Original Article

The Effects of Radiotherapy on Arterial Diameters in Patients with High-Grade Glial Tumors Who Have Undergone Adjuvant Radiotherapy

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Abstract

Background and Aims: Our purpose was to evaluate the M2 branch of the middle cerebral artery (MCA) in high-grade glial tumor patients who undergo adjuvant radiotherapy (RT). For this purpose, the diameter of the M2 branch was measured and evaluated by means of contrast-enhanced magnetic resonance imaging (CE-MRI) before and after RT. Post-radiotherapeutical measurements were made 1, 3, 5, and 7 months after the procedure; and vascular diameter alterations were evaluated. **Materials and Methods:** CE-MRI examinations were performed on the 32 patients enrolled in the study, who had undergone radiotherapy of the temporoparietal region. MRI examinations were performed prior to RT (RT0) and 1 (RT1), 3 (RT2), 5 (RT3), and 7 (RT4) months after RT. The M2 branch of the MCA was evaluated on MRI images, and the vessel diameter was measured in millimeters (mm), and then comparisons were made. **Results:** Statistically significant results were obtained during RT0-RT1, RT0-RT2, RT0-RT3, RT0-RT4, RT1-RT2, RT2-RT4, and RT3-RT4, and comparisons of the diameters of the M2 branch of the right MCA were performed ($P < 0.05$). When the same measurements and comparisons were made for the M2 branch of the left MCA, statistically significant results were found for the RT1-RT2, RT1-RT3, and RT1-RT4 comparisons ($P < 0.05$). **Conclusion:** Our study showed that the MCA M2 branch diminished in size following RT. This was demonstrated by means of CE-MRI controls performed up to 7 months after the completion of the RT procedures.

Keywords: *Adjuvant radiotherapy, high-grade glial tumor, radiologic follow-up*

Introduction

High-grade gliomas (HGGs) are the most frequent primary brain tumors of the central nervous system (CNS) of adults. The HGG tumors of the brain are of two main types: Grade 4 glioblastoma multiforme (GBM) and Grade 3 anaplastic glioma. HGGs comprise almost 80% of all malignant primary cranial tumors. The standard mode of therapy in HGG is maximum safety resection, followed by temozolomide (TMZ) administration and radiotherapy (RT). The overall survival (OS) rate had been very low in HGG; however, the recent advances made in surgical techniques, RT administration, and chemotherapy have led to the development of a better outcome, and the OS has risen to 2 years in 44% of the patients.[1]

In HGG of patients between 18 and 79 years of age, external curative RT is established by the application of an adjuvant dose of 60 Gy, administered by means of conventional fractionation. The adjuvant RT for HGG has undergone an evolution up to the present day. Initial

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applications comprised administration of radiation from both contralateral aspects in order to cover the whole brain volume. However, later, it was demonstrated in the Trial 80-01 Study of the Brain Tumor Cooperative Group that there was no statistically significant difference in terms of OS between patients who had received a whole brain RT and patients who had received a partial brain RT.[2] The contemporary method of RT application for HGG is the administration of a partial RT, performed with large margins, which are defined by the evaluation of the contrast-enhanced (CE) T1-weighted (T1W) images and the edema-demonstrating T2W and fluid-attenuated inversion recovery (FLAIR) and magnetic resonance imaging (MRI) images. During this partial RT administration, the M2 branch of the middle cerebral artery (MCA) is contained in the RT area at phase 1.

The MCA is the most frequently associated artery with stroke. This artery originates from the internal carotid artery (ICA) and trifurcates into the M1, M2, and M3 branches. These branches feed the frontal, temporal, and parietal lobes, together with the caudate nucleus, internal capsule, and thalamus, which constitute the deep cerebral structures. An occlusion of the MCA may well lead to hypoperfusion of these structures and cause neurologic symptoms.[3,4]

In this study, the diameters of the M2 branches of the MCAs of the patients undergoing curative-dose adjuvant external RT were measured and compared by means of evaluating the CE-MRI examinations performed prior to RT (RT0) and 1 month (RT1), 3 months (RT2), 5 months (RT3), and 7 months (RT4) after RT. In this study, all patients were given an adjuvant curative dose of RT after total surgical resection with the diagnosis of GBM. It was aimed to monitor the change in vessel diameter over time in the M2 branch of MCA and to clinically observe the patients from the neurological point of view.

Materials and Methods

Patients

The study was conducted retrospectively. The ethical approval was obtained from the Ethical Committee of the University of Cukurova School of Medicine prior to the study. A limited number of patients were included in this study because patients with a primary tumor and RT area in the temporoparietal region were included in this study. No co-morbidity was observed during the follow-up of the patients after RT. From the ethics committee of Çukurova University Faculty of Medicine, ethical approval was obtained with 96 meeting number and 74 decision number dated February 14, 2020. Thirty-two patients, of whom 14 (43.75%) were females and 18 (56.25%) were males, were enrolled in the study protocol. These patients had undergone an RT of the temporoparietal zone at the Adana City Training and Research Hospital, Department of Radiation Oncology, between May 2016 and January 2020. Twenty (62.5%) patients had been operated from the right temporoparietal zone, whereas 12 (37.5%) had been operated from the left temporoparietal zone. Eighteen (56.25%) patients had Grade 4, and 14 (43.75%) patients had Grade 3 diagnoses prior to RT.

All patients underwent a CE-MRI examination prior to and 1, 3, 5, and 7 months after the RT sessions. All MRI examinations were performed using a Philips Ingenia 1.5 T scanner (Philips, Eindhoven, The Netherlands). All patients underwent an initial basic enhanced scan, followed by a CE T1 imaging of the brain. All studies were evaluated on the workstation monitor of the MRI system. No neurological symptoms were detected at succeeding controls.

Radiotherapy management

Post-operative MRI examinations were taken as a reference for RT planning. The clinical target volume (CTV) was fixed as 0.5–2.0 cm^3, according to the physician's choice and marginal borders defined at the clinical studies. The planning target volume (PTV), on the other hand, was fixed on the basis of a 5-mm margin. The RT dose was adjusted as 46 Gy at phase 1 for the pre-boost CTV, which contained the area of peritumoral edema, which was demonstrated as a signal increase at the T2W and FLAIR sequences. At phase 2, on the other hand, an external curative RT of 60 Gy was administered by means of intensity-modulated radiation therapy (IMRT), which was focused on the residual tumor and resection cavity. TMZ was administered synchronously with the RT.[5,6] In all the patients, the M2 branch of the MCA was contained in the RT area during phase 1. All patients received curative dose RT with 60Gy IMRT treatment method, with a total of 30 fractions from 200cGy daily. RT was given to the patients using an Elekta Versa HD Linear Accelerator Device 6 MV photons Flattening Filter Free (FFF).

Statistical methods

Descriptive statistical analyses were performed by means of the median, standard deviation, minimum, and maximum values. Student's paired t test was utilized for comparing the pre- and post-RT values of these descriptive statistical definitions. The Pearson correlation coefficient was used in order to define the relation between these variables. The statistical significance was designated as 0.05. The SPSS statistical packet program was utilized for all statistical procedures.

Results

The mean age of the patients was 54.44 (34–72) years; however, the mean body weight was 71.13 (61–85) kg, and the mean height was 166.09 (157–179) cm.

Comparative descriptive analyses on the basis of gender are provided in Table 1. No statistically significant difference could be found between the genders in terms of right (R) and left (L) MCA diameters recorded at the RT0, RT1, RT2, RT3, and RT4 phases ($P > 0.05$).

Table 2 demonstrates the diameter measurements of the M2 branches of the MCA, performed prior to and 1, 3, 5, and 7, months after the radiotherapy session. The table also shows the comparisons of these values and their statistical analyses. The M2 diameter values are given as the right and left separately. As can be readily seen from Table 2, the M2 diameter values demonstrate a general decline after RT, in comparison to the pre-RT values. The differences between the right-sided pre-RT and RT1, RT2, RT3, and RT4 measurements of the M2 demonstrated statistical significance ($P < 0.05$). The measurements of the M2 disclosed a statistically significant decrease in diameter, following RT. Besides, right-sided measurements demonstrated statistically

Table 1: Comparative descriptive analyses on the basis of gender

	n	Mean	Std. Deviation	Min.	Max.	*P*
Age at Time of Diagnosis						
Female	14	54.07	7.721	41	72	0.855
Male	18	54.72	11.328	34	72	
Total	32	54.44	9.771	34	72	
Weight						
Female	14	72.79	5.659	65	85	0.149
Male	18	69.83	5.544	61	78	
Height						
Female	14	165.14	7.502	157	179	0.452
Male	18	166.83	5.044	159	178	
RTORMCA						
Female	14	2.3000	0.50394	1.49	3.12	0.980
Male	18	2.3056	0.70165	1.24	3.63	
RTOLMCA						
Female	14	2.3064	0.61482	1.35	3,50	0.885
Male	18	2.3422	0.74456	1.22	3.75	
RT1RMCA						
Female	14	2.2650	0.47584	1.48	3.05	0.939
Male	18	2.2817	0.68431	1.23	3.60	
RT1LMCA						
Female	14	2.3386	0.62457	1.35	3.52	0.933
Male	18	2.3178	0.73249	1.20	3.76	
RT2RMCA						
Female	14	2.22429	0.475665	1.460	3.000	0.541
Male	18	2.35762	0.671374	1.230	3.610	
RT2LMCA						
Female	14	2.3250	0.59747	1.33	3.48	0.766
Male	18	2.3975	0.70699	1.28	3.72	
RT3RMCA						
Female	14	2.2057	0.48587	1.40	3.00	0.512
Male	18	2.3500	0.67274	1.18	3.58	
RT3LMCA						
Female	14	2.3300	0.60281	1.38	3.49	0.856
Male	18	2.3744	0.70896	1.26	3.72	
RT4RMCA						
Female	14	2.1814	0.48731	1.37	3.00	0.497
Male	18	2.3325	0.68142	1.12	3.55	
RT4LMCA						
Female	14	2.3200	0.59201	1.39	3.47	0.752
Male	18	2.3993	0.73326	1.25	3.77	

Table 2: Comparative descriptive analyses of the differences and their results

	Mean	Std. Deviation	Difference	Std. Deviation	P
RTORMCA	2.3800	0.62043	0.02848	0.03572	0.001
RT1RMCA	2.2994	0.60123			
RTORMCA	2.3800	0.59921	0.058645	0.050816	0.001
RT2RMCA	2.32135	0.590529			
RTORMCA	2.3800	0.59921	0.07419	0.05303	0.001
RT3RMCA	2.3058	0.59192			
RTORMCA	2.3800	0.59921	0.09419	0.07094	0.001
RT4RMCA	2.2858	0.59860			
RTOLMCA	2.3536	0.68744	0.00030	0.10092	0.986
RT1LMCA	2.3533	0.68317			
RTOLMCA	2.4058	0.67130	0.01581	0.10408	0.404
RT2LMCA	2.3900	0.65376			
RTOLMCA	2.4058	0.67130	0.02516	0.11515	0.233
RT3LMCA	2.3806	0.65714			
RTOLMCA	2.4150	0.68078	0.02767	0.11215	0.187
RT4LMCA	2.3873	0.66257			
RT1RMCA	2.3494	0.58071	0.028000	0.044227	0.001
RT2RMCA	2.32135	0.590529			
RT1RMCA	2.3494	0.58071	0.04355	0.05823	0.001
RT3RMCA	2.3058	0.59192			
RT1RMCA	2.3494	0.58071	0.06355	0.07273	0.001
RT4RMCA	2.2858	0.59860			
RT1LMCA	2.4065	0.66518	0.01645	0.03545	0.015
RT2LMCA	2.3900	0.65376			
RT1LMCA	2.4065	0.66518	0.02581	0.05117	0.009
RT3LMCA	2.3806	0.65714			
RT1LMCA	2.4167	0.67407	0.02933	0.05317	0.005
RT4LMCA	2.3873	0.66257			
RT2RMCA	2.32135	0.590529	0.015548	0.043170	0.054
RT3RMCA	2.3058	0.59192			
RT2RMCA	2.32135	0.590529	0.035548	0.055109	0.001
RT4RMCA	2.2858	0.59860			
RT2LMCA	2.3900	0.65376	0.00935	0.03924	0.194
RT3LMCA	2.3806	0.65714			
RT2LMCA	2.4030	0.66085	0.01567	0.04477	0.065
RT4LMCA	2.3873	0.66257			
RT3RMCA	2.3058	0.59192	0.02000	0.03596	0.004
RT4RMCA	2.2858	0.59860			
RT3LMCA	2.3960	0.66269	0.00867	0.03003	0.125
RT4LMCA	2.3873	0.66257			

significant variations among the post-radiotherapeutic RT1, RT2, RT3, and RT4 phases ($P < 0.05$).

The left-sided post-RT measurements showed a tendency to decline, in comparison to the pre-RT measurements, but still, this difference was not found to be statistically significant. However, on the other hand, statistically significant differences were found between the RT1 and the remaining RT2, RT3, and RT4 measurements of the M2.

The correlation coefficients for the relations between the MCA M2 diameter measurements performed at the RT0, RT1, RT2, RT3, and RT4 phases and the variables of age, weight, and height are demonstrated in Table 3. As can be seen from the table, no statistically significant relations exist between the M2 measurements and the age and weight variables of the patients. However, on the other hand, a statistically significant but negative correlation was found between the RT0 and RT1 RMCA measurements and the heights of the patients ($P < 0.05$). This low-grade negative correlation points to a decline in the RT0 RMCA and RT1 RMCA values as the height values increase. However, on the other hand, positive and statistically highly significant correlations were

Table 3: Correlation coefficients between the variables

	Age	Weight	Height	RT0RMCA	RT0LMCA	RT1RMCA	RT1LMCA	RT2RMCA	RT2LMCA	RT3RMCA	RT3LMCA	RT4RMCA	RT4LMCA
Age	1												
Weight	0.191	1											
Height	0.004	-0.094	1										
RT0RMCA	0.138	-0.120	-0.349*	1									
RT0LMCA	0.259	-0.077	-0.094	0.867**	1								
RT1RMCA	0.149	-0.129	-0.344*	0.999**	0.869**	1							
RT1LMCA	0.273	-0.078	-0.123	0.871**	0.989**	0.872**	1						
RT2RMCA	0.169	-0.144	-0.355	0.996**	0.865**	0.997**	0.869**	1					
RT2LMCA	0.302	-0.086	-0.123	0.850**	0.988**	0.852**	0.999**	0.867**	1				
RT3RMCA	0.140	-0.139	-0.354	0.996**	0.863**	0.995**	0.868**	0.997**	0.865**	1			
RT3LMCA	0.302	-0.062	-0.135	0.847**	0.985**	0.849**	0.997**	0.864**	0.998**	0.860**	1		
RT4RMCA	0.142	-0.149	-0.349	0.993**	0.865**	0.993**	0.869**	0.996**	0.867**	0.998**	0.863**	1	
RT4LMCA	0.320	-0.047	-0.157	0.849**	0.986**	0.852**	0.997**	0.865**	0.998**	0.860**	0.999**	0.860**	1

*:$P<0.05$; **:$P<0.01$

found between the RMCA M2 values measured at the RT0, RT1, RT2, RT3, and RT4 phases.

Discussion

Randolph *et al*.[6] have performed the follow-ups of their HGG patients who had undergone RT, with MRI. We, too, performed the RT1, RT2, RT3, and RT4 follow-ups of our HGG patients by means of performing MRI examinations.

Byun *et al*.[7] have administered a single fractional 10 Gy RT into the oral cavities of rats and have reported anatomical damage to the immune system and the blood and lymph vessels of the buccal mucosa.

Haynes *et al*.,[8] on the other hand, have emphasized in their article that the risk of stroke may increase in patients with T1 larynx cancer who undergo an irradiation of the neck and receive a 3000 cGy anteromedial irradiation to the carotid artery, even in the absence of complications.

Choi *et al*.[9] have published an article in which they report the RT doses they used in early stage neck cancers. The authors emphasize in this study that they stabilized the "organ at risk volume dose" of the carotid arteries between V30 Gy <20% and V10 Gy <50% against the odds of a stroke risk.

Acute side effects in RT-related tissues arise during RT and 6 weeks after RT. Early delayed side effects come out during a period of up to 6 months after RT, and chronic side effects are seen after 6 months following RT.[10]

Silverberg *et al*.[11] performed a study in 1978 and irradiated the cervical lymph nodes of patients with different cancer types, applying different radiation doses of 4400, 5650, and 6820 rads. They then investigated the effects of these radiation doses on the carotid arteries and reported that the destruction which befell the carotid arteries was not dose-dependent but was associated with the ages and genders of the patients. In our study however, we could not find any statistically significant differences among the patients in regard to their ages and genders, concerning the radiation of the M2 branch of the MCA received during RT [Table 1].

Even though the mean diameters of the M2 branches of the MCA were found to be rather higher in males than females in the RT0, RT1, RT2, RT3, and RT4 phases, this difference was not statistically significant [Table 1].

During the recent years, a significant process has been achieved in the survival rates of patients with head and neck cancers, thanks to the substantial developments that have taken place in RT techniques. The rates of vascular injury and carotid stenosis have conspicuously decreased because of the same technical developments. Several authors have reported carotid artery stenoses and succeeding cerebral ischemic attacks and strokes, following RT. Lam *et al*.,[12] who have performed a study in which they compared the carotid arteries of patients who had undergone RT, with patients who had not. The RT patients were 71 nasopharynx cancer patients who had received RT, whereas the control group consisted of 51 newly diagnosed nasopharynx patients who had not received RT. The authors have reported that the RT patient group had developed significant arterial stenosis of the external branches of the carotid artery.

Cheng *et al*.[13] performed a study in which they irradiated the cervical lymph nodes of 96 nasopharyngeal cancer patients with differing doses of 45 Gy, 50 Gy, 60 Gy, and 66 Gy and compared the results with those from 96 healthy control individuals. The authors followed these patients for a mean period of 79.9 months and then evaluated their carotid arteries with duplex ultrasonography, and they detected a stenosis of 70% or more in 14 internal carotid arteries of 12 patients, six of whom had presented with an obstruction. On the other hand, a stenosis of 70% or more was detected in 11 carotid arteries of nine patients, four of whom had presented with an obstruction. In general, a critical stenosis of the common or internal carotid artery was found in 15 patients (16%). Twenty (21%) patients, on the other hand, had a mild stenosis. No stenosis of the carotid arteries was detected in the control group. A significant association was found between carotid steosis and a pre-RT history of smoking, cerebrovascular symptoms, age, and cardiac disease. The results of our study revealed statistically significant differences in terms of the diameters of the M2 branches of the MCA, when comparisons were made between the basal R0 and succeeding phases mentioned above ($P < 0.05$). It was found that the mean diameters of both the right and left M2 branches of the MCA demonstrated a statistically significant downward slope as phases continued up to the 7th month following the RT [Table 2]. On the other hand, the fact that statistically significant results were not obtained in other measurements may be attributed to the sample size of the study group [Table 2].

It was noted that the RT0 RMCA and RT1 RMCA values showed a tendency as heights increased; however, still highly positive correlations in vessel diameters were demonstrated between all the remaining phases of the follow-up period [Table 3].

Previous studies in the literature have demonstrated that a decrease in carotid artery diameter takes place following different doses of RT applied to the cervical lymph nodes of patients with head and neck cancers. Our study showed that the M2 branch of the MCA undergoes a stenosis during the RT1, RT2, RT3, and RT4 phases of radiotherapy.

As a conclusion, we would like to emphasize that in none of our patients could we detect a complete obstruction of the M2 branch of the MCA, following the RT1, RT2, RT3, and RT4 phases. The M2 branch showed some degree of narrowing, but still, the cerebrovascular blood supply was maintained. No neurologic damage could be found during the controls performed at the RT1, RT2, RT3, and RT4 applications. Our results have clearly indicated that the RT administered to patients with high-grade glial tumors does not cause an occlusion in the M2 branch of the MCA.

Up to our knowledge, no studies have been conducted up to now, concerning RT and cerebral artery diameters. Our study is the first of its kind to comprise chronic phase vascular alterations in cerebral RT. Although a limited number of patients were included in this study, it is a new and up-to-date study in terms of examining the change in diameter of the MCA after RT in the M2 branch and examining whether there is neurological damage in patients.

Conclusion

Statistically significant alterations in the diameters of the RMCA M2 branches contained in the phase 1 RT areas were detected during the follow-ups performed between the RT0 and RT 4 phases. On the other hand, additional statistically significant alterations in the diameters of the LMCA M2 branches contained in the phase1 RT area were detected in terms of the measurements performed at the RT1 and RT2, RT3, and RT4 phases.

As a conclusion, we would like to emphasize our finding that the M2 branch of the MCA was found to decrease in diameter in the follow-ups performed up to 7 months after RT. These alterations were demonstrated by MR and found to be statistically significant. This change in vessel diameter after a curative dose of 60Gy/30 fractions of RT did not cause any neurological side effects in the follow-up of the patients.

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Conflicts of interest

There are no conflicts of interest.

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