



Relationship of Serum Microsomal Prostaglandin E2 Levels with Residual Tumor Volume in Patients with Astrocytoma

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ABSTRACT

AIM: To investigate the relationship between tumor volume and serum microsomal prostaglandin E2 (mPGE2) levels in patients with astrocytic tumors.

MATERIAL and METHODS: The study included patients with astrocytic tumors who were treated at our clinic between August 2015 and December 2016. Preoperative and postoperative contrast-enhanced cranial magnetic resonance imaging (MRI) scans were performed (within the first 24 h), and preoperative and postoperative residual tumor volumes were calculated. Microsomal prostaglandin E2 (mPGE2) levels were measured and compared in the serum samples of the patients before surgery, on the first day after surgery, and at 1 week after the surgery.

RESULTS: The study included 20 patients, 13 of whom were males and 7 were females, with a mean age of 57.20 ± 14.66 yr. The mean postoperative tumor volume was $9,180.69 \text{ mm}^3$ (range, 0.00–41,961.60), which was significantly lower than the preoperative mean tumor volume of $37,323.84 \text{ mm}^3$ (range, 4,457.40–108,247.20; $z = -3.920$, $p < 0.001$). On the first postoperative day, the mean mPGE2 level was $1,776.50 \text{ pg/ml}$ (range, 771–5,010), which was similar to the preoperative mean mPGE2 level of $1,769.20 \text{ pg/ml}$ (range, 681–3,480). On the seventh postoperative day, the mean mPGE2 level was 955.50 pg/ml (range, 31–2,130), which was significantly lower than the preoperative and postoperative first-day mean mPGE2 levels ($p < 0.001$). No correlation was found between preoperative and postoperative tumor volumes and mPGE2 levels.

CONCLUSION: Compared with preoperative mPGE2 levels, mPGE2 levels decreased significantly on the seventh postoperative day. However, no correlation was observed between the tumor volume removed and decrease in mPGE2 levels.

KEYWORDS: Astrocytoma, mPGE2, Tumor volume, Prognostic marker

INTRODUCTION

Primary brain tumors have a poor prognosis and are one of the most devastating malignancies that negatively affect cognitive abilities of the patients, impair their quality of life, and account for approximately 2.5% of all cancer-related deaths (25). Glioma is one of the most aggressive types of brain cancer, which account for approximately 80.8% of malignant central nervous system tumors and affect millions of

people worldwide (20,27). According to the 2021 World Health Organization classification, gliomas can be divided into adult-type diffuse gliomas, astrocytoma (isocitrate dehydrogenase (IDH)-mutant), oligodendroglioma (IDH-mutant and 1p/19q-codeleted), and glioblastoma (GBM; IDH wild-type) subtypes (20). Apart from brain and vascular diseases, gliomas are the most common cause of death in the central nervous system. In patients with Glioblastoma Multiforme (GBM), a 5-yr overall survival rate of 6.8% has been reported (26).

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Researchers have focused on molecular mechanisms, such as tumor cell growth, proliferation, development, and metastasis, to provide effective treatment of tumors. The fate of tumor cells can be determined by factors, such as tumor microenvironment, tumor cell heterogeneity, tumor cell presence, and inflammatory mediators (1). Inflammatory mediators are very important in tumor development and progression (3,14,22). Prostaglandins and leukotrienes, both potent inflammatory mediators, play a role in tumorigenesis and progression (11,13,37). Cyclooxygenase-2 (COX-2) is associated with tumor cell proliferation, angiogenesis, apoptosis, invasion, and drug resistance (7,12,16,32). Furthermore, prostaglandin E2 (PGE2), which is the main product of COX-2, increases in colon, lung, breast, and head and neck cancers (10,17,23,31). Increased COX-2 and PGE2 levels are believed to be associated with a poor prognosis in malignant lesions (28).

Studies have been conducted to determine prognostic factors for all cancers, including brain cancers. Studies have shown that PGE2 levels increase in brain tumors (2,6,18). However, no study has been conducted so far to determine whether PGE2 can be used as a prognostic factor. Thus, this study aimed to determine preoperative and postoperative microsomal PGE2 (mPGE2) levels in patients with glioma and determine their relationship with tumor volume.

■ MATERIAL and METHODS

This prospective study was conducted at our clinic, with ethics approval granted by Izmir Bozyaka Education and Research Hospital Ethics Committee (approval number 26.06.2015/404-421), and all participants provided written informed consent in accordance with the Declaration of Helsinki. The study included 20 patients who were radiologically diagnosed with an astrocytic tumor and scheduled for surgery between August 2015 and December 2016. Pediatric patients (<18 years), patients with pathologically confirmed absence of astrocytic tumors, patients with recurrent tumors, patients previously treated with chemotherapy and/or radiotherapy, patients with active infection, and pregnant patients were excluded from the study.

The patients' magnetic resonance imaging (MRI) images were captured using a Philips Brilliance 230 1.5 Tesla MRI device (Philips Medical Systems, The Best, Netherlands). All patients underwent preoperative and postoperative contrast-enhanced cranial MRI. The following measurements were taken for the contrast-enhanced T1 sequence: TR/TE, 456/8.0; section thickness, 6 mm; section interval, 1 mm; NSA, 2 FOV; AP, 210; RL, 214; and FH, 253. The patients' preoperative tumor volumes were calculated as square millimeters of the contrast-enhanced tumor area in each section, beginning with the first section where the lesion was visible in the contrast-enhanced T1 sequence. Tumor volumes in cubic millimeters were calculated by multiplying the cross-sectional area of the contrast-enhanced tumor by its thickness. Therefore, three-dimensional tumor volumes in cubic millimeters were calculated from the two-dimensional cross-sectional areas of the irregularly shaped tumor tissue. The three-dimensional volumes of irregularly shaped tumor tissues (22) were calculated using the modified Cavalieri method (Figure 1).

To rule out infection, serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and white blood cell (WBC) counts were measured in patients. CRP, ESR, WBC, and serum mPGE2 levels were measured in patients preoperatively (before corticosteroid treatment), on the first postoperative day, and on the seventh postoperative day three times. To assess serum mPGE2 enzyme levels, an enzyme-linked immunosorbent assay (ELISA; Elabscience Cat. No. E-EL-0034) was used.

Statistical Analysis

SPSS 20 statistical software was used for the statistical analysis. Mean, standard deviation, frequency, and percentage are examples of descriptive statistics. The Shapiro–Wilk test and graphical examination were used to determine whether the quantitative data conformed to the normal distribution. The Friedman test was used to compare repeated measurements. If there was a difference in the measurements, the Wilcoxon test was used to compare them. For the correlation of numerical variables, Spearman correlation analysis was used. The significance level for all statistical analyses was set at $p < 0.05$.

■ RESULTS

The study included 13 male patients and 7 female patients, with a mean age of 57.20 ± 14.66 yr. Table I shows the demographic information for the patients. Seizures were the most common complaint (30%, $n=6$), followed by speech disorders (25%, $n=5$). Tumors were found in the left hemisphere in 10 patients and the right hemisphere in the other 10. There were 18 GBM patients and two oligodendroglioma patients.

Table II compares tumor volumes and mPGE2 levels before and after surgery. The postoperative mean tumor volume was $9,180.69 \text{ mm}^3$ (range, 0.00–41,961.60), which was significantly lower than the preoperative mean tumor volume of $37,323.84 \text{ mm}^3$ (range, 4,457.40–108,247.20; $z = -3.920$, $p < 0.001$). An average of $28,143.15 \text{ mm}^3$ (range, 4,457.40–73,434) of tumor tissue was removed during the operations.

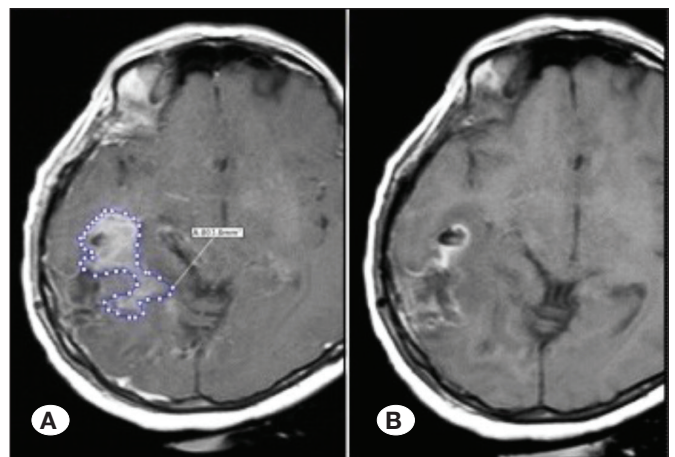


Figure 1: A) Preoperative, and B) postoperative contrast-enhanced T1W MRI sections for calculating tumor volume.

Table I: Demographic Characteristics of Patients

Characteristic	Value
Age (years, mean \pm SD)	57.20 \pm 14.66
Time of onset (days) (median, min–max)	30 (1–300)
Sex (n, %)	
Male	13 (65)
Female	7 (35)
Symptoms (n, %)	
Headache	4 (20)
Disorders of consciousness	3 (15)
Speech disorder	5 (25)
Motor deficit	2 (10)
Seizure	6 (30)
Lesion site (n, %)	
Right frontal	2 (10)
Right parietal	2 (10)
Right temporal	3 (15)
Right temporoparietal	3 (15)
Left frontal	3 (15)
Left frontoparietal	1 (5)
Left parietal	2 (10)
Left parieto-occipital	1 (5)
Left temporal	3 (15)
Tumor histology (n, %)	
Glioblastoma	18 (90)
Oligodendroglioma	2 (10)

Table II: Comparison of Preoperative and Postoperative Tumor Volumes and mPGE2 Levels

Variables	Mean \pm SD Median (min–max)	
Preoperative tumor volume	37,323.84 \pm 27,044.30 32,469.90 (4,457.40–108,247.20)	z = –3.920 p<0.001
Postoperative tumor volume	9,180.69 \pm 11,959.42 5,732.70 (0.00–41,961.60)	
mPGE2 (preoperative)	1,769.20 \pm 734.64 1,660 (681–3,480)	X ² = 56.200 p<0.001
mPGE2 (postoperative first day)	1,776.50 \pm 976.55 1,570 (771–5,010)	
mPGE2 (postoperative seventh day)	955.50 \pm 475.14 ^{a,b} 832 (31.00–2,130)	

X²: Friedman test, z: Wilcoxon test, **mPEG**: *Microsomal Prostaglandin E2*. ^ap<0.001 compared with mPGE2 (preoperative). ^bp<0.001 compared with mPGE2 (postoperative first day).

The preoperative mPGE2 level was 1,769.20 pg/ml on average (range, 681–3,480.00). On the first postoperative day, the mean mPGE2 level was 1,776.50 pg/ml (range, 771–5,010), which was comparable with the preoperative mean mPGE2 levels. On the seventh postoperative day, the mean mPGE2 level was 955.50 pg/ml (range 31.00–2,130.00), which was significantly lower than the preoperative and postoperative first-day mean mPGE2 levels (p<0.001). The mean mPGE2 level decreased by 813.70 pg/ml on the seventh postoperative day compared with the preoperative mean mPGE2 level.

Table III shows the relationship between preoperative and postoperative tumor volumes and mPGE2 levels. There was no relationship between preoperative mPGE2 levels and tumor volume. There was no correlation between the amount of tumor tissue left after surgery and mPGE2 levels measured on the first and seventh postoperative days.

Table IV shows the relationship between the surgically removed tumor mass and the difference in mPGE2. The surgically removed tumor mass did not correlate with either the postoperative first-day preoperative difference or the postoperative seventh-day preoperative difference. There were no correlations between preoperative and postoperative tumor volume, mPGE2 levels, age, gender, and tumor localization (Table V).

■ DISCUSSION

Herein, we investigated the relationship between tumor volume and mPGE2 in patients with glioma. Seven days after surgery, we detected a significant decrease in mPGE2 levels. However, no correlation was observed between the tumor volume removed and decrease in mPGE2 levels.

The COX pathway plays a pivotal role in tumor initiation, growth, and apoptosis. Studies have shown that COX isoforms are overexpressed in lung, liver, pancreatic, breast, colorectal, and head and neck cancers, renal cell carcinoma, leukemia, and lymphoma (8,24,39). Furthermore, many brain tumors ex-

Table III: Correlation Between Preoperative and Postoperative Tumor Volumes and mPGE2 Levels

	mPGE2 (preoperative)		mPGE2 (postoperative first day)		mPGE2 (postoperative seventh day)	
	ρ	p-value	ρ	p-value	ρ	p-value
Preoperative volume	0.115	0.629				
Postoperative volume	—	—	0.407	0.075	-0.274	0.242

ρ : Spearman correlation coefficient, mPEG: Microsomal prostoglandin E2.

Table IV: Correlation Between Surgically Removed Tumor Volume and Decrease in mPGE2 Levels

	mPGE2 (preoperative–postoperative first day)		mPGE2 (preoperative–postoperative seventh day)	
	ρ	p-value	ρ	p-value
Tumor volume	-0.214	0.366	-0.48	0.840

ρ : Spearman correlation coefficient.

Table V: Relationship Between Demographic Data and Tumor Volume and mPGE2 Levels

	Lesion site	Gender	Age
Preoperative volume	$\chi^2 = 7.562$ $p = 0.477$	$z = -0.357$ $p = 0.721$	$\rho = 0.125$ $p = 0.600$
Postoperative volume	$\chi^2 = 12.551$ $p = 0.128$	$z = -1.078$ $p = 0.281$	$\rho = -0.027$ $p = 0.911$
mPGE2 (preoperative)	$\chi^2 = 4.861$ $p = 0.772$	$z = -0.357$ $p = 0.721$	$\rho = -0.317$ $p = 0.173$
mPGE2 (postoperative first day)	$\chi^2 = 9.629$ $p = 0.292$	$z = -0.436$ $p = 0.663$	$\rho = -0.336$ $p = 0.147$
mPGE2 (postoperative seventh day)	$\chi^2 = 5.300$ $p = 0.725$	$z = -0.277$ $p = 0.782$	$\rho = -0.069$ $p = 0.771$

χ^2 : Kruskal–Wallis test; z : Mann–Whitney U test; ρ : Spearman correlation coefficient.

press high COX-2 levels (29). Anagnostopoulos-Schlepp et al. reported that PGE2 and PGF2 α are expressed by a variety of brain tumors, such as gliomas and meningiomas (2). Kokoglu et al. found that PGE2 levels in gliomas and meningiomas were significantly higher than in control tissues (18). Moreover, they documented that meningiomas had significantly higher PGE2 levels than gliomas. In their study on brain tumors, Venza et al. observed a positive correlation between PGE2 overproduction and IL-8 gene activation only in case of astrocytomas. The researchers also found that the positive correlation between mPGE synthase-1 and IL-8 mRNA levels was independent of tumor histological grade (36). Further, Casteli et al., while examining gliomas from different histological subgroups, reported that PGE2 production increased with anaplastic grade (6). Higher PGE2 levels in rapidly growing malignant brain tumors compared to slow-growing benign brain tumors have been associated with a poor prognosis (19).

A study of surgical specimens from 66 patients with astrocytomas found that high COX-2 expression, particularly in patients

with GBM, is associated with poor survival (33). In another study of 43 patients with GBM, patients with COX-2-negative glioblastoma had a median survival that was more than twice than in patients with COX-2-positive glioblastoma (5). Another study found that primary glioblastomas with high COX-2 expression had a shorter radiological recurrence than tumor cells with lower COX-2 expression levels (34). As a result, it has been proposed that COX-2 expression is a strong predictor of glioma aggressiveness and poor survival, independent of other variables (33). In another recent study, Panagopoulos et al. reported higher PGE2 content in GBM tumors than in low-grade gliomas. Furthermore, researchers found that the higher the PGE2 concentration, the lower the patient's survival (28). In vitro studies have shown that selective COX-2 inhibitors increase GBM susceptibility to chemotherapy and radiotherapy, increase apoptosis and cell death, and reduce tumor migration (15,29,35). In animal models, the administration of a COX-2 inhibitor together with temozolomide increases the cytotoxic effect of the drug on GBM and improves the average survival rate (21,38).

As with many cancer types, research into prognostic factors in gliomas is ongoing. O⁶-Methylguanine-DNA methyltransferase promoter methylation, isocitrate dehydrogenase mutations, epidermal growth factor receptor amplification/mutations, vascular endothelial growth factor overexpression, heat shock protein 10 overexpression, and adenosine A2A receptor gene expression have been associated with a poor prognosis in glioma (4,9,30).

This study aimed to determine the relationship between mPGE2 and prognosis by comparing the pre- and postoperative levels of mPGE2, which has previously been shown to be associated with a poor prognosis in gliomas. In our study, the tumor volume was reduced by surgery; however, the postoperative first-day mPGE2 values were found to be similar to the preoperative mPGE2 values. The mPGE2 values being similar to the preoperative mPGE2 values on the first postoperative day could be due to increased mPGE2 levels caused by the surgery that triggered inflammation. On postoperative day 7, mPGE2 levels were significantly lower than preoperative and postoperative mPGE2 levels. Surgical removal of approximately 75% of the tumor volume resulted in a 46% reduction in mPGE2 levels. PGE2 levels were reduced by 42% in cases where approximately 50% of the tumor volume was removed and 64% in cases where approximately 95%–100% of the tumor volume was removed. However, no correlation was observed between the removed tumor volume and decrease in mPGE2 levels. This, we believe, is due to the small patient population. In a similar study, Loh et al. observed significant decreases in PGE2 concentration 3 days after surgery. However, they did not examine the correlation between tumor volume removed and PGE2 reduction (19).

Our study has certain limitations. First, it was a single-centered study. Second, it had a small sample size. Last, it did not have a control group.

CONCLUSION

This study examined the relationship between tumor volume and mPGE2 levels in patients with glioma. mPGE2 levels decreased significantly on the seventh postoperative day compared with preoperative mPGE2 levels. However, no correlation was observed between the tumor volume removed and decrease in mPGE2 levels. The findings of our study should be re-evaluated in larger patient population studies.

Declarations

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Availability of data and materials: Data available on request from the authors: The data that support the findings of this study are available from the corresponding author, [author initials], upon reasonable request.

Disclosure: Authors declare no conflict of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: CA

Data collection: AY, MA

Analysis and interpretation of results: CA

Draft manuscript preparation: MA, CA

Critical revision of the article: AY

Other (study supervision, fundings, materials, etc...): AT, EK, OB

All authors (CA, MA, AT, EK, OB, AY) reviewed the results and approved the final version of the manuscript.

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