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Serum Fibroblast Growth Factor-2 Levels in Patients with Ocular Tumors: A Case-Control Study

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Abstract

Background: Ocular tumors comprise a heterogeneous group of benign and malignant lesions that may threaten vision and survival. FGF2 is a pro-angiogenic growth factor involved in cellular proliferation, migration, and tumor angiogenesis. However, evidence regarding serum FGF2 levels in patients with ocular tumors remains limited. This exploratory case-control study aimed to compare serum FGF2 levels between patients with ocular tumors and healthy controls and to evaluate differences in serum FGF2 levels between benign and malignant ocular tumors.

Methods: This study included 38 participants, consisting of 19 patients with ocular tumors and 19 controls without ocular or systemic tumors. All participants underwent ophthalmologic examination, and tumor diagnosis was determined based on clinical and pathological evaluation. Serum FGF2 levels were measured using an enzyme-linked immunosorbent assay. Data distribution was assessed using the Shapiro–Wilk test. Between-group comparisons were performed using the Mann–Whitney U test for non-normally distributed data.

Results: Serum FGF2 levels were significantly higher in patients with ocular tumors than in controls. The median FGF2 level was 431.39 (107.65-1291.38) pg/mL in the tumor group and 171.45 (100.59-933.61) pg/mLin the control group ($p = 0.040$). Among patients with ocular tumors, FGF2 levels were higher in malignant tumors than in benign tumors. The mean FGF2 level was 600.63 (419.34–1291. 38) pg/mL in malignant tumors and 171.23 (107.65–999.60) pg/mL in benign tumors ($p = 0.001$).

Conclusion: There is a significant association between FGF2 levels and the occurrence of ocular tumors. FGF2 also has potential as a biomarker to differentiate between benign and malignant ocular tumors.

1. INTRODUCTION

Ocular tumors can originate from either extraocular structure or intraocular components within the eye. These tumors may arise de novo (primary tumors) from native ocular tissues or may represent metastases (secondary tumors) from systemic malignancies, including breast, prostate, gastrointestinal, or pulmonary cancers. In clinical practice, secondary eye tumors are currently observed with greater frequency than primary ones.[1]

Epidemiologically, ocular tumors represent a rare and underreported subset of malignancies, with limited global data attributable to their low incidence and the absence of standardized classification systems. The most encountered primary ocular malignancies are ocular melanoma in adults and retinoblastoma in children.[2] In the United States, approximately 3,490 new cases of eye tumors were reported in 2023 (predominantly ocular melanoma) with a higher incidence among males and an age-related increase in risk. While the incidence of uveal melanoma has remained stable over recent decades, conjunctival melanoma has shown a rising trend.[3] In Asia, including Indonesia, epidemiological data are scarce and largely derived from single-center or regional hospital reports.[2] A retrospective study conducted at Dr. Wahidin Sudirohusodo Hospital in Makassar documented 70 cases between 2014 and 2016, with a

predominance in females and a high proportion of pediatric retinoblastoma, particularly in children under five years of age. Similar findings have been reported in other Indonesian centers, underscoring the predominance of retinoblastoma in early childhood and the need for broader epidemiological surveillance.[4,5,6]

Ocular tumors are complex entities that pose significant threats to both vision and survival, necessitating accurate diagnosis through comprehensive clinical evaluation and advanced imaging modalities. Despite their rarity, intraocular tumors require precise characterization due to their diverse presentations, ranging from benign, asymptomatic lesions to highly aggressive malignancies.[7,8] Diagnostic imaging tools, such as high-frequency ultrasonography, fluorescein angiography, optical coherence tomography (OCT), computed tomography (CT), and magnetic resonance imaging (MRI) are essential for assessing tumor dimensions, configuration, location, and extraocular extension. Ophthalmic ultrasonography, in particular, remains a valuable non-invasive and cost-effective modality.[9] Therapeutic decisions are influenced by tumor size, location, local invasion, and associated complications, with treatment options including observation, local excision, chemotherapy, radiation, or enucleation in advanced cases. Given the limitations of invasive biopsy procedures, increasing attention has been directed toward molecular biomarkers, such as FGF2, as adjuncts in diagnosis and personalized treatment planning.[10]

FGF2 is a potent angiogenic growth factor expressed in various normal tissues and tumor types. It exerts strong mitogenic effects not only on endothelial cells but also on a wide array of mesodermally derived cells. FGF2 shares sequence homology with oncogenes such as int-2, hst1/K-fgf, and keratinocyte growth factors. Prior studies have demonstrated elevated FGF2 expression in corneal tumors and related cell lines, implicating its involvement in tumor biology.[11,12] Physiologically, FGF2 contributes to embryogenesis, angiogenesis, tissue homeostasis, and wound healing by functioning as a paracrine, autocrine, or endocrine factor that activates FGF tyrosine kinase receptors. Aberrant FGF2 activation has been implicated in human cancers, promoting cellular proliferation, differentiation, migration, and survival.[13,14]

Uveal melanoma, the most prevalent primary intraocular malignancy, constitutive activation of the FGF2 signaling pathway fosters autocrine stimulation loops that sustain tumor progression.[15] Cancer stem-like cells (CSCs), a subpopulation responsible for tumor initiation, metastasis, chemoresistance, and recurrence, have been identified in uveal melanoma. Notably, these tumors exhibit resistance to conventional chemotherapy, underscoring the urgency for novel therapeutic approaches.[16]

Experimental studies using murine melanoma cell lines and human uveal melanoma models (UM Mel285, Mel270, 92.1, OMM2.3) have shown that inhibition of FGF2 signaling via molecules such as Long Pentraxin 3 (PTX3) or NSC12 effectively suppresses tumor proliferation, induces apoptosis, and impairs cell migration. These findings position FGF2 inhibitors as promising candidates for targeted therapy in ocular melanoma.[17]

Given the potential role of FGF2 in tumor proliferation and angiogenesis, this exploratory case-control study aimed to compare serum FGF2 levels between patients with ocular tumors and healthy controls. In addition, this study evaluated whether serum FGF2 levels differed between benign and malignant ocular tumors.

2. MATERIALS AND METHODS

Study Design and Setting

This study employed an observational case–control design to investigate the association between serum FGF2 levels and the incidence of ocular tumors. Data were collected cross-sectionally. The study was conducted at the Oculoplasty, Reconstructive, and Ocular Oncology Division of the Ophthalmology Outpatient Clinic, Prof. Dr. Chairuddin P. Lubis General Hospital, Universitas Sumatera Utara, and its affiliated network hospitals, in collaboration with the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara (FK USU), Medan, Indonesia. The study commenced in September 2024 and continued until the required sample size was achieved. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Sumatera Utara (Approval No. 64/KEP/USU/2024). All participants provided written informed consent.

Study Population and Subjects

Study Population

The target population consisted of all patients with ocular tumors and healthy individuals attending the outpatient clinics.

Study Subjects

Subjects were selected consecutively from the study population based on eligibility criteria. Only those who met both the inclusion and exclusion criteria and provided informed consent were included.

Participants

A total of 38 participants were enrolled, including 19 patients diagnosed with ocular tumors (case group) and 19 individuals without ocular or systemic tumors (control group). All participants were recruited consecutively from the Ophthalmology Outpatient Clinic of Prof. Dr. Chairuddin P. Lubis Hospital and its affiliated institutions.

The diagnosis of ocular tumors was established based on clinical ophthalmologic examination and pathological evaluation. Pathological confirmation was obtained using fine-needle aspiration biopsy, incisional biopsy, excisional biopsy, or histopathological examination, according to the clinical indication and tumor location. Tumors were classified as benign or malignant based on the final pathological diagnosis.

The tumor group consisted of heterogeneous ocular tumor entities. Basal cell carcinoma was the most frequent diagnosis, followed by epidermoid cysts. Other diagnoses included pleomorphic adenoma, pyogenic granuloma, retinoblastoma, sebaceous cell carcinoma, conjunctival cyst, malignant conjunctival melanoma, melanocytic nevus, papilloma, and uveal melanoma. Based on pathological classification, 10 cases were categorized as malignant tumors and 9 cases as benign tumors.

Eligibility Criteria

Participants were enrolled based on predefined inclusion and exclusion criteria. The case group included pediatric and adult patients diagnosed with ocular tumors who attended the ophthalmology outpatient clinic at Prof. Dr. Chairuddin P. Lubis General Hospital and its affiliated hospitals, and who provided informed consent to participate in the study. The control group consisted of individuals without a history of ocular tumors or tumors in other organ systems, who were confirmed to be free of malignancy and agreed to participate as controls. Participants were excluded from either group if they had active ocular inflammation or infection, a history of ocular trauma, prior ocular tumor surgery, or were pregnant at the time of enrollment. In addition, individuals who refused blood sampling or withdrew consent at any stage of the study were also excluded.

Sample Size

The minimum required sample size for this study was determined based on a comparative analytical design involving continuous numerical variables, with a significance level of 5% and a statistical power of 80%.50 Using previously reported values for the standard deviation and expected mean difference in FGF2 levels between groups, the calculation yielded a minimum of 18 participants per group. To account for potential dropouts, a total of 19 subjects were recruited for both the case and control groups.

Clinical Examination and Sample Collection

All participants underwent standardized ophthalmologic evaluation. Visual acuity was measured using a Snellen chart. Anterior segment examination was performed with slit-lamp biomicroscopy, and intraocular pressure was measured using a non-contact tonometer. Posterior segment evaluation was conducted via indirect ophthalmoscopy. Following clinical assessment, venous blood samples (3 mL) were collected from each subject under aseptic conditions.

The diagnosis of ocular tumors was established based on clinical ophthalmologic examination and pathological evaluation. Pathological confirmation was obtained using fine-needle aspiration biopsy, incisional biopsy, excisional biopsy, or histopathological examination, according to the clinical indication and tumor location. Tumors were classified as benign or malignant based on the final pathological diagnosis.

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conjunctival melanoma, melanocytic nevus, papilloma, and uveal melanoma. Based on pathological classification, 10 cases were categorized as malignant tumors and 9 cases as benign tumors.

Sample Processing and FGF2 Measurement

Blood samples were allowed to clot at room temperature, then centrifuged at 3,000 rpm for 15 minutes to separate serum. The serum was aliquoted and stored at −80°C until analysis. Quantitative measurement of serum FGF2 was conducted at the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara, using a commercially available sandwich ELISA kit (bFGF/FGF2, Santa Cruz Biotechnology, USA; Catalog No. sc-1006), following the manufacturer's instructions. All samples were analyzed in duplicate, and the mean value was used for analysis. The assay's sensitivity and precision were within accepted quality control standards.

Data Analysis

All data were entered into SPSS software (IBM SPSS Statistics, version 25) for analysis. Descriptive statistics were used to summarize demographic and clinical variables. Data distribution was tested for normality using the Shapiro–Wilk test. For normally distributed variables, group comparisons were performed using the independent samples t-test. For non-normally distributed data, the Mann–Whitney U test was applied. A p-value <0.05 was considered statistically significant.

3. RESULT

Participant Characteristics

A total of 38 participants were included in the study, comprising 19 patients with ocular tumors (case group) and 19 individuals without ocular or systemic tumors (control group). All participants met the inclusion and exclusion criteria. The demographic characteristics of both groups, including age and sex distribution, were recorded and summarized in Table 1. There were no statistically significant differences in age or gender between the case and control groups ($p > 0.05$), indicating comparability between the two groups.

Table 1. Participant Characteristic (n=38)

Demographic Characteristics	Case (n = 19)	Control (n = 19)	p
Sex, n (%)			
Male	7 (36.8)	6 (31.6)	0.732[a]
Female	12 (63.2)	13 (68.4)	
Age, year			
Mean ± SD	42.32 ± 25.61	40.74 ± 19.76	0.833[b]
Median (Min – Max)	45 (1 – 86)	38 (14 – 78)	

[a]Chi Square, [b]T Independent

Characteristics of Patients with Ocular Tumors

Table 2 summarizes the clinical and pathological characteristics of the 19 patients in the case group. With respect to occupational background, a slight majority of patients (57.9%) were employed in indoor environments, whereas the remaining 42.1% were engaged in outdoor occupations.

Histopathological examination based on fine-needle aspiration biopsy (FNAB) revealed diverse lesion types. The most frequently diagnosed tumor was basal cell carcinoma, accounting for 21.1% of cases, followed by epidermoid cysts (15.8%). Other lesions observed with equal frequency (10.5%) included pleomorphic adenoma, pyogenic granuloma, and retinoblastoma. Less frequently encountered tumors, each representing 5.3% of cases, comprised sebaceous cell carcinoma, conjunctival cyst, malignant conjunctival melanoma, melanocytic nevus, papilloma, and uveal melanoma.

Regarding tumor classification, malignant tumors were slightly more prevalent than benign tumors, with proportions of 52.6% and 47.4%, respectively. These findings reflect a heterogeneous spectrum of ocular tumor types and emphasize the need for precise pathological differentiation in clinical diagnosis.

Table 2 Clinical and Pathological Characteristics of Patients with Ocular Tumors (n = 19)

Characteristic	n = 19
Occupation, n (%)	
Indoor	11 (57,9)
Outdoor	8 (42,1)
Pathological Diagnosis	
Pleomorphic Adenoma	2 (10,5)
Basal Cell Carcinoma	4 (21,1)
Sebaceous Cell Carcinoma	1 (5,3)
Epidermoid Cyst	3 (15,8)
Conjunctival Cyst	1 (5,3)
Malignant Conjunctival Melanoma	1 (5,3)
Melanocytic Nevus	1 (5,3)
Papilloma	1 (5,3)
Pyogenic Granuloma	2 (10,5)
Retinoblastoma	2 (10,5)
Uveal Melanoma	1 (5,3)
Tumor Classification, n (%)	
Malignant Tumor	10 (52,6)
Benign Tumor	9 (47,4)

Serum FGF2 Levels

Quantitative analysis of serum fibroblast growth factor-2 (FGF2) levels was conducted for all participants (Figure 1). The median FGF2 level in the case group was 431.39 (107.65-1291.38) pg/mL, whereas in the control group was 171.45 (100.59-933.61) pg/mL. The distribution of FGF2 values was assessed for normality using the Shapiro–Wilk test and found to be non-normally distributed. Therefore, the Mann–Whitney U test was applied to compare the groups. The analysis revealed a statistically significant difference in FGF2 levels between the case and control groups ($p = 0.040$), indicating that FGF2 concentrations were significantly higher in patients with ocular tumors.

FGF2 Levels in Malignant and Benign Ocular Tumors

Quantitative analysis of serum fibroblast growth factor-2 (FGF2) levels was also performed within the case group to compare patients with malignant versus benign ocular tumors (Figure 2). The mean FGF2

concentration in the malignant tumor group was 772.9 ± 376.29 pg/mL, while the benign tumor group demonstrated a substantially lower mean concentration of 288.53 ± 284.46 pg/mL. The distribution of FGF2 levels was assessed using the Shapiro–Wilk test and found to be non-normally distributed. The statistical analysis revealed a significant difference in FGF2 levels between the two subgroups ($p = 0.001$), indicating that FGF2 concentrations were markedly higher in patients with malignant tumors.

In addition to mean values, median FGF2 levels further supported this observation: the malignant group had a median of 600.63 pg/mL (419.34–1291. 38), whereas the benign group showed a median of 171.23 pg/mL (107.65–999.60). These findings suggest that elevated FGF2 expression is more closely associated with malignant ocular tumor pathology, potentially reflecting increased proliferative and angiogenic signaling in tumor progression.

4. DISCUSSION

The central aim of this study was to investigate the association between FGF2 levels and the presence of ocular tumors. This was achieved by comparing serum FGF2 concentrations between patients with ocular tumors and healthy controls. The study enrolled a total of 38 subjects, comprising 19 patients with ocular tumors and 19 individuals without any ocular neoplasm. Demographic data revealed a balanced sex distribution across groups, with a predominance of female participants (63.2% in the tumor group and 68.4% in the control group). The mean age of patients with ocular tumors was 42.32 years, slightly higher than that of the control group (40.74 years), though this difference was not statistically significant. The age range of tumor patients was notably broad (1 to 86 years). Clinically, most tumor patients were employed in indoor environments (57.9%), and histopathological examination identified basal cell carcinoma (21.1%) as the most common lesion, followed by epidermoid cysts and other rarer tumor types. Malignant tumors accounted for 52.6% of the cases, while benign tumors comprised 47.4%.

Serum analysis demonstrated significantly higher FGF2 levels in the tumor group compared to controls, suggesting FGF2 involvement in ocular tumor pathophysiology. Furthermore, patients with malignant tumors exhibited significantly higher FGF2 concentrations than those with benign tumors, implying a possible correlation between elevated FGF2 levels and tumor aggressiveness, proliferation, and angiogenesis.

Several studies have supported the role of FGF2 in tumorigenesis, including its contribution to cell proliferation, invasion, and metastasis. Although research directly comparing FGF2 levels between ocular tumor patients and healthy individuals remains limited, mainly focused on retinoblastoma and uveal melanoma there is increasing interest in its broader oncogenic role. Loda et al. (2022) reported widespread expression of FGF2 and its receptors (FGFRs) in primary ocular tumors and surrounding stromal tissues, further linking increased FGF/FGFR expression with ocular neoplasms.[19]

Elevated FGF2 expression is thought to reflect the invasive nature of various tumors, including those of ocular origin, and is often associated with poor prognosis. FGF2 signaling activates pathways such as RAS/MAPK and PI3K/AKT, which facilitate tumor growth, angiogenesis, and therapy resistance.[20,21] In this study, significantly higher median FGF2 levels were observed in tumor patients versus controls (431.39 vs. 171.45 pg/mL), with even higher concentrations in patients with malignant tumors (600.63 vs. 171.23 pg/mL), reinforcing its association with tumor aggressiveness.

Wang et al. (2017) provided compelling evidence of FGF2's role in uveal melanoma by demonstrating its ability to promote both horizontal and vertical migration of MUM2B melanoma cells.[15] This effect was mediated via the store-operated calcium entry (SOCE) pathway through upregulation of STIM1 and ORAI1. Inhibition of this pathway using 2-APB suppressed the pro-migratory and pro-metastatic effects of FGF2, suggesting a potential therapeutic target in FGF2-mediated signaling.[22-24]

Flokis et al. (2023) offered further insights into the spatial and contextual behavior of FGF2, particularly in epithelial–mesenchymal transition (EMT). Their study showed that FGF2, in combination with TGF-β2, induced EMT in central lens epithelial cells while promoting lens fiber differentiation in peripheral cells. These findings highlight the context-dependent nature of FGF2's cellular effects and its dual roles in cell proliferation and transformation.[20,22,25]

Ocular tumors, especially uveal melanoma and retinoblastoma, are characterized by high angiogenic activity. Increased intraocular levels of vascular endothelial growth factor (VEGF) have been linked to tumor size and poor prognosis. FGF2, a potent pro-angiogenic factor, may act synergistically with VEGF in promoting neovascularization. Elevated FGF2 levels in the aqueous humor of patients with these malignancies support its role in tumor-associated angiogenesis.[15,19,26]

Outside ophthalmology, elevated FGF2 expression has been associated with poor prognosis and lymph node metastasis in esophageal squamous cell carcinoma (SCC) and gastric cancer. Patients with high FGF2 levels show reduced overall survival, with a more rapid progression to mortality compared to those with lower levels. Although ocular-specific studies are scarce, these systemic findings corroborate the association between FGF2 elevation and aggressive tumor behavior.[27,28]

A relevant comparative study by Mastronikolis et al. examined FGF2 expression in pterygium tissues using cell spot arrays. They reported a correlation between FGF2 activation and both the morphology and recurrence potential of pterygia. While not a neoplastic transformation, these findings underscore FGF2's involvement in cell differentiation, migration, and angiogenesis in ocular tissue, further validating its biological significance.[29]

Importantly, increased FGF2 levels are not confined to malignant conditions. FGF2 is also implicated in physiological responses such as wound healing, tissue repair, and metabolic regulation. Elevated expression is observed in conditions involving tissue injury or systemic metabolic disturbances, including obesity, diabetes, dyslipidemia, and hypertension. FGF21 and FGF1, for instance, rise in

response to hepatic stress, chronic kidney disease (CKD), and metabolic syndromes. Likewise, FGF23 regulates phosphate and vitamin D metabolism in CKD but is also linked to cardiovascular complications. Chronic inflammation, oxidative stress, and immune responses can also elevate FGF expression as part of tissue remodeling. Moreover, FGF family members play crucial roles in organ development, hormonal signaling (especially FGF19 subfamily), and stem cell maintenance. Thus, elevated FGF2 levels may sometimes reflect compensatory physiological processes rather than malignancy.[30,31,32]

From a translational standpoint, the FGF2–FGFR signaling axis holds promise as a therapeutic target in oncology. Several approaches including FGFR inhibitors, anti-FGF monoclonal antibodies, and calcium signaling modulators are currently under investigation. However, due to the pleiotropic and context-specific nature of FGF2, careful therapeutic design is required to avoid unintended disruption of normal tissue homeostasis.[20,26,33]

This study has several limitations. First, the ocular tumor group was heterogeneous and included different benign and malignant tumor entities with distinct biological behaviors. Therefore, the findings should not be interpreted as tumor-specific evidence for FGF2 expression. Second, the small sample size limited subgroup analyses according to tumor type or anatomical location. Third, the absence of diagnostic accuracy analysis prevents conclusions regarding the clinical utility of FGF2 as a biomarker. Accordingly, the present findings should be considered exploratory and hypothesis-generating, requiring validation in larger, multicenter studies with more homogeneous tumor cohorts.

5. CONCLUSION

Serum FGF2 levels were significantly higher in patients with ocular tumors than in healthy controls. Among patients with ocular tumors, FGF2 levels were also higher in malignant tumors than in benign tumors. These findings suggest that serum FGF2 may be associated with the presence and malignancy status of ocular tumors. However, due to the exploratory design, small sample size, and absence of diagnostic accuracy analysis, further studies are needed to determine the clinical utility of FGF2 in ocular oncology.

Declarations

6. COMPETING INTEREST

There is no competting interest

7. ETHICS DECLARATION

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of Universitas Sumatera Utara, Medan, Indonesia, with approval number **64/KEP/USU/2024**. All participants, or the parents/legal

guardians of pediatric participants, provided written informed consent before enrollment. The confidentiality and anonymity of all participants were maintained throughout the study.

8. CONFLICT OF INTEREST

The authors declare that they have no conflicts of interests

9. FUNDING

I confirm that i have not received any funding to support this work

10. AVAILABILITY OF DATA AND STATEMENT

Data are available upon reasonable request

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Figures

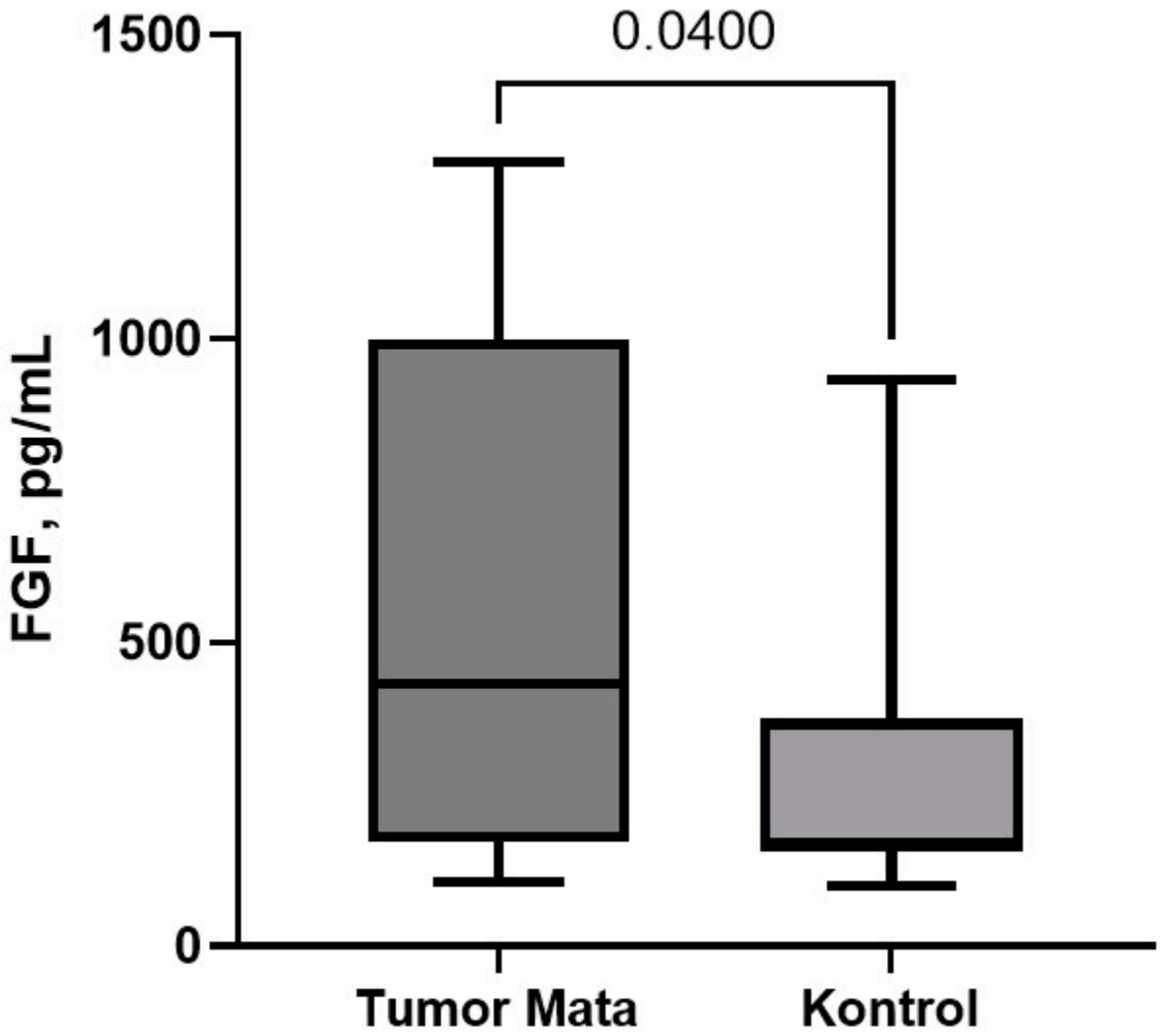


Figure 1

Comparison Of Serum FGF2 Levels Between Case and Control Groups

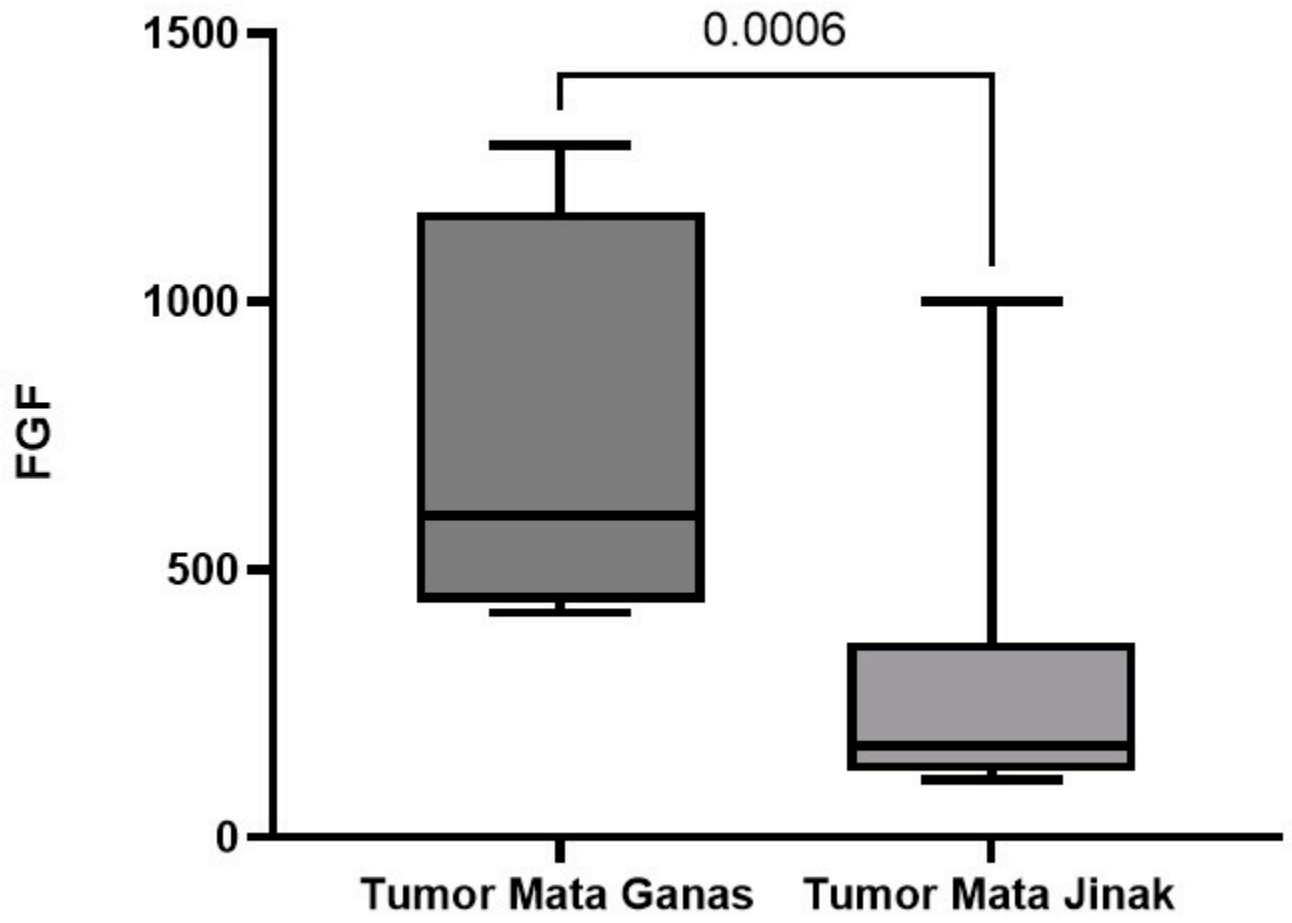


Figure 2

Comparison Of Serum FGF2 Levels Between Malignant and Benign Ocular Tumors