

# Orbital Neurogenic Tumors: An Eye Care Service Experience in Turkey

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## Abstract

**Aim:** This study aimed to evaluate the clinical and pathological features and treatment outcomes of neurogenic tumors developing in the orbit.

**Methods:** A retrospective study was conducted on the medical records of 23 patients diagnosed with orbital neurogenic tumors between 2008 and 2020 in the ophthalmology clinic. Clinicopathologic features and treatment results of this patient group were evaluated.

**Results:** Twenty-three patients, mean (SD) age 33.34±20.18 (min-max 4-60) years, were included in this study. Mean follow-up time was 56.7±42.7 (min-max 9-120) months. At the time of presentation, 15 (65%) patients had proptosis, eight (35%) patients had strabismus and reduced vision. Histopathologic diagnosis was made after lateral orbitotomy through the skin in 16 patients (69.5%) and medial orbitotomy through the conjunctiva in 4 patients (17.4%). Nine (39.1%) of the orbital neurogenic tumors were diagnosed as meningiomas based on histological and clinical findings, eight (34.8%) as optic nerve gliomas, and the other six (26%) as peripheral nerve origin tumors. Four (44.5%) of the meningiomas originated from the sphenoid wing, and five (55.5%) from the optic nerve sheath. As a treatment modality, external radiotherapy was administered to fifteen patients (65.2%), cyberknife radiosurgery to one patient (4.3%), chemotherapy to one patient (4.3%), and exenteration surgery to one patient (4.3%).

**Conclusions:** According to our study, meningioma, optic nerve glioma, and peripheral nerve sheath tumors were the most frequent neurogenic tumors of the orbit. With the treatments applied, survival and the visual prognosis were satisfactory.

**Keywords:** Meningioma, orbit, schwannoma, neurofibroma, optic nerve glioma

## 1. Introduction

Approximately 10% of all orbital tumors are primary neural tumors. Neurogenic tumors develop from cells such as leptomeningeal, schwann, ganglion, and melanocytes; they begin in the neural crest and neuroectoderm. Optic nerve/meningeal tumors accounted for 8% of all lesions in a retrospective case series of orbital tumors, while peripheral nerve tumors made up 2% of the cases<sup>1</sup>. Meningiomas, optic nerve gliomas, neurofibromas, schwannomas, malignant peripheral nerve sheath tumors, and granular cell tumors are among the various tumor types. Benign or malignant optic nerve gliomas and optic nerve sheath meningiomas are examples of optic nerve tumors. Neurofibromas, schwannomas, granular cell tumors, and malignant peripheral nerve sheath tumors are exam-

ples of peripheral nerve tumors in the orbit. All of these neural tumors are space occupying lesions that typically present with gradual vision loss and proptosis<sup>2</sup>. In this study, it was aimed to assess the clinical, pathological, and therapeutic outcomes of individuals with neurogenic tumors.

## 2. Materials and methods

This study included 23 patients with orbital neurogenic tumor (ONT) who were admitted to the ophthalmology department of Dr. Abdurrahman Yurtaslan Oncology T&R Hospital between January 2008 and January 2020. Approval for the study was obtained from the ethics committee of the hospital. Age, gender, clinical findings, tumor location, pathological diagnosis, course of treatment, and prognosis were all assessed retrospectively for each patient. A thorough eye exam was done prior to treatment. Radiological techniques like magnetic resonance imaging (MRI) and computed tomography (CT), the location, size, and relationship of the tumor to the surrounding tissues were assessed. For a conclusive diagnosis, most patients underwent biopsies.

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### 2.1. Statistical analysis

Statistical analyses were made using with IBM SPSS 19.0 for Windows Statistical software (SPSS, Chicago, IL). Frequency and percentage were used to represent categorical variables. The numerical variables were represented as min-max and mean±standard deviation (SD).

### 3. Results

The mean age of the patients was 33.34±20.18 (min-max 4-60) years. Of the patients, eight (34.8%) were men and 15 (65.2%) were women. The right eye was affected in 14 patients (60.9%) and the left eye in 9 patients (39.1%). The mean follow-up period of the patients was 56.7±42.7 (min-max 9-120) months. Table 1 shows the symptoms and examination findings of the patients.

Of the patients, 20 (87%) underwent surgery for diagnosis and treatment. Three patients (13%) were diagnosed without surgery using imaging techniques. Lateral orbitotomy was performed if the mass localization was intraconal and lateral to the optic nerve, and medial orbitotomy was performed through the skin or conjunctiva if the mass was medially localized. 16 (69.5%) patients underwent lateral orbitotomy through the skin and 4 (17.4%) patients underwent medial orbitotomy through the conjunctiva. Nine patients (39.1%) underwent incisional biopsy, ten patients (43.4%) underwent total excisional biopsy, and one patient (4.3%) underwent subtotal excisional biopsy, depending on the mass's location and characteristics.

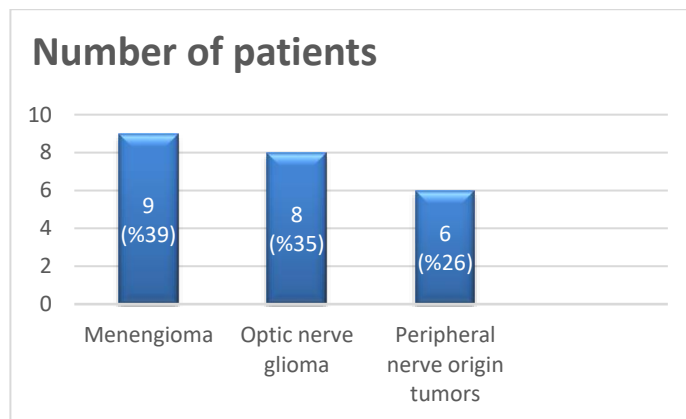
Figure 1 illustrates the distribution of orbital neurogenic tumors according to imaging and biopsy reports. Of the meningiomas, 4 (44.5%) were sphenoid wing meningiomas and 5 (55.5%) were optic nerve sheath meningiomas. Out of all the peripheral nerve tumors, plexiform neurofibroma 1 (16.7%), olfactory neuroblastoma 1 (16.7%), and schwannomas (66.6%) accounted for 4 of the tumors. Three patients (13%) had an associated type-1 neurofibromatosis (NF-1). One (4.3%) patient with NF-1 had plexiform neurofibroma, and two (8.7%) had optic nerve gliomas.

Fifteen patients (65.2%) received external radiation, one patient (4.3%), underwent cyberknife radiosurgery, and one patient (4.3%) received chemotherapy. The patient with olfactory neuroblastoma underwent exenteration because of their severe proptosis, large and diffuse localization of the mass, and lack of light sensation.

The patients pre- and post-treatment visual acuity varied from perception (-) to 5/10. A significant improvement in visual acuity was defined as a two line or greater increase in Snellen visual acuity following treatment. After treatment, 11 (48%) of the patients' visual acuity could be monitored. As a result, following treatment, two patients (9%), and nine patients (39%) reported decreased visual acuity. Two patients with sphenoid wing meningioma experienced recurrences during the follow-up period, but no deaths occurred.

Figure 1

Distribution of orbital neurogenic tumors



### 4. Discussions

Consistent with the previous reports of Shields<sup>1</sup> (37.5%) and Kızıltunç<sup>3</sup> (25.7%), optic nerve glioma was the most common neurogenic tumor in the orbit in this study (34.8%), followed by optic nerve sheath meningioma (21.7%) and sphenoid wing meningioma (17.4%). Similar rates to our study were also reported by Shields et al.<sup>1</sup> for optic nerve sheath meningioma in the second most common tumor (22.6%) and sphenoid wing meningioma in the third most common tumor (18.7%). The study revealed that the prevalence of schwannoma was 17.4%, whereas the rates of plexiform neurofibroma (4.3%) and olfactory neuroblastoma (4.3%) were found to be equal. Schwannoma (10.9%), plexiform neurofibroma (3.1%), and isolated neurofibroma (1.5%) were reported by Shields et al.<sup>1</sup> Kızıltunç et al. reported schwannoma (17.1%) and optic nerve sheath meningioma (17.1%) as the second most common tumor. In addition to perisellar meningioma (3%), they also reported sphenoid wing meningioma (14.3%), plexiform neurofibroma (11.4%), isolated neurofibroma (5.7%), and ectopic meningioma (5.7%)<sup>3</sup>.

Meningioma, schwannoma, and isolated neurofibroma are more common in adulthood, while optic nerve glioma and plexiform neurofibroma are more common in childhood<sup>4</sup>. The average age of patients with plexiform neurofibroma was 7 years, while the average age of patients with optic nerve glioma was 9 years (4–16). In adults, the mean age of orbital neurogenic tumors was 51 years for olfactory neuroblastoma, 47 years (40–52) for schwannoma, and 49 years (42–60) for meningioma.

Imaging methods are typically used to assess the diagnosis of optic nerve tumors, however certain tumor types may make the diagnosis more difficult<sup>3</sup>. In our study, all 9 cases of meningioma were identified through biopsy, compared to 3 of the 8 patients with optic nerve glioma who were identified through imaging methods.

Gliomas of the optic nerve that affect children are known as juvenile pilocytic astrocytomas and are typically benign. Nonetheless, adult cases of malignant glioblastoma, a type of optic nerve glioma, are possible. With a median age of five years and a clinical presentation that can occur anywhere from eight months to 38 years of age, 90% of optic nerve gliomas are diagnosed within the first two decades of life. Females account for 60% of cases of these lesions, which are typically unilateral and clinically manifest as unilateral painless visual loss, proptosis, optic disc edema, or optic atrophy<sup>5-6</sup>. Although sporadic in most cases, 10–70% of patients diagnosed with juvenile pilocytic astrocytomas have been reported to be associated

Table 1

Symptoms and examination findings of the patients

Symptoms and examination findings	Number of patients (%)
<b>Symptoms</b>	
Proptosis	15 (65,2)
Visual impairment	6 (26,1)
Strabismus	2 (8,7)
<b>Examination findings</b>	
Optic atrophy	8 (34,8)
Optic disc edema	4 (17,4)

with neurofibromatosis type 1 (NF-1). NF-1 is typically linked to bilateral optic nerve gliomas<sup>7-8</sup>. NF-1-related tumors typically grow slowly, but sporadic tumors typically progress quickly and manifest clinically. Since the chiasm is involved in more than half of the tumors, bilateral visual field defects may be observed<sup>9-11</sup>. Each patient's response to treatment for optic nerve glioma is unique due to the tumor's variable growth pattern. While some tumors show rapid or slow growth patterns for many years, others remain stable for years and do not grow at all<sup>9</sup>.

Surgery, chemotherapy, external radiation, and follow-up are all part of the treatment.

If an advanced proptosis, progressive loss of visual acuity, or an increase in tumor size is found during MRI follow-up, treatment of gliomas should be considered. Otherwise, follow-up is advised if the tumor size does not grow or progress. When a patient's tumor results in severe proptosis and deformity, severe visual loss, or severe keratopathy from lagophthalmos, surgery is performed to reduce the tumor<sup>2</sup>.

Chemotherapy may be the preferred course of treatment for pediatric patients in order to prevent side effects from radiation. Chemotherapy combined with vincristine and carboplatin is typically regarded as first-line therapy. This treatment does not raise the risk of treatment-related death or secondary cancer, and it offers about 70% progression-free survival. About 40% of patients experience hypersensitivity reactions to carboplatin, which is the primary side effect. Additional regimens for chemotherapy consist of temozolomide, cisplatin/etoposide, and thioguanine/procarbazine/CCNU/vincristine (TPCV). Although these regimens have comparable survival rates, they should not be used in NF-1 patients due to the increased risk of secondary leukemia<sup>12-13</sup>.

When chemotherapy is not an option for older children with refractory disease, external radiotherapy is advised. The goals of this treatment are to stop the tumor from growing larger and to avoid vision loss. There could be adverse effects on the central nervous system. In order to reduce the radiation dose to nearby structures, more advanced radiation therapy techniques have been developed. Conformal therapy, proton beam radiation therapy, fractionated stereotactic radiation therapy, and stereotactic radiosurgery (using a Gamma Knife) are some of these techniques<sup>13-14</sup>. It has been demonstrated that the VEGF inhibitor bevacizumab is useful in either halting or reducing the growth of optic nerve gliomas. It has been documented that bevacizumab is used both alone and in combination with other medications like irinotecan or vinblastine<sup>15</sup>. Inhibitors of the mitogen-activated protein kinase (MAPK) pathway are one class of molecularly targeted treatment that specifically targets the development and spread of cancer cells. With a specific focus on the MAPK pathway—which is hyperactive in certain cancer types—these treatments aim to slow the spread of cancer cells. The growth and division of cells depend on this pathway. Trametinib is the most commonly used MAPK inhibitor at the moment, but numerous other options are presently undergoing clinical trials<sup>12-14</sup>.

Eight patients with optic nerve gliomas were included in our study; one patient underwent chemotherapy, one patient underwent Gamma Knife radiosurgery, and six patients underwent external radiotherapy. The survival rate was 100% and there was no recurrence.

Rare benign tumors of the central nervous system are called optic nerve sheath meningiomas (ONSM). Their location is crucial for the patient because the tumor can directly impact the visual pathway and cause severe vision loss, despite their slow but progressive growth<sup>16-18</sup>. These are often more prevalent in women in their middle years. They are rare, but can occur in children, though they are usually more aggressive. Ninety-five percent of ONSMs are unilat-

eral. Patients diagnosed with type 2 neurofibromatosis may experience rare bilateral tumors. The gradual, painless, and progressive loss of vision in the affected eye is the hallmark of ONSM's natural course. This tumor can cause total blindness if treatment is not received<sup>19-20</sup>. Because of the tumor's close proximity to the optic nerve, it is challenging to remove the entire tumor without experiencing further complications or aftereffects. For this reason, the management of this condition is still deemed controversial. When a patient's vision is stable or good, especially when they have central visual acuity of 20/50 or better, observation is a suitable course of treatment. These patients receive close monitoring and are subjected to a thorough examination that includes optical coherence tomography of the papillary retinal nerve fibers and visual field<sup>21-22</sup>. Tumor follow-up with MRI is recommended every year<sup>18,23</sup>.

On the other hand, in cases of disfiguring proptosis with markedly diminished visual function or intracranial spread, surgical resection might be warranted. ONSM can be treated if the tumor is contained within the orbit and the affected eye lacks feeling in light. However, some surgeons recommend surgical excision of the tumor to stop it from spreading to other areas. The tumor and nerve should be removed if the eye is light-sensitive and there is intracranial spread. According to some authors, surgical intervention should be the first line of treatment because it can partially reverse existing visual impairment as well as stop the disease's progression and lower the risk of future vision loss<sup>24</sup>. It has been demonstrated that the recently suggested transnasal endoscopic optic nerve decompression can, in certain circumstances, stabilize the condition and enhance visual acuity<sup>25-26</sup>.

For many years, conventional radiation has been used both before and after surgery, and it has been noted that the treatment affects the preservation of visual acuity<sup>17,27</sup>.

Recently, surgery has been replaced with stereotactic radiotherapy (STR). Since STR provides the right amount of radiation to the tumor locally, it has become the method of choice in cases of reduced visual function. Risks of radiation-induced optic neuropathy or retinopathy are frequent<sup>28</sup>.

In our study, 5 patients with optic nerve sheath meningioma were treated with external radiotherapy. Visual acuity was stable and no recurrence was observed during a mean follow-up period of 27 months (15-72 months).

About 18% of all intracranial meningiomas are sphenoid wing meningiomas. Because of its unique anatomical location in the sphenoid bone, the tumor's nature frequently involves periorbital tissue and bones. On imaging, hyperostosis is frequently observed<sup>29-30</sup>. Because it is difficult to restore the dura mater and bony structure while maintaining key anatomical structures like the optic nerve, oculomotor nerve, trigeminal nerve, or internal carotid artery, surgical resection of sphenoid wing meningioma is technically difficult<sup>31-32</sup>. Recurrence after surgery is frequent. Treatment approaches include postoperative STR and maximal safe resection<sup>33</sup>.

Individuals who have small tumors without any symptoms and cavernous sinus meningiomas can undergo annual or biannual close observation. Serial imaging with brain MRI is usually recommended as part of the follow-up.

Adjuvant therapies may be necessary in cases of incompletely resected meningiomas as well as atypical or malignant meningiomas in order to lower the recurrence rate. Patients with anaplastic meningioma who receive bevacizumab, a type of chemotherapy that targets molecular changes of vascular endothelial growth factor, following surgical resection and radiation therapy have demonstrated successful tumor regression<sup>34</sup>. Four sphenoid wing meningioma patients in our study had stereotactic radiotherapy after surgery to reduce the tumor. While the visual acuities of the other patients re-



ceiving stereotactic radiotherapy remained stable, the visual acuities of the other two patients showed a decline. Recurrences occurred in two patients.

Although they are uncommon in the orbit, peripheral nerve sheath tumors (PNST) account for 2% of all orbital neoplasms. Of these, 50% of the tumors are schwannomas, which are the most prevalent type. Neurilemmomas, or Schwannomas, are benign, slowly growing encapsulated tumors that originate from the Schwann cells in the peripheral nerve sheath. Most adults who experience it are between the ages of 30 and 70. In addition to the oculomotor, trochlear, and abducens nerve branches, orbital schwannomas also commonly originate from sympathetic and parasympathetic fibers, as well as the trigeminal nerve's frontal branch. The genesis of orbital schwannomas elucidates their predominant distribution in the supraorbital domain<sup>35</sup>.

The preferred course of treatment is complete surgical resection. Even though the capsule is extremely thin, especially in tumors with cystic degeneration, the recurrence rate is almost nonexistent in the absence of a capsular breach. Restrictions on eye movement and permanent reduction in visual acuity have been reported; these depend on the surgical technique, tumor location, and degree of dissection. To assess recurrence, repeat MRIs performed over an extended period of time are advised<sup>36</sup>.

All four of the patients in our study had total excision, and there was no sign of recurrence.

Singular, diffuse, and plexiform neurofibromas are further classifications for neurofibromas. With the exception of pleural neurofibromas, which are diagnosed in half of cases between the ages of 1 and 5, the majority of benign PNSTs affect adults between the ages of 20 and 60. No racial or gender predisposition exists. 90% of singular orbital PNSTs are not associated with NF-1, despite neurofibromas being linked to it. Benign PNSTs are typically slow-growing, non-invasive tumors whose genesis is primarily determined by where they are located in the orbit. Granular cell tumors are another type of benign nerve tumor that can develop in the orbit and are derived from peripheral nerve tissue<sup>2</sup>.

It is uncommon for neurofibromas to transform malignantly. Plexiform neurofibromas can be challenging to completely remove due to their high vascular and infiltrative nature. Tumor reduction techniques can be used on kids who are susceptible to amblyopia. It is recommended to remove isolated benign neurofibromas completely without causing any damage to the capsule<sup>37</sup>.

In our study, the patient with plexiform neurofibroma underwent subtotal excision with mass reduction; during follow-up, no malignant transformation was found. Due to the olfactory neuroblastoma patient's large and diffuse localization of the mass, advanced proptosis, and lack of light sensation, exenteration was performed.

In summary, ONT is not an uncommon condition, and its manifestations can vary based on the kind and location of the tumor. During follow-up, patients' radiological and clinical findings should be carefully assessed. If in doubt, a biopsy ought to be done to get an accurate diagnosis<sup>1</sup>. Follow-up, external radiation therapy, and chemotherapy should all be part of the treatment plan for optic nerve gliomas and optic nerve sheath meningiomas, respectively. External radiation therapy and maximally safe resection are the recommended treatments for sphenoidal wing meningiomas. For well-circumscribed peripheral nerve sheath tumors, subtotal excision is recommended, whereas total excision is advised for infiltrative tumors<sup>2</sup>. After receiving the right care, the prognosis for survival and vision is satisfactory.

### Statement of ethics

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was approved by University

of Health Sciences, Dr. Abdurrahman Yurtaslan Oncology T&R Hospital 2016.

### Conflict of interest statement

Author declare that they have no financial conflict of interest with regard to the content of this report.

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