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Optic Pathway and Hypothalamic Gliomas (OPHG): Management and Controversies

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Introduction

Optic pathway gliomas are considered a rare tumor that originates in the optic nerve, optic tract, or optic chiasma[1]. These tumors account for around 3-5% of all paediatric brain tumors.[2] Multifocal location and female preponderance was also common in OPG associated with NF1. Their management poses significant challenges due to their proximity to and involvement of critical structures such as the optic pathways, hypothalamus, and surrounding neurovascular regions. The management paradigms are often complex, with the treatment goals balancing between tumor control and functional / visual preservation. While multimodal approaches incorporating chemotherapy, radiotherapy, and observation are often prioritized, surgery continues to play a vital role in specific scenarios.

This chapter explores the current concepts in the management of OPHGs, synthesizing findings from recent research and clinical experience.

Pathogenesis

Dysregulation of cell growth is involved in pathogenesis of both sporadic and NF1 associated low grade glioma. The Neurofibromin protein is defective in NF1, thereby affecting several downstream pathways of cell cycle regulation. *KIAA1549::BRAF* fusions, BRAF V600E mutations, *FGFR1* alterations and loss of function mutations of the neurofibromin 1 (*NF1*) gene are the most frequent molecular alterations.[3] The various factors on the cell surface that are involved in low grade glioma include FGFR, EGFR, VEGF, NTRK and the BRAF, MEK inhibitors work on the cytoplasm. B-raf is a proto oncogene that upregulates proliferating factor such as MAPK and MTOR.[4] Neurofibromin is affected in NF1 where the tumor suppressor gene NF1 is defective, therefore causing lack of control over RAS MAPK pathway. However, mutations in BRAF are commonly noted in sporadic cases of optic pathway glioma as well.

Classification

Optic pathway glioma, as the name suggests, can involve any part of the optic pathway with differential extent of involvement. The symptomatology and management often varies based on the location and extent of the involvement. The OPHG was classified by Dodge et al. into types A, B and C, based on the location namely, Dodge A tumors involved the optic nerves, Dodge B tumors involved optic chiasm and Dodge C tumors involved the post- chiasmal optic pathway and hypothalamus. This classification has been further modified by Taylor et al. into subgroups, which differentiated unilateral or bilateral involvement of optic nerves, asymmetric involvement etc. Hypothalamic involvement was separately denoted as well as presence of leptomeningeal metastases and the neurofibromatosis status of the patient.[5] This classification enabled us to compare the data across the studies more homogenously as well as plan management decisions.

Patients with NF1-associated OPHGs generally require less aggressive intervention due to their relatively indolent course. Studies (e.g., Goodden et al., 2014)[6] report better visual and endocrine outcomes in this subgroup, with fewer requiring active surgical or medical intervention.

Factors influencing management decision:

Management decisions in optic pathway glioma are dependent on multiple factors and are ideally taken after a multidisciplinary evaluation and discussion in a tumor board. Hill et al. (2021) emphasized the importance of patient selection and tailoring interventions to individual needs, particularly in challenging cases involving hypothalamic involvement.[7]

Key considerations include:

- Patient-Specific Factors: Age, NF1 status, visual status, features of mass effect and / or raised ICP and tumour location are critical in decision-making.
- Long-Term Morbidity: Surgical interventions must aim to minimize risks of visual, cognitive, and endocrine dysfunction.
- Multidisciplinary Approach: Collaboration among neurosurgeons, oncologists, endocrinologists, and ophthalmologists ensures comprehensive care[7].

Indications for Surgery

The role of surgery in OPHGs has evolved significantly over time. While complete resection is rarely feasible in these tumors in view of involvement of optic pathway, advances in techniques and technologies have made surgery safer and more effective. Surgical intervention in OPHGs is carefully considered due to the risks associated with operating in eloquent brain regions.

The following indications are commonly considered for surgery:

Symptomatic Hydrocephalus: Tumour-induced cerebrospinal fluid (CSF) obstruction often necessitates surgical debulking or shunt placement to relieve intracranial pressure.

- *Tumour Mass Effect*: Large tumors causing significant mass effect and symptoms such as visual deterioration or hypothalamic dysfunction may require debulking to reduce tumour burden.
- *Refractory Cases*: Surgery is employed in cases where chemotherapy or radiotherapy fails to halt tumour progression or where shunt complications, such as refractory ascites, occur.
- *Tissue Diagnosis*: Biopsies, either open or endoscopic, are conducted to confirm histopathological diagnosis and guide further treatment, particularly in non-neurofibromatosis type 1 (NF1) cases.

Surgical indications based on location:

The indications of surgery in optic nerve glioma are limited. In a patient with an optic nerve lesion with typical MRI imaging of optic nerve glioma, a biopsy is usually not warranted. Chemotherapy can be considered upfront to stabilise the lesion and preserve the residual vision. Surgical excision of the optic nerve glioma can be considered in patients with a complete visual loss, painful severe proptosis and tumor not involving the chiasm or the other optic nerve.

In case of chiasmal lesions, in the presence of NF1 or typical imaging, biopsy may not be indicated. However, in view of the emerging molecular characterisation of these tumors, biopsy would enable the clinician to molecularly type these tumors for further therapy. Surgical decompression of the chiasmal tumors can be considered in case of large exophytic lesions. Often these tumors can expand the optic nerves and chiasm and render tumor decompression challenging without causing damage to the optic fibres. Some authors have reported on the utility of optic nerve DTI in pre-operative identification of optic pathways in OPHG and postulated that these can be used for achieving safer resection.[8,9]

Tumors predominantly arising from hypothalamus are often indicated for surgery, since they present with mass effect and hydrocephalus. A significant amount of surgical decompression can be achieved in these tumors, with access to third ventricle component by interhemispheric approach. The surgery should aim at maximal decompression of the exophytic component and draining of cysts, while avoiding damage to the optic chiasma, hypothalamus and third ventricle floor.

The choice of surgical approach depends on tumor location and the specific clinical scenario. A trans-sylvian approach is the most commonly used for decompression / biopsy of the chiasmal lesion. Chiasmatic or hypothalamic tumors with large cisternal exophytic component can be managed by a trans-sylvian approach. Intra ventricular tumor component can be accessed through lamina terminalis. However, in view of expanded chiasm, this may be often difficult without causing chiasmal damage. Optic tract lesions can be accessed either by trans-sylvian pre-temporal, trans temporal horn suprachoroidal or subtemporal routes based on the size and extension of the lesion. Hypothalamic tumors with large third ventricle component can be decompressed with anterior inter-hemispheric transcallosal, trans foraminal or trans-velum interpositum approach. Endoscopic approach for obtaining tissue biopsy has been described in some cases.

Intraoperative MRI (ioMRI) is a significant advancement that allows surgeons to assess the extent of tumor resection in real time. Studies (e.g., Millward et al., 2015)[10] have shown

that ioMRI facilitates second-look surgeries during the same operation, enabling more extensive tumor removal without increasing morbidity. Neuronavigation systems further enhance precision, reducing risks of damage to adjacent critical structures.

Surgical Goals

The primary goals of surgical intervention in OPHG management include:

a) *Tumour Control*: Partial or subtotal resections aim to stabilize disease progression while minimizing risks to critical structures.
b) *Symptom Relief*: Debulking alleviates symptoms such as hydrocephalus, diencephalic syndrome, and visual impairment caused by tumour mass effects.
c) *Minimizing Morbidity*: The focus is on achieving functional preservation, especially regarding vision, endocrine function, and cognitive abilities.

Outcomes of Surgical Resection

Tumour Resection Rates

The tumor resection rates vary widely and are most often subtotal resection. Gross total resection is achievable in 23 to 36% cases, particularly for intraorbital tumors. However, for chiasmatic/hypothalamic tumors, GTR rates are much lower (9.6%) due to the risk of damaging critical structures[11,12]. Subtotal resection (50-90% tumour removal) and partial resection (<50%) are more common for hypothalamic or chiasmatic gliomas, with a focus on symptom management rather than curative intent.[13]

Surgery improves or stabilizes vision in most cases, with postoperative visual acuity improving in 24.6% and remaining stable in 68.2% of patients.[11] Vision outcomes are highly dependent on tumour location and the extent of preoperative visual impairment. Patients with hypothalamic involvement often require lifelong hormone replacement to address pituitary dysfunction. Regular ophthalmologic evaluations and interventions are necessary to monitor and manage changes in vision. Early intervention programs can help address cognitive and behavioural issues arising from both the tumour and its treatment. Continued surveillance for shunt-related complications, such as infections or malfunctions, is essential.

Complications following surgery include hydrocephalus (35.4%), often requiring postoperative shunting. Endocrine dysfunction, such as anterior pituitary dysfunction (19.6%) and diabetes insipidus (29%), often necessitates lifelong hormonal management.[11] Transient neurological complications, including seizures and hemiparesis, are also reported.

Role of Chemotherapy in Optic Pathway Glioma Tumors

Chemotherapy was introduced into protocol of management after anecdotal evidence of benefit in delaying radiotherapy in a few cases in early 1980's . However since a sustained response was documented with chemotherapy, it is currently the preferred first line management in children with low grade glioma. This also helps circumvent the long term side effects associated with Radiotherapy [14]. Several chemotherapy regimens have been utilized in the past. TPVC – Thioguanine, Procarbazine, Vincristine and Lomustine (CCNU) was one of the most effective regimens used for low grade gliomas. About 30% of these tumors occur in the background of Neurofibromatosis 1, use of alkylating agents such as procarbazine and lomustine can lead to increased risk of second cancers in them [4]. Carboplatin- Vincristine(CV) is a reliable regimen with good response rates irrespective of sporadic OPG or NF1 associated OPG. The response rates, stable tumor vs progression on chemotherapy were comparable in both the arms when CV was used. The randomized study between CV and TPVC with 71 and 67 patients respectively in each arm demonstrated a EFS of 44.5+ 5% and OS of 87 + 5% with no significant difference in outcomes based on chemotherapy regimen[15] . Cisplatin- Etoposide based regimens are less preferred due to long-term ototoxicity and nephrotoxicity with Cisplatin and risk of second malignancies with Etoposide. Packer and colleagues published a concurrent carboplatin and vincristine regimen in a 10-week induction phase, followed by 48 weeks of maintenance carboplatin- vincristine, which resulted in a PFS of 75% at 2 years and 50% at 5 years. Radiological evidence of tumor shrinkage was noted in 63% of patients[16]. Observation with close follow up is also a feasible option in NF1 associated OPG as they

often remain indolent and are associated with good outcomes. Combination of Surgery+/- chemotherapy/ radiotherapy is commonly used in sporadic cases of OPG. Chemotherapy effectively delayed disease progression in both groups, but patients without NF1 exhibited higher rates of radiologic and visual progression despite treatment[14].

Role of Targeted therapy

MEK inhibitors such as selumetinib, refametinib, trametinib and cobimetinib have shown promise in the treatment of progressive and recurrent low grade gliomas in children with a 2-year PFS of up to 69%. MEK1/2 Inhibitors are preferred to BRAF inhibitors which tend to result in paradoxical activation of the RAS/MAPK pathway[17]. They are likely to benefit patients with BRAF mutations. Pediatric Brain Tumor Consortium trial of selumetinib has been safely used up to 24 months in children with recurrent/progressive LGG. In the NF1 group, 10 of 25 patients (40%) achieved a sustained complete or partial response. The two-year PFS was 96%. In the non-NF1 patient group, there were 25 patients with recurrent/ progressive sporadic OPG or hypothalamic LGG. In this group, two year PFS was 74%.(Figure 1) Considering good response rates even in sporadic LGG, selumetinib has potential to replace carboplatin- vincristine based chemotherapy. About 12% of patients had to discontinue the drug due to dose limiting toxicity[18]. Ocular toxicity is of major concern with MEK inhibitors. There are reports of central vein occlusion, optic neuropathy, uveitis and neurosensory retinal detachment. These side effects are most prominent in adults while children tolerate them better. The major challenge with MEK inhibitors is the poor penetrance across the blood brain barrier and therefore the slow response to treatment. Targeting higher up in the pathway was therefore important to overcome the toxicity as well as to get desirable response. Selumetinib is active both in NF1-associated and sporadic OPGs.

BRAFV600E mutations are known to be associated with aggressive disease and poor response to treatment. Dabrafenib and Tramatenib have individually shown efficacy in progressive/ refractory LGG who have previously received chemotherapy. Dabrafenib is a potent and selective inhibitor of the V600-mutant form of the BRAF kinase. Initial results from a multicentre phase 1 clinical study using dabrafenib reported an ORR of 41% in patients with recurrent or progressive BRAFV600E mutant pLGG[3]. Usage of combination of the two drugs has been recently emphasized in upfront therapy for BRAFV600E mutated LGG in a phase II randomized controlled trial against carboplatin-vincristine arm, where preliminary results showed a median PFS of 20.1 months with dabrafenib-trametinib versus 7.4 months with carboplatin-vincristine, with a twelve-month progression free survival of 67% versus 26% respectively[19]. Tovrafenib, which is a PanRAF inhibitor has been studied in both BRAF fusion and mutated refractory LGG and has shown promising response. A randomised trial FIREFLY 2 has demonstrated overall response rate of 67% with better Brain penetrance and more tolerable side effect profile. Paradoxical activation of MAPK pathway was not noticed with Tovrafenib[20].

VEGF is abnormally expressed in glial tumors contributing to their increased vascularity. Therefore utilising this aspect to limit proliferation of cells and thereby growth of tumor

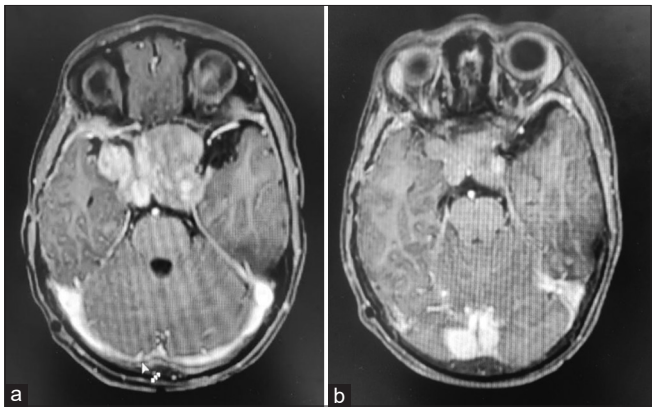

Figure 1: (a) Pre Chemotherapy : Heterogenous enhancing lesion 38x54x37 mm, epicentred in the supra sellar region involving optic chiasma, hypothalamus with encasement of cavernous segments of both ICA, effacing the interpeduncular cisterns. (b) Post Chemotherapy: Decrease in bulk in both cystic and solid components of the lobulated mass about 35x35x20 mm seen with persistent encasement of the ICA

size has been feasible with VEGF inhibitor, Bevacizumab[4]. This has shown efficacy even as monotherapy or in combination with conventional chemotherapeutic agents. Bevacizumab monotherapy has shown improvement in visual symptoms in upto 86% of progressive optic pathway gliomas with a 48% progression free interval in a case series. Common undesirable side effects of Bevacizumab are proteinuria, hypertension, fatigue and joint pains, which are reversible after stopping the drug. Incorporation of VEGF inhibitors in the early phase of treatment has shown benefit. Even those who did not have radiological improvement, preservation or restoration of vision was the most significant benefit noted[18].

A wait-and-watch approach may be deemed appropriate in children who have no visual symptoms or neurological deficits. Treatment may be considered in those with radiological progression of the lesion or with new visual/ neurological symptoms or signs. Considering the practical challenge of accurate vision assessment in very young children, the preferred first-line therapy would remain vincristine-carboplatin-based chemotherapy with close monitoring of visual function. Although there is reassuring data about upfront usage of targeted agents in low-grade glioma, paradoxical progression when treatment is discontinued, and duration of treatment are issues to be addressed before they can be incorporated into mainstream treatment in chemo-naïve children.

Long-term visual outcomes following therapy:
Risk factors for long-term visual deterioration are young age, chiasmatic/hypothalamic tumor site, and intraconal tumor site for the involved eye. The most desirable visual outcome for children with OPG after treatment with chemotherapy is improvement in vision, however stability is the most commonly achieved outcome[21]. Long term visual outcomes and stability maintained only with chemotherapy upto 2 years has been published in several small series, however progressive deterioration in vision has been documented over 5 year period[22,23] .

Infants especially had poor visual outcomes. The delay in diagnoses in pre-verbal children could be a contributing factor. Biology of tumor with more aggressive nature of disease and therefore extensive disease at presentation is seen in very young children. Chemotherapy being a subtle modality to stabilise or improve vision symptoms, consideration of targeted agents in this age group could be beneficial in terms of visual outcomes. However, it is noteworthy that those who achieved improvement in vision are likely to retain those gains than those with poor initial response to chemotherapy.

Hypothalamic and chiasmatic gliomas have poor visual outcomes owing to site of tumor. They tend to have bilateral vision loss with upto 45% of children blind in follow up[18]. Consideration of Bevacizumab in upfront or combination with chemotherapy may prove beneficial in these children as an upfront therapy[24]. Intraconal tumors were also a poor prognostic factor as many times debulking/ enucleation was done to reduce the disfigurement and provide symptomatic relief. In the absence of above mentioned risk factors long term stability in vision was achieved in 90% of children in follow up[21].

Its important to understand overall survival in pLGG is above 80% in most studies (17) particularly with the WHO designation of low-grade glioma (LGG. The recent focus is on attaining stability of the disease with chemotherapy and using radiotherapy only in recurrent cases. In OPG with Neurofibromatosis 1, radiotherapy is best avoided due to risk of vascular complications and second malignant neoplasms[14]. The table 1 illustrates the various studies with outcomes using surgery + chemotherapy +/- radiotherapy used in pLGG. Targeted therapy appears seamless, however lack of data on duration, the risk of paradoxical growth on stopping the drug and the cost of therapy, make chemotherapy the most affordable and effective option to attain stability and prevent progression upto 60 months or more. However one must understand that literature on long term outcomes with chemotherapy alone are sparse.

Role of Radiotherapy in Optic Pathway Glioma Tumors

Although OPHG are typically classified as a low-grade tumors, its progression can vary from slow growing to more aggressive forms. A multimodality approach including monitoring, surgery, chemotherapy, and radiation therapy (RT) remains the mainstay

Table 1: Outcomes with chemotherapy- Targeted therapy in pLGG/OPG

Study	Patient population	Treatment given	Chemotherapy regimen	Outcomes
Packer *et al*[16]	Twenty-three children with recurrent and 37 children with newly diagnosed LGG Chiasmal 18/23 recurrent and 30/37 Newly diagnosed LGG	10-week induction cycle of carboplatin and vincristine, followed by maintenance treatment with the same drugs; Radiation in recurrent cases	Carboplatin-vincristine	Greater than 50% reduction in tumor Recurrent disease ~ size in seven of 23 (30%) Newly diagnosed patients ~ 16 of 37 (43%)
Fawzy *et al*.[50]	Pediatric LGG ~227 OPG in 13/227	Surgery (GTR/STR/ Biopsy) 210/227 RT in none CT in 26/227	CCG A9952 Carboplatin - vincristine	3 years EFS: 65.5% 3 years OS: 87.30% OS in OPG ~ 66.9%
Papusha *et al*.[51]	Pediatric LGG BRAF mutated ~69	GTR/NTR:26 STR: 37 Biopsy: 4 RT :6 CT : 36	Targeted agents BRAF +/- MEK inhibitors	2 years EFS: 57.8% 2 years OS: 100% OPG ~ 7/69
Varan *et al*.[52]	Pediatric LGG ~55	GTR/NTR: 10 STR: 34 Biopsy: 11 RT : 41 CT : 12	COPP CCNU based CDDP + VP16	5 year OS: 93.3% OPG excluded from the study

in the management of these tumours.[1,25,26] While chemotherapy is often the first-line treatment in paediatric cases, RT remains an important therapeutic option in cases of disease progression or failure of other treatments.[27,28] As a result, RT remains a viable treatment option, particularly for cases where chemotherapy alone is insufficient. While concerns about late effects persist, modern radiation techniques aim to reduce these risks and enhance long-term outcomes for patients with optic pathway gliomas.[29-32]

The radiotherapy target typically includes the Gross tumor volume (GTV) with a margin of 0.5cm as the CTV (Clinical Target Volume) to which a geometric margin of 0.3-0.5cm is given as Planning Target Volume (PTV).[11,12] progression-free survival (PFS Radiotherapy doses routinely prescribed in these tumors range from 45Gy-54Gy at 1.8-2Gy per fraction based on the location and proximity of adjacent organs at risk.[33,34] Accurate immobilisation , MRI based planning , highly conformal planning , strict quality assurance and precise treatment delivery as illustrated in Figure 2 are integral in improving therapeutic ratio in these curable tumors.

Favourable radiological and visual outcomes were observed in 75% and 81% (95% CI: 75–86) of patients, respectively, who underwent various RT techniques.[26] Studies on low-grade gliomas have reported 5 to 10-year overall survival (OS) rates ranging from 79% to 96% and 5-year progression-free survival (PFS) rates between 48% and 100%.[28,29,32,33,35] with results from a few studies are summarised in the below Table 2.

Early versus delayed radiotherapy

Early Radiotherapy is considered as RT given either in the upfront setting or as first line salvage treatment and RT is considered as delayed if given after more than 2 cycles of chemotherapy.[31]The decision between early and delayed RT depends on multiple factors, including tumor progression, visual impairment, patient age, and underlying conditions such as Neurofibromatosis Type 1 (NF-1). Early RT is often considered in cases of progressive tumor

'or symptomatic and older patients particularly when rapid tumor control is necessary to preserve vision, neurological function and prevent hydrocephalus. Studies suggest that initiating RT at an early stage shows improvement in Blindness Free Survival (BFS)

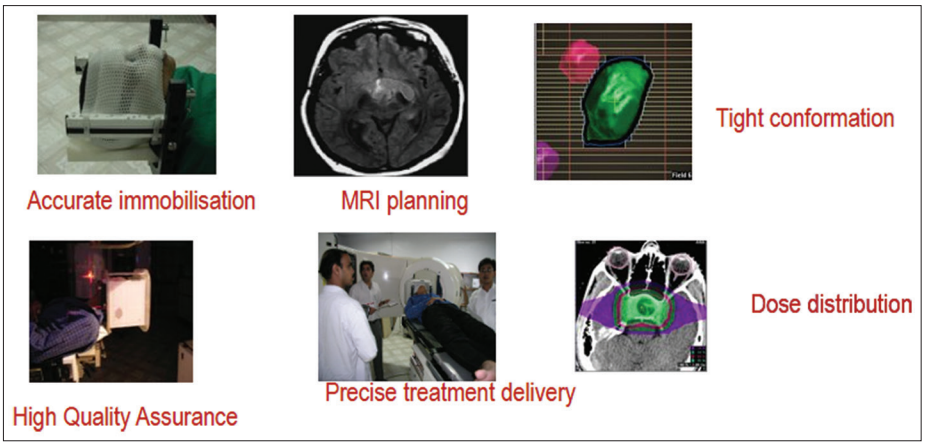

Figure 2: Integral process involved in the delivery of Conformal Radiotherapy

Table 2: Reported Clinical outcomes of Optic Pathway Glioma (OPG)

Study	Patients (*n*)	RT Modality	RT Dose (Gy)	PFS	OS
Cappelli *et al.*[53]	53	X-ray	50–55	5yr 82%	5yr 93%
Acharya *et al.*[36]	41	X-ray/Proton therapy	50–55	5yr 83%	5yr 98%
Tao *et al.*[54]	29	X-ray	50–54	10 year 89%	10yr 89%
Tsang *et al.*[55]	24	X-ray or proton therapy	45–54	5yr 88%	5yr 100%
Jalali et al. [29]	38	Xray	54	-	5-yr 86-91%

compared to delayed RT. [31,36,37]A delayed approach, with chemotherapy as initial treatment with the aim to defer RT for as long as possible is considered to minimize long-term toxicities. This strategy is particularly recommended for young children and NF-1 patients, who are at higher risk of radiation-induced complications.[38] The decision between early and delayed RT for optic pathway glioma should be individualized, balancing the benefits of early tumor control against the long-term risks of radiation toxicity.

Response assessment and monitoring in Optic Pathway Glioma

Evaluating treatment response is essential for determining whether to continue the current line of management or alteration in therapy is required. The RAPNO-LGG group has recently introduced widely accepted criteria and MRI sequencing guidelines for this purpose.[39] Follow-up assessments typically involve clinical evaluations, symptom monitoring, and visual acuity tests, complemented by MRI scans. The RAPNO guidelines recommend performing an MRI with T1W plain, contrast and T2 with spin echo with slice thickness of ≤3mm, preferably with no gap.[39] A unique aspect of these criteria is their consideration of the cystic and solid component of tumours in response assessment with percentage based classifications and recommendations in the management.[39,40] The use of APTw (Amide proton transfer weighted) imaging also aids in the diagnosis and response assessment of Optic pathway glioma. Figure 3, below, illustrates representative images of response to treatment. Visual assessment is an integral part of response and surveillance in the management of optic pathway glioma. High contrast visual acuity and visual fields are considered the gold standard for assessing visual function however, they require the child's cooperation, which can be challenging. Optical Coherence Tomography (OCT) is a non-invasive technique that measures retinal nerve fiber layer thickness and has a high correlation with high-contrast visual acuity (HCVA) and visual fields (VF). OCT allows for the early detection of changes in VA/VF defects, making it a valuable tool in monitoring optic pathway gliomas. Visual Evoked Potential (VEP) testing has limited accuracy and utility, particularly in cases where optic pathway gliomas involve the optic chiasm, preventing meaningful inter-eye comparisons. Additionally, the test's sensitivity can be affected by subtle changes, making it less reliable.

Role of Proton therapy in Optic Pathway Glioma

Multiple studies have explored ways to reduce the long-term toxic effects of radiation by implementing selective avoidance strategies, minimizing target volume sizes, and utilizing advanced radiation techniques.[29,30,33]Among these, proton therapy stands out as

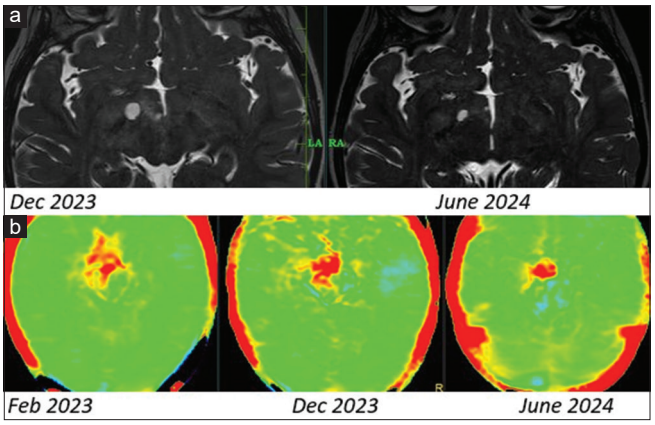

Figure 3: (a) T2 images showing decrease in cystic component over six months with observation; (b) APTw images used for response assessment

a highly promising approach, as it effectively limits radiation exposure to healthy tissues beyond the treatment area. The physical advantages of Proton Beam Therapy PBT over photon RT (X-ray) is based on the "Bragg peak" which could minimize unnecessary radiation exposure of normal organs and increase the therapeutic ratio.[41]As a result, the American Society for Radiation Oncology has classified pediatric low-grade gliomas (LGGs) as a 'Group 1' indication for proton therapy. Consequently, these paediatric low-grade tumours have emerged as one of the most frequently treated paediatric brain tumors using proton therapy worldwide. PBT produced comparable outcomes to conventional photon radiotherapy in terms of survival with the dosimetric advantage of reduced dose to normal brain tissue as illustrated in Figure 2. Indelicato analyzed 174 patients with low-grade gliomas, including 101 cases of optic pathway glioma (OPG), who underwent PBT at doses ranging from 50.4 to 54.0 GyE. After a median follow-up period of 4.4 years, the results for the OPG group were favourable, with 5-year local control, progression-free survival, and overall survival rates of 89%, 88%, and 93%, respectively. Furthermore, patients who received a dose of 54 Gy RBE demonstrated better progression-free survival compared to those who received lower doses (5-year local control: 91% vs. 67%, 5-year progression free survival of 90% vs 67%).[42] Current evidence, derived from indirect comparisons between proton therapy and conventional X-ray therapy, suggests that proton therapy can significantly reduce these toxicities such as moya-moya, endocrine dysfunction, visual defects and hypothalamic disorders.[28,32,43] However, randomized trials comparing the two are unlikely due to the rarity of these cancers and the ethical concerns of exposing children to potentially higher risks in one treatment arm. There are still uncertainties regarding the biological effects of proton therapy on certain healthy tissues, and proton therapy's availability is limited, particularly in developing countries. Nevertheless, as research progresses and the cost of proton therapy units decreases, it is expected that proton therapy will become more accessible and beneficial for children with CNS tumors.[41]

Treatment sequalae

Optic pathway gliomas present unique challenges in terms of treatment and long-term effects. It may affect the optic pathway and surrounding structures, leading to worsened visual function or other neurological symptoms. In pediatric patients with OPG, radiation-induced vasculitis and pseudoprogression are a concern because of the impact on vascular integrity and tissue health.[44] Endocrinopathy may arise because of damage to the hypothalamic-pituitary axis following radiation therapy or surgery. In OPG patients, this is particularly relevant, as the optic pathway is near the hypothalamus and pituitary gland. Endocrine dysfunction, including growth hormone deficiencies, hypothyroidism, and adrenal insufficiency, can occur. Regular monitoring of hormone levels is important for early detection and management. Neurocognitive impairment is another potential long-term effect, particularly with radiation treatment. Children who receive radiation for OPG may experience cognitive deficits affecting memory, attention, processing speed, and executive function.[27,45] The risk of second malignancies, especially secondary brain tumors, is a well-documented long-term risk for pediatric patients who undergo radiation therapy for OPG.

Current Guidelines for Diagnosis and Management of Optic Pathway Gliomas (OPGs)

Current guidelines for diagnosing and managing optic pathway gliomas (OPGs) emphasize a multidisciplinary approach that integrates clinical assessment, imaging, and molecular diagnostics. Diagnosis primarily relies on magnetic resonance imaging (MRI) with contrast, which helps define tumor location, size, and potential spread.[46] In addition to imaging, ophthalmic evaluations, including visual acuity tests and optical coherence tomography (OCT), play a crucial role in assessing disease impact on vision.[47] Histopathological and molecular analyses are also recommended, particularly for distinguishing sporadic OPGs from those associated with neurofibromatosis type 1 (NF1). Molecular markers, such as the BRAF V600E mutation and KIAA1549-BRAF fusion, provide insights into tumor behavior and potential targeted therapies.[47]

Management Strategies

Management strategies for OPGs depend on tumor progression, symptoms, and patient-specific factors. Observation is often the first-line approach for asymptomatic or slowly progressing tumors, particularly in NF1-associated cases, which tend to have a more indolent course.[47] If treatment is required due to significant visual deterioration, chemotherapy is the preferred initial therapy, with vincristine and carboplatin being the standard regimen.[46] Vinblastine monotherapy is an alternative, particularly in cases where toxicity concerns arise. Targeted therapies, such as MEK inhibitors (e.g., selumetinib and trametinib), have emerged as promising options, particularly for BRAF-mutated tumors.[47]

Radiotherapy, once a common first-line treatment for OPGs, is now reserved for cases where other therapies, such as chemotherapy and targeted agents, have failed or the tumor is rapidly progressing.[46] The shift away from radiotherapy is primarily due to its long-term adverse effects, particularly in young children whose developing brains are more vulnerable to radiation-induced damage.[47] Potential complications include neurocognitive deficits, endocrine dysfunction from hypothalamic-pituitary axis damage, and an increased risk of secondary malignancies, such as radiation-induced gliomas.[47] Additionally, radiation can exacerbate vasculopathies, leading to conditions like Moyamoya syndrome, which can cause strokes in pediatric patients.[47] Because of these risks, radiotherapy is typically considered only in older children or adolescents when the benefits outweigh the long-term consequences.[46]

Surgical Treatment of OPGs

Surgical intervention for optic pathway gliomas (OPGs) is generally reserved for specific cases where tumor debulking can relieve symptoms without significantly worsening vision. Indications for surgery include severe proptosis, hydrocephalus due to cerebrospinal fluid obstruction, or well-defined exophytic tumor components that can be safely removed. Biopsy may also be performed when molecular characterization is necessary for targeted therapy.[47] However, complete resection is usually not feasible due to the tumor's delicate location, and surgery is primarily used as an adjunct to other treatments.[46]

Follow-Up and Screening Regimen

Screening and follow-up timelines are crucial for early detection of disease progression and treatment monitoring. In children with NF1, annual ophthalmic evaluations with visual acuity testing are recommended until age 8, with at least biennial follow-ups until age 18.[47] In diagnosed cases, ophthalmic assessments, including visual acuity, OCT, and MRI, should be performed every 3 months for the first year post-diagnosis, followed by every 3–6 months in the second year and every 6–12 months thereafter based on clinical stability.[47] For patients receiving chemotherapy, MRI and ophthalmologic evaluations should be conducted every 3 months during treatment, with continued monitoring every 3–6 months for the first two years post-treatment.[46]

Patients who have undergone radiotherapy require long-term surveillance due to risks of tumor recurrence, endocrine dysfunction, and radiation-related complications. In the first two years, physical examinations, ophthalmologic assessments, and MRIs should be performed every 3–6 months, transitioning to annual follow-ups from the third year onward. Audiometry is recommended every 6–12 months for those at risk of radiation-

induced hearing loss. Endocrine evaluations should be conducted periodically, as radiation to the hypothalamic-pituitary axis may result in hormone deficiencies.[47]

This follow-up schedule ensures early detection and management of late treatment-related complications, maximizing long-term quality of life for pediatric OPG patients.

Future Directions

Advancements in surgical techniques and imaging technologies continue to refine the role of surgery in OPHG management. Future research should focus on long term outcomes with emphasis of quality of life , endocrine function, and cognitive development. A more comprehensive understanding of tumour biology, particularly in NF1-associated cases, could guide treatment decisions.

Development of targeted therapy is a great step in the right direction for these patients thereby enhancing the possibility of personalised medicine in future for these tumors. The fact that these tumors are a part of neurofibromatosis spectrum further highlights the opportunities ahead in exploring the molecular signature based targeted therapy. In future, one can expect that such molecular therapies will completely replace the conventional chemotherapy in these patients.

Older RT techniques and the use of larger target volume margins in the past have been associated with various side effects, including cognitive and growth impairments, neuroendocrine and vascular complications, vasculopathy, difficulties in social adaptation, an increased risk of secondary malignancies, musculoskeletal hypoplasia, hearing disturbances, and reduced quality of life.[48,49] Significant progress has been made in imaging technology, immobilization devices, and modern RT techniques, such as intensity-modulated RT (IMRT), 3D conformal RT, stereotactic radiosurgery, and proton RT. Additionally, improvements in in-room image guidance, tumor localization, and patient position verification have enabled a reduction in target volume margins while maintaining treatment efficacy and failure rates.[29,33] Despite concerns regarding late toxicities, these innovations offer hope for better tumor control, improved visual outcomes, and enhanced quality of life for patients with Optic pathway Gliomas.

Conclusion

Optic pathway glioma, a low grade glioma, occurring in children, commonly necessitates a thorough understanding of its natural history and treatment response in planning management. A multidisciplinary care is paramount is achieving the best outcome. Surgery remains an essential component in the management of OPHGs, particularly for symptomatic relief and cases refractory to other treatments. While the risks associated with operating near critical structures necessitate caution, advancements such as intraoperative MRI have significantly improved surgical safety and outcomes. A comprehensive approach ensures that each patient receives tailored care, balancing the goals of tumor control with the preservation of neurological, visual, and endocrine functions.

Chemotherapy is a safe first line modality with minimal long term toxicity. Targeted agents are promising with new data about their use as first line therapy is emerging. Early addition of VEGF inhibitors, especially in those with high risk of poor visual outcomes may benefit vision stability. Genetic testing to assess molecular profiling is mandatory to explore targeted therapy options available. Radiotherapy continues to play a crucial role, particularly in cases where surgical resection is not feasible, or chemotherapy alone proves insufficient.. For younger patients and those with NF-1, delaying RT in favor of initial chemotherapy may be preferable to reduce late side effects. However, for patients with rapid tumor progression or worsening vision, early RT may offer better disease control and visual preservation.

References

1. Jahraus CD, Tarbell NJ. Optic pathway gliomas. Pediatr Blood Cancer 2006;46:586-596.
2. Binning MJ, Liu JK, Kestle JR, Brockmeyer DL, Walker ML. Optic pathway gliomas: a review. Neurosurg Focus 2007;23:E2.

3. Al-Jilaihawi S, Lowis S. A Molecular Update and Review of Current Trials in Paediatric Low-Grade Gliomas. Pediatr Neurosurg 2023;58:290-298.
4. Farazdaghi MK, Katowitz WR, Avery RA. Current treatment of optic nerve gliomas. Curr Opin Ophthalmol 2019;30:356-363.
5. Taylor T, Jaspan T, Milano G, *et al*. Radiological classification of optic pathway gliomas: experience of a modified functional classification system. Br J Radiol 2008;81:761-766.
6. Goodden J, Pizer B, Pettorini B, *et al*. The role of surgery in optic pathway/hypothalamic gliomas in children. J Neurosurg Pediatr 2014;13:1-12.
7. Hill CS, Khan M, Phipps K, Green K, Hargrave D, Aquilina K. Neurosurgical experience of managing optic pathway gliomas. Child's Nervous System 2021;37:1917-1929.
8. Li S, Xiao W, Tong Z, Li L, Zhang Y. The Use of Diffusion Tensor Imaging in the Differentiation and Surgical Planning of Suprasellar Hypothalamic-Opticochiasmatic Glioma and Craniopharyngioma in Children. World Neurosurg 2025;193:474-482.
9. Lober RM, Guzman R, Cheshier SH, Fredrick DR, Edwards MS, Yeom KW. Application of diffusion tensor tractography in pediatric optic pathway glioma. J Neurosurg Pediatr 2012;10:273-280.
10. Millward CP, Perez Da Rosa S, Avula S, *et al*. The role of early intra-operative MRI in partial resection of optic pathway/hypothalamic gliomas in children. Childs Nerv Syst 2015;31:2055-2062.
11. Albalkhi I, Shafqat A, Bin-Alamer O, *et al*. Complications and visual outcomes following surgical resection of pediatric optic pathway/hypothalamic gliomas: a systematic review and meta-analysis. Childs Nerv Syst 2024;40:2033-2042.
12. Kwon Y, Jeon SR, Kim JH, *et al*. Analysis of the causes of treatment failure in gamma knife radiosurgery for intracranial arteriovenous malformations. J Neurosurg 2000;93 Suppl 3:104-106.
13. Kim JW, Phi JH, Lee JY, *et al*. Clinical Outcome of Optic Pathway and Hypothalamic Gliomas: A 20-Year Single-Institution Retrospective Study. World Neurosurg 2022;166:e451-e459.
14. Czyzyk E, Jóźwiak S, Roszkowski M, Schwartz RA. Optic pathway gliomas in children with and without neurofibromatosis 1. J Child Neurol 2003;18:471-478.
15. Ater JL, Zhou T, Holmes E, *et al*. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. J Clin Oncol 2012;30:2641-2647.
16. Packer RJ, Bilaniuk LT, Cohen BH, *et al*. Intracranial visual pathway gliomas in children with neurofibromatosis. Neurofibromatosis 1988;1:212-222.
17. Maheshwari A, Pakravan M, Charoenkijkajorn C, Beres SJ, Lee AG. Novel treatments in optic pathway gliomas. Front Ophthalmol (Lausanne) 2022;2:992673.
18. Yaman Bajin I, Bouffet E. Optic pathway and hypothalamic glioma, old problems, new paradigms. Pediatric Hematology Oncology Journal 2023;8:102-110.
19. Bouffet E, Hansford JR, Garrè ML, *et al*. Dabrafenib plus Trametinib in Pediatric Glioma with BRAF V600 Mutations. N Engl J Med 2023;389:1108-1120.
20. van Tilburg CM, Kilburn LB, Perreault S, *et al*. LOGGIC/FIREFLY-2: a phase 3, randomized trial of tovorafenib vs. chemotherapy in pediatric and young adult patients with newly diagnosed low-grade glioma harboring an activating RAF alteration. BMC Cancer 2024;24:147.
21. Dodgshun AJ, Elder JE, Hansford JR, Sullivan MJ. Long-term visual outcome after chemotherapy for optic pathway glioma in children: Site and age are strongly predictive. Cancer 2015;121:4190-4196.
22. Campagna M, Opocher E, Viscardi E, *et al*. Optic pathway glioma: long-term visual outcome in children without neurofibromatosis type-1. Pediatr Blood Cancer 2010;55:1083-1088.
23. Dalla Via P, Opocher E, Pinello ML, *et al*. Visual outcome of a cohort of children with neurofibromatosis type 1 and optic pathway glioma followed by a pediatric neuro-oncology program. Neuro Oncol 2007;9:430-437.
24. Avery RA, Hwang EI, Jakacki RI, Packer RJ. Marked recovery of vision in children with optic pathway gliomas treated with bevacizumab. JAMA Ophthalmol 2014;132:111-114.
25. Luo R, Zhang T, Yang W, *et al*. Spontaneous regression of tumor in a girl with optic pathway glioma with diencephalic syndrome. Pediatr Investig 2023;7:60-62.
26. Yousefi O, Azami P, Sabahi M, Dabecco R, Adada B, Borghei-Razavi H. Management of Optic Pathway Glioma: A Systematic Review and Meta-Analysis. Cancers (Basel) 2022;14.
27. Moreno L, Bautista F, Ashley S, Duncan C, Zacharoulis S. Does chemotherapy affect the visual outcome in children with optic pathway glioma? A systematic review of the evidence. Eur J Cancer 2010;46:2253-2259.
28. Awdeh RM, Kiehna EN, Drewry RD, *et al*. Visual outcomes in pediatric optic pathway glioma after conformal radiation therapy. Int J Radiat Oncol Biol Phys 2012;84:46-51.
29. Jalali R, Gupta T, Goda JS, *et al*. Efficacy of Stereotactic Conformal Radiotherapy vs Conventional Radiotherapy on Benign and Low-Grade Brain Tumors: A Randomized Clinical Trial. JAMA Oncol 2017;3:1368-1376.

30. Youn SH, Kim H, Lee SH, Kim JY. Regression and pseudoprogression of pediatric optic pathway glioma in patients treated with proton beam therapy. Pediatr Blood Cancer 2022;69:e29434.
31. Hanania AN, Paulino AC, Ludmir EB, *et al*. Early radiotherapy preserves vision in sporadic optic pathway glioma. Cancer 2021;127:2358-2367.
32. Terashima K, Chow K, Jones J, *et al*. Long-term outcome of centrally located low-grade glioma in children. Cancer 2013;119:2630-2638.
33. Cherlow JM, Shaw DWW, Margraf LR, *et al*. Conformal Radiation Therapy for Pediatric Patients with Low-Grade Glioma: Results from the Children's Oncology Group Phase 2 Study ACNS0221. Int J Radiat Oncol Biol Phys 2019;103:861-868.
34. Bansal I, Merchant TE. Radiotherapy for pediatric low-grade glioma. Childs Nerv Syst 2024;40:3277-3290.
35. Taveras JM, Mount LA, Wood EH. The value of radiation therapy in the management of glioma of the optic nerves and chiasm. Radiology 1956;66:518-528.
36. Acharya S, Quesada S, Coca K, *et al*. Long-term visual acuity outcomes after radiation therapy for sporadic optic pathway glioma. J Neurooncol 2019;144:603-610.
37. Kim N, Lim DH. Recent Updates on Radiation Therapy for Pediatric Optic Pathway Glioma. Brain Tumor Res Treat 2022;10:94-100.
38. José P, Couceiro R, Passos J, Jorge Teixeira F. Visual Outcomes of Optic Pathway Glioma Treated With Chemotherapy in Neurofibromatosis Type 1. J Pediatr Ophthalmol Strabismus 2022;59:128-135.
39. Fangusaro J, Witt O, Hernáiz Driever P, *et al*. Response assessment in paediatric low-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 2020;21:e305-e316.
40. van den Bent MJ, Wefel JS, Schiff D, et al. Response assessment in neuro-oncology (a report of the RANO group): assessment of outcome in trials of diffuse low-grade gliomas. Lancet Oncol 2011;12:583-593.
41. Gondi V, Yock TI, Mehta MP. Proton therapy for paediatric CNS tumours - improving treatment-related outcomes. Nat Rev Neurol 2016;12:334-345.
42. Indelicato DJ, Rotondo RL, Uezono H, *et al*. Outcomes Following Proton Therapy for Pediatric Low-Grade Glioma. Int J Radiat Oncol Biol Phys 2019;104:149-156.
43. Greenberger BA, Pulsifer MB, Ebb DH, *et al*. Clinical outcomes and late endocrine, neurocognitive, and visual profiles of proton radiation for pediatric low-grade gliomas. Int J Radiat Oncol Biol Phys 2014;89:1060-1068.
44. Omura M, Aida N, Sekido K, Kakehi M, Matsubara S. Large intracranial vessel occlusive vasculopathy after radiation therapy in children: clinical features and usefulness of magnetic resonance imaging. Int J Radiat Oncol Biol Phys 1997;38:241-249.
45. Passos J, Nzwalo H, Marques J, *et al*. Late Cerebrovascular Complications After Radiotherapy for Childhood Primary Central Nervous System Tumors. Pediatr Neurol 2015;53:211-215.
46. Roka K, Scheinemann, K., Avula, S., Maduro, J.H., Thomale, U.W., Sehested, A., Schouten-Van Meeteren, A.Y.N. European standard clinical practice recommendations for primary pediatric low-grade gliomas. EJC Paediatric Oncolog 2024;4.
47. Modrzejewska M, Olejnik-Wojciechowska J, Roszyk A, *et al*. Optic Pathway Gliomas in Pediatric Population-Current Approach in Diagnosis and Management: Literature Review. J Clin Med 2023;12.
48. Han TS, Gleeson HK. Long-term and late treatment consequences: endocrine and metabolic effects. Curr Opin Support Palliat Care 2017;11:205-213.
49. Williams NL, Rotondo RL, Bradley JA, *et al*. Late Effects After Radiotherapy for Childhood Low-grade Glioma. Am J Clin Oncol 2018;41:307-312.
50. Fawzy MA E-HA, Awad M E-BM, Zaghloul MS, Taha H,. Multidisciplinary treatment of pediatric low-grade glioma: Experience of children cancer hospital of Egypt. Indian J Med Paediatr Oncol 2018;39:488-492.
51. Papusha L.I. VEF, Druy A.E., Yasko L.A., Voronin K.A., Zaitseva M.A., Salnikova E.A., Raikina E.V., Novichkova G.A., Karachunsky A.I. Low-grade gliomas with the V600E mutation in the BRAF gene in children: features of the clinical course and treatment options. Pediatric Hematology/Oncology and Immunopathology Issues 2020;19:58-65.
52. Varan A, Akyüz C, Akalan N, *et al*. Astrocytic tumors in children: treatment results from a single institution. Childs Nerv Syst 2007;23:315-319.
53. Cappelli C, Grill J, Raquin M, et al. Long-term follow up of 69 patients treated for optic pathway tumours before the chemotherapy era. Arch Dis Child 1998;79:334-338.
54. Tao ML, Barnes PD, Billett AL, *et al*. Childhood optic chiasm gliomas: radiographic response following radiotherapy and long-term clinical outcome. Int J Radiat Oncol Biol Phys 1997;39:579-587.
55. Tsang DS, Murphy ES, Merchant TE. Radiation Therapy for Optic Pathway and Hypothalamic Low-Grade Gliomas in Children. Int J Radiat Oncol Biol Phys 2017;99:642-651.