Pediatric Optic Pathway/Hypothalamic Glioma

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Abstract

Optic pathway/hypothalamic gliomas (OP/HGs) are rare astrocytic tumors that appear more commonly among young children and are often unresectable. They comprise approximately 2% of all central nervous system tumors and account for 3–5% of pediatric intracranial tumors. Initial manifestations are often visual disturbances, endocrinopathies, and hypothalamic dysfunction such as the diencephalic syndrome, and sometimes hydrocephalus due to cerebrospinal fluid (CSF) outflow obstruction. In many cases, the tumors are diagnosed late in the clinical course because they silently enlarge. These tumors consist mostly of histologically benign, World Health Organization (WHO) grade I tumors represented by pilocytic astrocytomas (PA), the rest being pilomyxoid astrocytomas (PXA) – WHO grade II tumors. In young pediatric patients, however, PXA that show aggressive clinical course such as CSF dissemination. Our small series of 14 non-Neurofibromatosis type 1 (NF-1) OP/HGs PA patients underwent extended resection without any adjuvant treatments. The median age at initial treatment was 11.5 ± 6.90 years (range, 1–25 years) and median follow up 85.5 ± 25.0 months. Surgical resection for OP/HGs results in acceptable middle-term survival, tumor control and functional outcome equivalent to chemotherapy. There is, however, no longer doubt that chemotherapy with or without biopsy and as-needed debulking surgery remains the golden standard in management of OP/H. Clinical conditions and treatment plans for OP/HGs vary depending on their structure of origin.

Key words: optic pathway glioma, pilocytic astrocytoma, prognosis, chemotherapy, radiotherapy, surgery

Introduction

Among the variety of brain tumors, treatment plans depend on their histologically established types, precise location and some additional factors. For pediatric brain tumors, it is necessary to effectively choose and combine “surgery,” “radiotherapy” and “chemotherapy”. Optic pathway/hypothalamic gliomas (OP/HGs) accounts for 2% of all gliomas, and its main pathological types are pilocytic astrocytoma (PA) and pilomyxoid astrocytoma (PXA). Although the incidence of optic pathway gliomas (OPGs) ranges from 3% to 5% of pediatric brain tumors, it accounts for 20% of pediatric brain tumor patients who are two years old or younger.

To obtain an optimal long-term functional prognosis, it is necessary to have a comprehensive treatment strategy, particularly for a pediatric brain tumor patient. Radiotherapy and chemotherapy are typically effective against medulloblastoma and germ cell tumor. However, chemotherapy is also important for PA and PXA that have been developed in regions where complete tumor removal cannot be achieved. This paper will outline treatment strategy for OP/HGs.

Critical form of OP/HGs

Of the OP/HGs patients, 75% are children 10 years old or younger, and 90% are 20 years old or younger. The special characteristics of the symptoms of this disease include deteriorating visual acuity, narrowing of the visual field and pendular movement nystagmus. Because preschool children rarely complain about poor vision, such problems are often found and indicated as a result of a physical examination conducted when the child is about to start school. In the anterior-type (intraorbital) optic nerve tumor, if the tumor enlarges, it will cause exophthalmos (Fig. 1). Pendular movement nystagmus is an OP/HGs symptom that involves the optic chiasma and hypothalamus, and it is significant as a cause of acquired nystagmus. It can be seen in almost half
of child patients who are two years old or younger. However, it is rarely seen in those who are older than two, and by the time this symptom manifests, the disorders of vision have already progressed.

Once the tumor in the hypothalamus has progressed from the optic chiasma further toward the upper posterior side, it occludes the third ventricle and the foramen of Monro, thus causing hydrocephalus. If this occurs in a child under a year of age, the head will expand in circumference. It also causes dysfunction in the pituitary gland and hypothalamus, and in infants it develops concurrently with the diencephalic syndrome (Russell syndrome). Even though the patient has adequate quantity of oral intake, she/he will experience significant weight loss. A special characteristic of this syndrome is emaciation, which can be misconstrued as child abuse. From the laboratory, growth hormone shows increased levels. If the treatment is effective, the diencephalic syndrome can be improved. However, as OP/HGs patients become older, hypothalamic obesity can occur, and subsequently they tend to develop true precocious puberty.

Classification by sites of origin

OP/HGs occurs in the intraorbital optic nerve, intracanalicular optic nerve, intracranial optic nerve, optic chiasma, optic tract, lateral geniculate body and the hypothalamus; it can develop also adjacent the visual pathway and hypothalamus. It is considered that there are more anterior-type OPGs in Neurofibromatosis type 1(NF-1) patients and for tumors including optic chiasma, it accounts for 73% of the cases. In the cases considered sporadic (not related to NF-1), the posterior type occurs more frequently.

Dodge et al. classified OPG into the following three stages: A: limited to the optic nerve; B: involving optic chiasma (with or without extension to the optic nerve) and C: involvement of hypothalamus and other structures.

Pathology of OP/HGs

The most common pathological present of OPG is PA, WHO Grade 1. Considering the OPG origin in the optic nerve, nearly all cases are PA, which have an extremely slow growth rate. Of all PA cases, 10% to 50% are associated with NF-1, and most of them are bilateral type. Moreover, 11 to 30% of NF-1 patients develop OPG. Contrastingly, the incidence rates of other histological types of OPGs are higher in patients whose tumors are located in the optic chiasma and hypothalamus. Among infant patients, PXA, WHO Grade 2 is more commonly seen. Additionally, a disease concept of considering intermediate pilomyxoid tumors as transitional-type tumors between PA and PXA has also been advocated. However, in the WHO’s new classification published in 2016 all of the above types are classified as Grade 1 because the differences in gene abnormality and prognosis among these types of tumors and PA are unclear. Furthermore, in the posterior parts of optic chiasma, ganglioglioma and other similar tumors have been reported. Once children grow up to adulthood, the frequency of reported diffuse glioma increases.

For the onset of PA, activation of the mitogen-activated protein kinase (MARK) signal pathway such as RAS and RAF plays an important role. NF-1 gene controls the RAF-MEK-ERK signal pathway downstream by controlling RAS, thus activating ERK, which is a typical signal pathway of the MARK during NF-1 gene mutation. Furthermore, approximately 2Mb tandem duplications were observed at the site of 7q34 in more than 2/3 of PA cases. This abnormality is not seen in very aggressive gliomas, but the BRAF-KIAA1549 fusion gene activates MARK (ERK) as a cancer gene. Moreover, gene mutation of V600E of BRAF can be found at the frequency of approximately two thirds in pleomorphic xanthoastrocytoma and it has also been observed in PA. Regarding other gene mutations, gene mutation and fusion gene formation in FGFRI and fusion gene formation in the NTRK family have been reported. These abnormalities activate the MARK (ERK) signal pathway. Examining the relation between places of tumor origin and gene mutation patterns,
less BRAF-KIAA1549 fusion-gene formations and more BRAF V600E gene mutations are observed in PA developed on the optic pathway compared to the tumors developed in the cerebellum.\textsuperscript{15} It is hoped that the collection of those findings on gene abnormality will enable us to develop future more effective treatment methods.

**Chemotherapy for OP/HGs**

The so-called CV regimen using Carboplatin and Vincristine, as reported by Packer et al., is the most frequently recommended first-line chemotherapy, and it is considered to be the standard treatment of OPG.\textsuperscript{16} The treatment period is one year. Because OPG is a disease that should be treated by means of a long-term plan, it can be said that long-term chemotherapy is an advantage. However, the fact that chemotherapy must be continued for a long period could be a disadvantage to the patient.

In regard to Carboplatin, bone marrow suppression has been reported. Therefore, if the hemoglobin level is rapidly decreasing, the patient must be carefully monitored.\textsuperscript{17,18} In this treatment, it is necessary to remember that it takes certain period of time until the tumor reduction effect manifests. The regimen of Cisplatin and Vincristine has been reported by Sawamura et al. For this treatment, the patient must be hospitalized because the treatment intensity will increase with the use of Cisplatin instead of Carboplatin. The following are advantages in the use of Cisplatin: the therapeutic effect of Cisplatin manifests in the early stages as compared to Carboplatin; the success ratio is high; the treatment period can be reduced to almost half of that of Carboplatin.\textsuperscript{19} Although it has been reported that Temozolomide is effective as an OPG treatment option, its success ratio is not high. Therefore, it is not recommended as the first-line treatment, unlike situations in which it is used for aggressive gliomas.\textsuperscript{20} Temozolomide and Bevacizumab are covered by insurance in recurrent tumors, as they are considered to be a malignant glioma.

**Radiotherapy on OP/HGs**

The concept of “every effort should be taken to avoid radiotherapy” has gained consensus as the basic policy in the treatment of OPG. However, radiotherapy must be applied if the disease cannot be controlled by other regimens except external irradiation with fractionation. Despite the effectiveness that radiotherapy demonstrates against OPG, there are many problems of late effects such as hormonal dysfunction, angioopathy, progressive deterioration of cognitive function, development of secondary tumors (meningioma, glioblastoma) and cavernous angiomas, radiation gliosis and necrosis in the white matter. The younger the patient at the start of radiotherapy, the more serious the late effects will be. Therefore, the time to start radiotherapy should be aimed at the age of five to seven, or even older, while the patient is treated through other means, or it should be completely avoided if possible.\textsuperscript{21} In NF-1 patients, the risk of developing secondary tumors or Moyamoya disease as an angiopathy is increased.\textsuperscript{22} It has been reported that excessive postponement of radiotherapy may adversely affect endocrinological functions, such as decreased secretion of growth hormone.\textsuperscript{23} It has been reported that the prognosis for vision was better when radiotherapy was performed before chemotherapy than vice versa, but these are not long-term data.\textsuperscript{24} The non-recurrent 10 years survival rate after the administration of radiotherapy ranges from 70% to 90%, and the patients whose vision became stabilized during that period account for 69% to 81%.\textsuperscript{3} It is expected that the risk of occurrence of late effects will be diminished by reducing the amount of radiation dose to the normal peripheral tissues, which would be done by precision beam delivery radiotherapy – by intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT) or through the use of a proton beam.

**Surgical treatment of OP/HGs**

The topic of OPG surgery is controversial and the purpose and role of surgery must be carefully examined. Sawamura et al. have reported that if OPG can be confirmed through an image diagnosis, chemotherapy must be initiated immediately due to the reasons that mere surgery cannot cure OPG, and that chemotherapy is effective. They also claim that the surgery risk itself must be avoided, as well as the delay in the initiation of chemotherapy due to surgery.\textsuperscript{25} They also state that surgery must be performed only under unavoidable circumstances such that when the tumor has grown following chemotherapy. Furthermore, in the consensus announcement is stated that upon discovery of these tumors, ablative operation should not be considered for every single case and it is unnecessary to perform biopsy when the NF-1 patient has a typical OPG.\textsuperscript{26} Except when tumors are localized in the optic nerve on one side alone and curable even though the patient may lose the visual function of one side due to the ablation, this disease cannot be cured only by surgery.\textsuperscript{3} One should bear in mind the fact that tumors localized on the optic chiasma and diffuse infiltrating gliomas that have extended to the optic pathways cannot be subject to any surgery, including biopsy. It is essential to
carefully examine surgical indications considering the functional prognosis, especially for possible damages to the hypothalamus and visual function caused by surgery, risks of damage to vascular structures, consideration of the site of origin of the lesion and an existing context of NF-1. Once it has been determined that surgery will be performed, it is essential to devise an adequate plan and set goals in advance.

Another reason for the difficulty to determine treatment policy, including the surgical indication, is the natural course of PA, i.e., property changes in the tumors due to aging. PXA grow with the child's brain growth. Once the child brain is developed, the tumor may spontaneously regress at some point, depending on its nature. However, in the context of clinical practice it can be difficult to determine whether a tumor will spontaneously regress or therapeutic intervention will be required. Furthermore, due to the treatment and its changes over time, it is difficult to clearly define natural history. A certain fact is that many tumors are low grade, grow slowly and patients survive for a long period of time.

There is no doubt, however, that decompression through surgery is effective in the following situations: for large tumors, particularly those inducing hydrocephalus, for patients with visual impairment caused by the visual pathway tumor compression and in patients who have endocrine dysfunction. Particularly for infants, it is important that treatment harmful to the neural development be postponed by performing a debulking operation to reduce the tumor mass. Furthermore, on some occasions, tumors may naturally regress following debulking operation or a biopsy. In a group of young patients with poor prognosis, which is the so called high-risk group, it has been reported that a favorable treatment result can be achieved by conducting adequate decompression through surgery followed by chemotherapy. However, there is also an opposite opinion that for infants non-invasive treatment must be considered (such as chemotherapy) preceding whenever possible, considering the risk of surgery itself toward their neural development. When both surgery and chemotherapy were conducted on patients three years old or younger, the effectiveness of such treatment was not demonstrated as compared to chemotherapy alone. Thus, it can be assumed that each individual case must be sufficiently examined by a team of specialists.

The timing of surgery is not subject to any single consensus. However, it is thought that when the symptoms of exophthalmos, significantly poor vision, visual loss or a combination of the previous two are observed in a patient with a unilateral optic nerve lesion alone, it indicates that surgery must be performed. In a case of tumor protruding from the optic chiasma or hypothalamus, the presence of significant brain edema with mass effect or the appearance of hydrocephalus can be a surgical indication. Once a cyst is formed, it is also difficult to reduce it merely through means of chemotherapy. If it becomes symptomatic due to the mass effect, it is considered as a surgical indication. As for the vision, it is difficult to determine the proper timing of surgery. Moreover, it has been reported that changes in visual function do not indicate the tumor condition and that tumor growth is not necessarily related to the deterioration of visual function.

The following surgical approaches can be chosen, depending on the predominant localization and the presence of concurrent hypothalamic involvement: the interhemispheric trans-callosal, interhemispheric trans-lamina terminalis, trans-foraminal (cortical), pericallosal and endonasal trans-sphenoidal. Considering the preservation of vision in relation to surgery, a surgical approach is often chosen in consideration of the eye in which vision is already deteriorating. Because a tumor often grows asymmetrically, the most suitable approach must be chosen in accordance with a thorough preoperative examination for each individual case. It is recommended that, even after the tumor mass is significantly reduced, a follow-up imaging must be conducted every two months for the first six months in order to confirm whether the tumor continues to grow. If there is a tendency toward regrowth, it can be considered appropriate to start or resume chemotherapy.

In our series, nearly half of OP/HGs remain stable and not require any interventions. Progressive cases are usually treated with chemotherapy and sometimes with radiotherapy, but not with surgery alone because of their critical locations including optic tracts, hypothalamus and adjacent brain structures. Because of their rarity, there have been no definitive randomized clinical trials to evaluate chemotherapeutic protocols. Carboplatin (CBDCA) is a key chemotherapeutic agent for OP/HGs. Gnekow achieved high response rate with CBDCA/vincristine (VCR) regimen. Other protocols that include cisplatin (CDDP) and VCR are also effective. Though in a small number of cases, all the patients who received 6 to 8 cycles of CDDP/VCR every 4 weeks, achieved complete or partial remission, i.e. at least stable disease. Imatinib may be an alternative approach for progressive disease refractory to chemotherapy. Six patients with progressive hypothalamic/chiasmatic gliomas who had undergone surgical resection and chemotherapy were treated with imatinib.
and all of them achieved stable disease for 5 to 47 months. Chemotherapy is recommended as a primary treatment for OP/HGs, however does not provide complete cure alone. It plays a pivotal role in stabilization of tumor condition and not in its regression, and acts as a bridge between initial treatment and salvage surgery or late-stage radiotherapy.

**Discussion**

Radiation is often considered the treatment of choice for OP/HGs. But it has significant long-term complications including cognitive, visual and neuroendocrine dysfunction. Regarding its cognitive effects, it was reported that a dose of 54 Gy conformal radiation therapy (CRT) decreased psychological score, such as Wechsler Individual Achieve Test and Vineland Adaptive Behavior Scale, by an average of 8 points. In addition, radiotherapy may induce secondary neoplasms. Raikar reported that after CRT with dose ranging from 50 to 54 Gy, both the 3- and the 10-year overall survival (OS) were 100% whereas the 3- and the 10-year progression free survival (PFS) were 69% and 46%, respectively. The younger age at initiating radiation therapy and the tumor location, especially hypothalamus and optic pathways are high risk factors for progression. In a large, multicenter multidisciplinary treatment study for low-grade glioma, the 5-year and the 10-year PFS were 65% and 62%. It was indicated by multivariable analysis, the risk factors for tumor progression after radiation were non-pilocytic grade I and non-diffuse grade II histology, patient age at diagnosis <1 y and dissemination at diagnosis. Though the radiotherapy is effective, early irradiation is often accompanied by development of complications later in life. Radiation may therefore be useful for an adjuvant treatment in the case of chemotherapy refractory tumors (Table 1).

In many cases, the role of surgery is to acquire the accurate pathological diagnosis and debulking is performed only in a few cases. Gross total resection of low-grade glioma is strongly associated with improvement of both OS and PFS. Aggressive resection, however, often involves sacrifice including blindness, hypothalamic damage and cognitive dysfunctions. Hence, in a multidisciplinary consensus conference on pediatric neurosurgery in 2011, was published the statement that “It was agreed that attempted primary surgical resection of HCLGG (Hypothalamic Chiasmatic Low Grade Glioma) is not the current standard of care, however, it was also acknowledged that selected cases were amenable to attempted resection or debulking with low risk”.

Biopsy is recommended because accurate pathological diagnosis helps us to select therapeutic options when the imaging appearance is atypical even in patients not associated with NF-1. If the imaging is showing typical appearance, biopsy may not be necessary. In non-NF-1 patients, it is acceptable to perform biopsy after multidisciplinary discussion. Stereotactic biopsy, neuroendoscopic biopsy or open biopsy with craniotomy can be appropriate, but we have to choose the best approach for ensuring maximum safety.

Debulking surgery is controversial with regard to the timing of the surgical intervention. Goodden reported that the timing of surgery depends on tumor size, anatomical location and patient’s symptoms. Whether the tumor is associated with NF-1 or not is also an important decision factor for surgery. NF-1 associated OP/HGs are multifocal and often involve optic nerves, chiasma and optic radiations. They, in general, present in older than 1 year of age and have better outcome, whereas non-NF-1 cases present in younger age with large tumors. But non-NF-1 patients with lesions developed in later childhood frequently have small tumors. In younger age the tumors grow rapidly and cause visual disturbances, endocrinopathy and sometimes hydrocephalus by obstructing CSF outflow. Their growth, however, slows and arrests in late childhood. Therefore,

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<th>Table 1</th>
<th>Past OP/HGs report about the overall survival (OS) and the 5- and the 10-year progression-free survival (PFS) rate</th>
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<tr>
<td>Laitheir et al. J Clin Oncol 21, 2003</td>
<td>5-year OS: 89.0%</td>
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<tr>
<td>Cappelli et al. Arch Dis Child 79, 1998</td>
<td>10-year OS: 83.0%</td>
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<tr>
<td>Grabenbauer et al. Radiother Oncol 54, 2000</td>
<td>10-year OS: 94%</td>
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<tr>
<td>Nicolin et al. Pediatr Blood Cancer 53, 2009</td>
<td>5-year/10-year OS: 97.6%/94.6% (Cx, Debulking, GTR, Rx)</td>
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<tr>
<td>Nicolin et al. Pediatr Blood Cancer 53, 2009</td>
<td>There was no difference in PFS between Cx vs Cx+debulking vs debulking alone.</td>
</tr>
<tr>
<td>Our series of 14 non-NF-1 OP/HGs patients</td>
<td>5-year/10-year OS: 100%/100%</td>
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Cx: chemotherapy, Rx: Radiotherapy.
in the statements mentioned above, there is a sentence: “The overall aim of therapy in childhood and adolescent HCLGG is to gain time by controlling tumor progression and to preserve function”. Surgical strategy is of considerable significance. Once the debulking surgery is planned, the surgeon has to take maximum care not to develop surgical complications. Safer debulking surgery is achieved by removing the central core of the tumor, leaving the tumor rim with the surrounding brain structures. This approach enables the surgeon to avoid complications, including visual or hypothalamic injury.\cite{37}

The access route for surgical resection also needs consideration. It is considered that the two major approaches used for a tumor in this region are the pterional and the midline transcallosal-interfornicial approaches.\cite{36,37} The pterional approach works well for the patients whose tumors project laterally and compress optic nerves and chiasma. This approach has the advantage of being able to confirm the perforating branches from the anterior cerebral artery, but is unable to show the hypothalamic arteries. It is also difficult and dangerous to remove the tumor from posterior hypothalamus. The midline transcallosal-interfornicial approach is suitable for the tumors extending superiorly and to the third ventricle.\cite{37} Though this approach can provide narrow operative field, the anatomical orientation is relatively clear. The surgeon can distinguish the tumor from the third ventricle wall and spare the hypothalamus bilaterally.\cite{36} The inter-fornicial approach, however, involves the risk of injuring fornix bilaterally, resulting in intractable memory disturbance. In addition, through this surgical route a tumor derived from the optic nerve, chiasma or optic radiation could not be resected under direct surgical observation. In recent years, the indications for the extended endoscopic endonasal approach have been progressively expanded. Zoli et al. reported that this approach is useful in hypothalamic gliomas for central debulking and even gross-total removal of the tumor.\cite{36} Their initial experience may suggest that the endoscopic endonasal approach may allow the surgeon to remove the tumor with a microsurgical technique as well. However, their study includes only a small number of patients and the method remains only a possibility at this time.

Negative predictors of OPG include early age of onset (between one and three years old), the site of origin (posterior to the optic chiasma), diencephalic syndrome as a complication, non-NF-1 patient and BRAF V600E mutation. Regarding vision impairment in general, an early age of onset has negative prognosis. Tumor development posterior to chiasm has also negative prognosis regarding visual function.

In a report on patients to whom BB-SFOP (chemotherapy using the six drugs Carboplatin/Procarbazine, Etoposide/Cisplatin and Vincristine/Cyclophosphamide) was performed in France as a form of primary care, the long-term prognosis was not as favorable as was claimed in other previous reports.\cite{39} Although the data are biased because the cases treated surgically were excluded and only radiotherapy and other types of chemotherapies had been performed, it shows that the survival rate continues to decrease every five years and tumors were the leading cause of death. In addition, onset before the age of one and the presence of intracranial hypertension upon onset are negative predictors. However, male patients and patients who didn't develop diencephalic syndrome had better prognoses. Contrastingly, prognoses of the patients who had two or more of the following conditions were significantly worse and only about half of these patients survived for 18 years after receiving BB-SFOP therapy: (1) onset age younger than one year; (2) intracranial hypertension; and (3) female with diencephalic syndrome. Another interesting fact in this report was that although NF-1 patients' prognoses have been good initially, their survival curve began to overlap that of non-NF-1 patients during the long-term follow-up period of more than 15 years. It is considered that the number of patients who need therapeutic intervention is minimal because the OPG tumor characteristics of NF-1 patients are relatively benign. However, it is necessary to further investigate the question of long-term prognosis by accumulating case series.

In our institution, the treatment strategy for OP/HGs is surgical resection alone, with no adjuvant therapy including chemotherapy and irradiation. The goal of surgery is not a simple debulking but an extended resection, in other words – maximum safe resection. In the anterior type tumors which derive from optic nerves or chiasma, the exophytic part of the tumor is detached from surrounding brain structures and removed as much as possible while the tumor on the optic nerves and chiasma is carefully reduced as if the surgeon should reshape chiasma properly. The posterior type tumors including retro-chiasmatic and hypothalamic type often grow superiorly into the third ventricle. In this type, the surgeon can detach the tumor relatively safely from the lateral walls of the third ventricle. The technique to reduce the tumor on chiasma is as with the anterior type OP/HGs. The tumor under chiasma, however, cannot be resected safely. The surgical approach we commonly used is the anterior inter-hemispheric translaminaterminalis (AIHTL) approach or pterional approach. The AIHTL approach enables us to understand the anatomical relation between
the tumor and hypothalamus, while the space under the optic nerves and chiasma remains blind.

Our small series of 14 non-NF-1 OP/HGs patients underwent extended resection without any adjuvant treatments. The median age at initial treatment was 11.5 ± 6.90 years (range, 1–25 years) and median follow up 85.5 ± 25.0 months. Presenting symptoms were visual disturbance including loss of vision and visual field defect (92.9%), endocrine dysfunction (85.7%) and hydrocephalus (35.7%). All patients are alive at median follow-up of 86 months. The pathological diagnosis in all of them was PA. After surgery, visual and endocrine functions were deteriorated in 4 (28.6%) and 1 (7.1%), respectively (Table 2).

There was no remarkable functional improvement of vision and endocrinological function. Progression-free survival and overall survival at 5-years were 80.0 and 100%. Though there was no significant difference in PFS, gross-total removal showed better prognosis than a partial one. In four cases, re-growth of residual tumor was confirmed, and only one of them developed malignant change after the primary surgery and needed repeated surgical intervention.

Surgical resection for OP/HGs results in acceptable middle-term survival, tumor control and functional outcome equivalent to chemotherapy. There is, however, no longer doubt that chemotherapy with or without biopsy and as-needed debulking surgery remains the golden standard in the management of OP/HGs.

Future Prospects

In pediatric OPG cases it is important to determine the treatment policy with a long-term perspective in collaboration among various departments including neurosurgery, clinical neuro-oncology and pediatrics, and experts in tumors/endocrinology, radiotherapy, ophthalmology and other related medical fields. The treatment strategy thus devised must consider not only the findings of imaging but also the conditions of endocrinological functions, including the visual function, diencephalic syndrome, true precocious puberty and growth-hormone deficiency, while at the same time paying attention to complications and late effects. Hopefully, gene abnormalities of these tumors will be further elucidated and a molecular target agent will be developed in the future.

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