Fractionated stereotactic radiotherapy for optic nerve gliomas

Radioterapia estereotatica fracionada para o tratamento dos gliomas do nervo óptico

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ABSTRACT
Optic nerve gliomas represent approximately 5% of all pediatric intracranial tumors. Due to the highly variable clinical course optimal treatment is still discussed controversial. Since they often have little or no growth potential there is a strong recommendation for wait-and-see strategies. In patients with progressive loss of vision or local tumor progression in MR imaging, fractionated radiotherapy provides the greatest possibility of vision preservation. Radiotherapy plays an important role in these challenging tumors achieving high long-term local control rates and improved or stable visual function in approximately 90% of the cases. Recommended dose prescriptions vary between 45 and 54 Gy in standard fractionation. However, in children less than 5 years of age the role of radiotherapy is unclear. Here, chemotherapy is often used to delay radiotherapy treatment to avoid neuropsychological morbidity after irradiation during neurodevelopment. Typical late complications of radiotherapy include endocrinopathy, vasculopathy, cognitive deficits and cataracts, especially in younger patients. Modern high-precision radiotherapy techniques like fractionated stereotactic radiotherapy (FSRT) are capable to achieve high local control rates with reduced treatment related late morbidity. Prospective randomised trials are needed to further define the role of modern radiotherapy techniques, especially in younger patients in a multimodal treatment approach.

Key-words: Optic glioma, Fractionated stereotactic radiotherapy.

SUMÁRIO
Os gliomas do nervo óptico representam aproximadamente 5% de todos os tumores pediátricos intracranianos. O tratamento de escolha é ainda controverso devido a grande variabilidade de seu curso clínico. Em função do baixo índice de crescimento destes tumores, há uma grande tendência para a estratégia de tratamento conservador somente com observação. Em pacientes com perda visual progressiva ou crescimento tumoral na ressonância magnética, a radioterapia estereotáxica fracionada proporciona a maior possibilidade de preservação visual. A radioterapia desempenha um papel importante nestes tumores proporcionando altos índices de controle local a longo prazo e melhora ou estabilização da função visual em aproximadamente 90% dos casos. A dose de prescrição recomendada para o fracionamento varia entre 45 e 54 Gy. Em crianças com menos de 5 anos de idade o papel da radioterapia ainda não é definido. Nestes casos, a quimioterapia é frequentemente utilizada para retardar o tratamento radioterápico com o objetivo de evitar morbidade neuropsicológica após irradiação durante o desenvolvimento neurológico. Complicações tardias típicas da radioterapia incluem endocrinopatias, vasculopatias, déficit cognitivo e catarata, especialmente em pacientes mais jovens. Técnicas radioterápicas modernas de alta precisão como a radioterapia estereotáxica fracionada (FSRT) são capazes de proporcionar um alto índice de controle local com uma baixa morbidade relacionada ao tratamento. Estudos prospectivos randomizados são necessários para definir o papel das modernas técnicas de radioterapia, especialmente nos pacientes mais jovens, em uma abordagem terapêutica multidisciplinar.

Palavras-Chave: Glioma do nervo óptico, Radioterapia estereotáxica fracionada.
INTRODUCTION

Gliomas of the anterior optic pathway represent approximately 2% of all intracranial tumors\(^5\). Between 60 and 80% of these rare lesions occur in children during the first decade of life. After craniopharyngeoma, they are the most common supratentorial tumors in children accounting for about 5-7% of all intracranial pediatric tumors\(^3\). Optic nerve gliomas are often associated with neurofibromatosis type 1 (NF-1) occurring in up to 10% of children with NF-1. Between 33 and 70% of all optic nerve gliomas show clinical features of NF-1\(^14\). They are the most common intracranial tumor in NF-1, more common than meningioma of the optic sheath. A low-grade form (benign optic nerve glioma) occurs most often in children, whereas the aggressive glioma is most common in adults.

Typical clinical symptoms are visual impairment of the affected eye and even blindness, ocular movement abnormalities and proptosis. Further symptoms may be metabolic and endocrine disturbance, as well as increase of intracranial pressure and eventually death, unless they are treated properly in time. The optimal management of optic nerve gliomas is still discussed controversial with radiotherapy as being one of the treatment options. There is a strong recommendation for wait-and-see strategies, especially in asymptomatic smaller tumors. Patients presenting with visual loss, endocrine disturbance or mass effect may require aggressive intervention like surgical resection. However, high local control rates and improvement or stable visual function can be achieved with radiotherapy in up to 90% of all patients\(^13\). Radiotherapy is recommended by many authors as treatment of choice when resection is not possible with acceptable morbidity, or in recurrent disease. Whereas conventional radiotherapy techniques include substantial normal brain tissues, especially the pituitary gland and brain stem, modern techniques like fractionated stereotactic radiotherapy (FSRT), intensity modulated radiotherapy (IMRT) and proton radiotherapy are capable of reducing the dose to the surrounding normal radiosensitive tissues. Thus, potential late toxicity may be reduced.

This review gives an overview of the literature regarding modern radiotherapy treatment focused on FSRT in these rare and challenging tumors.

RADIOThERAPY TREATmENT PLANNING

Radiotherapy treatment planning of optic nerve gliomas is usually based on CT and MRI scans obtained under stereotactic guidance. The patient is immobilized in an individual head mask fixation system made of scotch cast. The accuracy of this system is measured to be 1-2mm\(^17\), thus resulting in only minimal safety margins in this radiosensitive region. Alternatively, commercial localization frames providing highly reproducible daily relocation may be used. CT scans are needed for exact dose calculation, however the tumor extent is better visible in MR imaging, especially regarding potential intracranial involvement. Target volume is delineated on contrast enhanced T1-weighted MRI scans. The clinical target volume (CTV) consists of the visible tumor plus a 5mm margin for microscopic spreading along the optic pathway. Saran et al\(^19\). suggests a safety margin of 3-8mm around the GTV in well demarcated pilocytic astrocytomas. In poorly defined non-pilocytic astrocytomas a 10mm margin is recommended. The planning target volume (PTV) consists of the CTV plus a 2mm safety margin, depending on the accuracy of the head fixation system.

Figure 1. Three-dimensional treatment planning for fractionated stereotactic radiotherapy (FSRT) in optic nerve glioma. Typical treatment plan with 4 isocentric beams. The portals are defined in beams-eye-view technique.

Figure 2. Exemplary dose distribution in a 6-years old girl with right optic nerve glioma treated with FSRT. The isodose lines are 100%, 90%, 80%, 70%, 50% and 10%.

Three-dimensional dose distributions are calculated using a 3-d planning system and portals are optimised using a beams-eye-view technique (figure 1). Technical aspects have been published by our research group previously\(^20\). However, several commercial 3-d planning systems are now available. For stereotactic conformal radiotherapy three to four non-coplanar isocentric irregularly shaped beams are usually defined. Beam sharing is done with a mid-size multi-leaf collimator with a leaf width of 5mm at isocenter. The resulting conformal dose distribution shows a steep dose fall-off to the surrounding normal radiosensitive tissues. Figure 2 shows a typical treatment plan. The prescribed total doses vary between 45 and 54 Gy applied daily, 5 times a week with 1.8 to 2 Gy per fraction. FSRT is delivered with a linear accelerator with 6 or 15 MeV energy.
LOCAL CONTROL AND SURVIVAL AFTER FSRT

Since 1956 radiotherapy plays a major role in the management of optic nerve gliomas. Taveras et al., first treated 34 patients with optic nerve glioma with primary radiotherapy and achieved an overall survival of 68%23,34. Visual acuity was improved in 11 of 22 patients without observing any morbidity associated with irradiation during follow-up. Today, radiotherapy is reserved for symptomatic or progressive optic nerve glioma in children older than 5 years. External beam radiotherapy is the most common approach used with good visual outcomes and progression-free survival4,8,22. For conventional radiotherapy large margins up to 1.5cm have been typically used. Modern radiotherapy techniques like stereotactic conformal radiotherapy permit smaller margins, thus improving sparing of critical radiosensitive structures.

In the study of Saran et al., 14 children with low-grade gliomas were treated with FSRT. In nine children the tumor was located at the optic chiasm. The 3-year local progression-free survival and overall survival rate after FSRT was 87% and 100%, respectively, compared with 89% and 98% for an historic control treated with conventional radiotherapy. Of the 12 patients where MRI were available for evaluation, two patients had a complete response, six a partial response and four stable disease. Twenty-eight children with low-grade astrocytomas were treated with FSRT at the Massachusetts General Hospital. Local control was 100% at 2 years with one child developing disseminated disease outside the treated volume. In a prospective trial16 to evaluate the efficacy of FSRT in low-grade gliomas 50 of 81 enrolled patients had low-grade astrocytoma, including optic gliomas. Progression-free survival rate for the children with low-grade gliomas was 82.5% at 5 years and 65% at 8 years. Overall survival rate was 97.8% at 5 years and 82% at 8 years. Six patients developed local progression 15-92 months after radiotherapy.

Debus et al.2 reported the initial results after FSRT in 10 patients with optic nerve glioma from our institution. Only one patient recurred after radiotherapy treated for recurrence after previous radiotherapy. A complete remission was achieved in 3/10 patients with subsequent improvement of visual acuity. Overall survival was 100% after a mean follow-up of 42 months. Our published long-term results in 15 patients showed a progression-free survival rate at 3 and 5 years of 92% and 72%, respectively1. Three out of 15 patients developed local tumor progression after a median follow-up of 97 months. The 3- and 5-year overall survival rate after FSRT was 100% and 90%, respectively. One patient with grade III astrocytoma died of continuous tumor progression with spinal dissemination.

TREATMENT RELATED TOXICITY OF FSRT

Treatment related toxicity must be weighted against the natural course of optic nerve gliomas. The natural history of these typically slow-growing and low-grade tumors is highly variable and especially depends on histology as well as the presence of NF-1. The prognosis is significantly better in patients presenting with NF-1 or in tumors with anterior location7,24. However, in younger children the prognosis is poorer23. Based on a study of mortality and morbidity in a cohort of optic nerve glioma patients with and without NF-1 published by Tow24 in 2003, patients should not be treated unless they demonstrate clear disease progression.

Typical treatment related late sequelae after radiotherapy for optic nerve gliomas include endocrine disturbances, neurocognitive dysfunction, vascular changes and radiotherapy induced second malignancies. With the introduction of modern radiotherapy techniques like FSRT, which limits the high dose area to the tumor itself, these late effects may be minimized. In the study of Saran et al.5 FSRT was well tolerated and transient hair loss was the only acute toxicity. At 6 months after FSRT 5 of 12 patients with neurological deficits improved and 5 remained stable. Vision improved in 2 of 8 children with visual deficits, remained stable in 4 and worsened in 2 children. New endocrine disturbances were seen in 2 of 14 children 20 and 23 months after radiotherapy. Neurocognitive evaluation was not performed, however, late neurocognitive sequelae were suspected in 2 of 14 children. One patient developed learning difficulties two years after radiotherapy and one patient was reported to have a reduction of short-term memory 6 months after irradiation. In our own series of 15 children2 vision improved in 6 of 14 patients with pre-existing visual impairments and remained stable in 7 patients. In only 2 patients vision was further impaired after FSRT. We observed new endocrine dysfunctions in only two patients. One patient with precocious puberty developed corticotropin deficiency 3 years after irradiation and one patient without hormonal alterations before radiotherapy developed precocious puberty 16 months after FSRT. We observed no second malignancy. However, in the study of Marcus et al.16 One child with low-grade glioma developed a primitive neuroectodermal tumor 6 years after FSRT within the irradiated volume. Four children with optic glioma developed Moya Moya syndrome at 23, 40, 57 and 83 months after FSRT. One of these children had also neurofibromatosis. According to the findings of Kestle et al.12 Particular children with neurofibromatosis appear to have an increased risk of developing the Moya Moya syndrome after radiotherapy.

NEW RADIOTHERAPY DEVELOPMENTS

With the development of more sophisticated radiotherapy techniques side effects due to irradiation may be further redu-
ced. Intensity-modulated radiotherapy (IMRT) is capable of improving target coverage while reducing total dose to normal brain tissue, brainstem and optic chiasm. In a dosimetric study of IMRT versus FSRT, the IMRT plan reduced the percent volume of brain stem receiving a dose greater than 45 Gy by 31% (p =0.004)15. Regarding the optic chiasm the percent volume receiving more than 45 Gy was also reduced by 30.4% (p =0.047). As compared with FSRT, IMRT significantly increased tumor control probability (p <0.005) and lowered the normal tissue complication rate for brain and brain stem (p <0.033).

Proton radiotherapy offers a high degree of conformity to target volumes and steep dose gradients leading to substantial normal tissue sparing in high- and low-dose areas in optic pathway gliomas compared with FSRT16. Merchant et al16. Determined the effects of radiation dose on cognitive outcomes (estimated IQ scores) using proton versus photon radiotherapy in pediatric brain tumors including optic nerve gliomas. Protons compared to photons consistently lower the distribution of low (0-20 Gy) and intermediate (20-40 Gy) doses to normal brain tissue in children irradiated for optic nerve gliomas. They concluded that differences in the overall dose distributions, as indicated by modeling changes in cognitive function, showed that a reduction in the lower-dose volumes or mean dose would have long-term clinical advantages for children e.g. with optic nerve gliomas.

### Conclusions

Since optic nerve gliomas often have little or no growth potential there is a strong recommendation for wait-and-see strategies. In patients with progressive loss of vision or local tumor progression in MR imaging, radiotherapy provides the greatest possibility of vision preservation. In children less than 5 years of age the indication for radiotherapy should be discussed very carefully. Here, chemotherapy should be considered as first line treatment modality. When irradiation is indicated, modern high-precision radiotherapy techniques like fractionated stereotactic radiotherapy (FSRT) offer the possibility of high local tumor control with reduced treatment-related late toxicity, especially in younger children. Recommended doses for FSRT vary between 40 and 54 Gy in 1.8 to 2 Gy per daily fraction. Most sophisticated techniques like intensity modulated radiotherapy (IMRT) may further improve sparing of radiosensitive structures. However, the integral dose to normal tissues is increased10 and the implication of this low-dose to a larger volume with regard to late effects, especially in younger children is still unclear. The role of proton radiotherapy has to be further defined in clinical trials. In small series it has been well tolerated. However, it is yet not broadly available.

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### References


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