Recent trends in the radiotherapy of pediatric gliomas

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Abstract

The management of pediatric gliomas is controversial, and is greatly influenced by the site of origin of the tumor. For example, cerebellar low grade tumors are often cured by surgery alone. This is in contrast to the hypothalamic and optic system tumors which are usually not amenable to complete resection. For the low grade astrocytomas, the usual indications for adjuvant treatment include: recurrent tumors after initial complete resection or symptomatic tumors that have been incompletely excised. In addition, treatment is generally indicated in tumors with growth on follow-up imaging, even in the absence of symptoms. In selecting the optimal treatment, the relative efficacies of surgery, chemotherapy and irradiation must be balanced against the potential complications of therapy. The potential risks of delayed intervention include irreversible neurologic impairment and potential lower probability of tumor control. This chapter reviews recent trends in the radiotherapeutic management of pediatric low-grade and malignant astrocytomas, particularly the new more conformal techniques that hold the promise of reduced toxicity in children requiring irradiation.

Introduction

The management of pediatric gliomas is controversial, and is greatly influenced by the site of origin of the tumor. For example, hemispheric lesions are often resectable. Recent pediatric reports [1] indicate that total removal is possible in up to 90% of cerebral hemispheric gliomas. Low recurrence rates are reported both for juvenile pilocytic astrocytomas (JPA) and for ordinary astrocytomas following total removal [1, 2]. This is in contrast to the hypothalamic and optic system tumors which are usually not amenable to complete resection. For the low-grade astrocytomas, the usual indications for adjuvant treatment include: recurrent tumors after an initial complete resection or symptomatic tumors that have been incompletely excised. In addition, in tumors with demonstrated growth on follow-up imaging, even in the absence of symptoms, treatment is generally indicated. In selecting the optimal treatment, the relative efficacies of surgery, chemotherapy and irradiation must be balanced against the potential complications of therapy. The risks of delayed intervention include irreversible neurologic impairment and a potentially lower probability of tumor control. This is particularly critical in the close follow-up frequently used in young patients with optic system tumors. This report will review recent trends in the radiotherapeutic management of pediatric low-grade and malignant astrocytomas, particularly the new more conformal techniques that may hold the promise of reduced toxicity in children requiring irradiation.

Conventional radiotherapy

Conventional radiotherapy is integral to the treatment of malignant gliomas. The irradiated volume
includes a significant amount of normal tissue, but the radiobiologic advantage of fractionation is incorporated to reduce the potential early and late complications. Most malignant gliomas are infiltrative. Therefore, the radiation field must cover not only the tumor bed (tumor volume) but also include tissue felt to be at risk for microscopic disease and tissue needed to allow for uncertainty in tumor definition and inconsistency in daily treatment set-up (target volume). The tolerance of the normal brain parenchyma and its vascular and supporting structures becomes the limiting parameter of external beam therapy, and the risk of acute and long-term sequelae are major dose-limiting factors. Permanent radiation injury can include cranial nerve damage and pituitary-hypothalamic dysfunction, as well as memory and intellectual deficits [3, 4]. White matter tends to be more sensitive than gray matter, and young children (less than two years of age) in whom myelinization is incomplete, are known to be at greater risk than adults [4-7]. With conventional fractionation schedules (180-200 cGy per day), total doses of up to 54 Gy are well tolerated for limited intracranial fields. Late effects appear in a predictable manner in terms of dose, volume and fractionation. Sheline et al. [8] have shown that frank radiation necrosis is a function of total dose and fraction size with threshold doses of approximately 4500 cGy in 10, 6000 cGy in 35, and 7000 cGy in 60 fractions, respectively. Thus, small volumes, low daily doses, and multiple fractions decrease the overall incidence of late effects associated with conventional external beam therapy.

Fractionated radiation therapy administers a high cumulative dose to the target volume in multiple treatments extending over several weeks. Fractionation exploits the differences in response to radiation between normal and tumor tissue, taking advantage of the well established radiobiologic fact that normal tissues can tolerate many small doses of irradiation much better than a single, large fraction [9]. Late reacting tissues, such as the relatively static parenchyma of the central nervous system, show an even greater protection by fractionation than acute responding tissues, emphasizing the sensitivity and importance of fractionated regimens for these tissues [10, 11].

**Hyperfractionation**

Hyperfractionated radiotherapy (HFRT) is defined as the delivery of multiple daily fractions in order to increase the total dose given over the same period of time compared to standard radiotherapy [12]. This treatment strategy takes advantage of the difference in sparing of early and late responding tissues by dose fractionation [13]. As radiation dose is divided into an increasing number of fractions, the total dose must be increased to maintain an equivalent biological dose. This increment in total dose necessary to compensate for dose fractionation is greater for slowly proliferating, late-responding normal tissues such as normal central nervous system (CNS) than for rapidly proliferating, early-responding tissues and tumor (Fig. 1) [14]. As the dose is fractionated, the differential sparing of normal structures allows delivery of a significantly higher biological tumor dose without increasing morbidity. Multiple daily doses (usually twice daily) are required in order to maintain the same overall treatment time. These multiple daily treatments must be separated by sufficient time to allow for full repair of radiation-induced damage between treatments. For normal CNS tissues this interval is generally

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**Fig. 1.** Biologically equivalent total doses for low a/b normal tissue and a tumor with high a/b. 60 Gy in 30 fractions is used as a reference treatment. Increasing the number of fractions given during the same overall time (6 weeks) allows an increased total dose based on normal tissue toxicity. The total dose allowed with hyperfractionated RT exceeds the dose that would be biologically equivalent to 60 Gy in 30 treatments for the tumor.