JHN Journal

Volume 4 | Issue 3 Article 4

July 2009

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The use of chemotherapy in low-grade gliomas has been very thoroughly studied in the setting of oligodendrogliomas and oligoastrocytomas. According to the Radiation Oncology staff here at Thomas Jefferson University Hospital, the current practices in our institution are as follows: Three-dimensional conformal radiation is provided in patients with low-grade gliomas 2-4 weeks post-operatively. The total dose ranges between 50 and 54 Gy and is delivered in 1.8 fractions at five fractions per week. In the presence of recurrence, a stereotactic boost with or without re-operation is provided. For the most part, these practices are similar to the aforementioned recommendations. However, factors such as the age of the patient, and optimal timing of the radiation are not considered in our institution at this given time.

Chemotherapy is restricted to patients with known pathology of oligodendroglioma. PCV is the chemotherapeutic agent of choice in both research recommendations and our clinical practice. Specifically, the use of PCV in an established oligodendroglioma case has shown to increase the time to progression and provide a statistically significant survival benefit. Furthermore, this response is augmented in patients with chromosomal analysis positive for the 1p and 19q allele mutation. For these patients, further chromosomal analysis is performed in order to predict the chemotherapy response rate. Recurrent disease is managed on a patient specific basis.

There is no level I evidence on the use of chemotherapy in the remaining categories of low-grade gliomas. A single randomized prospective trial by the South West Oncology Group studied the effect of post-operative radiation with and without lomustine (CCNU) in low-grade gliomas; although the median survival time of patients were 4.5 and 7.4 years respectively, the results did not reach statistical significance and the study closed early due to slow patient accrual. The increasing use of Temazolamide in malignant gliomas and its minimal cumulative toxicity have triggered additional research in its use in low-grade gliomas.

An extensive medical literature search was performed on the topic of adjuvant treatment in the management of low-grade gliomas. Although no specific guidelines were found, several papers were reviewed that included recommendations for clinical practice. The two sets of guidelines that were investigated were the use of adjuvant chemotherapy and radiation in low-grade gliomas. The following five references were reviewed:

1. Lang FF, Gilbert MR: Diffusely Infiltrative Low-Grade Gliomas in Adults. J Clin Neuro 2006; 24 (8): 1236-1245.
2. Frappaz D, Chinot O, et al: Summary Version of the Standards, Options and Recommendations for the Management of Adult Patients with Intracranial Glioma. British J of Cancer 2003; 89 (Supp I): 73-83.
3. Lesser G: Chemotherapy of Low-Grade Gliomas. Sem Rad Onc 2001; 11 (2): 138-144.
4. Dropohe E: Low-Grade Gliomas in Adults. Curr Treatm Options Neuro 2004; 6: 265-271.
5. Mason WP: Advances in the Management of Low-Grade Gliomas. Can J Neuro Sciences 2005; 32: 18-26.

A thorough review of these research articles has shown that although there are no specific standards (guidelines) for the adjuvant treatment of low-grade gliomas, there are multiple options and recommendations. Specifically, in the use of radiation therapy, the recommended dose is low (between 50 and 55 Gy in daily fractions between 1.8 and 2.0 Gy at five fractions per week). This optimal dose was reached from Class I evidence of least toxicity with equal survival benefit (EORTC study 2284). The timing of radiotherapy was also studied and Class I data from the second EORTC study showed that early post-operative radiotherapy prolonged the time to tumor progression at a five-year estimate from 37% (in observation control group) to 44%. However, the benefit in overall survival of the patients did not reach statistical significance. Being that radiation toxicity in this setting has not been adequately studied, mixed options were found proposing immediate post-operative radiation versus radiation at the time of progression only. A useful recommendation was to use radiation in patients greater than 40 years of age only; this protects the younger patient from radiation toxicity, being that the natural progression of the disease has a more favorable outcome in this age bracket. The fundamental question of whether radiation should be given in patients with low-grade-gliomas was not addressed in most of these studies. Most studies provided with Class II evidence (at best) with retrospective studies showing a five-year survival benefit from 10% (with surgery alone) to 32% (with surgery and radiation). However, most of these series have many flaws and no options or recommendations could be extracted from them. Most of these studies investigated the incidence and treatment of these tumors in the adult population. The guidelines are different in the pediatric population were the incidence of low-grade gliomas is much higher, and radiation options extremely limited secondary to the harmful effects of radiation in the developing brain.

Similarly to radiation, all these recommendations were made for the adult population, which is the main target population in our institution. Chemotherapeutic agents, regimens, and overall therapy are different in the pediatric population.

This document describes a clinical guideline for the treatment of patients with low-grade gliomas with radiation and chemotherapy following surgical resection. The patient population targeted is adults ranging from 18 to 70 years of age. All patients will be post-operative from lesion resection the final pathology of which should be consistent with low-grade glioma.

Overall, radiation therapy should not be delivered routinely following initial resection. Based on the review paper by WP Mason,

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radiation therapy benefits counteract the deleterious effects on the brain in patients with recurrent low-grade gliomas only. Therefore, radiation therapy should be delivered in patients who present with either clinical or radiographic recurrence.

Based on level I clinical evidence provided in the Summary Guidelines published in the British Journal of Cancer, the total radiation dose should be between 50 and 54 Gy divided in 1.8 Gy fractions delivered at five fractions per week. In the setting of the initial post-operative period, an exception is made in older patients (greater than 40 years of age), with two or more of the following negative prognostic indicators: contrast enhancement, post-operative residual of large size with continuing mass effect, rapidly increasing volume in follow-up imaging, uncontrolled epilepsy, and involvement of deeper or functional structures. Radiation therapy should be delivered in this setting according to the aforementioned dosing guidelines.

Chemotherapy should be delivered in all patients with post-operative pathology consistent with either oligodendroglioma or oligoastrocytoma. In addition, all these patients should undergo chromosomal analysis for the 1p 19q allele mutation. The agent of choice is the PCV chemotherapeutic combination. In the remaining group of low-grade gliomas, post-operative chemotherapy should be administered in patients presenting with recurrence and who have had post-operative radiation either following the initial resection or the recurrence. The agent of choice is also PCV, although temazolamide should be used if recurrence is characterized by either contrast enhancement in radiographic imaging or a higher Ki-67 labeling index upon re-resection. Sophisticated analysis of the RTOG 98-02 results will further refine or change the aforementioned guidelines.

These guidelines should be reviewed overall and in an individual patient basis by an organized oncological clinical team comprised of neurosurgeons, radiation oncologists, and medical oncologists. Careful adjustments should be made on a patient-specific basis and overall, as further research and data accrue over the years. Careful implementation could be achieved starting at the Medical Records office. Patients with a post-operative diagnosis of low-grade gliomas should be given a specific code or tag so that if they have not been assigned to an integrated oncological team as an inpatient, during their post-operative office visit, they could be referred to an oncologist (radiation and medical) at the registration desk. Due to the economical restrictions of such referrals, triage nurses, guided by the neurosurgeon's recommendations, could decide based on these guidelines whether one, both, or neither referrals should be made. The oncological team should keep frequent correspondence on the patient clinical status and meet at scheduled intervals to discuss the treatment plan and adjustments thereof.

Future guidelines on adjuvant chemotherapy will be refined from the results of the RTOG study, which investigates the outcome of high-risk patients with low-grade gliomas in the setting of radiation with and without chemotherapy (PCV). This trial closed in 2002 and the results are still maturing. The suggested clinical guidelines provide a strong foundation upon which additional research and clinical testing will further refine standard of treatment.

https://jdc.jefferson.edu/jhnj/vol4/iss3/4
DOI: https://doi.org/10.29046/JHNJ.004.3.004