High Grade Glioma & Glioblastoma

Cancer Centre of Southeastern Ontario
Standard Management Guidelines

For use by Clinicians and Health Care Providers involved in the Management or Referral of patients with high-grade glioma and glioblastoma

Section	Activity	Activity Description	Details	Reference(s)
AA	Cancer Centre Referrals		• All patients with a potential or confirmed high-grade glioma & glioblastoma should be considered for referral • Malignant glioma which comprises glioblastoma [World Health Organization (WHO) grade IV], anaplastic astrocytoma (WHO grade III), mixed anaplastic oligoastrocytoma (WHO grade III) and anaplastic oligodendroglioma (WHO grade III) • Management of patients with glioblastoma (GBM) should be individualized and take a multidisciplinary approach involving neuro-oncology, neurosurgery, radiation oncology, neuroradiology, and pathology, to optimize treatment outcomes. Patients and caregivers should be kept informed of the progress of treatment at every stage.	
A	Diagnosis		• Malignant Gliomas can be identified and localized by CT scans and MRI with contrast agents. The radiologic diagnosis is not considered reliable enough to initiate radiation and chemotherapy except in extenuating circumstances. In routine cases surgery is required obtaining of tissue for diagnosis. • Whenever possible, safe, maximal resection is preferred in the management of High-grade glioma and GBM rather than a biopsy. This can improve symptoms and gives a specimen that can be better characterized.	
B	History and Physical Exam		• Standard history and physical exam including disease related symptoms, ECOG performance status.	

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C	Investigations		• Baseline investigations to be obtained prior to therapy: 1. CBC and differential, electrolytes, creatinine PT and PTT 2. MRI or brain (pre-operative and post-operative) • Imaging: o The preoperative imagine of choice is MRI with gadolinium o Post-operative MRI is recommended within 72 hours of surgery to evaluate the extent of resection	
D	Pathology of diagnostic specimen and/or resection specimen	Synoptic Report	• World Health Organization Grading of Central Nervous System Tumours • Molecular Markers: 1. Genetic loss on chromosomes 1p/19q (co-deletion or loss of heterozygosity [LOH] 1p/19q) (LOH 1p/19q should be evaluated to support a diagnosis of oligodendroglioma) 2. Mutations of the isocitrate dehydrogenase gene (IDH) 3. Epigenetic silencing of the methyl-guanine methyl transferase (MGMT) gene promoter by gene promoter methylation	See: https://www.cancer.gov/types/brain/hp/adult-brain-treatment-pdq#section/_5
E	Post-Investigation Management	Staging	• Distant metastases are extremely rare; thus, only imaging of the brain by magnetic resonance imaging (MRI) is required.	
		General Management	• Corticosteroids (e.g. dexamethasone 16 mg/day) allow for rapid reduction of tumour-associated oedema and improve clinical symptoms. Accompanying H2 or proton pump blockade may be given to prevent gastric ulceration. • Anti-epileptic therapy is indicated in patients presenting with or at risk of developing seizures. Prophylactic use of anticonvulsants outside	

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			the perioperative phase is not indicated. (Third Generation antiepileptic drugs such as lamotrigine, levetiracetam or pregabalin lacosamide, are preferred) • DVT and pulmonary embolism prophylaxis in hospital and surveillance post-operatively	
		Surgery	• Whenever possible, maximal resection is preferred provided that neurological function is not compromised • When surgical resection is not safe (e.g. due to location of the tumour or impaired clinical condition of the patient), a stereotactic biopsy should be performed	
		Chemo-radiation Therapy	• Chemo-radiation therapy is the standard of care following surgery for patients with newly diagnosed High-grade glioma and GBM • Surgery should be followed by radiotherapy and concurrent temozolomide chemotherapy, followed by six cycles of adjuvant temozolomide. (Patient age and performance status to be considered) • External beam radiation therapy: o Postoperative external-beam radiotherapy in a dose of 60 Gy in 30 fractions. The recommended clinical target volume should be identified with gadolinium-enhanced T1-weighted MRI, with a margin in the order of 2–3 cm. Target volumes should be determined based on a postsurgical planning MRI. • During RT, temozolomide 75 mg/m2 daily should be administered concurrently for the full duration of radiotherapy, typically 42 days. Temozolomide should be given approximately 1 hour before radiation	

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			therapy, and at the same time on the days that no RT is scheduled. • Adjuvant temozolomide 150 mg/m2, in a 5/28-day schedule, is recommended for cycle 1, followed by 5 cycles if well tolerated. Additional cycles may be considered in partial responders. The dose should be increased to 200 mg/m2 at cycle 2 if well tolerated. • Prior to each chemotherapy: 1. Brief history and physical examination to evaluate disease status, toxicity and performance status 2. CBC, differential +/- electrolytes, creatinine, ALT/AST, total bilirubin 3. Weekly monitoring of blood count is advised during chemoradiation therapy in patients with a low white blood cell count.	
		Special Considerations	• Elderly patients (≥65 years old): o Concurrent Radiotherapy and Temozolomide: A shorter course (4000 cGy in 15 fractions) radiotherapy and concurrent and adjuvant Temozolomide chemotherapy in newly diagnosed patients older than 65 years of age with a good performance status (KPS > 70). (Perry et al, 2017) o A shorter course of radiation (4000 cGy in 15 fractions) may be considered • Elderly and/or frail o Short-course radiation (25 Gy in 5 daily fractions over 1 wk) • Poor performance status:	[7]

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			○ A shorter course of radiation (4000 cGy in 15 fractions) may be considered for patients with poor performance status • Anaplastic glioma: Adjuvant chemotherapy alone is equivalent to the standard initial radiotherapy. NOTE: IDH-1 wild type anaplastic gliomas are considered as "molecular gliobastomas" and are treated as GBM. • Anaplastic oligodendroglioma: should receive radiotherapy and adjuvant chemotherapy • Other considerations ○ Driving or loss of driver's license ○ Work ○ Difficulty accessing care ○ Cognitive impairment ○ Social isolation ○ Palliative care	
F	Follow-up with no Evidence of Disease		• Patients should be followed clinically every 4 – 6 months for the first year and then every 6 months for three years. If clinically indicated, may be followed-up longer and more frequently at CCSEO. Then, discharged to their family physician for ongoing annual surveillance. • Brief history and physical examination & performance status to evaluate disease status and toxicity. Follow up by MRI Perfusion Sequence of Brain: 12 weeks after the radiation treatment and then every 6 months, unless more frequent	

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			monitoring is clinically indicated (see controversies below).	
G	Controversies		1) Evidence of tumour progression on MRI 12 weeks after the end of radiotherapy may be due to pseudoprogression as opposed to true progression. This should be re-evaluated 12 weeks later with a second MRI. Apparent increase in tumour size after the end of radiotherapy should not lead to discontinuation of chemotherapy. Use of MR perfusion will help differentiate radiation necrosis from tumour progression. 2) Treatment of Recurrent Disease a) Resection: repeat resection when the situation appears favourable based on an assessment of individual patient factors such as medical history, functional status, and location of the tumour. b) Re-irradiation: the role of repeat radiation after disease progression or the development of radiation-induced cancers is also ill defined. Interpretation if difficult because the literature is limited to small retrospective case series. The decision must be made carefully because of the risk of neurocognitive deficits and radiation necrosis c) Localized chemotherapy (Carmustine wafer): Carmustine wafers have been investigated for the treatment of recurrent malignant gliomas, but the impact on survival is less clear than at the time of initial diagnosis and resection d) Chemotherapy: some benefit of chemotherapy has been shown for patients with an adequate performance status who have not	

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			received prior adjuvant cytotoxic therapy. Anaplastic astrocytomas are more likely than glioblastoma to respond to TMZ chemotherapy. For patients progressing after prior chemotherapy, there is no standard chemotherapy regimen and patients are best treated within investigational clinical protocols. Single-agent nitrosourea therapy may achieve tumour control in some patients. e) Bevacizumab: improved objective response rates observed in two trials. On the basis of these data and FDA approval, bevacizumab monotherapy has become a standard therapy for recurrent glioblastoma for patients with insurance coverage 3) OPTUNE (Electric field generator, newly diagnosed GBM improved survival in patients with newly diagnosed GBM) 4) Other imaging modalities, such as positron emission tomography (PET) with [18F]-fluoro-deoxy-D-glucose, may be considered in selected cases 5) Although radiation with PCV is based on level 1 evidence, concurrent chemotherapy and radiation with temozolomide is also considered a standard in treating grade II and grade III gliomas in Ontario	
H	Clinical Trials		Link to Cancer Centre of Southeastern Ontario Clinical Trials	

References

1. Cancer Care Ontario (CCO), British Columbia Cancer Agency (BCCA), Cancer Care Nova Scotia (CCNS), the National Comprehensive Cancer Network (NCCN), the National Cancer Institute (NCI), the National Institute for Health and Clinical Excellence (NICE), the Australian Cancer Network
2. Alberta Health Services Clinical Practice Guideline CNS 001 Version 3 Glioblastoma Sept 2012
3. High-grade malignant glioma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. R. Stupp1, J.-C.
4. The use of Prophylactic Anticonvulsants in Patients with Brain Tumors: A Clinical Practice Guideline. Cancer Care Ontario evidence Based Series 9
5. Roa et al, J Clin Oncol. 2004;22(9):1583–8.
6. https://www.optune.com/hcp/newly-diagnosed-glioblastoma/efficacy
7. Perry J et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma N Engl J Med. 2017 Mar 16;376(11):1027-1037. [back]
8. International Atomic Energy Agency Randomized Phase III Study of Radiation Therapy in Elderly and/or Frail Patients with Newly Diagnosed Glioblastoma Multiforme, Wilson Roa, http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2015.62.6606

Revisions

1. Initial Guideline templated October 20, 2016 – Alison Young
2. Revisions October 21, 2016 – Dr. Pokrupa via Alison Young
3. Revisions October 25, 2016 – Dr. Thain via Alison Young
4. Revisions June 2017 – Dr. Thain & Dr. Eisenhauer Edits with addition of links