Provincial Central Nervous System Cancer Treatment Guidelines

(Approved at Provincial CNS meeting on September 24, 2011)

Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace Physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. SCA disclaims all liability for the use of guidelines except as expressly permitted by SCA. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from SCA.

Benefits and risk of the proposed should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

Screening:

None

Work up

- History, physical and basic labs (including serum sodium and Glucose)
- Adequate pathologic specimen, from maximal safe resection when possible
- MRI (as imaging of choice)[1].
- If metastatic disease to the brain is suspected: whole body imaging to search for 'primary'

[1] CT scan to be used only if MRI is not available

ASTROCYTOMAS

HIGH GRADE ASTROCYTOMAS (WHO Grade III & IV)- Initial Rx

Assess for Maximal safe Resection:

Maximal safe Resection Possible: Proceed with surgery. Follow up MRI within 72 hours post-surgery.

Maximal safe resection Not Possible: Perform open biopsy or stereotactic biopsy

Adjuvant Treatment:

GLIOBLASTOMA (WHO Grade IV):

- Good Performance Status (KPS >70): Fractionated External Beam RT (59.4Gy/33Fx-60 Gy/30Fx) within 4 weeks after surgery with concurrent Temozolomide followed by adjuvant Temozolomide[2]. Duration of adjuvant Temozolomide; 6-12 cycles per physician discretion[3]
- Poor Performance status (KPS <70): Standard or Hypofractionated (40Gy/15Fx, 30Gy/10Fx or whole brain 20Gy/5Fx) external beam RT.
- Best Supportive care

ANAPLASTIC ASTROCYTOMA (WHO Grade III)

Good Performance status (KPS >70):

Fractionated external Beam RT (59.4 Gy/33Fx), 60Gy/30Fxis also an option. Combined

[2] Stupp R, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for Glioblastoma. N Engl J Med 2005; 352:987.

[3] Most Ongoing clinical trials are using 12 months of Temozolomide in the standard arm.

Temozolomide -RT OR Temozolomide[4]

Poor performance Status <70: Standard or hypofractionated external beam RT (40Gy/15Fx, or whole brain 20Gy/5f) OR Chemotherapy OR Best supportive care.

HIGH GRADE ASTROCYTOMAS (WHO Grades III & IV) – Recurrence[5]

Localized recurrence (resectable):

- Perform resection in selected pts followed by:
- Chemotherapy (antiangiogenic therapy-Bevacizumab[6-7], Temozolomide rechallange or metronomic chemotherapy[8] or nitrosourea based regimen PCV[9]) OR
- Consider re irradiation in selected patients OR
- Best supportive care if poor performance status.(KPS<70)

Localized recurrence (unresectable):

- Chemotherapy (metronomic chemotherapy, Temozolomide rechallange or antiangiogenic therapy-Bevacizumab or nitrosourea based regimen PCV). The optimal chemotherapeutic strategy for patients who progress following concurrent chemoradiation has not been determined.
- Consider re irradiation by stereotactic radiosurgery, IMRT or 3D conformal RT in carefully selected cases
- Best supportive care if poor performance status.

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[4] The role of adjuvant chemotherapy is less clear then in GBM. The EORTC-NCIC trial was limited to patients with GBM.

[5] Ensure true progression versus pseudoprogression (i.e. Treatment effect on MRI). If clinically stable, continue treatment unless clinically deteriorated or further imaging shows progressive disease. We suggest that first MRI post RT preferably done after 3months from completion of RT to minimize this issue.

[6] Friedman HS, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol 2009; 27:4733.

[7] Cloughesy, T, et al. Updated safety and survival of patients with relapsed glioblastoma treated with Bevacizumab in the BRAIN study (ASCO 2010- abstract #2008).

[8] James R. Perry et al. 'RESCUE study'. J Clin Oncol, 2010:28:2051-2057

[9] Schmidt F, et al. PCV chemotherapy for recurrent glioblastoma. Neurology 2006; 66:587.

Diffuse or Multiple sites recurrence:

- Chemotherapy (metronomic chemotherapy, Temozolomide rechallange or antiangiogenic therapy-Bevacizumab or nitrosourea based regimen PCV)
- Surgery for selected pts (e.g. Symptomatic large lesions)
- Best supportive care if poor performance status.

ADULT LOW GRADE ASTROCYTOMAS (WHO Grade II) -Initial Rx

Assess for Maximal safe Resection: [10]

Maximal Safe Resection Possible: Proceed with surgery.

Maximal Safe Resection not possible: Perform subtotal resection, or Open Biopsy or Stereotactic biopsy (preferably 1 cm2 specimen)

Additional therapy:

After maximal safe resection:

May observe if age <40 or Low risk.

- For patients >40 and High risk patients : Fractionated external beam RT[11] (50.4Gy/28Fx - 54 Gy/30Fx)
- chemotherapy[12-13] in highly selected patients consider nitrousea or alkylators

Maximal safe resection was not possible:

[10] Issue of immediate vs. delayed surgery is controversial. Most Neurosurgeons favor maximal safe resection at diagnosis because of trend towards improved survival. Surgery provides enough tissue to assess for areas of higher grade tumor and is also therapeutic. In highly selected patients, serial observations are appropriate without surgery or biopsy.

[11] Van den Bent MJ, et al. Long-term efficacy of early versus delayed radiotherapy for low-grade astrocytoma and oligodendroglioma in adults: the EORTC 22845 randomized trial. Lancet 2005; 366:985.

[12] Whereas chemotherapy is effective in low grade Oligodendrogliomas, its role in low grade Astrocytoma is less clear. RTOG 9802 showed improvement in PFS when PCV was added to RT. *'We suggest not routinely administering routine adjuvant chemotherapy following surgery. Temozolomide or PCV regimen should be reserved for symptomatic patients with substantial residual tumor or progressive symptoms following RT' (Uptodate v 19.2 May 2011)*

[13] Shaw, EG, et al. Final report of RTOG protocol 9802: Radiation therapy (RT) versus RT + Procarbazine, CCNU, and Vincristine (PCV) chemotherapy for adult low-grade glioma (LGG) (abstract). J Clin Oncol 2008; 26:90s

- If Uncontrolled Progressive symptoms: Fractionated EBRT OR Chemotherapy
- If Stable or Controlled symptoms: Consider fractionated EBRT OR Chemotherapy OR Observation

(Note: Surgery is recommended for low grade Astrocytoma, but serial observations are appropriate for highly selected patients without surgery or biopsy. For patients with brain stem or intramedullary spinal lesions lesions with no biopsy - RT is an option)

ADULT LOW GRADE ASTROCYTOMAS (WHO Grade II) - Recurrence[14]

Treatment of recurrent disease is based on whether the patient has or has not received radiation treatment in the past.

If prior RT:

-Resect if possible, followed by Chemotherapy[15-16,17]or observation

On further progression;

-consider biopsy/resection and/or

-changing chemotherapy regimen

-Consider re-irradiation in select cases, esp. if progression free survival is >2 years after prior RT or if new lesion outside of previously irradiated field, or if recurrence is small and geometrically favorable

- Best supportive care.

If No prior RT:

[14] To differentiate between true recurrence versus treatment effect can be difficult on an MRI. Tissue Biopsy may be required.

[15] Limited data available on chemotherapy in recurrent setting. Phase II trials with Temozolomide have shown respo nse rates of 47-61%.

[16] Quinn JA et al. Phase II trial of Temozolomide in patients with progressive low grade glioma. J Clin Oncol 2003:21: 646

[17] Pace A et al. Temozolomide chemotherapy for progressive low grade glioma. Ann Oncol 2003; 14: 1722

-Resectable: Surgery followed by observation or fractionated external beam RT OR Chemotherapy

-Unresectable: Fractionated external beam RT OR Chemotherapy OR Observation

OLIGODENDROGLIOMAS

ANAPLASTIC OLIGODENDROGLIOMA (WHO Grade III) – Initial Rx

Assess for maximal safe resection:[18]

- Maximal safe Resection possible: Proceed with surgery. After maximal safe resection or subtotal resection, obtain an MRI exam within 72 hours
- Maximal safe resection NOT possible: Perform open biopsy or stereotactic biopsy.

Additional Therapy:[19]

- Consider 1p19q analysis[20]
- Good Performance status (KPS >70): Fractionated external beam RT[21] (59.4Gy/33Fx) OR Chemo -RT [22] OR Chemotherapy
- Poor Performance Status (KPS <70) : Standard or Hypofractionated RT (40Gy/15Fx, or whole brain 20Gy/5Fx) OR Chemotherapy OR Best supportive care.

[18] Surgery is the initial treatment for most patients and generally recommended. There are no randomized trials that have established the benefit of maximal surgical resection, and such studies are unlikely to be conducted.
[19] Additional treatment (RT or Chemotherapy) is an important concept in Oligodendroglioma

[20] Many of these tumors contain a characteristic co-deletion of the short arm of chromosome 1 (1p) and the long arm of chromosome 19 (19q), which if present, has been correlated with both a striking sensitivity to chemotherapy and a more prolonged natural history, independent of specific treatment.
[21] Adjuvant RT in high grade 'Gliomas' has shown survival benefit. Although effectiveness of RT has not been assessed in randomized trial specifically looking at Oligodendroglioma, RT has been considered an integral component of the treatment for patients with anaplastic lesions.
[22] Temozolomide preferred because of ease and favourable toxicity profile (Not head to head compared with PCV)

ANAPLASTIC OLIGODENDROGLIOMA (WHO Grade III) – Recurrence

Localized recurrence (resectable):

- Perform resection followed by
- Chemotherapy: Both Temozolomide[23-24] and PCV [25] and are active treatments. (There is emerging data for antiangiogenic therapy-Bevacizumab).[26]
- Radiation Therapy: Consider re irradiation
- Best supportive care if poor performance status.

Localized recurrence (unresectable):

- Chemotherapy (Temozolomide or nitrosourea based regimen PCV or antiangiogenic therapy-Bevacizumab) OR
- Consider re irradiation by sterotactic radiosurgery, IMRT or 3D conformal RT in carefully selected cases OR
- Best supportive care if poor performance status.

Diffuse or Multiple sites recurrence:

- Chemotherapy (Temozolomide or nitrosourea based regimen PCV or antiangiogenic therapy-Bevacizumab) OR
- Surgery for symptomatic large lesion OR
- Best supportive care if poor performance status.

[23] van den Bent MJ et al. Temozolomide chemotherapy in recurrent oligodendroglioma. Neurology 2001; 57:340.
[24] Chinot OL, Honore S, Dufour H, et al. Safety and efficacy of Temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. J Clin Oncol 2001; 19:2449.
[25] Triebels VH et al. Salvage PCV chemotherapy for Temozolomide – resistant oligodendrogliomas. Neurology; 2004:63:904

[26] Chamberlain MC. Bevacizumab for recurrent alkylator-refractory anaplastic oligodendroglioma. Cancer 2009;

Low Grade Oligodendroglioma (WHO Grade II)

Assess for maximal safe resection: [27]

- Consider 1p19q analysis
- Maximal safe resection possible: Proceed with resection
- Maximal safe resection NOT possible: Perform subtotal resection or open biopsy or stereotactic biopsy

Additional Therapy :[28]

After maximal safe resection:

- May observe if age <40 or Low risk.
- For patients >40 and High risk patients : Fractionated external beam RT (50.4Gy/28Fx 54 Gy/30Fx) OR chemotherapy [29]

Maximal safe resection was not possible:

- If Uncontrolled progressive symptoms: Fractionated EBRT OR Temozolomide Rx
- If Stable or controlled symptoms: Consider fractionated EBRT OR Temozolomide OR Observation

[27] Surgery generally indicated for symptomatic patients. Uncontrolled studies have shown that outcome is better with surgery. Serial observations are appropriate in selected patients.

[28] After surgical resection, further treatment (RT or Chemotherapy) may be deferred until there is evidence of recurrence or progression of symptoms. Consider additional Rx (RT or Chemotherapy) if focal deficits persist, there is a residual lesion with mass effect, and if foci containing anaplastic tumor are identified.

[29] Particularly those with co deletion of 1p/19q(these patients are reported to be sensitive to alkylator therapy).

FOLLOW UP OF GLIOMA PATIENTS

Anaplastic gliomas or glioblastoma:

MRI at 1 and 3 months after RT,

then every 2-4 months for 2-3 years

then less frequently.

Low grade glioma including oligodendroglioma:

MRI every 6 months for the first 2-3 years then at least annually thereafter

CHEMOTHERAPY REGIMENS

Adjuvant Temozolomide[30] : 75 mg/m2 daily during RT then six cycles of 150 to 200 mg/m2 daily for 5 days, every 28 days

Temozolomide[31]**:** 150 to 200 mg/m2 daily for five days Every 4 weeks

Irinotecan-Bevacizumab [32]**:** Irinotecan 125 mg/m2 (non EIAED) or 340 mg/m2 (EIAED) iv over 90 min

Bevacizumab 10 mg/kg iv over 30-90 min Q2w

PCV[33] Procarbazine 60 mg/m2 po daily on days 8 to 21 Every 6 to 8 weeks , Lomustine 110 mg/m2 po on day 1, Vincristine 1.4 mg/m2 (maximum 2 mg) days 8 and 29. Cycle every 6 weeks.

Carmustine (BCNU)[34] 150 to 200 mg/m2 day 1 Every 6 weeks

Carmustine (BCNU)[35] 80 mg/m2 iv d1-3 Q8w x 6 cycles

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[30] Stupp, R et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med 2005; 3 52:987

[31] Chinot, JL et al. Safety and efficacy of Temozolomide in patients with recurrent anaplastic oligodendrogliomas after standard radiotherapy and chemotherapy. J Clin Oncol 2001; 19:2449

[32] Vredenburgh JJ et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 2007; 25: 4722

[33] Cancer 2004; 101:2079

[34] Shapiro WR et al. Randomized trial of three chemotherapy regimens and two radiotherapy regimens in postoperative treatment of malignant glioma. Brain Tumor Cooperative Group Trial 8001. J Neurosurg 1989; 71:1

[35] Brandes, AA et al. How effective is BCNU in recurrent glioblastoma in the modern era? A phase II trial. Neurology 2004; 63:1281

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