Thames Valley Cancer Network
Central Nervous System Tumour Site Specific Group

Adult CNS Non-surgical Oncology Guidelines

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Please see www.BNOS.org.uk for Rare Brain and CNS Tumours Guidelines: British Neuro-Oncology Society in collaboration with the National Cancer Action Team.

- Guidelines on the diagnosis and management of Adult PNETs
- Guidelines on the diagnosis and management of Optic Pathway Glioma (OPG)
- Guidelines on the diagnosis and management of primary CNS and intra-ocular Lymphoma (PCNSL)
- Guidelines on the Diagnosis and Management of Adult Pineal Area Tumours

TVCN Adult CNS non- surgical oncology guidelines cover:

High Grade Glioma
- Glioblastoma
- Anaplastic astrocytoma

Low Grade Glioma

Ologodendroglioma
- Anaplastic oligodendroglioma
- Oligodendroglioma

Ependymoma
- Low grade ependymoma
- Anaplastic ependymoma

Meningioma

Pituitary Adenoma

CNS Metastases are covered in a separate guideline.

High Grade Gliomas:

- **Anaplastic Astrocytoma - WHO Grade 3**
- **Glioblastoma Multiforme (+ variants) - WHO Grade 4**

Prognostic factors

- **histological grade**
- **age**
- **performance status**
- extent of resection *(RTOG / ECOG studies Chang et al 1983, Bleehan et al 1991)*
- length of history of fits (none = worse prognosis. *Bleehan et al 1991*).

Prognosis

	Median survival	**2 yr surv**
without treatment	3-4 months	0%
Radical RT alone GBM	12 months	10%
Radical RT + temozolamide (GBM)	14 months	26%
age < 50, grade 3, complete resection (60Gy RT)	23-36 months	47%
>65, poor performance status (30Gy RT)	6 months	

Post operative Management

- For grade 3 and 4 glioma: Gliadel wafer implant at time of initial surgical resection, improves median survival by 2.5 months. NICE guidance June 2007 See surgical guidelines on Gliadel wafers.

- **Post op CT or MRI scan** - *ideally within 48 hours of operation. .*
- **Patients >70 PS 0,1 check Meth MGMT on pathology**

Glioblastoma Multiforme

Age	WHO Performance status = 0,1	PS = 2	PS = 3,4
< 70	60 Gy / 30# + temozolamide	60 Gy/30#	30 Gy/6# over 2 weeks
>70	Meth MGMT+ Temozolamide Meth MGMT- 34/10# planned vol	30 Gy/6# over 2 weeks	No RT

WHO Performance status

0 Normal activity without restriction
1 Restricted in physically strenuous activity but ambulatory and able to carry out light work
2 Ambulatory and self-caring but unable to work. Up >50% of waking hours
3 Limited self care. Confined to bed or chair for >50% of waking hours
4 Completely disabled. No self-care. Confined to bed/chair.

Glioblastoma:

1. Concomitant temozolamide + RT + 6 cycles temozolamide subsequently. Stupp et al: NEJM 2005 (vol352:987).. . Stupp et al Lancet Oncol 2009
2. Age>70, PS 0,1 Meth MGMT positive. Give single agent temozolamide.
3. Age >70 PS 0,1 Meth MGMT negative. RT 34 Gy/10# planned volume has equivalent survival to radical RT (Nordic trial and NOA08)
4. Age <70: If PS 3-4, Age >70 PS 2. Palliative RT 30 Gy in 6# over 2 weeks.

See TVCN CNS chemotherapy protocol

Anaplastic Astrocytoma:

Consider entry into the BR14 study for patients without 1p19q co-deletion (register patient on study and central lab analysis of 1p19q undertaken).
Trial is RT (59.4 Gy +/- concomitant temozolamide +/- adjuvant temozolamide.

Otherwise if 1p19q co-deletion is present: options are: RT 60 Gy in 30 fractions or 59.4 Gy in 33 fractions. Or initial PCV chemo (NOA 4 trial 2009 showed no difference in overall survival between the two treatment options).

RT Guidelines

For treatment dose and planning details see TVCN CNS TSSG Radiotherapy Protocols:

1. Cranial RT

2. Spinal RT

Steroid Use

Management of acute raised ICP

1. Dexamethasone 8mg bd (usually orally) and reducing dose every few days or in an acute situation 16-24mg IV.
2. If no improvement consider mannitol 1mg / kg over 30 minutes, 2-3 times daily with daily U&E's. Stop/Review after 24 hours.
3. If there is suspicion of hydrocephalus, request urgent CT and if demonstrated, refer to neurosurgery.

Corticosteroid use (usually dexamethasone) - Indications:

1. Symptoms of raised ICP
2. Severe papilloedema with risk of visual impairment
3. Steroid responsive neurological deficit

Patients are often on a reducing course of dexamethasone post op. Continue reduction, but increase dose if neurological /RICP symptoms worsen. Try to avoid large rises in steroid dose.

Monitor during RT. Try to reduce gradually after first week if tolerating RT well. Aim to maintain on lowest dose possible. On completion of RT, aim to reduce gradually (usually 1-2 mg reduction every 7 days). It may be possible to avoid steroids during RT in selected cases.

In patients who are on Dexamethasone for a prolonged period of time - constantly review dose. Attempt to reduce and titrate against symptoms. Avoid giving second dose in late afternoon/evening in order not to disturb sleep pattern.
Cover with H2 blockers or proton pump inhibitors. Routine check of urine/blood glucose levels (Dexamethasone) if prolonged use. Check oral cavity for candidiasis. Consider also bisphosphonates and calcium supplementation.

Follow Up

- 3-4 weeks (ORH,RBBH) or 6 weeks (NGH) after completing RT to check dexamethasone / acute toxicity.
- Note adjuvant temozolamide will commence 4 weeks after RT and be given every 4/52 for 6 months.
- Post RT MRI scan with contrast at least 2 months after completing RT. (Scan in JR West wing for ORH patients, GWH, BHT, RBFT, NGH patients scan locally). And 1 month after completing adjuvant temozolamide if appropriate.
- FU 2 -3 monthly thereafter in year 1, increase to 3-6 monthly year 2 then 6-12 monthly.
- Refer appropriate cases for palliative care support, Disability living allowance (DS1500) etc.
- Further scans ONLY if clinical deterioration AND further treatment is appropriate.
- For long term survivors: monitor pituitary function annually if pituitary in/near field. (may drop up to 10-15 years post RT).

Relapse / progression

- Re-image with MRI + contrast.

- If >12 months since RT consider radionecrosis in differential diagnosis of relapse. – Discuss PET / MRI SPECT at ORH MDT. NB pseudoprogression following temozolamide + RT occurs in 25% or more of patients, and can occur as soon as 2 months after RT /chemo so continue chemotherapy if clinically stable even if scan suggests progression.

- Consider re-operation if mass effect and raised ICP symptoms (headache, vomiting) or cystic component. Consider use of Gliadel wafers following second resection. Low priority by South Central SHA apply to PCT for individual patients on case by case application.

- Consider chemotherapy (PS 0-2), age < 65.
    - **SEE TVCN CNS TSSG CHEMOTHERAPY PROTOCOLS for details.**

    - PCV 1st line X 2-3 cycles then repeat imaging, continue if stable disease or response and tolerated well. Usually 6 cycles maximum due to myelosuppression.

    - CCNU/BCNU single agent is an option.

    - If disease progression during or following 1st line treatment consider second line temozolamide **(NICE approved indication)** repeat imaging every 3 cycles and continue if stable disease or response and tolerated well until disease progression (may be more than 6 cycles).

    - Carboplatin AUC5 is 3rd line option

    - Bevacizumab option for very fit patients as 3rd line. Apply to Cancer Drugs Fund individual funding request.

- If **long** disease free interval (> 5 years) since previous radical RT cautious re-treatment of a carefully planned volume to 30-40 Gy in 1.6 Gy # could be considered.

Low Grade Gliomas

Prognosis

- **Overall median survival 6 years *(Leighton 1997), EORTC 22845 study***

  Grade 1 - Complete resection alone - 100% 10 year survival.
  Subtotal resection and RT - 74% 10 year progression free survival
  Grade 2 - Glioma median survival 7.5 years, 62% 5year survival *(Leighton 1997)*
  Patients were treated with either immediate or delayed RT.

RT indications

Two randomised trials looking at post op RT in low grade gliomas.

1. MRC BR04/EORTC 22845 trial
   - Immediate vs delayed (at sign of disease progression) post op RT in low grade glioma / oligdendroglioma
   - 311 patients
   - No difference in overall survival (5 year survival 60%, median survival 6 years).
   - 14 month improvement in progression free survival for early RT group.
   - Majority or relapses were high grade which were more difficult to treat in the RT group.
   - No difference in the frequency of high grade relapses in the 2 treatment groups i.e. no evidence that RT **causes** high grade relapse.

2. EORTC trial of immediate RT 45Gy vs 60 Gy
   a. No difference in 5 year survival (60%)
   b. Reduced toxicity with 45Gy.

Therefore use following guidelines for timing of RT:

- Following complete excision of grade 1, observe and reserve RT for relapse.
- Patients presenting with fits only, which are medically controlled, and not suitable for resection, observe and reserve RT for radiological +- symptomatic progression.
- Following incomplete excision or biopsy give RT on symptomatic progression.
- Recurrent disease or progressive disease not previously irradiated give RT.
- Patients with neurological impairment, tumour in critical site or tumour progression on scan give RT
- RT should only be administered following a positive diagnostic biopsy. If 2 x biopsy are negative but radiologically diagnostic of low grade glioma with definite disease progression, RT can be considered.

RT Guidelines

For treatment dose and planning details see TVCN CNS TSSG Radiotherapy Protocols:
1. Cranial RT
2. Spine RT

- Dose for cerebral LGG see RT guidelines

- **Dexamethasone**

Only if significant oedema on post op scans. Guidelines as for high grade gliomas.

Follow Up

- 3-4 weeks (ORH, RBFT) or 6 weeks (NGH) after completing RT to check dexamethasone / acute toxicity.
- Post RT MRI scan at 3-6 months after completing RT to act as baseline post RT.
- Clinical FU 6 monthly to 3 years then annually
- ORH - Scans annually until 5 years then only if symptomatic change RBFT/NGH scan at 1 year then only if symptom change
- Monitor pituitary function annually if pituitary in/near field. (levels may drop up to 10-15 years post RT).
- IF patients are NOT GIVEN RT – scan at 6 months post op, annually x 2 years then 2 yearly x 2 then only if symptomatic change. No FU scans for completely resected Dyembryoplastic Neuroepithelial Tumour (DNET).

Adjuvant Chemotherapy

Generally NO role for first line chemotherapy in <u>low grade</u> gliomas or oligodendrogliomas *(Chang 1995).* Can be considered in rare situation if patient not suitable for RT but could tolerate chemotherapy. PCV may have a specific role in low grade oligodendroglioma in this situation.

Relapse / progression

- Re-image with MRI + contrast.

- If >12 months since RT consider radionecrosis in differential diagnosis of relapse. – Discuss PET / MRI SPECT at RI MDT.

- Consider re-operation if mass effect and raised ICP symptoms (headache, vomiting)

- Consider Biopsy if resection not possible to define new grade of tumour.

- Consider stereotactic RT if young, good PS , < 5 cm diameter lesion.

- If **long** disease free interval (> 5 years) since previous radical RT cautious re-treatment of a carefully planned volume to 30-40 Gy in 1.6 Gy # could be considered.
- If fit enough for chemotherapy (PS 0-2), age < 65.
    - **SEE TVCN CNS TSSG CHEMOTHERAPY PROTOCOLS.**
    - PCV 1st line X 2-3 cycles then repeat imaging, continue if stable disease or response and tolerated well. Usually 6 cycles maximum due to myelosuppression.
    - If disease progression during or following 1st line treatment consider second line Temozolamide **if high grade relapse demonstrated at biopsy (NICE approved indication)** repeat imaging every 3 cycles and continue if stable disease or response and tolerated well until disease progression (may be more than 6 cycles). Start with standard 5 day dosing, but consider 21 day schedule if disease progression occurs and patient still fit enough to continue chemotherapy.
- Refer appropriate cases for palliative care support, Disability living allowance (DS1500) etc.

Glioma - Special sites:

- **Brain stem**: 50 - 55 Gy in 30-33 fractions. Lateral opposed fields.
  Prognosis - median survival 9 months with RT. Better for low grade.
- **Spinal cord**: 50 - 55 Gy in 30-33 fractions.
- **Gliomatosis Cerebrei:** multifocal usually low grade glioma. 50 - 55 Gy in 30-33 fractions to cover all sites of disease + margin. Avoid whole brain RT if possible. Often only possible to deliver palliative dose of 30 Gy in 6-10#. OR consider primary chemotherapy.
- **Optic Glioma:** See www.BNOS.org.uk for national guidelines.

Oligodendroglioma

- Oligo dendroglioma
- Anaplastic Oligodendroglioma
- Mixed oligo-astrocytoma

Prognosis

		3 yr surv	5 year survival
Low grade:	resection alone		43%
	resection + RT		58%
High grade:	resection + RT	50%	
	resection + RT+PCV	57%	
High grade mixed tumour			
	resection + RT+PCV	80%	

Overall better for oligodendroglioma and mixed tumours than gliomas both for low grade and high grade.

RT + Follow up

- **Dose as for low and high grade glioma as appropriate**

For treatment dose and planning details see TVCN CNS TSSG Radiotherapy Protocols:
1. Cranial RT
2. Spine RT

Adjuvant /Relapse Chemotherapy

Anaplastic Oligodendroglioma or oligoastrocytoma:

- Consider entry into the BR14 study for patients without 1p19q co-deletion (register patient on study and central lab analysis of 1p19q undertaken). Trial is RT (59.4 Gy +/- concomitant temozolamide +/- adjuvant temozolamide.

- 6 cycles of adjuvant PCV chemotherapy improves overall survival for patients **with Anaplastic Oligdendroglioma with 1p19q codeletion**. Addition of chemo improves median survival from 9 years (RT alone) to >12 years (RT + 6xPCV). (EORTC trial 26981. Van den Bent 2013). IDH1 mutation and methylation MGMT also predict for better outcome. RTOG 9402 study confirms findings. (Cairncross 2013)

- High (70%ORR, 38% CR, 38% PR) response rate to PCV chemotherapy as initial treatment and on recurrence for anaplastic oligodendroglioma (Cairncross 1994).

- Consider PCV for low grade oligodendroglioma on disease progression following RT, or possibly prior to RT in selected cases with extensive disease
- Second line therapy with temozolamide as per high grade glioma above.

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Ependymoma

Ependymoma (low grade)
Anaplastic Ependmoma (High grade)

Prognosis

Low grade - 60-80% 5 year survival
High grade (anaplastic) - 10-47% 5 year survival

Staging investigations

for high grade:
MRI of craniospinal axis
CSF cytology

RT guidelines

For treatment dose and planning details see TVCN CNS TSSG Radiotherapy Protocols:
1. Cranial RT
2. Spine RT
2. Whole CNS

Metastatic Disease only – ie not high grade infratentorial aswell.

Cranio-spinal axis - 35 Gy in 21# (prescribed to anterior dura)
Boost to pre-op primary volume +3 cm margin - 20 Gy in 12 #
Boost to spinal seedlings to 50 Gy total.

All other cases:

Localised radiotherapy - 54 Gy in 30# for cerebral lesions and 50-54 Gy in 30# for spinal lesions.
Myxopapillary ependymomas arising from the conus have a very good prognosis and <u>are not</u> irradiated if completely resected.

Meningioma

Meningioma WHO grade 1
Atypical Meningioma WHO Grade 2
Malignant Meningioma WHO Grade 3

Prognosis

Grade 1 tumours	5 year relapse	15 year relapse	10 year survival
total resection	7%	32%	93%
subtotal resection	30-60%	90%	49%
subtotal resection + RT	22%	44%	81%

Grade 3 tumours	**Recurrence rates**	**median survival**
total resection	33%	
total resection + RT	12%	
subtotal resection	100%	7 months
subtotal resection + RT	55%	?

RT Guidelines

Indications:

- WHO grade 3 (following complete or partial resection).
- Incompletely resected grade 1/2 with evidence of disease progression post op OR post -op if critical site involved
- recurrence following second resection
- tumour unresectable or patient medically inoperable and fit enough for radical RT

For treatment dose and planning details see TVCN CNS TSSG Radiotherapy Protocols:
1. Cranial RT
2. Spine RT

Dose:

WHO Grade 1,2	54 Gy in 30 #
WHO Grade 3	60 Gy in 30 #,

Consider 30Gy in 6-10# if not fit enough for radical RT

For relapse following surgery and radiotherapy.
Consider Hydroxycarbamide chemotherapy, initially 500mg od increase to 1000mg od.

References Meningioma

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Pituitary Adenomas

All adenomas except prolactinomas

1. Trans-sphenoidal / (trans cranial surgery) if:

- Mass effect
- Secreting tumours

2. No further treatment if:

- tumour completely excised (may be difficult to decide for non-functioning adenomas).
- 4 hormone levels fall to average GH < 5 mU/l and IGF_1 normal.

3. Post operative RT if:

- For non-functioning adenomas:
  - Definate tumour persists on scan particularly if extra-sellar extension (60% recurrence rate falls to 5% post RT)
  - All non-functioning adenomas with extra-sellar extension pre-op.
  - For recurrent disease (+/- following second operation).
  - For inoperable disease if fit enough for RT (caution in elderly and when tumour pressing on chiasm).
- For Functioning adenomas if medical therapy with octreotide or metyrapone as appropriate is not effective
  - Hormone levels do not fall to normal post-op or recur
    - for acromegaly
      - mean GH > 5mU/l
      - IGF_1 levels elevated above age related normal range.

Prolactinomas

- Dopamine agonists (cabergoline, bromocriptine, quinagolide or pergolide) return prolactin to normal in over 90% and shrink tumour in most patients.
- Surgery is used in rare cases intolerant of or unresponsive to dopamine agonists and in situations with a worsening visual field defect (v. rare with dopamine agonist therapy).
- Radiotherapy used for macroadenomas only, once there has been shrinkage into fossa with dopamine agonist therapy (normalises PL in 50% at 5 years) or lack of response to DA agonist. (Histological proof not required if PL elevated and macroadenoma seen on scan.

RT Guidelines

Investigations:

Pre and post op MRI scan of pituitary fossa
Document visual field perimetry
Pituitary function tests:
For secreting tumours - baseline pre RT levels:
- Prolactin
- GH day curve, GTT and IGF_1
- Cortisol + urine cortisol

Radiotherapy technique:

See TVCN CNS TSSG Radiotherapy Protocols for treatment and planning details:
1. Cranial RT

Dose:
Standard dose - 45 Gy in 25 fractions

Extensive inoperable disease, **extensive** post op residual (infiltrating). Optic nerve gliomas, meningiomas. - 50 Gy in 30 fractions.

Sterotactic Radiotherapy/ radiosurgery can be considered for relapse if sufficient margin (>3mm) from optic chiasm/nerve.

Expected effect of RT on disease

- Controls disease in 94% of cases at 10 years and 88% at 20 years.
- Relapse (tumour enlargement or rise in hormone levels) occurs a median of 10 years post RT.
- reduces local recurrence from 60% with surgery alone to 5% (surgery + RT).
- reduces hormone secretion in 90% cases of acromegaly, but median 4 ½ years to normalisation of hormone levels (continue to fall for 15 years). Will still need somatostatin / bromocriptine / metyrapone until then. Trial off treatment yearly.
- controls hormone secretion in 50-75% of Cushing's. 6-9/12 to respond.
- Acromegalic features usually improve slowly, soft tissue swelling first.
- 55% of patients with impaired visual fields or acuity notice improvement following surgery and RT. RT not used if field defect caused by persistent tumour pressing on chiasm.
- See pituitary radiotherapy patient information leaflet – www.pituitary.org.uk/resources/pituitaryradiotherapy

Complications

Acute:

- hair loss and skin erythema (temporal and occipital beam entry and exit sites)
- headache (rare - use dexamethasone with caution)
- watch visual fields during RT (rare cases of deterioration).

Chronic:

- Hypopituitarism. 30% of patients by 10 years, 50% by 19 years. Need annual pituitary function tests. Common order of loss of function is GH, LH/FSH, ACTH then TSH.
- Optic nerve damage. <1% of cases show some visual deterioration. Blindness is very rare, most reported cases received >2Gy per fraction or >50Gy total dose.
- Brain necrosis. Not described with this dose, fractionation and 3 field technique.
- 2nd malignancy. 1.9% at 20 years in RMH series of 411 patients. 57 cases reported worldwide. Meningioma, glioma and sarcoma. No increased incidence in series from St. Bartholomews (Jones et al).

Post RT Follow up

In radiotherapy department:
4 weeks after completion of RT (ORH, RBBH), 6 weeks in NGH.
Then refer back to endocrinology. RBBH see at 1 year.

Endocrinology: Hormone levels and stimulation tests to assess response.

- Annual Pituitary function screen:

SH,T3,T4
Oestradiol / testosterone
LH, FSH
Prolactin
am cortisol and ITT test if low.

- Annual MRI until 5 years, then 2 yearly till 11 years - only for patients **NOT irradiated.**
- Visual field perimetry

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Craniopharyngioma

Management (adults)

- **Initial radical surgery occasionally indicated ~ 29% risk of recurrence**

For patients treated with radical surgery, reserve RT for recurrence

- **If initial limited surgery ~ 73% recurrence rate**
  - drainage of hydrocephalus
  - aspiration of cyst
  - minor debulking

- **Follow this with radiotherapy ~ reduces recurrence rate to 17% with improved survival (77% vs 37% 10 year survival)**

See TVCN CNS TSSG Radiotherapy Protocols for treatment and planning details: Brain/Spine Radical Brain

Dose: 50 Gy in 30# to 55Gy in 35#

- **Follow up post RT**

  Post RT MRI scan at 3 months. Regular 3-6 monthly FU.
  Endocrine FU and ophthalmology FU (if needed).

- **For recurrent cyst following RT**

Consider instillation of 32P Chromic Phosphate to deliver 200Gy to cyst surface.

Background

Data from Brada and Thomas, 1993. Overview of 34 published reports.

Prognosis:	**actuarial survival**	
	5 year	**10 year**
Complete Surgery alone	81%	69%
Incomplete surgery alone	**53%**	**37%**
Incomplete Surgery + RT	89%	77%

Tumour control:	**progression free survival 10 year**	**recurrence rate**
Complete Surgery alone	N/A	29%
Incomplete surgery alone	**31%**	**73%**
Incomplete Surgery + RT	83%	17%

Treatment related toxicity:

Radical surgery:

- operative mortality 12% (range 2-43%)
- hypothalamic damage 40% (range 30-57%)
- post op visual impairment 19% (range 10-35%)
- following radical surgery - majority of patients require hormone replacement and long term treatment o f DI.

Limited surgery (drainage of hydrocephalus, aspiration of cyst, minor debulking)

- operative mortality 1%

Radiotherapy (if ≤55 Gy at ≤1.8 Gy per #)

- No hypothalamic damage
- visual impairment 1-1.5%
- second malignancy 1-2% at 20 years (in RT for pituitary adenomas)
- long term pituitary failure needing replacement therapy in most patients

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