Radiation Oncology and Brain Tumours
Current guidelines, recent advances and future directions

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Overview

- For many years neuro-oncology was the “poor cousin” - recent improvements in outcome for high grade glioma and the use of TMZ has improved situation dramatically
- Need to adopt the paediatric oncology model of large proportion of patients on clinical trials
- Outline current tx protocols, areas of uncertainty and current research
Types of radiotherapy

- External beam radiotherapy
- Unsealed sources e.g. gliasite
- Brachytherapy - usually iridium wire
- Particles ..... 
  - protons
  - carbon ions
Current guidelines

- High grade glioma
- Low grade glioma
- Cerebral metastases
GBM

Glioblastoma multiforme (GBM)

Treated with BCNU wafer

No BCNU wafer

Fractionated external beam RT\(^f\) ± concurrent and adjuvant temozolomide (category 2B)\(^{g,h}\)

Fractionated external beam RT\(^f\) + concurrent and adjuvant temozolomide (category 1)\(^{g,i,j}\)

- Age < 70 y
- Good performance status (KPS > 60)

MRI 2-6 wk after RT, then every 2-3 mo for 2-3 y

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Combination of agents may lead to increased toxicity or radiographic changes.


Duration of treatment for glioblastomas beyond 6 months is unknown. Duration of therapy for anaplastic astrocytoma is unknown.

See Principles of Brain Tumor Imaging (BRAIN-D)

See Principles of Brain Tumor Radiation Therapy (BRAIN-B)

See Principles of Brain Tumor Chemotherapy (BRAIN-C)
RTOG studies and the current trial. Therefore, we adapted the class definitions. Both the original and adapted definitions are presented in Table 1. The most important differences are as follows: EORTC classes III through V include GBM only, whereas RTOG classes III and IV include both anaplastic astrocytomas (WHO grade 3) and GBM; EORTC uses WHO performance status, whereas RTOG uses the Karnofsky index; and neurologic function in the RTOG RPA classification is defined as either "good" in RPA III or "neurologic function that inhibits the ability to work" in RPA IV, and mental status is described as "normal" or "abnormal," whereas the EORTC classification uses the Mini-Mental Status Examination (MMSE).

The MMSE is a brief, standardized tool used to grade cognitive function. It contains an assessment of orientation to place and time, a memory test, a substraction test, and an aphasia and apraxia evaluation. The maximum score that can be achieved is 30 points. In an analysis of a North Central Cancer Treatment Group trial, an abnormal MMSE score was characterized as /H11349/26, and these patients had a significantly worse prognosis.

Statistical Analysis

The prognostic value for survival, independent of treatment received, according to the RPA classification was estimated using the Kaplan-Meier method. This technique was also used to assess the efficacy of RT with or without TMZ in the three classes. The trend test was used to assess the ordering of the classes. The log-rank test was used for each treatment comparison. The interaction tests (heterogeneity and trend tests) were also computed.

RESULTS

Patient Demographics

Patient characteristics are presented in Table 2. RT and RT/TMZ treatment arms were well balanced for the repartition of RPA classes, with 14% and 15% of patients in class III, 52% and 53% in class IV, and 34% and 32% in class V, respectively. The percentage of patients receiving corticosteroids at the time of random assignment was slightly higher in the RT group than in the RT/TMZ group.

Fig 1. Kaplan-Meier estimates of overall survival according to Radiation Therapy Oncology Group (RTOG)/European Organisation for Research and Treatment of Cancer (EORTC) recursive partitioning analysis (RPA) class.

Table 2. Baseline Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RT (N=286)</th>
<th>RT/TMZ (N=287)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>50 81</td>
<td>50 205</td>
</tr>
<tr>
<td>Sex</td>
<td>175 61</td>
<td>185 64</td>
</tr>
<tr>
<td>WHO PS</td>
<td>110 38</td>
<td>113 39</td>
</tr>
<tr>
<td>1 141 49</td>
<td>136 47</td>
<td></td>
</tr>
<tr>
<td>2 35 12</td>
<td>38 13</td>
<td></td>
</tr>
<tr>
<td>Extent of surgery</td>
<td>Biopsy 45 16</td>
<td>48 17</td>
</tr>
<tr>
<td>Partial resection</td>
<td>128 45</td>
<td>126 44</td>
</tr>
<tr>
<td>Complete resection</td>
<td>113 40</td>
<td>113 49</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>215 75</td>
<td>193 67</td>
</tr>
<tr>
<td>Baseline MMSE</td>
<td>30 92</td>
<td>32 100</td>
</tr>
<tr>
<td>27-29 97 34</td>
<td>96 33</td>
<td></td>
</tr>
<tr>
<td>26 86 30</td>
<td>81 28</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>12 4</td>
<td>10 3</td>
</tr>
<tr>
<td>EORTC RPA class</td>
<td>III 39 14</td>
<td>42 15</td>
</tr>
<tr>
<td>IV 150 52</td>
<td>152 53</td>
<td></td>
</tr>
<tr>
<td>V 97 34</td>
<td>93 32</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: RT, radiotherapy; TMZ, temozolomide; PS, performance status; MMSE, Mini-Mental Status Examination; EORTC, European Organisation for Research and Treatment of Cancer; RPA, recursive partitioning analysis.
Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Diffuse or multiple Resectable Unresectable

Progression

Best supportive care if poor performance status or Systemic chemotherapy or Surgery for symptomatic, large lesion

Consider reirradiation (category 2B) or Systemic chemotherapy or Reirradiation

Consider reirradiation or Systemic chemotherapy

- Observe or Post RT chemotherapy
- Age < 70 y
- Good performance status (KPS > 60)
- AO > AA

Combination of agents may lead to increased toxicity or radiographic changes.


Duration of treatment for glioblastomas beyond 6 months is unknown. Duration of therapy for anaplastic astrocytoma is unknown.

- MRI 2-6 wk after RT, then every 2-3 mo for 2-3 y

See Principles of Brain Tumor Imaging (BRAIN-D)
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See Principles of Brain Tumor Chemotherapy (BRAIN-C)

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Anaplastic Astrocytoma/Anaplastic Oligodendroglioma/Glioblastoma Multiforme

GLIO-3

Anaplastic astrocytoma (AA)
Anaplastic oligodendroglioma (AO)
Glioblastoma multiforme (GBM)

No BCNU wafer Treated with BCNU wafer

Fractionated external beam RT ± concurrent and adjuvant temozolomide (category 2B)

Duration of treatment for glioblastomas beyond 6 months is unknown. Duration of therapy for anaplastic astrocytoma is unknown.

See Principles of Brain Tumor Imaging (BRAIN-D)
See Principles of Brain Tumor Radiation Therapy (BRAIN-B)
See Principles of Brain Tumor Chemotherapy (BRAIN-C).
GBM - areas of uncertainty

- Older patients
- much worse prognosis
- currently trying to back-titrate treatment protocols
- NCIC study locally (TROG 08.02)
  - 40Gy in 15 fractions
  - +/- chemotherapy
Trial outline

F-DOPA PET MRI

Surgery

Chemo-radiotherapy

F-DOPA PET MRI

Chemotherapy

F-DOPA PET MRI
CT MR fusion
Anaplastic Astrocytoma

**PATHOLOGY**
- Anaplastic astrocytoma (AA)
- Anaplastic oligodendroglioma (AO)

**TREATMENT**
- Treated with BCNU wafer
- No BCNU wafer

**ADJUVANT TREATMENT**
- Fractionated external beam RT ± chemotherapy (category 2B)

**FOLLOW-UP**
- Observe or Post RT chemotherapy
  - Age < 70 y
  - Good performance status (KPS > 60)
  - AO > AA

*Note: All recommendations are category 2A unless otherwise indicated.*

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Low grade glioma

**RADIOLOGIC PRESENTATION**

- **MRI compatible with primary brain tumor**
  - Maximal safe resection feasible
  - Observation
  - Maximal safe resection not feasible
  - Stereotactic biopsy or open biopsy or subtotal resection

**CLINICAL IMPRESSION**

- Maximal safe resection feasible
- Maximal excision
- MRI

**SURGERY**

- Maximal safe resection feasible
- Maximal excision
- MRI
- Age > 45 y
- Observe
- Fractionated external beam RT
- Consider chemotherapy
- Category 2B

**ADJUVANT TREATMENT**

- Uncontrolled or progressive symptoms
- Fractionated external beam RT
- Chemotherapy
- Category 2B

**FOLLOW-UP**

- Stable or controlled symptoms
- Observation
- Fractionated external beam RT
- Chemotherapy
- Category 2B

- MRI every 3-6 mo for at least 5 y then annually
- MRI every 3-6 mo for at least 5 y then annually

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**Notes:**
- All recommendations are category 2A unless otherwise indicated.
- Post-operative MRI should be done within 72 hours after surgery.
- Regular follow-up is essential for patients receiving observation alone after resection.
- Consider testing for deletions in 1p19q if tumor has components of oligodendroglioma for prognostic purposes.
Low grade glioma

- Long clinical course
- Frequently young patients
- Clinical problem is when to intervene? and with what?
- Locally - EORTC / TROG 06.01 trial
  - Biopsy or resection up front
  - Tx delayed until progression / neurology / seizures
  - Randomised to RT or TMZ
Brain metastases

CLINICAL PRESENTATION

Small cell lung systemic cancer or lymphoma (Non-PCNS) or Disseminated systemic disease with poor systemic treatment options

Stable systemic disease or Reasonable systemic treatment options

Resectable

Surgical resection, followed by WBRT (category 1 for 1 metastasis, and category 2A for 2-3 metastases) or Stereotactic radiosurgery (SRS), + WBRT (category 1 for 1 metastasis, category 2A for 2-3 metastases) or Stereotactic radiosurgery alone (category 2B)

Unresectable

WBRT and/or radiosurgery

PRIMARY TREATMENT

WBRT

Brain MRI

WBRT

WBRT and/or
radiosurgery

WBRT and/or
radiosurgery

Note: All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Current trials - brain mets

- Concerns regarding toxicity
- TROG / ANZMTG whole brain melanoma trial
- 1-3 mets
- All resected or stereotactic radiosurgery to all lesions
- Randomised to whole brain RT or observation
Induced malignancies

- median latency = 7 years
- thought to arise from incompletely repaired damage from ionising radiation
- can arise in any tissue irradiated
- often on the edge of the radiotherapy field (penumbra)
Pseudoprogression

Fig. 1. Clinical course of pseudoprogression in a 65-year-old patient with glioblastoma multiforme. (A) Presurgical MRI scan. (B) Postsurgical MRI scan. (C) MRI scan performed 1 month after combined temozolomide (TMZ)/radiotherapy; adjuvant TMZ was continued. (D) Four months later, during administration of maintenance TMZ. (E) Eight months later, during administration of maintenance TMZ.
Pseudoprogression

• MR scans being done early post chemo-RT

• frequently seen at one month

• blood brain barrier disruption occurs with RT and may enhance delivery of chemotx (and then gadolinium) making the lesion appear larger than prior to RT

• MR spectroscopy can be helpful in investigating
Choline, creatine and NAA peaks are important

General recommendation is to continue treatment plan

Steroids may help

HBO and bevacuzimab are experimental

Fig. 2. MR spectroscopic imaging 10 months after temozolomide plus radiotherapy. Choline:creatine and N-acetylaspartate:choline ratios were 1.3 and 0.92, respectively, suggesting a residual non-neoplastic lesion.
Helical TomoTherapy
Dose painting
Conclusions

- Renewed interest in brain tumour treatment
- Current clinical priorities are delineating tumour and individualising treatment
- New technologies will allow higher doses of radiation to be delivered more safely
- Involvement in clinical trials is the key to progress