Metaanalysis of Radiotherapy in Brain Tumors

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Diagnostic Imaging

<table>
<thead>
<tr>
<th>Imaging</th>
<th>Remarks</th>
<th>PROS</th>
<th>CONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CECT BRAIN</td>
<td>FIRST LINE</td>
<td>1. Fast</td>
<td>1. Limited Reconstruction ability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Can be used with metallic object</td>
<td>2. Poor Resolution</td>
</tr>
<tr>
<td>MRI Brain</td>
<td>Gold Standard</td>
<td>1. True Multiphasic</td>
<td>1. Motion Artefacts, Metallic objects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Unparalleled Resolution</td>
<td>2. Noisy</td>
</tr>
<tr>
<td>MR Spectroscopy</td>
<td>Brain</td>
<td>Tumor metabolites can be assessed</td>
<td>1. Limited utility near bone, vessels, air space</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can differentiate radiation necrosis and tumor</td>
<td>2. Variability in interpretation</td>
</tr>
<tr>
<td>MR Perfusion</td>
<td>Blood flow and volume is assessed</td>
<td>Can differentiate from radiation necrosis and tumor Progression</td>
<td>Limited utility near bone, vessels.</td>
</tr>
</tbody>
</table>

Meta-Analysis of MR Spectroscopy in diagnosis of Brain Tumors

- 24 studies
- Total of 1013 participants

<table>
<thead>
<tr>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>80.85%</td>
<td>78.46%</td>
</tr>
<tr>
<td>(95% CI: 75.97%–83.59%)</td>
<td>(95% CI: 73.40%–82.78%)</td>
</tr>
</tbody>
</table>

- Stratified meta-analysis showed higher sensitivity and specificity in child than adult. CSI (Chemical shift imaging) had higher sensitivity and single voxel (SV) had higher specificity.
- Current evidence suggests that MR may be a valuable adjunct to magnetic resonance imaging for diagnosing brain tumors, but requires selection of suitable technique and TE value. (Echo Times)

A. Abubakar et al. Magnetic resonance imaging in radiotherapy treatment target volumes definition for brain tumours: a systematic review and meta-analysis

Studies included were only those that quantitatively compared computed tomography (CT) and MRI in target volume definition for radiotherapy of brain tumours.

Five studies with a total number of 72 patients were included in this review.

**Conclusion:** Brain tumour volumes measured using MRI-based method for radiotherapy treatment planning were larger compared with CT defined volumes but the difference lacks statistical significance.

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Intraoperative Magnetic Resonance Imaging (iMRI)

Defines the tumour’s location, edema, and involvement of eloquent areas which are crucial tools to determine the appropriate surgical intervention in every patient.

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Surgery

- Retrospective systematic meta-analysis study
- 41,000 newly diagnosed GBM patients

Gross total resection (GTR) of high grade gliomas (HGG) and low grade gliomas (LGG) increases the median survival rate by 200% and 160% respectively, when compared to survival rates for patients subjected to a subtotal resection (STR):

- GTR proved superior over STR
- 61% increase in likelihood of a one-year survival
- 51% likelihood of a 12-month progression free survival

Montserrat Lara-Velazquez et al. Advances in Brain Tumor Surgery for Glioblastoma in Adults.
When maximal resection is not feasible, supramarginal resection (SMR) of the tumor is an option.

SMR is doing resection beyond tumor mass enhancement displayed by the imaging techniques.

Innovation in Neurosurgery
- Obtaining a maximal cytoreduction while preserving functional pathways.
- Radiographic analysis such as Intraoperative Magnetic Resonance Imaging (Imri).

Awake Craniotomy
- Permits the surgeon to monitor and rely on the functionality of patient while the patient is awake, and thereby increase the extent of resection.
- Cortical mapping of these areas through a set of direct electrodes that stimulate or inhibit cortical functions remains the optimal option to delineate the relationship of tumor to eloquent cortex in order to avoid damage of tissue that can compromise language or movement skills in patients.
WBRT versus Partial Brain RT

Multiple studies, including the Brain Tumor Cooperative Group 80-01 randomized trial, compared WBRT with partial-brain irradiation concluded that there was no advantage of WBRT

Standard: Partial-brain RT treatment

LOW GRADE GLIOMAS

Liang Xia, Chenyan Fang et al. Relationship between the extent of resection and the survival of patients with low-grade gliomas: a systematic review and meta-analysis.

- Relationship between the extent of resection and the prognosis of low-grade gliomas updated until March 2017 were systematically searched in two databases (Pubmed and EMBASE).

Twenty articles (Pubmed and EMBASE). Total of 2128 patients were identified.
Forest Plot of 10-Year Overall Survival for Gross Total Resection (GTR) vs Subtotal Resection (STR)

Forest Plot of 10-Year Overall Survival for Gross Total Resection (GTR) vs Biopsy (BX)

Forest Plot of 10-Year Overall Survival for Subtotal Resection (STR) vs Biopsy (BX)
The meta-analysis showed that the 5-year and 10-year associated with gross total resection (GTR) were higher than those associated with subtotal resection (STR). Similarly, as compared with biopsy (BX), the 5-year and 10-year OS were higher after either GTR.

Conclusions
A greater extent of resection could significantly increase the OS of patients with low-grade gliomas.

Optimal timing of radiotherapy

Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta
Dose of radiotherapy 54 Gy/30 #, 1.8 Gy per #, 5# per week

<table>
<thead>
<tr>
<th>EARLY RT</th>
<th>DELAYED RT</th>
<th>OS</th>
<th>PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.2 YEARS</td>
<td>7.4 YEARS</td>
<td>Log-rank P value = 0.873; HR 0.97, 95% CI 0.71 to 1.33</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>EARLY RT DELAYED RT</td>
<td></td>
</tr>
<tr>
<td>5.3 YEARS</td>
<td>3.4 YEARS</td>
<td>Log-rank P value &lt; 0.0001; HR 0.59, 95% CI 0.45 to 0.77</td>
<td></td>
</tr>
</tbody>
</table>

Seizures

<table>
<thead>
<tr>
<th>EARLY RT</th>
<th>DELAYED RT</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>41%</td>
<td>0.0329</td>
</tr>
</tbody>
</table>

Meta-analysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>Eligibility</th>
<th>Treatment</th>
<th>Phase</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG9802</td>
<td>WHO grade II glioma &lt; 40 &amp; neurosurgeon-determined GTR n=111</td>
<td>Post-operative observation</td>
<td>II</td>
<td>PFS at 5 y: 48%, OS at 5 y: 93%</td>
</tr>
<tr>
<td></td>
<td>WHO grade II glioma ≥ 40 or STR / PR / Biopsy n=254</td>
<td>RT vs RT + PCV</td>
<td>III</td>
<td>Median PFS (whole): 4.8 y vs. 16.4 y, HR 0.50, P &lt; 0.001</td>
</tr>
<tr>
<td>EORTC22033-26033</td>
<td>WHO grade II glioma n=477</td>
<td>RT vs Dose-intensified TMZ (21/28)</td>
<td>III</td>
<td>Median PFS (whole): RT 46 m vs TMZ 39 m, HR of TMZ vs RT: 1.16, P = 0.22</td>
</tr>
</tbody>
</table>
### Treatment Recommendations for Adult Patients with Diffuse Gliomas of Grades III According to the New WHO Classification in 2016

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<th>Eligibility</th>
<th>Treatment</th>
<th>Phase</th>
<th>Main Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NOA-04</td>
<td>WHO grade III glioma n = 318</td>
<td>RT vs Chemotherapy (PCV or TMZ)</td>
<td>III</td>
<td>Median PFS (whole): RT 30.6 m vs chemo 31.9 m, HR 1.0, P = 0.437</td>
</tr>
<tr>
<td>RTOG 9802</td>
<td>Anaplastic oligodendroglia / oligoastrocytoma n = 280</td>
<td>RT or PCV 4 + RT</td>
<td>III</td>
<td>Median PFS (whole): RT 1.7 y vs PCV + RT 2.4 y, HR 0.9, P = 0.046</td>
</tr>
<tr>
<td>EORTC 26951</td>
<td>Anaplastic oligodendroglia / oligoastrocytoma n = 360</td>
<td>RT vs PCV 6</td>
<td>III</td>
<td>Median PFS (whole): RT 13.2 m vs RT + PCV 23.8 m, HR 0.66, P = 0.0063</td>
</tr>
<tr>
<td>CATNON</td>
<td>Anaplastic glioma without 1p/19q codeletion n = 745</td>
<td>RT vs RT/TMZ vs RT/TMZ + TMZ 12 vs RT/TMZ + TMZ 12</td>
<td>III</td>
<td>Adjusted OS (adjuvant TMZ): HR 0.645, P = 0.0014</td>
</tr>
</tbody>
</table>

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### Evidence-based standard of care and treatment recommendation for adult diffuse gliomas

**WHO 2016**

<table>
<thead>
<tr>
<th>Grade II</th>
<th>Evidence-based standard of care</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligodendroglioma, IDH-mutant and 1p/19q-codeleted</td>
<td>RTL → PCV 6 courses</td>
<td>RTL → PAV 4–6 courses or TMZ 4 courses or RTL × PAV 3–6 courses</td>
</tr>
<tr>
<td>Diffuse astrocytoma, IDH-mutant</td>
<td>unknown (may be)</td>
<td>RTL → PCV 6 courses</td>
</tr>
</tbody>
</table>

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### Evidence-based standard of care and treatment recommendation for adult diffuse gliomas

**WHO 2016**

<table>
<thead>
<tr>
<th>Grade III</th>
<th>Evidence-based standard of care</th>
<th>Treatment recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaplastic oligodendroglia, IDH-mutant and 1p/19q-codeleted</td>
<td>PCV 4 courses → RTL or RTL → PCV 6 courses</td>
<td>PAV 4 courses → RTL or RTL → TMZ 6–12 courses</td>
</tr>
<tr>
<td>Anaplastic astrocytoma, IDH-mutant</td>
<td>unknown (may be)</td>
<td>RTL → TMZ 12 courses or RTL/TMZ → TMZ 12 courses</td>
</tr>
</tbody>
</table>

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**RT**: radiotherapy 50–54 Gy in 1.8–2.0 Gy fraction, **RT²**: radiotherapy 59.4–60 Gy in 1.8–2.0 Gy fraction, **PAV**: radiotherapy 3–6 courses**: for elderly patients or patients with minimal residual disease, "The number of treatment courses may be personalized dependent on efficacy, toxicity, and MGMT status."
Adult Diffuse Glioma Grade II or III

Resectable Lesion (Non-Eloquent area)
- Awake Surgery
  - Maximum Safe Resection
  - GTR/NTR
  - Debulking/Residual
  - Histomorphology, grading, molecular diagnosis (IDH Mutation and ATRX) 1p 19q for ODG

Maximum Safe Resection
- Not amenable to Stereotactic Biopsy
- Histomorphology, grading, molecular diagnosis (IDH Mutation and ATRX) 1p 19q for ODG

Stereotactic Biopsy
- Not amenable to Stereotactic Biopsy
- Histomorphology, grading, molecular diagnosis (IDH Mutation and ATRX) 1p 19q for ODG

Confirmed Adult Diffuse Glioma Grade II or III

GTR/NTR
- Debulking/Residual
- Histomorphology, grading, molecular diagnosis (IDH Mutation and ATRX) 1p 19q for ODG

Clinico-Radiological Observation
- Progression without Transformation
- Repeat Surgery if feasible
- Progression with Transformation to high grade

Fav LGG Grade II
- Unfav / Aggressive LGG Grade II
- Anaplastic (Grade III)

RT+ TMZ followed by 12 CYCLES Adjuvant TMZ (55.8GY/31#)
- RT+ TMZ followed by 12 CYCLES Adjuvant TMZ (59.4GY/33#)

Salvage RT+ TMZ followed by 12 CYCLES Adjuvant TMZ (59.4GY/33#)
- Salvage RT+ TMZ followed by 12 CYCLES Adjuvant TMZ (55.8GY/31#)

Glioblastoma Multiformae

Rare spinal GBM case report female snake.
RT treatment volume for GBM

Co-registration of pre- and postoperative MRI with planning CT images

<table>
<thead>
<tr>
<th>Glioblastoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certain brain tumors, e.g., glioma have a distinct appearance on MRI scans. With irregular borders and necrotic center.</td>
</tr>
</tbody>
</table>

EORTC treatment volumes (EORTC 22981/22961, 26071/22072 (Centric), 26981–22981, and AVAglio trials)

<table>
<thead>
<tr>
<th>Phase 1 (to 60 Gy in 30 fractions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV = Surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans).</td>
</tr>
<tr>
<td>CTV = GTV plus a margin of 2 cm</td>
</tr>
<tr>
<td>PTV = CTV plus a margin of 3–5 mm</td>
</tr>
</tbody>
</table>

80%–90% of treatment failures occur within this margin

RTOG treatment volumes (RTOG 0525, 0825, 0913, and AVAglio trials)

<table>
<thead>
<tr>
<th>Phase 1 (to 46 Gy in 23 fractions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GTV1 = Surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scans) plus surrounding oedema (hyperintensity on T2 or FLAIR MRI scans).</td>
</tr>
<tr>
<td>CTV1 = GTV1 plus a margin of 2 cm if no surrounding oedema is present, the CTV is the contrast enhancing tumour plus 2.5 cm.</td>
</tr>
<tr>
<td>PTV1 = CTV1 plus a margin of 3–5 mm</td>
</tr>
</tbody>
</table>

Phase 2 (14 Gy boost in 7 fractions)

| GTV2 = Surgical resection cavity plus any residual enhancing tumour (postcontrast T1 weighted MRI scan) |
| CTV2 = GTV2 plus a margin of 2 cm |
| PTV2 = CTV2 plus a margin of 3–5 mm |

Margins up to 3 cm were allowed in 22981/22961 trial, and 1.5 cm in 26981–22981 trial.
One phase Target Delineation for GBM

MRI image, gross total resection. The GTV includes surgical cavity and residual enhancement based on the axial T1 sequence with gadolinium (red line) and CTV is a 2 cm expansion in all directions (green line).

Two phase Target Delineation for GBM

The initial GTV includes postoperative peritumoral edema based on the axial T2 fluid-attenuated inversion recovery sequence (red line); the initial CTV (green line) includes postoperative peritumoral edema plus a 2 cm expansion in all directions. The boost GTV includes the surgical cavity and residual enhancement based on the axial T1 sequence with gadolinium (red line) and the boost CTV is a 2 cm expansion in all directions (green line).

Contouring guidelines

- WTSG
- Phase 1-CTV: postoperative peritumoral edema plus a 2 cm margin (low grade 1 cm)
- Phase 2-CTV: residual tumor plus 2 cm margin
- EORTC: 2-3 cm dosimetric margin around the tumor (as evaluated by MRI)
The University of Texas MD Anderson Cancer Center uses a 2 cm margin around the gross tumor volume (GTV), which consists of the resection cavity and any residual contrast enhancing tumor, but ignoring any edema.

Conclusion of Studies (Post operative GBM)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burger et al; Halperin et al</td>
<td>The distribution of cells of a GBM cannot be inferred from CT images, since the peritumoral area of low density can over- or underestimate the extent of the lesion.</td>
</tr>
<tr>
<td>Chang et al; Minniti et al; McDonald et al; Dobelbower et al</td>
<td>There were no significant differences in relapse patterns between the two target delineation techniques.</td>
</tr>
<tr>
<td></td>
<td>The use of this limited-margin RT can significantly decrease the volume of normal brain tissue that is irritated.</td>
</tr>
</tbody>
</table>

TEMORADIATION

<table>
<thead>
<tr>
<th>Treatment Schedule</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concomitant</td>
<td>TMZ/RT</td>
</tr>
<tr>
<td></td>
<td>adjuvant TMZ</td>
</tr>
<tr>
<td>RT</td>
<td>0 6 10 14 18 22 26 30 weeks</td>
</tr>
<tr>
<td>TMZ</td>
<td>Temozolomide 75 mg/m²/d po during RT, and 150–200 mg/m² po days 1–5 / 26 for 6 cycles</td>
</tr>
<tr>
<td></td>
<td>RT— 30 fractions x 200 cGy</td>
</tr>
<tr>
<td></td>
<td>Total dose 60 Gy</td>
</tr>
</tbody>
</table>

Stupp et al. NEJM 2005.
Five RCTs (1655 patients) were eligible in this study.

Statistical information and characteristics of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjuvant therapy</th>
<th>Time from randomization</th>
<th>Survival (OS)</th>
<th>OS HR (95% CI)</th>
<th>OS P-value</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pappas 2006</td>
<td>Adjuvant</td>
<td>24.2</td>
<td>0.67</td>
<td>0.41-0.91</td>
<td>0.021</td>
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<td>24.2</td>
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</table>

Adjuvant therapy.

<table>
<thead>
<tr>
<th>All patients</th>
<th>CT patients</th>
<th>Eligible brainstem</th>
<th>Eligible body</th>
<th>Eligible tumor</th>
<th>Eligible 2D</th>
<th>Eligible 3D</th>
<th>Eligible 4D</th>
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Meta-analyses result of survival rate

Subgroup Analysis Of OS

CTRT were associated with a significant improvement in OS compared with that of RT. Besides, the risk of death was reduced by 30% in those received combination of chemotherapy and radiotherapy.

STUPP Trial for Elderly GBM

Elderly GBM – Nordic Trial (Age >60yrs)

Nordic Trial Design

Temozolomide may be an alternative to RT
Oral chemotherapy combined with radiotherapy contributes to the survival in patients with newly diagnosed GBM.

Adjuvant chemotherapy confers a survival benefit in patients newly diagnosed with GBM.

Target dose coverage with IMRT planning was better than 3DCRT planning. If PTV is distant to optical nerves, chiasm and brainstem, 3D conformal technique can be applied, and if the PTV is nearby OAR, intensity-modulated treatment technique should be used.

Tumors adjacent to (or partially overlapping with) critical structures, IMRT dramatically spared the volume of the critical structures to be irradiated.

For large and spherical brain tumors, the smaller collimator leaf widths give no significant benefit.
RTOG 9305: Newly Diagnosed GBM Stereotactic Radiosurgery Phase III Trial

Arm 1
RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then Gliadel for 6 cycles

Arm 2
SRS followed by
RT – 60Gy / 30 #
BCNU 80mg/m2 D1-3 of RT then Gliadel for 6 cycles

SRS Dose
24 Gy – Lesion < 2cm
18 Gy – Lesion 2.1 – 3 cm
15 Gy – Lesion 3.1 – 4 cm

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**Imaging features of GBM**

- Resectable lesion in non eloquent cortex
- Awake surgery with Electrophysiological guidance
- Maximum Safe Resection
- Stereotactic Biopsy
- Non Amenable to Stereotactic Biopsy

- Confirmed GBM or variant on Histopathology
- MGMT IDH only if age < 50 year or prior H/o LGG

**GBM RPA Modified**

- Poor Prognosis
- Other class V and class VI
  - Palliative Hypofractionated Radiotherapy
  - If Good Response adjuvant TMZ
- Favourable Prognosis
- Class III-IV
  - Selected Class V
  - Radical Concurrent CTRT with TMZ 60Gy/30#/6 weekly Adjuvant 6-12 cycles of TMZ (methylated) Adjuvant 6 cycles of TMZ (unmethylated)

**BRAINSTEM GLIOMAS**

- National Cancer Grid (INDIA)
- Poor Prognosis
- Other class V and class VI
  - Palliative Hypofractionated Radiotherapy
  - If Good Response adjuvant TMZ
- Favourable Prognosis
- Class III-IV
  - Selected Class V
  - Radical Concurrent CTRT with TMZ 60Gy/30#/6 weekly Adjuvant 6-12 cycles of TMZ (methylated) Adjuvant 6 cycles of TMZ (unmethylated)
Between 1997 and 2007, 104 patients (age > 18 years) with histologically proven gliomas of the brainstem were included in this study from five German centres.

- **Brain Stem Gliomas**
  - Tectal Plate
  - Focal or Dorsal Exophytic
  - Diffuse Intrinsic Glioma (Radiologically)

- **Rx of Hydrocephalus**
  - Observation
  - Progression
  - Biopsy if amenable

- **EBRT**
  - 54Gy/30 #/6 weeks

- **Electrophysiology guided resection or biopsy**
  - GTR
  - STR/Biopsy

- **GTR**
  - 54Gy/30 #/6 weeks

- **Grade II to IV**
  - Observation
  - RT for Grade II (54Gy/30#/6wk)
  - Grade III-IV (55.8Gy/31#/6.5 week)

- **Pilocytic**
  - Observation
  - LGG chemo protocol (Vcr, carboplatin)
  - 54Gy/30#

- **Michael C. Oh, Michael E. Ivan et al**
  - Adjuvant radiotherapy delays recurrence following subtotal resection of spinal cord Ependymomas.

  - GTR provides the best PFS, which was significantly longer, compared with STR and STR + RT groups (log rank, P <001).

  - The median survival time (50% PFS) for the STR + RT group was twice as long (96 months), compared with the STR group (48 months).
No difference in OS between the STR and STR + RT groups.


Ependymoma after Maximal safe resection

Low grade

Postop EBRT 54Gy/30 #x/6 wk

High Grade

Anaplastic

Neuroaxis staging
MRI Spine, CSF

MRI Spine, CSF

Negative

Positive

59.4 Gy/33#/6.5 wk
In young children or tumor close to critical structures 55.8Gy/33#

Craniospinal irradiation+ local boost+ adjuvant chemotherapy

Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta
**Recommended MRI protocol for suspected medulloblastoma**

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<tbody>
<tr>
<td>Axial, T1. T2 and FLAIR images of the brain</td>
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<tr>
<td>Axial, coronal and sagittal T2 images of the brain using thin sections (1mm with 0.5-mm gap) with small field of view and high matrix</td>
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<tr>
<td>Post-contrast T1 spin-echo imaging of the brain in at least one plane followed by 3D FSPGR with contrast. Reconstruction of the 3D images should be done using 3 mm sections with 0.5-mm gap to match the pre-contrast thin sections</td>
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<tr>
<td>Axial diffusion-weighted imaging of the brain</td>
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<tr>
<td>Post-contrast, T1, sagittal imaging of the entire spine</td>
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<tr>
<td>Post-contrast T1, sagittal imaging of the entire spine if the lesion extends beyond the midline</td>
</tr>
<tr>
<td>Pre and post-contrast T2 weighted imaging of the posterior fossa</td>
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</tbody>
</table>
| Gradient-echo MRI perfusion imaging of brain during contrast (
| Axial 3D susceptibility-weighted imaging of the brain |
| 
| SPACE occupying lesions. |
| sagittal T1 spin-echo imaging of the entire spine |
| T1 weighted and axial imaging of the posterior fossa |
| Any contrast enhancement for further characterization in unlesioned spinal magnetic resonance. |

**Intraoperative Photograph**

Space occupying lesion in midline posterior fossa nearly filling the fourth ventricle.

**Spinal MRI**

- Most sensitive for spinal cord metastases.
- Frequency of spinal seeding at diagnosis is 30-35%.
- M-C seen in the lumbosacral and thoracic areas and are best seen on **post-contrast T1-weighted images**.
- MRI spine should be obtained whenever possible pre-operatively or else at least 2/3 weeks post-operatively.
Neurosurgery

Routine pre-operative ventriculo-peritoneal (VP) shunt should generally be avoided as definitive surgical resection readily relieves the obstruction by opening the cerebrospinal fluid (CSF) pathways.

Surgical exposure

- Complete surgical resection is ideal, but this may not always be safe or feasible.
- In such cases, it is recommended to attempt maximal safe resection leaving residual tumor behind rather than aggressive surgical resection that can precipitate significant morbidity.

Post-operative Neuro-imaging

- Post-operative MRI of the brain be acquired immediately (within 24-48 hours of surgical resection) to accurately identify the extent of resection and quantify the status of the residual disease.
- Whenever immediate post-operative neuro-imaging has not been obtained, it is recommended to wait for 2-3 weeks (but no later than 4-weeks) to allow resolution of post-operative changes.
**CSF cytology**

Mandatory

- Staging
- Risk Stratification

50% of patients with positive spine MRI studies are asymptomatic and have negative cytologic results.

**Recommended testing by diagnostic pathology laboratories for medulloblastoma (Minimum desirable mandatory tests)**

- Hematoxylin and eosin (H&E) staining
- Reticulin staining
- MIB-1 Labelling index (using Ki-67)

**Medulloblastoma, Grade IV tumors (WHO Classification)**

- Medulloblastoma, classic
- Desmoplastic/nodular medulloblastoma
- Medulloblastoma with extensive nodularity
- Large-cell/anaplastic medulloblastoma
- Medulloblastoma, not otherwise specified (NOS)
Medulloblastoma, genetically defined

- Medulloblastoma, WNT-activated
- Medulloblastoma, SHH-activated and TP53-mutant
- Medulloblastoma, SHH-activated and TP53-wildtype
- Medulloblastoma, non-WNT/non-SHH
  - Medulloblastoma, group 3
  - Medulloblastoma, group 4

Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta

How are postoperative radiotherapy care patterns changing in young children with medulloblastoma, and what are the survival implications?

In this national database analysis of 816 children with medulloblastoma, ages 3 to 8 years, who received postoperative chemotherapy, there was a 15.1% rate of postoperative radiotherapy deferral overall, and deferral rate increased from 2004 to 2012.

Postoperative radiotherapy deferral was associated with decreased overall survival in this population.

The analysis suggests that postoperative radiotherapy deferral is associated with worse survival in this age group, even in the modern era of chemotherapy.

Treatment of the entire neuraxis, i.e. craniospinal irradiation (CSI) followed by boost irradiation of the tumor bed/posterior fossa is recommended

- CSF Dissemination 14-16%
- Being Radiosensitive, Radiotherapy is curative up to 70% of standard risk patients
Unavailability of linear accelerators locally, children should ideally be referred in time to an appropriate higher centre with adequate RT facility and infrastructure to prevent unnecessary delays.

Indian Society of Neuro-Oncology consensus guidelines for the contemporary management of medulloblastomas

CT-based three-dimensional (3D) simulation

- Supine position is now being increasingly used.
- Target volume coverage is more easily assured and delivery more reproducible with CT-planned supine CSI.
- Axial planning CT images should be acquired from the vertex till the upper thigh region using 5mm slice thickness.

| CTV brain | Brain and its covering meninges till the C2 |
| PTV brain | 5mm isotropic margin around CTV-brain. |
| CTV spine | Spinal thecal sac and exiting nerve roots from the C2 cervical spine till the lower end of the thecal sac |
| PTV spine | 8-10mm isotropic margin is recommended around the CTV-spine |

Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta
Organs-at-risk (OARs) for CSI should include but may not be limited to eyes, lens, cochlea, mandible, parotids, thyroid, esophagus, lungs, heart, liver, kidneys, bowel bag, rectum, bladder, gonads (ovaries/testes), and vertebral bodies plus pelvis (surrogate for red bone marrow).

Boost irradiation planning

| Low Risk And Standard Risk | Pre-operative Tumor-bed With Appropriate Margins (Typically 1-1.5cm Around The Tumor Bed). |
| High Risk And Very High Risk Disease | Irradiation Of The Entire Posterior Fossa Is Presently Recommended |

Posterior Fossa Boost
CSI and boost plans be summated to produce a composite treatment plan and final dose-distribution.

3DCRT with multileaf collimators

CSI in supine position

Fixed-field geometry for supine craniospinal irradiation with set-up isocentre fixed at mid-body of C2-vertebra.
The field junction over the cervical cord is usually moved weekly ("feathered") to avoid over- or underdosage.

The anterior fields are shown and the gap can be measured directly from the image.

Tumor-bed Boost Following Craniospinal Irradiation
Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta

**Radiotherapy prescription**

**Infants**
Age < 3 years

**CHEMOTHERAPY**

**Radiotherapy deferred till 3 years**

**Children 3-18 years**

<table>
<thead>
<tr>
<th>ISNO guidelines</th>
<th>NCG Guidelines</th>
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<tr>
<td><strong>Low Risk Disease</strong></td>
<td>Reduced dose of CSI Reduced chemotherapy intensity</td>
</tr>
<tr>
<td><strong>Standard Risk Disease</strong></td>
<td>Reduced dose CSI weekly VCR CSI: 23.4 Gy/13#/3wks PF Boost: 12.6 Gy/7#/1.5 wks Tx Bed Boost: 18 Gy/10#/2wks Followed by 6 cycles of adjuvant chemotherapy</td>
</tr>
<tr>
<td><strong>High Risk Disease/Very High Risk Disease</strong></td>
<td>Standard CSI 35 Gy/21#/4 week concurrent carboplatin during CSI and tumor bed boost: 19.8 Gy/11#/2.5wks</td>
</tr>
<tr>
<td></td>
<td>Boost to gross metastatic deposit: 5.4-9 Gy/3-5#</td>
</tr>
</tbody>
</table>

HFRT
CSI: 36 Gy/36#/1Gy B.I.D (6-8 hrs gap in between 2 daily fractions)
Tx Bed Boost: 32 Gy/32#/1Gy B.I.D
Results: Mean values of planning target volume (PTV), PTV95% and PTV5% in IMRT were 97.19% and 106.07% and for 3DCRT were 96.57% and 105.33%, respectively. The dose homogeneity was better in IMRT (1.091) as compared to 3DCRT (1.100), but was not statistically significant (P = 0.341). Conformity index was comparable in both the plans, i.e., 3DCRT (0.979) and IMRT (0.976) with P = 0.049. IMRT plan provided reduced mean dose to cochlea relative to the 3DCRT plan with P = 0.032 for the right cochlea and 0.020 for the left cochlea. IMRT showed no advantage over 3DCRT in sparing the anterior cranial structures where mean doses to the right and left lens were 0.61 Gy and 0.56 Gy for IMRT and 0.16 Gy and 0.09 Gy for 3DCRT, respectively.

Conclusions: IMRT technique was able to improve homogeneity index, spare the cochleae, but 3DCRT plans were superior in sparing anterior cranial structures without compromising the dose to PTV.
Yes, that's right. There is a light that stops at a certain point and releases all of its energy and disappears.

As soon as the proton beam reaches the cancer tissues, it destroys the cancer tissues with maximum energy and subsequently, it becomes completely annihilated.
Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta

Proton Craniospinal Radiation Therapy: Rationale and Clinical Evidence
Anita Mahajan, MD University of Texas MD Anderson Cancer Center, Houston, TX, USA

Abstract Purpose: To review the existing evidence that supports the use of proton craniospinal irradiation (p-CSI) in pediatric patients.

Conclusions: Based on the theoretical and early clinical outcomes, p-CSI appears to provide equal tumor control with potentially reduced risk of side effects when compared with data. Ongoing efforts will continue to evaluate these advantages.

Proton CSI improved normal tissue sparing while providing more homogeneous target coverage than photon CSI for patients across a wide age and BMI spectrum. Of the 24 parameters (V_5, V_10, V_15, and V_20 in the esophagus, heart, liver, thyroid, kidneys, and lungs), Wilcoxon signed rank test results indicated 20 were significantly higher for photon CSI compared to proton (p ≤ 0.05).

Comparison of therapeutic dosimetric data from passively scattered proton and photon craniospinal irradiations for medulloblastoma. Rebecca M Howell, Anita et al. MD Anderson Cancer Center

Technology comparison
Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta
Medulloblastoma, composite of craniospinal plus posterior fossa

Novel Hybrid Scattering- and Scanning-Beam Proton Therapy Approach

Chemotherapy

- Adjuvant chemotherapy following RT
- Adjuvant chemotherapy following surgery in infant medulloblastoma (<3-years)
- Pre-irradiation chemotherapy in infant medulloblastoma to defer RT (till 3-years)
- High-dose chemotherapy with autologous stem-cell rescue
- Concurrent chemotherapy with RTSalvage therapy in relapsed/recurrent medulloblastoma.
Metaanalysis of Radiotherapy in Brain Tumors: Dr. Meenu Gupta