Diagnosis and Treatment of Intracranial Tumors: Overview

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Clinical and Research Training in Tokyo Women’s Medical University Japanese Language Classes, Research Student, Doctorate Candidate, Doctorate Degree (博士) in March 2000, IREIIMS Postdoctoral Fellow, JSPS Postdoctoral Fellow (October 2000 – March 2012),

Assistant Professor in Faculty of Advanced Techno-Surgery and Department of Neurosurgery of the Tokyo Women’s Medical University (from April 2012)
What is Common in These Celebrities?
Brain Tumors

- Gliomas Tumor
- Meningioma Tumors
- Pituitary Adenomas
- Schwannomas (Acoustic Neuromas)
High-grade gliomas account for approximately 80% of adult primary malignant brain tumors diagnosed in the United States each year.

The most common type of glioma is glioblastoma multiforme (GBM), which ranges in age-adjusted incidence rate from 0.6 to 3.7 per 100,000 persons, with the greatest incidence among those aged 75-84 years.

The incidence of gliomas in pediatric population (0-14 years) in the United States (2007-2011) is 2.8 per 100,000 persons; pilocytic astrocytoma is the most common type of pediatric glioma, with an incidence of 0.9 per 100,000.
Gliomas: Risk Factors

Ionizing Radiation Studies
- Preston
- Sadetzki
- Neglia
- Pearce

Risk Ratio and 95% CI
- Excess Risk Ratio: 0.56 (0.2 – 2.0)
- Relative Risk: 2.6 (0.8 – 8.6)
- Odds Ratio: 6.78 (1.5 – 30)
- Relative Risk: 2.8 (1.3 – 5)

Allergy Studies
- Interphone
- Allergy Meta-analysis
- Scheurer
- Schwartzbaum

Cellular Phone Studies
- Frei (men)
- Frei (women)
- Benson (women)
- Hardell
- Coureau

Relative Risk: 1 (0.8 – 1.3)
Relative Risk: 1 (0.6 – 2)
Relative Risk: 0.8 (0.5 – 1.1)
Odds Ratio: 1.6 (1 – 2.7)
Odds Ratio: 1.2 (0.9 – 1.8)
### WHO Classification (2016)

#### Diffuse astrocytic and oligodendroglial tumours

- **Diffuse astrocytoma, IDH-mutant**
  - Gemistocytic astrocytoma, IDH-mutant*
- **Diffuse astrocytoma, IDH wild-type**
- Diffuse astrocytoma, NOS

- Anaplastic astrocytoma, IDH-mutant
- **Anaplastic astrocytoma, IDH wild-type**
- Anaplastic astrocytoma, NOS

- Glioblastoma, IDH wild-type
  - Giant cell glioblastoma*
  - Gliosarcoma*
  - Epithelioid glioblastoma*
- Glioblastoma, IDH-mutant
- Glioblastoma, NOS

- **Diffuse midline glioma, H3-K27M-mutant**

- Oligodendroglioma, IDH-mutant and 1p/19q co-deleted
- Oligodendroglioma, NOS

- Anaplastic oligodendroglioma, IDH-mutant and 1p/19q co-deleted
- Anaplastic oligodendroglioma, NOS

- **Oligoastrocytoma, NOS**
- **Anaplastic oligoastrocytoma, NOS**

#### Other astrocytic tumours

- Pilocytic astrocytoma
- **Pilomyxoid astrocytoma***
- Subependymal giant cell astrocytoma
- Pleomorphic xanthoastrocytoma
- Anaplastic pleomorphic xanthoastrocytoma

#### Ependymal tumours

- Subependymoma
- Myxopapillary ependymoma
- Ependymoma
  - Papillary ependymoma*
  - Clear cell ependymoma*
  - Tanyctic ependymoma*
- Ependymoma, RELA fusion-positive
- Anaplastic ependymoma

#### Other gliomas

- Chordoid glioma of the third ventricle
- Angiocentric glioma
- Astroblastoma

* NOS: not otherwise specified (no genetic testing done)
* Italics: provisional entities
* Blue: new genetic-based nomenclatures
* Red: new entities or variants
* * A variant
Gliomagenesis

Infiltrating gliomas

Normal cells

Circumscribed astrocytomas

CDKN2A mt / HD

TP53 mt

IDH1/IDH2 mt

MGMT meth

ATRX mt

TERT mt

1p/19q co-deletion

BRAF fusion

BRAF mt

PA

PXA

CIC/FUBP1 mt

DA

OA

OD

AA

AOA

AOD

TERT mt

PTEN mt / HD

EGFR amp

primary glioblastoma

secondary glioblastoma

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O6-methylguanine-DNA-methyltransferase (MGMT) - endogenous DNA repair protein, which removes alkyl groups produced on DNA by alkylating agents.

1p/19q co-deletion – molecular signature of oligodendrogliomas.

Isocitrate dehydrogenase genes 1 and 2 (IDH-1/IDH-2) mutation - almost exclusively associated with the glial phenotype.

<table>
<thead>
<tr>
<th>Molecular Marker</th>
<th>Histopathological Tumor Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-grade Gliomas (WHO Grade II)</td>
</tr>
<tr>
<td>MGMT Promoter Methylation</td>
<td>Uncertain prognostic/predictive value</td>
</tr>
<tr>
<td>1p/19q Co-deletion</td>
<td>Favorable prognostic value</td>
</tr>
<tr>
<td>IDH-1 or IDH-2 Mutation</td>
<td>Favorable prognostic value</td>
</tr>
</tbody>
</table>
Structural MRI
Advanced MRI
Positron Emission Tomography
Summary of Prognostic Factors

Patient-related:
- Age
- Performance status / Mental status / Neurological function
- Duration of symptoms

Tumor-related:
- Imaging characteristics (size, location, enhancement, edema, crossing midline, necroses, metabolic parameters, multiplicity)
- Grade / Type
- Molecular and genetic markers

Treatment-related:
- Need of steroid therapy at baseline
- Aggressive surgery (EOR, Residual volume) / Advanced surgical adjuncts
- Standard adjuvant therapy
Stereotactic Biopsy
Age, KPS, extent of resection were independent predictors of survival.

A significant survival advantage was seen at 78% EOR and stepwise improvement was noted even between 95% and 100% resection.
# Extent of Resection - Low-grade Gliomas

## Low-grade gliomas in adults

A review

Nader Sanai, M.D., Susan Chang, M.D., and Mitchel S. Berger, M.D.

*J Neurosurg 115:948–965, 2011*

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### Table: Extent of Resection for Low-grade Gliomas

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>EOR Methodology</th>
<th>PFS Benefit</th>
<th>OS Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whitton &amp; Bloom, 1990</td>
<td>88</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>no</td>
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<tr>
<td>North et al., 1990</td>
<td>77</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>yes</td>
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<tr>
<td>Philippson et al., 1993</td>
<td>179</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>yes</td>
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<tr>
<td>Rajan et al., 1994</td>
<td>82</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>Leighton et al., 1997</td>
<td>167</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>van Veelen et al., 1998</td>
<td>75</td>
<td>volumetric</td>
<td>NA</td>
<td>yes</td>
</tr>
<tr>
<td>Bauman et al., 1999</td>
<td>401</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>no</td>
</tr>
<tr>
<td>Nakamura et al., 2000</td>
<td>88</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>yes</td>
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<tr>
<td>Johannesen et al., 2003</td>
<td>993</td>
<td>nonvolumetric</td>
<td>NA</td>
<td>no</td>
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<tr>
<td>Yeh et al., 2005</td>
<td>93</td>
<td>nonvolumetric</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Claus et al., 2005</td>
<td>156</td>
<td>volumetric</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>Smith et al., 2008</td>
<td>216</td>
<td>volumetric</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>McGirt et al., 2008</td>
<td>170</td>
<td>nonvolumetric</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Sanai et al., 2010</td>
<td>104</td>
<td>volumetric</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>Rezvan et al., 2009</td>
<td>130</td>
<td>nonvolumetric</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Chaichana et al., 2010</td>
<td>191</td>
<td>nonvolumetric</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
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![Cumulative Survival Graph](image-url)
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Less Aggressive Resection for OD/AOD may be Acceptable

OS stratified by postoperative volume for all patients with supratentorial LGG (N = 228)  

OS stratified by postoperative volume for patients with supratentorial OD (N = 93)  

Neuro Oncol (in press)
Maximal Safe Resection of Gliomas

- $^{11}$C-methionine uptake – very extensive tumors
- Contrast-enhanced area on T1-weighted MRI
- T2/FLAIR hyperintensity
- Supramarginal resection (Hugh Duffau)
### Tumor Location (Sawaya Functional Grade)

**Grading of intraparenchymal tumors according to functional location***

<table>
<thead>
<tr>
<th>Grade</th>
<th>Functional Location</th>
</tr>
</thead>
</table>
| I: noneloquent brain | frontal or temporal pole of cerebrum  
|                 | rt parietooccipital lobe  
|                 | cerebellar hemisphere                                                                 |
| II: near eloquent brain | near motor or sensory cortex†  
|                 | near calcarine fissure  
|                 | near speech center  
|                 | corpus callosum  
|                 | near dentate nucleus  
|                 | near brainstem                                                                 |
| III: eloquent brain  | motor or sensory cortex  
|                  | visual center  
|                  | speech center  
|                  | internal capsule  
|                  | basal ganglia  
|                  | hypothalamus or thalamus  
|                  | brainstem  
|                  | dentate nucleus                                                                 |

* + pre- and intraoperative functional brain mapping
Modern Intraoperative Technologies

Computers

Intraoperative MRI

Neuronavigation System

Robotics
Treatment in Specialized Centers
Intraoperative Technologies

The best tools for improving Extent of Resection in glioma:

- **5-ALA** (6-month PFS 41% vs. 21%; Stummer et al., 2006)
- **DTI functional neuronavigation** (median survival 21.2 mos vs. 14.0 mos; Wu et al. 2007)
- **intraopertive MRI** (improvement of EOR and PFS; Senft et al., 2011)
- **neurophysiological monitoring** (intraoperative brain mapping) / awake craniotomy
Intraoperative Technologies

VIDEO
Surgical Strategy in TWMU

Information-guided Surgery for Glioma

- higher resection rate + lower complication rate

Intraoperative information

Anatomical Information
- iMRI, updated navigation

updated navigation/
diffusion imaging

image-guided surgery

Priority
- functional > histological
- > anatomical information

Functional Information
- mapping (awake)/monitoring (MEP, SEP)

Histological Information
- histology on frozen sections
Results of Aggressive Resection of Gliomas in TWMU

Rate of radiologically total resection of cerebral gliomas, 45-97% (TWMU, 46%)
Postoperative Radiotherapy
573 patients (18-70 years old) with newly diagnosed, histologically confirmed GBM, who were randomized to either FRT alone (focal irradiation to a total dose of 60 Gy in 30 daily fractions of 2 Gy each given 5 days per week for 6 weeks) or FRT with continuous TMZ (75 mg/ m\(^2\) given daily for 42 days concurrent with irradiation), followed by up to 6 cycles of adjuvant TMZ (150 mg/m\(^2\) for cycle 1 with further escalation to 200 mg/m\(^2\) for 5 days every 28 days; median survival 12.1 vs. 14.6 months.

The 5-year outcome analysis of this study was reported recently and showed improved overall survival rate at 2 years (27.2% vs. 10.9%) and 5 years (9.8% vs. 1.9%) for patients treated with FRT and TMZ in comparison to those who received FRT alone (HR, 0.6; 95% CI: 0.5 - 0.7; P < 0.0001).

The subpopulation of patients with MGMT promoter methylation in their tumors showed the best survival outcomes.
PCV Chemotherapy for Low-grade Gliomas

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402
Gregory Cairncross, Melissa Wang, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Soutelli, Normand Lapierre, Walter Curran, and Miuch Mehta

Radiation plus Procarbazine, CCNU, and Vincristine in Low-Grade Glioma
Jan C. Buckner, M.D., Edward G. Shaw, M.D., Stephanie L. Pugh, Ph.D., Arnab Chakravarti, M.D., Mark R. Gilbert, M.D., Geoffrey R. Barger, M.D., Stephen Coons, M.D., Peter Ricci, M.D., Dennis Bullard, M.D., Paul D. Brown, M.D., Keith Stelzer, M.D., David Brachman, M.D., John H. Suh, M.D., Christopher J. Schultz, M.D., Jean-Paul Bahary, M.D., Barbara J. Fisher, M.D., Harold Kim, M.D., Albert D. Murtha, M.D., Erica H. Bell, Ph.D., Minhee Won, M.A., Minesh P. Mehta, M.D., and Walter J. Curran, Jr., M.D.
Antiangiogenic Therapy for Recurrent GBM
Photodynamic Therapy

Phase II clinical study on intraoperative photodynamic therapy with talaporfin sodium and semiconductor laser in patients with malignant brain tumors

Local Chemotherapy

- Placebo-controlled Phase III trial recurrent malignant gliomas (222 patients from 27 institutions): median survival, 31 weeks vs. 23 weeks (Brem et al., 1995)

- Placebo-controlled Phase III trial newly diagnosed malignant gliomas (240 patients): median survival, 13.9 vs. 11.6 months (Westphal et al., 2003, 2006)

Other methods of local drug delivery: CED, microchips, gels, nanocarriers
Brachytherapy
### Vaccine Therapy

<table>
<thead>
<tr>
<th>Type of vaccine</th>
<th>Antigen / target</th>
<th>Related references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptide vaccines targeting specific tumor-associated antigens</td>
<td>Epidermal Growth Factor Receptor variant III (EGFReIII)</td>
<td>Sampson et al., 2010[17]</td>
</tr>
<tr>
<td></td>
<td>Wilms tumor 1 (WT1) protein</td>
<td>Del Vecchio et al., 2012 [20]</td>
</tr>
<tr>
<td></td>
<td>Ephrin type-A receptor 2 (EphA2)</td>
<td>Schuster et al., 2015 [25]</td>
</tr>
<tr>
<td></td>
<td>Interleukin-13 receptor alpha 2 (IL-13Ra2)</td>
<td></td>
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<tr>
<td></td>
<td>Survivin</td>
<td></td>
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<tr>
<td>Personalized peptide vaccines (PPV)</td>
<td>Screening for appropriate peptide antigens for vaccination and selection optimal candidates in each individual patient based on the pre-existing host immunity.</td>
<td>Yajima et al., 2005 [13]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terasaki et al., 2011 [19]</td>
</tr>
<tr>
<td>Heat Shock Protein (HSP) vaccines</td>
<td>Autologous tumor-derived HSP96-peptides complexes</td>
<td>Bloch et al., 2014 [21]</td>
</tr>
<tr>
<td>Autologous tumor cell vaccines, including AFTV</td>
<td>Autologous (formalin-fixed) whole tumor tissue</td>
<td></td>
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<tr>
<td>AFTV, autologous formalin-fixed tumor vaccine</td>
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</tbody>
</table>
A 42-year-old man suffered from epilepsy, mild aphasia and decline of performance status (KPS score 70). Contrast-enhanced MRI revealed ring-enhanced mass in the left temporal lobe (A). The patient underwent ≥98% lesion resection leaving the residual tumor within subcortical language-related structures (B). Histopathological investigation revealed typical glioblastoma with negative immunostaining for IDH-1 and p53. Postoperative course was uneventful with improvement of performance status (KPS score 90). Upon completion of chemoradiotherapy and before first course of vaccination contrast-enhanced MRI demonstrated heterogeneous enhancement of the wall of the surgical cavity (C), which gradually decreased in size at 7 (D) and 16 months (E), and fully disappeared at 20 months (F) after surgery. This complete response lasted until 35 months after tumor removal. The patient died from disease 49.7 months after initial resection of the neoplasm.
Innovative Modalities

BNCT

LITT

Cryodestruction

HIFU

TTF
Edited by M.F. Chernov, Y. Muragaki, S. Kesari, and I.E. McCutcheon.

In total 44 chapters.

International contributors from North America (25 chapters), Japan (10 chapters), West Europe (8 chapters), Russia (1 chapter).

Scheduled publication due: 1st 2018

Very reasonable pre-publication price.
How to Treat Such Patients?

Jugular foramen meningioma

Cerebellar AVM

Multiple metastases
RADIOSURGERY!!!

Gamma Knife

Linear Accelerator

Proton Beam

Cyber Knife
History of Gamma Knife

- **1951** – first X-ray radiosurgical procedure for trigeminal neuralgia
- **1968** – development of Gamma Knife prototype for management of tumors and vascular malformations (use of 196 sources of Co$^{60}$)
- **May 1990** – first Gamma Knife is installed in Japan (professor Kintomo Takakura; University of Tokyo)
- **April 2005** – first Gamma Knife is installed in Russia (Burdenko Neurosurgical Institute; Moscow)
- **April 2010** – installation of the 55th Gamma Knife Unit in Japan

Lars Leksell
(1907 – 1986)
Evolution of Gamma Knife

1968
The first prototype of Leksell Gamma Knife was installed in Karolinska University, Stockholm, Sweden

2006
The latest Leksell Gamma Knife model (“Perfexion”) was installed in La Timone Hospital, Marseille, France
Stereotactic Localization of the Target
Frame Fixation

VIDEO
Treatment Planning
Conformal and Selective Treatment

Scheme of treatment plan for Koos grade III vestibular schwannoma based on the concept of “robotic microradiosurgery”
Radiosurgical Treatment

VIDEO
Vestibular Schwannoma

At the time of treatment

36 months after Gamma Knife radiosurgery
Cavernous Sinus Meningioma

Marginal dose, 12 Gy

Resolution of symptoms within 4 months

Tumor shrinkage at 3 years, asymptomatic
Craniopharyngioma
Cavernous Sinus Hemangioma

18-22 Gy in 3-4 fractions

No major complications

from Wang et al. ; J Neurosurg (in press)
Malignant Lymphoma

Before treatment

6 months after GKS (marginal dose 10 Gy)

16 months after GKS

Novosibirsk 2017

Courtesy of Dr. Pavel Ivanov
Recurrent Glioblastoma

- Recurrent GBM: survival after salvage SRS, 5.3 – 17.9 months; adverse radiation effects, 0-31%; favorable prognostic factors: tumor volume < 14 cc; marginal dose ≥15 Gy; recurrent (vs. residual tumor). Problem: target localization.

- Novel approach: SRS + BVZ

- Pilocytic astrocytomas, 10-year survival 97.4%; oligodendrogliomas, 5-year survival, 81.5%; WHO grade II astrocytomas, 10-year survival, 65%; prognostic factors: size, cysts.
Conclusion

Management of intracranial tumors should be preferably performed in specialized Brain Tumor Centers, where availability of various diagnostic and therapeutic options and multidisciplinary team of doctors would permit selection of the most appropriate treatment strategy for each individual patient.
Meshalkin Institute of Circulation Pathology

ISRS

Educational Course
December 7-8, 2017; Novosibirsk, Russia