Seminar in the Institute of Cytology and Genetics

December 6, 2017; Novosibirsk, Russia

Diagnosis and Treatment of Intracranial Tumors: Overview

Mikhail Chernov, M.D., D.Med.Sci.

Faculty of Advanced Techno-Surgery

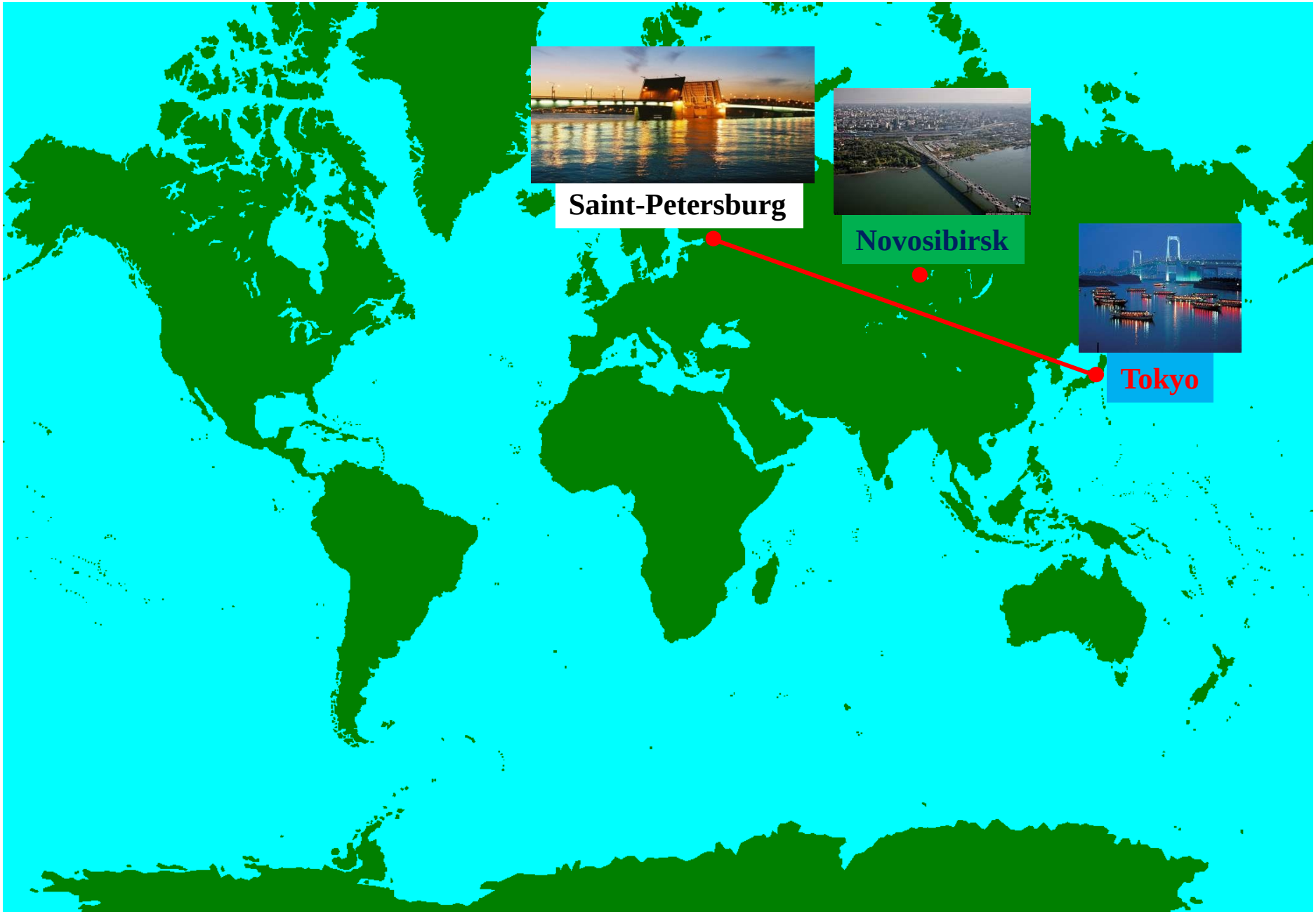
Tokyo Women`s Medical University, Tokyo, Japan

FATS Faculty of Advanced Techno-Surgery TWMU

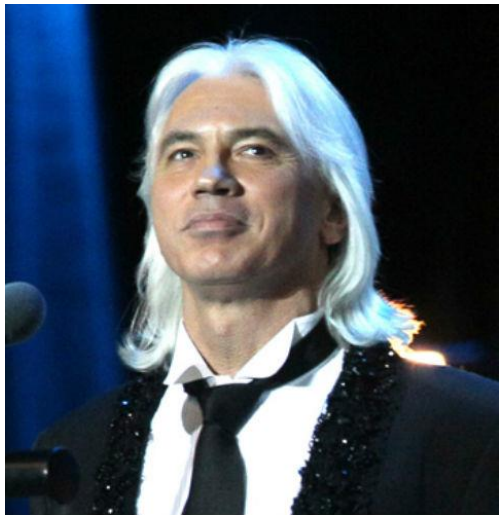
TOKYO WOMEN'S MEDICAL UNIVERSITY TWMU FOUNDED IN 1900

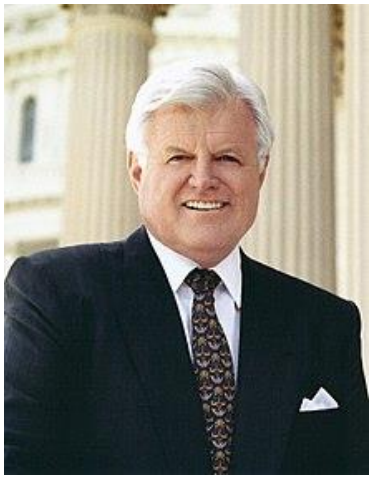
Mikhail Felixovich Chernov

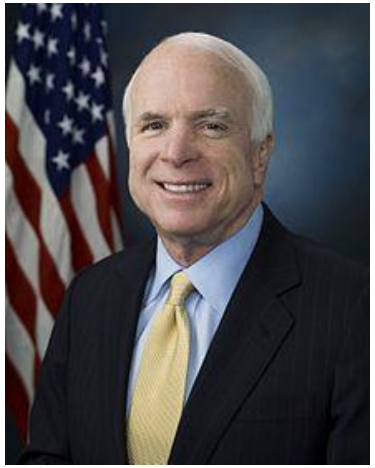
- **Medical Education** Faculty of Medicine, First Leningrad Medical Institute (State Medical Academy) named after I. P. Pavlov, Leningrad, 1983 – 1989
- **Neurosurgical Training** (Internship, Clinical Ordinatura, Aspirantura) Leningrad Regional Clinical Hospital, Medical Academy for Postgraduate Medical Education, Russian A.L. Polenov Neurosurgical Institute, Saint Petersburg, 1989 – 1995
- **Candidate of Medical Sciences** Russian A.L. Polenov Neurosurgical Institute, Saint Petersburg, September 1995
- **Neurosurgeon and Senior Research Assistant in Neurosurgery** Department of Surgical Neuro-Oncology, Russian A.L. Polenov Neurosurgical Institute, Saint Petersburg, 1995 – 2000
- **Visiting Fellow** (1) Gough-Cooper Department of Neurological Surgery, National Hospital for Neurology and Neurosurgery, Queen Square, London, UK, October 1996 – March 1997; (2) Department of Neurosurgery, MD Anderson Cancer Center, Houston, TX, U.S.A., March 2000 – August 2000
- **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)


Saint-Petersburg
Novosibirsk
Tokyo

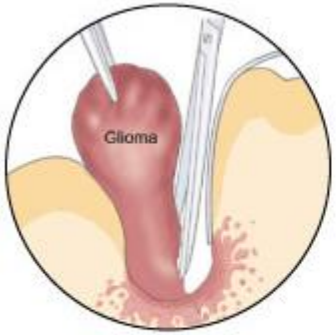
What is Common in These Celebrities?





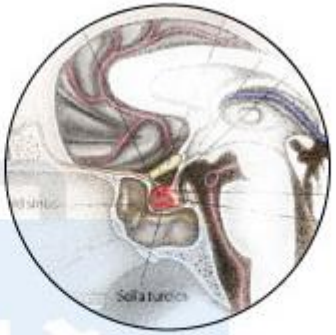


Brain Tumors

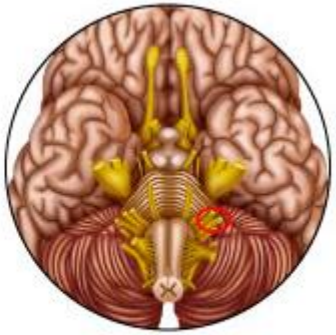


Gliomas
Tumor

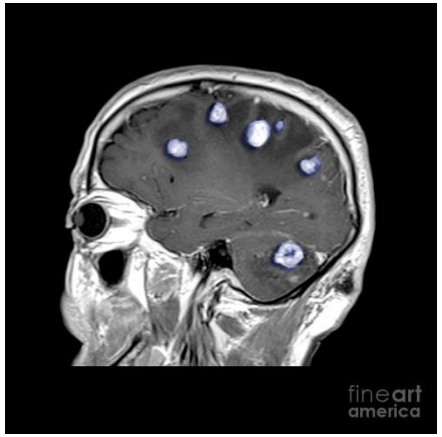
Meningioma
Tumors



Pituitary
Adenomas



Schwannomas
(Acoustic Neuromas)



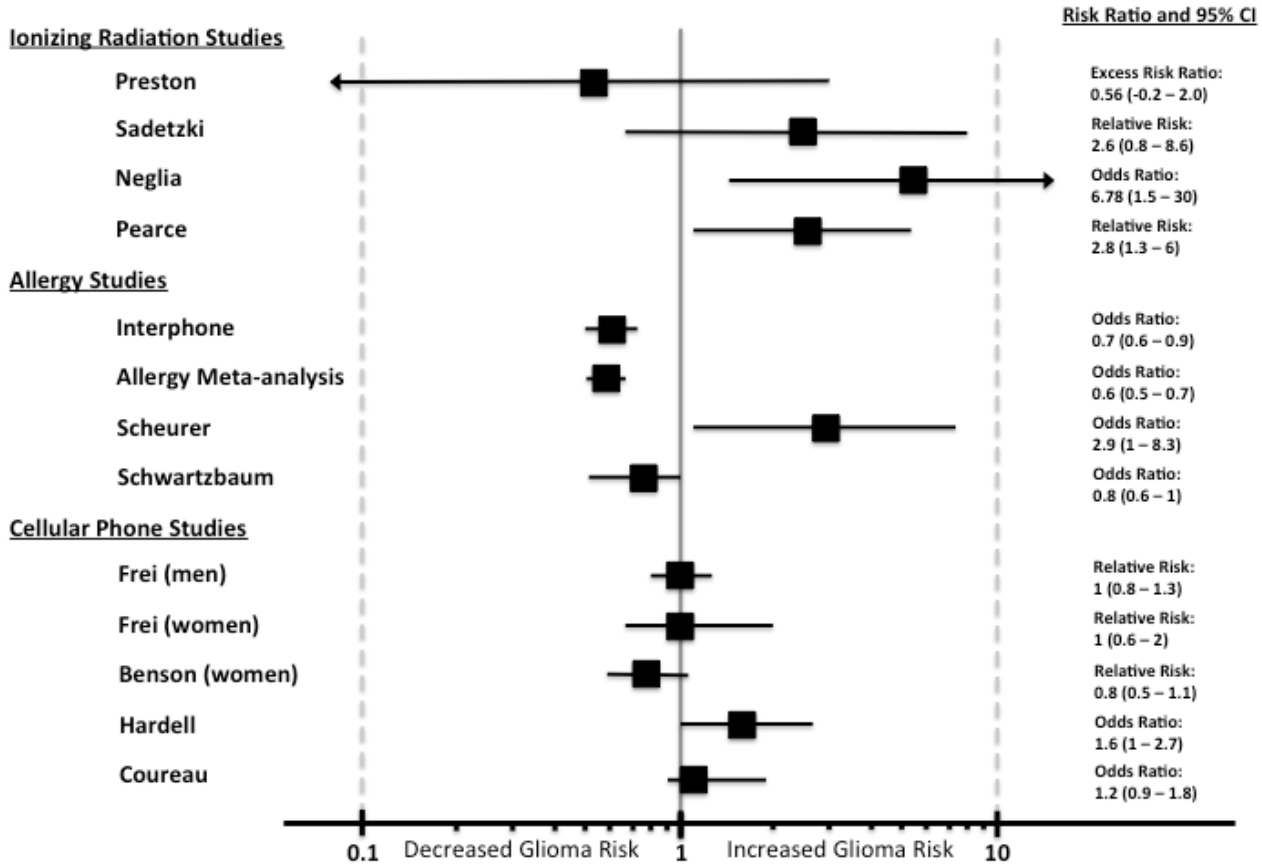
Gliomas: Incidence

- 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



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*
- Tanycitic ependymoma*

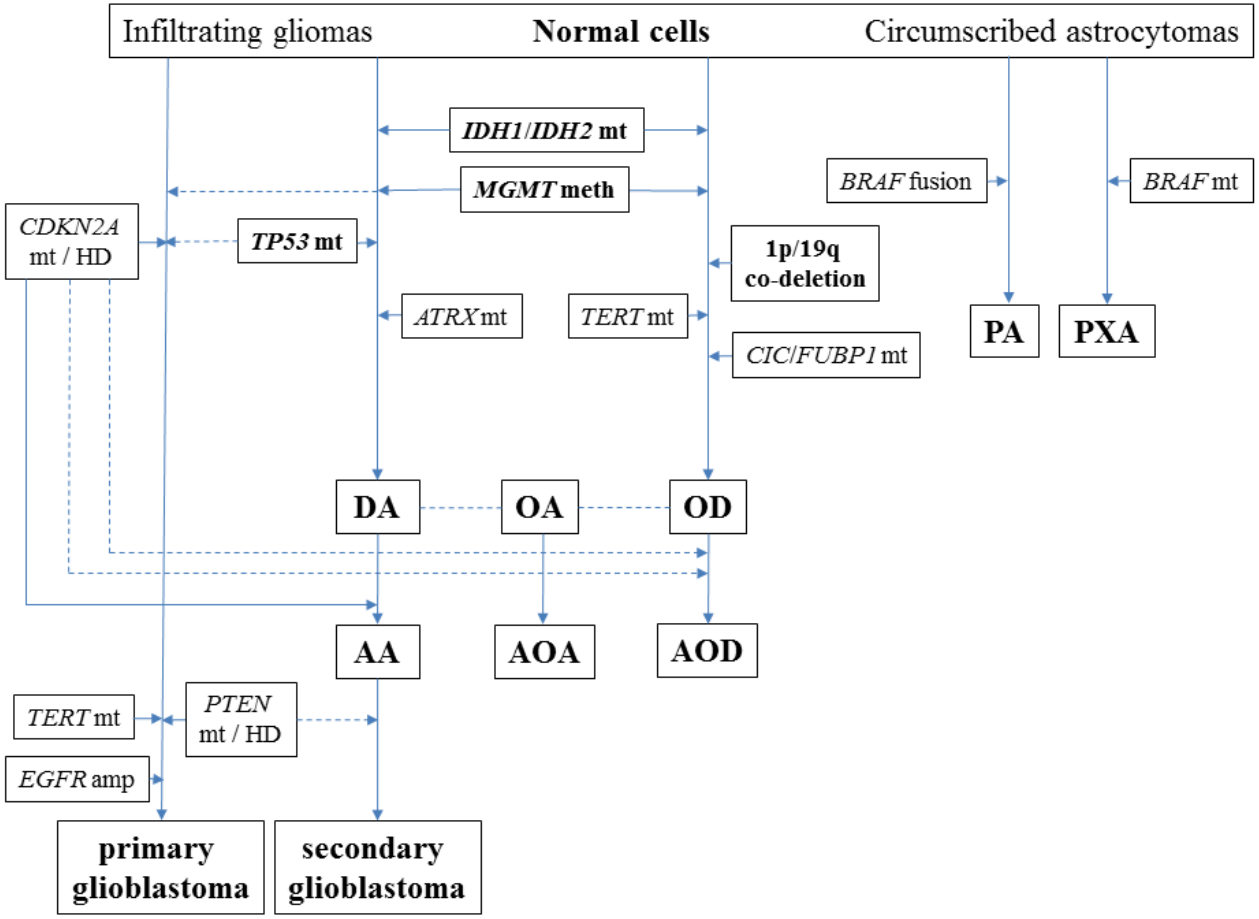
Ependymoma, RELA fusion-positive
Anaplastic ependymoma

Other gliomas

Chordoid glioma of the third ventricle
Angiocentric glioma
Astroblastoma

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

Gliomagenesis

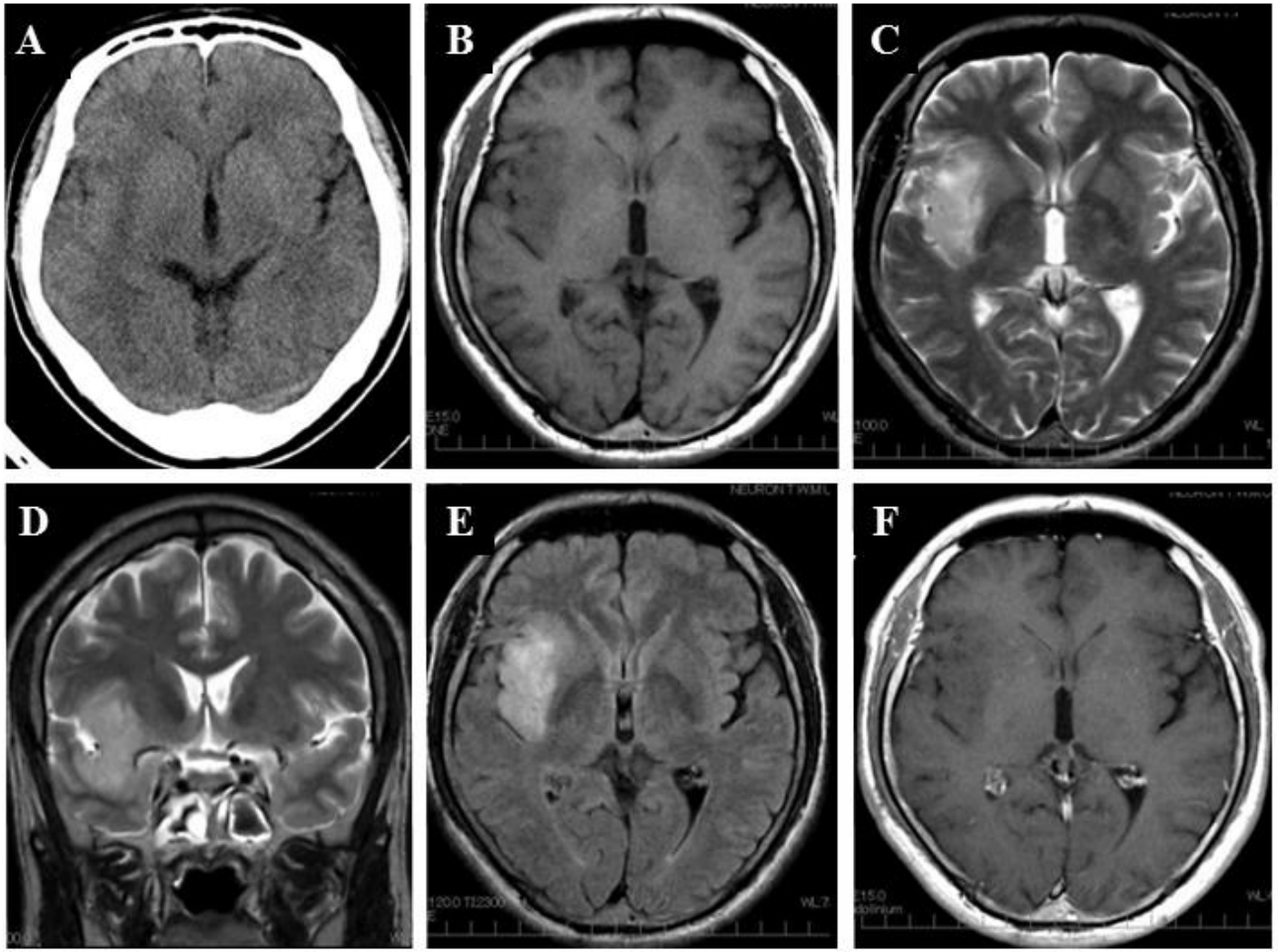


Molecular Markers

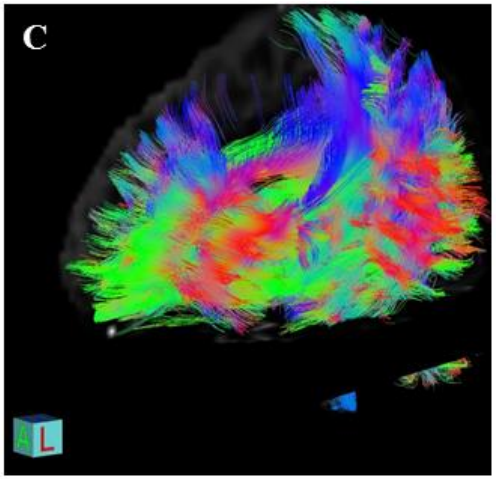
- O6-methylguanine-DNA-methyltranferase (**MGMT**) - endogenous DNA repair protein, which removes alkyl groups produced on DNA by alkylating agents.
- **1p/19q** co-deletion – molecular signature of oligodendrogliomas.
- isocitrate dehydrogenase genes 1 and 2 (**IDH-1/IDH-2**) mutation - almost exclusively associated with the glial phonotype

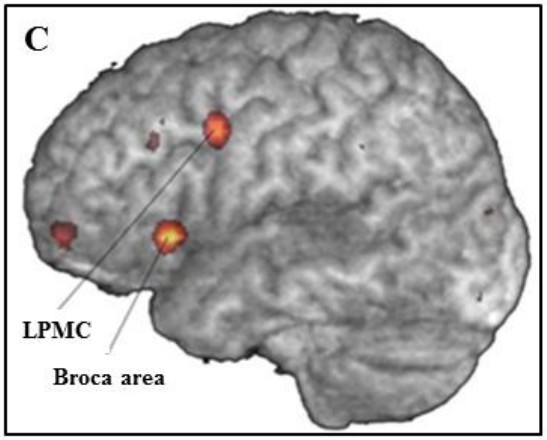
Molecular Marker	Histopathological Tumor Grade		
	Low-grade Gliomas (WHO Grade II)	Anaplastic Gliomas (WHO Grade III)	Glioblastomas (WHO Grade IV)
MGMT Promoter Methylation	Uncertain prognostic/predictive value	Probable favorable prognostic/predictive value	Predictive for response to chemotherapy with alkylating agents
1p/19q Co-deletion	Favorable prognostic value	Favorable prognostic value; predictive for response to PCV chemotherapy	None
IDH-1 or IDH-2 Mutation	Favorable prognostic value	Favorable prognostic value	Favorable prognostic value

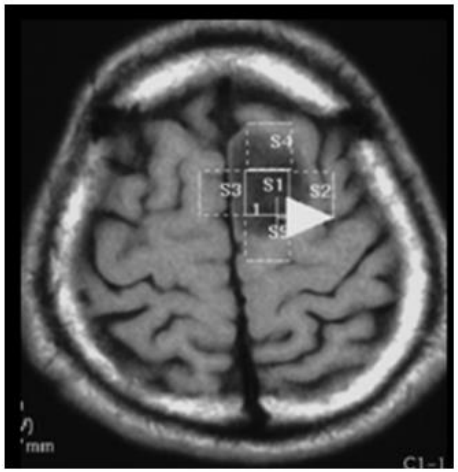
Structural MRI

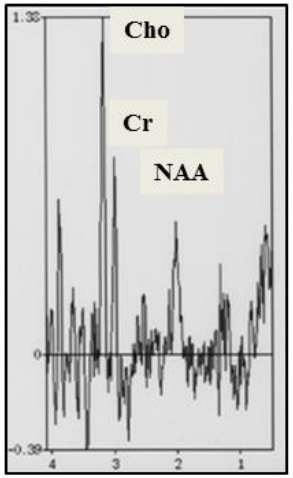


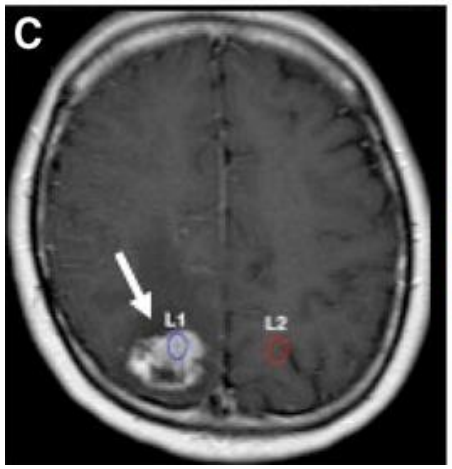
Advanced MRI

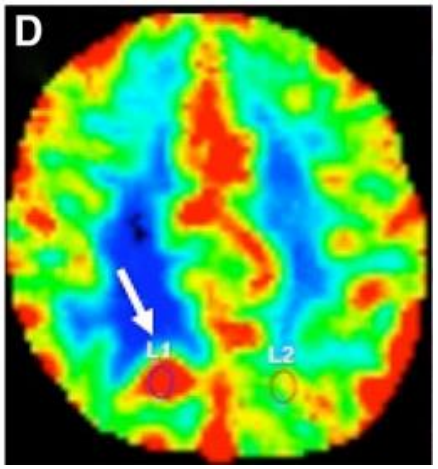




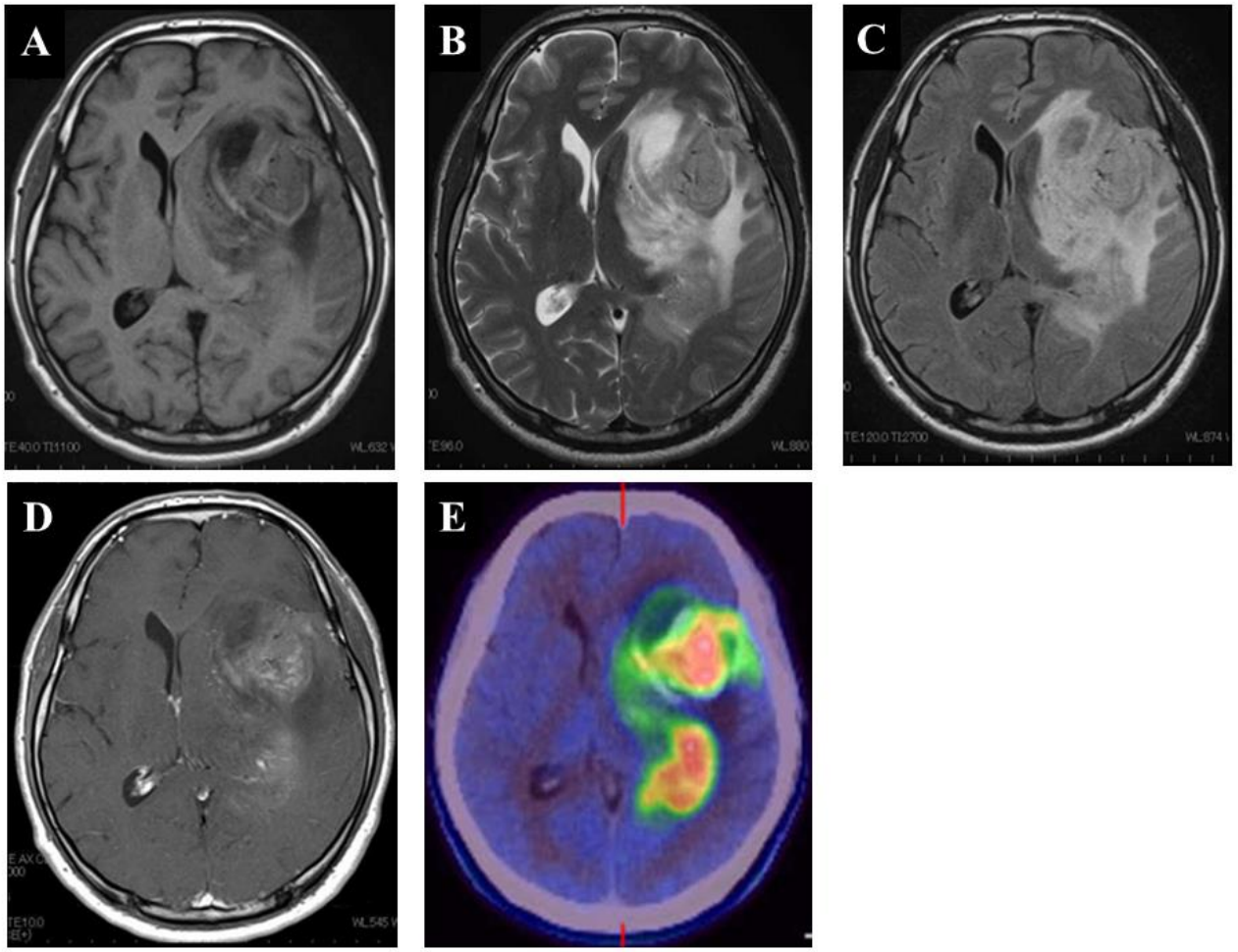








Positron Emission Tomography



Summary of Prognostic Factors

Patient-related:

- Age
- Performance status / Mental status / Neurological function
- Duration of symptoms

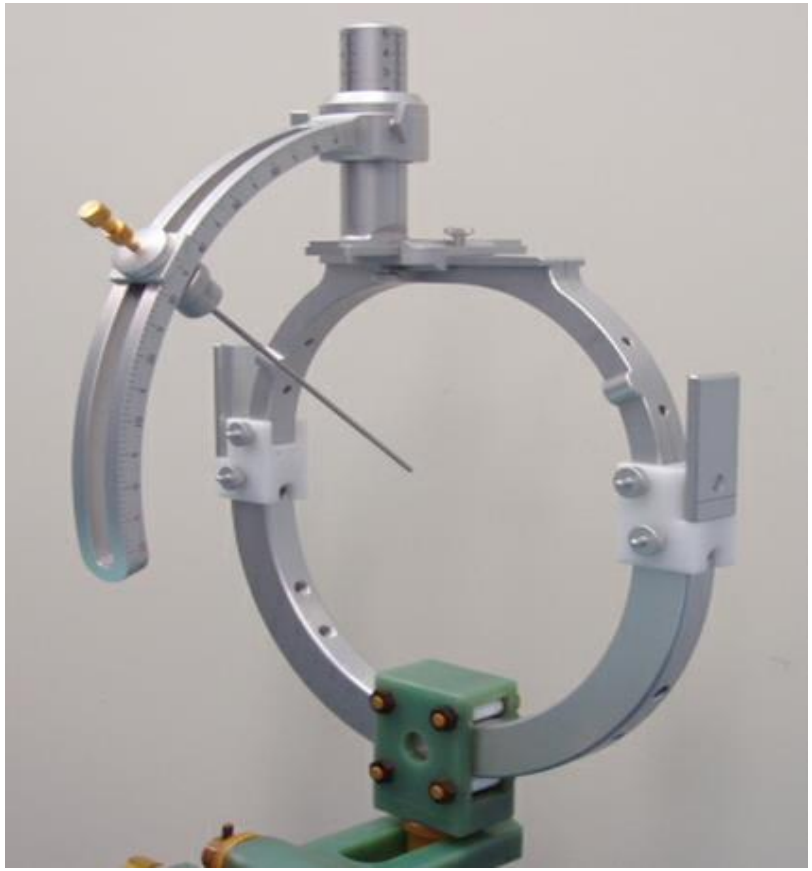
Tumor-related:

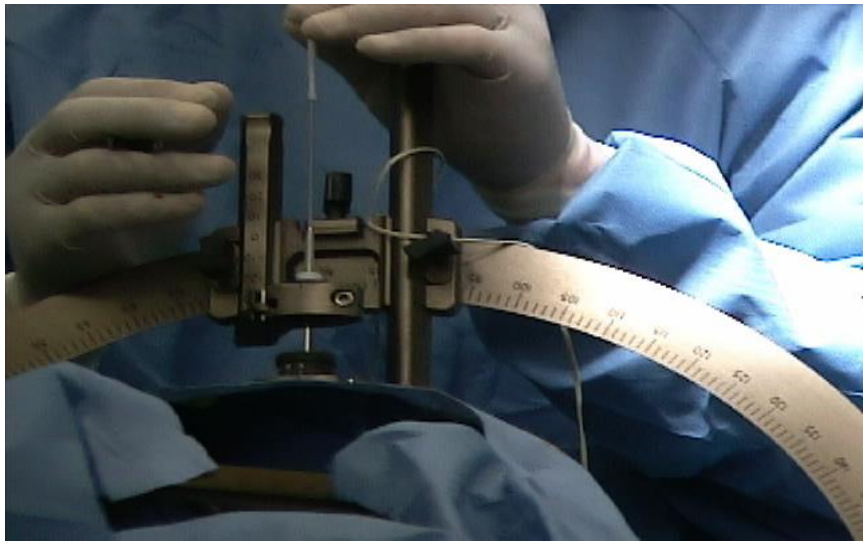
- Imaging characteristics (size, location, enhancement, edema, crossing midline, necroses, metabolic parameters, multiplicity)
- Grade / Type
- Molecular and genetic markers

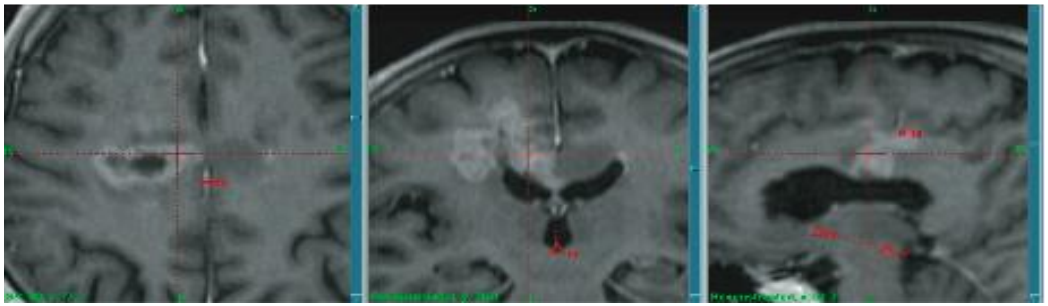
Treatment-related:

- Need of steroid therapy at baseline
- **Aggressive surgery** (EOR, Residual volume) / Advanced surgical adjuncts
- Standard adjuvant therapy

Stereotactic Biopsy







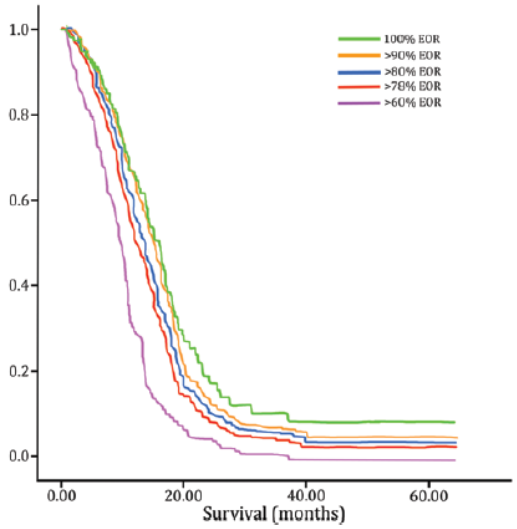
Aggressive Surgery for Glioblastoma

An extent of resection threshold for newly diagnosed glioblastomas

J Neurosurg 115:3–8, 2011

Clinical article

Nader Sanai, M.D.,[1] Mei-Yin Polley, Ph.D.,[2] Michael W. McDermott, M.D.,[1] Andrew T. Parsa, M.D., Ph.D.,[1] and Mitchel S. Berger, M.D.[1]



- 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

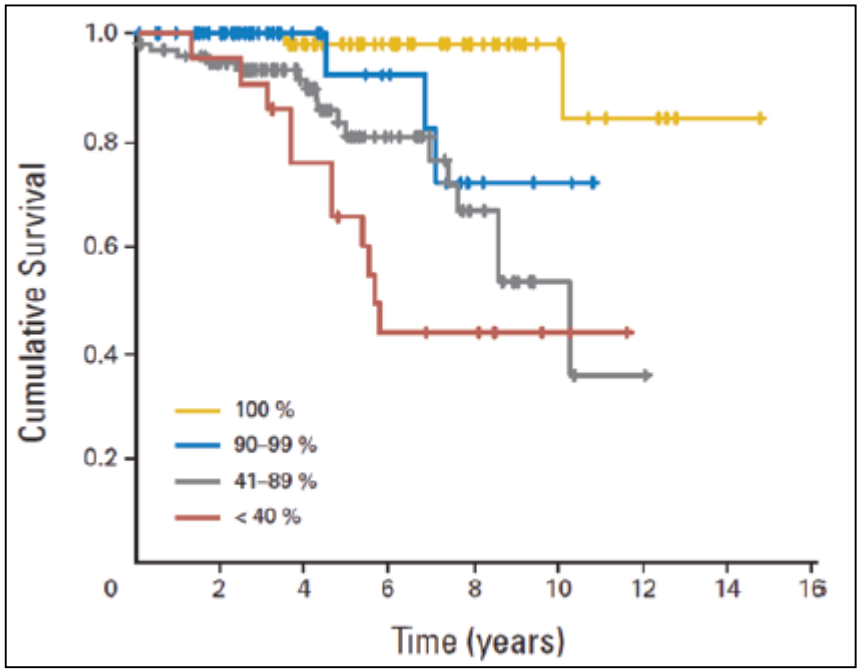
Low-grade gliomas in adults

A review

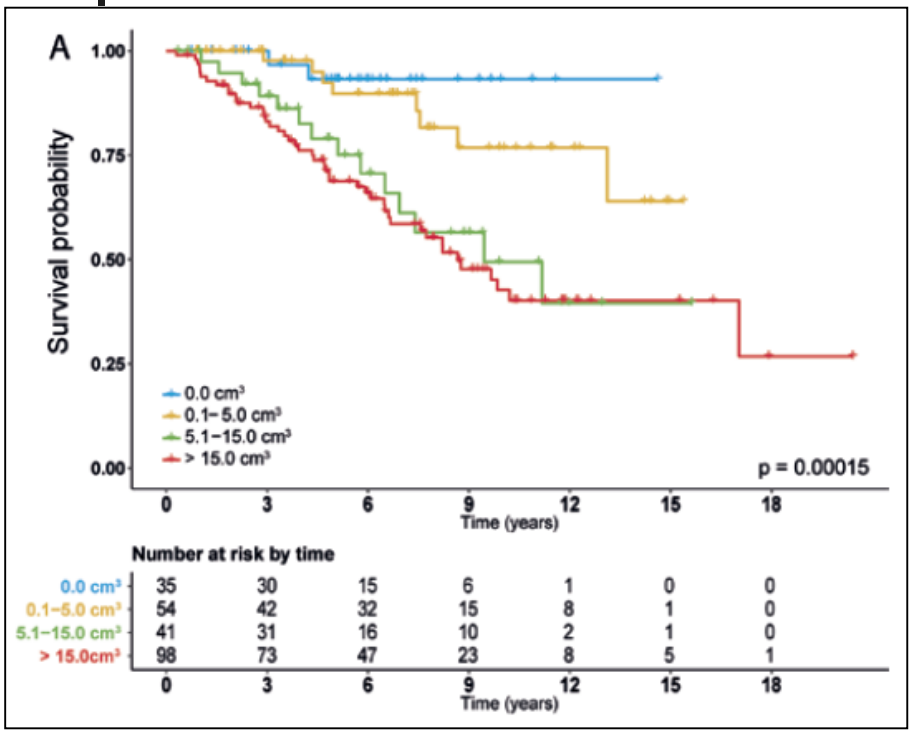
J Neurosurg 115:948–965, 2011

NADER SANAI, M.D.,[1] SUSAN CHANG, M.D.,[2] AND MITCHEL S. BERGER, M.D.[2]

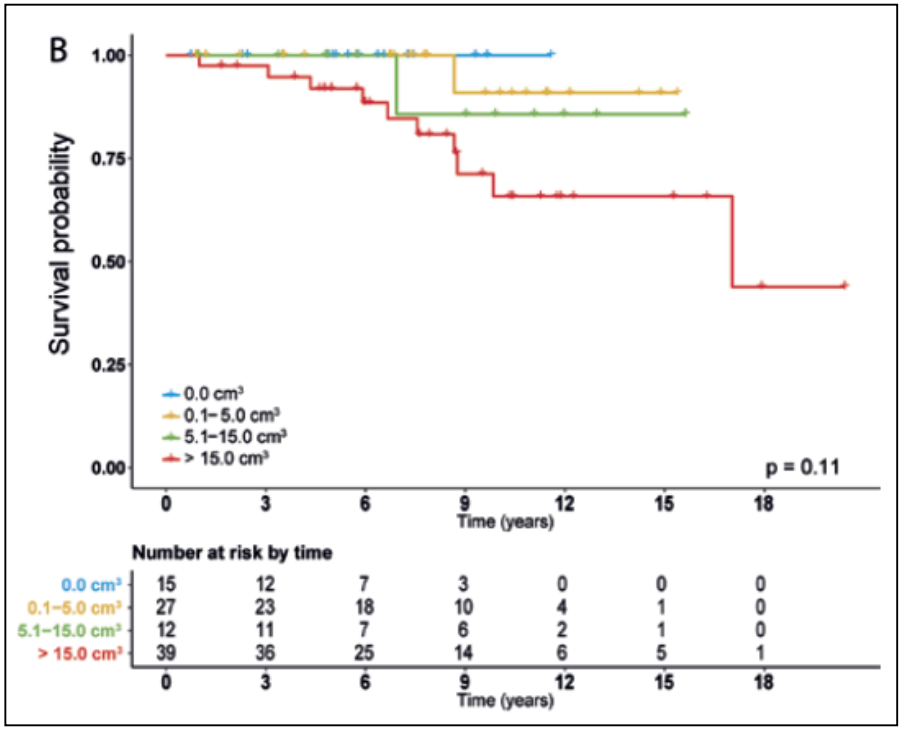
Authors & Year	No. of Pts	EOR Methodology	PFS Benefit	OS Benefit
Whitton & Bloom, 1990	88	nonvolumetric	NA	no
North et al., 1990	77	nonvolumetric	NA	yes
Philippon et al., 1993	179	nonvolumetric	NA	yes
Rajan et al., 1994	82	nonvolumetric	NA	yes
Leighton et al., 1997	167	nonvolumetric	NA	yes
van Veelen et al., 1998	75	volumetric	NA	yes
Bauman et al., 1999	401	nonvolumetric	NA	no
Nakamura et al., 2000	88	nonvolumetric	NA	yes
Johannesen et al., 2003	993	nonvolumetric	NA	no
Yeh et al., 2005	93	nonvolumetric	yes	yes
Claus et al., 2005	156	volumetric	yes	yes
Smith et al., 2008	216	volumetric	yes	yes
McGirt et al., 2008	170	nonvolumetric	yes	yes
Sanai et al., 2010	104	volumetric	yes	yes
Rezvan et al., 2009	130	nonvolumetric	yes	yes
Chaichana et al., 2010	191	nonvolumetric	yes	yes



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**

Grade	Functional Location
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

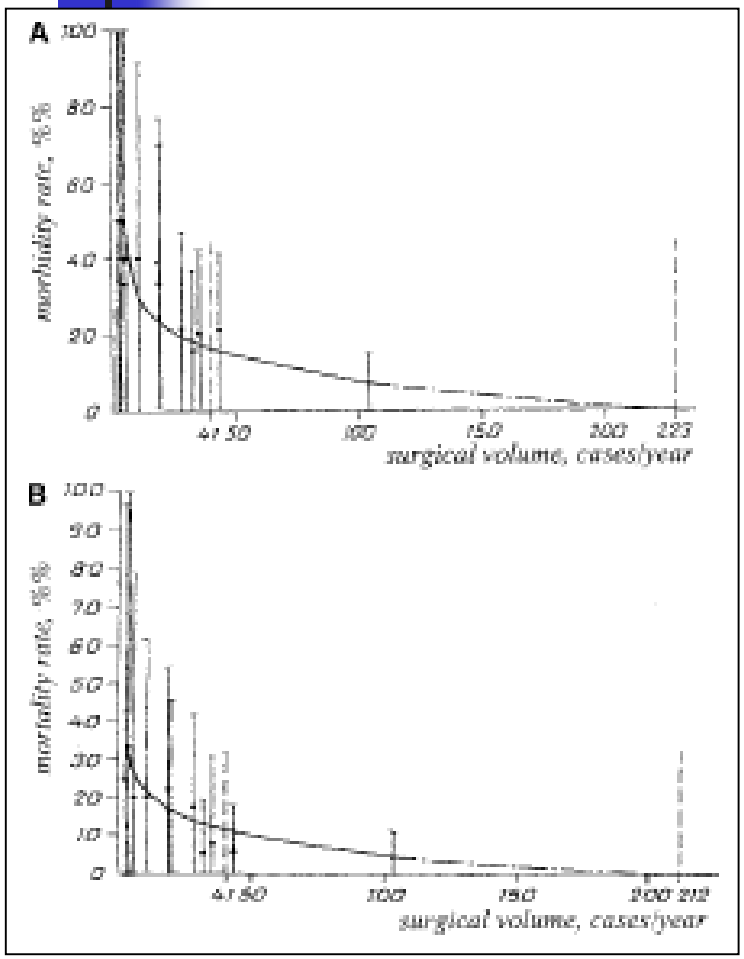
Computers

Intraoperative MRI

Neuronavigation System

Robotics

Treatment in Specialized Centers



Neurosurgery 54: 1027-1028, 2004

Donlin M. Long, M.D., Ph.D.
Department of Neurosurgery, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Outcome and Cost of Craniotomy Performed to Treat Tumors in Regional Academic Referral Centers

TABLE 1. Hospital group classification and characteristics of patients undergoing craniotomy for tumor

Volume (cases/yr)	Hospital volume group	No. of hospitals	Total cases	Average cases/hospital/yr
≤50	Low	31	1933	8.9 (40.9%)
>50	High	2	2790	199.3 (59.1%)
Total		33	4723	20.4 (100.0%)

Mortality	Statewide	Hospital volume group	
		High	Low
Benign			
Unadjusted (%)	2.1%	1.3%	3.7%
Unadjusted relative risk	NA	1.0	2.9[b]
Adjusted relative risk[c]	NA	1.0	1.9[d]
Primary malignant			
Unadjusted	4.1%	3.7%	4.7%
Unadjusted relative risk	NA	1.0	1.3[d]
Adjusted relative risk[c]	NA	1.0	1.0[d]
Secondary malignant			
Unadjusted	4.9%	3.0%	6.5%
Unadjusted relative risk	NA	1.0	2.2[e]
Adjusted relative risk[c]	NA	1.0	2.1[e]

Neurosurgery 52: 1056-1065, 2003

Intraoperative Technologies

Intraoperative assistive technologies and extent of resection in glioma surgery: a systematic review of prospective controlled studies

Neurosurg Rev (2015) 38:217–227

Breno José Alencar Pires Barbosa · Eric Domingos Mariano · Chary Marquez Batista · Suely Kazue Nagahashi Marie · Manoel Jacobsen Teixeira · Carlos Umberto Pereira · Marcos Soares Tatagiba · Guilherme Alves Lepski

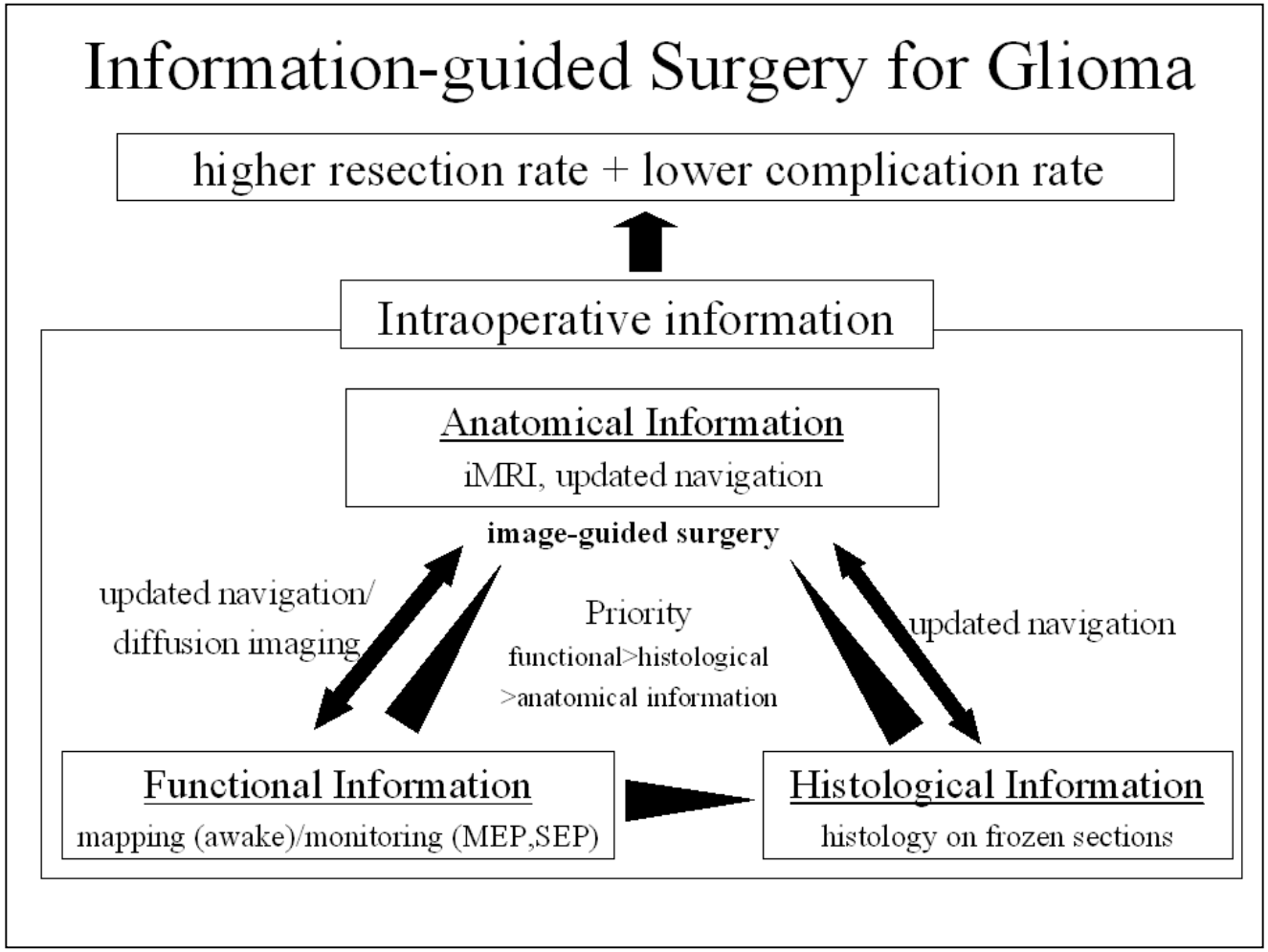
The best tools for improving Extent of Resection in glioma:

- 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

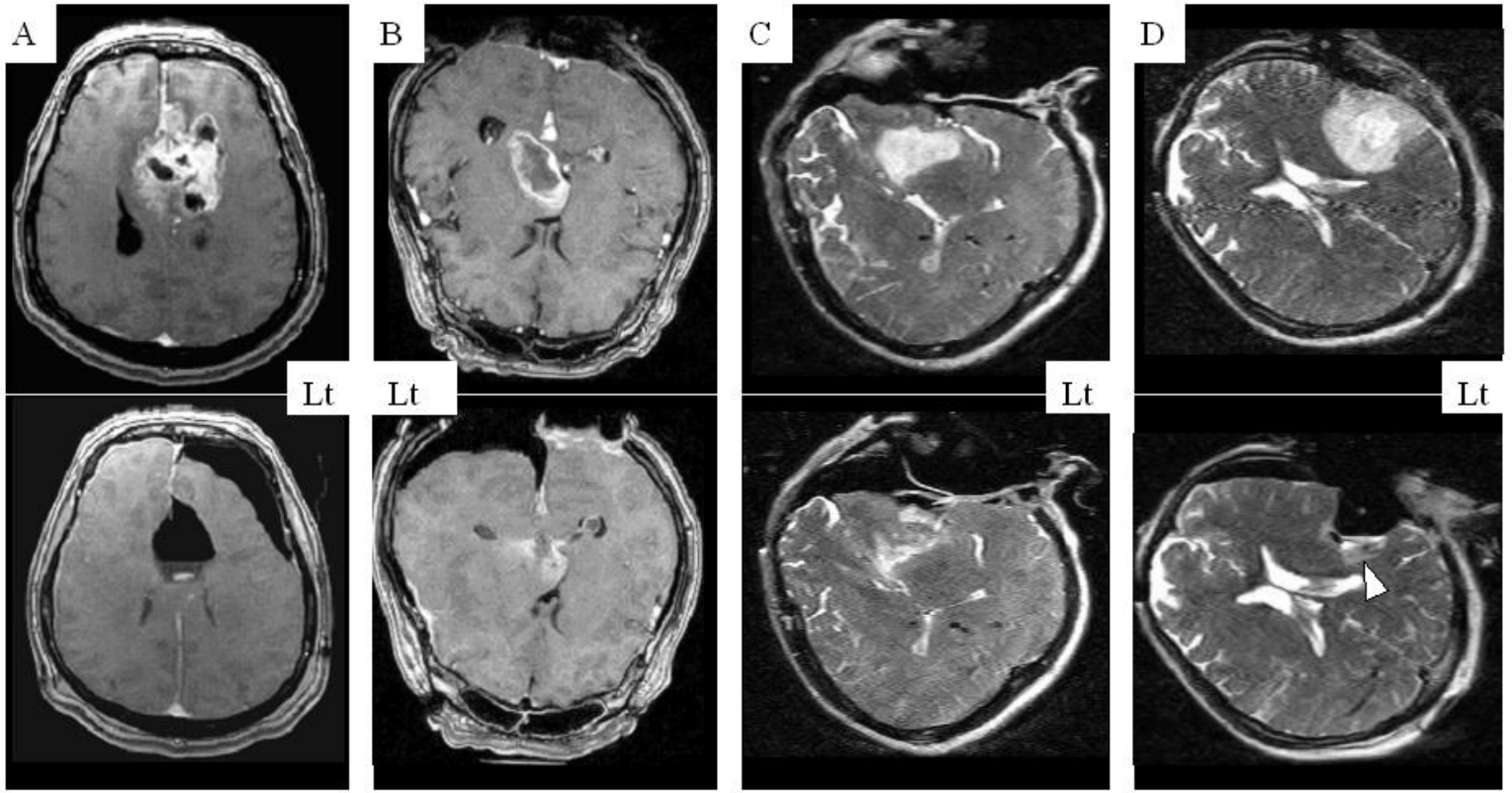
Intraoperative Technologies

VIDEO

Surgical Strategy in TWMU

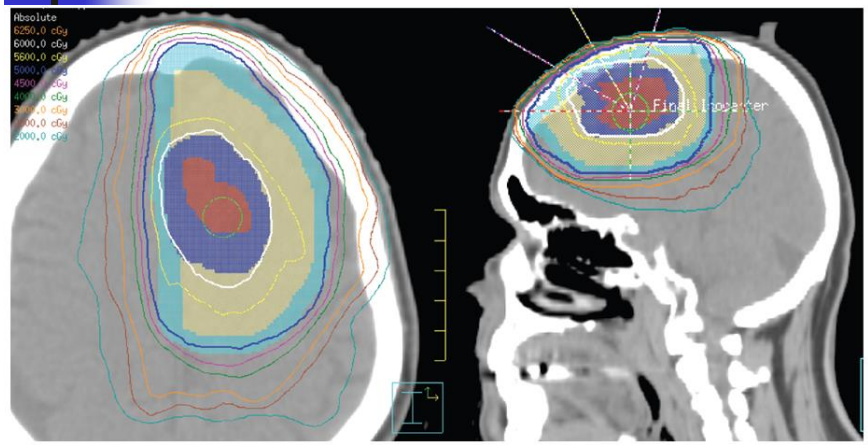


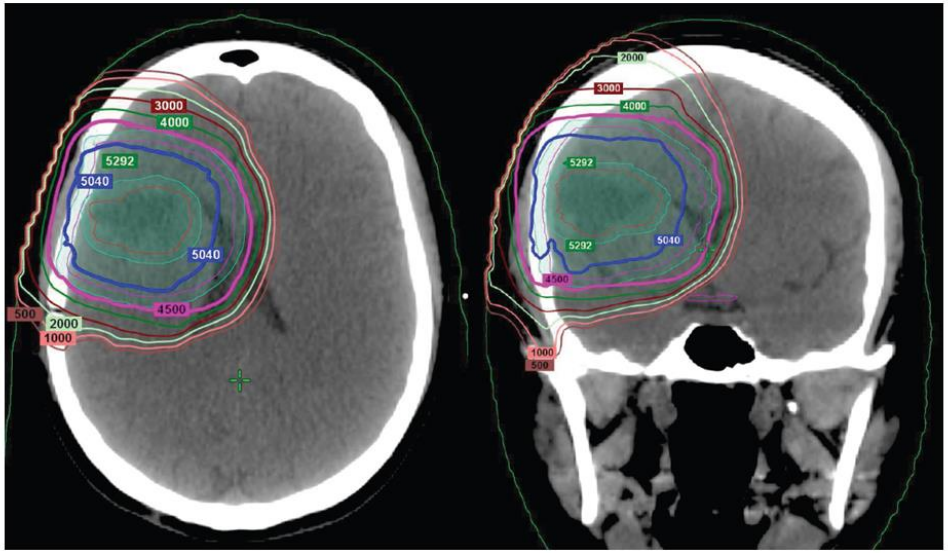
Results of Aggressive Resection of Gliomas in TWMU



Rate of radiologically total resection of cerebral gliomas, 45-97% (TWMU, 46%)

Postoperative Radiotherapy



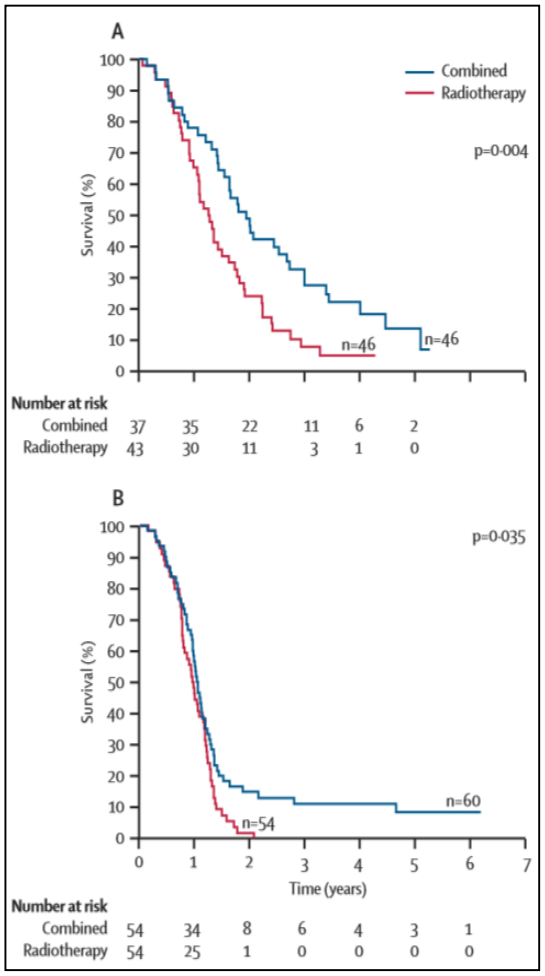


"Stupp Protocol" for Newly Diagnosed GBM

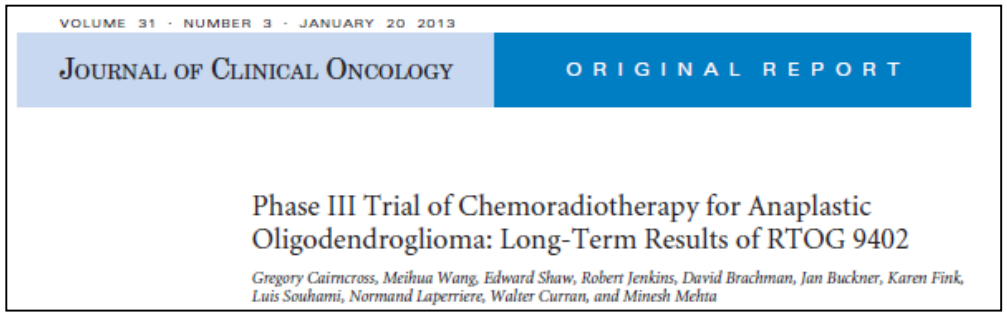
- 573 patients (18-70 years old) with newly diagnosed, histologically confirmed GBM, who were randomized to either FRT alone (focal irradiation to a total dose of 60 Gy in 30 daily fractions of 2 Gy each given 5 days per week for 6 weeks) or FRT with continuous TMZ (75 mg/ m^2 given daily for 42 days 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



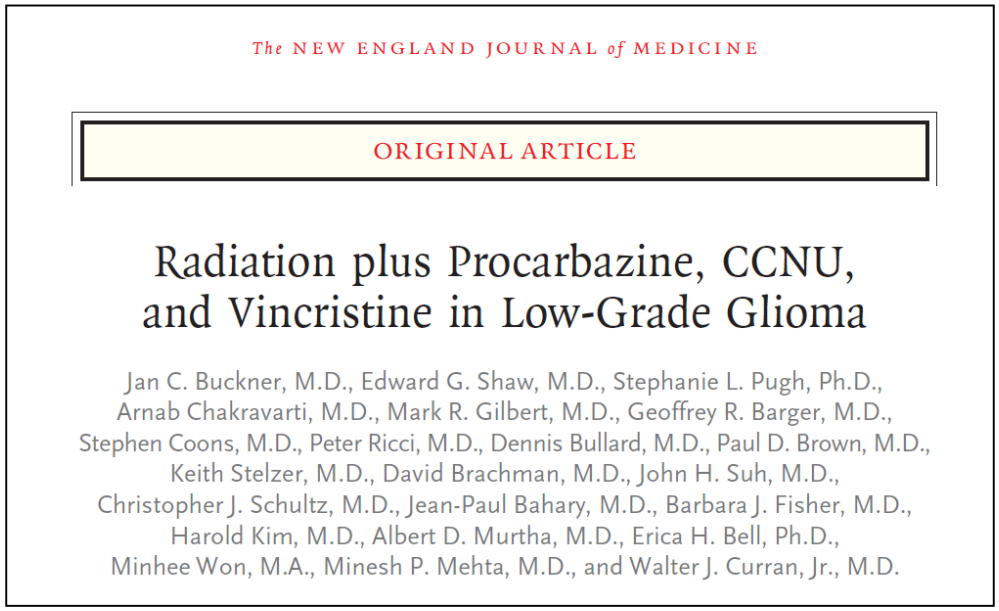
VOLUME 31 · NUMBER 3 · JANUARY 20 2013

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Phase III Trial of Chemoradiotherapy for Anaplastic Oligodendroglioma: Long-Term Results of RTOG 9402

Gregory Cairncross, Meihua Wang, Edward Shaw, Robert Jenkins, David Brachman, Jan Buckner, Karen Fink, Luis Souhami, Normand Laperriere, Walter Curran, and Minesh Mehta



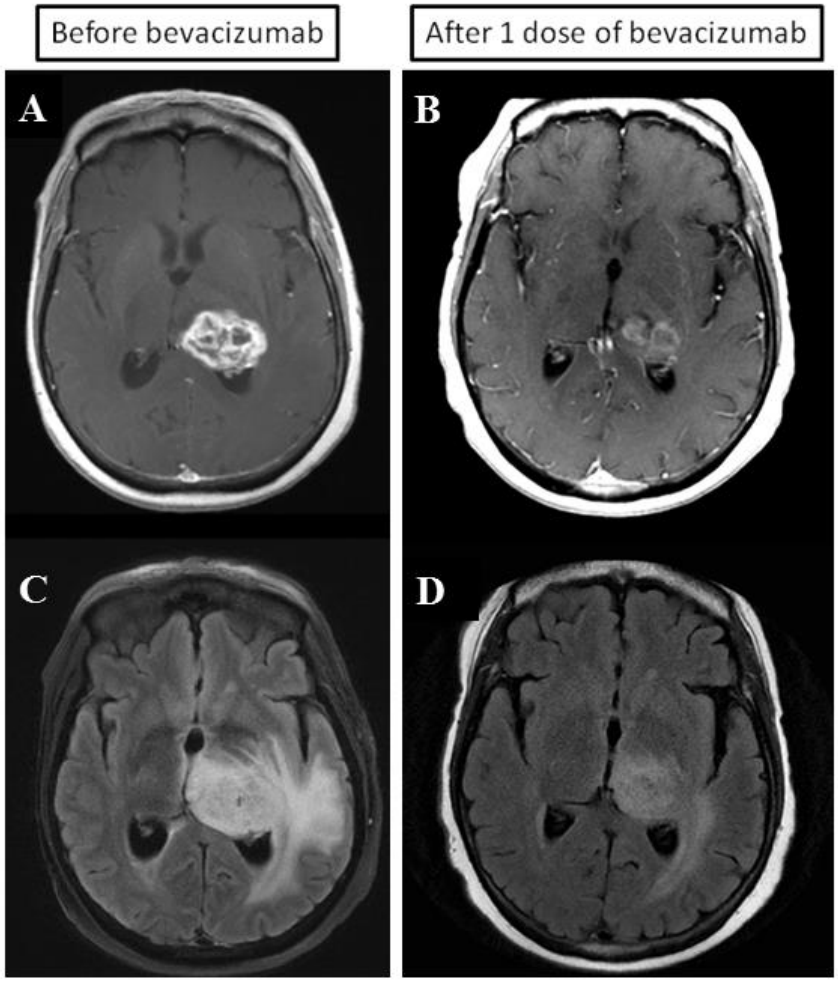
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

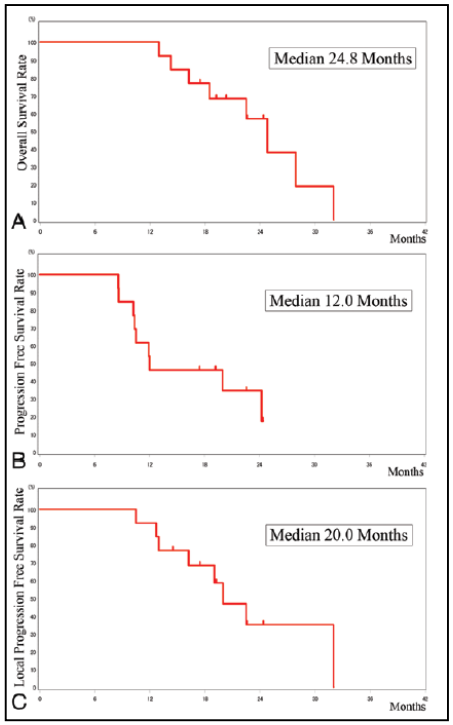


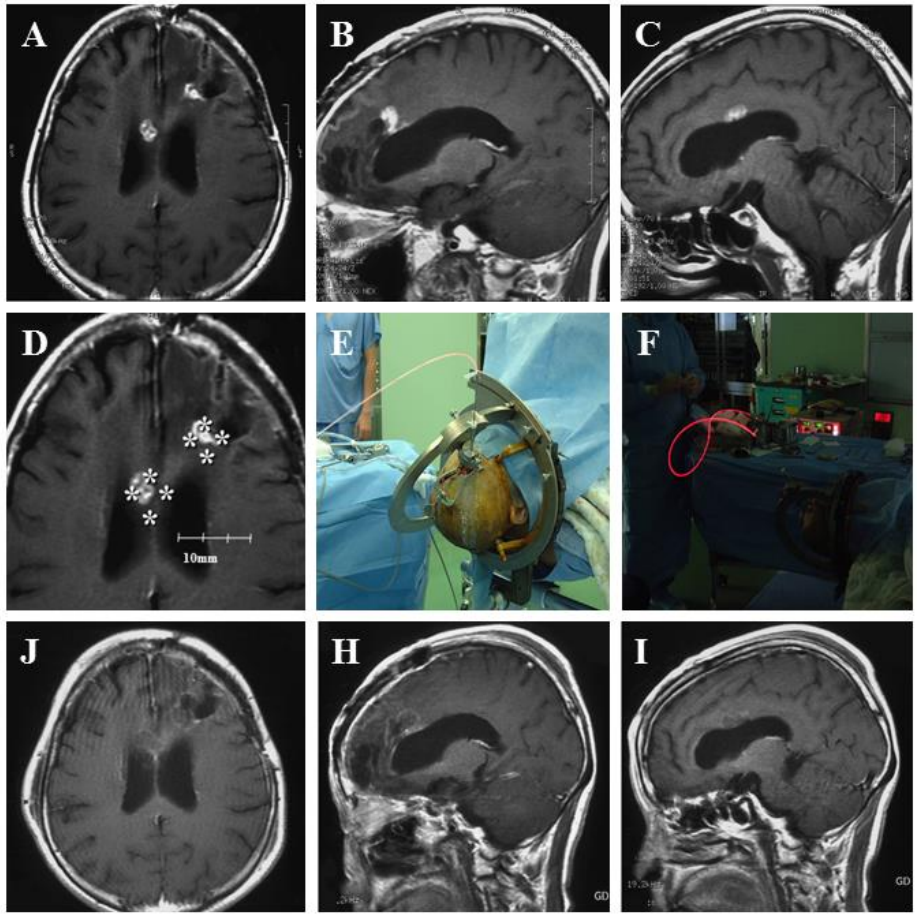
Photodynamic Therapy

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

Clinical article

J Neurosurg 119: 845-852, 2013

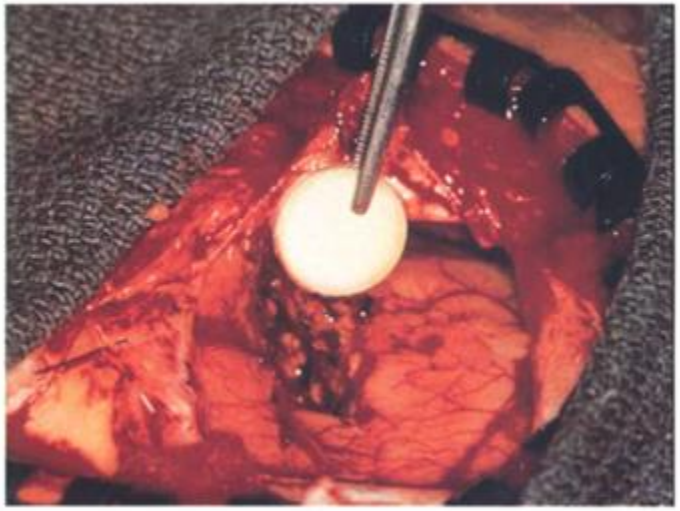


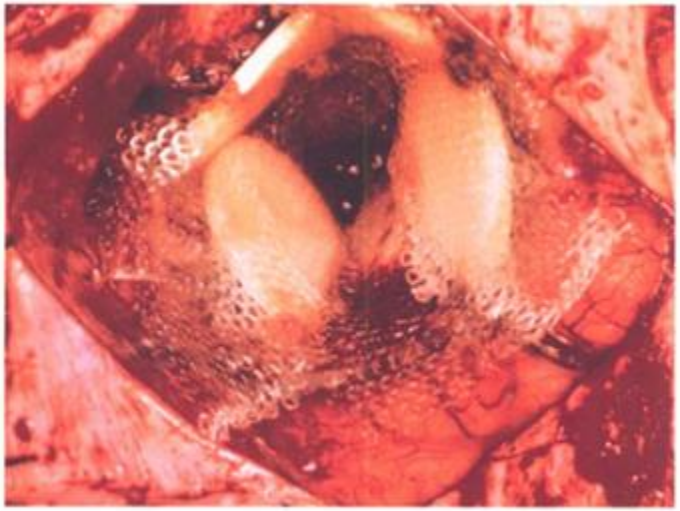


Local Chemotherapy

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

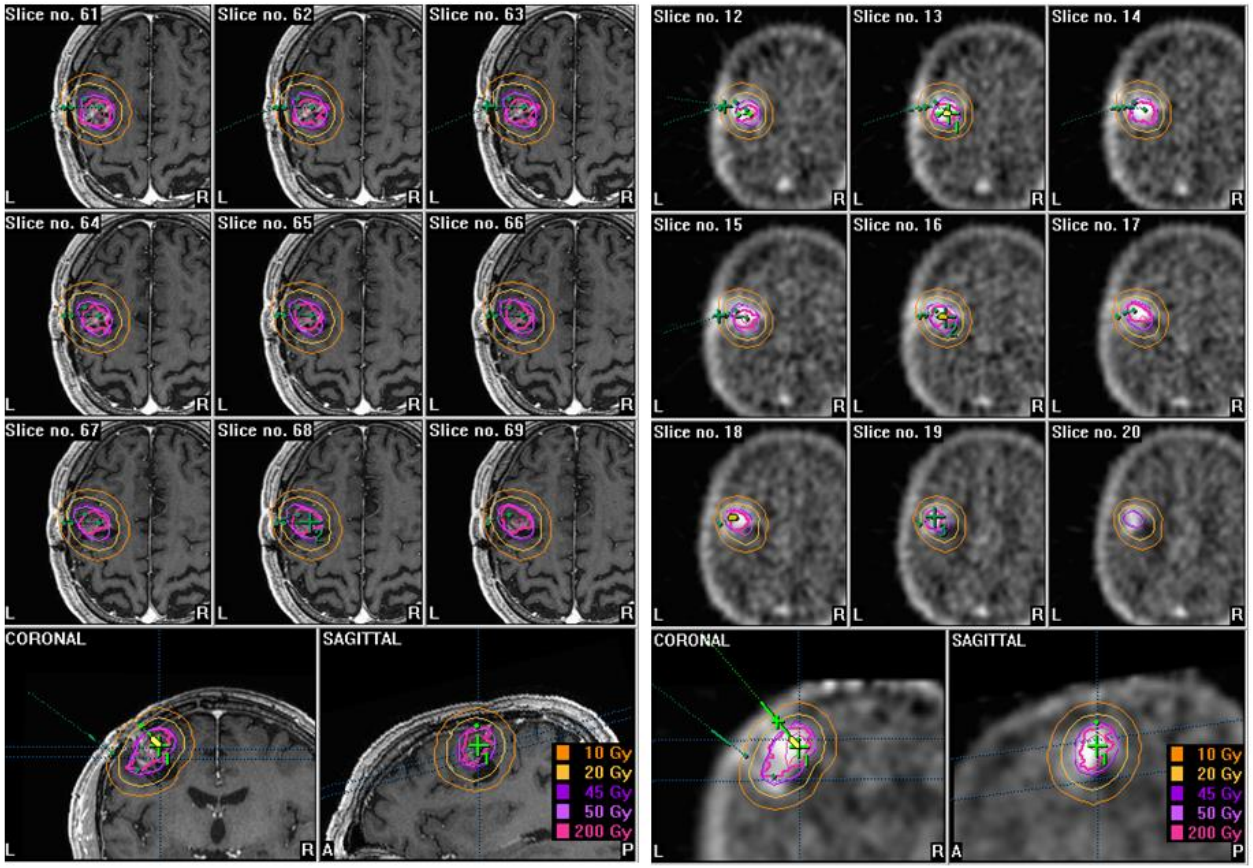
- Placebo-controlled Phase III trial newly diagnosed malignant gliomas (240 patients): median survival, 13.9 vs. 11.6 months (Westphal et al., 2003, 2006)





Other methods of local drug delivery: CED, microchips, gels, nanocarriers

Brachytherapy

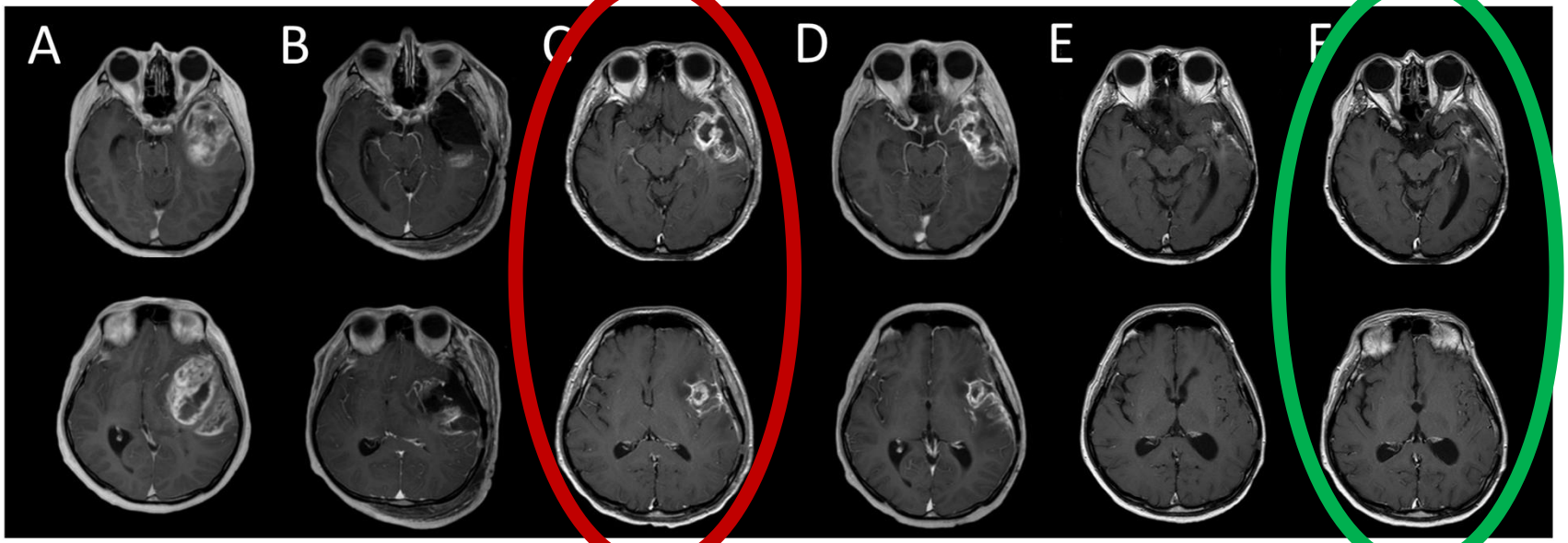


Vaccine Therapy

Type of vaccine	Antigen / target	Related references
Peptide vaccines targeting specific tumor-associated antigens	Epidermal Growth Factor Receptor variant III (EGFRvIII)	Sampson et al., 2010[17] Del Vecchio et al., 2012 [20] Schuster et al., 2015 [25]
	Wilms tumor 1 (WT1) protein	Izumoto et al., 2008 [16]
	Ephrin type-A receptor 2 (EphA2) Interleukin-13 receptor alpha 2 (IL-13Rα2) Survivin	Pollack et al., 2014 [23]
Personalized peptide vaccines (PPV)	Screening for appropriate peptide antigens for vaccination and selection optimal candidates in each individual patient based on the pre-existing host immunity.	Yajima et al., 2005 [13] Terasaki et al., 2011 [19]
Heat Shock Protein (HSP) vaccines	Autologous tumor-derived HSP96-peptides complexes	Bloch et al., 2014 [21]
Autologous tumor cell vaccines, including AFTV	Autologous (formalin-fixed) whole tumor tissue	Ishikawa et al., 2007 [14] Muragaki et al., 2011 [18] Ishikawa et al., 2014 [22]

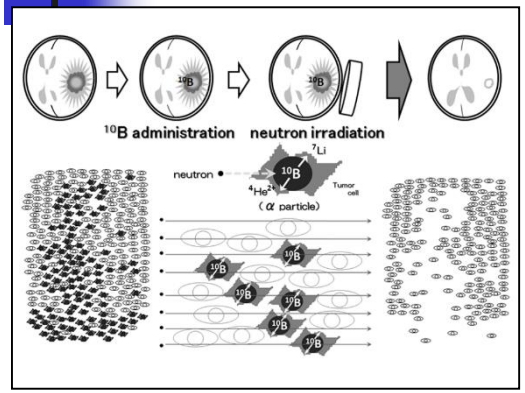
AFTV, autologous formalin-fixed tumor vaccine

AFTV

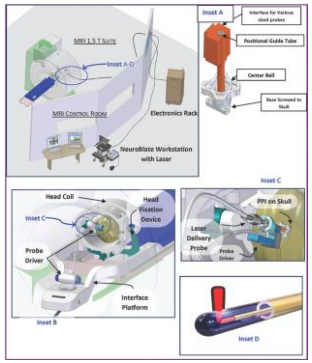


A 42-year-old man suffered from epilepsy, mild aphasia and decline of performance status (KPS score 70). Contrast-enhanced MRI revealed ring-enhanced mass in the left temporal lobe (A). The patient underwent ≥98% lesion resection leaving the residual tumor within subcortical language-related structures (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.

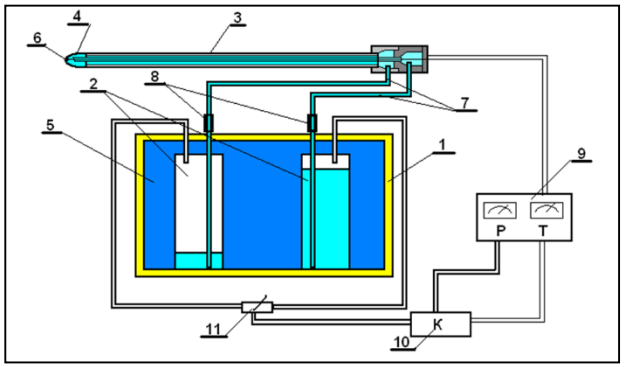
Innovative Modalities



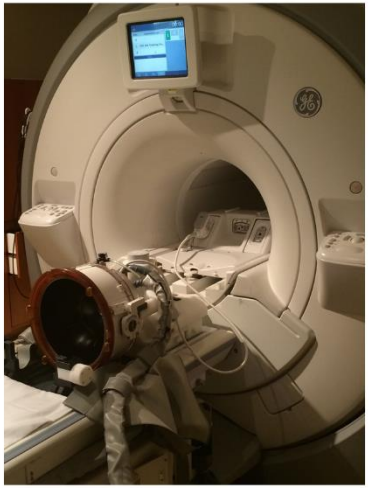
BNCT



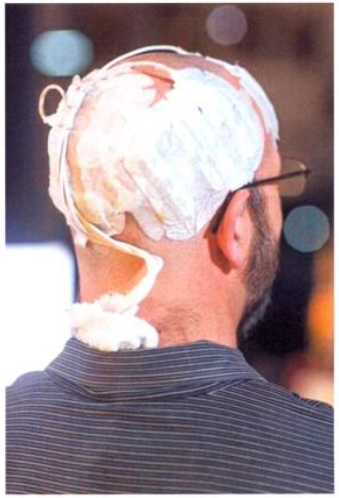
LITT



Cryodestruction

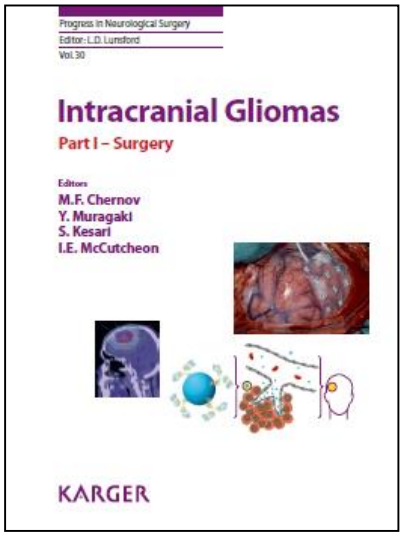


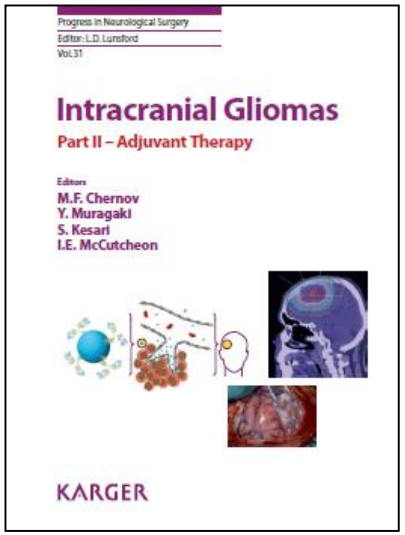
HIFU

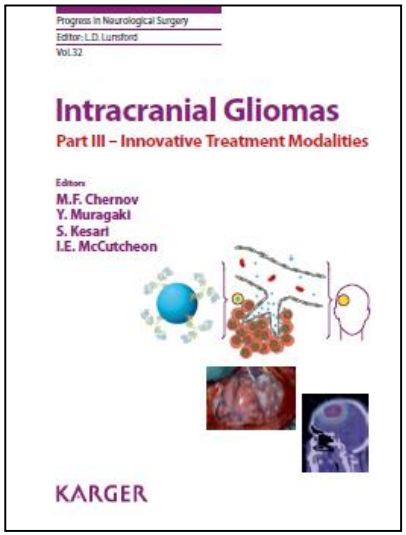


TTF

Progress of Neurological Surgery (KARGER)

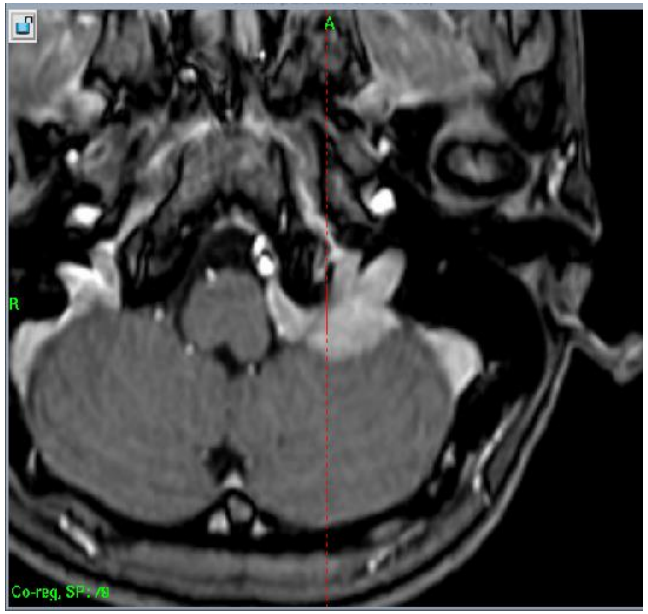




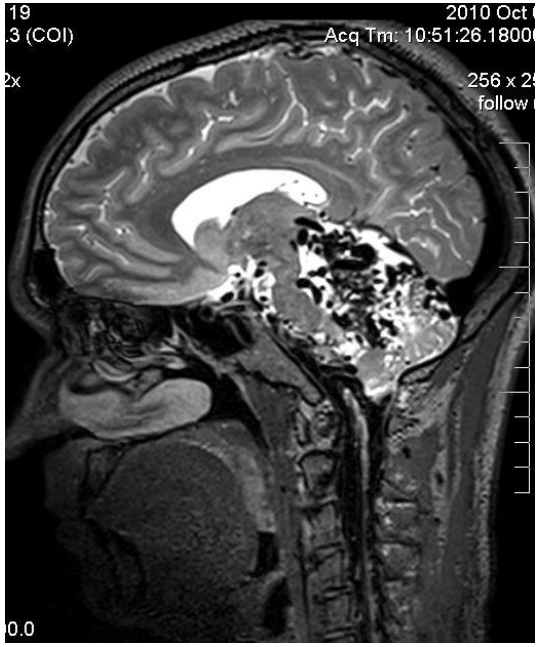


- Edited by M.F. Chernov, Y.Muragaki, S. Kesari, and I.E. McCutcheon.
- In total 44 chapters.
- International contributors from North America (25 chapters), Japan (10 chapters), West Europe (8 chapters), Russia (1 chapter).
- Scheduled publication due: 1st 2018
- Very reasonable pre-publication price.

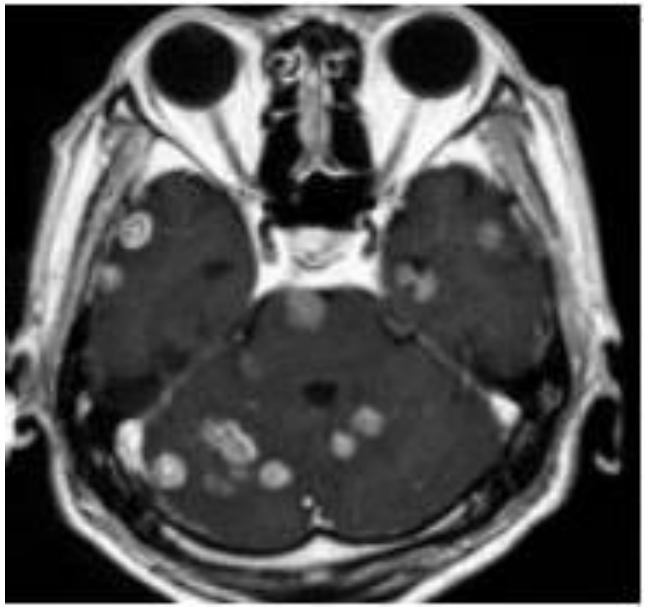
How to Treat Such Patients?



Jugular foramen meningioma

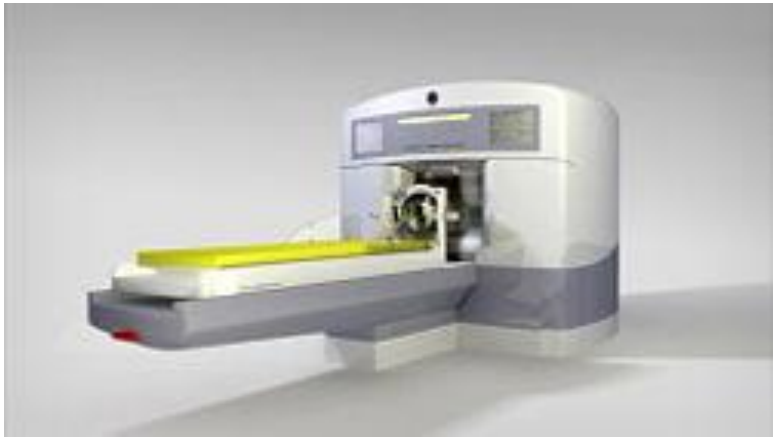


Cerebellar AVM



Multiple metastases

RADIOSURGERY!!!



Gamma Knife

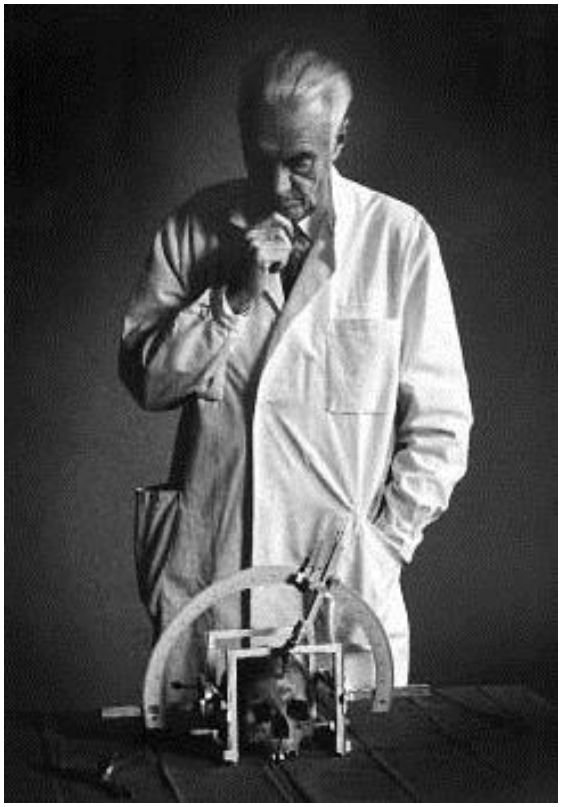
Linear Accelerator

Proton Beam

Cyber Knife

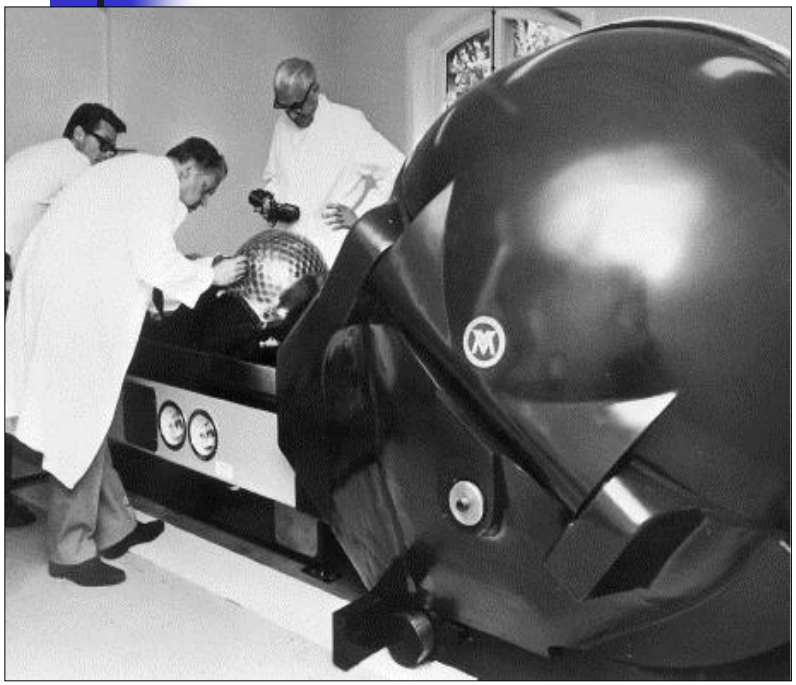
History of Gamma Knife

- **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 55^{th} Gamma Knife Unit in Japan



Lars Leksell
(1907 – 1986)

Evolution of Gamma Knife



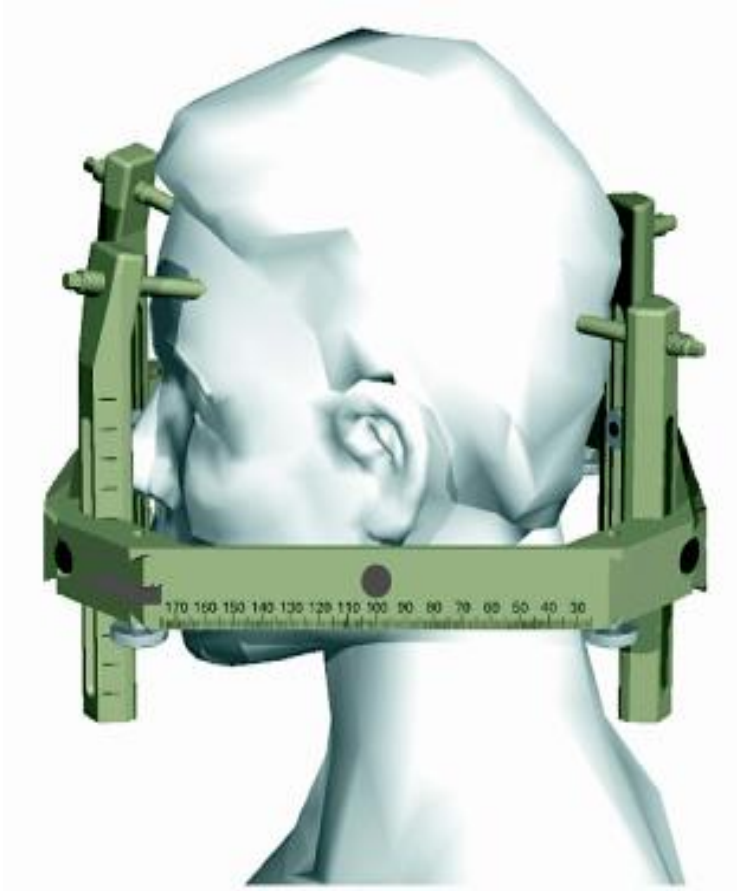
1968

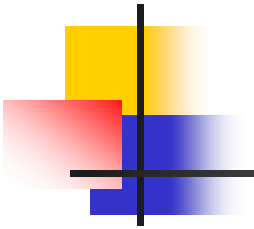
The first prototype of Leksell Gamma Knife was installed in Karolinska University, Stockholm, Sweden

2006

The latest Leksell Gamma Knife model (“Perfexion”) was installed in La Timone Hospital, Marseiile, France

Stereotactic Localization of the Target

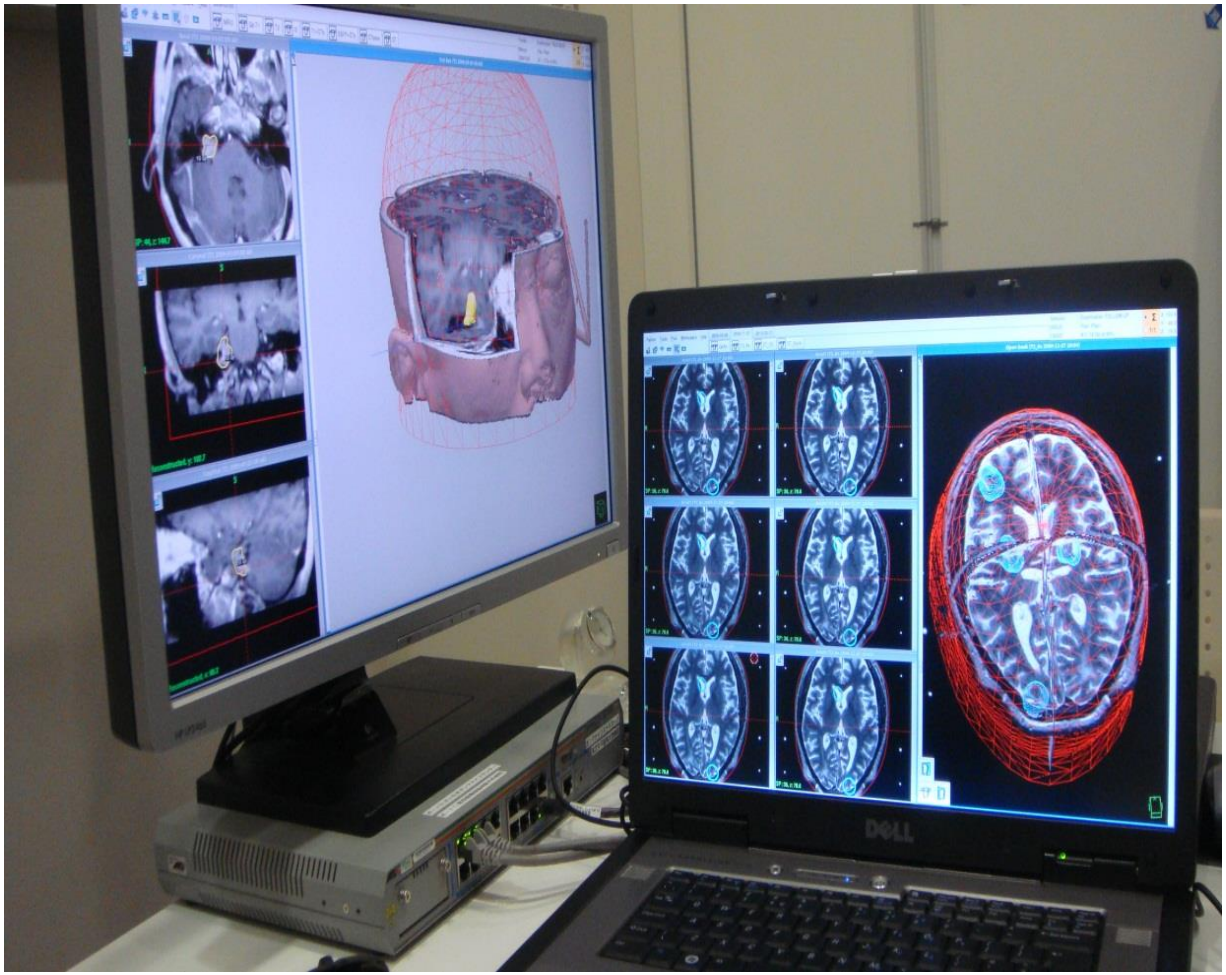




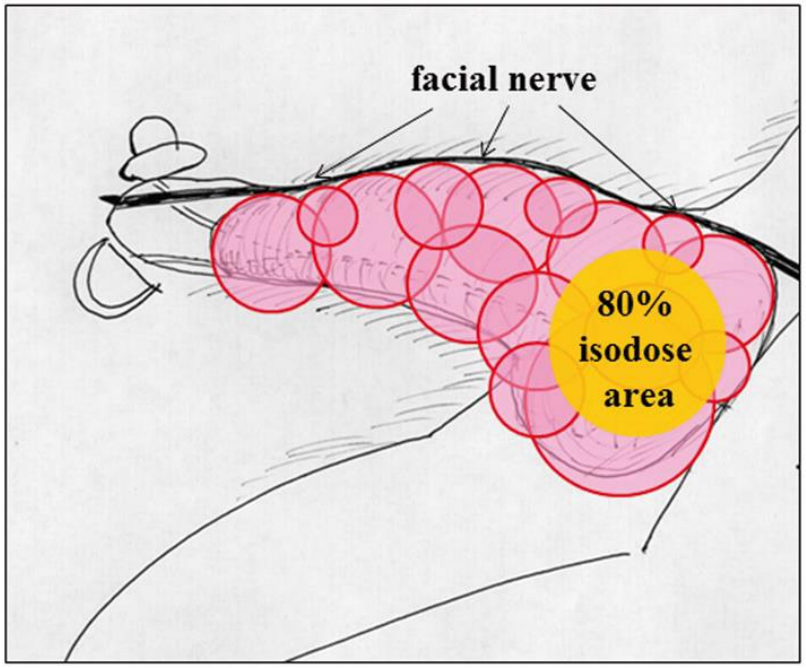
Frame Fixation

VIDEO

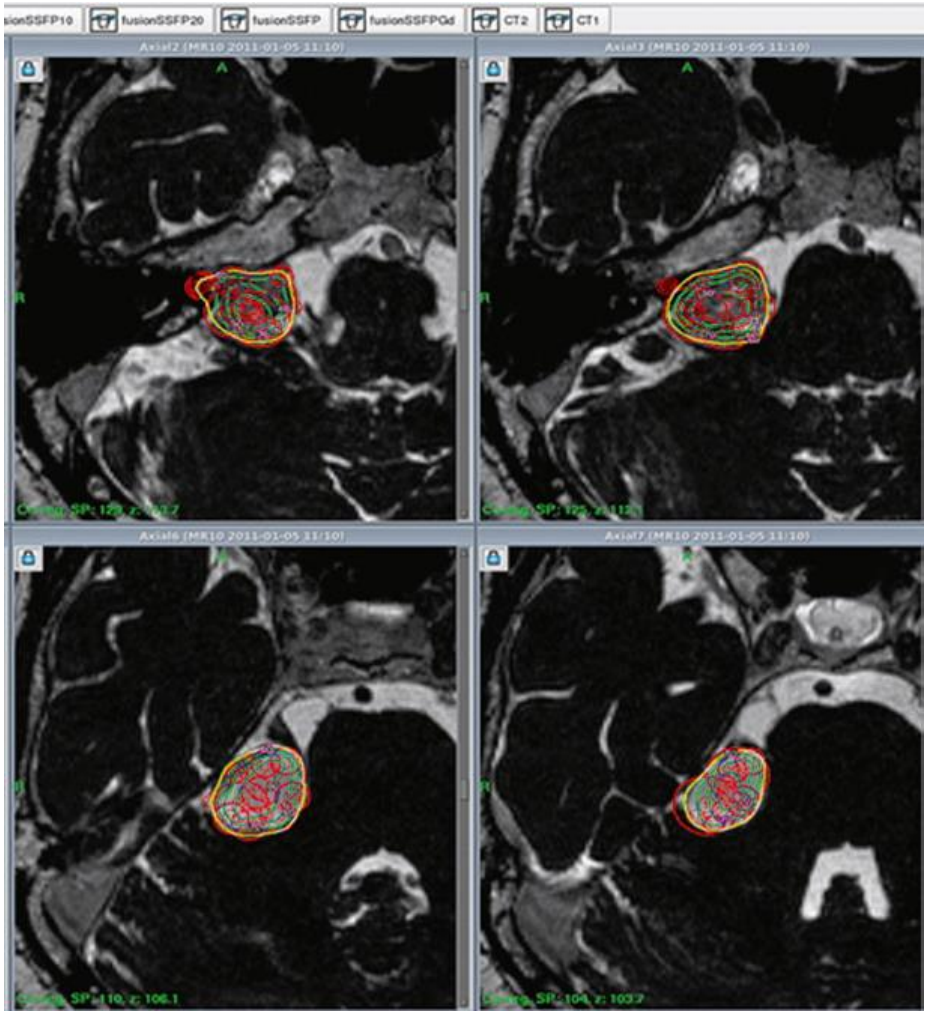
Treatment Planning



Conformal and Selective Treatment



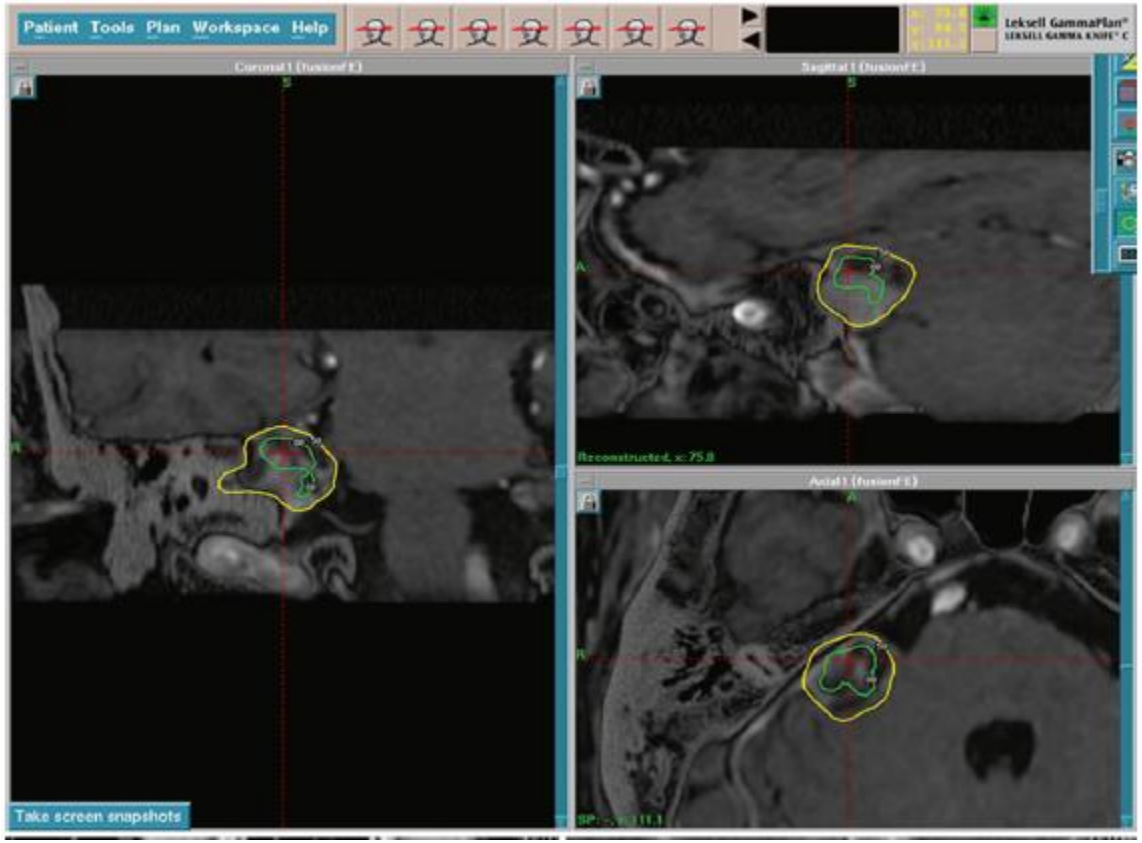
Scheme of treatment plan for
Koos grade III vestibular schwannoma
based on the concept of
“robotic microradiosurgery”



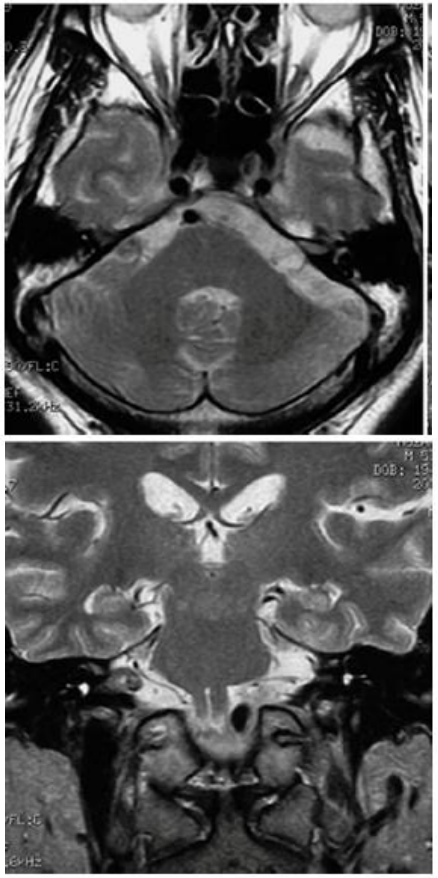
Radiosurgical Treatment

VIDEO

Vestibular Schwannoma

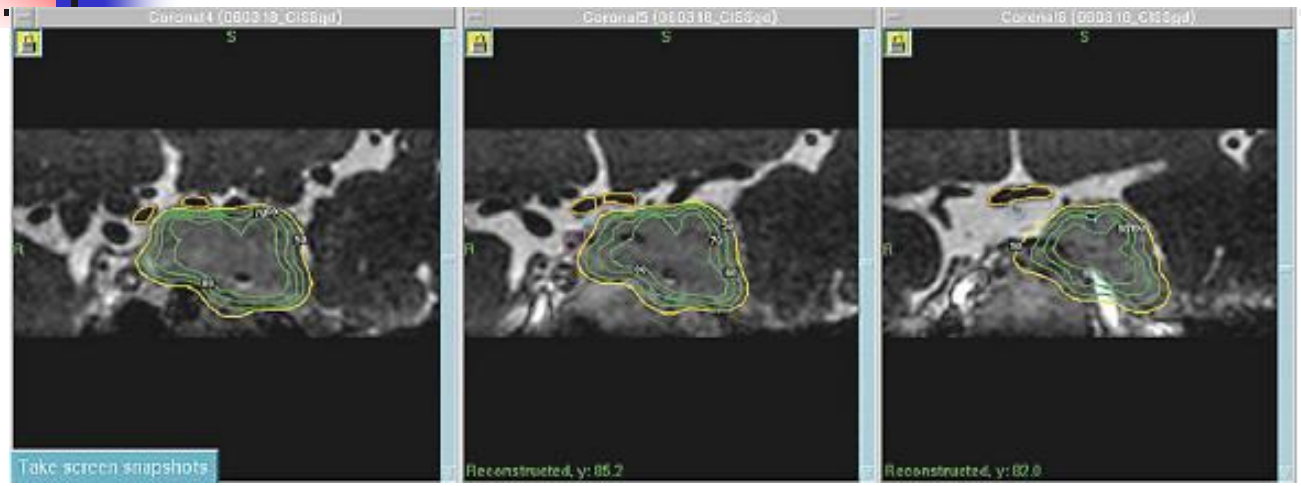


At the time of treatment



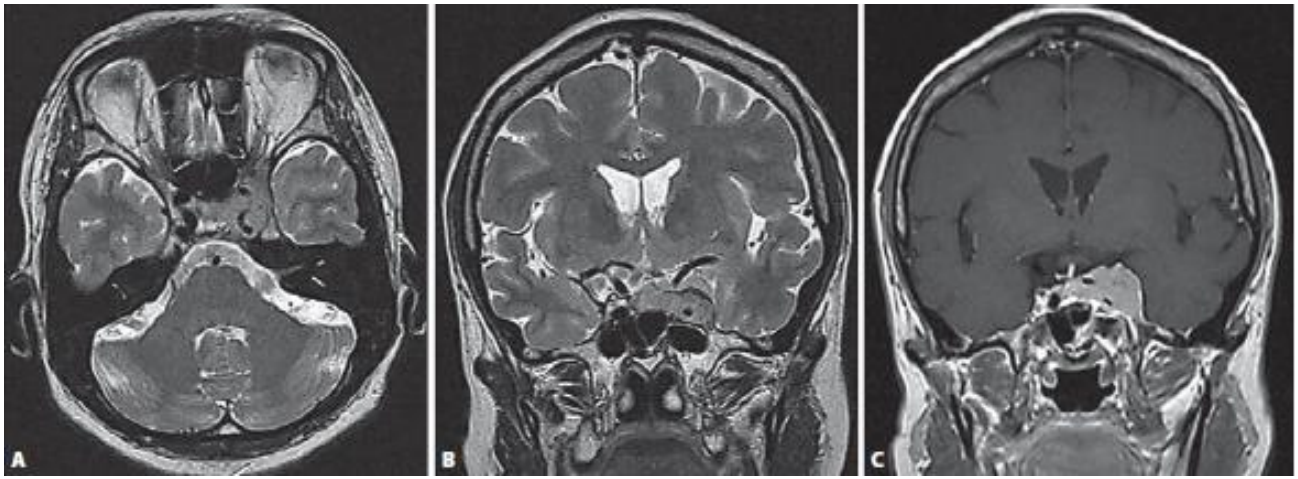
36 months after
Gamma Knife radiosurgery

Cavernous Sinus Meningioma



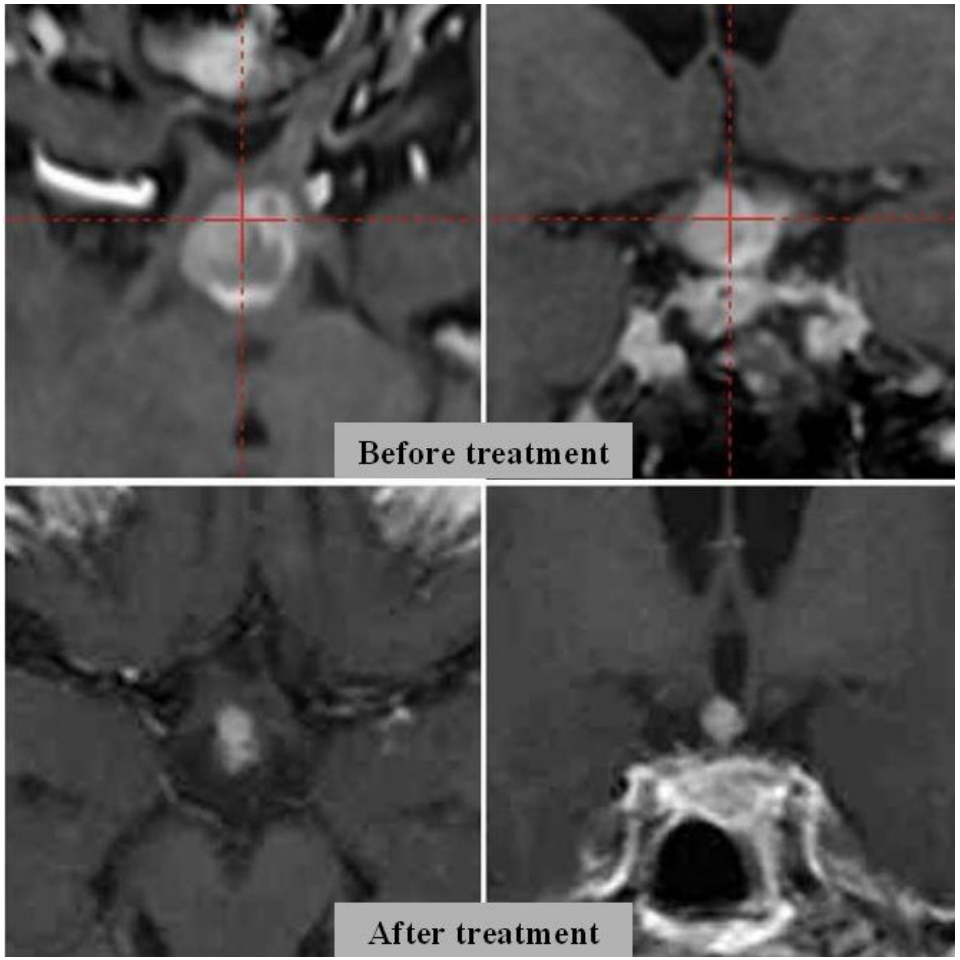
Marginal dose, 12 Gy

Resolution of symptoms within 4 months



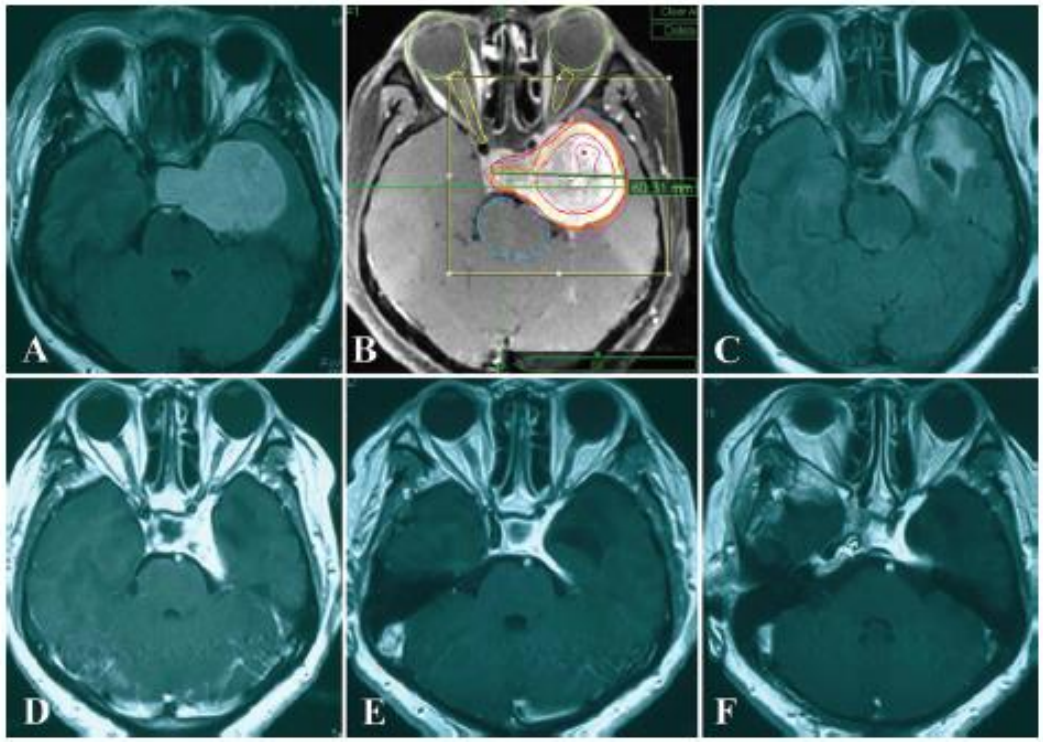
Tumor shrinkage at 3 years, asymptomatic

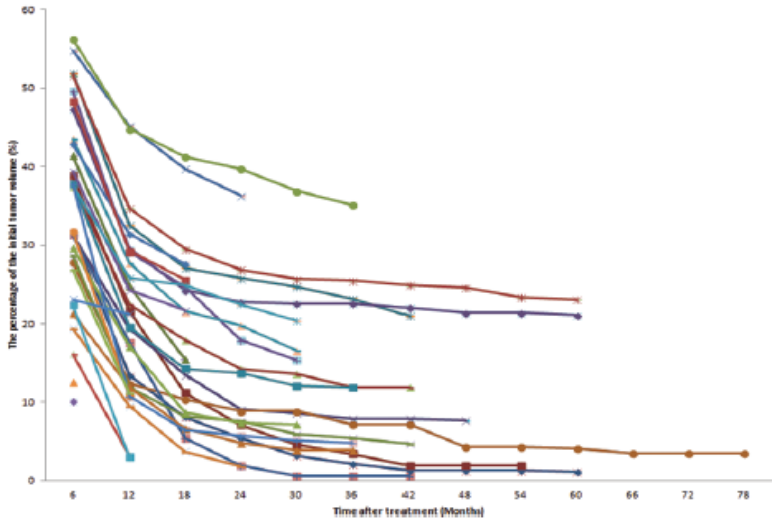
Craniopharyngioma



Cavernous Sinus Hemangioma

18-22 Gy in 3-4 fractions

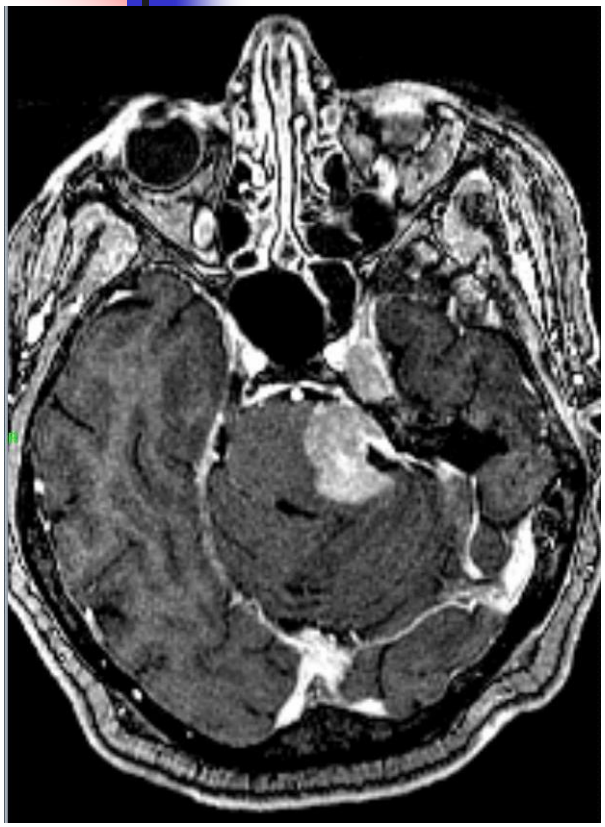




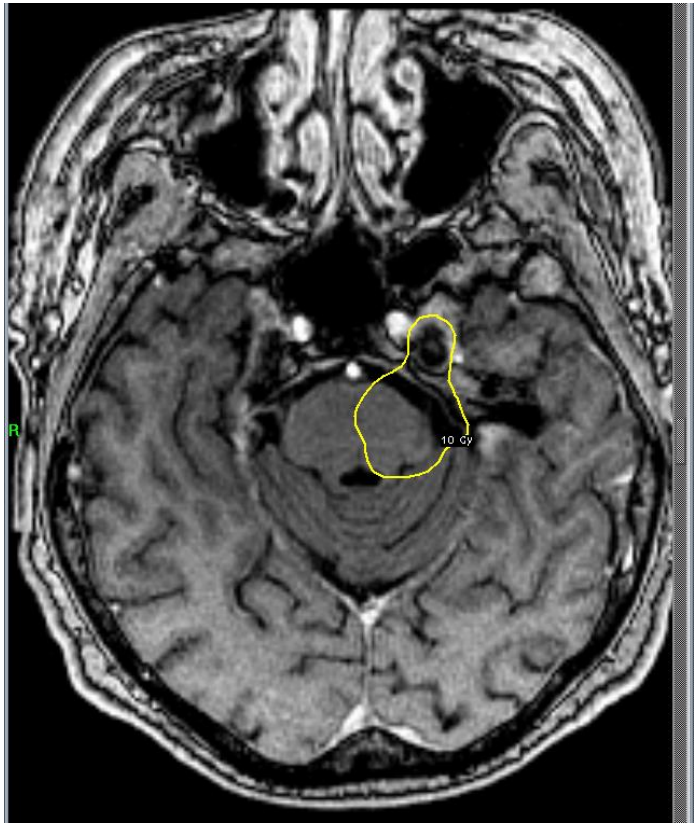
No major complications

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

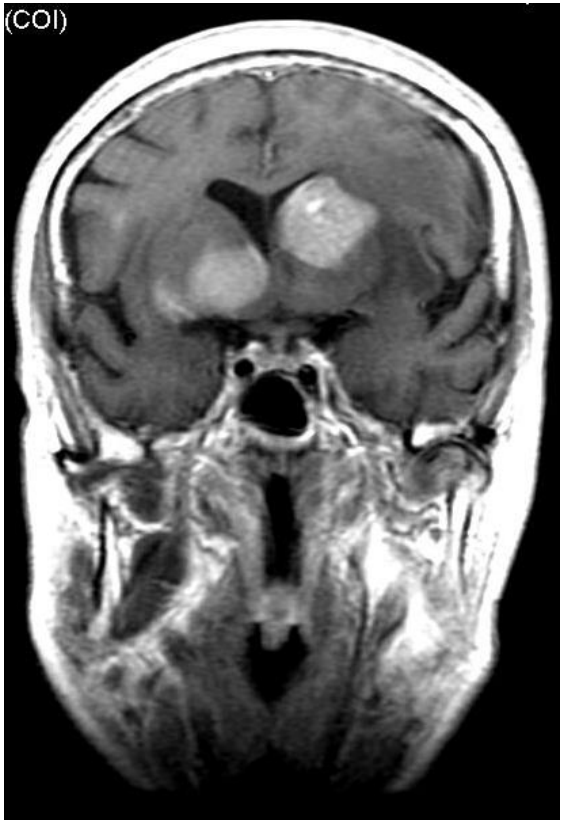
Malignant Lymphoma



Before treatment



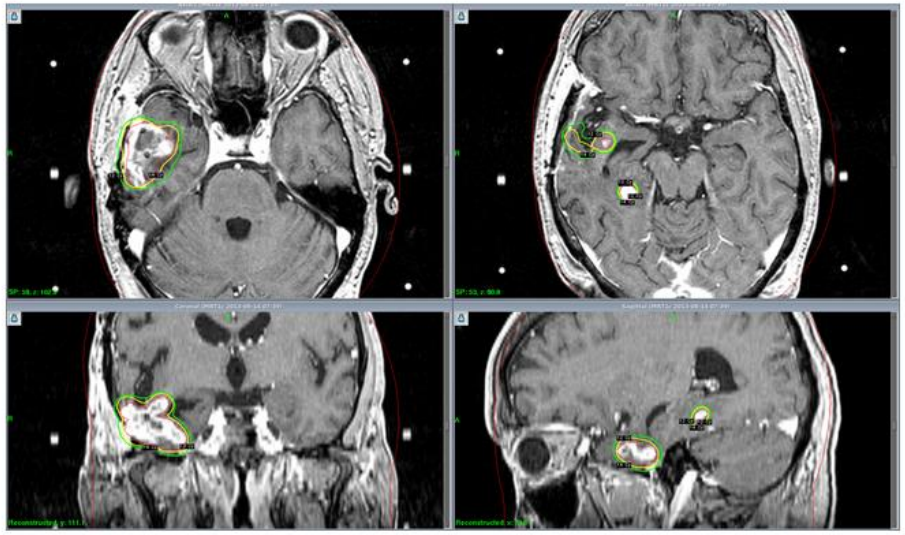
6 months after GKS
(marginal dose 10 Gy)

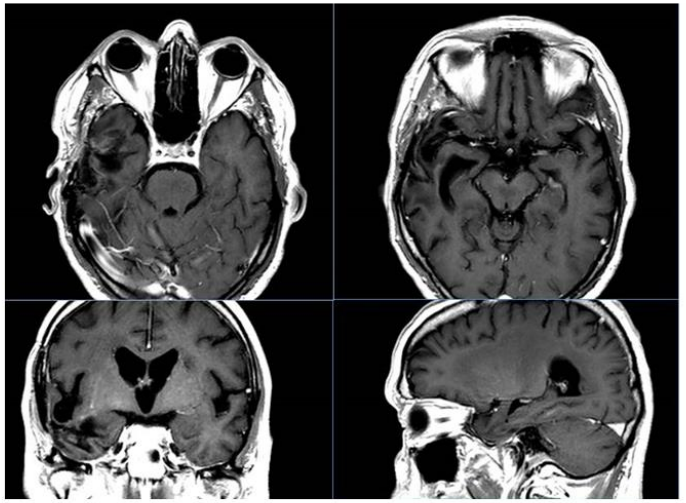


16 months after GKS

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.

Novosibirsk 2017

Meshalkin Institute of Circulation Pathology

ISRS

EDUCATIONAL COURSE

SRS/SRT COMBINED WITH IMMUNOTHERAPY IN MANAGEMENT OF BRAIN METASTASES, INTRACRANIAL GLIOMAS, AND SOMATIC CANCERS. MEDICAL PHYSICS FOR RADIOSURGERY.

DECEMBER 7-8, 2017; NOVOSIBIRSK, RUSSIA