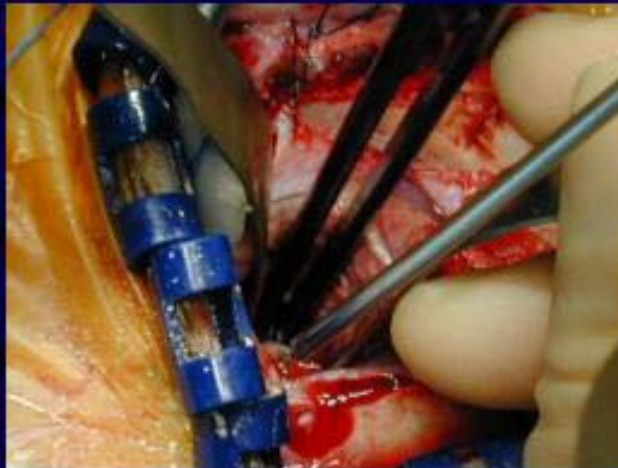


Integrated Image Guided Diagnosis and Therapy

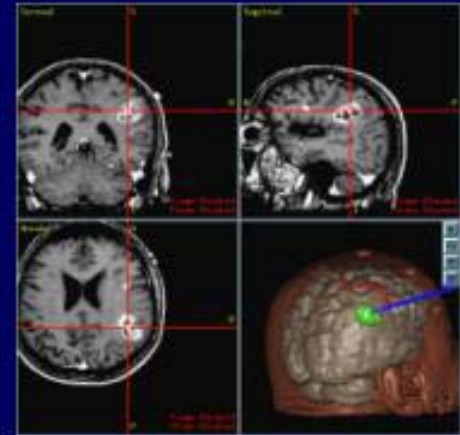
Timothy Ryken, MD



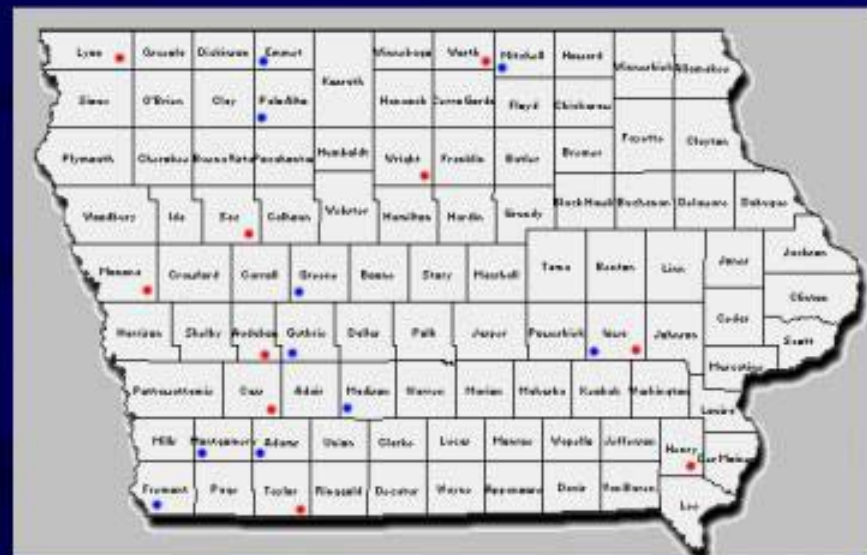
Brain Tumor Treatment Group
Molecular Neurosurgery Laboratory
Department of Neurosurgery
Holden Comprehensive Clinical Cancer Center
University of Iowa Hospitals and Clinics

Primary Malignant Brain Tumors

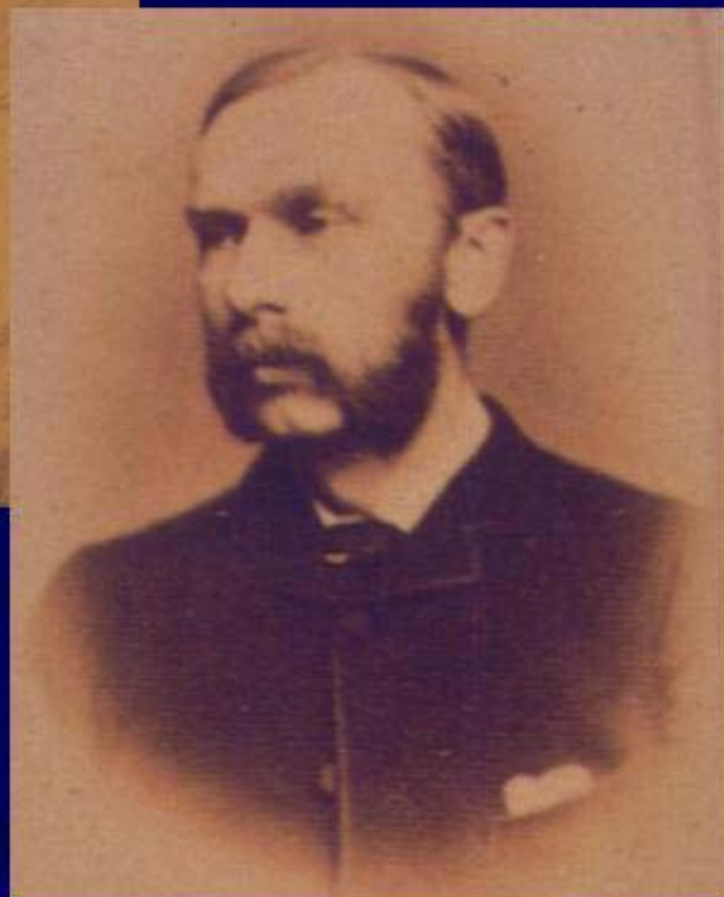
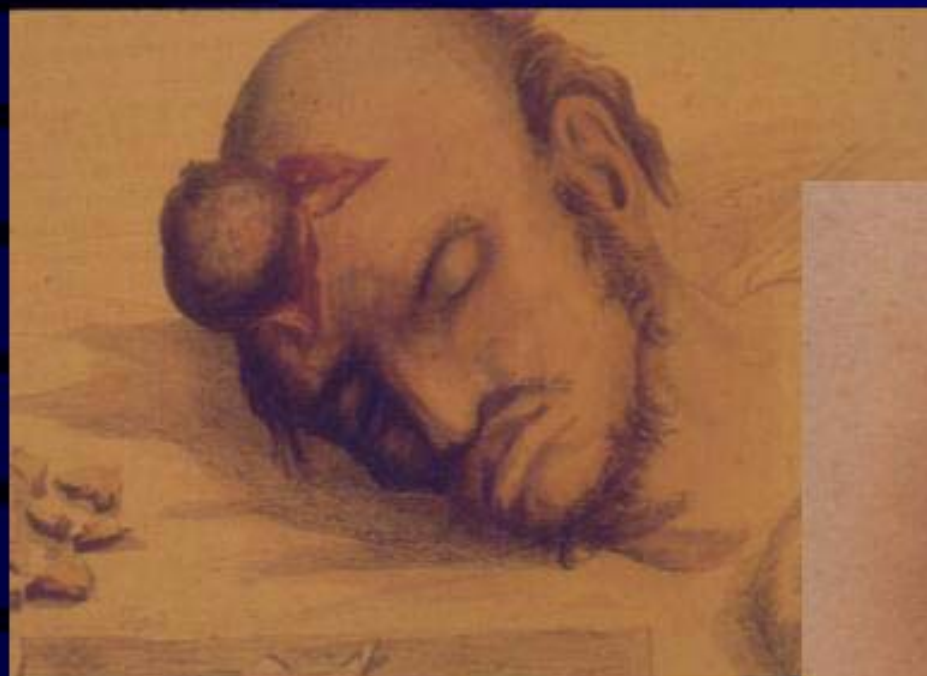
15,000 to 20,000 per year (USA)



(Iowa 250 per year)

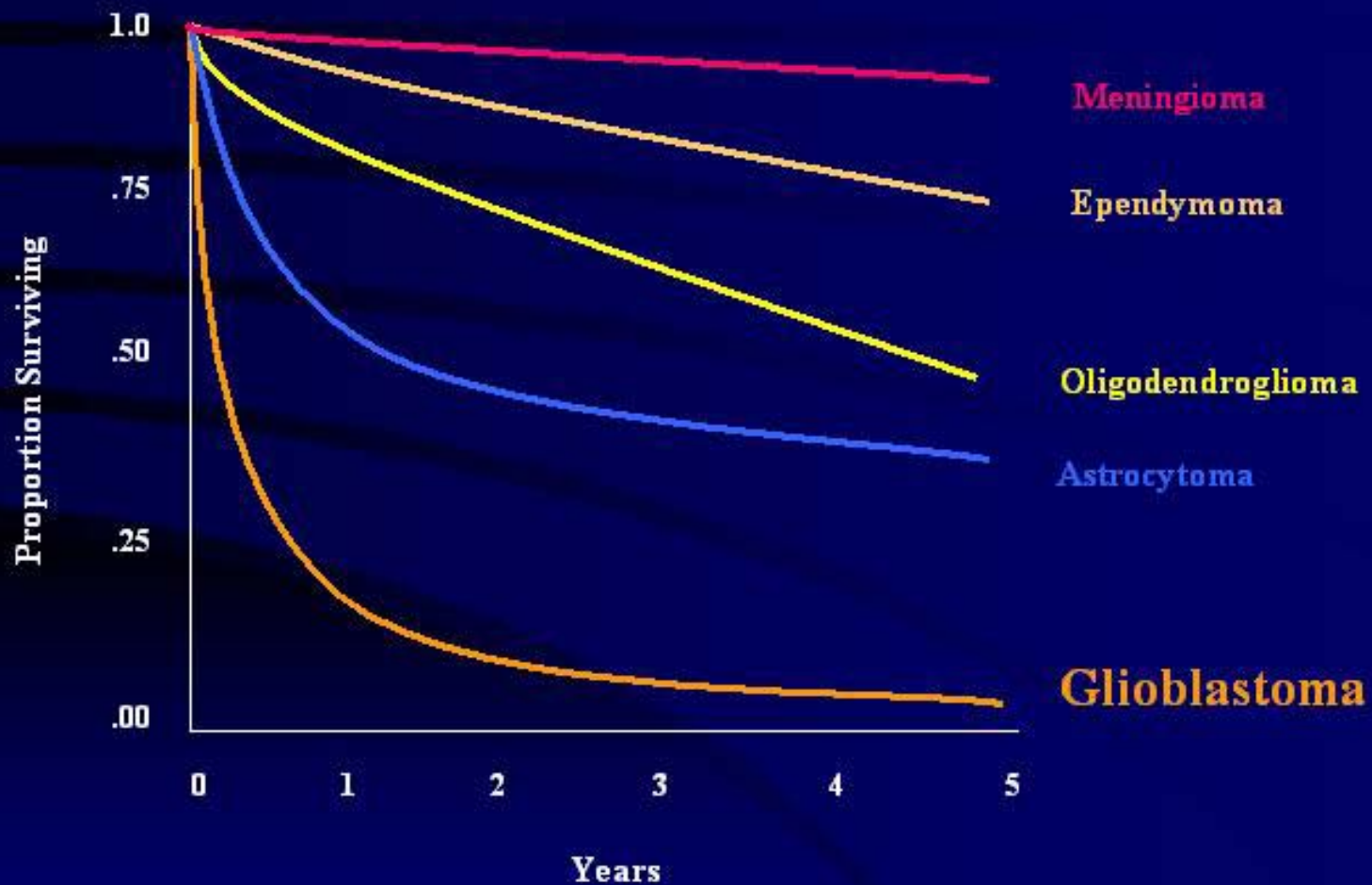


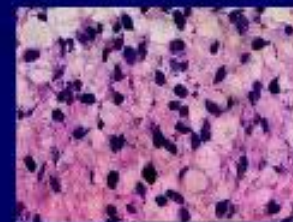
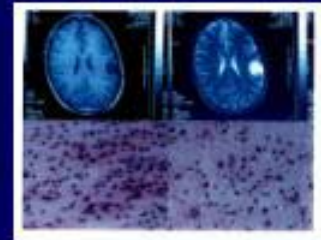
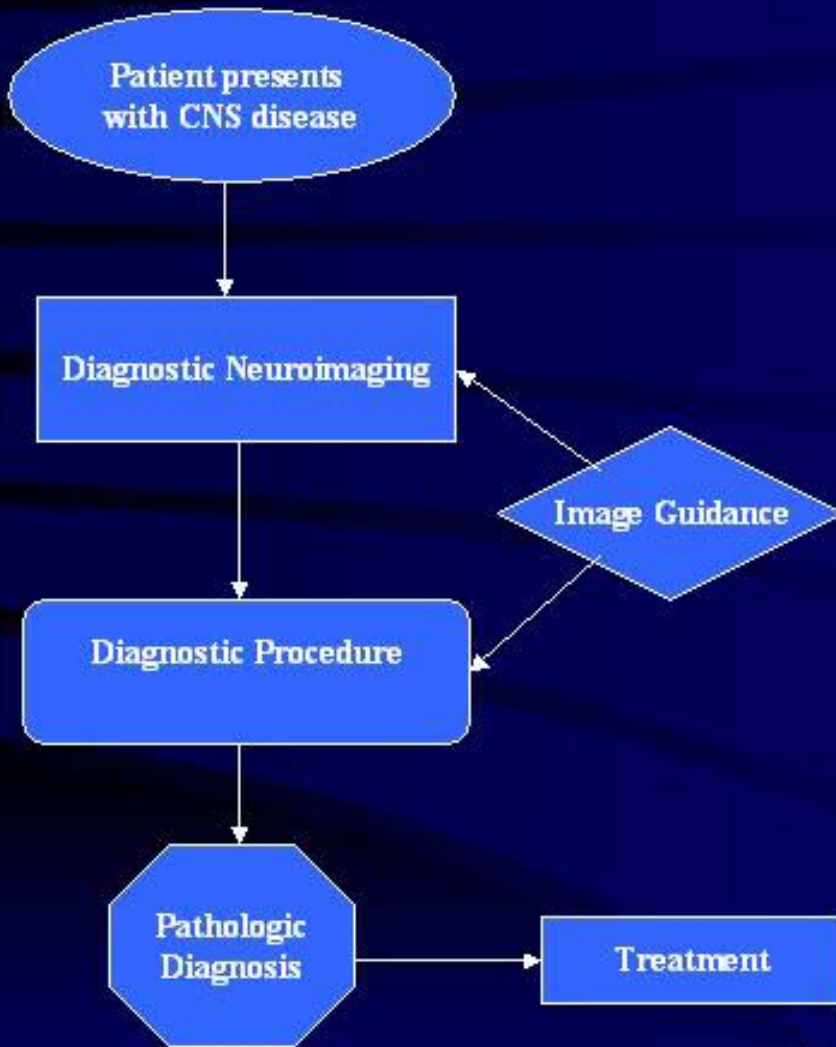
Malignant Glioma Incidence (per capita by county)
Red – Top Ten 1974-1985 Blue – Top Ten 1984-1995



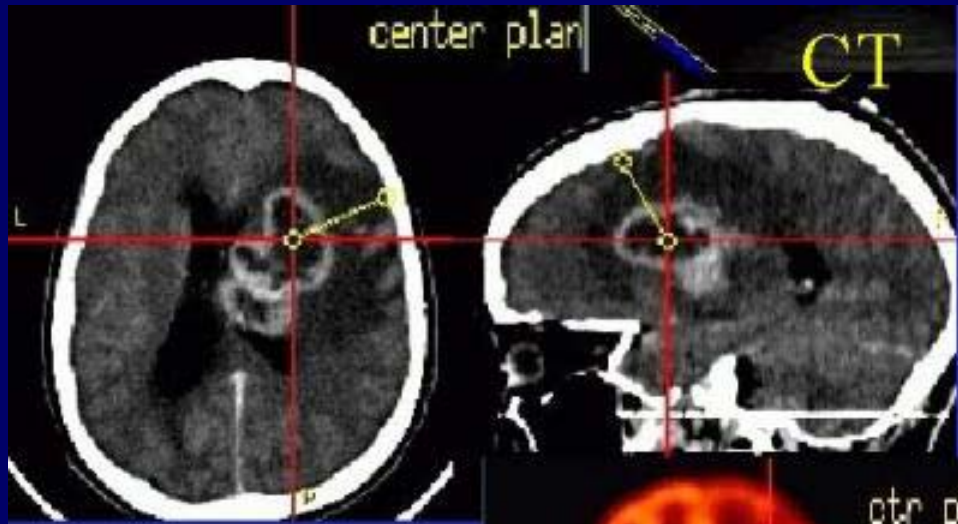
1884

Primary Glial Tumors: General Survival Trends

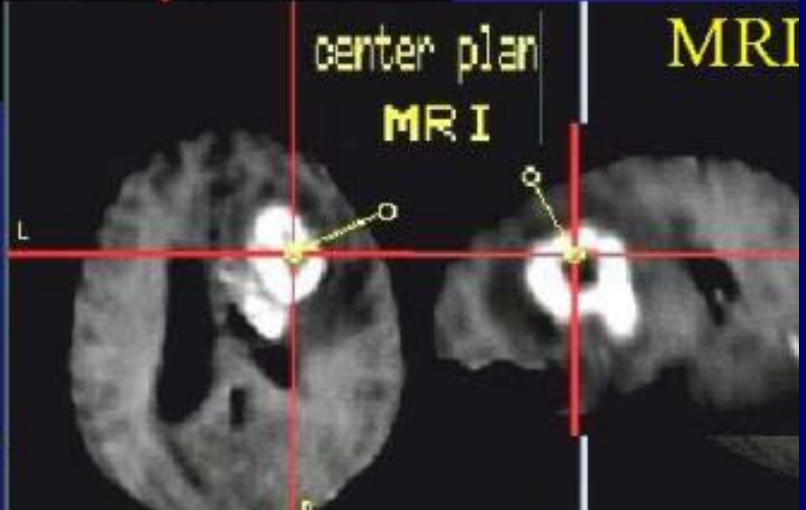




1995

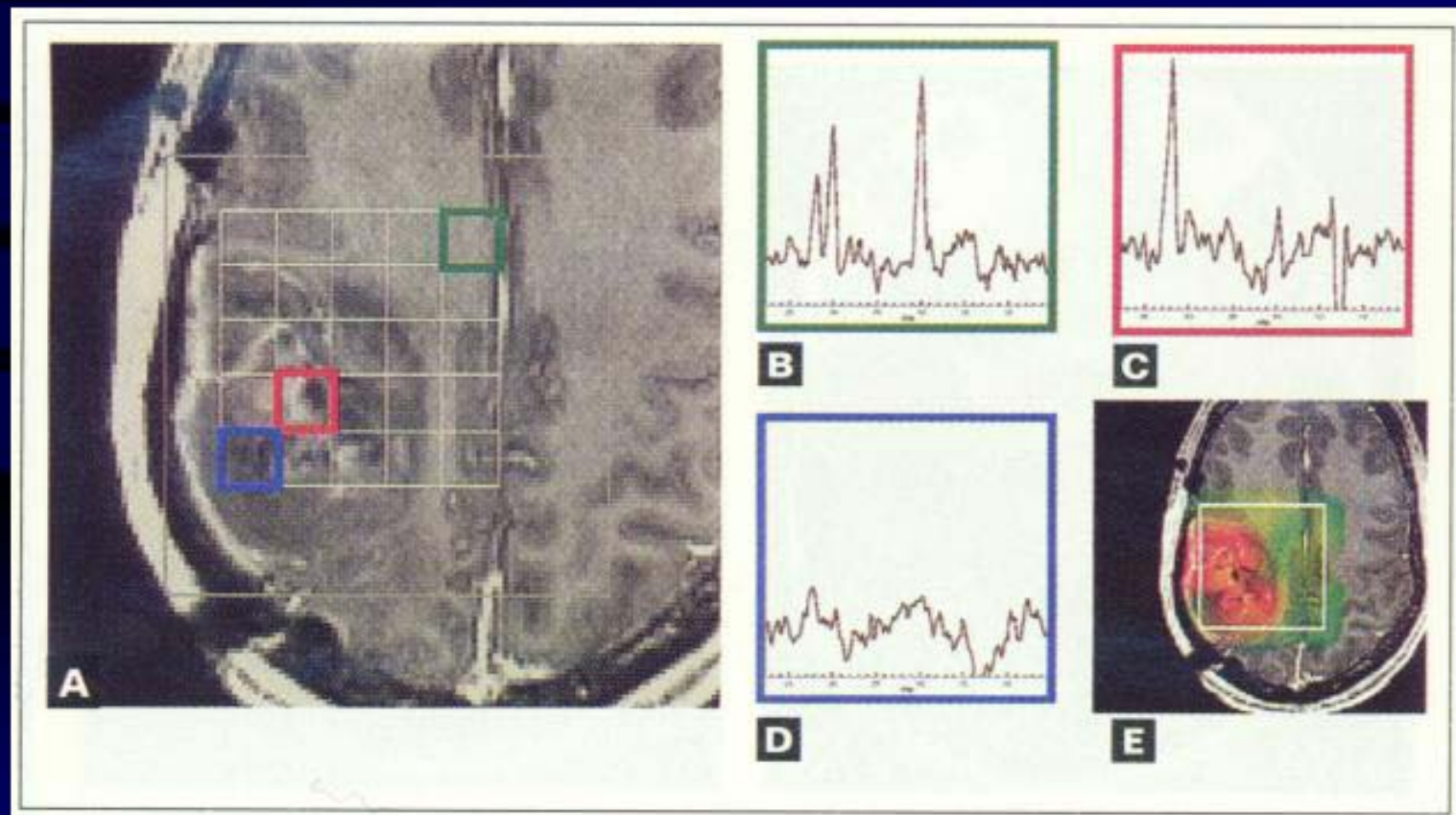


CENTER OF LESION BIC
CT, PET, & MRI

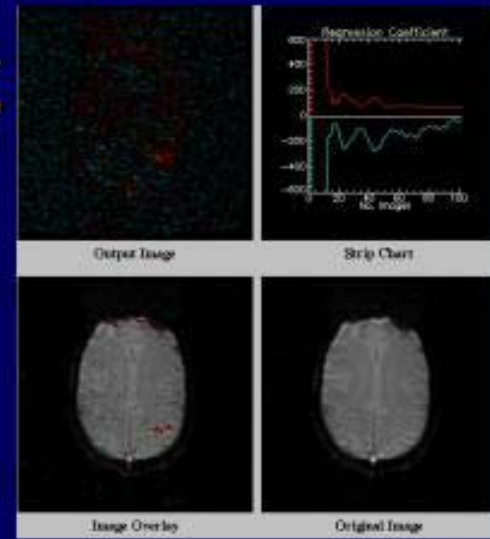
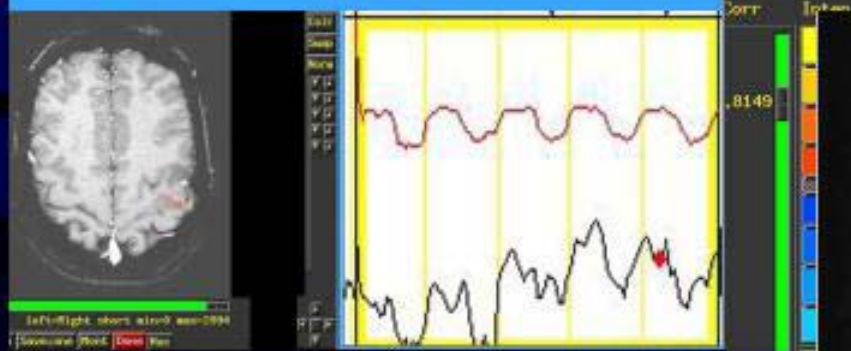
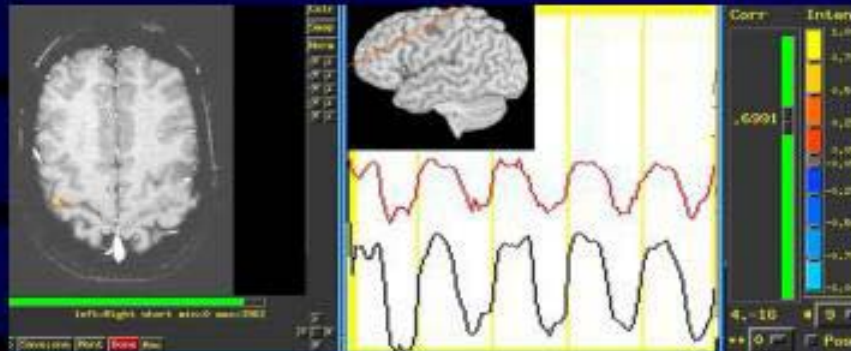


Patient 3-JR: Glioblastoma

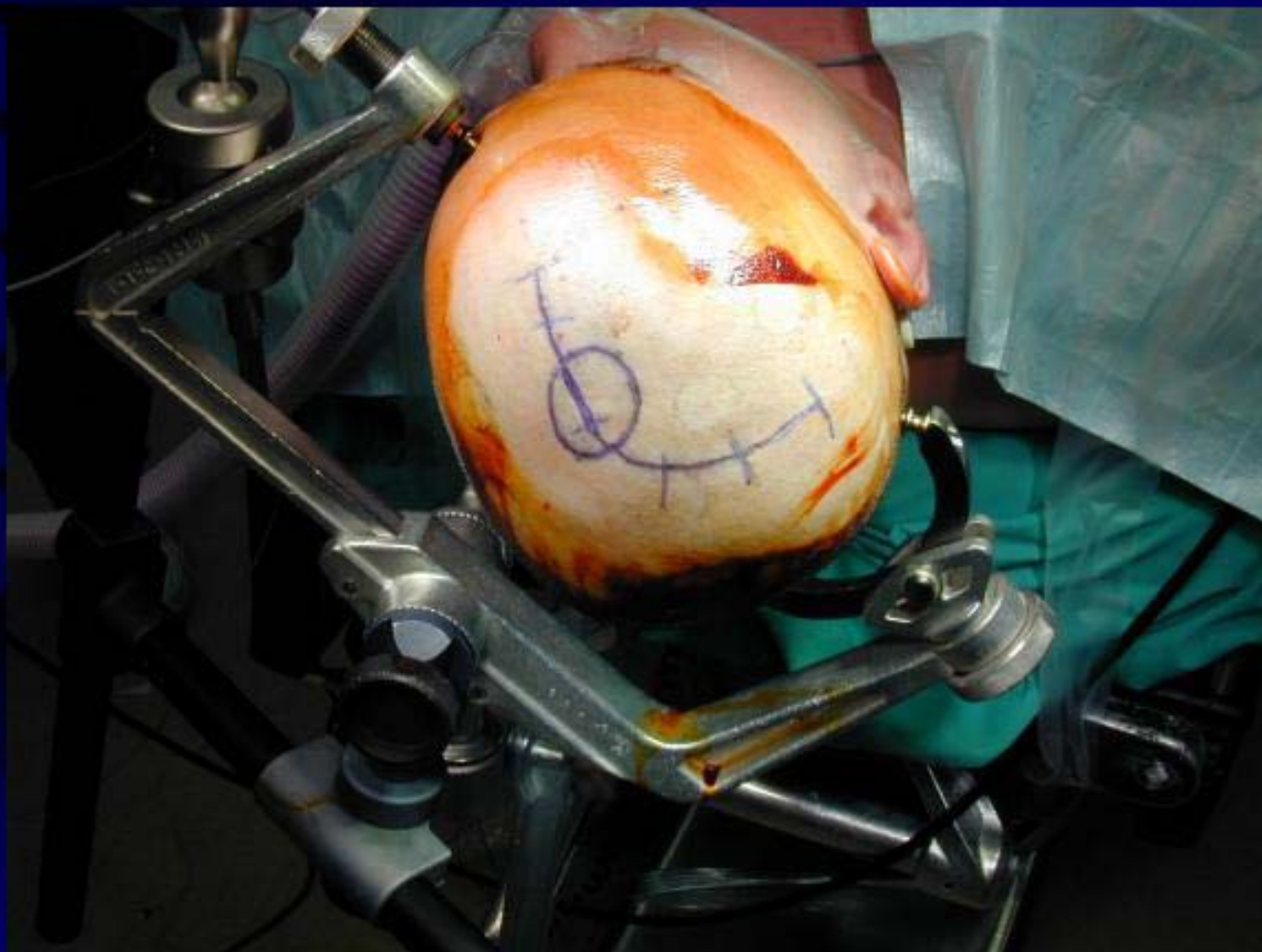
Imaging: Magnetic Resonance Spectroscopy

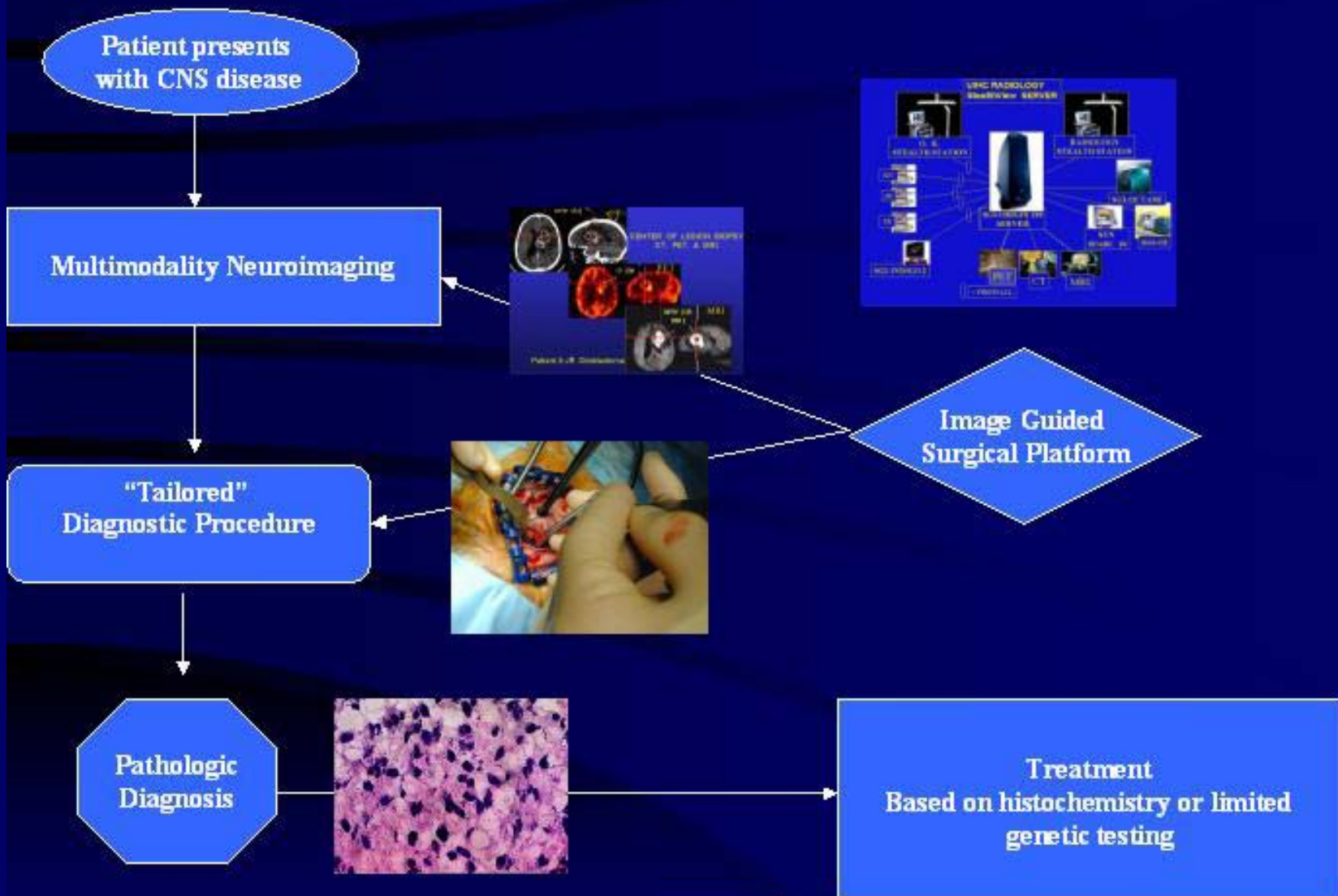


MRI – Functional Mapping



(Whoops !)





2002

Image-guided Neurosurgical Treatment Platforms

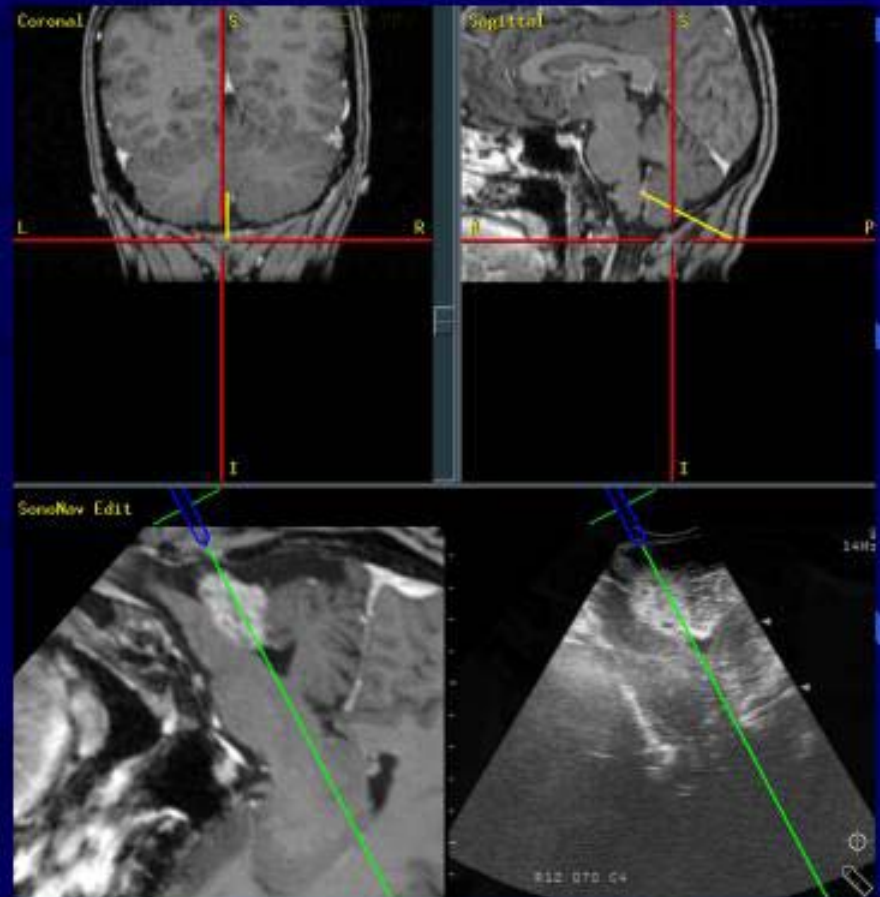


University of Iowa

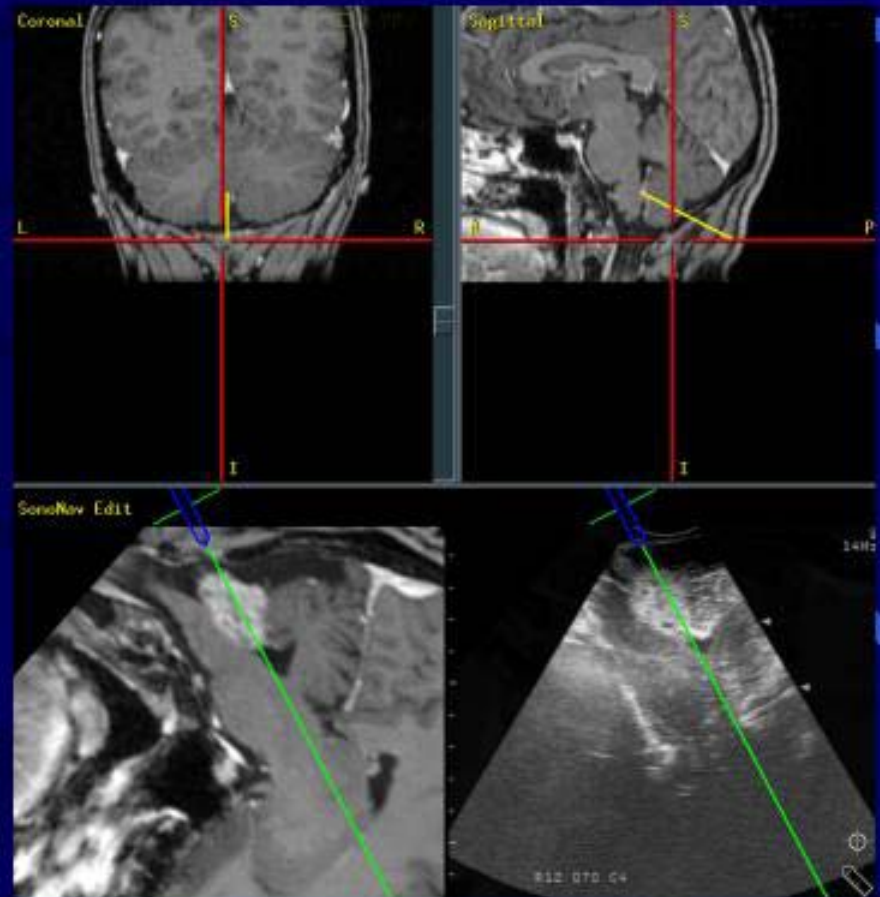
(circa – 2001)



Ultrasound-linked image guided navigation



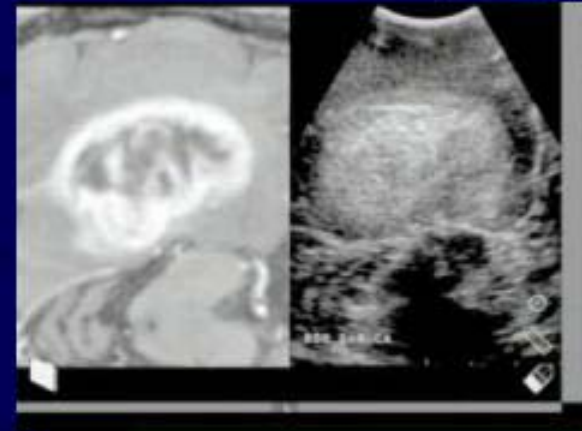
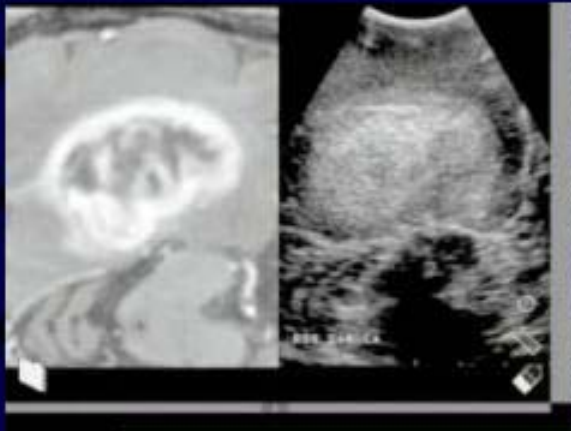
Ultrasound-linked image guided navigation



Ultrasound-linked image guided navigation



Pre-resection assessment



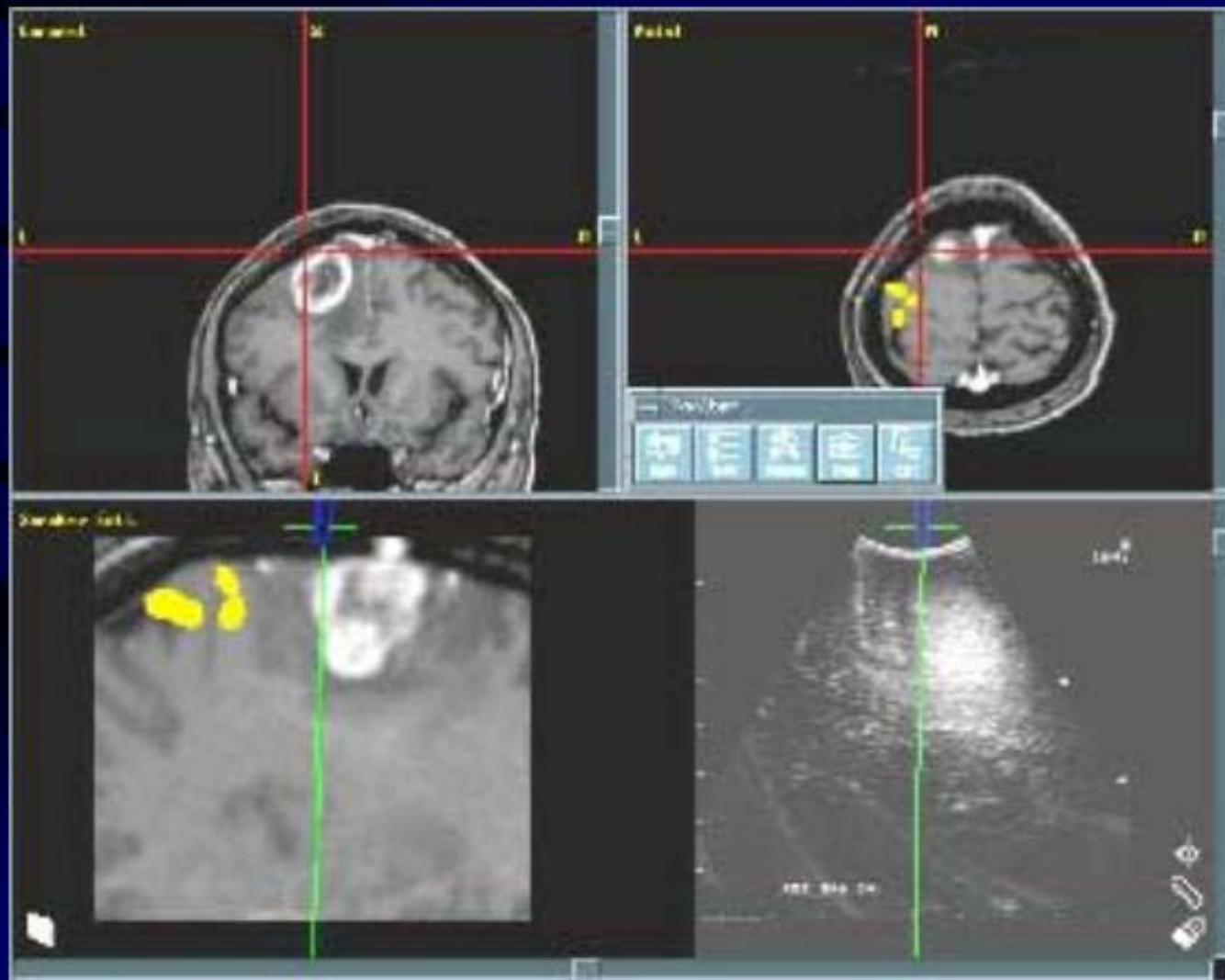
Intraoperative shift



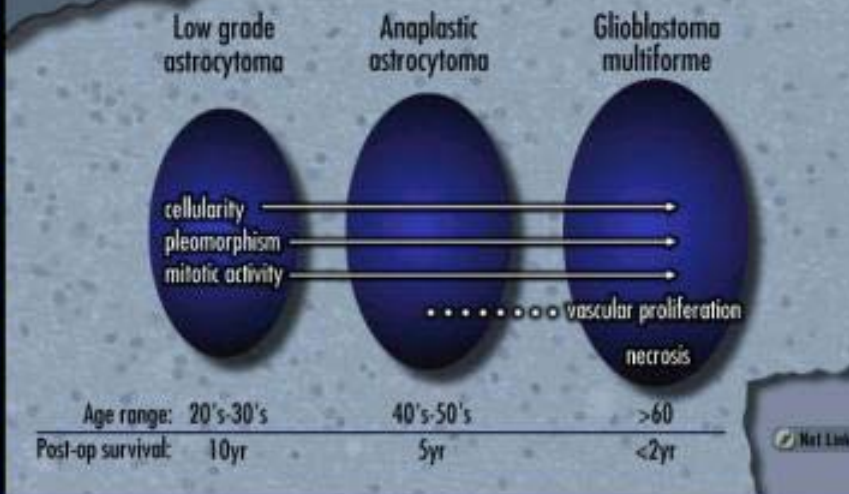
Resection assessment



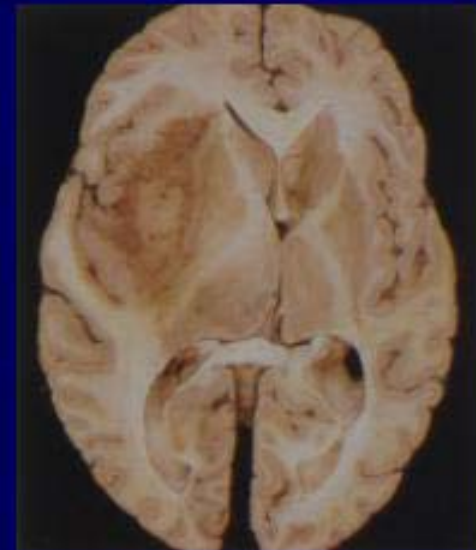
Image fusion – fMRI, MRI, US



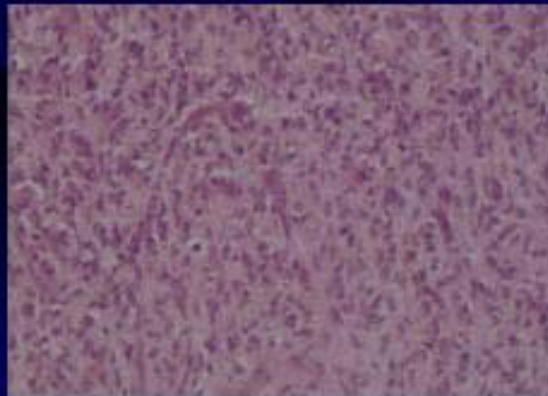
Classification Systems



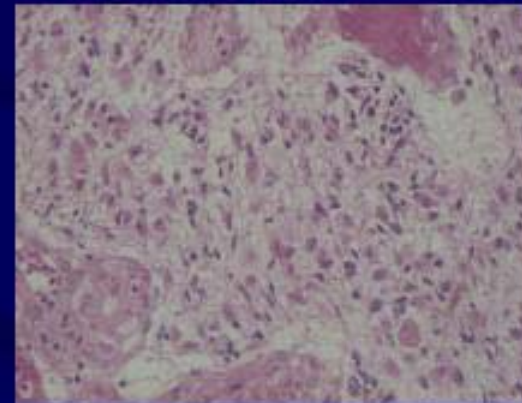
Gross Pathology:



Histopathology:



Anaplastic Astrocytoma

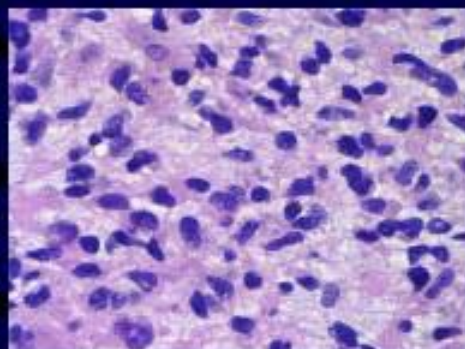


Glioblastoma

X-Cyt Project

(Nick Street, Ph.D. – University of Iowa)

Digitized Image



Segmented Cell Nuclei

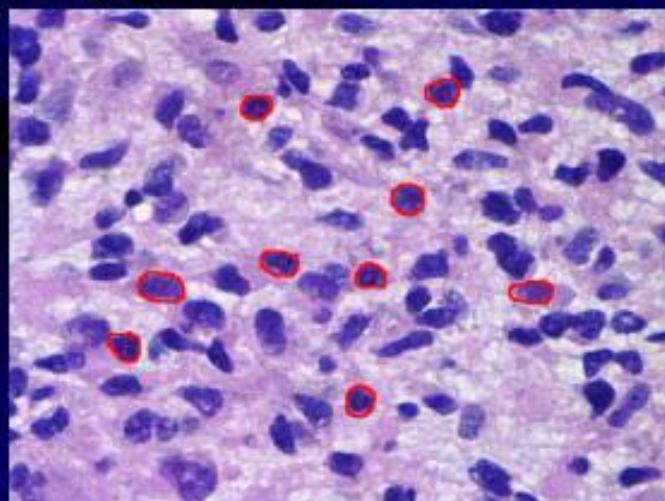


Image Analysis

TABLE 1. DIAGNOSTIC FEATURES

	BENIGN (n=39)		MALIGNANT (n=27)	
	Mean	SD	Mean	SD
	Mean Radius (µm)	11.7852 ±	2.0901	11.7714 ±
Mean Texture	17.2192 ±	4.285	27.7285 ±	9.7497
Mean Perimeter (µm)	76.3515 ±	14.0874	78.0541 ±	12.3022
Mean Area (µm ²)	455.4103 ±	196.6025	434.4111 ±	128.6403
Mean Smoothness	0.1043 ±	0.0163	0.1192 ±	0.015
Mean Compactness	0.1045 ±	0.0967	0.174 ±	0.0733
Mean Concavity	0.0888 ±	0.0589	0.1217 ±	0.0593
Mean Concave Points	0.043 ±	0.027	0.0668 ±	0.0322
Mean Symmetry	0.2012 ±	0.0292	0.223 ±	0.0287
Mean Fractal Dimension	0.067 ±	0.0077	0.0796 ±	0.0079
SE Radius (µm)	0.5237 ±	0.4828	0.4137 ±	0.1327
SE Texture	0.7324 ±	0.3421	1.7877 ±	0.9776
SE Perimeter (µm)	3.6096 ±	3.3335	3.0572 ±	0.967
SE Area (µm ²)	45.431 ±	55.4045	31.3467 ±	14.1543
SE Smoothness	0.008 ±	0.0018	0.0064 ±	0.0013
SE Compactness	0.027 ±	0.0183	0.0314 ±	0.0096
SE Concavity	0.0347 ±	0.0245	0.0313 ±	0.0098
SE Concave Points	0.0115 ±	0.0053	0.012 ±	0.0024
SE Symmetry	0.0208 ±	0.0058	0.0194 ±	0.0029
SE Fractal Dimension	0.0041 ±	0.0019	0.0041 ±	0.0009
Extreme Value - Radius (µm)	15.0115 ±	3.6484	15.6822 ±	2.5923
Extreme Value - Texture	22.4664 ±	5.6151	43.6733 ±	16.6618
Extreme Value - Perimeter (µm)	99.2349 ±	25.3583	106.9496 ±	19.1705
Extreme Value - Area (µm ²)	733.2897 ±	422.0634	751.1593 ±	257.0683
Extreme Value - Smoothness	0.1678 ±	0.0225	0.1744 ±	0.0217
Extreme Value - Compactness	0.3437 ±	0.2065	0.5158 ±	0.168
Extreme Value - Concavity	0.3827 ±	0.2109	0.4741 ±	0.1549
Extreme Value - Concave Point	0.1375 ±	0.0445	0.1843 ±	0.0406
Extreme Value - Symmetry	0.3542 ±	0.065	0.4047 ±	0.0611
Extreme Value - Fractal Dimension	0.1033 ±	0.0225	0.1191 ±	0.0175

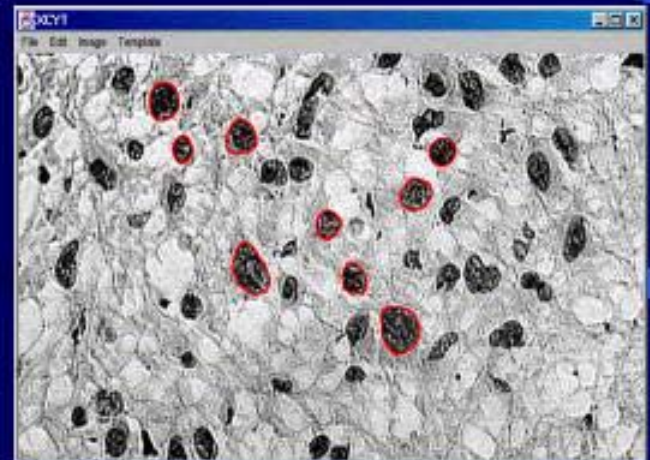
Note: SE = standard error; SD = standard deviation

Inductive Machine Learning

- Classification procedure uses linear programming
- Decision tree model to categorize new cases
- Accuracy determined by 10-fold cross-validation

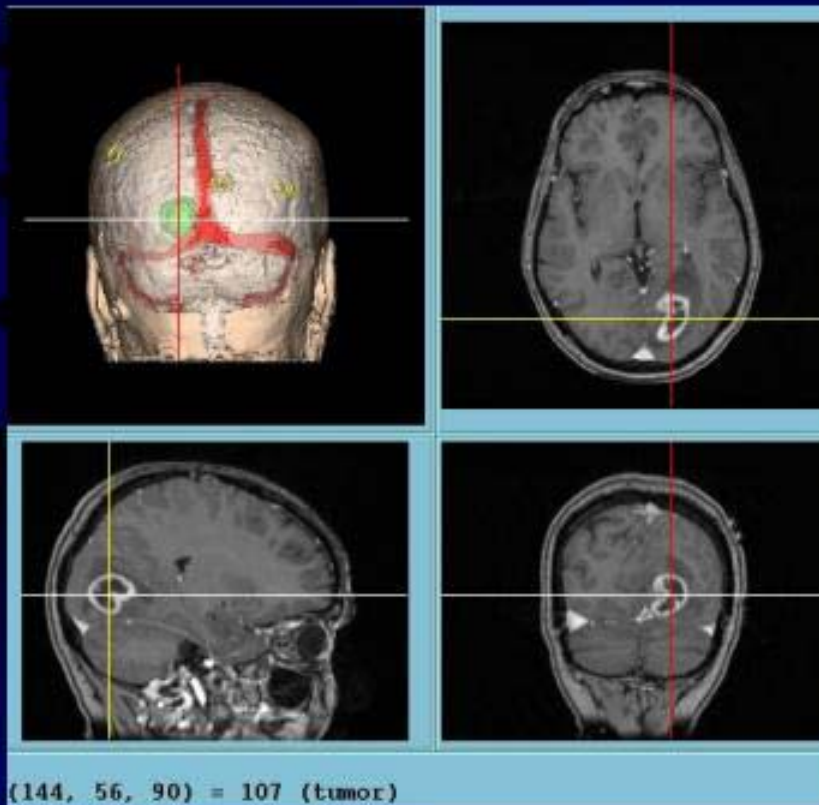
“Malignancy” Index

- Limited training data set
- Total 66 samples
- 27 glioblastoma specimens
- 39 normal brain specimens
- Accuracy using Xcyt program was 92.4%



Digital Analysis of Radiographic Images

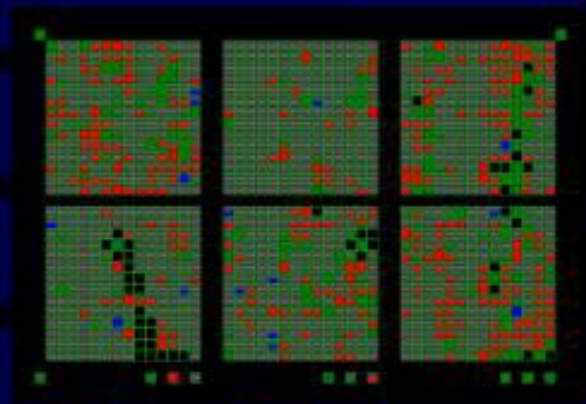
Create "smart software" -
resulting in a searchable
archive to assist in analysis



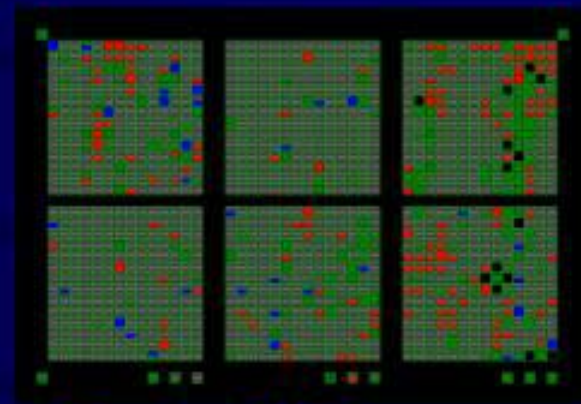
Diagnosis

Prognosis

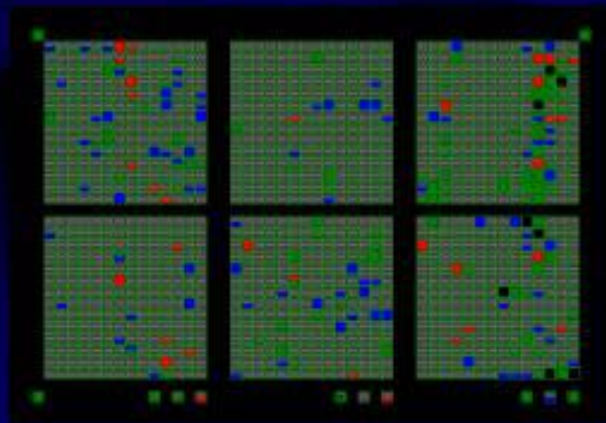
Comparison of Multiple Patients all with Pathologic Diagnosis of Glioblastoma



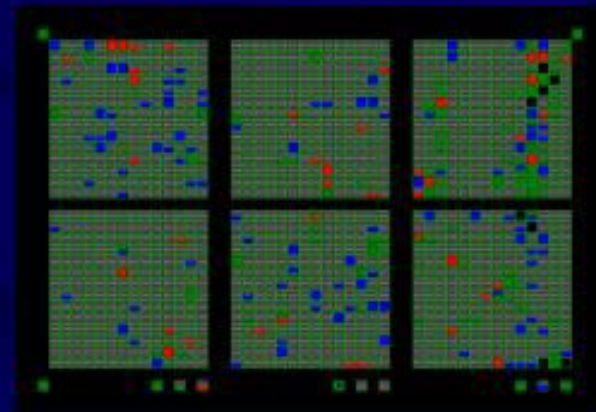
Patient GSR



Patient RSC



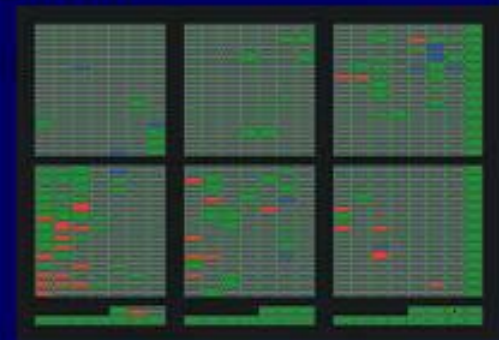
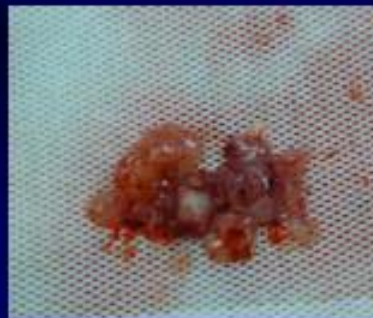
Patient TCW



Patient KJE

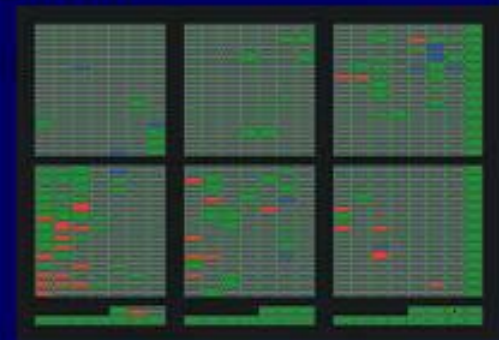
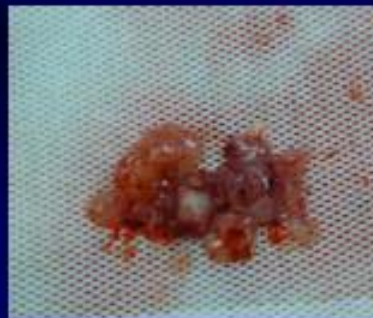
Analysis of Digital Pathologic Diagnosis and Genetic Transcription Profiles in Patients with Malignant Glioma treated with Implantable BCNU

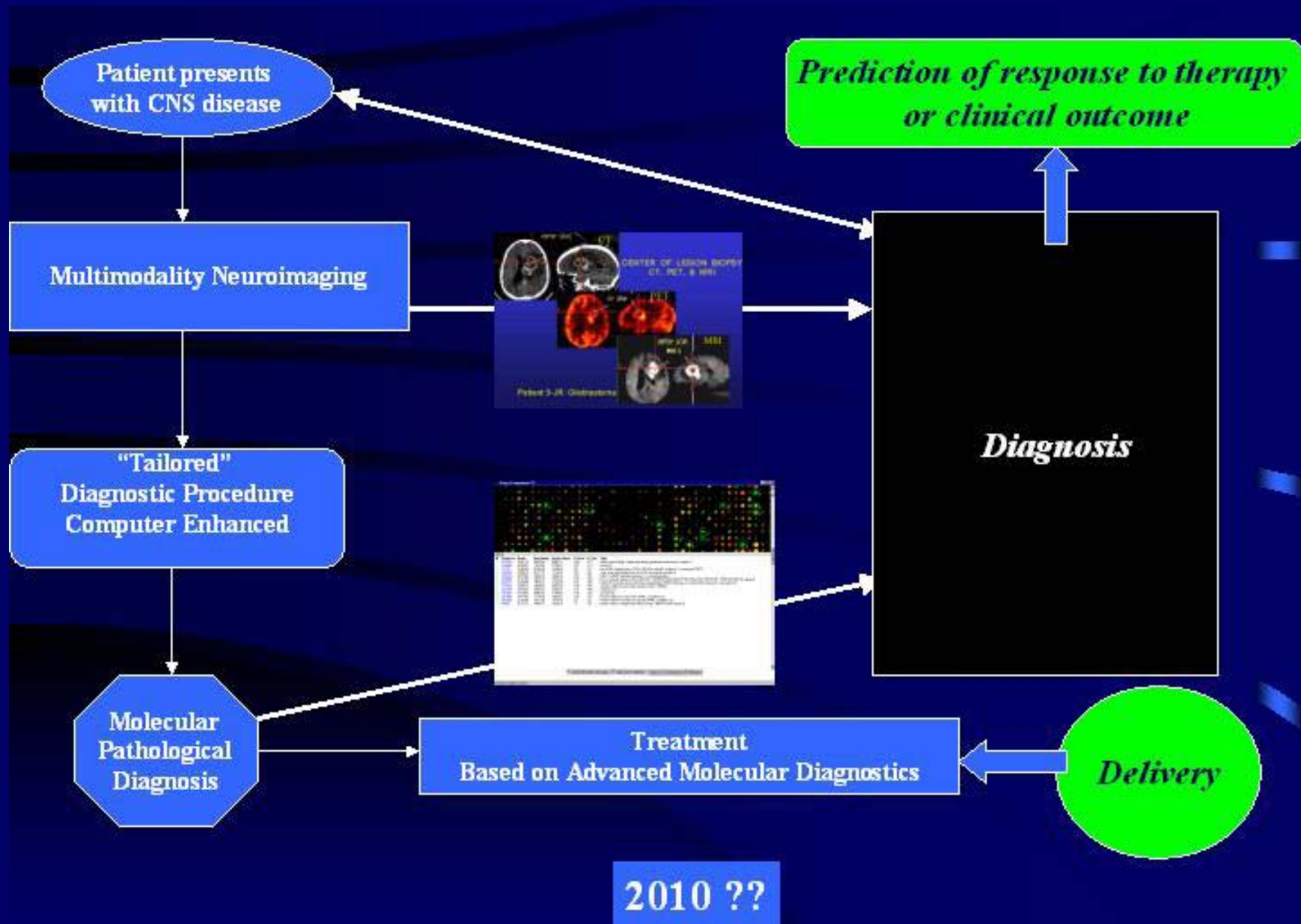
- 25 patients with malignant glioma
- Implanted with BCNU polymer
- Tumor tissue cultured and genetic transcription profile obtained
- Goal is to identify any trends in tumor response linked with gene expression
- Special interest in those undergoing reoperation



Analysis of Digital Pathologic Diagnosis and Genetic Transcription Profiles in Patients with Malignant Glioma treated with Implantable BCNU

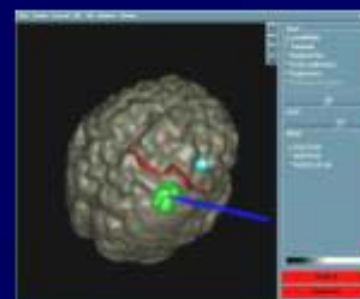
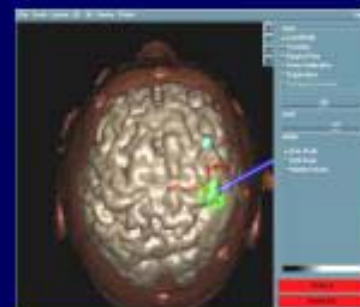
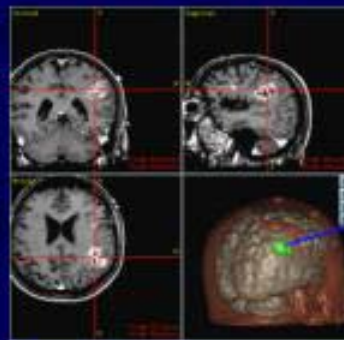
- 25 patients with malignant glioma
- Implanted with BCNU polymer
- Tumor tissue cultured and genetic transcription profile obtained
- Goal is to identify any trends in tumor response linked with gene expression
- Special interest in those undergoing reoperation





Delivery

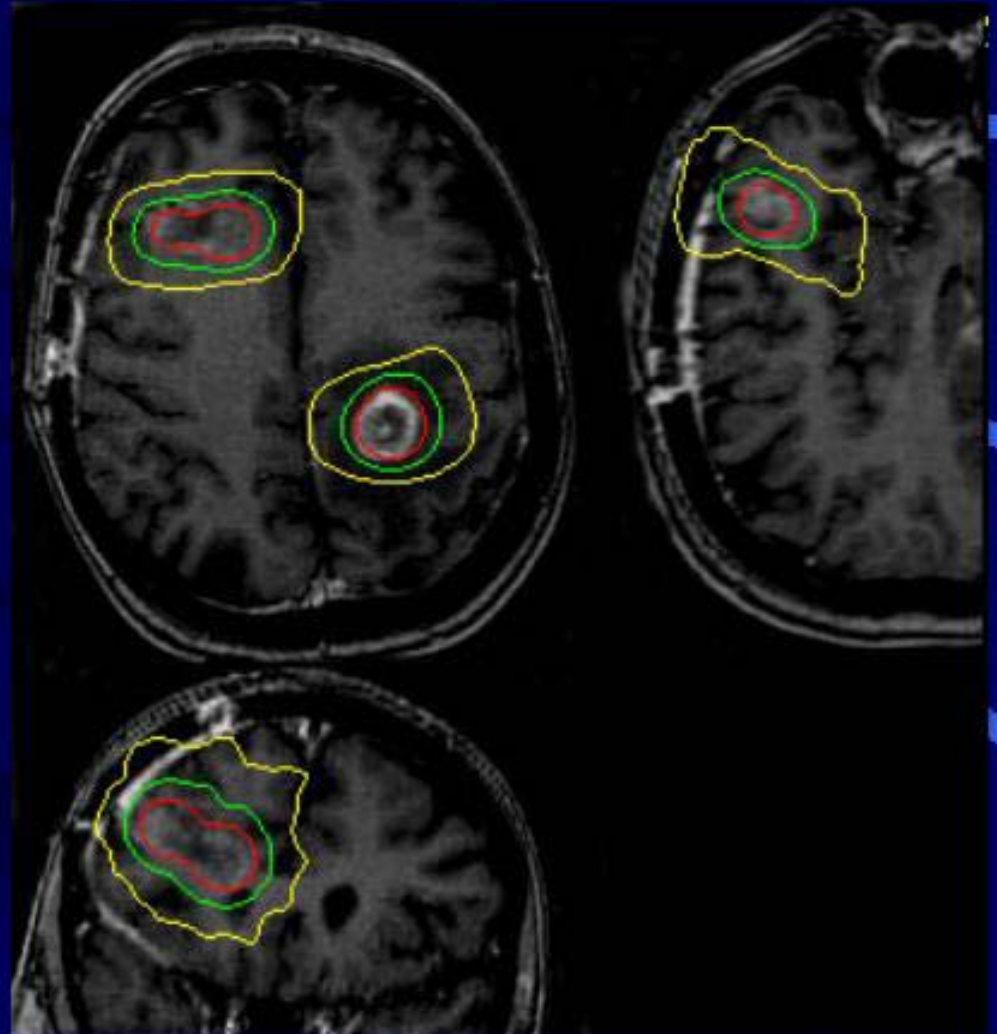
- Image guided surgery
- Stereotactic radiosurgery
- Brachytherapy
- Local drug delivery
 - Polymeric delivery
 - Infusion
- Subselective arterial delivery



Stereotactic Radiosurgery

Framed
Frameless

Cranial
Extracranial



Gliasite – Brachytherapy Catheter



Image Guided Craniotomy: Debulking and Implants

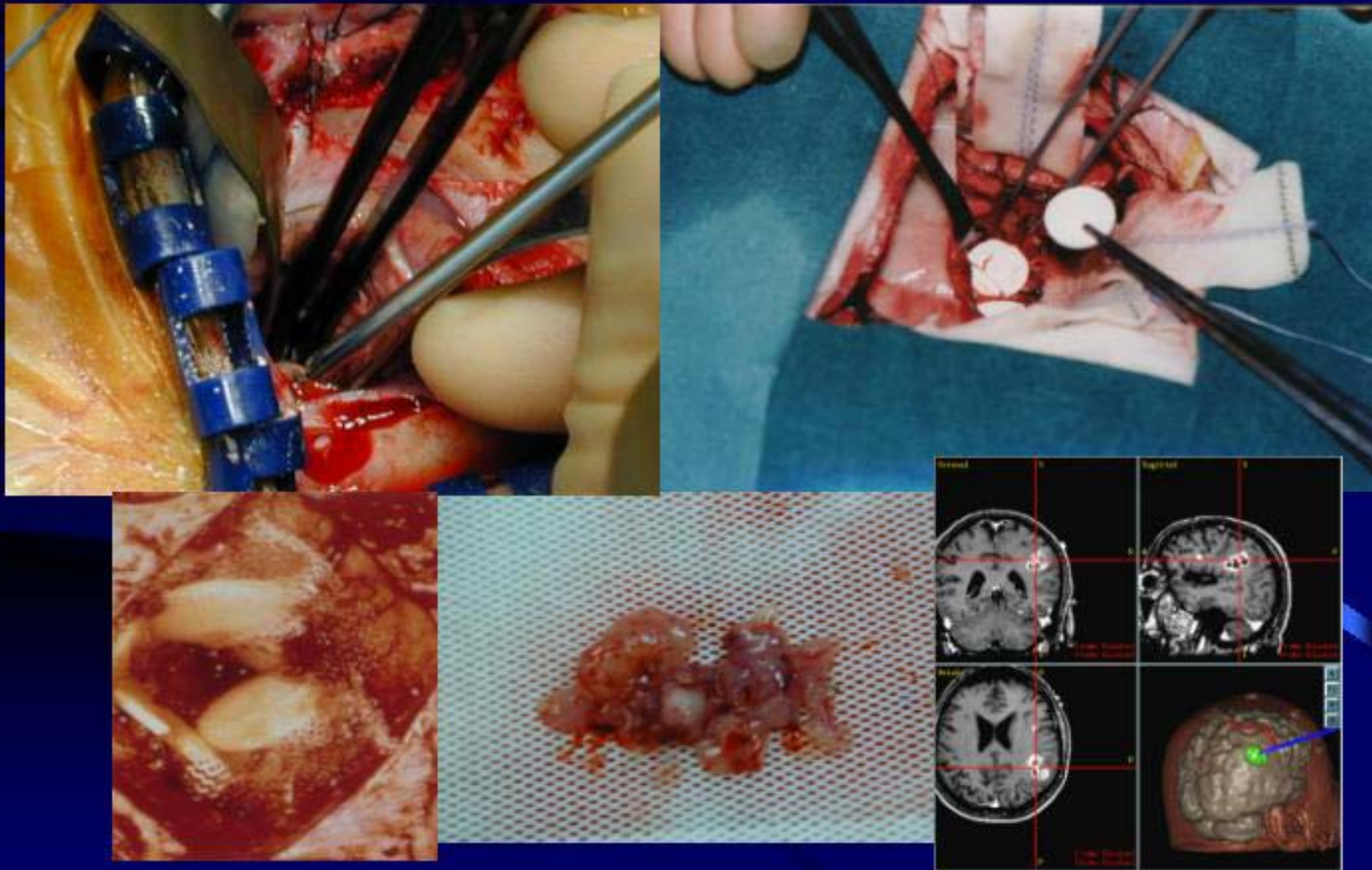
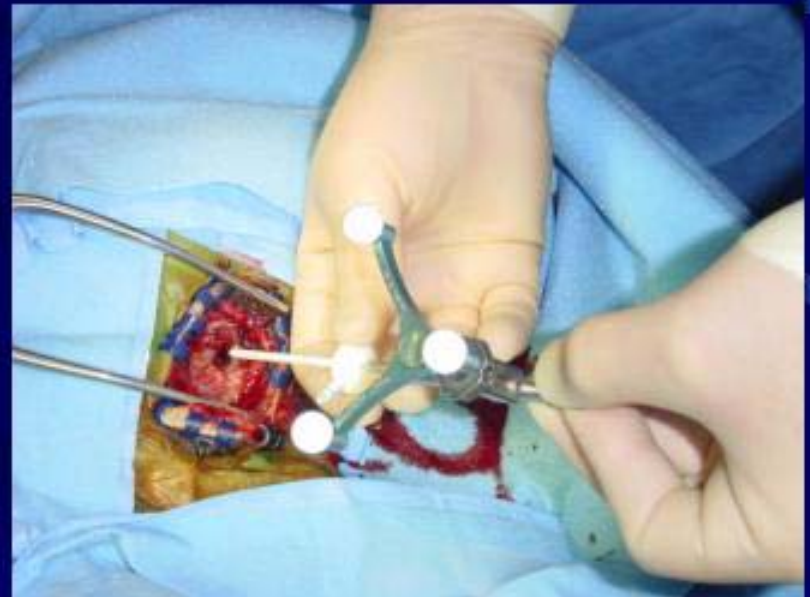
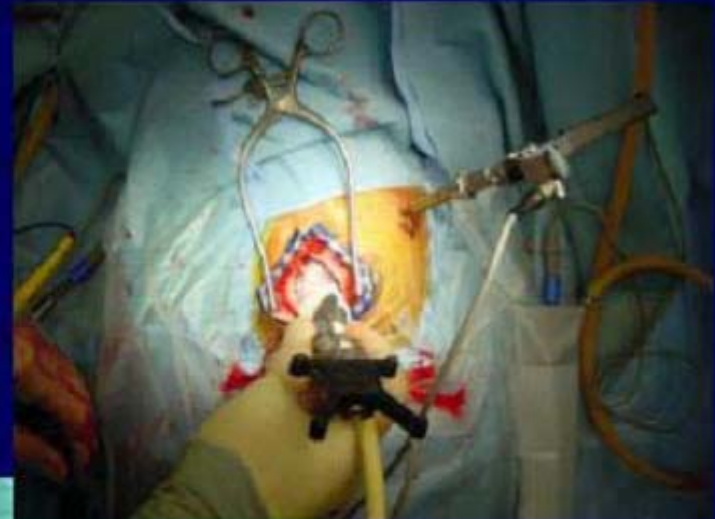


Image Guided Therapy

Equipment modification for real-time tracking



Direct Cranial Fixation for Image Guidance – Awake Craniotomy



Delivery of Genetic Material to the Central Nervous System

Image Guidance



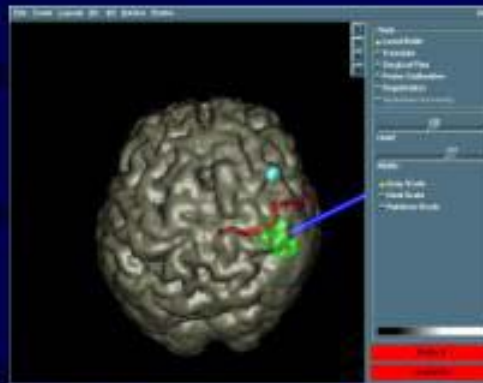
Macroscopic delivery

Injection

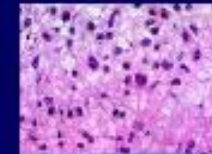
Infusion

Particle delivery

Regional electroporation



Site Specific Delivery



Cellular level (transfection)

Vectors

Cell-mediated

Effectors

Promoters

Transcription factors

Immunomodulation

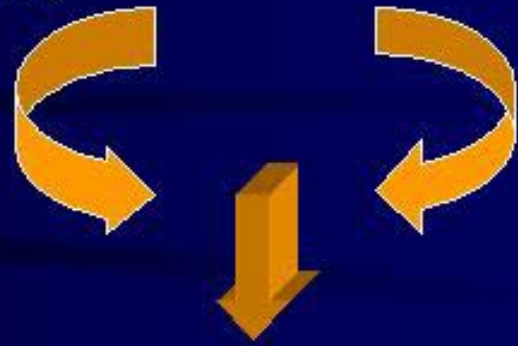
Treatment of CNS Disease:

Gene replacement

Polymeric delivery

Growth factor inhibitors

Viral vectors



Immuno-modulation

Anti-sense vectors

Apoptosis agents

Biological inhibitors

Cell implants

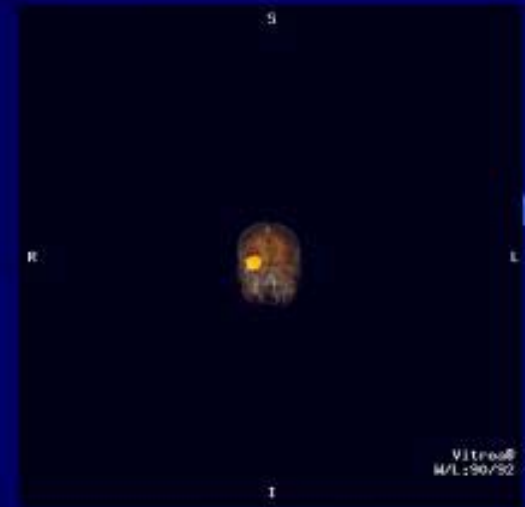
Neurosurgery

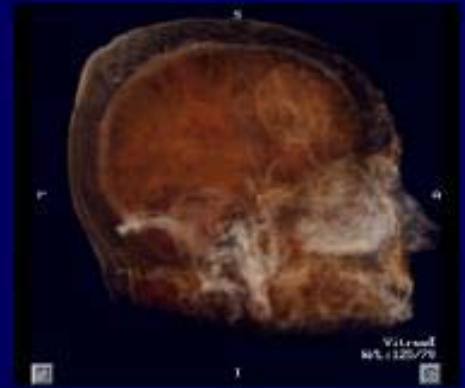
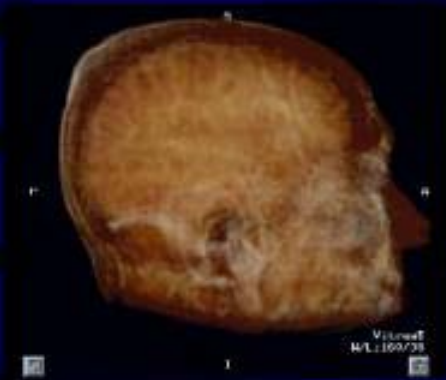
Image Guidance



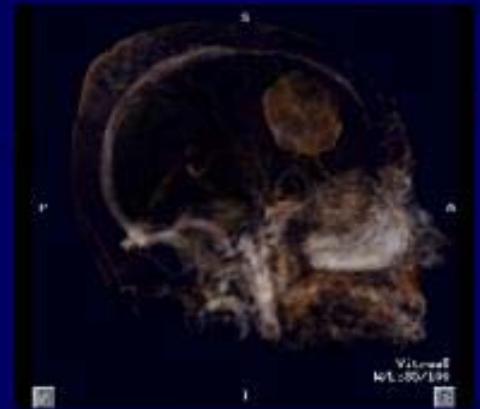
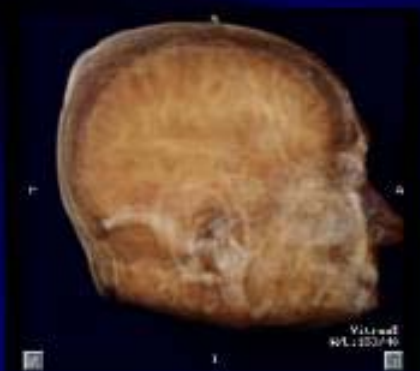
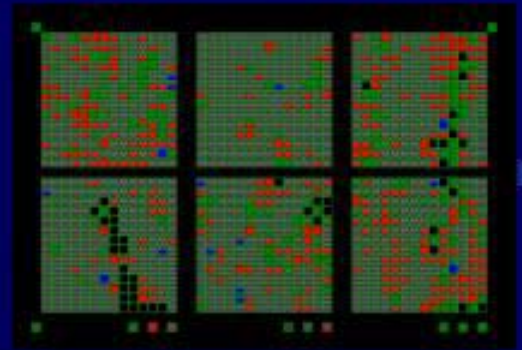
Treatment

Targetted CNS Delivery





2084 ?



Thank you.