EU Integrated Project eTUMOUR

Project acronym: eTUMOUR
Project full title:
WEB ACCESSIBLE MR DECISION SUPPORT SYSTEM FOR BRAIN TUMOUR DIAGNOSIS AND PROGNOSIS, INCORPORATING IN VIVO AND EX VIVO GENOMIC AND METABOLOMIC DATA
(FP6-2002-LIFESCIHEALTH 503094)

Programme:
SIXTH FRAMEWORK PROGRAMME PRIORITY LSH-2002-2.2.0-5
Molecular imaging for early detection of tumours and monitoring of treatment

Period: February 1, 2004 till January 31 2009 (5 years)
Budget: 7.5 million € EU financing; 9.633 million € Overall
Participants: 21 partners (14 public institutions and 7 companies)
Coordinator: Prof. Dr. Bernardo Celda, Univ. de Valencia, Spain
Website: http://www.uv.es/etumour

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Antecedentes

- Los tumores cerebrales afectan a una ↑ % de la población europea aumentando al incrementarse las expectativas de vida.
- Los tumores del SNC es hoy en día la causa de mortalidad líder en niños por debajo de 15 años y la segunda causa de muerte por cáncer para edades comprendidas entre 15-34 años.
- Diagnóstico y tratamiento de tumores del SNC está basado en la clínica, radiología y histopatología.
- La respuesta a la terapia de tumores con características Histológicas o radiológicas similares es muy variable, especialmente en tumores pediátricos.

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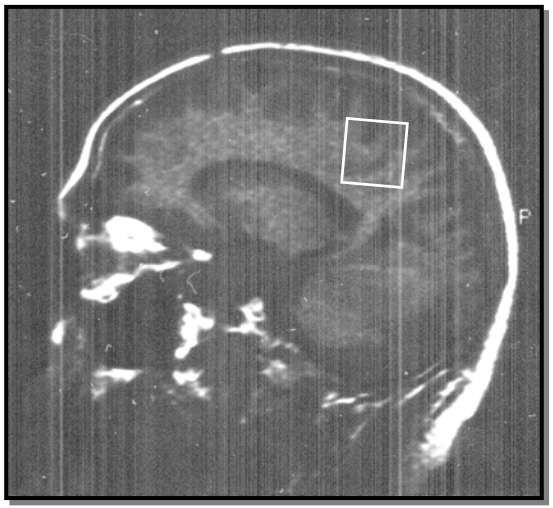
Antecedentes

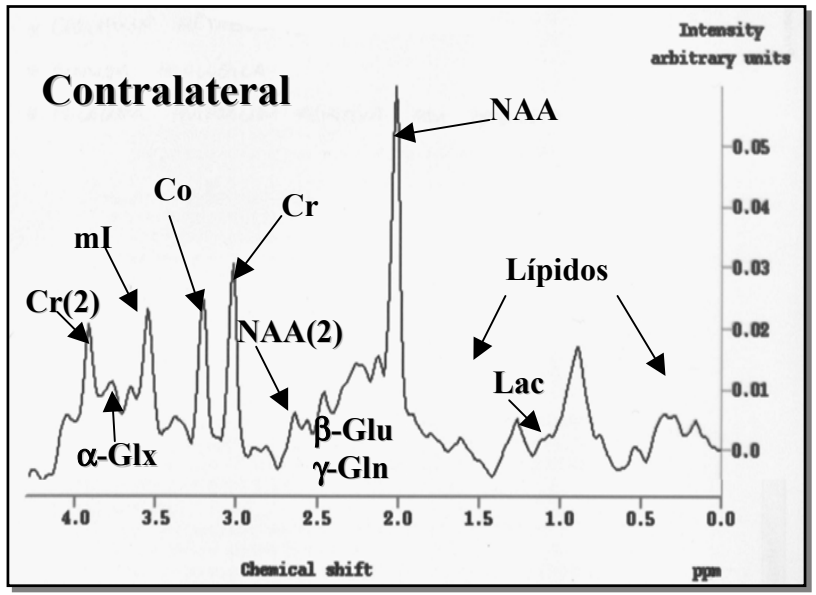
- El diagnóstico no cruento por la imagen (RMI) sólo alcanza 60-90% de precisión en función del tipo de tumor y grado.
- Actual "gold standard" → histopatología de biopsias implica un proceso quirúrgico "invasivo" con un riesgo 1-2% de mortalidad.
- Necesario una mejora para la clasificación y gradación no cruenta para diagnóstico y pronóstico de tumores de SNC

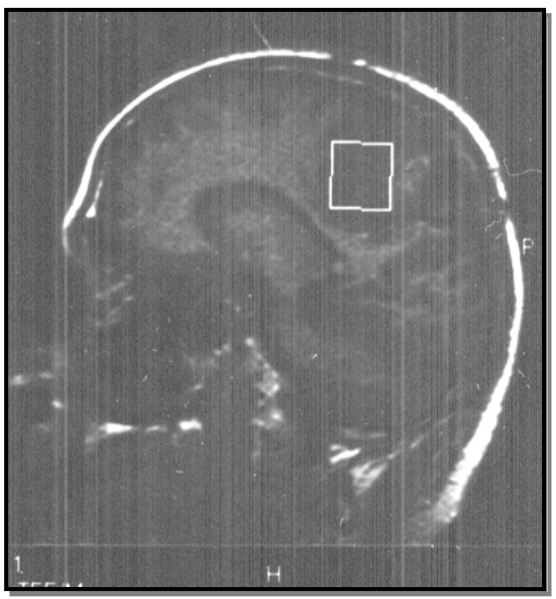
- Tres técnicas disponibles:
  1) ERM in vivo no cruenta
  2) HR-MAS ex vivo → METABOLÓMICA
  3) Chips ADN ex vivo → TRANSCRIPTÓMICA

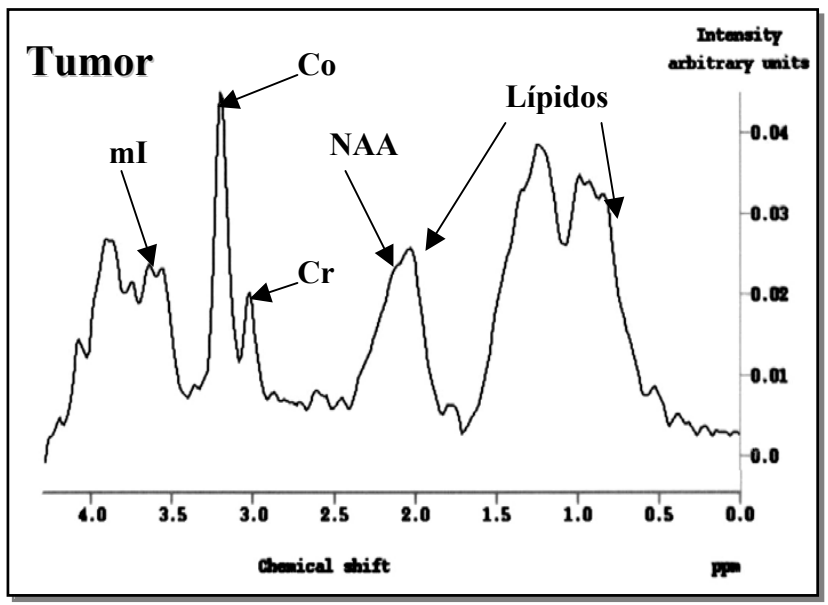
GLIOMA IV

VOI Tumor y contralateral









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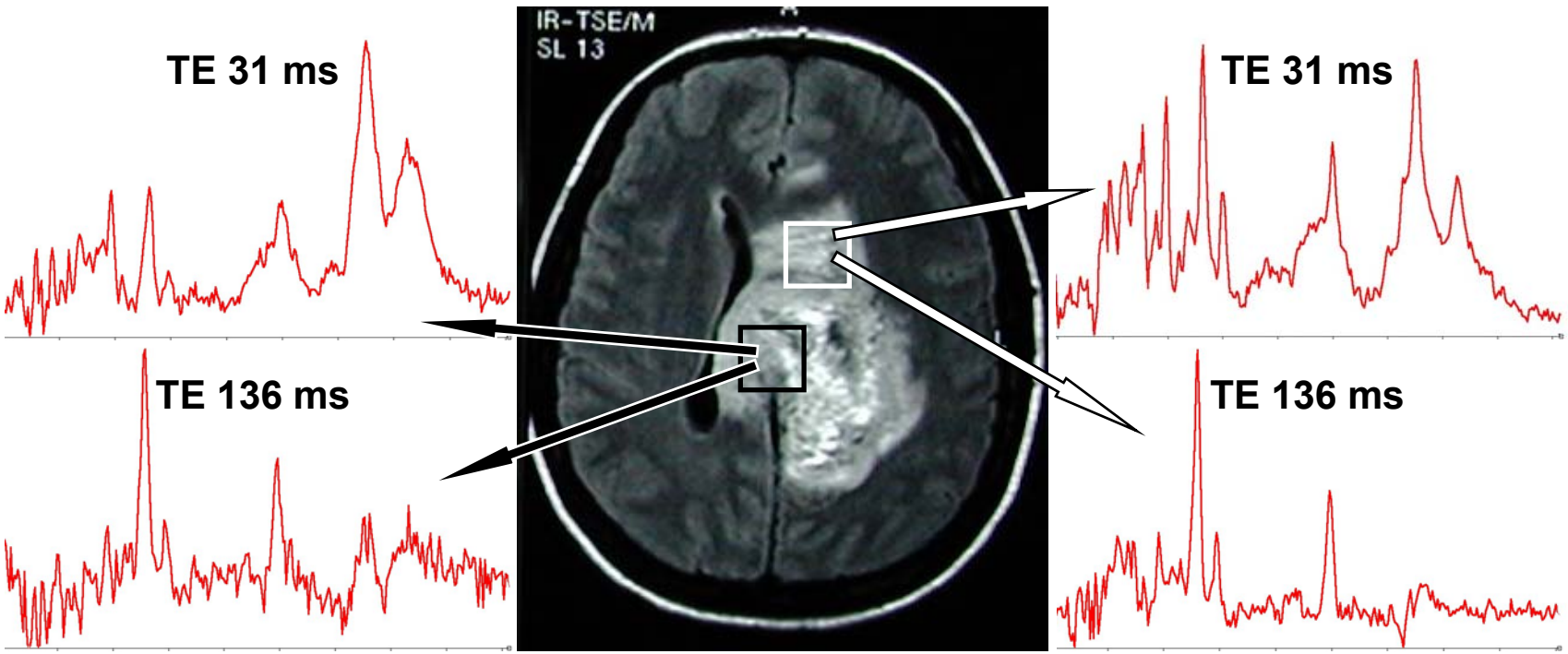
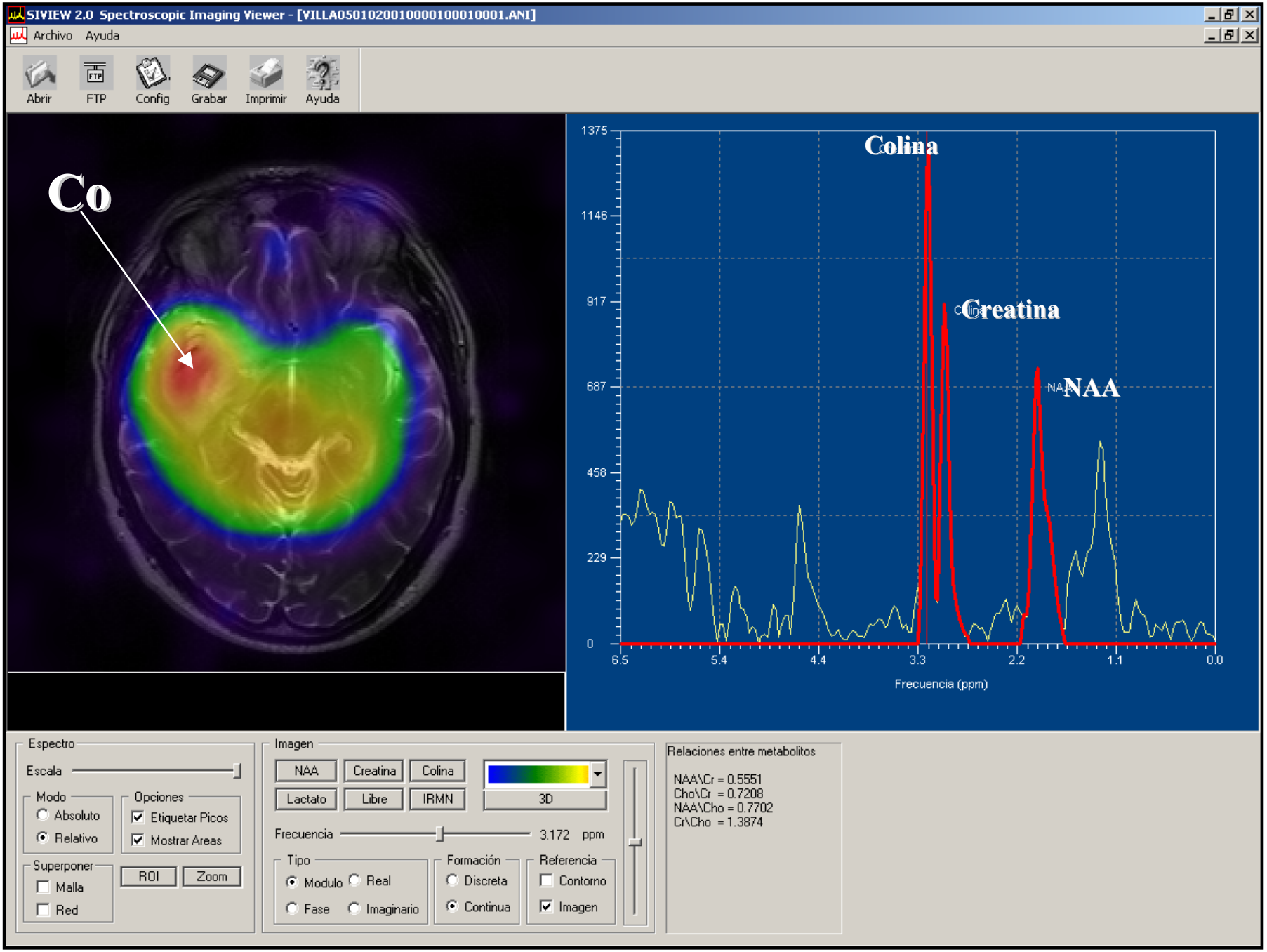
Tumor in vivo ^{1}H ERM a 1,5 T




SIVIEW 2.0 Spectroscopic Imaging Viewer - [VILLA05010200100001000010001.ANI]
Archivo Ayuda
Abrir FTP Config Grabar Imprimir Ayuda
Co
Colina
Creatina
NAA
1375
1146
917
687
458
229
0
6.5 5.4 4.4 3.3 2.2 1.1 0.0
Frecuencia (ppm)
Espectro
Escala
Modo
Absoluto
Relativo
Opciones
Etiquetar Picos
Mostrar Areas
Superponer
Malla
Red
ROI
Zoom
Imagen
NAA
Creatina
Colina
Lactato
Libre
IRMN
3D
Frecuencia
3.172 ppm
Tipo
Modulo
Real
Fase
Imaginario
Formación
Discreta
Continua
Referencia
Contorno
Imagen
Relaciones entre metabolitos
NAA\Cr = 0.5551
Cho\Cr = 0.7208
NAA\Cho = 0.7702
Cr\Cho = 1.3874

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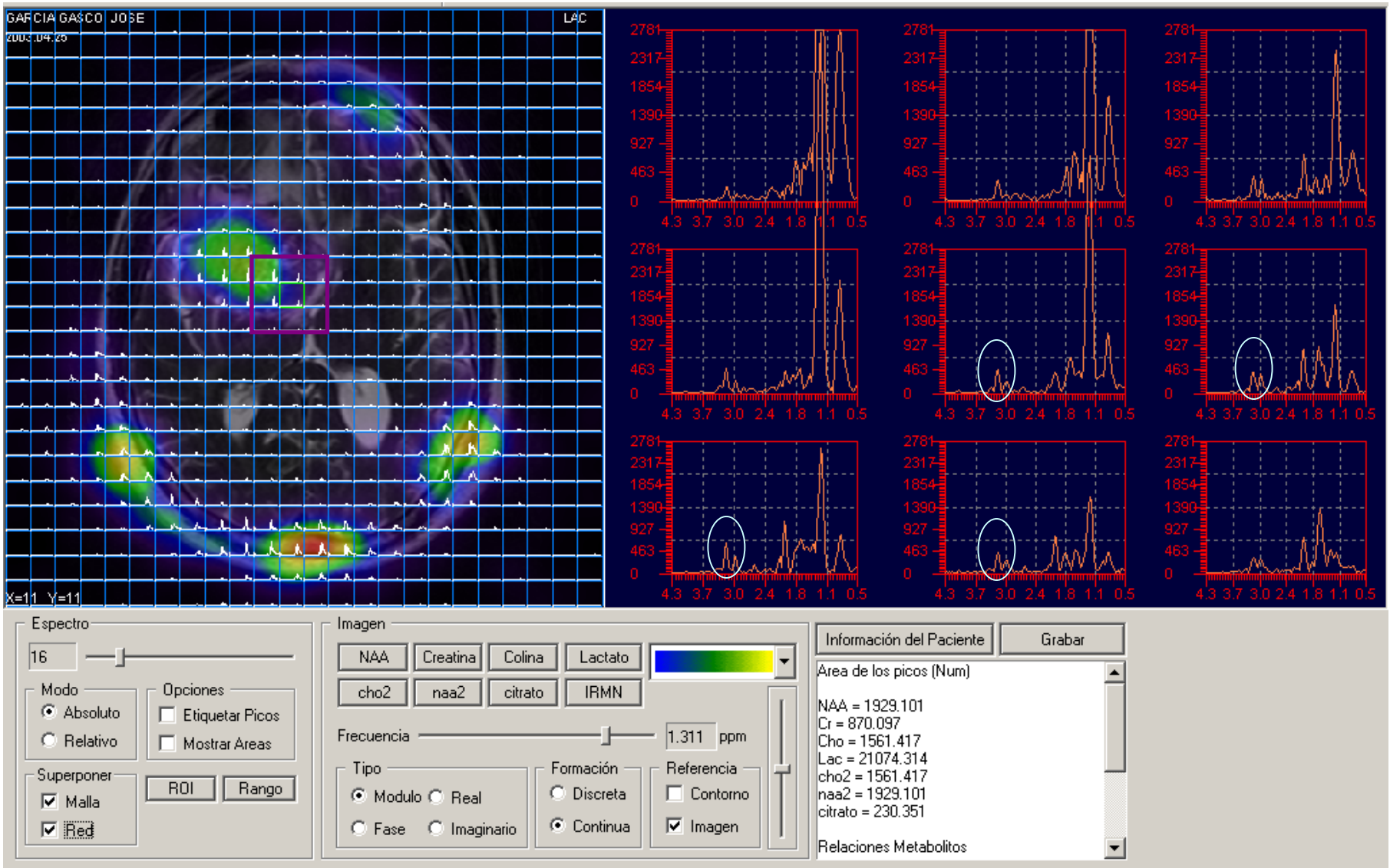
Metástasis



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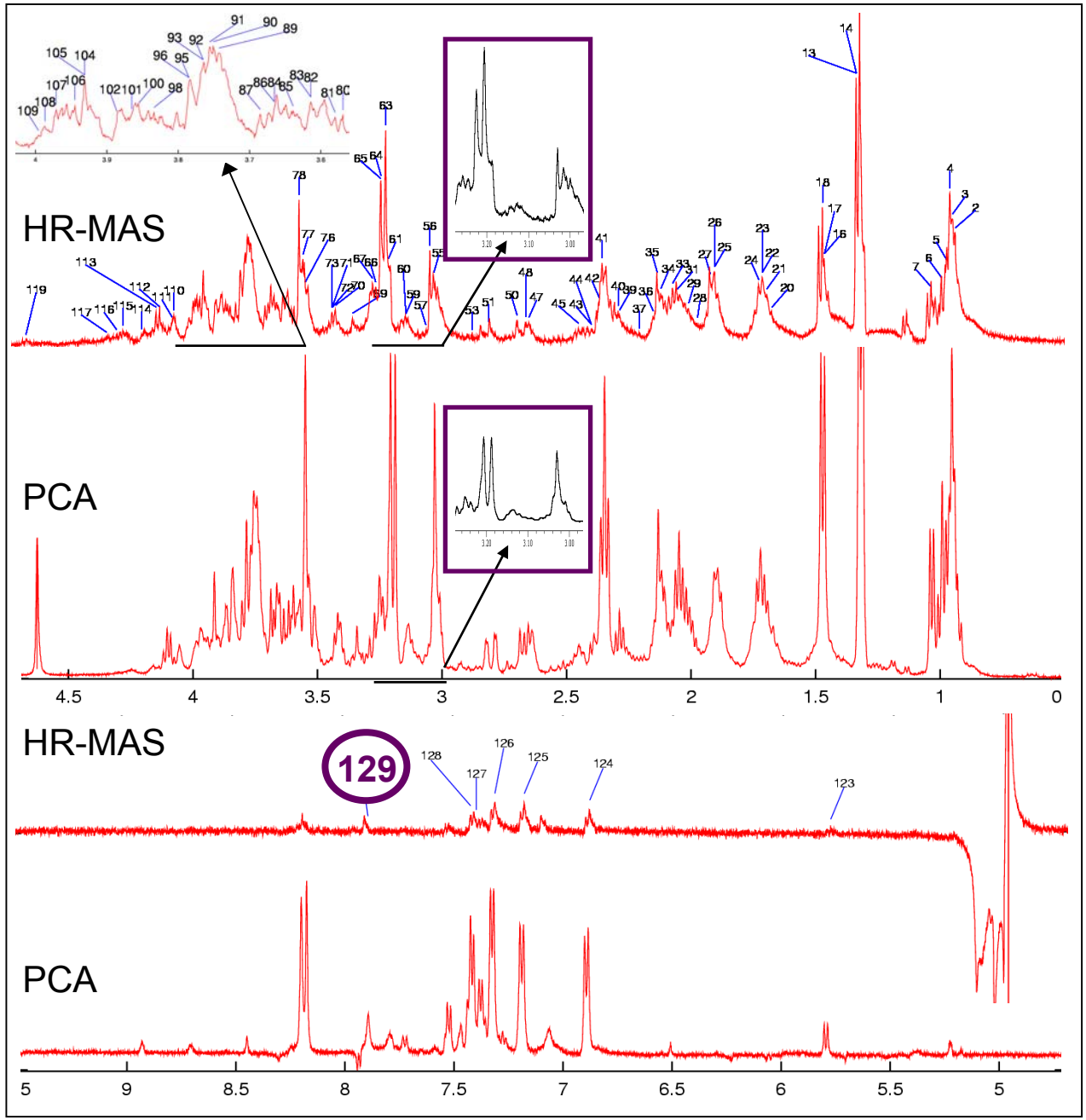
METABOLÓMICA

Estudio de biopsias con HR-MAS (ex vivo)

- T=0 C (4 C interior)
- 4500 Hz
- Aprox. 20 mg de tejido
- Rotor cilíndrico (50 µl)
- (PCA aprox. 2g)
- D_2O ajuste del campo y movilidad



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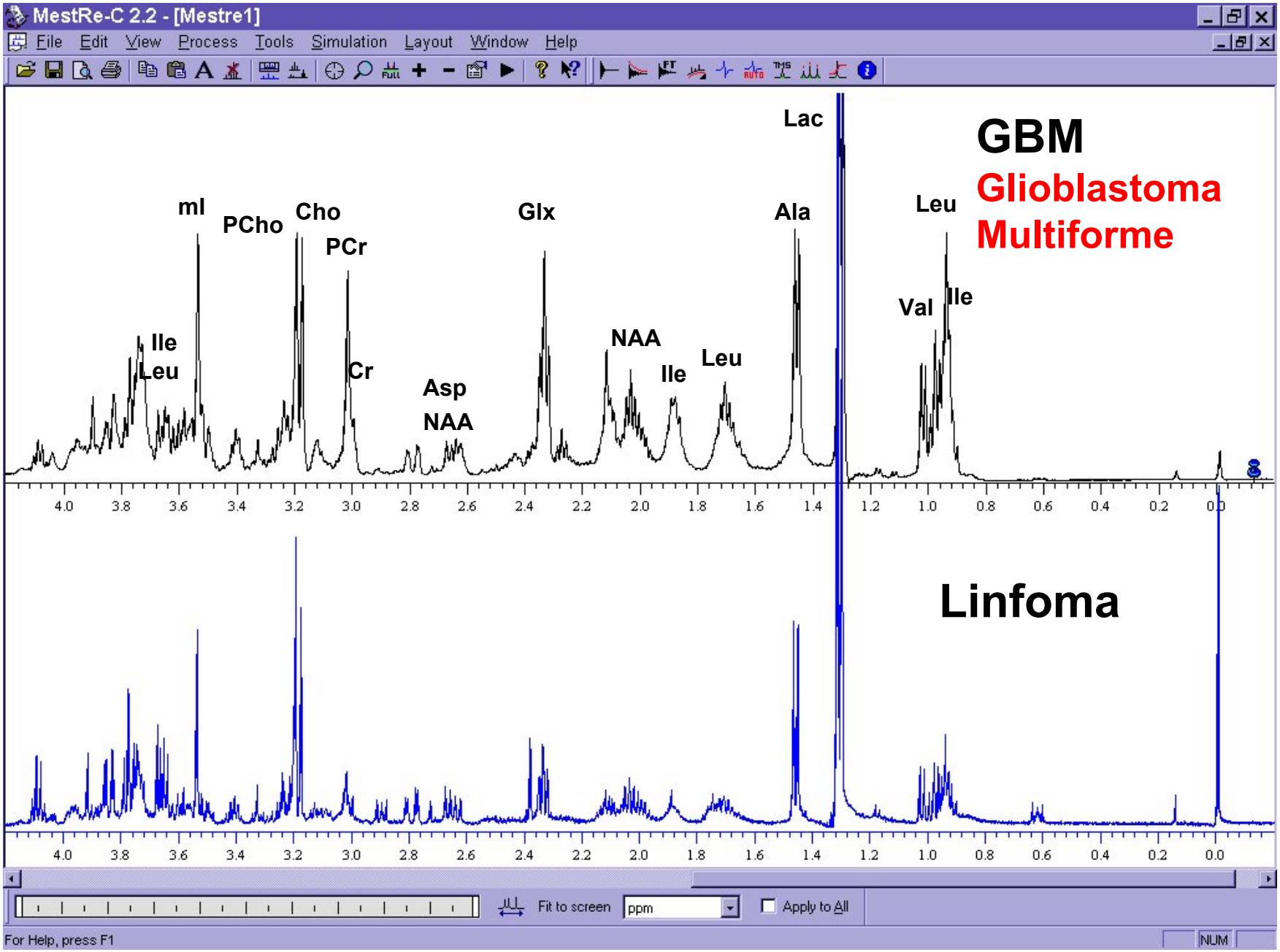
[NMR in Biomedicine, Martínez-Bisbal et al. 2004;17:1-15(2004)]


MestRe-C 2.2 - [Mestre1]
File Edit View Process Tools Simulation Layout Window Help
GBM
Glioblastoma
Multiforme
Lac
mI
PCho
Cho
PCr
Glx
Ala
Leu
Val
Ile
Ile
Leu
Cr
Asp
NAA
NAA
Ile
Leu
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0
Linfoma
4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4 0.2 0.0
Fit to screen
ppm
Apply to All
For Help, press F1
NUM

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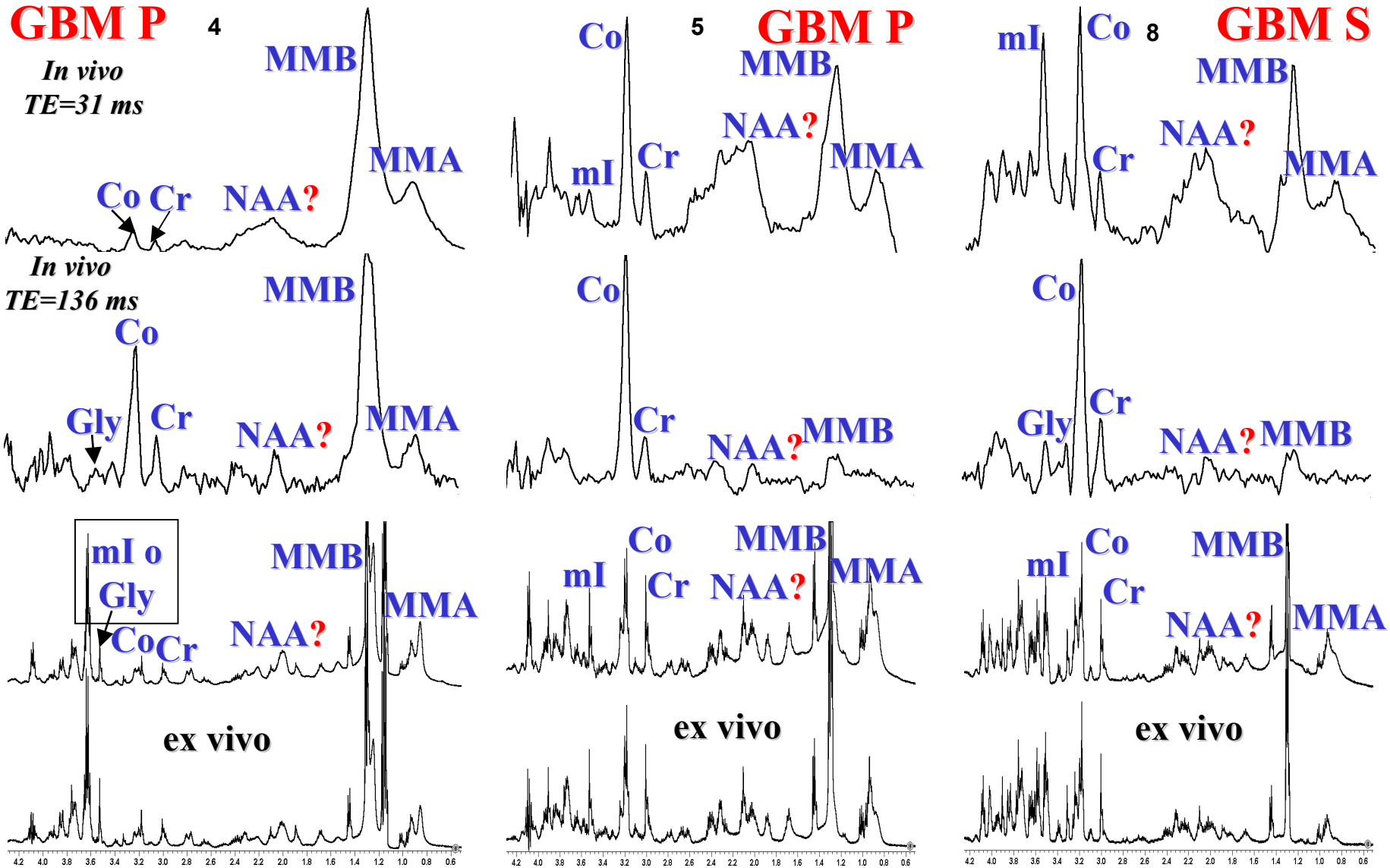

[NMR in Biomedicine, Martínez-Bisbal et al. 2004;17:1-15(2004)]

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University Medical Center Nijmegen
The Netherlands

Gradación de gliomas: características histopatológicas

- polimorfismo nuclear
- actividad mitótica
- necrosis
- proliferación microvascular
- celularidad

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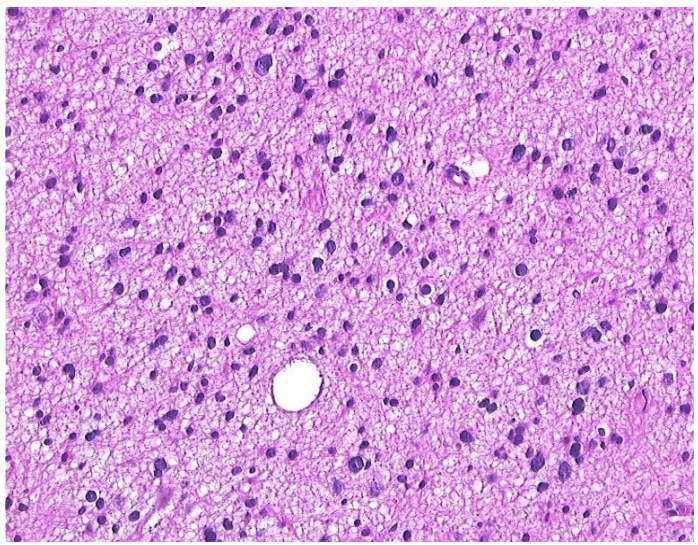
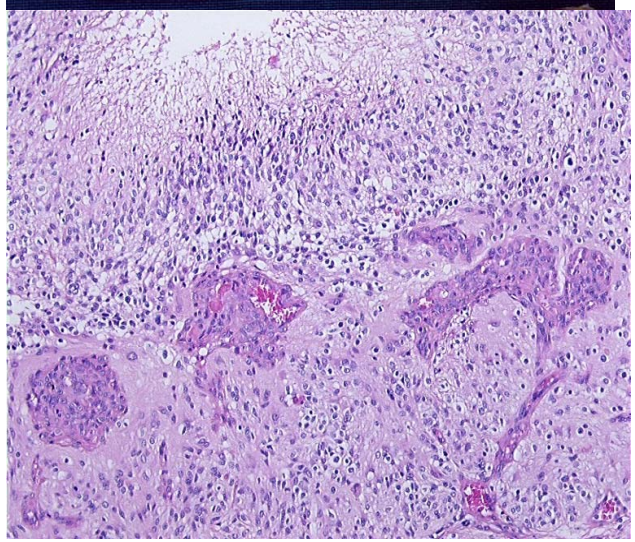
A

GBM





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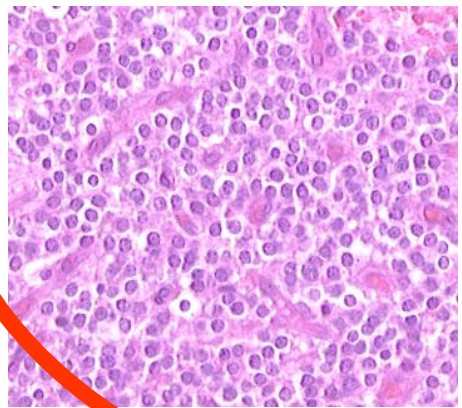
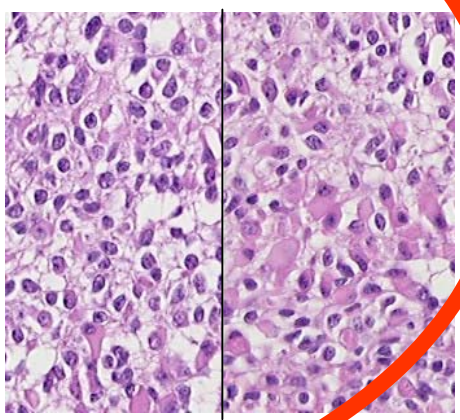
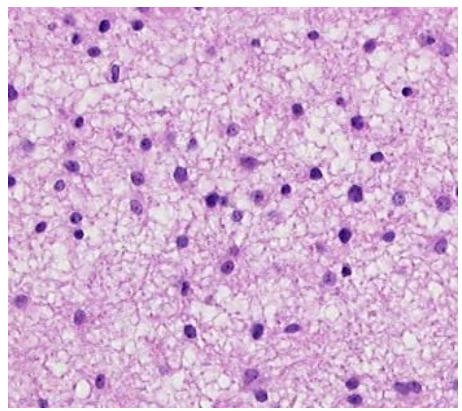
Clasificación Histopatológica de gliomas

Os ⟷ OAs ⟷ As







Oligodendroglial Tumors (OTs)

* Sensible a quimioterapia
* Mejor pronóstico

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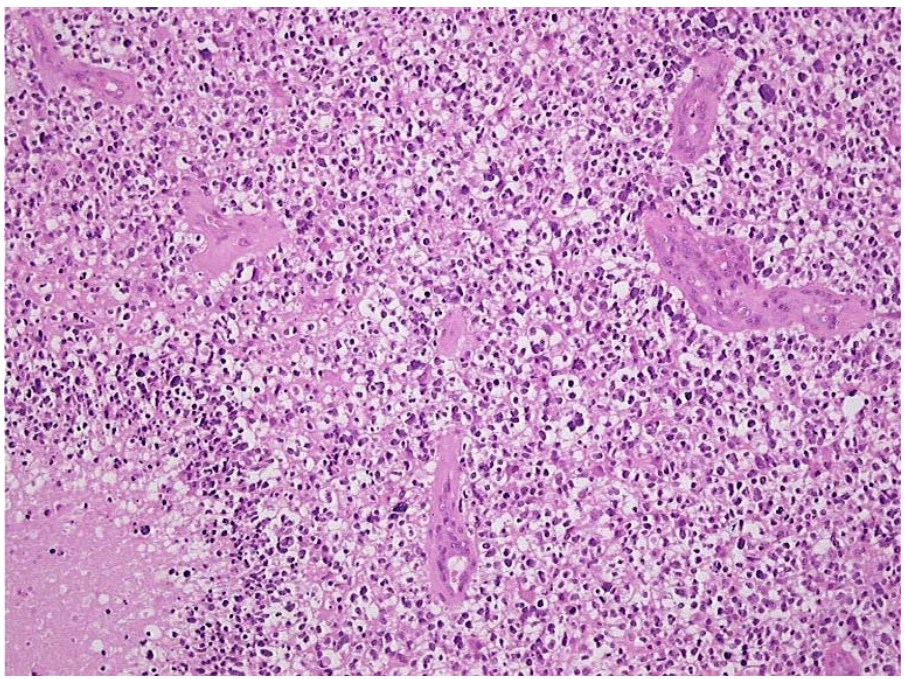
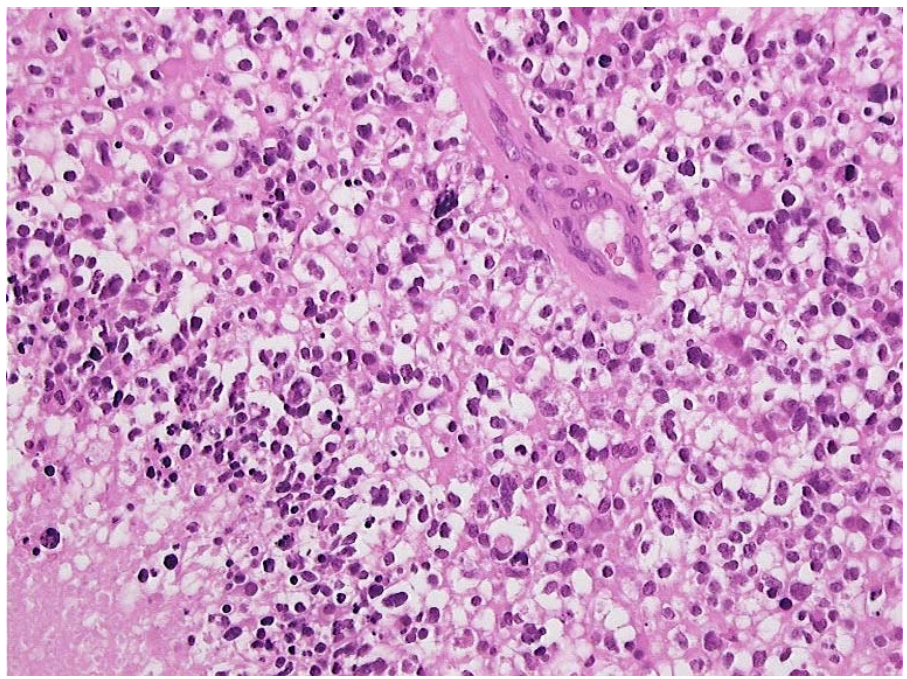
Oligodendroglioma Maligno?
O GBM con características de oligo?





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Genética de los Tumores del SNC

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Subtipos Genéticos de GBMs

Progresión / Secundario evolución

Astrocito Normal

↓ LOH 17p
↓ P53 mutacion (17p13)

Astrocitoma

↓ LOH 19q
↓ LOH 13q
↓ LOH 9p

Astrocitoma Anaplásico

↓ LOH 10q
↓ PTEN mutacóon (10q23)

GBM

De novo / Primario evolución

Astrocito Normal

↓ Amplificación :

EGFR (7p12)
MDM2 (12q14-15)

↓ Deleción (LOH) o mutación :

p16 (9p21)
10p and 10q
RB1 (13q14)

GBM

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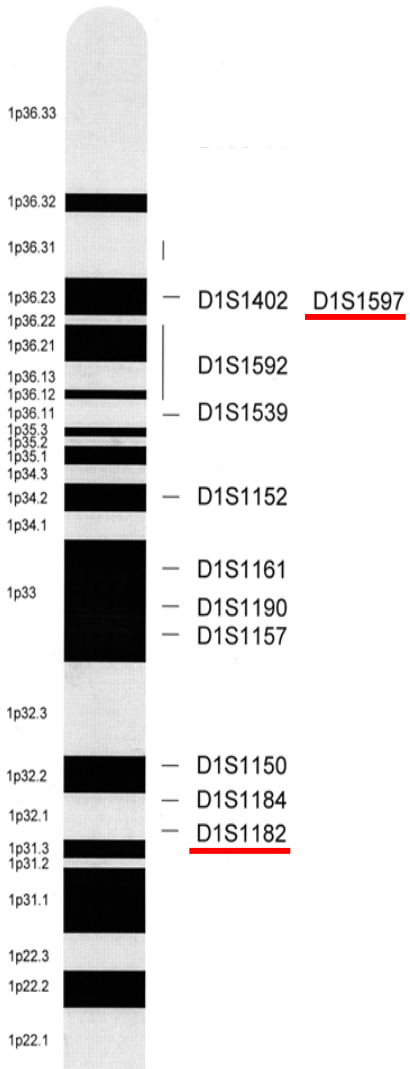
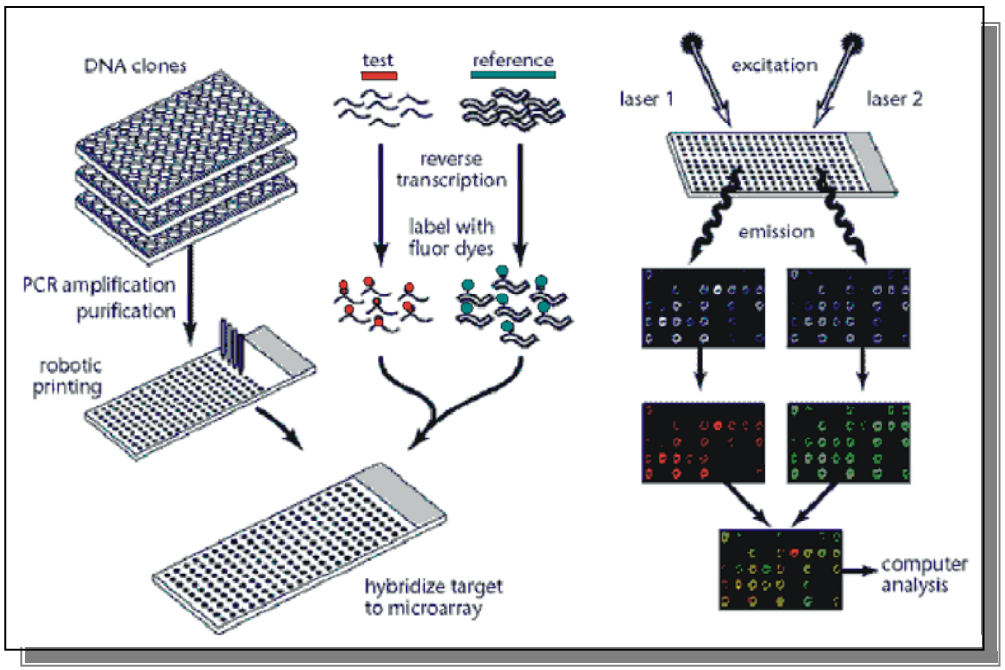
LOH 1p

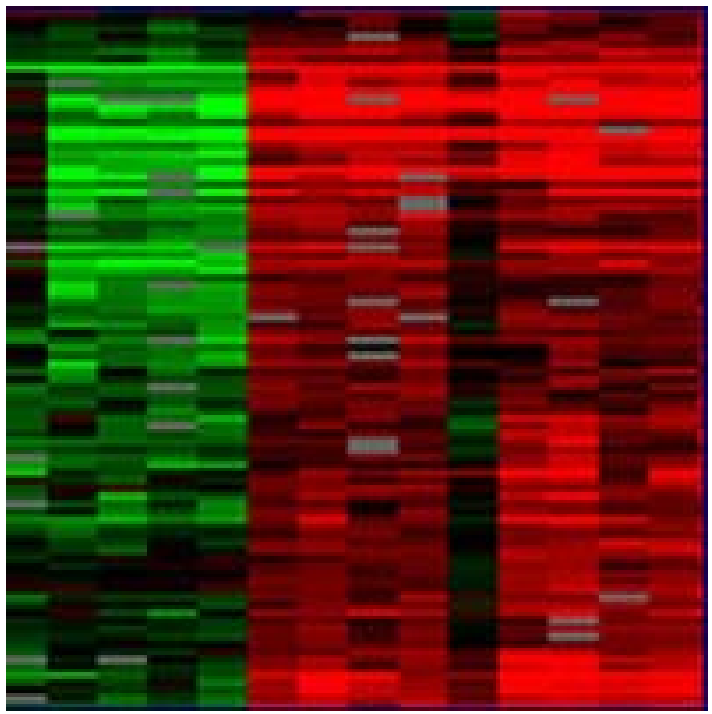


ID 23462
Oligoastrocitoma
WHO Grado II

ID 23434
Anaplásico
oligodendroglioma
WHO Grado III

Transcriptómica eTUMOUR





EU Integrated Project eTUMOUR

eTUMOUR GENERAL OBJECTIVES

- eTUMOUR aims to create a comprehensive Web-accessible Decision Support System (DSS) for analysis and interpretation of in vivo Magnetic Resonance Spectroscopy and Imaging (MRS & MRI) data of brain tumours
- includes a database of clinical, histological, metabolic (NMR HR-MAS) and molecular phenotype data from brain tumour patients
- the DSS will facilitate evidence-based clinical decision-making using MR and include new criteria such as genetic based tumour classifications
- the DSS will be also designed with Agent Technology to create a secure distributed database accessible trans-nationally by collaborating centres

EU Integrated Project eTUMOUR

eTUMOUR PARTICULAR OBJECTIVES (1)

- Acquire *in vivo* MRS/MRI and clinical (histopathology, treatment response and patient outcome) data from brain tumour patients
- Acquire *ex vivo* HR MAS (metabolomic) and DNA microarray (transcriptomic) data from tumour biopsies
- Correlate metabolomic with transcriptomic profiles of tumours and correlate these with clinical data
- Implement pattern recognition methods for classification and analysis of in vivo MRS and ex vivo HR-MAS and microarray data
- Develop transcriptomic based tumour classifications
- Develop new microarrays specific to tumour classification

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eTUMOUR PARTICULAR OBJECTIVES (2)

- Improve our classification of *in vivo* molecular MRS imaging of tumours and understanding of tumour biology by using *ex vivo* metabolomic and transcriptomic data
- Develop automated processing, analysis and display for molecular imaging by MRS
- Use Agent Technology to securely integrate multi-site data for access by the DSS, for pattern recognition (PR)
- Analysis on distributed data, for data sharing and for DSS updating
- Create a web-based Decision Support System (DSS) with a distributed database that incorporates clinical, metabolomic, transcriptomic data and the MRS processing and classification prototype
- Prospectively evaluate the DSS in a clinical demonstration of added value

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SCIENTIFIC OBJECTIVES	Users of the outcomes (apart from partners)
Clinical demonstration of the added value of combined MRI/MRS use in the DSS for diagnostic accuracy support over conventional radiology.	Clinicians. Government Agencies. MR companies.
Introduction of DNA microarray analysis of tumour biopsies as an adjuvant in tumour classification.	Pathology services at major hospitals. Pharmaceutical companies.
High field MRS of biopsy tissue to improve under-standing of tumour biology, classification and grading, and to aid diagnosis and prognosis using new high field (≥3T) whole body MR systems.	Cancer researchers. Pharmaceutical companies. High-field ex vivo MRS researchers and users of new high-field in vivo MR systems. Developers of DSS upgrades
Publications and PhD's	Scientific and industrial MR community

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TECHNOLOGICAL OBJECTIVES	Users of the outcomes (apart from partners)
Development of a secure distributed database using Agent Technology with web server DSS access	Clinical centres worldwide (≈ 5600) with 1.5 T (and 3T) MRI/MRS scanners
The development of the GUI as a learning tool for proper MRS use by radiologists	Teaching institutions. Radiology departments. Data-mining groups
Automated processing & analysis software for incorporation of molecular imaging by MRS into the DSS in real time.	Future users of the DSS
GUI guided advice on optimal MRI and MRS acquisition protocols for differential diagnosis.	Clinical MR centres. Companies making MR scanners.
Contribution to the development of a DICOM MRS standard.	Companies developing MR scanners and postprocessing software for MRI/MRS.
Consensus protocols for acquisition of all MRS/MRI data compatible with DSS use.	Future DSS users. Researchers into MR diagnosis of other abnormal brain masses and neuro-degenerative diseases.
MR system and patient data quality control protocols for data acceptance into the DSS.	MR clinical centres. Future DSS users. MR Industry.

EU Integrated Project eTUMOUR

List of Participants

CO	1	Prof. Dr.Bernardo Celda, Universitat de Valencia – Estudi General	UVEG	Spain
CR	2	Prof Carles Arús, Universitat Autònoma de Barcelona	UAB	Spain
CR	3	Dr Franklyn Arron Howe, St George's Hospital Medical School	SGHMS	United Kingdom
CR	4	Prof Arend Heerschap, University Medical Centre Nijmegen	UMCN	The Netherlands
CR	5	Prof Lutgarde Buydens, Stichting Katholieke Universiteit	KUN	The Netherlands
CR	6	Dr Anne Ziegler, INSERM U594	U594	France
CR	7	Mr Magí Lluch, MICROART, S.L.	MICROART	Spain

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List of Participants

CR	8	Dr Antoni Capdevila, Hospital San Joan de Deu	HSJD	Spain
CR	9	Dr Fernando Geijo, Pharma Quality Europe, s.r.l.	PQE	Italy
CR	10	Dr Luigi Visani, Hyperphar Group SpA	HG	Italy
CR	11	Prof. Sabine van Huffel, Katholieke Universiteit Leuven Research & Development	KUL	Belgium
CR	12	Dr Ruud de Boer, Philips Medical Systems Nederland B.V	Philips	The Netherlands
CR	13	Dr Peter Kreisler, Siemens AG, Medical Solutions	Siemens	Germany
CR	14	Dr Arno Klaassen, SCITO, S.A.	SCITO	France

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List of Participants

CR	15	Dra. Montserrat Robles, Universidad Politécnica de Valencia	UPVLC	Spain
CR	16	Prof Semmler Wolfhard, Deutsche Krebsforschun-gszentrum Heidelberg	DKFZ	Germany
CR	17	Dr Christian Brevard, BRUKER BIOSPIN SA	Bruker	France
CR	18	Dr Richard Grundy, Institute of Child Health, University of Birmingham	BU	United Kingdom
CR	19	Dr François Berger, INSERM U318	U318	France
CR	20	Dr Jorge Calvar, FLENI	FLENI	Argentina
CR	21	Dr Witold Gajewicz, Medical University Lodz	MUL	Poland

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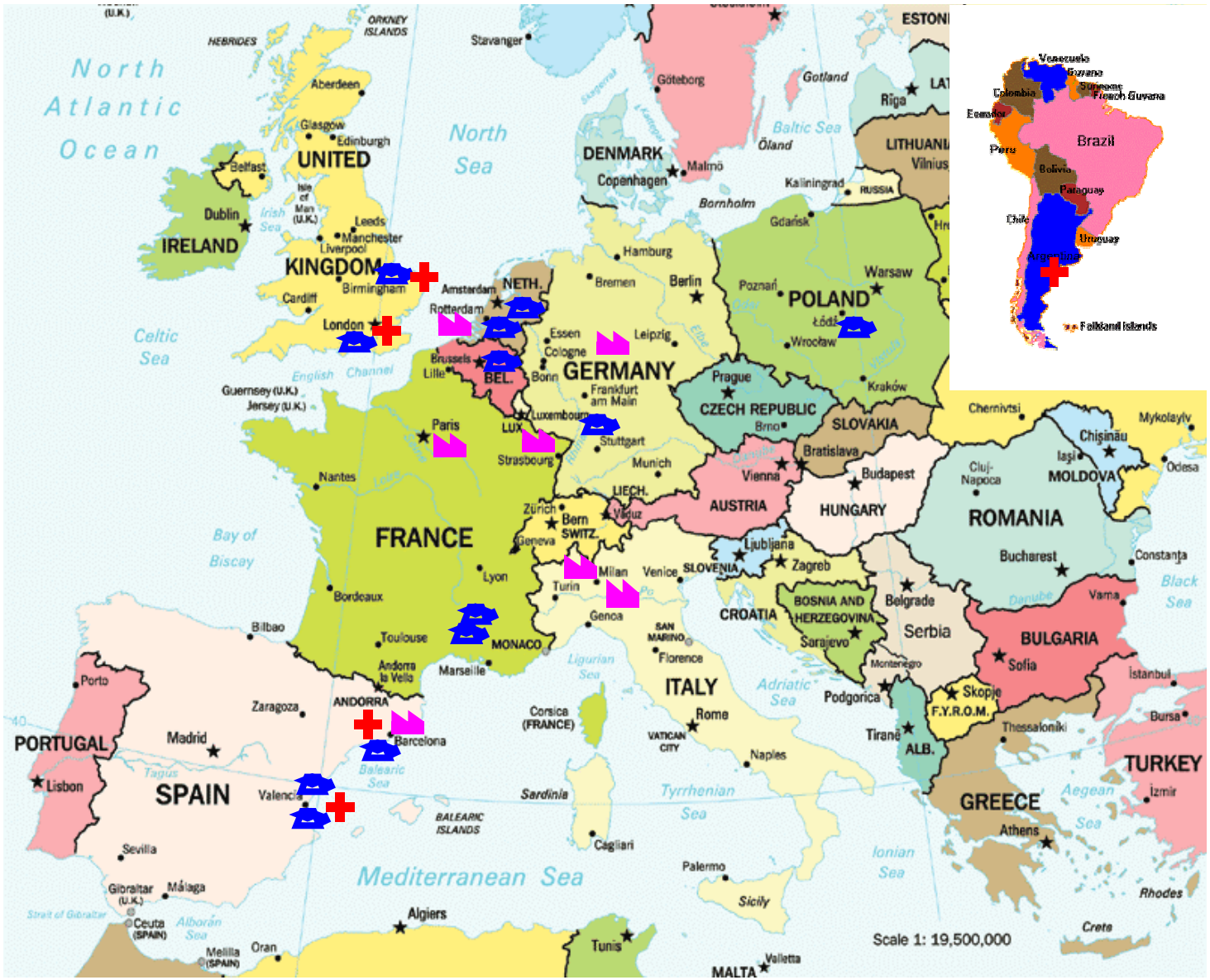

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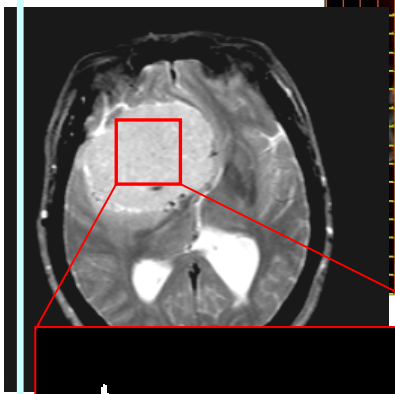
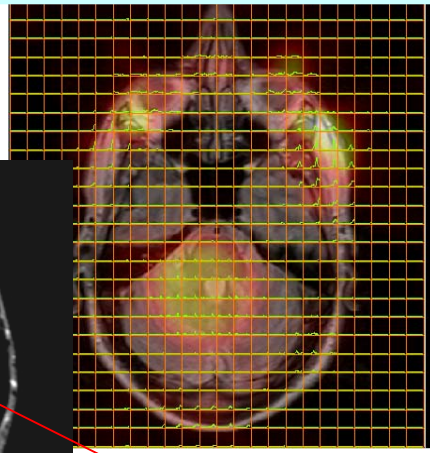
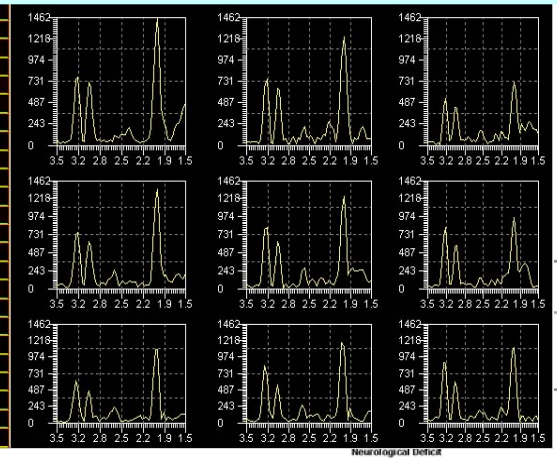
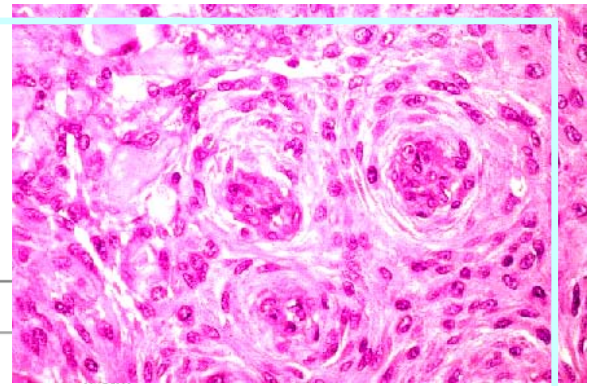
Workpackage Description

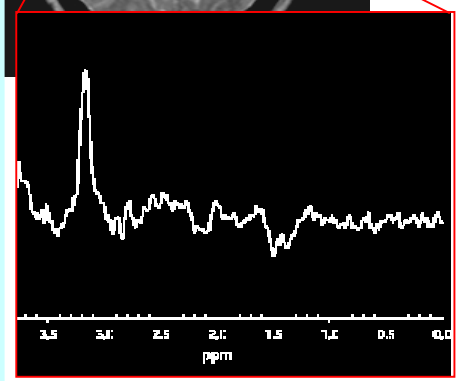
Workpackage	Description	Leader
WP1	Management	Prof. Bernardo Celda
WP2	Data	Prof. Carles Arús
WP3	Pattern Recognition	Dr. Montserrat Robles
WP4	DSS Development	Dr. Anne Ziegler
WP5	Clinical Demonstration Added Value	Dr. Luigi Visani
WP6	Quality Assessment	Dr. Gilda D'Incerti
WP7	Diffusion and Implementation	Mr. Magí Lluch
WP8	Industrialization and CE Marketing	Dr. Arno Klaassen











Neurological Deficit

Coma (G CS less or equal to 8)

Medication at Time of Spectroscopy

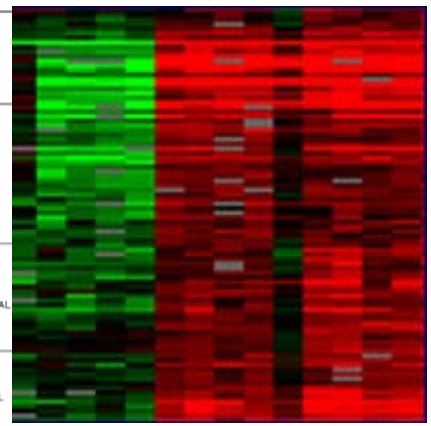
		Drug taken:
Steroids	NO	DEXAMETASONA
Anticonvulsants	NO	NA
Gadolinium	NO	
Anæsthetic Agents	NO	NA
Mannitol	NO	

Radiology - MRI or CT Scan Findings

Bleed into Tumour	NO
Tumour Location	RIGHT FRONTAL
Tumour Size (Diameter mm)	65
Radiological Diagnosis	MENINGIOMA

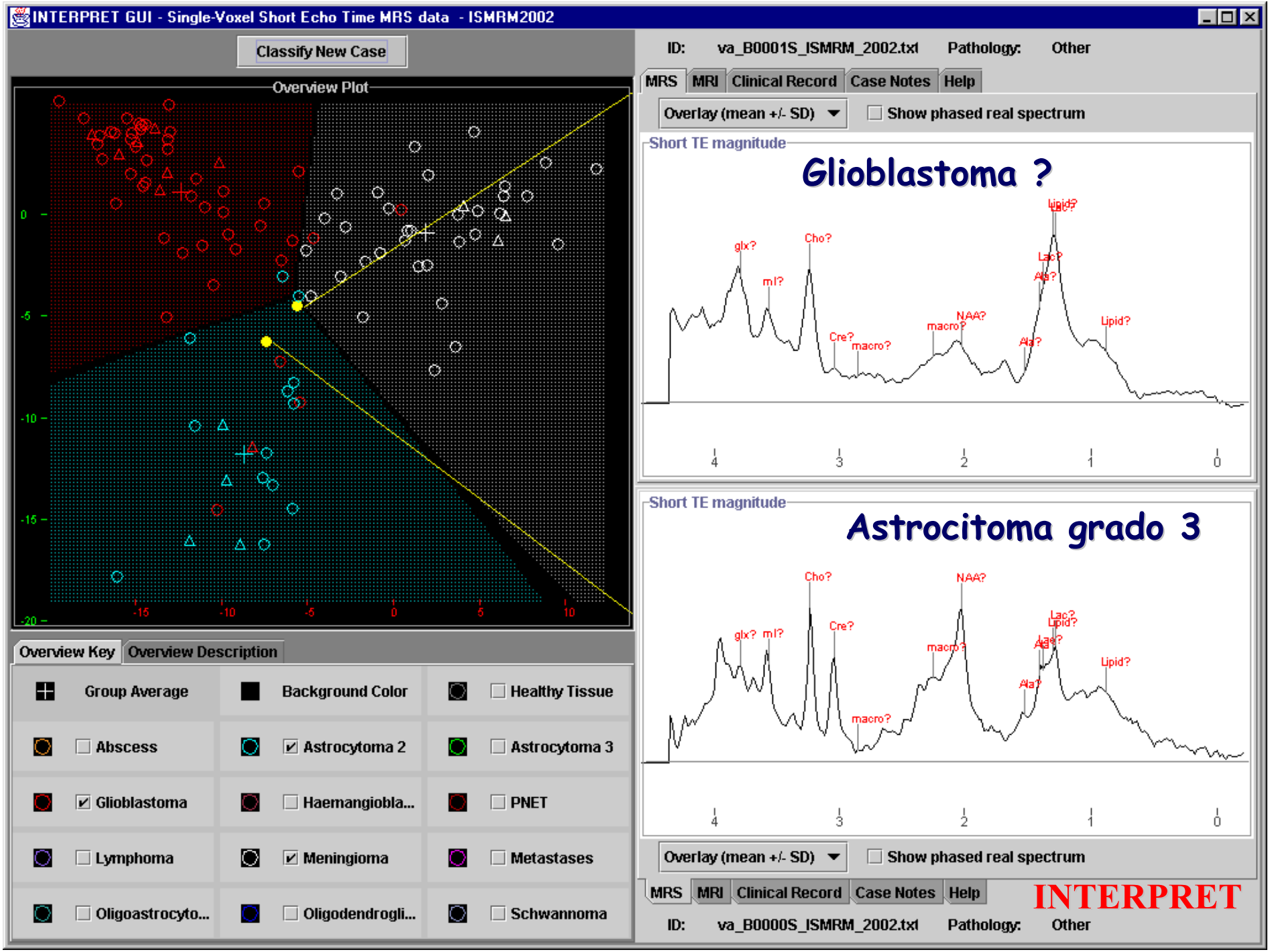
Surgery

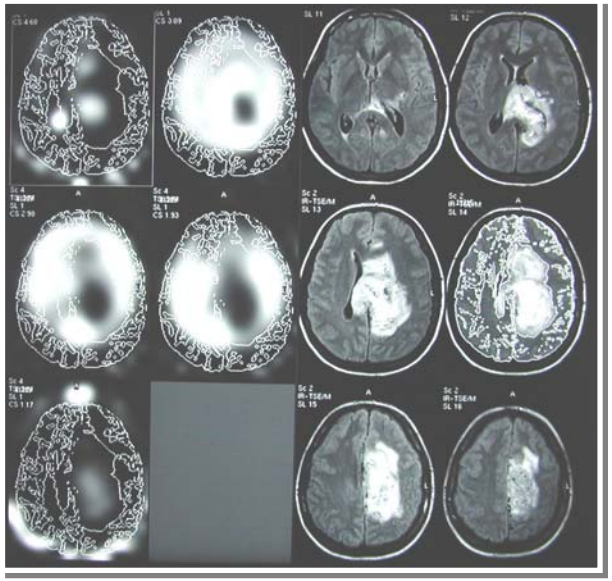
Site of Operation	FRONTOTEMPORAL
Total Tumour Removal	NO
Subtotal Tumour Removal	NO
Stereotactic Biopsy	NO

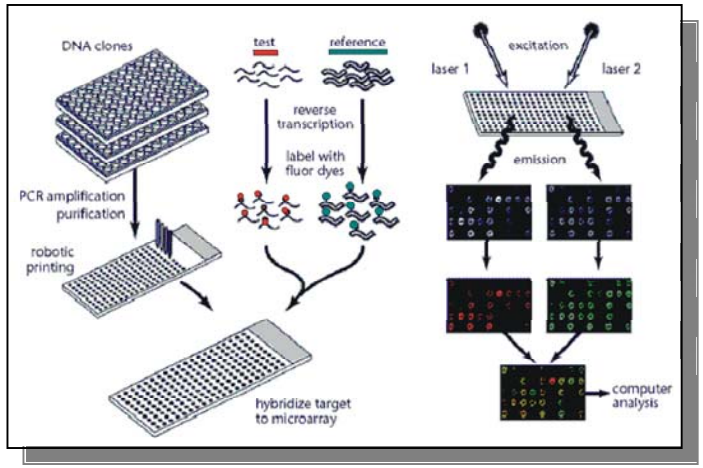


SECURE WEB-BASED DISTRIBUTED DATABASE

DECISION SUPPORT TOOL


INTERPRET GUI - Single-Voxel Short Echo Time MRS data - ISMRM2002
Classify New Case
Overview Plot
ID: va_B0001S_ISMRM_2002.txt Pathology: Other
MRS MRI Clinical Record Case Notes Help
Overlay (mean +/- SD)
Show phased real spectrum
Short TE magnitude
Glioblastoma ?
glx?
mI?
Cho?
Cre?
macro?
NAA?
Lipid?
Short TE magnitude
Astrocitoma grado 3
Overview Key
Overview Description
Group Average
Background Color
Healthy Tissue
Abscess
Astrocytoma 2
Astrocytoma 3
Glioblastoma
Haemangiobla...
PNET
Lymphoma
Meningioma
Metastases
Oligoastrocyto...
Oligodendrogli...
Schwannoma
INTERPRET





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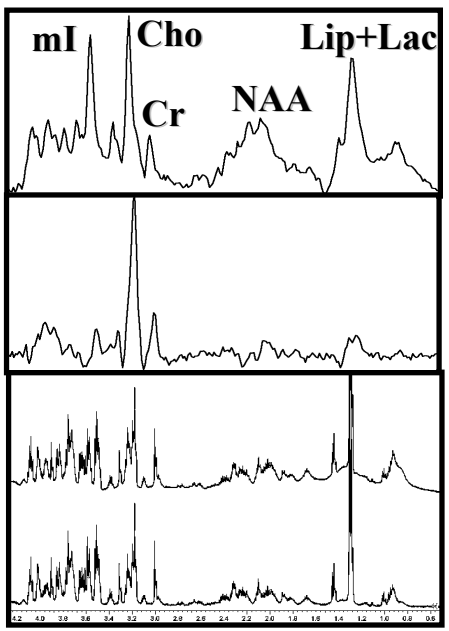

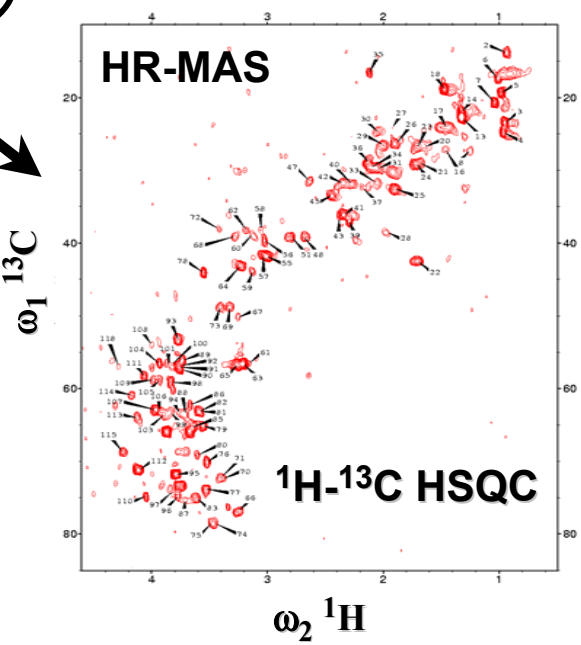

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