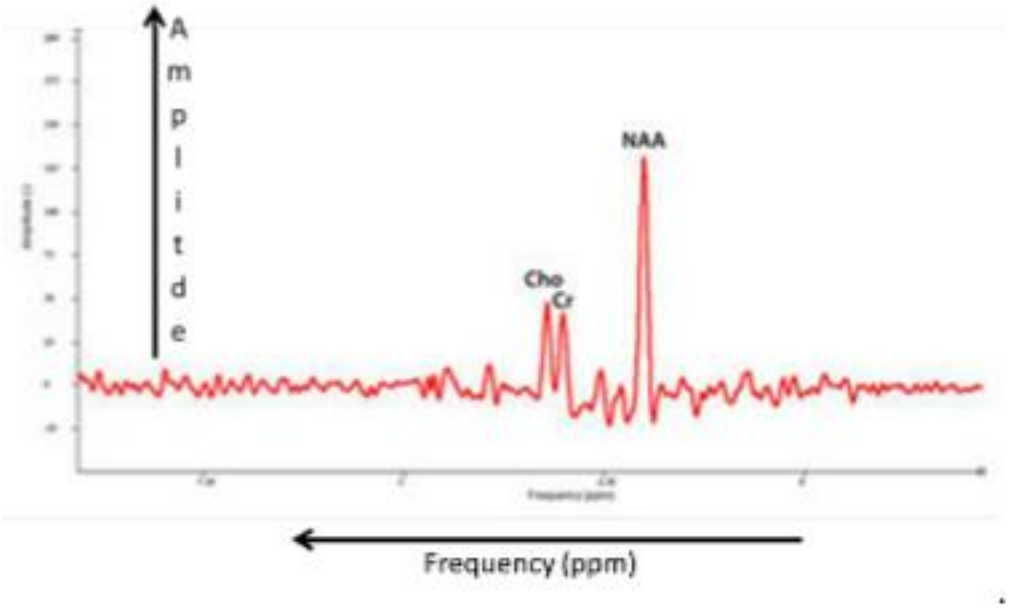
Introduction

- ***Basics***
  - *MR spectra may be obtained from different nuclei. Protons (1H) are the most used nuclei for clinical applications in the human brain mainly because of its high sensitivity and abundance.*
  - *When a tissue is exposed to an external magnetic field, its nuclei will resonate at a frequency (f) that is given by the Larmor equation.*
  - *he chemical shift position of a nucleus is ideally expressed in ppm because it is independent of the field strength (choline, for example, will be positioned at 3.22 ppm at 1.5T or 7T).*



  - *H-MRS acquisition usually starts with anatomical images, which are used to select a volume of interest (VOI), where the spectrum will be acquired.*
  - *For the spectrum acquisition, different techniques may be used including single- and multi-voxel imaging using both long and short echo times (TE).*

Techniques

- ***Single-Voxel Spectroscopy***
  - ***Single voxel spectroscopy (SVS)*** *the signal is obtained from a voxel previously selected.*
  - *Mainly, two techniques are used for acquisition of SVS H-MRS spectra: pointed-resolved spectroscopy (PRESS) and stimulated echo acquisition mode (STEAM).*

- *The most used SVS technique **is PRESS.***

Magnetic Resonance Spectroscopy Imaging (MRSI)

- *MRSI, also called spectroscopic imaging or chemical shift imaging, is a multi- voxel technique.*
- *The result of a 2D MRSI is a matrix, called a spectroscopy grid.*
- *The size of this grid corresponds to the field of view (FOV) previously determined.*
- *Spatial resolution is also determined by the FOV size (smaller FOV gives better spatial resolution) and by point of spread function (PSF).*
- *PSF on an optical system is defined as the distribution of light from a single point source.*
- *For MRSI the PSF is related to voxel contamination with signals from adjacent voxels, also called voxel "bleeding".*

SVS VS MRSI

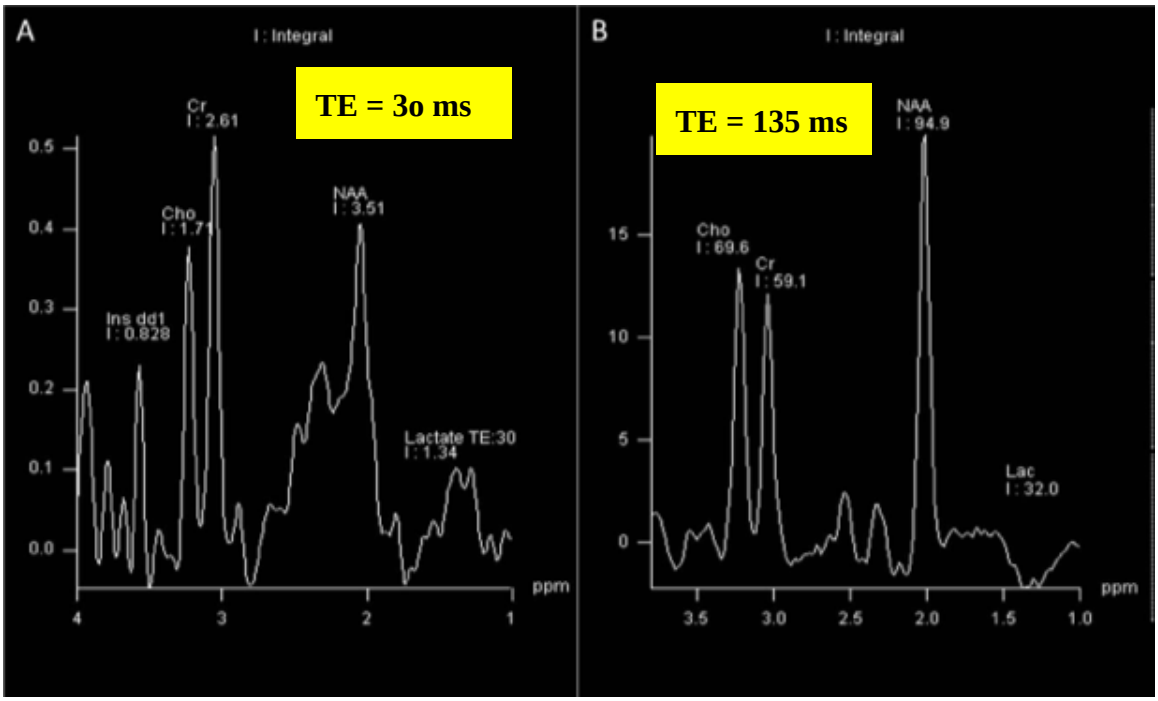
- *SVS technique is usually obtained with short TE since longer TE has decreased signal due to T2 relaxation.*
- *The main advantage of MRSI is spatial distribution compared to SVS technique that only acquires the spectrum in a limited brain region.*
- *Moreover, the grid obtained with MRSI allows voxels to be repositioned during post processing.*
- *On the other hand, the quantification of the metabolites is not as precise when using MRSI technique because of voxel bleeding.*

SVS	MRSI
Short TE	Long TE
One voxel	Multi-voxel
Limited region	Many data collected
Fixed grid	Grid may be shifted after acquisition
More accurate	Voxel bleeding
Quantitative measurement	Spatial distribution

Short TE VS Long TE

- *Short TE refers to a study in which it varies from 20 to 40 ms.*
- *These short TE properties result in a spectrum with more metabolites peaks, such as myoinositol and glutamine-glutamate , which are not detected with long TE.*

- *Nevertheless, since more peaks are shown on the spectrum, overlap is much more common and care must be taken when quantifying the peaks of metabolites.*



- ***Water Suppression***
  - *Water is the most abundant and thus its signal in MRS spectrum is much higher than that of other metabolites (the signal of water is 100.000 times greater than that of other metabolites).*
  - *To avoid this high peak from water to be superimpose on the signal of other brain metabolites, water suppression techniques are needed (fig. 9).*
  - ***Chemical shift selective water suppression (CHESS)** – most common technique*
- ***Artifacts***
  - *MRS is prone to artifacts. Motion, poor water or lipid suppressions, field inhomogeneity, eddy currents, and chemical shift displacement are some examples of factors that introduce artifacts into spectra.*
  - *One of the most important factors that predict the quality of a spectrum is the homogeneity of the magnetic field.*
  - *Poor field homogeneity results in a lower SNR and broadening of the width of the peaks.*
  - *For brain MRS, some regions are more susceptible to this artifact, including those near bone structures and air tissue- interfaces.*

- *Therefore placement of the VOI should be avoided near areas such as anterior temporal and frontal lobes.*

Spectra and Metabolites

- ***Spectra***
  - *The metabolite changes often precede structural abnormalities and MRS can demonstrate abnormalities before MRI does.*
  - *The ppm increases from right to left.*
  - *Long TE sequences result in less noise than short TE sequences but several metabolites are better demonstrated with short TE.*
  - *Long TE sequences **(TE = 135-288 ms)** detect*
    - NAA
    - Cr
    - Cho
    - Lac
    - Possibly Ala
  - *Short TE sequences (**TE = 20-40 ms)** demonstrate the metabolites seen with long TE acquisitions and in addition*
    - Lip
    - Myo
    - Glx,
    - Glucose
    - Some macromolecular proteins
- ***Brain metabolites***
  - ***N-acetylaspartate (NAA) (2.02 (ppm))***
    - Peak of NAA is the highest peak in normal brain.
    - Synthesized in the mitochondria of neurons then transported into neuronal cytoplasm and along axons.
    - Exclusively found in the nervous system (peripheral and central) and is detected in both grey and white matter.
    - It is a marker of neuronal and axonal viability and density.
    - Absence or decreased concentration of NAA is a sign of neuronal loss or degradation.
    - Neuronal destruction from malignant neoplasms and many white matter diseases result in decreased concentration of NAA.
    - In contrast, increased NAA is nearly specific for Canavan disease.
    - NAA is not demonstrated in extra-axial lesions such as meningiomas or intra-axial ones originating from outside of the brain such as metastases.
  - ***Creatine (Cr) 3.03 ppm***
    - Combination of molecules containing creatine and phosphocreatine.

- Cr is a marker of energetic systems and intracellular metabolism.
- Concentration of Cr is relatively constant and it is considered a most stable cerebral metabolite.
- Therefore it is used as an internal reference for calculating metabolite ratios.
- In brain tumors, there is a reduced Cr signal.
- Gliosis may cause minimally increased Cr due to increased density of glial cells (glial proliferation).
- Creatine and phosphocreatine are metabolized to creatinine then the creatinine is excreted via kidneys . Systemic disease (e.g. renal disease) may also affect Cr levels in the brain.

o ***Choline (Cho) 3.22 ppm***
- Cho is a marker of cellular membrane turnover (phospholipids synthesis and degradation) reflecting cellular proliferation.
- In tumors, Cho levels correlate with degree of malignancy reflecting of cellularity.
- Increase Cho may be seen in infarction (from gliosis or ischemic damage to myelin) or inflammation (glial proliferation) hence elevated Cho is nonspecific.

o ***Lactate (Lac) 1.33 ppm***
- Not seen or is hardly visualized in the normal brain.
- The peak of Lac is a doublet at 1.33 ppm which projects above the baseline on short/long TE acquisition and inverts below the baseline at **TE of 135-144 msec.**
- Product of anaerobic glycolysis so its concentration increases under anaerobic metabolism such as cerebral hypoxia, ischemia, seizures and metabolic disorders (especially mitochondrial ones).
- Increased also occur with macrophage accumulation (e.g. acute inflammation). Lac also accumulates in tissues with poor washout such as cysts, normal pressure hydrocephalus, and necrotic and cystic tumors.

o ***Lipids (Lip)***
- Lipids are components of cell membranes not visualized on long TE because of their very short relaxation time. There are two peaks of lipids: methylene protons at 1.3 ppm and methyl protons at 0.9 ppm (van der Graaf, 2010).
- These peaks are absent in the normal brain, but presence of lipids may result from improper voxel selection causing voxel contamination from adjacent fatty tissues (e.g. fat in subcutaneous tissue, scalp and diploic space).
- Lipid peak scan be seen when there is cellular membrane breakdown or necrosis such as in metastases or primary malignant tumors.

o ***Myoinositol (Myo)*** *3.56 ppm*
- Is a simple sugar

- Considered a glial marker because it is primarily synthesized in glial cells, almost only in **astrocytes.**
- May represent a product of myelin degradation.
- Elevated Myo occurs with proliferation of glial cells or with increased glial-cell size as found in inflammation. Elevated in gliosis astrocytosis and in Alzheimer's disease.

o ***Alanine (Ala) 1.48 ppm***
- This peak is located above the baseline in spectra obtained with short/long TE and **inverts below the baseline on acquisition using TE= 135-144 msec .**
- Its peak may be obscured by Lac (at 1.33 ppm). The function of Ala is uncertain but it plays a role in the citric acid cycle .
- Increased concentration of Ala may occur in oxidative metabolism defects
- **In tumors, elevated level of Ala is specific for meningiomas.**

o ***Glutamate-Glutamine (Glx)*** *2.05-2.50 ppm*
- These metabolite peaks are difficult to separate at 1.5 T. Glu is an important excitatory neurotransmitter and also plays a role in the redox cycle.
- Elevated concentration of Gln is found in a few diseases such as hepatic encephalopathy.

Clinical application

❑ ***Brain Tumors***

o *Brain tumors are currently the main application of H-MRS.*

o *This technique is usually used as a complement to conventional MRI, along with other advanced techniques, such as perfusion.*

o *The most relevant parameter when facing is TE (Short TE allows for recognition of more peaks than long TE, which may be important for differential diagnosis of brain masses and for grading tumors.*

o ***Myo is a marker for low grade gliomas****, only seen on short TE acquisitions.*

o *Hence, the choice of TE may be difficult and one solution is to acquire two different spectra using both TEs. In clinical practice two H-MRS acquisitions are rarely feasible due to time constraints.*

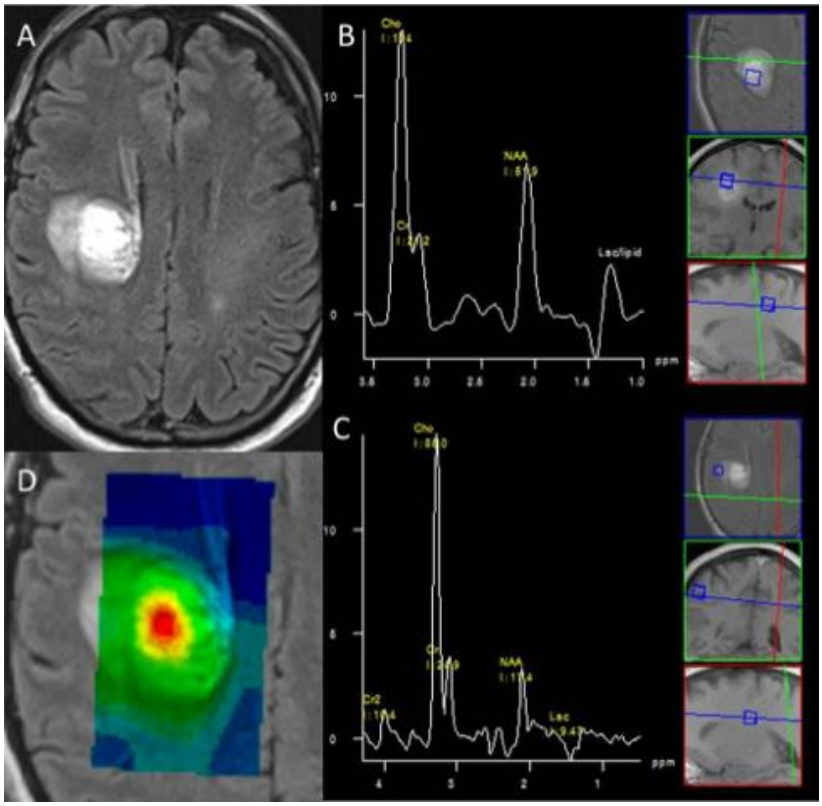
o *MRSI is usually preferable to SVS because of its spatial distribution.*

o *However, MRSI is generally combined with long TE instead of short TE.*

o *SVS, on the other hand, is faster and can be obtained using both long and short TEs. When using SVS, the VOI should be placed within the mass, avoiding contamination from adjacent tissues.*

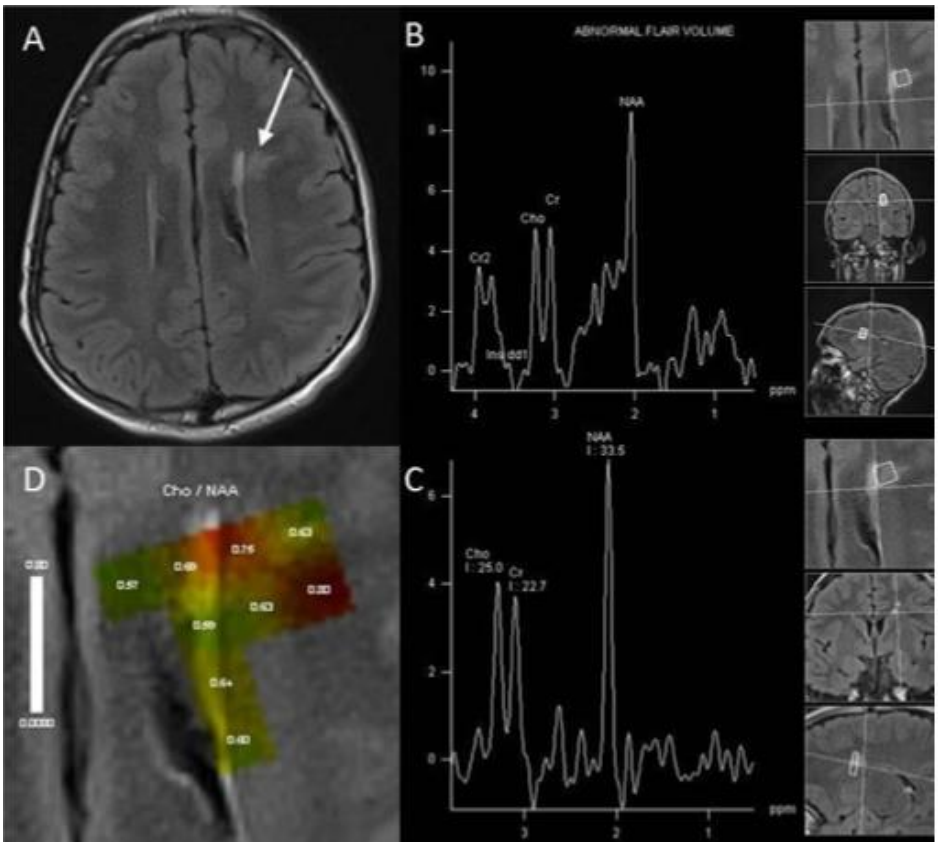
o *An identical VOI must be positioned on the homologous region of the contralateral hemisphere for comparison, whenever possible.*

- ***Elevation of Cho is seen in all neoplastic lesions.***
- *Cho peak may help with treatment response, diagnosis and progression of tumor. Its increase has been attributed to cellular membrane turnover, which reflects cellular proliferation.*
- *Cho signal is consistently low in necrotic areas.*
- *Another H-MRS feature seen in brain tumors is decrease NAA.*
- *Its reduction denotes destruction and displacement of normal tissue.*
- *Absence of NAA in an intra-axial tumor generally implies an origin outside of the central nervous system (metastasis) or a highly malignant tumor that has destroyed all neurons in that location.*
- *Cr signal, on the other hand, is slightly variable in brain tumors. It changes according to tumor type and grade.*
- ***Typical H-MRS spectrum for a brain tumor is one of high level of Cho, low NAA and minor changes in Cr.***



- *The use of H-MRS in specific cases improves accuracy and level of confidence in differentiating neoplastic from non- neoplastic masses .*
- *The differentiation of a low grade glioma from stroke or focal cortical dysplasia may be difficult or impossible using conventional MRI.*
- *In these cases, increased levels of Cho make diagnosis of neoplasm much more likely.*

- *In some cases of focal cortical dysplasia, Cho may be moderately increased probably as a result of intrinsic epileptic ictal activity.*



- *10 year-old boy with intractable seizures.*
  - A= Focal high signal intensity in the white matter.
  - B =H-MRS with TE= 35ms
  - C = TE=144 demonstrate normal Cho and NAA peaks.
  - Color metabolite map (D) demonstrate normal Cho/NAA ratio.
  - These findings are suggestive of a cortical dysplasia with adjacent abnormal white matter.

❑ *Demyelinating Disease*

- *H-MRS spectrum of a **giant demyelinating plaque** usually shows high Cho and low NAA levels.*
- *In the acute stage of a demyelinating disease, increase Lac can also be seen and may reflect the metabolism of inflammatory cells. Increase in glutamate and Myo also noted in multiple sclerosis.*

❑ *Brain abscess*

- *If the VOI is positioned in the enhancing area, presence of Cho favors a neoplasm.*
- *If the VOI is positioned in the cystic area of a lesion, abscess and tumor both demonstrate high peak of lactate.*

- *Nonetheless, presence of acetate, succinate, and amino acids (AAs) such as valine, alanine, and leucine in the core of the lesion have high sensitivity for pyogenic abscess These peaks are not seen in tumors.*
- *It is important to be aware that in patients with pyogenic brain abscess that are under antibiotic therapy these peaks may be absent.*

Metastasis

- *H-MRS can also help in the differentiation of high grade gliomas from solitary metastasis.*
- *Both lesions show the same H- MRS pattern, with high Cho and low NAA.*
- *However, the high signal intensity on T2 weighted imaging seen in the perilesional area demonstrates elevated Cho/Cr ratio only in high grade glioma.*
- *This feature is consistent with the pathological findings of infiltrating tumor cells in areas of edema not seen in metastases.*

Grading Tumors

- ***High grade gliomas***
  - Marked elevation of Cho, decreased NAA
  - Presence of Lac and Lip.
- *Myo is high in low grade gliomas and decreases with increasing grades of tumors.*

- ***Astrocytomas***
  - Classified into low grade (grade I and II, benign) and high grade (grade III and IV, malignant).
  - High grade gliomas (anaplastic gliomas or grade III, and glioblastoma multiforme or grade IV) have higher Cho and lower NAA than low grade ones. Elevated Cho correlates with cellular proliferation and density.
  - Though, threshold values of metabolite ratios for grading of gliomas are not well established.
  - Cho/Cr is the most frequently used ratio.
  - Some institutions use a threshold value of 2.0 for Cho/Cr to differentiate low grade from high grade gliomas while some use a cutoff value of 2.5.
  - Presence of Lip and Lac correlate with necrosis in high-grade gliomas. Low grade gliomas show higher Myo levels compared with high grade gliomas.
- ***Gliomatosis cerebri***
  - This rare disease is characterized by diffuse infiltration of glial cell neoplasm throughout the brain.
  - Gliomatosis cerebri has various histological subtypes (astrocytoma, oligodendroglioma, or mixed glioma).

- The WHO classification denotes grades II, III and IV gliomatosis cerebri. Therefore patients with this tumor have a widely variable prognosis.
- **Marked elevation of Myo and Cr has been found in gliomatosis cerebri**
- This may be attributed to glial activation rather than glial proliferation because Cho level is moderately elevated, suggesting low glial cell density.

- ***Oligodendroglioma***
  - Subgroup of gliomas which has a better response to treatment (chemosensitive) and better prognosis than glioblastoma.
  - This distinct tumor is devided into 2 groups according to the WHO classification: grades II and III.
  - It originates from oligodendrocytes but often contains a mixed population of cells, particularly astrocytes.
  - On dynamic contrast-enhanced MR perfusion, low grade oligodendrogliomas may demonstrate high rCBV because they contain a dense network of branching capillaries
  - A number of oligodendrogliomas can be misinterpreted as high grade tumors because of their high rCBV, which contributes to decrease reliability of rCBV in diffentiating the high vs. from low grade gliomas.
  - Among the low grade gliomas, low grade oligodendrogliomas also exhibit significantly higher rCBV on dymamic- contrast MR perfusion.
  - Oligodendroglial tumors, MRI studies have found that contrast enhancement is not suggestive of anaplasia as it is in astrocytomas.
  - The results of MRS studies in oligodendrogliomas are more consistent than those of MR perfusion studies.
  - Similarly to astrocytomas, MRS of oligodendrogliomas demonstrates significantly higher Cho, Cho/Cr ratio, and a higher incidence of Lac and Lip in high grade than in low grade tumors.
  - Apart from higher rCBV, the level of glutamine plus glutamate is significantly higher in low grade than in low grade astrocytomas and may help to distinguish these tumors from each other.

- ***Radiation Necrosis***
  - *Cho/Cr and/or Cho/NAA ratios are significantly higher in recurrent tumor than in radiation injury)*
  - *Lac/Cr ratio was significantly higher in recurrent tumor than in radiation injury*
  - *Lip/Cr ratio was significantly lower in recurrent tumor than in radiation injury.*
  - *Another study showed that Lac or Lip signal alone was not helpful in differentiating these two conditions.*

	Cho	NAA	Lac	Lip	Myo	Glu	Suc	Acet	Ala	Aa
Low grade tumor	↑	↓			↑					
High grade tumor	↑	↓	↑	↑						
Metastasis	↑	absent[1]	↑	↑						
Oligodendroglioma	↑	↓	↑[2]							
Meningioma	↑	absent							↑	
Gliomatosis cerebri	↑	↓								
Lymphoma	↑	absent[1]		↑						
Radionecrosis	↓	↓	↑	↑						
Abscess	N	↓	↑	↑			↑	↑	↑	↑
Demyelination	↑	↓	↑[3]	↑	↑	↑[3]				