



# Role of Magnetic Resonance Spectroscopy in Clinical Management of Brain Tumors

# 5

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## 5.1 Introduction

### 5.1.1 Basic Principles

Magnetic resonance spectroscopy (MRS) analyzes the frequency of different atomic groups of molecules. Each atomic group corresponds to a free induction decay signal (FID) in the time domain.

In a molecule as well as in cerebral tissue, several different atomic groups correspond to different FIDs resonating at different frequencies after Fourier transform. Each atomic group, and thus FID, appears as a peak at a particular frequency allowing biochemical characterization. MRS has therefore become a useful analytical and diagnostic tool in biomedicine.

In the past two decades, human localized MRS (single voxel or multivoxel-spectroscopy or spectroscopic imaging) has emerged as an *in vivo* MR-based spectroscopic approach to translational and clinical research of parenchymal human tissues of interest.

One of the greatest advantages of cerebral MRS techniques is their ability to detect multiple tissue-specific physicochemical metabolites in a single experiment compared to Positron-emission

tomography (PET) tracers (with membrane receptor affinity assumptions or hypotheses). The quantitative nature and translational component of *in vivo* MRS biomarkers come from the spectral and metabolic biomarkers discovered in *in vitro/ex vivo* and preclinical research studies. For these reasons, these *in vivo* MRS biomarkers can be easily translated and integrated into noninvasive spectroscopic and cerebral imaging protocols.

Disadvantages of *in vivo* MRS include low sensitivity, poor spectral resolution due to the inherently wider lines of “*in vivo*” metabolites, and B0 and B1 inhomogeneities. This will lead to overlapping resonances that are difficult to model and measure very accurately. It also suffers from poor time resolution, therefore offering fewer metabolic biomarkers to be measured and followed *in vivo*. Other disadvantages of the technique could be the difficulty in integrating all MRS measurements into a clinical protocol because it sometimes is perceived as taking too long.

In this chapter, we will reiterate several known MRS techniques and situations and provide considerations for establishing reliable indications and protocols, metabolite detection, measurement and quantification of *in vivo* brain tumor MR spectra. We will also explain how these techniques can contribute to diagnosis, follow-up, prediction, and monitoring of brain tumors. In this chapter, we will also present an overview of the role of cerebral MRS and when MRS could be used, and we will provide practical

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tables and examples of clinical cases of brain tumor spectroscopy.

### 5.1.2 Basic Protocol

For 3 T and 1.5 T, perform 1 min of calibration that encompasses the rough setup of the center frequency, then the optimization of the transmit and receiver gains, then the fine setup of center frequency, then the optimization of water suppression, and finally the single voxel MRS acquisition with 2 or 3 Echo Times (TEs):

- 35 ms (with 64 acquisitions for 2min12)
- 144 ms (with 96 acquisitions for 3min00)
- 288 ms (with 128 acquisitions for 3min48) = total 6–10 min

For new 3 T (with more head coil elements and better signal-to-noise ratios):

- 35 ms (with 16 or 32 acquisitions for 32 s or 1min34)
- 144 ms (with 64 acquisitions for 2min10)
- 288 ms (with 96 acquisitions for 3min00) = total 5–7 min

Monovoxel acquisition and processing are fast and relatively easy. However, there is not enough

information about the extension and the heterogeneity of the tumor. On the other hand, we can easily quantitate, using monovoxel MRS, the most aggressive part of the tumor, which is most often used along with anatomic-pathology, to predict the prognosis the treatment response and make therapeutic decisions during the neuro-oncologic multidisciplinary staff meeting.

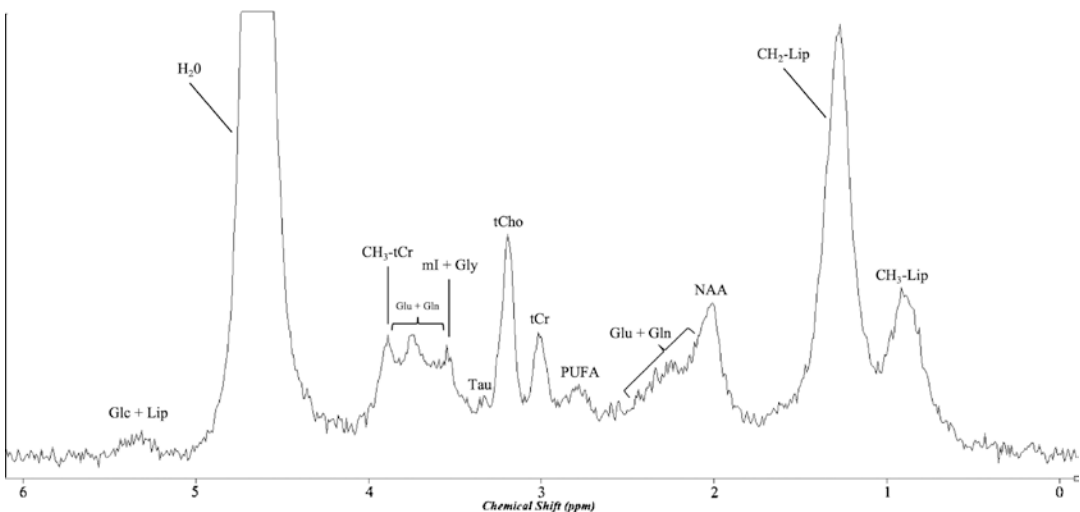
The basic protocol in multivoxel MRS could be Chemical Shift Imaging (CSI) of one slice with  $12 \times 12$  or  $16 \times 16$  phase encoding at TE 144 ms in 3 min with a 1min30 calibration.

Basic and frequent applications are brain tumors, metabolic brain diseases, inflammation and demyelination diseases, intensive care unit and epilepsy patients (cf. Chap. 3).

## 5.2 Important Metabolites Affecting Clinical Management

### 5.2.1 Metabolites

The main metabolites detected in proton MRS, in brain tumors, are, as you can see in Fig. 5.1, from 0 to 6 ppm: CH<sub>3</sub>-Lipids (CH<sub>3</sub>-Lip → 0.9 ppm), CH<sub>2</sub>-Lipids + Lactate (CH<sub>2</sub>-Lip + Lac → 1.3 ppm), *N*-Acetylaspartic Acid (NAA → 2.02 ppm), Glutamate + Glutamine (Glu + Gln → from 2.05



**Fig. 5.1** Representative proton spectrum (TE/TR = 35/1500 ms) of the aggressive part of a Glioblastoma (GBM) with the main metabolite described above

to 2.55 ppm), PolyUnsaturated Fatty Acid (PUFA  $\rightarrow$  2.8 ppm), CH<sub>3</sub>-Total Creatine (CH<sub>3</sub>-tCr  $\rightarrow$  3.03 ppm), Total Choline (tCho  $\rightarrow$  3.22 ppm), Taurine (Tau  $\rightarrow$  3.4 ppm), Myoinositol + Glycine (mI + Gly  $\rightarrow$  3.56 ppm), Glutamate + Glutamine (Glu + Gln  $\rightarrow$  from 3.6 to 3.9 ppm), CH<sub>2</sub>-Total Creatine (CH<sub>2</sub>-tCr  $\rightarrow$  3.93 ppm), Water (H<sub>2</sub>O  $\rightarrow$  from 4.5 to 4.9 ppm), Glucose + Lipids (Glc + Lip  $\rightarrow$  5.24 ppm).

All metabolites are often measured as ratios over Creatine because this is the most stable metabolite in the brain in the most common brain diseases.

### 5.2.1.1 Cho/Cr and Cho/NAA

The first ratio to measure is the Choline/Creatine ratio (Cho/Cr), which is estimated at TE = 144 ms [1] (cf. Fig. 5.2). This ratio corresponds to tumor proliferation: the higher the ratio (above 2.5), the more proliferation and the mitotic index (Ki-67) reflecting proliferative activity is elevated [2]. We determine the grade of glioma based primarily on this ratio [3]. The ratio of Cho/NAA also allows us to confirm the tumor grade [1].

### 5.2.1.2 Lactate and Lac/Cr

The presence of lactate in a tumor lesion gives us information about the aggressiveness of the tumor. Its presence in large quantities can sometimes differentiate a lymphoma from a GBM and a transition to a higher grade of a glioma [4].

The detection of lactate is particular because its resonance frequency is located at the same frequency position as a part of necrotic CH<sub>2</sub> phos-

pholipids (1.3 ppm). For this, several TEs are needed as shown in Fig. 5.3: a TE at 35 ms to detect the presence of lactate and lipids, both at 1.3 ppm, at TE = 144 ms: if the 1.3 ppm signal goes negative, then there is more lactate than necrotic CH<sub>2</sub> phospholipids. The concentration can be estimated at TE = 288 ms [5]. We should be cautious on 3 T MRS because the lactate detection is decreased at TE = 144 ms [5, 6]. Its concentration is therefore underestimated because of the chemical shift error and the PRESS sequence. We should thus use a third TE at 288 ms.

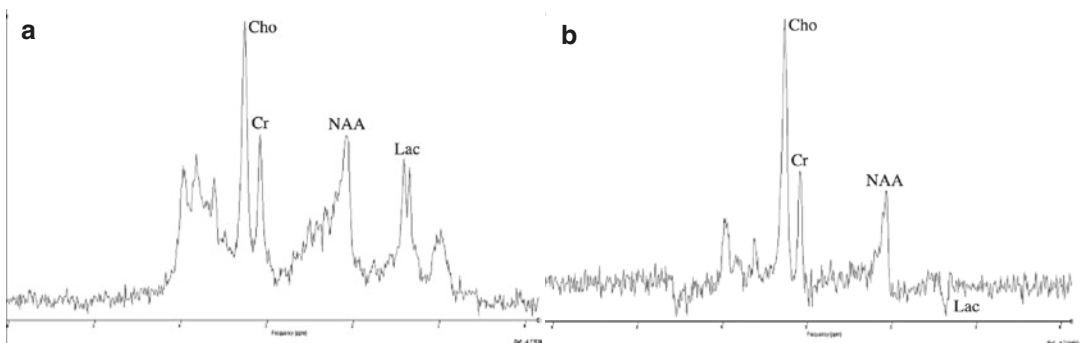
It is important, especially in low-grade gliomas, to associate Cho/Cr and Lac/Cr. When the glycolytic metabolism (Lac/Cr) is increased (>12 Mmol as in Fig. 5.3), it is a sign that a glioma transformation has resulted in a high-grade glioma, even though there is limited proliferation and almost no contrast enhancement.

### 5.2.1.3 Glucose

The amount of glucose [7] in a tumor is usually related to lactate [8].

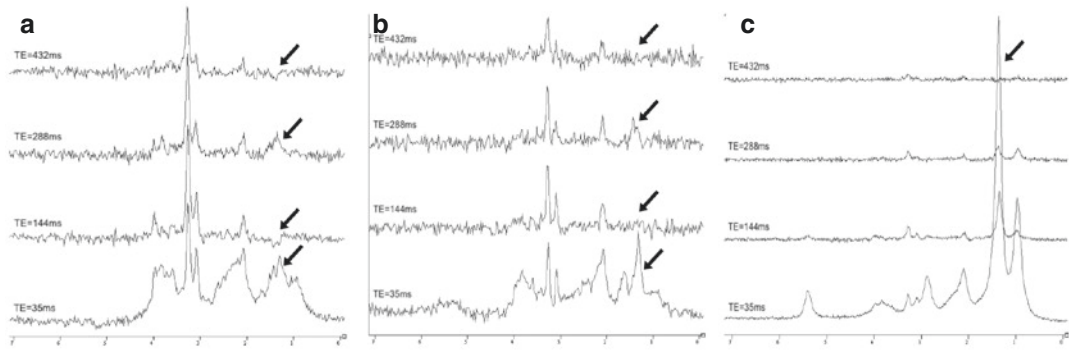
### 5.2.1.4 Glutamine

The glutaminergic complex also confirms the aggressiveness of a tumor [9]. Its detection and measurement without processing software is more complex for distinguishing difference between glutamate and glutamine in particular [10] because of the overlapping resonances. They are added most of the time, but it is possible to differentiate them. The most useful energetic proton tumor



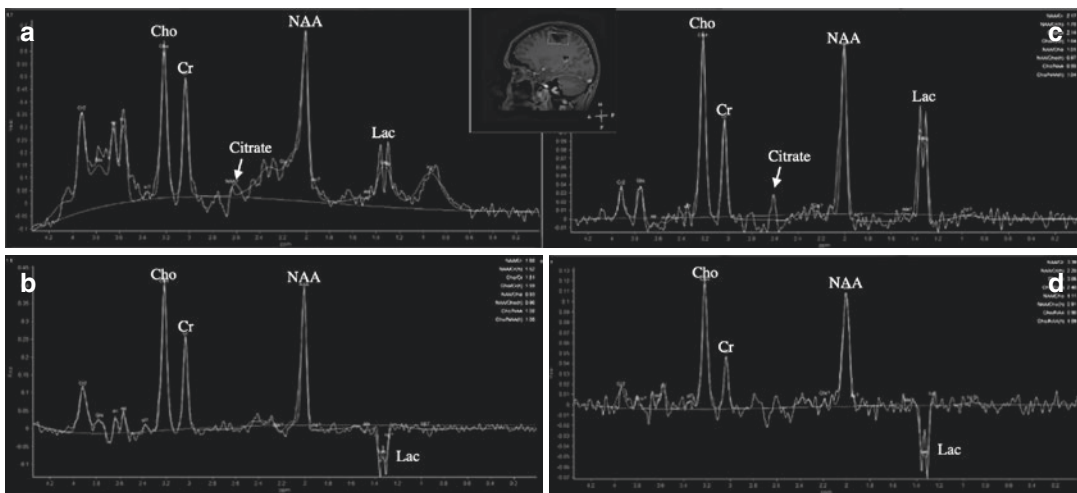
**Fig. 5.2** Spectrum of a glioblastoma at TE/TR = 35/1500 ms (a) and TE/TR = 144/1500 ms (b) The ratio of Cho/Cr is measured by the neuroradiologist on the

TE/TR = 144/1500 ms and correspond to the ratios of areas under the resonances of Choline (3.22 ppm) and Creatine (3.03 ppm). Here, the Cho/Cr ratio is a little above 2



**Fig. 5.3** A multi-TE study (TE = 35, 144, 288 and 432 ms) can, in some cases, help with the quantification of lactate and the differentiation between Lipids and lactate. If at TE = 144 ms the lactate doublet appears (a), it means that

the lactate is predominant in the Volume of Interest (VOI). If it does not appear, it is that the resonances are of the same intensity (b). If, on the contrary, the resonance remains positive, it is that the lipids are still predominant (c)



**Fig. 5.4** MRS Glioblastoma spectra with citrate at TE/TR = 35/1500 ms (a); at TE/TR = 144/1500 ms (b); at TE/TR = 288/1500 ms (c); and at TE/TR = 432/1500 ms (d).

Where we can detect citrate at 2.6 ppm, more visible at TEs 35ms and 288 ms

biomarker for detection is glutamine, which is closer to CH<sub>2</sub> creatine (while glutamate is closer to the higher mI resonance at 3.56 ppm). Glutamine shows the metabolic activity of the tumors and is predictive of future proliferation [11].

### 5.2.1.5 CH<sub>2</sub>-Lipids

CH<sub>2</sub> phospholipids are not present in substantial quantity in the normal human brain. The presence of lipids and the amount of CH<sub>2</sub>-Phospholipids (1.3 ppm) tells us about several elements. Before treatment initiation, they allow us to estimate the grade of the tumor. The higher they are, the higher the grade is. After treatment has been started, if the

ratios detected are significantly different, they can indicate the effectiveness of the treatment [12] in producing necrosis [13].

### 5.2.1.6 Taurine

The Glucose/Taurine peaks (3.40 ppm), positioned to the left of Choline (3.22 ppm), can also indicate tumor grade [14].

### 5.2.1.7 Citrate

Citrate can be found in aggressive pediatric glial tumors [15] and active glioblastomas as in Fig. 5.4 below, and can be correlated to citrate synthase activity.

### 5.2.1.8 Alanine

When alanine is detected at 1.47 ppm in cerebral tumors, we should suspect meningioma [16].

### 5.2.1.9 Miscellaneous

Polyamines (between creatine and choline at 35 ms) could help to follow embolization and therapies of some GBM.

Myoinositol (at 35 ms) and glycine (at 35 and 144 ms) at around 3.56 ppm are elevated in glial tumors.

Polyunsaturated fatty acids (PUFA) at 2.8 ppm could be detected [17].

## 5.2.2 Etiologies

Table 5.1 below is giving a brief overview of main metabolites and ratios in main etiologies of

brain tumors. It is sometimes important to consider spectral frequency resonances of metastases that could be detected in tumors, necrosis, and edema. This may suggest etiologic types of metastasis, or when the scale of the intensity changes, could give us information on the distribution. In the future, pharmacokinetics of some concentrated therapies such as Solumedrol, Diprivan, or antiepileptics could be followed.

## 5.2.3 Importance of Analysis of the Whole Spectral Profile

All of these ratios can be analyzed together (by multidimensional analysis with main compound analysis (MCA), correspondence factorial analysis (CFA) with discriminant analysis, or hierarchical classification), increasing the discriminative

**Table 5.1** Brief overview of main metabolites and ratios in brain tumors

Metabolites	Etiologies
Cho/Cr	<ul style="list-style-type: none"> <li>– Tumor proliferation (Cho/Cr &gt;3)</li> <li>– Malignant (glial tumor, metastasis) or benign (meningioma) tumor setting: Clinical MRI</li> </ul>
NAA/Cr	<ul style="list-style-type: none"> <li>– Infiltration</li> </ul>
Cho/NAA	<ul style="list-style-type: none"> <li>– Tumor grade, proliferation, and infiltration</li> </ul>
Lac/Cr	<ul style="list-style-type: none"> <li>– Tumoral glycolytic metabolism</li> <li>– Intensive sport practice → Lactate &lt;4 Mmol/L (288 ms)</li> <li>– Ischemia (stroke, vasospasm of subarachnoid hemorrhage, embolization) → Lactate &gt;15 Mmol/L (288 ms)</li> <li>– Mitochondrial disease → Lactate often &gt;20 Mmol/L (288 ms)</li> <li>– Inflammation, macrophages → Lactate between 5 and 10 Mmol/L (288 ms)</li> </ul>
Glucose	<ul style="list-style-type: none"> <li>– Glucose infusion, food, diabetes (ketone bodies) (35 ms)</li> </ul>
Glutamine, glutamate	<ul style="list-style-type: none"> <li>– Glial tumors and metabolic disease → Gln between 5 and 15 Mmol/L (35 ms)</li> <li>– Seizures → Glx &gt;10 Mmol/L (35 ms)</li> <li>– Hepatic encephalopathy → Glx &gt;15 Mmol/L (35 ms)</li> <li>– Excitotoxicity → Glu &gt;15 Mmol/L (35 ms)</li> </ul>
CH2 lipids (before treatment)	<ul style="list-style-type: none"> <li>– Tumoral necrosis (Glial) → 15 &gt;CH2Lip/Cr &gt;2 (35 ms)</li> <li>– Tumoral necrosis (metastasis) → CH2Lip/Cr &gt;15 (35 ms)</li> <li>– Infectious necrosis → CH2Lip/Cr &gt;15 (35 ms) (e.g., bacterial, toxoplasmosis)</li> <li>– Demyelination (stroke) → CH2Lip/Cr &lt;10 (35 ms)</li> <li>– Demyelination (MS) → 2 &gt;CH2Lip/Cr &gt;0.5 (35 ms)</li> <li>– Mental retardation → 10 &gt;CH2Lip/Cr &gt;5 (35 ms)</li> <li>– Apoptosis → CH2Lip/Cr &lt;1 (35 ms)</li> <li>– Drug (alcohol) → CH2Lip/Cr &lt;1 (35 ms)</li> </ul>
Taurine	<ul style="list-style-type: none"> <li>– Low-grade tumor and inflammation → Tau/Cr between 0.1 and 0.4 (35 ms)</li> <li>– Energetic drinks (e.g., Red Bull) → Tau/Cr between 0.2 and 0.6 (35 ms)</li> </ul>
Citrate	<ul style="list-style-type: none"> <li>– Pediatric tumor cases → Cit/Cr between 0.1 and 0.3 (35 ms)</li> <li>– Aggressive tumors (GBM) → Cit/Cr 0.2 (±0.1) (35 ms)</li> </ul>
Alanine	<ul style="list-style-type: none"> <li>– Meningioma → Ala/Cr = 0.4 (±0.3) (35 ms)</li> <li>– Intensive care unit patients Ala/Cr = 0.2 (±0.1) (35 ms)</li> </ul>
Miscellaneous	<ul style="list-style-type: none"> <li>– Polyamine between Cr and Cho (35 ms)</li> <li>– Myoinositol and glycine (at 3.56 ppm) increased</li> <li>– Polyunsaturated fatty acids (PUFA) (at 2.8 ppm)</li> </ul>

If the TE is not indicated, it is at TE = 144 ms ratio

power of MRS. Performing multiple TEs at different sites of the tumor and brain allows for better differentiation of coupled spins from noise. It also allows the collection of as much relevant information as possible from tumoral processes, differential diagnoses, and treatment responses (included in contralateral normal appearing brain). Artificial intelligence and neuronal networks as well as deep learning could, of course, be helpful after evaluation and validation of a sufficient number of relevant and well-labeled data.

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### 5.3 Role of MRS in Clinical Management of Brain Tumors

MRS provides additional quantitative information about the aggressive part of the tumor and the different pathological processes, acquired within a regular MR examination in 3–5 min.

MRS facilitates additional metabolic analysis far more inexpensively and quickly than PET, with physicochemical measurements, independent of the affinity of the receptor, and in real time (and with membrane changes). MRS is sometimes diagnostic, particularly for necrotic masses and for distinguishing tumoral from infectious processes, notably bacterial infection. For other tumoral conditions, and after registration, association with morphologic MRI 3D sequences, perfusion, and different PET tracers are always informative.

Once the tumoral process is confirmed (Cho/Cr >3), MRS used along with MRI increases the likelihood of detecting malignant tumors in some cases. It could help to measure the spectral and metabolic treatment response *in vivo* and monitor some highly concentrated treatments. In the future, monitoring biomarkers for responses to treatment could be possible. These biomarkers and their combinations could allow us to predict early survival (if the patient is still alive at 6, 8, or 10 months after relapse) and to predict the response to costly therapies such as antiangiogenics. It is particularly useful when contrast enhancement and hyperperfusion disappear while proliferation continues [18] or with anti-hypoxia or antimetabolite therapies. It could be

possible to follow therapies in real time and monitor metabolic pharmacology [19].

MRS, which detects tumoral processes (Cho/Cr >3), allows early detection of brain tumors, the extension of their progression, and their boundaries, in CSI or multivoxel for glial tumors and their relapses under treatment, MRS can detect early response to specific treatments and their combinations (e.g., costly antiangiogenics, signaling pathway inhibitors, and new sources of radiation). Therefore, this technique is able to change the monitoring and treatment combinations used in brain tumor patients. MRS techniques and sequences should be adapted to the clinical question: Is there a malignant or benign tumor process? What is the extension assessment and stage? How is the tumor lesion progressing under therapy (degree of proliferation, necrosis, glycolytic, and glutamatergic metabolism)?

In metastasis, MRS will help to first differentiate multiple lesions, MS lesions, or vascular lesions from metastasis, then with more difficulty from some infectious diseases. In cases of unique necrotic masses, as we will see below, MRS helps to differentiate metastasis from abscess and GBM. In addition, in some cases it could help to evaluate or monitor treatment effectiveness, e.g., Solumedrol effectiveness.

Moreover, MRS is useful for better understanding and following the physiopathology of brain tumors and the different pathological processes that occur over time, particularly in treatment responses. Indeed, the volumetric response criteria (RECIST, RANO) are often not sufficient although they are used in clinical research protocols because they are more reproducible and quantifiable than clinical criteria. More sensitive, discriminant, and informative (regarding the pathological processes) measurements, such as multidimensional analysis of the different spectroscopic ratios and spectral profiles and their combinations over time, are needed. Artificial intelligence, neuronal networks, and deep learning could naturally be helpful after evaluation and validation of enough relevant and well-labeled data.



## 5.4 Clinical Features in Which MRS Will Be Used for Clinical Management

### 5.4.1 MRS Before Brainstem Biopsies of Brainstem Lesions with Mass Effect

Spectroscopy with perfusion and diffusion first helps to rule out differential diagnoses of brain tumor processes such as infectious, inflammatory, granulomatous, or autoimmune diseases [20].

Among brainstem tumors, we can justify differentiating between lymphomas, metastases, and necrotic or non-necrotic lesions, with increased CH<sub>2</sub> phospholipids. Spectroscopy could subsequently predict the grade and the progression as well as short-term survival of the patients, followed by the differentiation between low-grade and high-grade gliomas.

### 5.4.2 Differentiation of Necrotic Masses

Diffusion and spectroscopy (with acetate, valine, leucine, isoleucine, and succinate) will confirm the diagnosis of abscesses with an accuracy rate of more than 99% [21, 22].

In non-treated necrotic masses, spectroscopy results with a CH<sub>2</sub> phospholipids to creatine ratio >15 and a Cho/Cr ratio <3, in metastasis can help to differentiate them from glioblastomas.

Spectroscopy showing the amount of lactate, CH<sub>2</sub> phospholipids and the value of Cho/Cr and mI/Cr, could help to differentiate GBM from lymphomas, especially when there is involvement of the corpus callosum in both cases.

### 5.4.3 Prediction of Survival, Tumor Activity, Early Progression, and Treatment Response

Usually, in cancer, four kinds of responses are used to evaluate treatment efficacy: complete and partial response, stability, and progression. To be classified into one of these responses, size comparisons using previous exams are done.

Two imaging exams are often used: the initial exam (baseline, before treatment) and the NADIR (the imaging exam in which the patient achieved the best treatment response). If the size increases by more than 20% compared to the NADIR, we classify it into “tumor progression,” which often leads to a treatment change. In the same way, spectroscopy criteria could be set up and optimized to define best tumoral progression. For example, comparisons between two exams, or between the last exam and the initial or first one after treatment or the NADIR. Thus, these criteria are easier for proliferation and glycolytic metabolites, but more difficult for glutamine and other metabolites. To find MRS differences between necrosis and apoptosis in a clinical setting is still very challenging.

The complete response in spectroscopy is not seen often because the different tumoral pathological processes do not disappear quickly and easily. In contrast, we can see various combinations of changes, therefore the tumoral stability is difficult to define and the partial response needs further MRS/MRI studies and evaluations.

Within heterogeneous glial tumors, we can try to define target(s) such as the most aggressive parts of the tumor that could be good target(s) for localizing therapies such as stereotaxic radiation, boost radiation, or intra-tumoral therapy delivery. MRS in GBM and in metastasis could be predictive of volumetric changes.

Segmentation in the VOI to obtain a percentage of gray/white matter and the different tumoral compartments is useful in multivoxel and in monovoxel as well, allowing the correction of certain effects of the partial volume effect.

Any sign of spectral, or metabolic, progression needs to be thoroughly evaluated when there is no proliferation and when there is a combination of spectral changes. As mentioned before, it could be useful to study the relationship between the volume of necrosis in post-gadolinium T1-weighted imaging and the CH<sub>2</sub> necrotic phospholipids to creatine ratio.

#### 5.4.3.1 Chemotherapy (Temozolomide)

It is possible to detect Temozolomide (TMZ) in vitro and, in some cases, in vivo during glioma and GBM chemotherapy [23].

### 5.4.3.2 New Sources of Radiation

MRS could help to monitor stereotaxic, proton and Hadron therapy and to detect proliferation and relapse from radio-necrosis or pseudo-progression, or tissular antioxidant level [24].

### 5.4.3.3 Antiangiogenic Therapy

Some tumors, such as GBM, after genomic analysis with functional assays for identifying patients specific targetable alterations [25], can respond well to antiangiogenic therapy, with disappearance of hyper-perfusion and contrast enhancement. However, the glycolytic metabolism and proliferation persist [18]. Some other GBM have nevertheless shown decreased neo-angiogenesis (with disappearance of contrast enhancement and hyper-perfusion). They have, however, increased in size, mostly due to necrosis (in T1-weighted imaging post-gadolinium), and are confirmed by a markedly increased quantity of CH2 necrotic phospholipids without proliferation or glycolytic metabolism.

### 5.4.3.4 Immunotherapy: Detection of Inflammation and Immune Response

MRS, in some cases, can detect inflammation and immuno-response secondary to immunotherapy.

### 5.4.4 Interventional Therapeutic Monitoring of Tumors

Biopsies could be studied with HR-MAS. Tumoral ablation could be studied by thermo or cryoablation, focus ultrasound, or lasers, and could be monitor by spectroscopy.

Embolization in tumors such as meningiomas [16] could be monitored by MRS to follow experimental ischemia, embolization agents, metabolism changes, and glial tumor follow-up with glucose and polyamine. MRS could help to follow venous perfusion of medication, intra-arterial or intra-tumoral chemotherapy, or therapy delivery such as microbubbles and nanoparticles under ultrasound, laser, or radiation.

### 5.4.5 Symptomatic Treatment

MRS could detect and measure in vitro and in vivo symptomatic treatments such as antiepileptics, antibiotics, mannitol, steroids (Solumedrol), and Diprivan.

### 5.4.6 Summary of Clinical Features of Brain Tumors Pathologies for Which MRS Is Useful

Table 5.2 below is giving a summary of the main clinical features of brain tumors pathologies with metabolic changes for which MRS is useful.

**Table 5.2** Summary of the main clinical features of brain tumor pathologies for which MRS is useful

Clinical management used	Pathologies	Metabolites
Brainstem biopsy	Brainstem tumors and their differential diagnosis	Cho/Cr, acetate, leucine, isoleucine, valine, CH2 phospholipids, CH3/Cr, Glx/Cr, ml/Cr
Necrotic masses	Abscesses, metastases, GBM, lymphoma	Acetate, leucine, isoleucine, valine, succinate, CH2 Creatine >15, Cho/Cr >3
Survival and tumor progression prediction	GBM, low-grade gliomas	Cho/Cr, Lac/Cr, Gln/Cr, Glc/Cr, ratio combinations
Monitoring treatment response	GBM, low-grade gliomas	Cho/Cr, Lac/Cr, Gln/Cr, CH2/Cr, NAA/Cr
Chemotherapy	GBM, low-grade gliomas	Cho/Cr, Lac/Cr, Gln/Cr, NAA/Cr, TMZ/Cr
Radiotherapy (stereotaxic, proton)	GBM	Cho/Cr, CH2/Cr, NAA/Cr
Antiangiogenics	GBM	Cho/Cr, Lac/Cr, Gln/Cr
Immunotherapy, inflammation	GBM	Cho/Cr, Lac/Cr
Interventional therapies	Meningioma embolization	Glucose, Cho/Cr, Lac/Cr, Glx/Cr, Gln/Cr, polyamines
Treatments	GBM, low-grade gliomas	TMZ, antiepileptics, antibiotics, Mannitol, Solumedrol, Diprivan



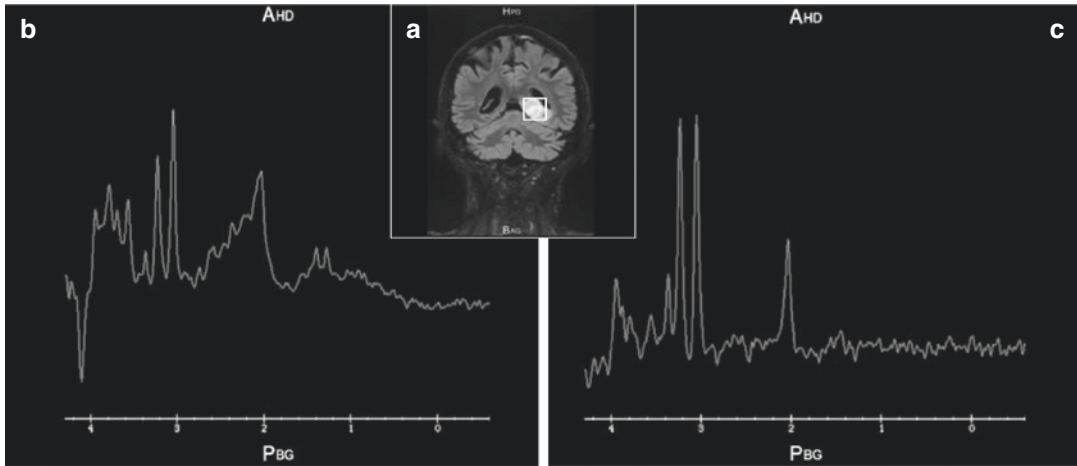
## 5.5 Brief Overview of Practical Clinical Cases: Examples of Brain Tumor MRS

For each pathology, a brief summary of the usefulness of MRS with examples are reviewed. Then, necrotic tumors and differential diagnosis of brain tumors will be discussed.

### 5.5.1 Glioblastoma

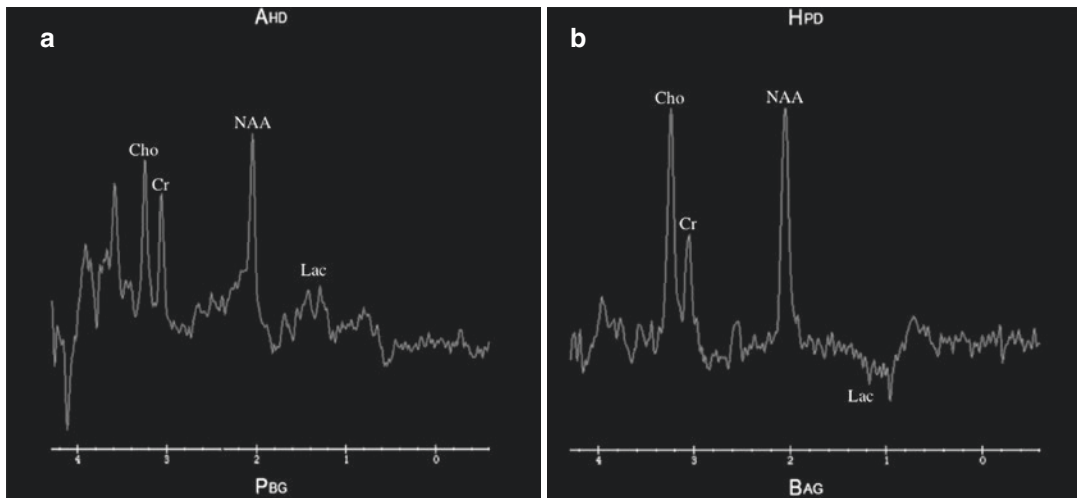
The usefulness of conventional, advanced MR imaging and MRS become clear when the biopsies are negative as in these two cases (Figs. 5.5 and 5.6).

The study of the agreement with anatomopathology features is also essential (Fig. 5.7).



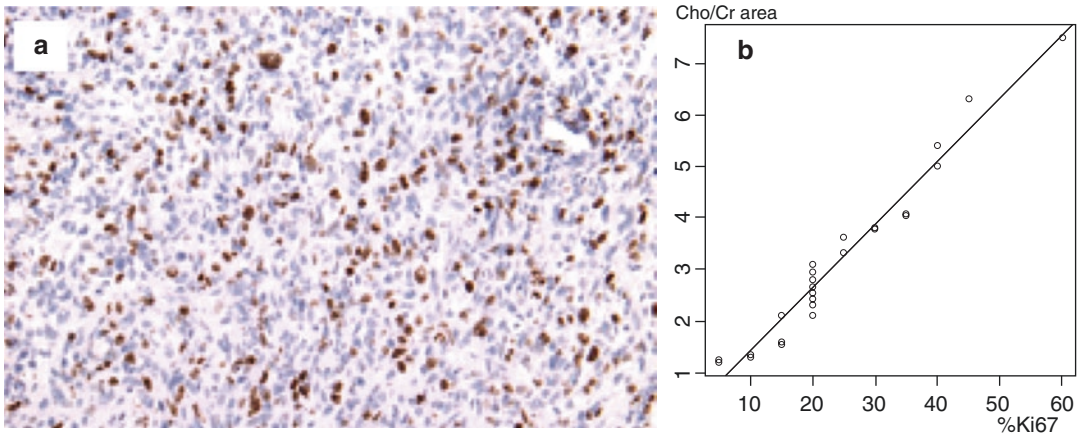
**Fig. 5.5** MRI and MRS of a glioblastoma secondary to a glial tumor, with a negative biopsy and no proliferation T2 FLAIR (a) with infiltration, no proliferation (TE/TR = 144/2500 ms (c)), Glutamine and glycolytic metab-

olism (MRS TE/TR = 35/1500 ms (b)) Glucose - Taurine resonances can be seen around 3.4 ppm. If the glucose peak appears at 5.24 ppm, glucose is predominant



**Fig. 5.6** MRI and MRS of a glioblastoma with a negative first biopsy. Although there is no significant infiltration, the proliferation (Cho/Cr at TE/TR = 144/1500 ms (b))

and the lactate (TE/TR = 35/1500 ms (a) and (b)) confirm the metabolic activity in high grade glioma (GBM confirmed by a 2nd biopsy)



**Fig. 5.7** There is good agreement between Ki-67 reflecting the number and percentage of mitosis found in anatomopathology (a) and the Cho/Cr ratio (b)

It would be useful to do a longitudinal spectral variation follow-up to predict survival, progression, and proliferation (Fig. 5.8), glycolytic (Fig. 5.9) metabolism, and treatment monitoring.

Usefulness of separation of short responders from long responders (Fig. 5.10).

### 5.5.2 Low- and High-Grade Gliomas

Usefulness of perfusion and spectral profiles in predicting progression or improvement, particularly in low-grade and diffuse infiltrative gliomas (Fig. 5.11).

### 5.5.3 Metastasis

MRI and MRS are useful for differential diagnosis of multiple lesions (number and size), edema assessment (Fig. 5.12), for treatment, prognosis prediction, and sometimes type of the metastasis.

### 5.5.4 Lymphoma

Lymphoma (Fig. 5.13) is a differential diagnosis from gliomas [26]. Lymphoma can also be differentiated from toxoplasmosis (Fig. 5.14).

### 5.5.5 Meningioma

MRS is helpful in the diagnosis of meningioma by showing the presence of alanine and sometimes very low Cr (Fig. 5.15). There are at least five meningioma spectra profile types showing different metabolic activity [16]. MRS could also be useful in following treatment (embolization, surgery, and/or radiation).

### 5.5.6 Necrotic Tumors

In front of necrotic tumors MRS could be very useful to distinguish abscesses from metastasis and GBM.

#### 5.5.6.1 Abscess

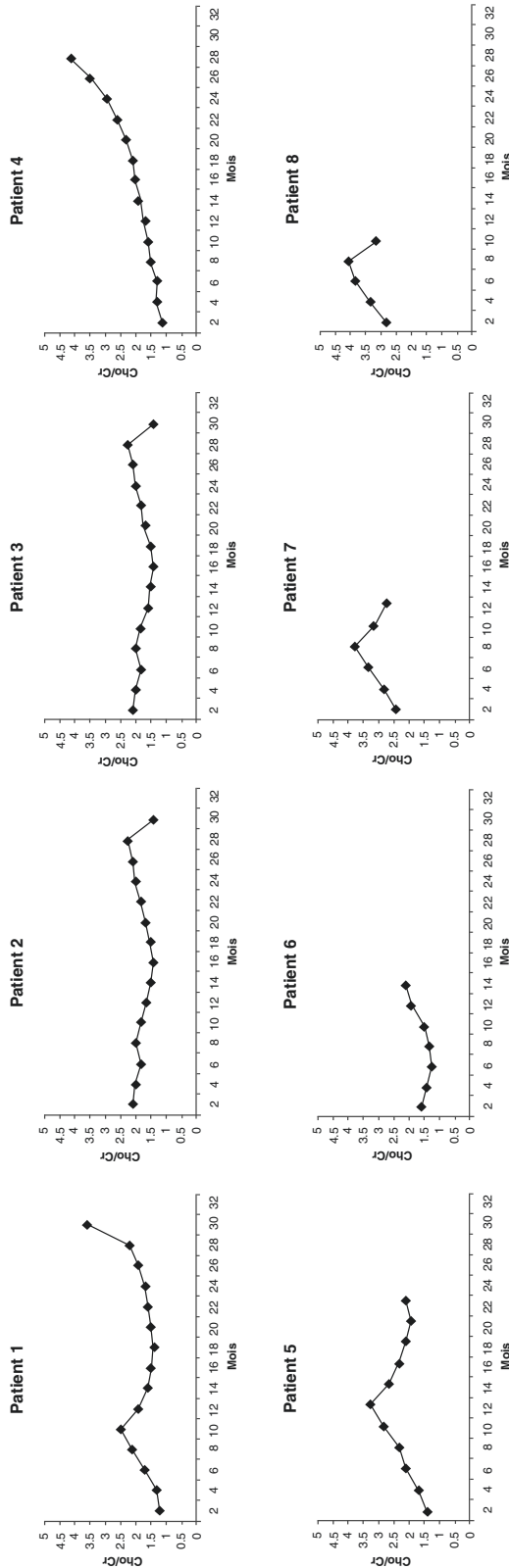
Together with diffusion imaging, MRS with branched amino acid, acetate, and succinate (Fig. 5.16) helps to recognize bacterial abscess.

#### 5.5.6.2 Metastasis

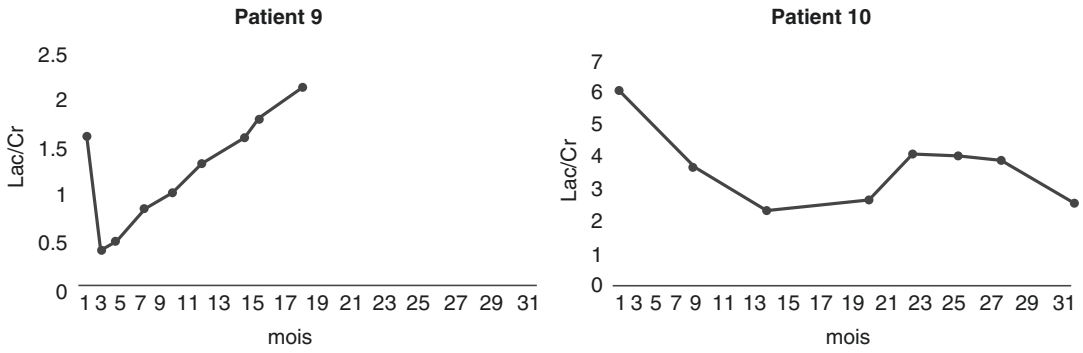
MRS shows usually a very high quantity of necrotic CH<sub>2</sub>-Phospholipids (Fig. 5.17).

#### 5.5.6.3 Glioblastoma

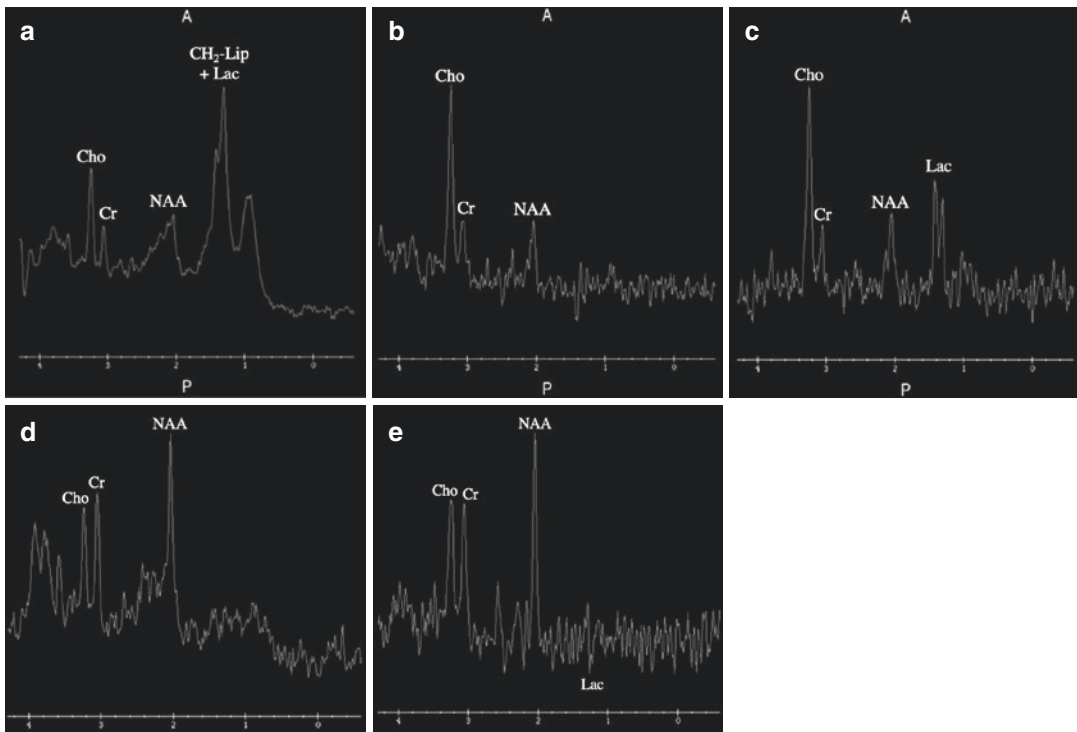
MRS from GBM shows usually high proliferation and relatively low CH<sub>2</sub>-Phospholipids before treatment (Fig. 5.18).



**Fig. 5.8** Follow-up of Cho/Cr ratio in 8 patients showing periods of proliferation with increased Cho/Cr ratio in a long period for long responders (patients 1 to 5) and a short period for short responders (patients 6, 7 and 8)

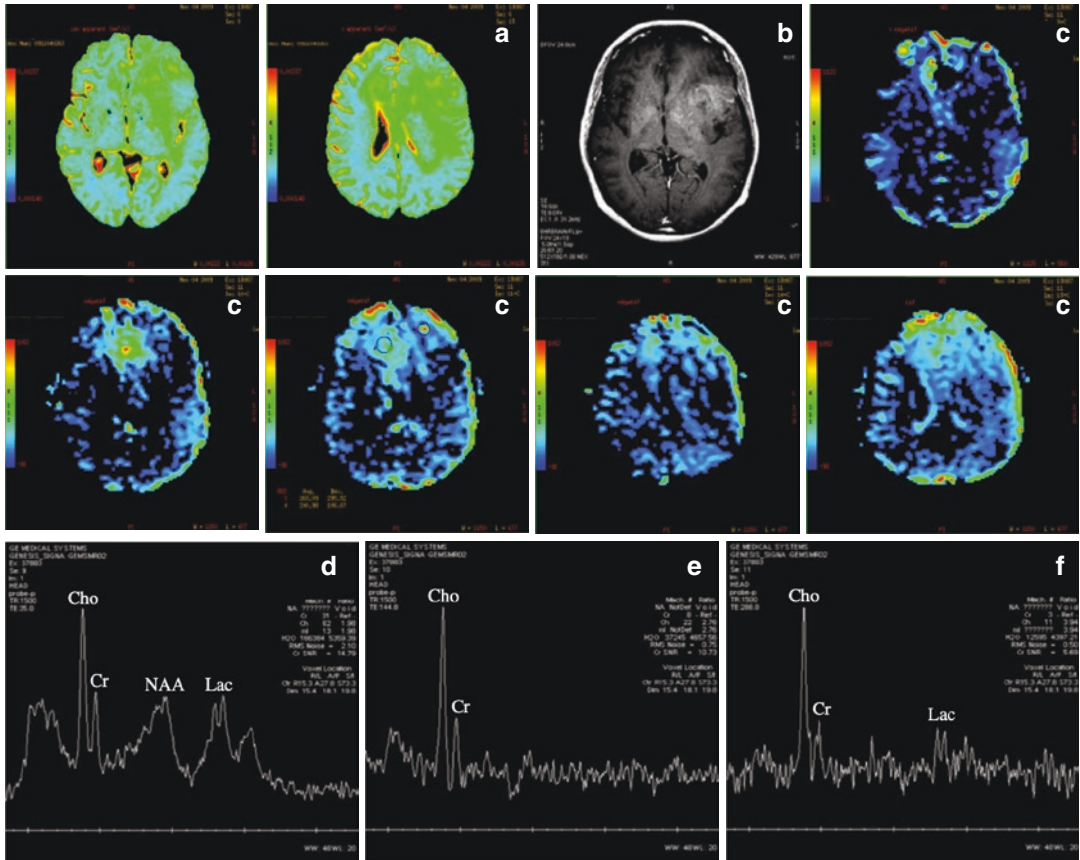


**Fig. 5.9** Follow-up of Lac/Cr ratio in 2 patients showing increased and variable glycolytic metabolism

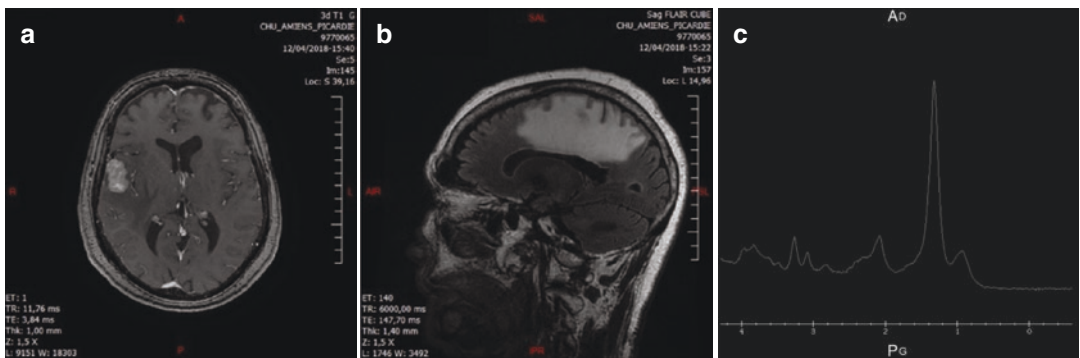


**Fig. 5.10** MRS of short responder patient with glioblastoma with high metabolic activity (higher proliferation, higher lactate and glutamine) at TE/TR = 35/1500 ms (a); TE/TR = 144/1500 ms (b); TE/TR = 288/1500 ms (c)

Compared to GBM long responder patient TE/TR = 35/1500 ms (d) and TE/TR = 144/1500 ms (e) without proliferation or high lactate



**Fig. 5.11** Stability of ADC map (a), Disappearance of significant contrast enhancement (b) and not any more hyper perfusion (c) under antiangiogenics, but with persistence of glycolytic metabolism followed by increased proliferation. (TE/TR = 35/1500 ms (d); TE/TR = 144/1500 ms (e); TE/TR = 288/1500 ms (f))



**Fig. 5.12** MRI of metastasis (d), (e) and (f) images were done 3 months after (a), (b) and (c) Hyper Signal FLAIR (Edema) is reduced due to Cyber Knife treatment (like the proliferation, the CH2-Phospholipids and the Glx in the metastasis spectra)

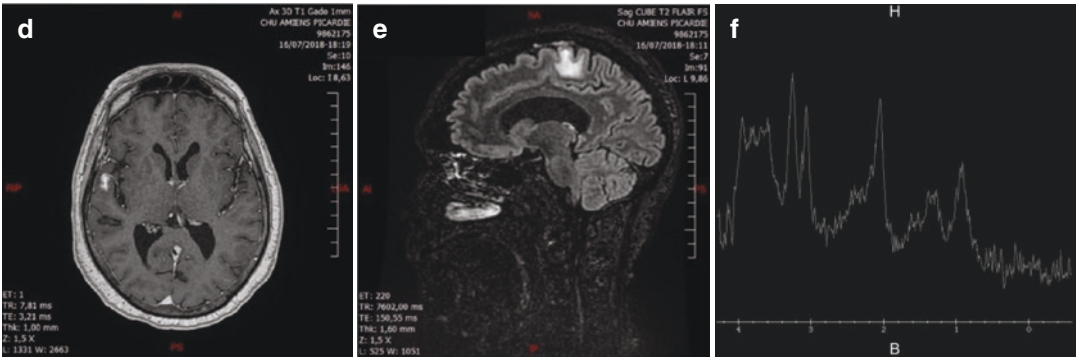


Fig. 5.12 (continued)

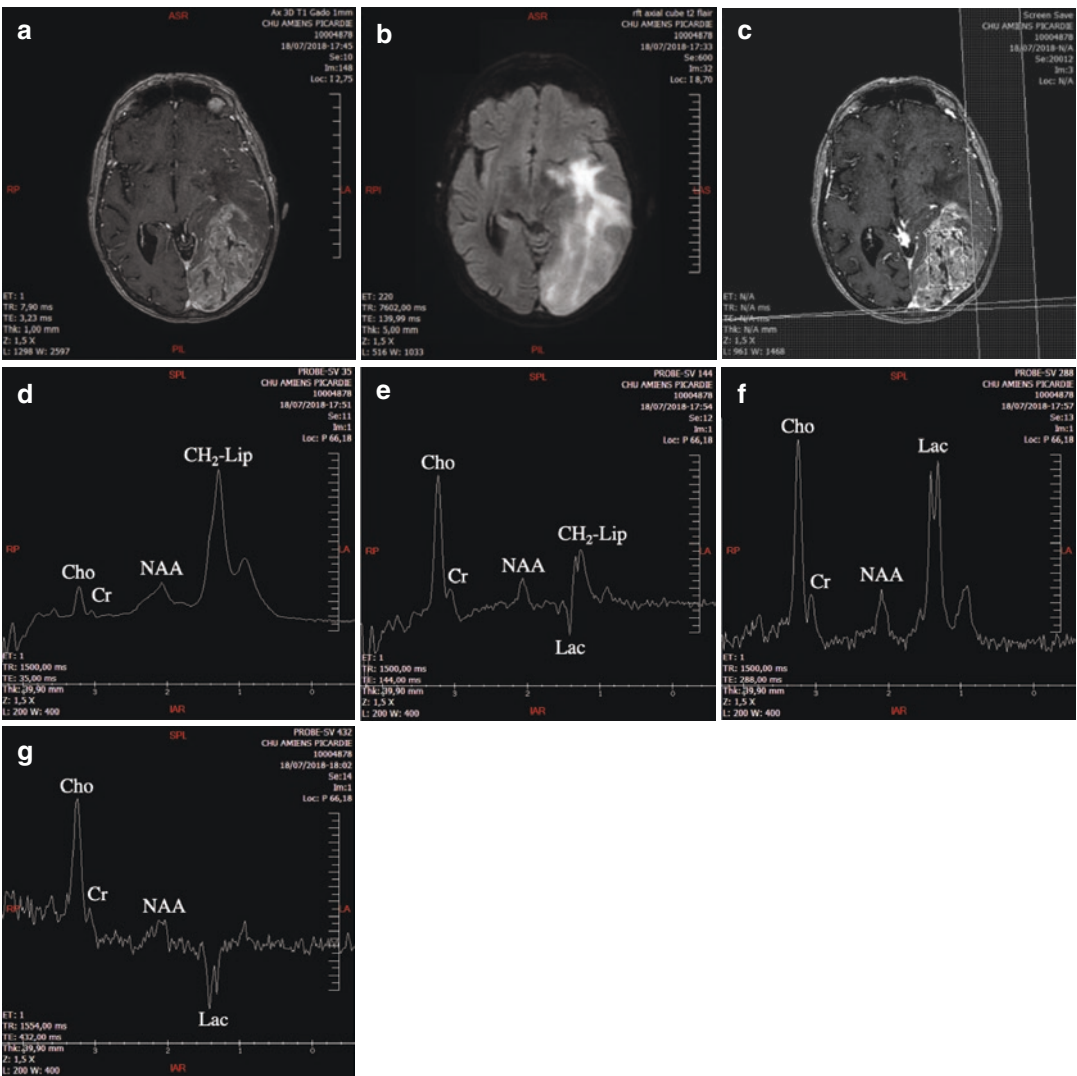
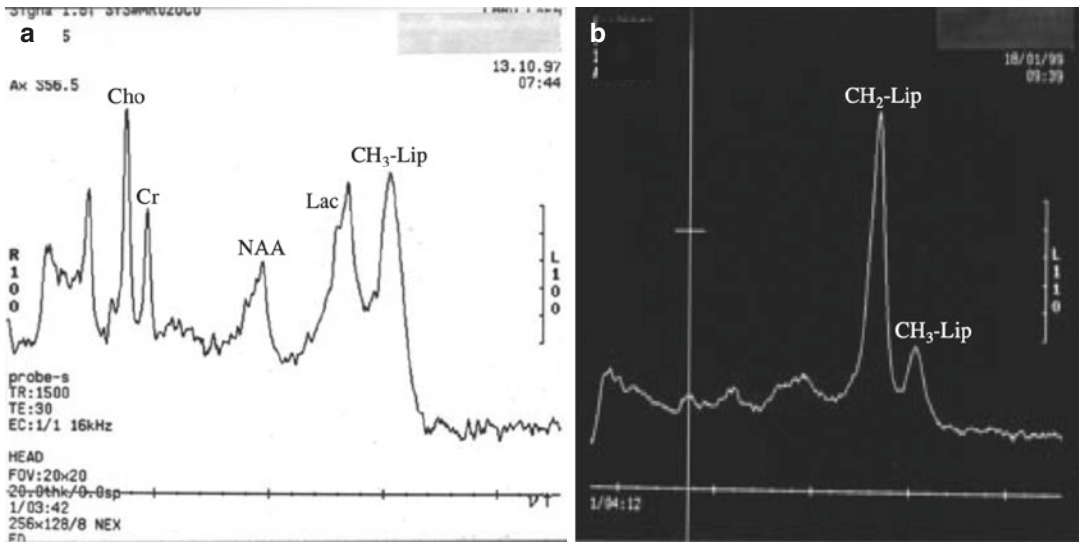
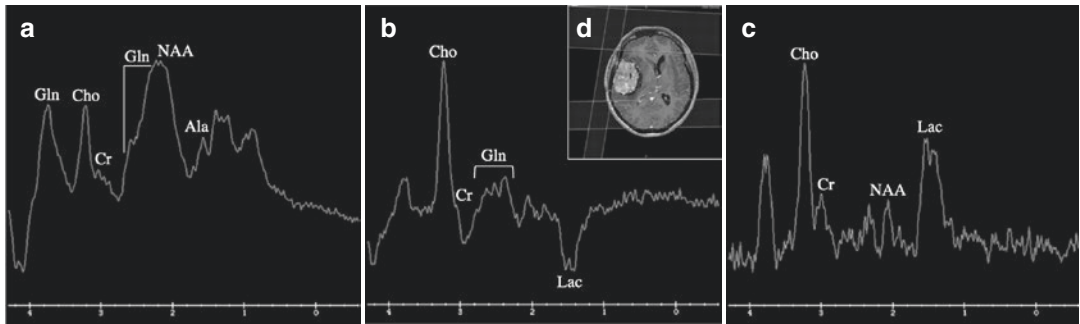


Fig. 5.13 MRS of patient with lymphoma at T1 gado (a); 144/1500 ms (e); 288/1500 ms with high lactate (f); Axial FLAIR (b); Voxel placement with saturation bands (c); 1H-NMR Spectroscopy at TE/TR = 35/1500 ms (d);

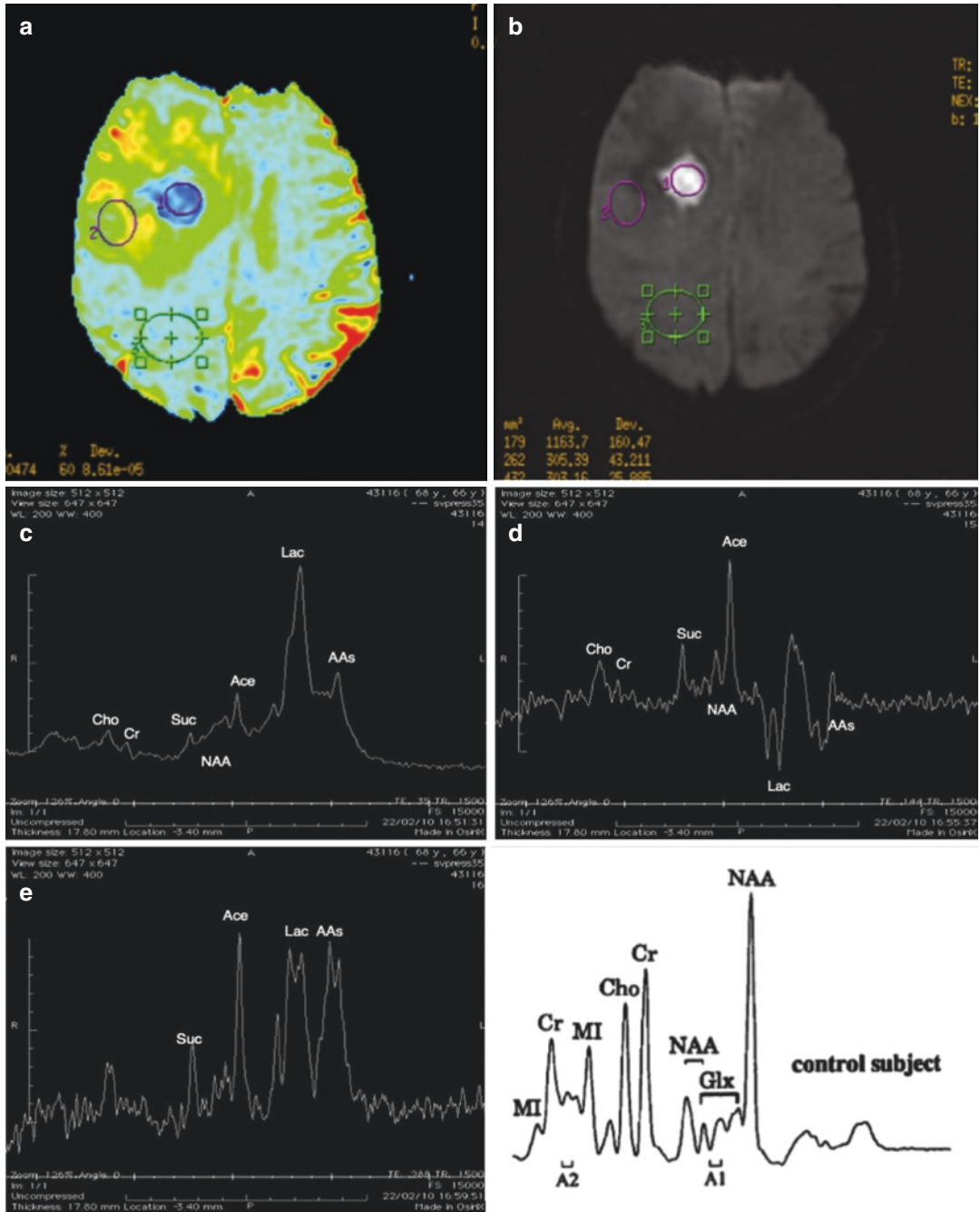




**Fig. 5.14** When necrosis is present: More lactate at 1.27–1.33 ppm and CH<sub>3</sub> lipids (0.9 ppm) in Lymphoma at TE/TR = 35/1500 ms (a); More CH<sub>2</sub>-Lipids in necrotic toxoplasmosis (b). The lactate doublet (a) can be seen on the left of the CH<sub>2</sub> lipids resonances

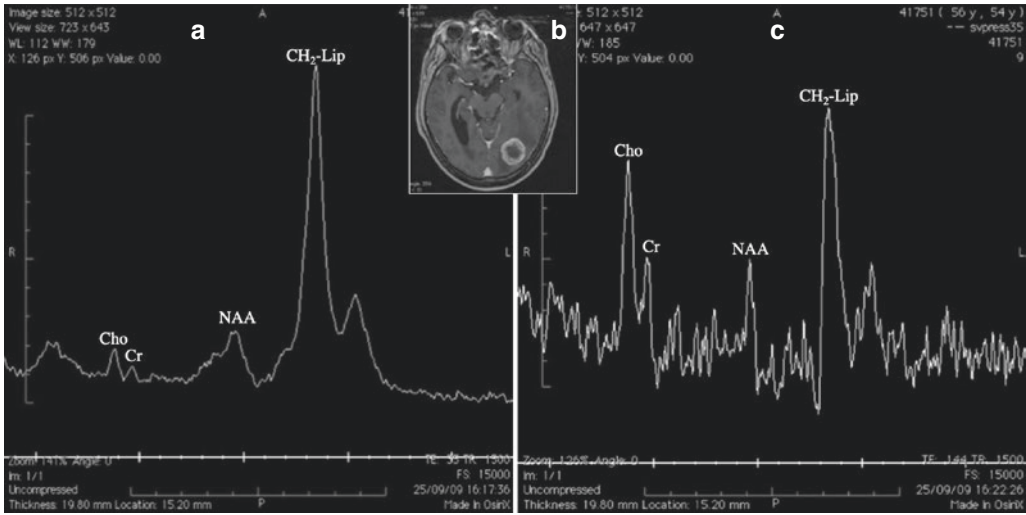


**Fig. 5.15** Spectra from a meningioma at TE/TR = 35/1500 ms (a); TE/TR = 144/1500 ms (b); TE/TR = 288/1500 ms (c); Axial T1 Gado (d) Alanine is detected at 1.47 ppm (to the left of Lactate) at TE = 35 ms In this type of meningioma, glutamine is very high and creatine is very low

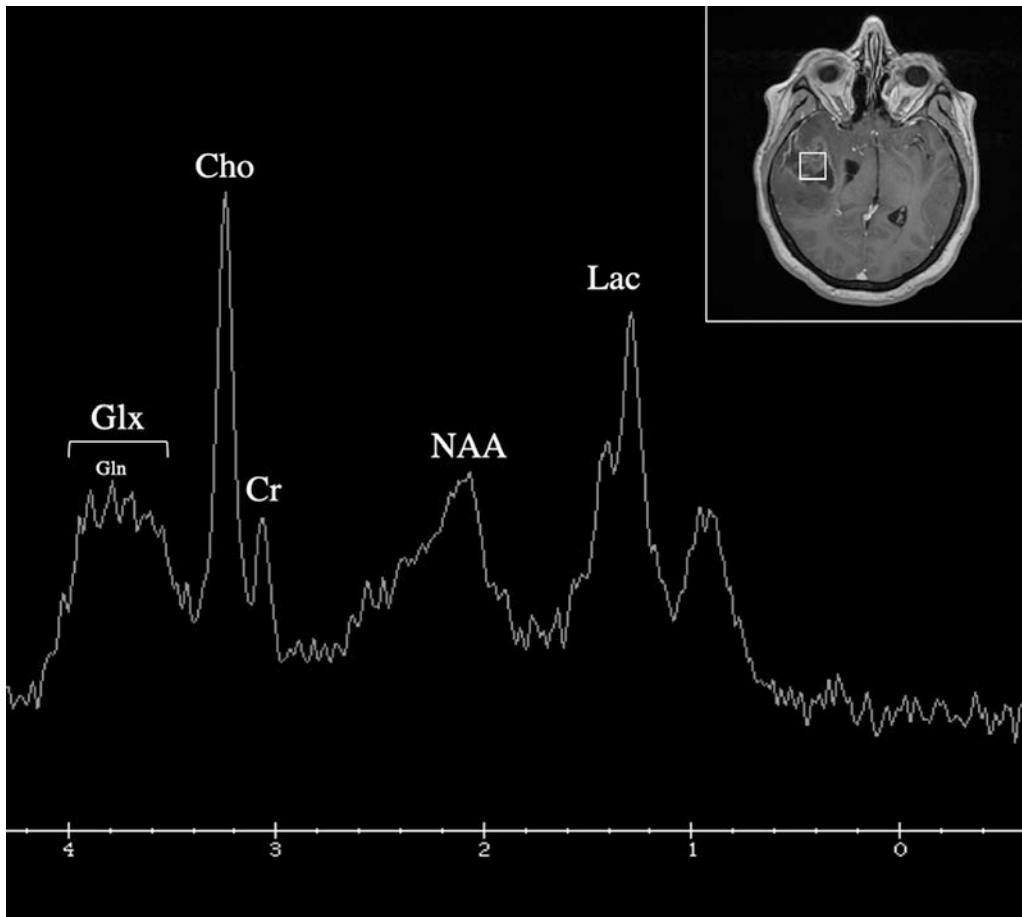


**Fig. 5.16** ADC (a) and diffusion imaging (b), MRS from a necrotic bacterial abscess (TE/TR = 35/1500 ms (c); TE/TR = 144/1500 ms (d); TE/TR = 288/1500 ms (e)) and normal spectra from a healthy control subject (f). The abscess spectra are not normal. Very high resonances of acetate, lactate, and branched amino acids (leucine, iso-

leucine, and valine) that are coupled (positive at TE = 35 ms (c), negative at TE = 144 ms (d) and again positive at TE = 288 ms (e)) are seen. Acetate and branched amino acids specific for bacterial abscesses are seen. In addition, the elevated succinate resonance seen here are indicative of anaerobic bacteria



**Fig. 5.17** TE/TR = 35/1500 ms (a) and TE/TR = 144/1500 ms (c) from a metastasis with a typical MRI appearance (b). There is a very high quantity of necrotic  $CH_2$ -PhosphoLipids ( $CH_2-Lip/Cr$  ratio greater than 24 (a)) and a Cho/Cr ratio less than 3 (c)



**Fig. 5.18** TE/TR = 35/1500 ms spectrum from a GBM. High Cho/Cr ratio (over 4), high Glx and glutamine, high lactate (Lac/Cr over 2), and low  $CH_2-Lip/Cr$  (under 2) are seen

**Table 5.3** Main and frequent ratio variations for the most frequently encountered brain tumors

Pathologies	MRS main metabolites ratios variations found
GBM	<ul style="list-style-type: none"> <li>– Proliferation:               <ul style="list-style-type: none"> <li>• Cho/Cr &gt;3 → High</li> <li>• Cho/Cr &lt;1.8 → Stable or in regression</li> </ul> </li> <li>– Glycolytic metabolism:               <ul style="list-style-type: none"> <li>• High Lac/Cr (288 ms)</li> <li>• High Glc/Cr (35 ms)</li> </ul> </li> <li>– Glutaminergic metabolism:               <ul style="list-style-type: none"> <li>• High Gln/Cr (35 ms)</li> <li>• High Glx/Cr (35 ms)</li> </ul> </li> <li>– High CH2PLip/Cr (&gt;2) before treatment (35 ms)</li> <li>– Short responder (versus long responder):               <ul style="list-style-type: none"> <li>• Higher Cho/Cr, Glc/Cr (35 ms), and Lac/Cr (288 ms)</li> <li>• Higher Lip/Cr before treatment (35)</li> </ul> </li> </ul>
High- and low-grade gliomas	<ul style="list-style-type: none"> <li>– Low grade:               <ul style="list-style-type: none"> <li>• Cho/Cr &gt;1.5</li> <li>• NAA/Cr &gt;1.2</li> <li>• Lac/Cr &lt;0.5 (288 or 35 ms)</li> <li>• mI/Cr &lt;0.9 (35 ms)</li> </ul> </li> <li>– High grade:               <ul style="list-style-type: none"> <li>• Cho/Cr &gt;3</li> <li>• NAA/Cr &lt;0.8</li> <li>• Lac/Cr &gt;2 (35 ms)</li> <li>• mI/Cr &gt;1 (35 ms)</li> </ul> </li> </ul>
Lymphoma	<ul style="list-style-type: none"> <li>– CH2Lip/Cr and CH3Lip/Cr high (35 ms)</li> <li>– Lac/Cr high (288 ms)</li> <li>– mI/Cr &lt;0.9 (35 ms)</li> </ul>
Meningiomas	<ul style="list-style-type: none"> <li>– Ala/Cr &gt;0.4 (35 ms)</li> <li>– Glx/Cr &gt;2 (35 ms)</li> <li>– Lac/Cr &gt;1 (288 ms)</li> <li>– Low creatine (Cr/Cho &lt;0.3)</li> </ul>
Necrotic tumors (metastasis and glial)	<ul style="list-style-type: none"> <li>– Tumoral necrosis (metastasis)               <ul style="list-style-type: none"> <li>• CH2Lip/Cr &gt;15 (35 ms)</li> </ul> </li> <li>– Tumoral necrosis (glial) →               <ul style="list-style-type: none"> <li>• 10 &gt;CH2Lip/Cr &gt;5 (35 ms)</li> <li>• Cho/Cr &gt;3</li> </ul> </li> </ul>

If TE is not indicated, it is a TE = 144 ms ratio

### 5.5.7 Summary of Main Metabolite Ratios Variations

Table 5.3 shows the summary of the main metabolite ratios variations found for the most frequently encountered brain tumors.

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