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REVIEW

Clinical pitfalls related to short and long echo times in cerebral MR spectroscopy

Pièges cliniques liés aux temps d'écho long et court en spectroscopie RM cérébrale

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Summary MR-spectroscopy (MRS) is a multiparameter diagnostic tool and modification of each parameter results in spectrum morphology changes. In particular, changing the echo time (TE) represents a useful tool to highlight different diagnostic elements, but also has significant impact on the spectrum morphology. Diagnostic errors can result if the role of TE is not properly considered. This article reviews the four most common TE-related pitfalls of MRS interpretation. Clinical practical methods to avoid such pitfalls are also suggested.
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Introduction

Magnetic resonance spectroscopy (MRS) is a non-invasive technique that provides metabolic information on a tissue of interest, and complements the anatomic information obtained with magnetic resonance imaging. MRS has subsequently acquired an important role in the diagnosis and follow-up of intracranial pathologies. This added value is particularly evident for the characterization of focal pathology, especially brain tumors [1—11].

With the advent of semi-automatic data acquisition, data processing and quantitation, the utility of MRS in clinical practice has increased, and the threshold for non-experts to use MRS clinically has been drastically lowered [12]. As such, interpretation of MRS data has become an increasingly necessary and useful task for radiologists in clinical practice. Nevertheless, correct interpretation of spectra and avoidance of pitfalls presently requires in-depth understanding of the underlying MR physics and chemistry phenomena. Thus, a more simplified clinically relevant analysis of potential pitfalls is needed.

Different parameters may be varied to optimize MRS data acquisition. These parameters determine not only the appearance of the spectrum but also the information that can be extracted from it. One of the most relevant MRS parameters is the echo-time (TE). The TE used for clinical

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MRS ranges between 18 and 288 ms. Within this range, spectra are broadly divided into short and long TE, with short TE ranging between 18 and 45 ms and long TE between 120 and 288 ms. Different TE values highlight different aspects of the spectra, and arguments have been made for and against every option. Pitfalls associated with short TE MRS include an irregular fluctuating baseline due to underlying resonances of cellular macromolecules and possible artifactual elevation of N-acetyl aspartate (NAA) due to overlap with an elevated glutamine/glutamate (Glx) peak. Pitfalls associated with a long TE MRS include non-detection of short T1/T2 metabolites such as lipids (Lip), Glx, and myoinositol (mI) with an overall lower signal to noise ratio of the spectra and most importantly possible artifactual elevation of the choline (Cho): creatine (Cr) ratio. As an example, one of the most widely used applications of clinical MRS is the evaluation of intracranial tumors. The basic metabolic changes common to brain neoplasms include elevation in Cho, lactate (Lac), and Lip, as well as a decrease in NAA (and Cr in necrotic tumors). As automated peak identification algorithms in clinical spectroscopy becomes more sophisticated, additional metabolites identified with short TE MRS, such as mI and Glx, are also becoming important in increasing the specificity of MRS in brain tumor evaluation [13].

Detailed knowledge of all physical parameters and variables pertaining to all these metabolites is cumbersome for the practicing clinical radiologist. In this perspective paper we broadly identify four common pitfalls related to the choice of echo time, which the clinical radiologist evaluating MRS studies must be aware.

Discussion

In routine clinical MRS studies (TE range: 30—288 ms) adapting the TE parameter is a useful technique to obtain different diagnostic information, but at the same time this affects the morphology of the MRS spectra (Fig. 1) and results in potential pitfalls. These pitfalls have been broadly divided into four categories as summarized in Table 1.

Pitfall No. 1: metabolite quantization error due to irregular or fluctuating baseline on short TE

Spectra acquired at short TE are characterized by higher signal-to-noise ratio and by the visibility of more metabolite resonances, but sometimes this is at the expense of distorting the spectrum's baseline. An ideal baseline is flat. Baseline distortion is represented by an irregular, wavy, or fluctuating appearance of the baseline, especially between 2 and 4 ppm. If successful baseline correction and fitting

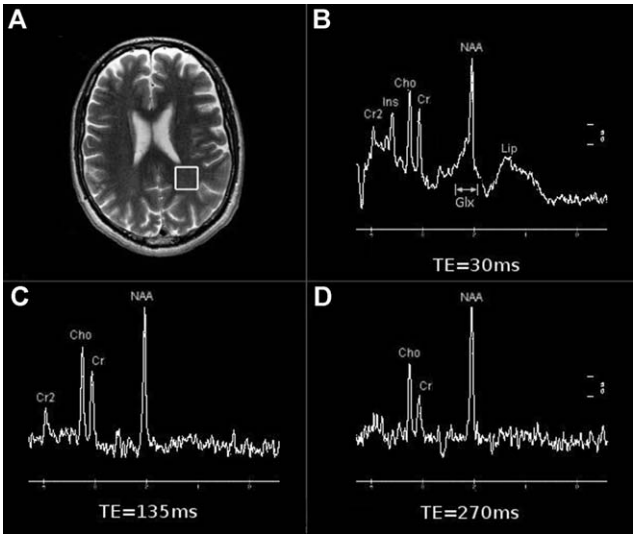

Figure 1 T2-weighted axial scan of a healthy subject's brain at the level of the lateral ventricles showing the voxel localizer (A). Single voxel PRESS MR spectroscopy (MRS) performed at three different echo times: 30 ms (B), 135 ms (C), and 270 ms (D), showing the wide variation in spectrum shape. At short TE (B) there is evidence of a greater number of metabolite peaks, whereas at longer TE (C & D) the short T2 metabolites are no longer evident. Moreover, a trend toward increased Cho/Cr ratio is visible at longer TEs.

is not achieved, the height and predicted area under the curve (AUC) of a metabolite peak located at an elevated or depressed portion of the baseline, can be erroneously estimated leading to errors in both absolute and relative metabolite quantitation. These errors could potentially propagate to result in mis-diagnosis of the underlying pathology. For example, in the case where the elevated Cho/Cr ratio is considered a hallmark of neoplasm, a wavy baseline can lead to an underestimation of the concentration of one of the metabolites and an overestimation of the other resulting in an erroneous Cho/Cr ratio. An area containing tumor might then be considered normal or conversely, an otherwise normal metabolite ratio might be misrepresented as pathologic. This artifact can be minimized by advanced post-processing with successful baseline correction and curve fitting. Not all automated MRS quantitation systems include such post-processing and those that do can not be expected to achieve successful baseline correction every time. Therefore, it is essential that the clinical radiologist not rely solely on the numerical metabolite measurements and ratios offered by automated software, but interpret these in conjunction with visual analysis of the

Table 1 Four common MRS pitfalls related to short and long TE time.

Pitfall No.	TE	Description
1	Short	Metabolite quantization error due to irregular or fluctuating baseline
2	Short	''artifactual'' elevation of NAA due to overlap with elevated Glx peak
3	Long	non-detection of metabolites with short T2 (i.e.: mI, Glx, Lip)
4	Long	''artifactual'' increase in the relative measurements of the Cho peak

TE: echo time.

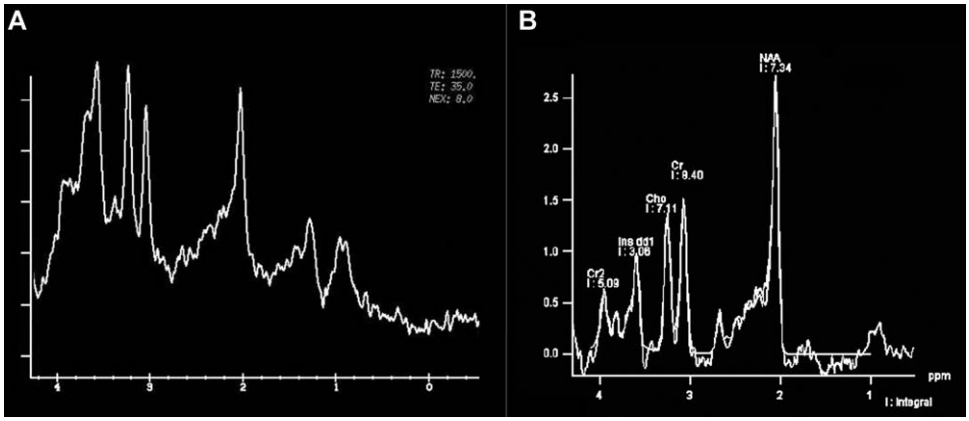

Figure 2 Single voxel PRESS MR Spectroscopy (MRS) performed at short TE (35 ms) showing baseline fluctuation. In (A) the spectrum shows a wavy and fluctuating baseline (note the high MI peak, the slightly elevated Cho peak and the reduced NAA peak), due to poor baseline correction and fitting, compared to the spectrum in (B), showing no abnormalities and obtained after baseline correction. Not all commercial MRS post-processing software used in clinical practice achieve an efficient curve fitting.

spectral baseline. When manual measurements of peak size are performed, and the baseline is not perfectly fitted, the height should be calculated starting from the interpolated baseline level at the exact location of the peak (Fig. 2).

Pitfall No. 2: ''artefactual'' elevation of NAA due to overlap with an elevated Glx peak on short TE

At short TE, glutamine, glutamate, and GABA show multiple resonance peaks between 2.05 and 2.45 ppm partially superimposed on the NAA peak [14]. The glutamine, glutamate and GABA metabolites are not separable at 1.5 T. The broad peak, encompassing these metabolites, is called the Glx complex. In normal conditions the Glx/Cr peak height ratio should not exceed 0.5, but increased concentrations are seen in hepatic encephalopathy as well as pathologic processes with anaerobic metabolism. Elevated Glx has also been reported in demyelinating and inflammatory diseases of the brain [15], in meningiomas [16] and in some low-grade oligodendroglioma [17]. In normal conditions, a small shoulder representing Glx is seen at the base of the NAA peak. Occasionally, the Glx peak can mask the base of the NAA peak, causing an erroneous underestimation of NAA concentration. More frequently, however, an elevated Glx peak can artifactually elevate the measured NAA peak due to the overlap of the peak locations of these two metabolites in the short TE spectra (Fig. 3). In the setting of a tumor with inflammatory response or a tumefactive demyelinating lesion, this elevation of the NAA peak could result in a normal Cho/NAA peak ratio and a false-negative interpretation. Since Glx has a very short T2, on long TE MRS it has marked signal decay and its resonance is not visualized. In cases where a large Glx resonance is noted on short TE MRS, we recommend verifying the height of the NAA peak on long TE MRS.

Pitfall No. 3: non-detection of metabolites with short T2 at long TE

The T2-weighting of the MRS sequence is directly proportional to the TE chosen by the operator. Some metabolites and macromolecules have a very short T2 decay time, such

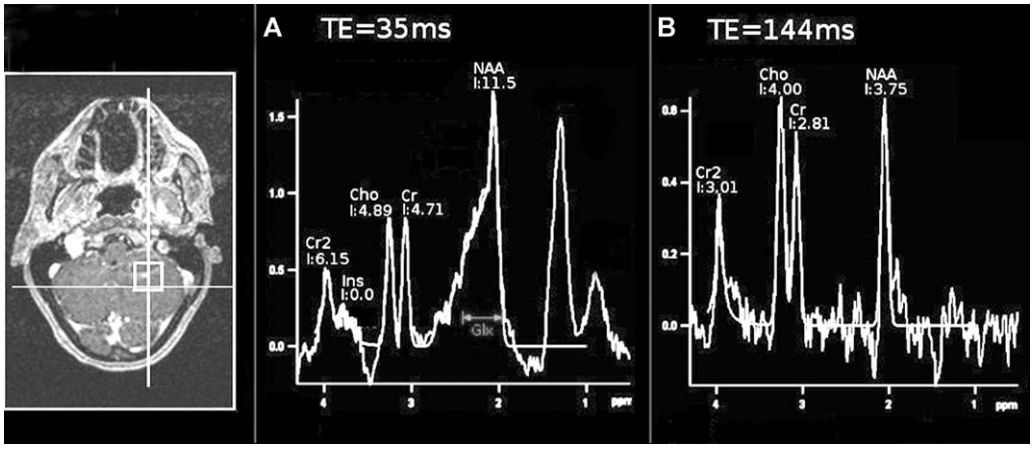

Figure 3 In this patient with left cerebellar cryptococcal abscess, the short TE MR spectrum (A) shows a large Glx shoulder artifactually elevating the NAA peak as confirmed at longer TE (B). At longer TE (B) the Glx and lipid components are no longer evident due to their short T2.

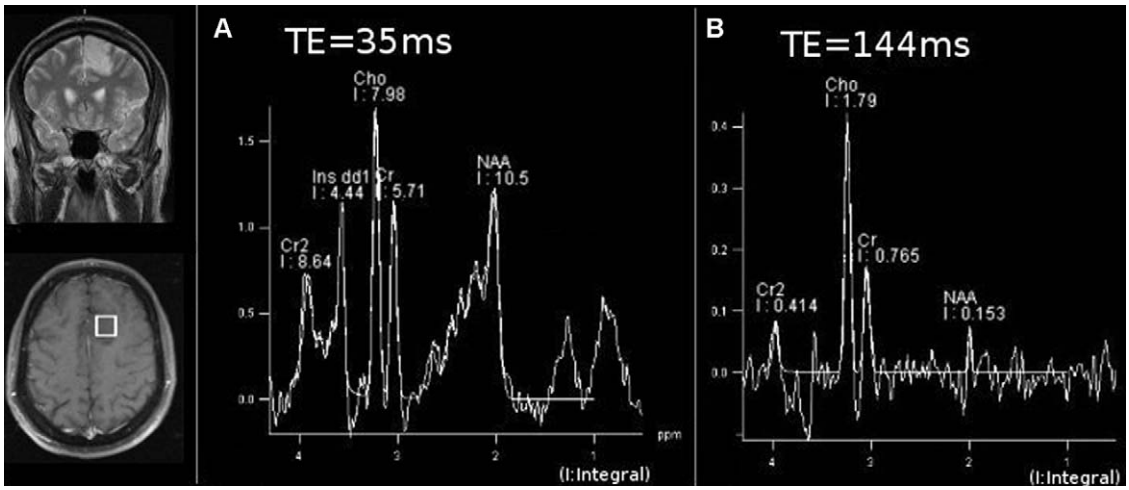

Figure 4 In this patient with biopsy proven low grade glioma the long TE spectrum (B) shows significant elevation of the Cho:Cr ratio due to the longer Cho T2, when compared to the short TE spectrum (A). Obtaining only a long TE spectrum might have resulted in a misinterpretation for high grade glioma. Elevated mI on the short TE spectrum suggests a low-grade neoplasm.

that their resonance peak is only visible in the spectra acquired at short TE and become non-detectable, due to signal decay, in the long TE MRS sequences. Some of these metabolites, such as MI, Glx and Lip may help increase the diagnostic specificity of MRS. MI, resonating at 3.56 ppm, has been shown to be a marker of astrogliosis. In normal conditions MI/Cr peak height ratio should not exceed 0.5, but elevation of this ratio has been described in different metabolic disorders including hypernatremia and Alzheimer's disease as well as in lesions with significant associated gliosis. Elevated MI is also a potential marker of neoplasms, such as low-grade gliomas or gliomatosis cerebri, but not high-grade gliomas [18]. MI therefore is an important additional diagnostic metabolite useful to differentiate low-grade versus high-grade neoplasm when the Cho/Cr ratio is borderline (Fig. 4) or to differentiate low-grade glioma versus a non-neoplastic lesion in cases without elevated Cho.

The Lip peak is a large resonance between 0.9 and 1.3 ppm, usually best seen at short TE, and not detectable in normal brain tissue. Lip resonance correlates with necrosis in high-grade gliomas, in metastases and in some infectious lesions; in the latter case associated with macromolecular amino acidic resonances. Lipids might be a hallmark of necrosis, even when macroscopic evidence of necrosis is lacking [19]. Since necrosis is one of the key radiologic diagnostic criterion and decisive prognostic factors for glioblastoma multiform [20—22], reliable assessment of necrotic foci in neoplasms would be of value in determining management and prognosis. Due to the short T2 of lipids, short TE MRS sequences are the most appropriate technique to visualize their peaks. Lipid has primary resonances for CH2 and CH3 at 1.2 and 0.9 ppm. Secondary resonances are also seen at 2 ppm, which, due to their overlap with the 2 ppm NAA peak, may additionally artifactually increase the NAA signal. Also, since lipid is easily visualized at short TE acquisitions, careful voxel placement is mandatory because any overlap between the voxel and adjacent subcutaneous fat or fatty calvarial bone marrow will contaminate the spectra and erroneously show an abnormal lipid peak.

Glx resonance is visible only at short TE, and seems to be a marker of inflammatory lesions [15]. Since inflammatory processes such as tumefactive demyelinating lesions can show confounding elevation of Cho peak (erroneously suggesting a neoplastic lesion etiology) [23,24], a marker to differentiate them from neoplasm is of great utility. With acquisition of only long TE spectra, the Glx peak is not seen and thus cannot help to distinguish inflammatory from neoplastic processes unless the short TE spectra of a given voxel are also acquired (Fig. 5).

Pitfall No. 4: ''artifactual'' increase in the relative measurements of the Cho peak at long TE

As stated above, metabolites visible on brain MRS have different T2 decay times, with relative differences ranging between 20 and 30% among the main metabolites Cho, Cr and NAA in normal brain tissue. When TE is long, metabolites have more time to dephase and lose signal, and those with short T2 do so more rapidly than metabolites with longer T2 values. Cr peak, for clinical purposes, is considered to be relatively stable in normal brain and in the presence of disease, thus representing the internal reference for most relative measurements in MRS. That notwithstanding, creatine's T2 decay is significantly shorter than choline's T2. A normal Cho/Cr ratio seen on short TE MRS, where the T2-weighting is minimal, can appear artifactually increased on long TE MRS because the increased T2-weighting causes a disproportionate amount of signal loss for Cr compared to Cho. The Cho/Cr ratio is the parameter most commonly used to identify, characterize, and grade neoplasms. An increased Cho/Cr ratio on long TE MRS could be caused solely by this T2 effect and may lead to erroneous diagnosis of brain neoplasm or to an overestimate of tumor grade unless an additional short TE spectra is simultaneously acquired (Figs. 1, 3—5). This phenomenon is even more prevalent (and thus more problematic) when a very long TE (270—288 ms) spectra is acquired compared to using a more ''intermediate'' value for the long TE (135—144 ms) spectra (Fig. 1).

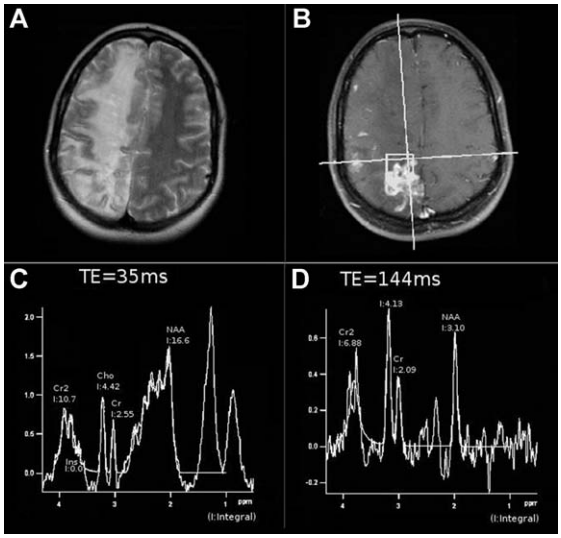

Figure 5 Biopsy proven lymphocitic vasculitis, a rare inflammatory CNS disease, causing extensive edematous changes, infiltrates and blood brain barrier disruption as seen on the axial T2-weighted (A) and post-contrast T1-weighted (B) images. The evidence of a large Glx shoulder resonating between 2.0 and 2.45 ppm in the short TE spectrum (C) orients towards the diagnosis of an inflammatory disease. On the long TE spectrum (D) the more greatly elevated Cho:Cr ratio, although compatible with an inflammatory lesion, might also be misinterpreted as a brain neoplasm.

It is relevant to note that if different metabolite T2 values alone determined changes in metabolite ratio at different TEs, the relationship between TE and a metabolites' peak height should be linear. In practice, this relationship is less predictable. A metabolite's T2 value differs between normal brain and brain with edema or tumor, most likely due to complex biochemical interactions with the surrounding environment [25—31]. A metabolite's T2 value also differs between individuals. Multiple studies evaluating T2 values of major metabolites in brain MRS show different measurements [25—29]. To avoid overestimating the Cho peak or Cho/Cr ratio at long TE, one should be aware of the T2 effect and, when possible, acquire an additional short TE spectrum. Alternatively, one could obtain a contralateral spectrum as a control.

Additionally, the Cr peak is not stable in many disease processes (such as ischemia, high-grade neoplasm, meningioma, etc.) especially when tissue necrosis is present. Thus, when interpreting long TE MRS studies, the ratio of Cho/NAA might be a more reliable index to follow than that of Cho/Cr. Also, the T2 values of NAA and Cho more closely match than do the T2 values of Cho and Cr. With similar T2 values, the effects of T2 decay on the NAA and Cho signal at long TE will be similar, and therefore their ratio (Cho/NAA) will show less TE dependence than will the ratio of Cho/Cr [4,32—36]. Using this Cho/NAA ratio can also increase the sensitivity to detect subtle metabolite abnormalities since the simultaneous Cho increase from cellular proliferation and the NAA decrease from loss of normal neuronal tissue results in a magnified numerical value when calculated together as a ratio. It should, however, again be noted that at short TE the Cho/NAA ratio may not be accurate due to the Glx effect on NAA, and so the Cho/Cr ratio is still the more appropriate index to consider at short TE. Thus, metabolite ratio depends not only on metabolite concentration but also on metabolite T2 decay time. Although this phenomenon has been described previously [4,18,21,26,32,37—39] and MRS experts may take it for granted, the implications for clinical radiological diagnosis are not always obvious and lack of this knowledge may result in misinterpretation of the spectra.

These discussed pitfalls are common to all MR spectra irrespective of the magnetic field strength of the MR imaging unit. There are; however, additional issues that arise when imaging at ultra-high magnetic field strength, such as 3 Tesla, that the operator should also be aware. For example, care should be taken when assessing spectra for a lactate peak at the ''intermediate'' long TE of 144 ms when using the usual point resolved spectroscopy (PRESS) acquisition at 3T. Due to anomalous j-modulation of the inverted lactate doublet, which results in chemical shift displacement artifact and subsequent signal cancellation, the expected peak amplitude is markedly diminished leading to potential underestimation of lactate concentration/presence. This loss of signal is roughly equivalent to the square of the B0 magnetic field strength. In this case, using an echo time of 288 ms for long TE spectra should provide better lactate conspicuity since there is no peak inversion at this echo time and therefore almost no signal cancellation occurs [40].

In summary, the optimal TE for brain tumor MRS is still under discussion [5,32,41]. MRS can be conducted at short TE (18-45 ms) with minimal T2-weighting and at long TE (120—288 ms) with greater T2-weighting. Short TE spectra have the advantage of higher signal to noise ratio (SNR) and reveal more metabolites than the long TE spectra. At short TE; however, metabolite areas could be artificially elevated due to metabolite signal overlap or incorrect baseline determination [27]. Long TE spectra are easier to analyse because there is little metabolite signal overlap, a more accurate baseline, and less contamination from lipid signal but subsequently provide less overall metabolite information. Additionally, because of the significantly shorter T2 relaxation time of Cr compared to that of Cho or NAA, the analysis of a long TE MRS without properly correcting for metabolite T2 differences, can lead to an incorrect estimate of both relative (metabolite/Cr) and absolute metabolite concentrations [27].

Conclusions

In clinical practice the choice of appropriate sequences for a thorough MRS evaluation is influenced by scanning time, patient tolerance and cost. There is no consensus on the optimal spectroscopy sequence or sequences to be utilized. The common use of a single sequence (usually a long TE MRS) poses significant risks of misdiagnosis. Since the metabolite information contained in the short TE and long TE spectra are actually complementary (and not superfluous), we strongly suggest performing both a short TE sequence and a long TE sequence whenever possible, and certainly in the doubtful cases. In some instances, comparison with contralateral normal brain is also advisable. In brief, the short TE spectra offer more complete metabolic information of

the tissue under study and present overall less confounding effects related to the T2-weighting while the long TE spectra have a flatter baseline and no peak overlap.

It is important to consider the underlying physical and biochemical phenomena when interpreting MRS spectra of the brain, based on different tissues, regions and acquisition parameters. Multiple techniques and different parameters can be chosen to obtain the most appropriate information. The different appearances of the MRS spectra with different TE values cause potential pitfalls. While increasing imaging time, clinical diagnostic accuracy is improved by combining information from both short and long TE MRS sequences.

Conflict of interest statement

We declare that we have no conflict of interest.

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