Magnetic Resonance Spectroscopic Analysis in Brain Tumors

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2.1 Introduction

Brain tumors are one of the most health problems in the world, and tumor grading is critical for the determination of appropriate treatment approaches [1]. Indeed, patients with some types of brain tumors (e.g., glioblastoma) have poor prognosis, and the time to progression and median survival can be mediated for selected subpopulations of patients by applying aggressive therapy [2, 3]. In fact, decide on the treatment which has highest suitable effects on a patient, and leading that therapy to the region of active tumor is very crucial for achievement of the appropriate results. Some critical considerations for analyzing prognosis are tumors type, grade, and volume [4, 5]. Considering the brilliant soft tissue contrast obtained by magnetic resonance imaging (MRI), the sensitivity and specificity with which this modality defines tumor type and grade is restricted. This is partially attributable to the presence of gadolinium (Gd)-enhanced necrosis which might be incorrect for tumor and partially to the inconvenience in differentiating between tumor, edema, and non-specific treatment consequences in the section of hypointensity on T2-weighted images [6, 7]. Overcoming these important challenges needs the development of new imaging modalities which highlight functional or metabolic characteristics of tumors. Though some researches about positron emission tomography and single photon emission tomography for such evaluation have been

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stated, there would be an important saving in cost and patient suffering, if above-mentioned challenging information could be described by using magnetic resonance methodologies [8–10]. For instance, two methods of imaging investigated for this application are perfusion-weighted and diffusion-weighted MRI. These make applying echo planar pulse sequences to study the architecture of tissues and microvasculature in the lesion and surrounding brain parenchyma. They offer information of physiological characteristics of tumors linked to cellularity, structural integrity, and angiogenesis; however, they are applied irregularly for clinical management of patients [11, 12].

In this chapter, MRS technique in diagnosis, follow-up and characterization of brain tumors, and grading of primary brain tumors has been discussed with latest developments; the efficiency of MRS in evaluation of treatment response of brain tumors is highlighted.

2.2 Important Brain Metabolites Detected by MRS

Magnetic resonance spectroscopy (MRS) technique can be applied for detecting metabolites, including N-acetyl aspartate (NAA), choline (Cho)-containing compounds, creatine (Cr)/phosphocreatine, and lactate (Lac) (Fig. 2.1) [13]. Presently, many studies in this field applied echo times of 144 or 270 ms, that offer spectra dominated by five various metabolite peaks: Cho; Cr; NAA; Lac; and lipid. The Cho peaks consist of different Cho-containing compounds, and demonstrate membrane synthesis and turnover. Cr is important in cellular energetics, and NAA is a neuronal marker. Lac indicates anaerobic metabolism, and LP can be detected in regions of cellular breakdown produced by necrosis [13]. Brandão and Castillo comprehensively reviewed the clinical applications of MRS in adult brain tumors [14]. Important MRS applications and crucial concerns in initial analysis of brain tumors

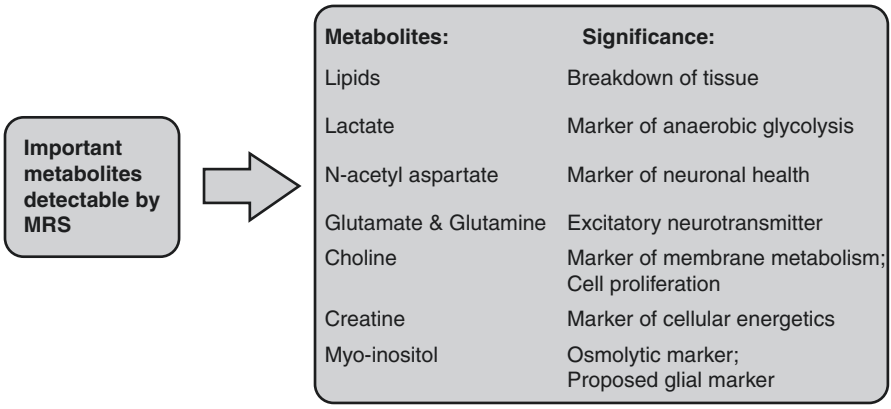

Fig. 2.1 Important metabolites detected by MRS

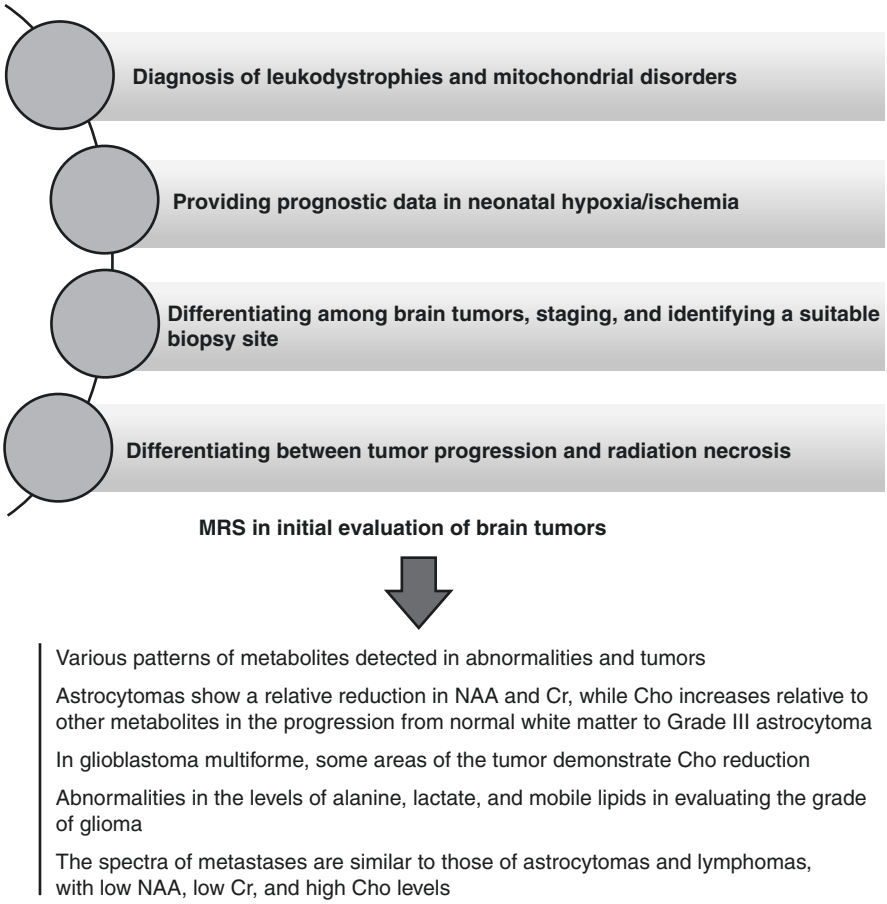

Fig. 2.2 Some important examples of clinical applications of MRS; important issues in initial evaluation of brain tumors are highlighted

are highlighted in Fig. 2.2 [1–12]. MRS can supply exclusive information for the researchers about the neurobiological substrates of brain functions in health and disease [15, 16]. Indeed, two categories of spatial localization techniques are existed for MRS; single-voxel (SV) techniques, frequently applied approaches include PRESS and STEAM, that record spectra from single region of the brain at a time, or multi-voxel techniques (magnetic resonance spectroscopic imaging (MRSI)), also recognized as chemical shift imaging (CSI) that concurrently record spectra from multiple regions and thus can be applied for mapping the spatial metabolite distribution inside the brain [17–19]. MRSI is typically performed in 2- or 3-dimensions, but does not regularly have full brain coverage. It should be noticed that important concern for brain tumors is their metabolic inhomogeneity [19]. For instance, the MRSI spectrum from the necrotic core of a high-grade brain tumor is entirely dissimilar from a spectrum of the actively growing rim, although peri-tumoral edema

is different from tumor invasion into surrounding brain tissue; thus, high-resolution MRSI is often preferred for analyzing brain tumor metabolism [20]. It was shown that proton MRSI may have a promising role in differentiating pediatric brain lesions, and crucial diagnostic value, especially for inoperable or inaccessible lesions [20]. Studying all potential metabolite ratios combinations, the best discriminant function for differentiating between non-brain tumors and neoplastic lesions was found to include only the ratio of Cho/Cr. The best discriminant function for differentiating between high- and low-grade tumors involved the ratios of NAA/Cr and Cho $_{norm}$. Cr levels in low-grade tumors were considerably lower than or comparable to control regions and ranged from 53 to 165% of the control values in high-grade tumors [20].

It was established that approximately all kinds of brain tumors show reduced NAA signals, frequently show accelerated Cho levels, and make an accelerated Cho/NAA ratios. The reduction of NAA is widely elucidated as the dysfunction, loss, or displacement of normal neuronal tissue, because NAA is identified to be mainly of neuronal and axonal origin [21]. Indeed, the Cho signal contains involvements from various Cho-containing compounds, which are contributed in membrane synthesis and degradation; it is increased in brain tumors by reason of accelerated membrane turnover. In vitro study showed that the increased Cho signal in brain tumors is because of accelerated phosphor choline levels. Additionally, it was suggested that MRSI can be applied for mapping Cho levels, and therefore been offered as a defining technique for tumor boundaries in the process of treatment [19].

Other usual metabolic alterations in human brain tumors consist of increased signals in the Lac and lipid region of the spectrum, and accelerated myo-inositol (mI) levels in short echo time (TE) spectra. The acceleration in Lac is almost certainly the consequence of anaerobic glycolysis. Furthermore, it can be due to inadequate blood flow that makes the ischemia or because of the necrosis. The detection of increased lipid levels is supposed to be related with necrosis and membrane breakdown. Accelerated levels of mI can be due to the elevated numbers of glial cells containing high levels of mI, and especially have been reported to be high in grade II gliomas. Additionally, patients with gliomatosis cerebri may show accelerated inositol levels, even in the absence of elevated Cho [19, 22]. MRS efficacy in diagnosis and assessment of treatment response of brain tumors has been widely reported, but this technique has not been typically established as a routine clinical tool. Robust and automated techniques are required to collect the information, evaluate the spectra, and show the consequences, comprehensively. Standardization across sites and various vendors of acquisition and evaluation technique is very critical. Additionally, carefully created, multicenter trials complying with criteria of evidence-based medicine have not been completed until now, and consequently, MRS is only comparatively infrequently applied for evaluating tumor by researchers in the field [19].

H-MRS can be applied in tumor histology and grading and may better describe tumor extension and the appropriate site for biopsy compared with conventional MRI. Combination of H-MRS with other developed imaging techniques, including

diffusion-weighted imaging, perfusion-weighted imaging, and permeability maps enhances the diagnostic accuracy for intra-axial brain tumors. Short echo time allows for detecting higher amounts of metabolites compared with long echo time, which is crucial for differential analysis of brain masses and grading tumors. Additionally, higher Cho levels and lower mI/Cr ratio are detected in more malignant tumors compared with lower-grade tumors. Lac is precisely related with brain tumor grading. Though, Lac is found in basically all pediatric brain tumors regardless of histologic grade. Gliomas are often invasive and show enhanced Cho levels in surrounding tissues, and thus, this can be applied for differentiating these lesions from metastases. It appears that lymphoma should be stated, when LP and Lac are found in a solid lesion. A prominent lipid peak is detected in lymphomatosis cerebri, while a considerable acceleration in mI is characteristic of gliomatosis cerebri. High acceleration in the Cho peak and the existence of LP and Lac are normally detected in pilocytic astrocytoma, a grade I tumor. Characteristically, higher levels of Cho happen in grade III gliomas; while, in glioblastoma multiforme, the Cho levels may be much lower because of the necrosis. If the Cho/NAA ratio is accelerated outside the area of enhancement, tumor infiltration can be detected. An enhancement in Cho-containing compounds after radiation therapy may be observed in radiation necrosis misclassified as tumors. H-MRS in exclusive cases enhances the accuracy and level of confidence in differentiating neoplastic from non-neoplastic masses [14].

2.3 Applications of MRS Metabolite Analysis in Brain Tumors

MRS offers significant and valuable clinical data permitting more precise diagnosis including differentiating the brain tumors from abscesses, defining the tumoral characteristic of the investigated lesion and better evaluation of brain tumors, and determining an extended local evaluation of morphological abnormalities detected in conventional MRI [23]. It can be applied for the therapeutic follow-up of evaluating the most active area in lesion, guiding and optimizing the biopsy, and differentiating the recurrent tumor. Additionally, MRS is suitable in radiosurgery as a criterion for representing the acceleration or reduction of the irradiation during tumor radiotherapy [13, 24]. In earlier differentiation between tumor and radionecrosis, MRS offers significant consequences. Accordingly, the lesion persistence or evolvement is recognized by an enhanced Cho, while a radionecrosis is stated by spectra where all metabolisms disappeared except free lipids (LP) [25].

The diagnostic variations between MRS and the conventional MRI analogue image, i.e., the accuracy and sensitivity of MRS, MRI, and CT relative to histological section, were reported. Consequently, brain tumors signify an incidence of 54% in Sudan during 2014–2017 with an increasing factor of 7.2/year. MRS demonstrated outstanding diagnostic achievement relative to standard (histology) with accuracy, sensitivity, and specificity as 93%, 90%, and 85%, respectively, and the diagnosis of analogue MRI by radiologists revealed 91%, 83%, and 76% for

accuracy, sensitivity, and specificity, correspondingly, while CT revealed 80%, 75%, and 15% for accuracy, sensitivity, and specificity, correspondingly. MRS typically surpasses MRI compared with the standard (histology) and the T-test showed a substantial point of 0.5, depending on the level of Cho, NAA, Cr/phosphocreatine, and Lac [26]. In another study, MRS was applied for differential analysis of brain tumors and inflammatory brain lesions. The examinations of 81 individuals by brain MRS evaluation have been performed. The patients with ages between 10 and 80 years old were separated into two groups. Group A consisted of 42 individuals with diagnoses of cerebral toxoplasmosis and Group B was formed of 39 individuals with diagnosis of glial neoplasms. On analyzing the ROC curve, the discriminatory boundary for the Cho/Cr ratio between inflammatory lesions and tumors was 1.97, and for the NAA/Cr ratio it was 1.12. MRS can be applied in the distinction of inflammatory brain lesions and high-degree tumors when the Cho/Cr ratio is higher than 1.97 and the NAA/Cr ratio is less than 1.12 [27]. Additionally, in two patients with heterogeneous intracranial tumors, in vivo 1H MRS and in vitro biochemical evaluations have been performed. Histology established the tumor heterogeneity. Cho was raised in the cellular portion of both tumors, but reduced in the necrotic or cystic portions. Cr was diffusely reduced while Lac was accelerated in all regions of both tumors. Furthermore, the acceleration in the choline peak on 1H MRS appeared to be due to upsurges in water-soluble Cho compounds [28].

2.4 Combining MRS and MRI-Based Diagnosis of Brain Tumors

Indeed, for metastatic lesions, the volume of Gd acceleration on T1-weighted spin echo or gradient echo images is reported to encompass the entire active tumor. In many cases, there are also central regions of hypointensity within the enhancing lesion which correspond to necrosis. The region of hypointensity on the T1-weighted image and corresponding hyperintensity on T2-weighted images that characteristically surrounds the enhancing volume is reported to correspond to edema or generic treatment consequences rather than to infiltrative tumor. Diagnosis of small lesions and enhanced visualization of larger enhancing lesions is possible using double or triple doses of Gd [29]. The number and size of metastatic lesions within the brain affects the decision as to whether the most appropriate treatment is surgery, radiosurgery, or whole brain radiation therapy. Other important issues are the status of the primary lesion and metastases in other organs. Definition of grade is based upon histological analysis of tissue samples obtained by biopsy or during surgical resection. Because it is typical for there to be regions of different tumor grade within the same lesion, directing the surgeon to the region that is possibly to be of highest grade is crucial to achieve typical experiments for histological evaluation. While tumor cells are recognized to be outside the MRI-defined lesion as well, the enhancing lesion is extensively applied as the target for surgery resection or for planning radiation therapy [7].

Generally, it is challenging to make a correct diagnosis of ring-like enhanced lesions on Gd-enhanced MR brain images. For differentiating these lesions using proton 1H MRS, the correlation between the 1H-MR spectra and histopathological results was evaluated, retrospectively. Additionally, proton MR spectra obtained from the lesions in 45 patients, including metastasis ($n = 19$), glioblastoma ($n = 10$), radiation necrosis ($n = 7$), brain abscess ($n = 5$), and cerebral infarction ($n = 4$) were evaluated. Consequently, the misdiagnosis rate was lowest at the threshold level of 2.48 for the (Cho-containing compounds)/ (Cho/Cr) detected from the whole lesions, which consist of the enhanced rim and the non-enhanced inner region. The positive predictive values of a Cho/Cr greater than 2.48 for detecting metastasis or glioblastoma was 88.9% and 60.0%, respectively, and the positive predictive value of a Cho/Cr less than 2.48 for detecting radiation necrosis or cerebral infarction was 71.4% and 100%, respectively. For additional differentiation between metastasis and glioblastoma, information about the existence and absence of an NAA peak and lipid- or Lac-dominant peak was helpful. In 73.7% of metastasis cases, a lipid-dominant peak was reported in the whole lesion without an NAA peak in the inner region, while the same pattern was detected in only 10% of the glioblastoma cases. The correlation with the histopathological consequences showed that a high Cho signal is suggestive of neoplasm. Lipid signal in the non-enhanced central region was correlated to necrosis. Lac signals were often found in glioblastoma, abscess, and sometimes metastasis, presumably reflecting the anaerobic glycolysis by the living cells in the ring-like enhanced rim. It was suggested that single-voxel proton MRS can be applied as a valuable technique for providing suitable data of differentiating ring-like enhanced lesions which cannot be detected properly by only applying improved magnetic resonance images [25].

The combination of MRS and perfusion-weighted imaging might develop assessment and evaluation of brain lesions [30]. The efficiency of perfusion and MRS in analysis and characterization of brain tumors was reported. Distribution of tumor territory in the brain site has significant relation with age. Astrocytomas were reported in 58 (45.3%) cases; gliomatosis cerebri, glioblastoma multiforme (GBM), and oligodendroglioma were in 44 (34.4%) cases; and the lymphoma and meningioma were detected in 2 (1.6%) and 8 (6.3%) cases, respectively, where the metastases constitute 3 (2.3%). Significant results have been reported between the perfusion findings and the MRS values regarding Cho/NAA and Cho/Cr. Astrocytomas demonstrated a relative decrease in NAA and Cr, and Cho comparing with the lymphoma. The spectra of metastases are similar to those of meningioma, gliomatosis cerebri, and ependymal tumors, with low NAA, low Cr, and high Cho levels. The difference was reported meaningful in the NAA values at various brain lesions with no significant reduction or increasing in Cho and Cr. Cho/Cr had major impact in differentiation of lymphoma from other lesions at p value = 0.004, where the other factors including Cho/NAA, NAA/Cr, Lac, and lipid showed no major relations. By combining both MRS and perfusion-MRI, the diagnosis of lesions was improved with value of 0.94 ± 0.89 for NAA and 1.83 ± 1.22 for Cho/NAA. Perfusion-MRI and MRS are beneficial for providing the differential diagnosis between brain metastases and brain tumors. Both have significant role in differentiation and diagnosis of brain tumors [30].

2.5 Gliomas and MRS

Gliomas are the most common shape of central nervous system neoplasm which come from glial cells, and are regular in all primary brain tumors [1]. The efficacy of 1H MRS in preoperative quantitative assessment of intracranial gliomas was evaluated [1, 31–33]. MRS has been suggested as an alternative modality for grading of brain tumors [34]. For a dependable MRS technique, spectroscopic localization approaches and data acquisition should be appropriately controlled [35]. Another critical parameter which can largely influence the spectrum is the TE. At short TE, it is possible to detect more metabolites. However, there are several disadvantages, including the distortion of the spectra baseline under the effects of eddy current, water contamination, and the overlapped LP and Lac peaks, resulting in higher shimming demands. On the contrary, intermediate TE MRS may be selected to distinguish the metabolites of longer relaxation times with little or no contamination of residual water, LP, or fat tissue and thus without baseline distortions. Limited investigations are focused on the influences of both short and intermediate TE MRS for tumor grading [36–38]. In order to evaluate the efficacy of MRS in grading of primary brain tumors, MRS was performed in 22 patients with primary brain tumors. Metabolite ratios of Cho/NAA, Cho/Cr, Cho + Cr/NAA, LP and Lac/Cr were evaluated and analyzed at short and intermediate echo times. Additionally, ratio of mI/Cr was analyzed at short echo time. On the basis of histopathology, tumors were subdivided into low grades and high grade. Receiver operating characteristic evaluation of metabolite ratios was achieved to find cutoff values between high- and low-grade tumors. The resulting sensitivity, specificity, and accuracy were assessed. Consequently, at intermediate echo time, Cho/NAA, Cho + Cr/NAA, and Cho/Cr were considerably higher in high-grade tumors than in low-grade tumor. At short echo time, Cho/Cr and Lac/Cr ratios were meaningfully higher in high-grade tumors than in low-grade tumor. The diagnostic accuracy of metabolite ratios at intermediate echo time was 86% while at short echo time the diagnostic accuracy was 75%. The combination of both echo times showed a diagnostic accuracy of 88%. Cho/NAA, Cho + Cr/NAA, and Cho/Cr are dependable in evaluating the grade of tumors. Lac/Cr is significantly associated with high-grade tumors. The combination of both short and intermediate echo times offers better accuracy, in grading of brain neoplasm, compared to that when applying each echo time alone [39].

Two-dimensional 1-H MRSI was applied for determining an outstanding classification of patients via a multivariate pattern recognition assessment of peaks corresponding to Cho, Cr, NAA, Lac, lipid, and alanine [40]. From looking at the metabolite levels in each class, it was well-defined that meningiomas were exclusively differentiated as they were the only lesions which had alanine. Grade 2 gliomas tended to have low Lac and lipid, some NAA, and some Cr. Grade 3 gliomas tended to have low Lac and lipid, less NAA and Cr, with higher Cho. Grade 4 gliomas tended toward high Lac and lipid, with very low NAA. Another possible important clinical role for 1-H MRSI is the capability of making an early assessment of whether a lesion has responded to treatment. If this were achievable, it can permit

tailoring therapy to each individual patient and moderating an unsuccessful treatment approach before the lesion shows a large increase in volume. It can also be possible to avoid giving unnecessary treatment in the case which acceleration in enhancing volume is attributable to generation of treatment-induced necrosis as opposed to recurrent or residual tumor. For 1-H MRSI to be involved in the clinical managing of the patient in this manner, it is crucial to map out both the temporal and spatial distribution of metabolite alterations in response to the therapy of interest. This involves the application of three-dimensional 1-H MRSI, and is most simply obtained for the case of focal treatments such as surgery or radiation [41]. Registration of the MR images and 1-H MRSI findings are critical for correlating data from such sequential analyses [42].

2.6 Single-Voxel and Multi-voxel MRS

Single-voxel proton MRS was applied for analyzing the metabolic signatures of brain tumors [32, 43, 44]. There is robust indication for a decrease in NAA and acceleration in Cho-containing compounds in tumor compared with normal brain parenchyma [28, 45]. Additionally, typically for some metastatic lesions and for high-grade gliomas, there are resonances corresponding to Lac or LP [44, 46]. Early investigations regarding the potential for single-voxel MRS in tumor grading offered different consequences with a large variability in information quality between institutions [47]. With the presentation of automated packages for performing single-voxel proton MRI on clinical scanners, the quality and reproducibility of the information were developed. Multivariate statistical evaluation procedures were applied for detecting patterns which explain exact tumor types and grades [48, 49]. Additionally, researches have showed the acquisition of spectra with both short and long echo times, and consequently levels of mI, glutamine, and glutamate can be involved in the assessment and provide the potential for better discrimination between various types of lesions [40, 50]. While single-voxel proton MRS is a relatively fast approach for obtaining information and indications about the metabolism in a 4–8-cm^3 region within the lesion, it does not address spatial heterogeneity and is not able to contribute in defining the spatial extent of the lesion. These factors are mainly crucial for planning focal treatments such as radiation and surgical resection and for following reaction to treatment. For representing these subjects, it is vital to consider multi-voxel proton MRSI (1-H) [32].

One of the best analytical approaches for generalizing single-voxel MRS is to select a larger volume of interest and then apply phase encoding to gain localization to a one-, two-, or three-dimensional array of voxels [51]. Multi-voxel MRS offers high spatial coverage and may be more valuable than single-voxel approaches for gaining a metabolic map of a large size of tumors [32]. PRESS and stimulated echo acquisition mode (STEAM) are the two most usual techniques applied for volume selection, with PRESS being preferred when the TE allows due to its intrinsically higher signal to noise ratio [52, 53]. Two-dimensional or three-dimensional array of spectra demonstrated some benefits, such as observation of heterogeneity within the

lesion and examination of surrounding tissue that may appear normal on MRI. This offers a reference for comparing metabolite levels in the tumor and permits to distinguish regions of abnormal metabolism outside the morphological lesion [51, 52]. For treatment planning and long-term follow-up, it is crucial to analyze tumor progression, and it is very critical to obtain three-dimensional coverage of a large volume of interest [54]. The normal brain has NAA which is about twice the intensity of Cho and Cr. Because of the nominal voxel size for a volume head coil at 1.5 T is 1 cm^3, individual voxels may consist of a mixture of tumor, necrosis, and normal brain tissue [51].

While it is possible to gain three-dimensional 1-H MRSI information with chemical shift selective water suppression and conventional volume selection radiofrequency pulses, there are numerous conditions where the water and lipid suppression are insufficient and compromise the quality of the data achieved. This is particularly true for patients who have had surgical resection and can be a severe problem for patients treated by brachytherapy using permanent radioactive seeds. For improving the quality of water suppression, it is possible to implement alternative radiofrequency pulses which are capable of offering improved spatial and frequency selection [55]. Another important technique for gaining full coverage of the lesion and for sharpening the edges of the selected volume has been the implementation of very spatially selective saturation bands. These have a very sharp transition band and can be applied parallel to the edges of the selective volume to make it more cubic in shape or at an oblique orientation to conform the volume to the anatomy [56].

Other approaches for gaining volumetric coverage of the lesion are to apply multislice and multiple TE approaches for offering spatial localization in a time effective fashion [57]. In this case, lipid suppression has characteristically been offered by spatial and frequency selective pulses, inversion recovery, and spatial saturation pulses. These methods have the advantage of gaining complete in-plane coverage but may be restricted close to the sinuses or surgery cavities due to susceptibility artifacts. For multislice acquisitions, it is essential to have a slice gap to avoid crosstalk, and two acquisitions are needed to offer complete coverage of the lesion. Another approach for gaining volumetric coverage of the brain with a rational acquisition time is to apply echo planar spectroscopic imaging with either oscillating gradients in one spatial dimension or spiral sampling within a given plane [58]. This has been shown to offer good data quality for normal volunteers and patients with neurodegenerative diseases but may be restricted for patients with brain tumors once they have undergone surgical resection. Additional researches are focused on the application of a hybrid PRESS-echo planar spectroscopic imaging technique with spatially selective saturation bands which allow greater k-space coverage but completely remove signals from regions that are likely to cause susceptibility artifacts.

The reconstruction of 1-H MRSI information and assessment of the resulting arrays of spectra combines Fourier transforms and apodization (an optimal filtering technique) with automated techniques of spectral processing to offer information that can be elucidated by visual inspection or quantified to produce maps of the

spatial distribution of various metabolites. The first step is applying an apodization function to the k-space-free induction decays and making a Fourier transform to produce k-space spectra [59]. The next step is to reconstruct the spatial dependence of the information. For spiral or irregular k-space sampling, the technique is to first re-grid the k-space data onto a rectangular array. For conventional phase encoding, this step is not essential. To center the information at the most suitable spatial location, it is achievable to phase-weight the k-space array with the proper voxel shift. This is followed by applying any needed spatial apodization and then performing the spatial Fourier transformations. The resulting array of spectra will characteristically have spatially dependent frequency and phase errors that need to be adjusted, in addition to the baseline variations because of residual water [60].

Various techniques for assessing frequency, phase, and baseline corrections for spectral information were reported. Characteristics of the 1-H MRSI information which guide the choice of methodology are the larger number of spectra that are essential to be considered, and the need for whatever technique is chosen to be robust to differences in signal to noise and peak configurations corresponding to various tissue types. One approach is to acquire a separate dataset with no water suppression. This is time consuming, but the high signal to noise of the water resonance permits for an accurate assessment of frequency and phase factors. Provided that the data acquisition window is timed correctly, there should be no necessity for frequency-dependent phase correction, and the phase of the water in each voxel may be the same as for the other metabolites [61]. A substitute for obtaining a separate water reference dataset is to deliberately limit the water suppression to leave behind a relatively large water peak in the spectrum. The accuracy of this technique depends upon the quality of the volume selection and out of voxel suppression due to incomplete suppression of water outside the excited volume may cause spurious peaks with various frequency and phase to be folded into the selected volume. Another method is applying prior information of possible peak locations, obtaining estimates of corrections from metabolite peaks in voxels that have sufficient signal to noise, and then applying spatial interpolation to fill in corrections for voxels with low signal to noise [59, 61].

More quantitative assessment of the information needs the valuation of peak locations, heights, and areas. Earlier data of relative peak locations are beneficial for accomplishing this evaluation, and offer the basis for a robust technique which recognizes statistically major peaks, analyzes peak heights, and calculates peak areas by integration inside a defined range of frequencies for each metabolite. Additionally, more sophisticated fitting algorithms can be applied to spectra which have adequate signals to noise for the optimization routines to be reliable. The yield of the assessment is a number of spatial maps of metabolite parameters applied to distinguish regions of abnormal and normal metabolisms. Further corrections for spatial variations in intensity produced by the information acquisition processes may also be needed if comparing relative intensities of metabolites such as Cho, Cr, NAA, Lac, and lipid [59]. It was reported that the relative acceleration in Cho and decrease in NAA are crucial for identifying the spatial extent of the metabolic abnormality corresponding to active tumor [62].

One of the critical issues in 1-H MRSI for evaluating brain tumors is whether the spatial extent of the metabolic lesion is diverse from the Gd-enhancing region and hyperintensity on T2-weighted images [63]. If there is no distinction between these lesions, there might be no extra value for the 1-H MRSI information over and above conventional MR images. For metastases, the focus is on distinguishing between regions of tumor and enhancing necrosis. In practice, it is hard to get definitive evidence, because it is infrequent for such lesions to be biopsied. Assessment of a lesion corresponding to active tumor is characteristically based on whether it consequently gets larger on Gd-enhanced MRI. Another complication was described that the lesion gets larger, it generates central necrosis and, with a voxel size of 1–2 cm^3, it is complicated for obtaining spectra free from partial volume of tumor and necrosis. In a study of eighteen patients with brain metastases treated with gamma knife radiosurgery, it was described that all but two of the lesions had reduced NAA, in addition to a peak corresponding to Lac or lipid. Of the lesions followed after treatment, all lesions which demonstrated reductions in the volume of the enhancing lesion also exhibited decrease in Lac, lipid, and Cho peaks. There were also three lesions which demonstrated decreased metabolism but had stable or slightly increasing volume. Lesions that demonstrated accelerated enhancement on long-term follow-up also had a corresponding enhancement in Cho and Lac or lipid peaks [63]. The situation is more complex for patients with gliomas as there is the need to separate tumor from necrosis and to distinguish non-enhancing tumor from edema and treatment consequences. For evaluating the viability of applying 1-H MRSI in this way, the alterations in anatomical and metabolic lesions in patients with recently detected gliomas scanned before surgical resection should be concerned [64].

2.7 Conclusion

In conclusion, MRS is a diagnostic technique which provides a noninvasive vision into the biochemical profiles of the brain tumors, and it can provide extra diagnostic information for improvement of managing and treating patients with brain tumors. But it has low sensitivity and can only detect selected nuclei. This technique is a challenging method and can be used when spectral data will provide clinical data which is not gained by other imaging approaches. The technique is very sensitive to inhomogeneities in the magnetic field, requires careful manual regulation to ensure field uniformity, and is also very sensitive to motion. Due to the smaller voxel size and restrictions in the length of time of image acquisition, MRSI information is noisier than single-voxel MRS. In order to overcome the aforementioned limitations of MRS, clinical researchers have moved their investigations to higher field strengths to gain signal-to-noise ratio and to detect additional metabolites more reliably. Furthermore, they focused on faster MRSI sequences to overcome low spatial resolution and lengthy data acquisitions, and applied motion corrected MRS acquisitions. 1-H MRSI as a suitable technique for anatomical imaging in analysis of tumor types and grading, and in evaluation of the treatment outcomes. Though, the prognostic value of this method is yet under investigations, but it can offer useful

information regarding the selection of the appropriate treatment strategies for patients and for recognizing the mechanistic aspects of treatments (successful or unsuccessful therapies). This is especially crucial for evaluating treatments based upon the biological characteristics of tumors, where it is very important to distinguish whether the insufficiency of response was due to the agent being unable to approach the tumor or to the lesion being insensitive to that particular method. Potentials for refining the sensitivity and specificity of the 1-H MRSI data contain the application of shorter echo times and radiofrequency coils with better-qualified signal to noise and of magnets with advanced field strength.

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