European Journal of Radiology 81 (2012) 566–577

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Review

Molecular imaging of cancer: MR spectroscopy and beyond

K. Pinker[a], A. Stadlbauer[c], W. Bogner[b], S. Gruber[b], T.H. Helbich[a,b,*]

[a] Department of Radiology, Division of Molecular and Gender Imaging, Medical University Vienna, Austria
[b] MR Centre of Excellence, Department of Radiology, Medical University Vienna, Austria
[c] Department of Neurosurgery, Neurocenter, University of Erlangen-Nuremberg, Erlangen, Germany

ARTICLE INFO

Article history:
Received 12 March 2010
Received in revised form 25 April 2010
Accepted 27 April 2010

Keywords:
Molecular imaging
MR spectroscopy
Cancer
Sodium imaging
Diffusion-weighted imaging
Breast
Prostate
Brain

ABSTRACT

Proton magnetic resonance spectroscopic imaging is a non-invasive diagnostic tool for the investigation of cancer metabolism. As an adjunct to morphologic and dynamic magnetic resonance imaging, it is routinely used for the staging, assessment of treatment response, and therapy monitoring in brain, breast, and prostate cancer. Recently, its application was extended to other cancerous diseases, such as malignant soft-tissue tumours, gastrointestinal and gynecological cancers, as well as nodal metastasis. In this review, we discuss the current and evolving clinical applications of proton magnetic resonance spectroscopic imaging. In addition, we will briefly discuss other evolving techniques, such as phosphorus magnetic resonance spectroscopic imaging, sodium imaging and diffusion-weighted imaging in cancer assessment.

1. Introduction

Since the 1980s, two complementary techniques – magnetic resonance imaging (MRI) and proton magnetic resonance spectroscopic imaging (^{1}H-MRSI) – have emerged. MRI investigates anatomic changes associated with neoplastic disease, while ^{1}H-MRSI is able to examine the biochemistry of tissue and to detect spatial deviations from normal biochemistry in neoplastic tissues. Although the evolution of ^{1}H-MRSI over the past 25 years in the clinical setting has been rather slow, MRI has matured more rapidly and now plays a key role in the assessment and therapeutic monitoring of neoplastic disease. However, with advances in technology within recent years, ^{1}H-MRSI has entered the clinical routine [1,2] and is now routinely used as an adjunct method to MRI for the pre-therapeutic diagnosis, assessment of therapy response, and therapeutic monitoring of brain [3–9], breast [10–14], and prostate [15–20] cancer. In addition, within the past few years, the application of ^{1}H-MRSI is now expanding to the investigation of other malignant processes, such as the assessment of soft-tissue tumours [21,22], cervical [23–25] and ovarian cancer [26], and lymph node involvement [27].

This article will discuss the role of molecular imaging with ^{1}H-MRSI in brain, breast, and prostate cancer, as well as new emerging applications of ^{1}H-MRSI. In addition, we will briefly discuss other evolving techniques which allows insight in molecular imaging, such as phosphorus magnetic resonance spectroscopic imaging, sodium imaging, and diffusion-weighted imaging in cancer assessment.

2. Primary brain tumours

The accurate grading of brain tumours has important prognostic and therapeutic implications, as high-grade lesions are treated differently from low-grade lesions. Patients with high-grade lesions, both resectable and unresectable, receive either radiotherapy or combined radio–chemotherapy [28,29]. Low-grade gliomas (WHO grade I and II) are amenable to (radio) surgical resection with curative intent, and adjuvant radio/chemotherapy is only recommended for patients with incompletely resected grade II tumours or for patients older than 40 years of age, regardless of the extent of resection [30,31]. In an effort to preoperatively differentiate between high-grade and low-grade lesions and to determine the optimal patient treatment, a stereotactic biopsy is often performed preoperatively [31]. Burger et al. found that among histopathological features, such as cell frequency, nuclear atypia and mitotic activity, and necrosis and vascular proliferation, only vascular proliferation differentially predicted both the short- and long-term survival in patients with anaplastic astrocytomas [32].

* Corresponding author at: Department of Radiology, Medical University Vienna, Waehringer Guertel 18-20, 1090 Vienna, Austria.
E-mail address: Thomas.Helbich@meduniwien.ac.at (T.H. Helbich).

0720-048X/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ejrad.2010.04.028

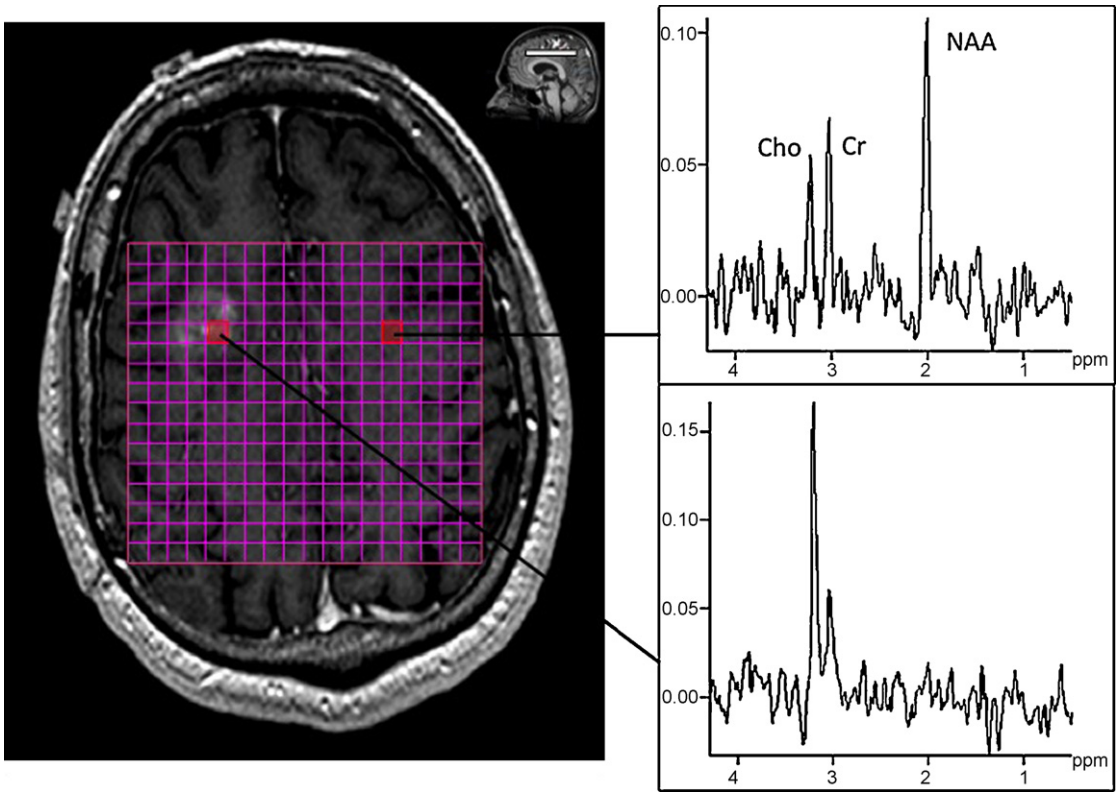

Fig. 1. Transverse, contrast-enhanced, T1-weighted MR images in a 34-year-old patient with an oligoastrocytoma WHO grade II of the right hemisphere, with the volume of interest of the MR spectroscopic examination (point-resolved spectroscopy box, pink). a) ^{1}H-MRS spectrum of healthy brain parenchyma of the contralateral side. b) Typical ^{1}H-MRS pattern of a primary brain tumour: increased levels of choline-containing compounds (Cho) and a reduction in the signal intensity of the *N*acetylaspartate (NAA) and creatine (Cr).(For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

Contrast-enhanced MRI is the current gold standard for the guidance of brain biopsies for diagnosis and grading of primary malignant brain tumours. However, this method can be ambiguous, as the absence or presence of contrast-enhancement does not necessarily coincide with high-grade. Therefore, a more accurate technique for the guidance of brain biopsy to the most metabolically active part of the lesion, and thus, a more accurate grading, is warranted.

2.1. Improved and accurate pre-therapeutic diagnosis

^{1}H-MRSI is a non-invasive tool for investigating the spatial distribution of metabolic changes in malignant primary brain tumours. Although there is no tumour-specific metabolite *per se*, there are specific patterns in the changes of metabolite concentrations in tumourous tissue compared to normal brain, which can be assessed by ^{1}H-MRSI (Fig. 1). Numerous studies have reported increased levels of choline-containing compounds (Cho at 3.2 ppm) and a reduction in the signal intensity of *N*-acetylaspartate (NAA at 2.0 ppm) and creatine (Cr 3.0 ppm) in brain tumours [33–40]. The total choline signal observed in ^{1}H-MRS is composed of choline, phosphocholine, and glycerophosphocholine, and is thought to be a marker for increased membrane turnover or higher cellular density [41,42]. NAA is regarded as a neuronal marker primarily contained within neurons [43]. The total Cr peak is the summed signal from both Cr and phosphocreatine and plays a role in tissue energy metabolism [44]. The range of Cho increase and NAA decrease is compatible with the range of tumour infiltration [44,45]. For pathologic conditions that mimic brain tumours at MRI, variations in the changes of these three metabolites and others (myo-inositol, lactate, lipids, glutamine, and/or glutamate, and alanine) can be used for differential diagnosis [8,39,40,46–48]. Numerous studies have demonstrated that the differentiation of the degree of malignancy of brain tumours is feasible [49,50]. In a recent study, Stadlbauer et al. [51] investigated high-spatial resolution ^{1}H-MRSI for the preoperative grading of suspected WHO grades II and III gliomas. In this study, 26 patients with suspected gliomas and 26 age- and sex-matched healthy control subjects underwent ^{1}H-MRSI before stereotactic ^{1}H-MRSI guided brain biopsy. The absolute metabolic concentrations for Cho, Cr, NAA, as well as metabolic maps of Cho/NAA ratios, were calculated. The metabolic maps were used for the stereotactic ^{1}H-MRSI-guided brain biopsy (Fig. 2). They concluded that ^{1}H-MRSI, with a high-spatial resolution, segmentation, and absolute quantification of metabolic changes, provides valuable information and allows a preoperative grading of gliomas. Surgical biopsies are the gold standard for diagnosis of tumour type and grade, but targeting the most appropriate tumour region can be difficult [39,40,52,53]. Several studies have confirmed that aiming the biopsy at the area of the maximum Cho/NAA ratio in ^{1}H-MRSI improves diagnosis [52–56].

2.2. Assessment and monitoring of response to treatment

A decrease in Cho, and an increase in Lactate (Lac) and/or lipids are indicative of response to therapy and reflect tumour necrosis. Moreover, a total absence of metabolites in the former tumour region is indicative of necrotic tissue. As gliomas are highly likely to recur after treatment, a diagnostic method for the early detection of recurrence is necessary. Currently, MRI is the method of choice for follow-up; however, as in primary diagnosis, the MRI findings at follow-up can be ambiguous. In equivocal cases, ^{1}H-MRSI can provide predictive information, as changes in Cho/Cr prior to a subsequent increase in contrast-enhancement hint at tumour progression or recurrence. In serial studies, Wald et al. [57] and