Annals of Clinical Case Reports

Research Article
Published: 25 Aug, 2023

Effect of Time of Echo on ^{1}H-Magnetic Resonance Spectroscopy Imaging of Metabolites in Maxillofacial Carcinoma

*Wang B[1,2#], Shangguan C[3#], Liu S[4], Wu J[5] and Mi J[1]**

[1]Department of Biochemistry and Molecular Cell Biology, Shanghai Jiao Tong University School of Medicine, China

[2]Department of Radiological Imaging, Ninth Hospital affiliated with Shanghai Jiao Tong University School of Medicine, China

[3]Department of Oncology, Shanghai Ruijin Hospital affiliated with Shanghai Jiao Tong University School of Medicine, China

[4]Department of Maxillofacial Surgery, Ninth Hospital affiliated with Shanghai Jiao Tong University School of Medicine, China

[5]Department of Radiological Imaging, Sixth Hospital affiliated with Shanghai Jiao Tong University School of Medicine, China

[#]These authors contributed equally to this work

Abstract

Background: This study aims to evaluate the effect of Time of Echo (TE) on Magnetic Resonance Spectroscopy Imaging (MRSI) of metabolites in maxillofacial carcinoma.

Methods: Twenty maxillofacial carcinoma patients and 10 healthy volunteers were recruited to undergo 1.5-Tesla high-resolution routine MRI and multi-voxel MRSI with a TE of 35 ms and 144 ms. An automated MRSI processing protocol calculated the metabolite peak area, which was analyzed to compare the patients and the volunteers.

Results: Although proton MRS with a 144 ms TE could detect choline with better sensitivity than MRS with a 35 ms TE, the choline content was lower in patients than that in volunteers, and the sensitivity of MRS with a 35 ms TE to lactate/lipids was significantly higher than that of 144 ms MRS. The detection baseline of MRS was more constant in the 35 ms MRS than in the 144 ms MRS. Regardless of the subtype of maxillofacial carcinoma, the content of lactate/lipid appeared to be increased in the 20 patients ($p<0.001$) compared to that in the healthy volunteers. One year after treatment, the content of lactate/lipid returned to the baseline level in 8 patients and was reduced in 5 patients.

Conclusion: Our data have demonstrated that MRSI with a 35 ms TE better reveals the content of tumor metabolites, specifically lactate/lipid, suggesting that MRSI with a 35 ms TE can be used to monitor specific metabolites for tumor diagnosis and assess therapeutic response.

Keywords: ^{1}H-Magnetic resonance spectroscopy; Metabolites; Time of echo; Maxillofacial carcinoma

OPEN ACCESS

Correspondence:
Jun Mi, Department of Biochemistry and Molecular Cell Biology, Shanghai Jiao Tong University School of Medicine, 280 South Chongqing Rd., Shanghai 200025, China

Received Date: *10 Aug 2023*
Accepted Date: *21 Aug 2023*
Published Date: *25 Aug 2023*

Citation:
Wang B, Shangguan C, Liu S, Wu J, Mi J. Effect of Time of Echo on ^{1}H-Magnetic Resonance Spectroscopy Imaging of Metabolites in Maxillofacial Carcinoma. Ann Clin Case Rep. 2023; 8: 2460.

ISSN: 2474-1655.

Introduction

Metabolic reprogramming is a hallmark of cancer [1]. Glucose and glutamate uptake are dramatically enhanced to meet the demands of rapidly growing malignant tumor cells [2]. A shift from oxidative phosphorylation to glycolysis and the conversion of pyruvate to lactate for energy production is favored by cancer cells even in the presence of freely available oxygen. This phenotype, termed aerobic glycolysis, is also known as the "Warburg effect" [3] and is a widely accepted metabolic feature of cancer [1]. Metabolites catalyzed by nutrients, such as lactate and choline, are increased in a tumor. Therefore, these abnormally accumulated metabolites could be used to monitor tumor treatment or serve as biomarkers for diagnosis and prognosis.

Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS) are complementary techniques applied in clinical practice. MRI displays tumor morphology, while MRS provides the biochemical information necessary for understanding the disease's physiology and

metabolism [4]. Choline, creatine and lactate/lipid are metabolites often detected in tumors by MRS. Elevated lactate levels have been found by ^{1}H-MRS in cancers such as brain, lung, thyroid [1,2], colorectal and breast [5-9]. *In vivo* Magnetic Resonance Spectroscopy Imaging (MRSI) provides a non-invasive modality for detecting metabolite changes in malignant tumors. Furthermore, lactate levels have been identified as strong indicators of tumor grade and poor prognosis in cancers of the brain, breast, lung, and liver [10-13]. Although MRSI was initially developed for the assessment of brain tumors in terms of diagnosis and treatment response monitoring, MRSI is an established imaging technique in multiple tumors including those in the brain, prostate, and breast [14].

The incidence of head and neck carcinoma is increasing, with approximately 650,000 new cases reported annually, and accounts for 2% to 4% of all malignancies worldwide [15]. Maxillofacial carcinoma is a major subtype of head and neck tumors; the shallow location of these tumors reduces the noise due to lipid, air and large vessels in MRS signals. Although MR/CT imaging is used to detect the dimension, invasion and metastasis of tumors, chemical changes in patients can be detected only by MRS. Therefore, maxillofacial carcinoma was chosen for the MRS-based analysis of metabolite alteration.

In this study, patients with maxillofacial carcinoma were examined by MRS, and the effect of the Time of Echo (TE) parameter (35 ms and 144 ms) on ^{1}H- MRS imaging of lactate/lipids was analyzed and optimized. The distribution of lactate/lipids in maxillofacial carcinoma before and after therapy will also be analyzed by ^{1}H-MRS imaging.

Methods and Materials

Patients

Twenty participants, recruited from June 15th, 2016 to December 30th, 2017, were informed of the content of the present study and gave consent for all procedures. All maxillofacial tumor patients involved in this study were pathologically diagnosed. The control group consisted of 10 healthy volunteers from a physical examination center who had no personal or family history of tumor or traumatic diseases. The 20 patients were diagnosed with primary adenocarcinoma or Squamous Cell Carcinoma (SCC) of grade I or II-III by punch biopsy. The age range of patients was between 20 and 85 years (Table 1). Subjects who could not complete the exam were excluded. Reasons for exclusion included the presence of motion artifact, metal implants, cardiac pacemakers, and claustrophobia. Thirteen patients were followed up for 12 months after surgery and radiotherapy. Detailed treatment information was available in the patients' files.

Inclusion criteria

(1) Patients with primary oral squamous cell carcinoma confirmed by pathologic diagnosis and healthy volunteers, whose ages were from 25 to 80 years old, were selected for this study. (2) Candidates were without mental history, metal implants, and excessive drinking or smoking habits. (3) The tumor patients have not administrated any anticancer drugs within one month.

Exclusion criteria

(1) Patients with any oral occupy lesions suspected to be a metastatic tumor within 3 years; (2) Any pathologically confirmed non-neoplastic occupy lesions; (3) Any patients failed to complete the examination or under certain condition affecting the imaging, such as metal implants, motion artifacts, pacemakers, claustrophobia, etc.

MR methods

All patients were positioned on a cotton mat and scanned with a full series of images. All tumors were scanned on a 1.5 Tesla high-resolution MRI scanner (GE Medical Systems, USA) with an 8-channel birdcage transmit-receive head coil. The protocol consisted of 1) a 3-plane localization sequence, 2) an axial T1 Weighted Imaging (T1WI) sequence, 3) an axial T2 Weighted Imaging (T2WI) sequence, 4) an axial T1WI contrast-enhanced sequence for reference, 5) an axial MRSI sequence with multi-voxel PRESS. The PRESS scan parameters were as follows: Voxel thickness =10 mm, TE=35/144 ms, TR=1000 ms, Field of View (FOV) =18 cm, matrix = 18×18, scan time =5'28", peak SAR=1.0. All tumors were scanned by MRS at two TE values, 35 ms and 144 ms. Except for the TE value, all other parameters were held constant between the short TE and long TE scanning sequences. The manual uniform magnetic field was used before scanning to ensure the water formant Full Width at Half Maximum (FWHM) was less than 20 Hz.

Data analysis

Three Regions of Interest (ROI) inside the tumors of all patients were sampled. The data from the PRESS sequence were processed and analyzed on a Sun workstation (GE Medical Systems, USA). The data are presented as the mean ± Standard Deviation (mean ± SD). All data were statistically analyzed by the SPSS 22.0 software (IBM Analytics, USA). The differences between groups were assessed by Student's t-test; $p<0.01$ for all reported differences unless otherwise stated.

Results

MRS with 35 ms TE is more sensitive than MRS with long TE for the detection of lactate/lipid

All maxillofacial carcinomas in this study, 6 of which were from females and 14 of which were from males, were primary tumors. The 10 healthy volunteers included 5 females and 5 males. To determine the effect of the TE (Time of Echo) parameter on the detection of metabolites by Magnetic Resonance Spectroscopy (MRS), Choline (Cho), Creatine (Cr) and Lactate/Lipid (LL) were examined by MRS in maxillofacial carcinomas, which are in a body location that may reduce the noise from lipid, air and large vessels in the MRS signal.

All subjects were first scanned by routine MRI. The Regions of Interest (ROI) inside the tumor were selected based on the MRI imaging results. The levels of Cho, Cr and LL were analyzed by MRS with a TE of both 144 ms and 35 ms. As shown in Figure 1A, the baseline was uneven and the peaks of the three metabolites were low in the control group for a 144 ms TE. The lactate/lipid peak increased in the maxillofacial carcinoma group and formed a large bidirectional peak between 1.21 and 1.45 ppm for a 144 ms TE (Figure 1B). When the TE was changed to 35 ms, the signal baseline became steady, and the peaks for two of the metabolites were still low in the controls (Figure 1C). The LL peak changed into a single peak that was significantly higher in the maxillofacial carcinoma group than in the control group (Figure 1D), suggesting that a 35 ms TE is more sensitive than a 144 ms TE for the detection of lactate/lipid by MRS.

Lactate/lipid content is increased in maxillofacial carcinoma

To determine whether the differences in metabolite content as measured by MRS with the two TE parameter values of 35 ms and

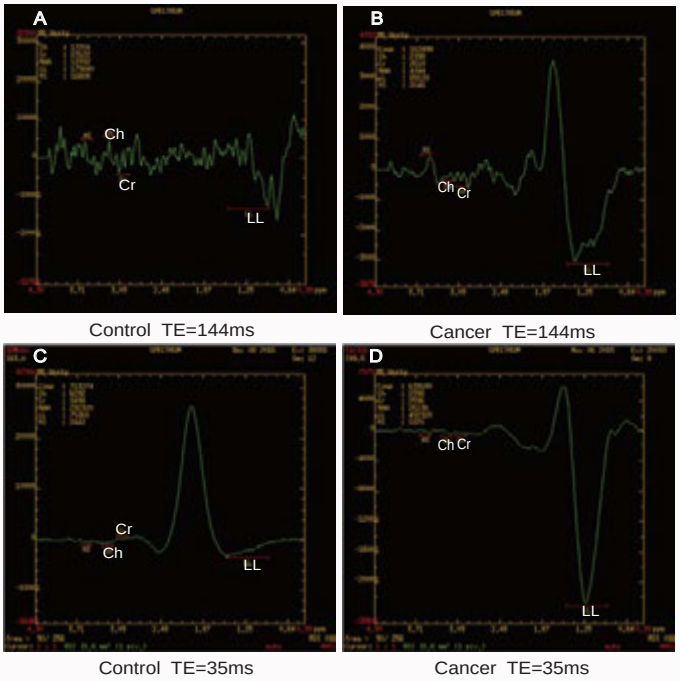
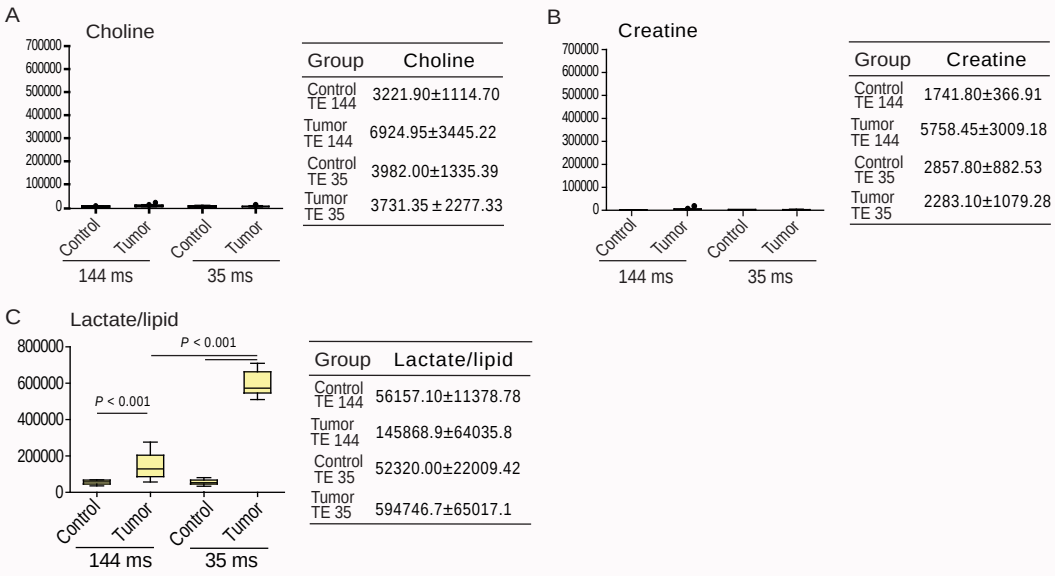


Figure 1: MRS with a 35 ms TE is more sensitive than MRS with a long TE for the detection of lactate/lipid.
A & B: The lactate content was analyzed in the tongues of the controls by MRS scanning with a 35 ms TE and a 144 ms TE. **C & D:** The lactate content was analyzed in the maxillofacial carcinoma by MRS scanning with a 35 ms TE and a 144 ms TE.



Group	Choline
Control TE 144	3221.90±1114.70
Tumor TE 144	6924.95±3445.22
Control TE 35	3982.00±1335.39
Tumor TE 35	3731.35 ± 2277.33

Group	Creatine
Control TE 144	1741.80±366.91
Tumor TE 144	5758.45±3009.18
Control TE 35	2857.80±882.53
Tumor TE 35	2283.10±1079.28

Group	Lactate/lipid
Control TE 144	56157.10±11378.78
Tumor TE 144	145868.9±64035.8
Control TE 35	52320.00±22009.42
Tumor TE 35	594746.7±65017.1

Figure 2: The content of lactate/lipid is increased in maxillofacial carcinoma.
Metabolite content was analyzed in the controls and maxillofacial carcinoma patients by MRS scanning with a 35 ms TE and a 144 ms TE. A: Choline; B: Creatine; C: Lactate/lipid.

144 ms were significant, the content of choline, creatine and lactate/lipid were assessed *in situ* and analyzed by the functions of the AW 4.6 software. As shown in Figure 2, the amount of lactate/lipid was substantial and varied between 52320.00 ± 22009.42 and 594746.7 ± 65017.1, while the amounts of choline and creatine were very low and ranged from 1741.80 ± 366.91 to 6924.95 ± 3445.22 for both long and short TE. Thus, the lactate/lipid content was further analyzed.

As shown in Figure 2C, MRS with a 35 ms TE was more sensitive than MRS with a 144 ms TE for the detection of lactate/lipid. Moreover, the lactate/lipid content was dramatically increased in tumor patients compared to the healthy volunteers (Figure 2C). This observation suggested that MRS analysis with a 35 ms TE is more suitable than MRS with a 144 ms TE for lactate/lipid detection.

Lactate/lipid is more identifiable by MRS imaging with a short TE than with a long TE

To visualize the distribution and concentration of lactate, MRS Images (MRSI) were generated based on the location and the lactate/lipid concentration. Accurate MRSI information enables tumor

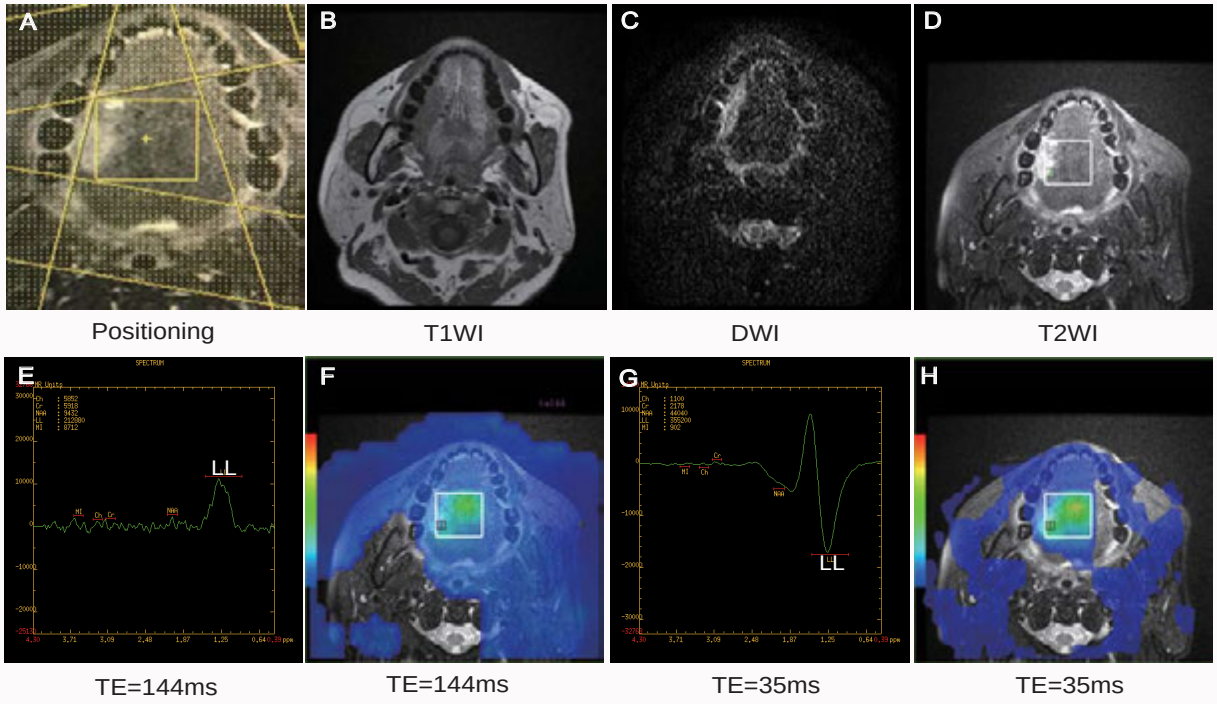


Figure 3: MRS imaging of lactate/lipid is clearer with a short TE than with a long TE.
A) 3-plane localization; B) T1 weighted image; C) diffusion weighted image; D) T2 weighted image; E & F) Multi-voxel MRS and MRSI for a 144 ms TE; G & H) Multi-voxel MRS and MRSI for a 35 ms TE.

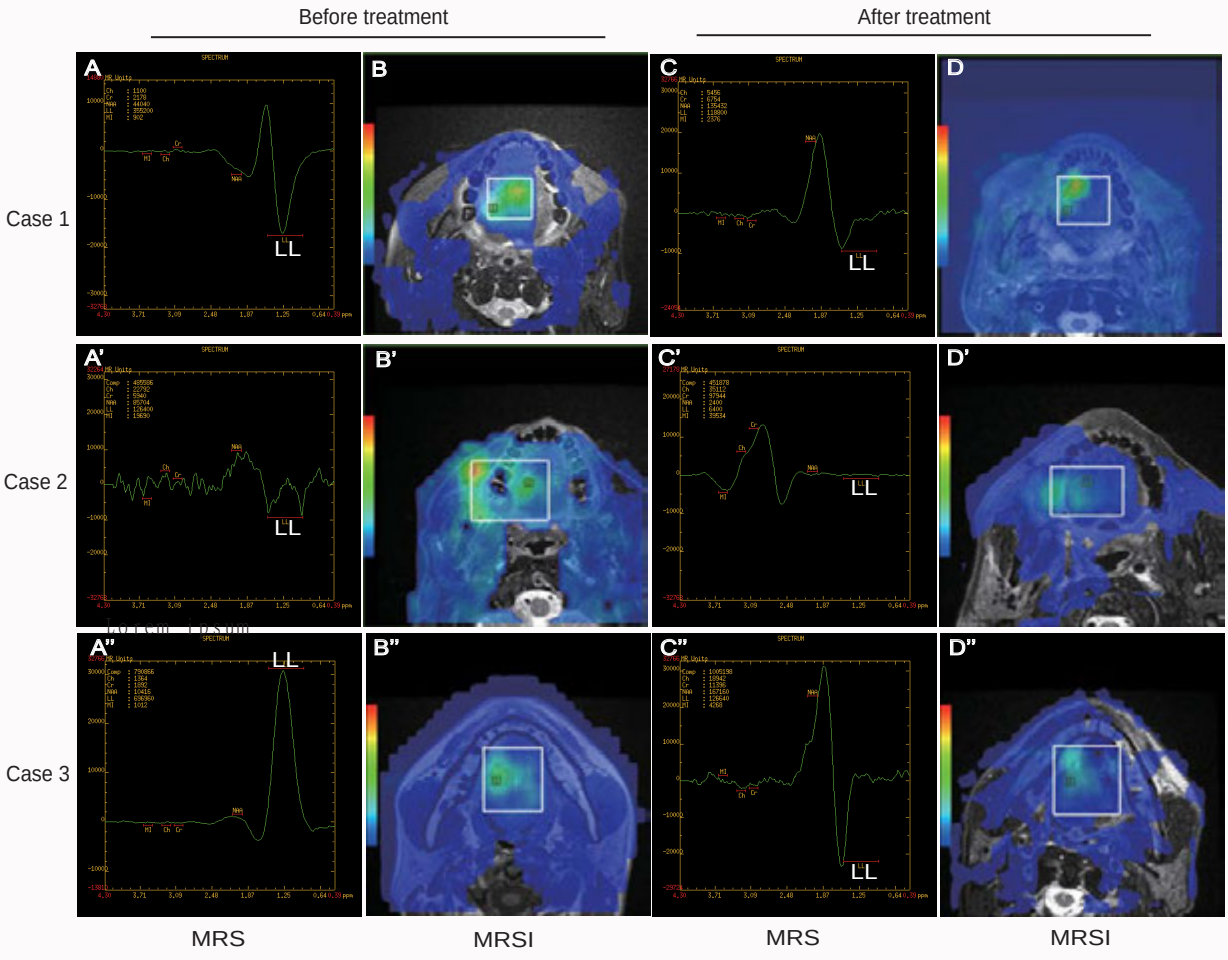


Figure 4: Lactate/lipid levels were closely correlated with progression of maxillofacial carcinoma.
Lactate was analyzed by MRS before and after therapy in three representative cases of maxillofacial carcinomas. A and C: MRS spectra; B and D: pseudo color MRS images.

Table 1: Detailed patient and volunteer characteristics.

		Cancer patients	Volunteers
Gender	Male	14	5
	Female	6	5
Age		57.3 ± 11.1	50.5 ± 15.24
Histology	SCC	17	
	Adenocarcinoma	3	
Pathological Grade	I	1	
	I-II	15	
	II	2	
	II-III	1	
Location	Lingual mucosa	13	
	Mandible	3	
	Floor of the mouth	4	

Note: SCC: Squamous Cell Carcinoma; IHC: Immunohistochemistry

boundary delineation, clinical diagnosis, treatment and prognosis [16]. The localization of each voxel was based on clinical evaluation, including pathology, T2WI or T1WI contrast-enhanced MR imaging (Figure 3A-3D). As shown in Figure 3E-3H, the MRS images visualized the lactate/lipid concentration and correctly displayed the lactate/lipid distribution. Consistent with the previous finding that changing the TE values changed the pattern of the MRSI [17], the lactate/lipid concentration and distribution in the MRSI based on MRS with a 35 ms TE was more identifiable than that in the MRSI based on the longer TE (Figure 3G, 3H).

Lactate/lipid levels were closely correlated with progression of maxillofacial carcinoma

Lactate content, as well as FDG uptake, is often used to distinguish benign tumors from malignant tumors. Moreover, lactate content is also a prognostic marker in cancer patients. Thus, we are particularly interested in the MRS detection of lactate in tumors. Since the lipid around the maxillofacial tumor is less changed in patients, the lactate/lipid signal most likely represents the lactate content variation, although we cannot separate the lactate signal from the lipid signal.

The correlation between lactate content and tumor progression was determined by MR spectroscopy in maxillofacial tumors. Thirteen patients were followed up, and lactate content was analyzed by MRS before and after surgery and radiotherapy. As shown in Figure 4, the lactate level was significantly decreased in all patients after therapy, suggesting that the tumors were effectively removed or eradicated and indicating a favorable prognosis.

Discussion

Magnetic Resonance Imaging (MRI) is a mature technology for the investigation of anatomical changes associated with malignant disease. Moreover, MR with Diffusion-Weighted Imaging (DWI) is used to evaluate tissue organization, while MR with Dynamic Contrast-Enhanced (DCE) imaging is utilized to assess tumor vascularity. Although PET is a major diagnostic method applied to detect chemical alterations in tumors, Magnetic Resonance Spectroscopy (MRS)/Spectroscopic Imaging (MRSI) and dynamic nuclear polarization (DNP) offer the possibility to obtain more functional information about features such as tumor metabolites [18]. Thus, MRS/MRSI is very useful to clinicians.

MRS is based on the fact that protons in different molecules resonate at slightly different frequencies. This difference is secondary to the differences in the local electron clouds, which may shield the nucleus from the main magnetic field. Magnetic Resonance Spectroscopy (MRS) can provide the structure, dynamics, reaction state and chemical environment of molecules based on the changes in resonance frequency from the spins of active nuclei (such as ^{1}H, ^{31}P, ^{13}C, and ^{19}F) activated by an external magnetic field. Different metabolites with the same nucleus exhibit characteristic shifts in resonance frequency. Due to the abundance and universal distribution of hydrogen in the human body, ^{1}H MRS is mainly used in the clinic to analyze steady-state metabolites in a noninvasive way that provides data complementary to the anatomic and structural information generated by MRI [19,20]. Multi-voxel MRS imaging enables the investigation of a larger volume and multiple regions of a lesion.

Abnormally increased metabolites are potential tumor biomarkers [21,22]. MRS can directly assess metabolic changes in tumors [23]. For example, MRS has been applied for the initial diagnosis, tumor grading, imaging-guided biopsy and treatment response assessment of brain tumors [24]. In this study, multi-voxel MRSI was applied to examine the content of lactate in maxillofacial carcinoma and to monitor the therapeutic response. Our data showed that the lactate content at the tumor site was significantly decreased after surgery and radiotherapy.

Long TEs suppress the noise from air and lipids in tissues and are commonly used for metabolite detection [25]. However, MRS with a long TE is not sensitive to lactate/lipid. Short TE (Time of Echo) MRSI has been applied in brain tumors but has seldom been used in maxillofacial carcinoma. Here, we showed that lactate, a potential tumor biomarker, was more sensitive to detection with a short TE than with a long TE and that its signal was a single positive peak between 1.20 and 1.35 ppm. Furthermore, the short TE more accurately represents the accurate content of lactate content, and results in a better image quality. However, the MRS detection on lactate is limited to specific tumor type due to the noses from blood vessel and air.

Conclusion

As a non-invasive examination technique, ^{1}H MRS can accurately detect various metabolites in or around carcinomas. Using a 35 ms TE, the metabolite detection baseline was steadier and more sensitive than with a 144 ms TE. The pseudo color map directly revealed the density and distribution of lactate. Our prospective study showed that the density and distribution of lactate were closely correlated with tumor progression and outcome, suggesting that lactate content could be a useful biomarker for the prognosis of maxillofacial carcinoma.

Acknowledgment

This study was supported by grants from the Shanghai Committee of Science and Technology (11DZ2260200) and the National Natural Science Foundation of China (81372194 and 81572300) to Dr. Mi and from the National Natural Science Foundation of China (81602509) to Dr. Xu.

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144:646-74.

2. Ward PS, Thompson CB. Metabolic reprogramming: A cancer hallmark even warburg did not anticipate. Cancer Cell. 2012;21:297-308.

3. Warburg O. On respiratory impairment in cancer cells. Science. 1956;124:269-70.

4. Martin Noguerol T, Sanchez-Gonzalez J, Martinez Barbero JP, Garcia-Figueiras R, Baleato-Gonzalez S, Luna A. Clinical imaging of tumor metabolism with ^{1}H magnetic resonance spectroscopy. Magn Reson Imaging Clin N Am. 2016;24:57-86.

5. Torregrossa L, Shintu L, Nambiath Chandran J, Tintaru A, Ugolini C, Magalhaes A, et al. Toward the reliable diagnosis of indeterminate thyroid lesions: A HRMAS NMR-based metabolomics case of study. J Proteome Res. 2012;11:3317-25.

6. Jimenez B, Mirnezami R, Kinross J, Cloarec O, Keun HC, Holmes E, et al. ^{1}H HR-MAS NMR spectroscopy of tumor-induced local metabolic "field-effects" enables colorectal cancer staging and prognostication. J Proteome Res. 2013;12:959-68.

7. Rocha CM, Barros AS, Gil AM, Goodfellow BJ, Humpfer E, Spraul M, et al. Metabolic profiling of human lung cancer tissue by ^{1}H High Resolution Magic Angle Spinning (HRMAS) NMR spectroscopy. J Proteome Res. 2010;9:319-32.

8. Chen W, Lou H, Zhang H, Nie X, Lan W, Yang Y, et al. Grade classification of neuroepithelial tumors using high-resolution magic-angle spinning proton nuclear magnetic resonance spectroscopy and pattern recognition. Sci China Life Sci. 2011;54:606-16.

9. Cao MD, Lamichhane S, Lundgren S, Bofin A, Fjosne H, Giskeodegard GF, et al. Metabolic characterization of triple negative breast cancer. BMC Cancer. 2014;14:941.

10. Czernicki Z, Horsztynski D, Jankowski W, Grieb P, Walecki J. Malignancy of brain tumors evaluated by proton Magnetic Resonance Spectroscopy (^{1}H-MRS) *in vitro*. Acta Neurochir Suppl. 2000;76:17-20.

11. Sharma U, Mehta A, Seenu V, Jagannathan NR. Biochemical characterization of metastatic lymph nodes of breast cancer patients by *in vitro* 1H magnetic resonance spectroscopy: A pilot study. Magnetic resonance imaging. 2004;22:697-706.

12. Yokota H, Guo J, Matoba M, Higashi K, Tonami H, Nagao Y. Lactate, choline, and creatine levels measured by vitro 1H-MRS as prognostic parameters in patients with non-small-cell lung cancer. J Magn Reson Imaging. 2007;25:992-9.

13. Yang Y, Li C, Nie X, Feng X, Chen W, Yue Y, et al. Metabonomic studies of human hepatocellular carcinoma using high-resolution magic-angle spinning ^{1}H NMR spectroscopy in conjunction with multivariate data analysis. J Proteome Res. 2007;6:2605-14.

14. Kwock L, Smith JK, Castillo M, Ewend MG, Collichio F, Morris DE, et al. Clinical role of proton magnetic resonance spectroscopy in oncology: brain, breast, and prostate cancer. Lancet Oncol. 2006;7:859-68.

15. Chai RC, Lambie D, Verma M, Punyadeera C. Current trends in the etiology and diagnosis of HPV-related head and neck cancers. Cancer Med. 2015;4:596-607.

16. Rosi A, Grande S, Luciani AM, Barone P, Mlynarik V, Viti V, et al. (1H) MRS studies of signals from mobile lipids and from lipid metabolites: Comparison of the behavior in cultured tumor cells and in spheroids. NMR Biomed. 2004;17:76-91.

17. Szulc A, Galinska B, Tarasow E, Kubas B, Dzienis W, Konarzewska B, et al. N-acetylaspartate (NAA) levels in selected areas of the brain in patients with chronic schizophrenia treated with typical and atypical neuroleptics: A proton Magnetic Resonance Spectroscopy (1H MRS) study. Med Sci Monit. 2007;13 Suppl 1:17-22.

18. Benz MR, Vargas HA, Sala E. Functional MR imaging techniques in oncology in the era of personalized medicine. Magn Reson Imaging Clin N Am. 2016;24:1-10.

19. Hajek M, Dezortova M. Introduction to clinical *in vivo* MR spectroscopy. Eur J Radiol. 2008;67:185-93.

20. McKnight TR. Proton magnetic resonance spectroscopic evaluation of brain tumor metabolism. Semin Oncol. 2004;31:605-17.

21. Chaumeil MM, Ozawa T, Park I, Scott K, James CD, Nelson SJ, et al. Hyperpolarized 13C MR spectroscopic imaging can be used to monitor Everolimus treatment in vivo in an orthotopic rodent model of glioblastoma. NeuroImage. 2012;59:193-201.

22. Wang AS, Lodi A, Rivera LB, Izquierdo-Garcia JL, Firpo MA, Mulvihill SJ, et al. HR-MAS MRS of the pancreas reveals reduced lipid and elevated lactate and taurine associated with early pancreatic cancer. NMR Biomed. 2014;27:1361-70.

23. Glunde K, Bhujwalla ZM, Ronen SM. Choline metabolism in malignant transformation. Nat Rev Cancer. 2011;11:835-48.

24. Hollingworth W, Medina LS, Lenkinski RE, Shibata DK, Bernal B, Zurakowski D, et al. A systematic literature review of magnetic resonance spectroscopy for the characterization of brain tumors. AJNR Am J Neuroradiol. 2006;27:1404-11.

25. Kelley DA, Wald LL, Star-Lack JM. Lactate detection at 3T: Compensating J coupling effects with BASING. J Magn Reson Imaging. 1999;9:732-7.