European Review for Medical and Pharmacological Sciences 2015; 19: 3345-3350

Preliminary study of IVIM-DWI and DCE-MRI in early diagnosis of esophageal cancer

J. LEI[1,2], Y. TIAN[3], S.-C. ZHU[2], Q. HAN[2], Y. WEI[2], S. YANG[2], D.-P. SHI[2]

[1]Xinxiang Medical University, Xinxiang, China
[2]Henan Provincial People's Hospital, Zhengzhou, China
[3]Department of Histology and Embryology, Changzhi Medical College, Changzhi, China

Jing Lei and *Yun Tian* should be regarded as co-first Authors

Abstract. – OBJECTIVE: To investigate the application value of double exponential model diffusion weighted imaging (IVIM-DWI) and dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) in the diagnosis of early esophageal cancer.

PATIENTS AND METHODS: 30 cases of patients with early esophageal cancer confirmed by pathology were collected. They were performed MRI plain scan, IVIM-DWI and DCE-MRI scan. The normal esophageal tissue, SlowADC value in tumor focus, FastADC value, F value, Ktrans, Kep and Ve values were measured. The difference between cancer tissue and normal tissue was compared using two independent sample t test. The prediction parameters and diagnostic threshold were compared by drawing receiver operating characteristic curve (ROC).

RESULTS: The average F, Ktrans and Kep values in esophageal cancer and normal esophageal tissue were: (0.48 ± 0.19), (0.64 ± 0.08); (0.45 ± 0.19)/min, (0.14 ± 0.04)/min and (1.14 ± 0.42)/min, (0.56 ± 0.25)/min respectively. Compared with normal esophageal tissue, esophageal cancer F value decreased, Ktrans value increased, Kep value increased, and the difference was statistically significant ($p < 0.05$); There was no difference in SlowADC, FastADC, Ve values of esophageal cancer and those in normal esophageal tissues ($p > 0.05$). The areas under ROC curve F, Ktrans and Kep values were 0.90, 0.98 and 0.92 respectively. They had the higher diagnostic efficiency.

CONCLUSIONS: IVIM-DWI and DCE-MRI can be used as the imaging method to diagnose esophageal malignant tumor, which has the higher diagnostic value.

Key Words:
Esophageal carcinoma, Dynamic contrast enhanced magnetic resonance imaging, Quantitative analysis.

Abbreviations

IVIM-DWI = intra-voxel incoherent motion-diffusion weighted imaging; DCE = dynamic contrast-enhanced; EPI = echo planar imaging; ADC = apparent diffusion coefficient; T2WI = T2 weighted image; FLAIR = fluid-attenuated inversion recovery; EES = extracellular extravascular space.

Introduction

Esophageal cancer is one of the common malignant tumors in China[1]. Squamous carcinoma is the main type. It is characteristic of high degree of malignancy, rapid development, poor therapeutic effect, and high recurrence rate[2]. Early diagnosis and treatment have important clinical significance on its prognosis. Endoscopic biopsy combined with pathological examination are the main method of preliminary diagnosis of esophageal cancer, especially early esophageal cancer. Its pathological change is occult, and there are significant differences in tumor size and shape. Therefore, the misdiagnosis phenomenon of esophageal cancer guided by gastroscope biopsy is to be considered as the recognized defects. The traditional imaging examination analyzed esophageal pathological changes only from morphology[3-5]. It was not easy to observe the early pathological changes. How to diagnose the disease accurately is the challenge which the imaging examination needs to face. The characteristics of early malignant esophageal tumor were investigated from the molecular level using functional magnetic resonance quantitative imaging technique, and whether the quantitative functional magnetic resonance IVIM-DWI and DCE-MRI could provide the early information for clinical diagnosis was explored in this study.

Corresponding Author: Shaocheng Zhu, MD; e-mail: shaochengzhucn@126.com

Patients and Methods

Clinical Data

34 cases of patients with esophageal cancer in our hospital from April 2013 to April 2014 were included in the study. Inclusion criteria: (1) early esophageal cancer confirmed by operation and pathology. The pathological changes were confined to the mucosa, submucosa and other positions; (2) MRI plain scan, IVIM-DWI and DCE-MRI were undertaken under the same magnetic resonance instrument; (3) A total of 34 patients were enrolled, The larger internal necrosis range of tumor (1 case), severe mobile artifacts (3 cases) were excluded. Eventually, 30 cases of patients with esophageal cancer were included into the group, including 16 female and 14 males. The age was 52 to 80 years old, and the median age was 68 years old. 30 esophageal cancer masses and corresponding normal esophageal tissues were obtained. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Henan Provincial People's Hospital. Written informed consent was obtained from all participants.

Inspection Method

8-channel phased array body coil was used for GE 3.0T high field magnetic resonance instrument (Discovery MR 750). The patients were supine. The patients conducted shallow slow breath training before the examination. The signal was acquired using respiratory gating free breathing for the patients with even breath. The signal was acquired using single shot acquisition for the patients with uneven breath.

The conventional MRI scanning sequences included: esophageal local axial and coronal fat suppressed fast spin echo (FSE) T2WI scan: TR 3500 ms, TE85 ms, echo train length (ETL) 19, thickness 5 mm, interval between the layer 0.5 mm, field of view (FOV) 24 cm*24 cm, incentive times (NEX) 4, matrix 320*256; esophageal local axial T1WI scan: TR 450 ms, TE 12 ms, thickness of layer 5 mm, interlayer distance 0.5 mm, reverse angle 5°, FOV 24 cm*24 cm, NEX 2, matrix 256*192.

IVIM-DWI scanning was axial plane two-dimensional scanning; scanning options: EPI, diffusion, parallel acquisition technology; echo time 57.8 ms, repetition time 8571 ms, flip angle N/A, saturation pulse N/A, field of view (FOV) 28-32 cm, thickness of layer 5.0 mm, interlayer spacing 1.0 mm, phase encoding 96 mm, frequency encoding 96 mm, excitation times 1-10, frequency encoding direction: anterior and posterior, the direction of diffusion: all directions, 9 b values (0 50 100 200 400 600 800 1000 and 1500 s/mm^2). Divided into nine groups for the analysis, interval 300 s/mm^2; scanning time 5 minutes and 51 seconds. After breathing freely, the scan was finished. Nine groups of images of 0-1500s/mm^2 were obtained by b value diffusion weighted imaging.

Omniscan (gadodiamide injection) was used as the contrast for DCE-MRI scan, and the amount was 0.5 mmol/kg. The vein of upper limb was given rapid injection 0.1 mmol/L through elbow vein indwelling catheter with high-pressure injector, followed by intravenous bolus injection of 25 ml saline for flushing. The vacant scan was conducted for 6 phases before injection of contrast agent. Then the contrast was injected, and scan was continued, sequential scan 60 cycles. 60 dynamics were collected for esophageal dynamic enhanced MRI scan. 16 images were acquired for each dynamic, 6 seconds in each stage. Finally, 960 dynamic enhanced images were obtained. Dynamic enhanced scanning was conducted by LAVA (liver acquisition with volume acceleration) sequence. The scanning parameters: TR 4 ms, TE 1.9 ms, thickness of layer 3.8 mm, interlayer spacing 1.8 mm, FOV 34 cm*34 cm, matrix 256*192.

Data Acquisition

DWI original image was processed using GE ADW4.5 workstation and post-processed by Functool workstation to obtain ADC map. The region of interest (ROI) was selected in the maximum level of axial tumor area with b value was 0. ROI range was 30 mm^2-50 mm^2. The signal intensity curve, SlowADC, FastADC and F diagram were obtained by calculation. The corresponding SlowADC, FastADC, and F value were measured using a double exponential model. The same size of ROI was outlined in normal location outside the mass correspondingly and measured. The difference between each parameter value of lesion and normal esophageal tissue was compared.

The measurement and calculation of all the original data parameter were completed using OmniKinetics software hemodynamics Tofts two compartment model (GE Healthcare, Bethesda, MD, USA). The esophageal arteries were not easily found, so this experiment adopted Population AIF for parameter calculation. The same size of

ROI was correspondingly outlined in normal location outside the mass and measured. Three parameters K^{trans}, K_{ep} and V_e were calculated. The difference between each parameter value of lesion and normal esophageal tissue was compared. Three doctor's average parameter was obtained finally. The specific method was that the strongest enhancement region was outlined on the maximum level of dynamic enhanced sagittal tumor as ROI. ROI range was 30 mm^2-50 mm^2. K^{trans}, K_{ep} and V_e value were calculated on the level.

T2WI and FLAIR images needed to be referred at the same time when ROI was set. The cystic degeneration, necrosis, hemorrhage and region containing normal blood vessels and nerve should be avoided. The tumor parenchyma referred to the region where plain scan T2 showed slightly higher signal, T1WI showed low signal intensity, and could be strengthened after enhancement; For tumor parenchyma region which the enhancement was not obvious, T1WI showed slightly low signal, T2WI and FLAIR showed slightly higher signal. Three abdominal imaging doctors with rich work experience repeatedly manually set ROI in the same lesion.

Statistical Analysis

All the parameter values of esophageal cancer and normal esophageal tissues were compared by two independent samples *t* test using SPSS 19.0 statistical software (SPSS Inc., Chicago, IL, USA). The parameters which had significant significance can be used to diagnose esophageal cancer. The parameters of which with the significant differences were drawn into diagnosis esophageal cancer receiver operating curve (ROC). $p < 0.05$ showed the difference had significant significance.

Results

Pathological Types

In 30 patients with stage I esophageal cancer, there were 27 cases of squamous cell carcinoma, 2 cases of adenocarcinoma and 1 case of small cell esophageal carcinoma diagnosed by pathology. 17 cases were erosion type, 4 cases were plaque type, 7 cases were papillary type, and 2 cases were flat type.

Characteristics of Lesion Signal

T1WI scan showed slightly low signal; T2WI showed equisignal or higher signal. The characteristic of lesion enhancement was that in the fourth stage of drug injection, namely after drug injection for 24s, strengthening began. The lesions showed heterogeneous enhancement, ring-enhancement or homogeneous enhancement (Figure 1).

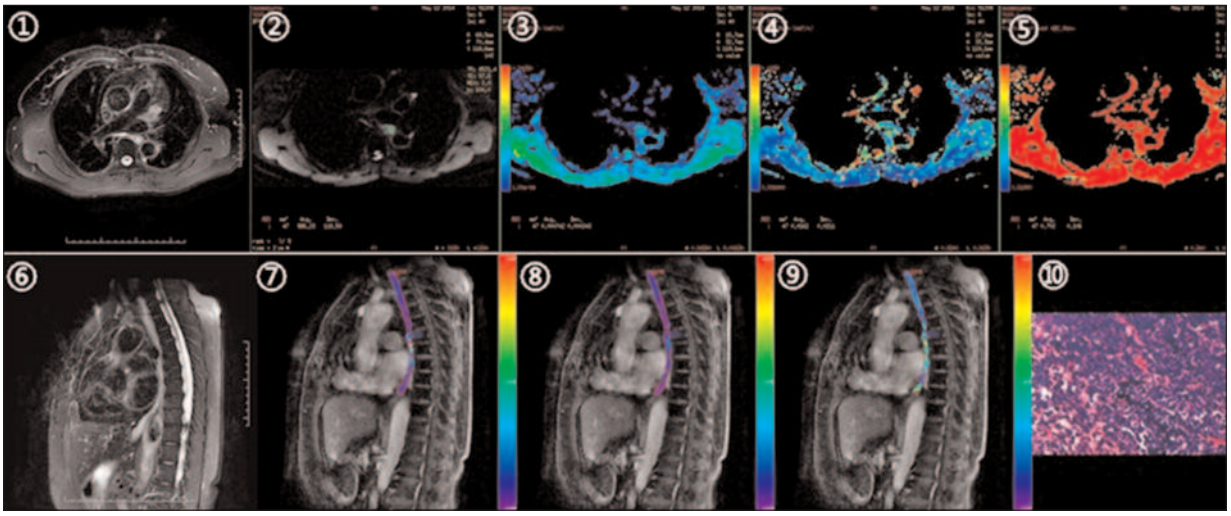

Figure 1. Characteristics of lesion signal. ***(1)*** Axial fat suppressed T2, there were no serious abnormalities noted on T2WI; ***(2)*** b = 1000, DWI map, there were slightly high signals on DWI; ***(3)*** Display range of SlowADC, graph: e-0.4-0.00250; ***(4)*** Display range of FastADC, graph: 0.001-0.0250; ***(5)*** Display range of F graph: 0.001-0.250; ***(6)*** Sagittal fat suppressed T2, there were no serious abnormalities noted on T2WI; ***(7)*** Display range of Ktrans graph: 0.000-1.000; ***(8)*** Display range of Kep graph: 0.000-5.000; ***(9)*** Display range of Ve graph: 0.000-1.000; ***(10)*** was squamous cell carcinoma (HE×100). The higher pseudo warm value color, the greater representative number in pseudo color map.

The Consistency Estimation

The minimum Kappa value of ROI was set as 0.8175, and the maximum was 0.9838. *p* values were less than 0.0001. The average was 0.9176. The consistency was the best.

Difference of IVIM-DWI Parameter Value in Two Experimental Groups

The SlowADC, FastADC and F values in esophageal cancer group were $(0.86 \pm 0.28)*10^{-3}$ mm^2/s, (0.13 ± 0.01) mm^{-2}/s and (0.48 ± 0.19) respectively; Those in normal esophageal group were $(0.81 \pm 0.29)*10^{-3}$ mm^2/s, (0.02 ± 0.01) mm^2/s and (0.64 ± 0.08) respectively. The result showed that F value in esophageal cancer group was lower than that in normal esophageal group (t = -2.391, p = 0.024), and the difference was statistically significant. But there was no significant difference between SlowADC and FastADC values (Table I).

Difference of DCE-MRI Parameter Value in Two Experimental Groups

K^{trans}, K_{ep} and V_e values in esophageal cancer group were (0.45 ± 0.19)/min, (1.14 ± 0.42)/min and (0.37 ± 0.17) respectively; Those in normal esophageal group were (0.14 ± 0.04)/min, (0.56± 0.25)/min and (0.27 ± 0.11) respectively. The result showed that K^{trans} and K_{ep} value in two groups were higher than those in norma group (t = 4.525, $p < 0.05$; t = 4.585, $p < 0.05$), and the difference was statistically significant. However, there was no significant difference about V_e value (Table II).

Area Under ROC Curve of Parameter Values with Diagnostic Value

The F, K^{trans} and K_{ep} values had the higher diagnostic efficiency. The areas under the curve were 0.90, 0.98 and 0.92 respectively (Table III).

Discussion

Intra voxel incoherent motion (IVIM) imaging can more accurately quantify two motion components in DWI image, including simple water molecule diffusion and blood perfusion[6,7]. The SlowADC value was pure diffusion coefficient, represented diffusion motion of pure water molecules (slow diffusion motion component); FastADC value was false diffusion coefficient, represented incoherent motion intra voxel microcirculation perfusion, namely perfusion related diffusion motion (fast diffusion motion component); F value represented perfusion proportion. Since Le Bihan et al[6] firstly put forward DWI imaging method based on IVIM in 1986, IVIM gradually developed into the later application in heart, liver, pancreas, kidney, prostate, placenta and anti-tumor efficacy monitoring from the initial application in head and neck[8-12]. With the appearance of MR echo-planar imaging (EPI), combined with parallel acquisition imaging technology (ASSET), multiple signal average technique solved the problems of large noise, poor contrast, artifacts and image deformation, and more and more studies were focused on esophagus. The study was to study the application value of IVIM-DWI in the diagnosis of early esophageal cancer using double exponential model. The result showed that SlowADC and FastADC could not differentiate between esophageal cancer and normal esophagus, but F value could do it. We used 9 b values to calculate F value. F value of esophageal cancer group was significantly lower than that of normal esophageal group, which suggesting that blood perfusion ratio of esophageal cancer was lower than that of normal esophageal tissues. This may be related to that tumor cell proliferation was faster than vascular formation. This study firstly applied IVIM-DWI technology in esophagus and evaluated its value in early diagnosis of esophageal cancer. The study showed that the areas under ROC curve of esophageal cancer K^{trans} and K_{ep} values were 0.90, the diagnostic threshold was 0.545. Studies

Table I. IVIM-DWI parameter value distribution in esophageal cancer group and normal esophagus group and *t* test analysis.

Groups	Slow ADC (10^{-3} mm^2/s)	FastADC (mm^{-2}/s)	F (%)
Esophageal cancer group	0.86 ± 0.28	0.13 ± 0.01	0.48 ± 0.19
Normal esophagus group	0.81 ± 0.29	0.02 ± 0.01	0.64 ± 0.08
t	0.220	-1.366	-2.391
p	0.827	0.188	0.024

Table II. DCE-MRI parameter value distribution in esophageal cancer group and normal esophagus group and *t* test analysis.

Groups	K^{trans} (/min)	K_{ep} (/min)	V_e
Esophageal cancer group	0.45 ± 0.19	1.14 ± 0.42	0.37 ± 0.17
Normal esophagus group	0.14 ± 0.04	0.56 ± 0.25	0.27 ± 0.11
t	4.525	4.585	1.871
p	< 0.05	< 0.05	0.077

Table III. ROC related parameters of esophageal cancer diagnosis.

Parameters	Area under the curve	Maximum youden index	Diagnostic threshold	Sensitivity (%)	Specificity (%)
K_{trans}	0.98	0.70	0.156	0.95	0.75
K_{ep}	0.92	0.70	0.622	0.95	0.75
F	0.90	-0.30	0.545	0.90	0.70

showed that its application success rate in esophagus was higher than that of traditional DWI technology[13,14], suggesting that IVIM-DWI could be applied in the diagnosis of early malignant tumor of esophagus.

MR dynamic enhanced scan quantitative analysis is to study the regularity of concentration of contrast agent in tissue along with time variation and the exchange process of contrast agent inside and outside the vessels on the molecular level using dynamic enhancement image and pharmacokinetic model, and then quantitatively describe hemodynamic information of tumor micro-angiogenesis and permeability[15]. Quantitative parameters include: (1) Volume transfer constant (K^{trans}): velocity of distribution from plasma to EES for contrast agent; (2) Rate constant (K_{ep}): rate of contrast agent which diffuses to EES back to plasma; (3) Extracellular extravascular space volume ratio (V_e): volume in unit volume tissue between plasma and EES; It has been used in the qualitative diagnosis of nervous system, digestive system, urinary, reproductive system and breast and stage at home and abroad[16-18]. American Chang et al[19] did the pilot study on 5 cases of esophageal adenocarcinoma, the results showed that DCE-MRI quantitative imaging technique could distinguish normal esophagus and esophageal malignant tumor. In China, esophageal squamous cell carcinoma is the most common type in esophageal cancer, accounting for about 90%[14]. This research showed that K^{trans} and K_{ep} values of esophageal cancer were higher than those of normal esophageal tissue, suggesting that dynamic enhanced quantitative imaging technique could be applied in the diagnosis of early esophageal cancer, this may be relevant to tumor formation of the immature vessles. The increase of VEGF can induce the proliferation and migration of tumor vascular endothelial cells, the increase of permeability of microvasculature[20]. Couvelard et al[21] have confirmed that overexpression of VEGF can lead to the occurrence of tumor. Compared with normal vessels, neoplastic tumor microvessels were not mature, the basement membrane was not complete, endothelial cell space widened. The vascular endothelium, pericyte coverage and abnormal basement membrane will lead to the increase of microvascular permeability. The study showed that the areas under ROC curve of esophageal cancer K^{trans} and K_{ep} values were 0.98 and 0.92 respectively, diagnostic threshold were 0.156 and 0.622. Its diagnosis efficiency to esophageal cancer is high, suggesting that quantitative DCE-MRI functional imaging, as a quantitative, noninvasive and economic examination, can be used for early diagnosis of esophageal cancer.

The shortcomings in this study including: (1) The quantitative DCE-MRI was affected by pharmacokinetic model, and had little difference with real human environment, so the result might have a certain bias; (2) The b value selection of IVIM also affected the result; (3) The two quantitative functional magnetic resonance scanning directions were different, their sizes of effectiveness were not comparable. The next research direction is to unify the standard, and compare the diagnostic efficacy of the two kinds of technologies.

Conclusions

IVIM-DWI and DCE-MRI can be used in early diagnosis of esophageal cancer. They can provide early lesion information for clinical and increase the cure rate of the disease.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

References

1) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: CLOBOCAN 2008. Int J Cancer 2010; 127: 2893-2917.
2) Shibata A, Matsuda T, Ajiki W, Sobue T. Trend in incidence of adenocarcinoma of the esophagus in Japan, 1993-2001. Jpn J Clin Oncol 2008; 38: 464-468.
3) Flamen P, Lerut T, Haustermans K, Van Cutsem E, Mortelmans L. Position of positron emission tomography and other imaging diagnostic modalities in esophageal cancer. Q J Nucl Med Mol Imaging 2004; 48: 96-108.
4) Pokieser P, Memarsadeghi M, Danzer M, Prokesch R, Partik B, Wenzl E. Staging of carcinomas of the upper gastrointestinal tract. The current status of diagnostic imaging. Radiologe 1999; 39: 555-561.
5) Giacoia A, Thomas P, Giovannini M, Hannou-Lévy JM, Garbe L, Thirion X, Lécuyer J, Giudicelli R, Seitz JF, Fuentes P. Ecoendoscopy in the assessment of esophageal neoplasms. Acta Gastroenterol Latinoam 1998; 28: 299-304.
6) Le Bihan D, Breton E, Lallemand D, Grenier P, Cabanis E, Laval-Jeantet M. MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders. Radiology 1986; 161: 401-407.
7) Luciani A, Vignaud A, Cavet M, Nhieu JT, Mallat A, Ruel L, Laurent A, Deux JF, Brugieres P, Rahmouni A. Liver cirrhosis: intravoxel incoherent motion MR imaging--pilot study. Radiology 2008; 249: 891-899.
8) Yin Y, Gan J. Intravoxel incoherent motion imaging. Journal of China Clinic Medical Imaging 2013; 25: 353-356.
9) Le Bihan D. Diffusion, confusion and functional MRI. Neuroimage 2012; 62: 1131-1136.
10) Sumi M, Nakamura T. Head and neck tumors:assessent of perfusion-related parameters and diffusion coefficients based on the intravoxel incoherent motion model. AJNR Am J Neuroradiol 2013; 34: 410-416.
11) Lu Y, Jansen JF, Mazaheri Y, Stambuk HE, Koutcher JA, Shukla-Dave A. Extension of the intravoxel incoherent motion model to non-gaussian diffusion in head and neck cancer. J Magn Reson Imaging 2012; 36: 1088-1096.
12) Zhang SX, Jia QJ, Zhang ZP, Liang CH, Qiu QH, Chen WB, Guo MY. Intravoxel incoherent motion diffusion-weighted imaging in differential diagnosis of primary nasopharyngeal carcinoma and nasopharyngeal hyperplasia. Chinese Journal of Radiology 2013; 47: 617-621.
13) Aoyagi T, Shuto K, Okazumi S, Hayano K, Satoh A, Saitoh H, Shimada H, Nabeya Y, Kazama T, Matsubara H. Apparent diffusion coefficient correlation with esophageal tumour stroma and angiogenesis. Eur Radiol 2012; 22: 1172-1177.
14) Lu J, Xue LY, Lu N, Zou SM, Liu XY, Wen P. Superficial primary small cell carcinoma of the esophagus: clinicopathological and immunohistochemical analysis of 15 cases. Dis Esophagus 2010; 23: 153-159.
15) Oberholzer K, Pohlmann A, Schreiber W, Mildenberger P, Kunz P, Schmidberger H, Junginger T, Düber C. Assessment of tumor microcirculation with dynamic contrast-enhanced MRI in patients with esophageal cancer: initial experience. J Magn Reson Imaging 2008; 27: 1296-1301.
16) Zhang N, Zhang L, Qiu B, Meng L, Wang X, Hou BL. Correlation of volume transfer coefficient Ktrans with histopathologic grades of gliomas. J Magn Reson Inmging 2012; 36: 355-363.
17) Huang W, Tudorica LA, Li X, Thakur SB, Chen Y, Morris EA, Tagge IJ, Korenblit ME, Rooney WD, Koutcher JA, Springer CS Jr. Discrimination of benign and malignant breast lesions by using shutter-speed dynamic contrast-enhanced MR imaging. Radiology 2011; 261: 394-403.
18) Sommer WH, Sourbron S, Huppertz A, Ingrisch M, Reiser MF, Zech CJ. Contrast agents as a biological marker in magnetic resonance imaging of the liver: conventional and new approaches. Abdom Imaging 2012; 37: 164-179.
19) Chang EY, Li X, Jerosch-Herold M, Priest RA, Enestvedt CK, Xu J, Springer CS Jr, Jobe BA. The evaluation of esophageal adenocarcinoma using dynamic contrast-enhanced magnetic resonance imaging. J Gastrointest Surg 2008; 12: 166-175.
20) Möbius C, Freire J, Becker I, Feith M, Brücher BL, Hennig M, Siewert JR, Stein HJ. VEGF-C expression in squamous cell carcinoma and adenocarcinoma of the esophagus. World J Surg 2007; 31: 1773-1774.
21) Couvelard A, Paraf F, Gratio V, Scoazec JY, Hénin D, Degott C, Fléjou JF. Angiogenesis in the neoplastic sequence of Barrett's esophagus. Correlation with VEGF expression. J Pathol 2000; 192: 14-18.