



The Blood Oxygenation T_2^* Values of Resectable Esophageal Squamous Cell Carcinomas as Measured by 3T Magnetic Resonance Imaging: Association with Tumor Stage

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Objective: To explore the association between the blood oxygenation T_2^* values of resectable esophageal squamous cell carcinomas (ESCCs) and tumor stages.

Materials and Methods: This study included 48 ESCC patients and 20 healthy participants who had undergone esophageal T_2^* -weighted imaging to obtain T_2^* values of the tumors and normal esophagi. ESCC patients underwent surgical resections less than one week after imaging. Statistical analyses were performed to identify the association between T_2^* values of ESCCs and tumor stages.

Results: One-way ANOVA and Student-Newman-Keuls tests revealed that the T_2^* value could differentiate stage T1 ESCCs (17.7 ± 3.3 ms) from stage T2 and T3 tumors (24.6 ± 2.7 ms and 27.8 ± 5.6 ms, respectively; all $p_s < 0.001$). Receiver operating curve (ROC) analysis showed the suitable cutoff T_2^* value of 21.3 ms for either differentiation. The former statistical tests demonstrated that the T_2^* value could not differentiate between stages T2 and T3 (24.6 ± 2.7 ms vs. 27.8 ± 5.6 ms, respectively, $p > 0.05$) or between N stages (N1 vs. N2 vs. N3: 24.7 ± 6.9 ms vs. 25.4 ± 4.5 ms vs. 26.8 ± 3.9 ms, respectively; all $p_s > 0.05$). The former tests illustrated that the T_2^* value could differentiate anatomic stages I and II (18.8 ± 4.8 ms and 26.9 ± 5.9 ms, respectively) or stages I and III (27.3 ± 3.6 ms). ROC analysis depicted the same cutoff T_2^* value of 21.3 ms for either differentiation. In addition, the Student's t test revealed that the T_2^* value could determine grouped T stages (T0 vs. T1–3: 17.0 ± 2.9 ms vs. 25.2 ± 6.2 ms; T0–1 vs. T2–3: 17.3 ± 3.0 ms vs. 27.1 ± 5.3 ms; and T0–2 vs. T3: 18.8 ± 4.2 ms vs. 27.8 ± 5.6 ms, all $p_s < 0.001$). ROC analysis indicated that the T_2^* value could detect ESCCs (cutoff, 20 ms), and discriminate between stages T0–1 and T2–3 (cutoff, 21.3 ms) and between T0–2 and T3 (cutoff, 20.4 ms).

Conclusion: The T_2^* value can be an additional quantitative indicator for detecting ESCC except for stage T1 cancer, and can preoperatively discriminate between some T stages and between anatomic stages of this tumor.

Keywords: Esophagus; Neoplasm; Carcinoma; Squamous cell; Magnetic resonance; Staging

Received May 29, 2016; accepted after revision November 22, 2016.

This work was supported by the National Natural Science Foundation of China (grant no. 81571645), the Sichuan Province Special Project for Youth Team of Science and Technology Innovation (grant no. 2015TD0029), and The Construction Plan for Scientific Research Team of Sichuan Provincial Colleges and Universities (grant no. 15TD0023).

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INTRODUCTION

Esophageal carcinoma is the eighth most common malignancy in the world. Esophageal squamous cell carcinoma (ESCC) accounts for more than 90% of these, and is the predominant histological subtype (1-5). Surgery for stage I esophageal cancers, neoadjuvant chemotherapy (NAC) or chemoradiotherapy (CRT) followed by surgery for stages II/III (except for T4) diseases, and preoperative CRT for inoperable esophageal cancers are considered the current standard treatments for esophageal cancer in clinical settings (6-8). One study (7) revealed that the survival outcomes were better for patients with stage III resectable esophageal carcinomas who underwent NAC followed by surgery than for those who underwent CRT. However, for stages I, II, and IV disease, the survival outcomes were not significantly different between the treatments. Hence, the accurate staging of esophageal cancer prior to treatment is extremely important for selecting the appropriate treatment strategy (9).

The current practice guidelines for accurately staging esophageal cancer before treatment include computed tomography and endoscopic ultrasonography. However, computed tomography and endoscopic ultrasonography cannot identify the histologic layers of the esophageal wall (10, 11). Magnetic resonance imaging (MRI) can overcome the limitation of these other modalities and can demonstrate the histologic layers of the esophageal wall. With the development of advanced techniques, such as faster scanning, respiratory and cardiac gating, and use of surface coils, the diagnostic efficacy of MRI for T staging has improved considerably (12, 13). The relatively new MRI technique of the multi-echo gradient recalled echo (GRE) T₂*-weighted imaging (T₂*WI) sequence requires a highly uniform magnetic field, and can improve the detection rate of small lesions. Additionally, T₂* values can indirectly reflect changes in tissue biochemical components, such as the amounts of oxy- and deoxyhemoglobin in the vessels and their surrounding tissues (14, 15). The published literatures (16-18) have reported that there is a linear relation between the transverse relaxation rate and the deoxyhemoglobin concentration. This technique has been applied to evaluate tissue oxygenation in hepatocellular carcinomas, renal carcinomas, breast cancers and prostate cancers (19-22). Therefore, we hypothesize that T₂* values could reflect the contents of oxy- and deoxyhemoglobin in ESCC. To our knowledge, GRE T₂*WI has not been used to evaluate tissue

oxygenation in esophageal carcinomas. Therefore, this study was conducted to investigate the association of the T₂* values of resectable ESCCs with tumor stages.

MATERIALS AND METHODS

Participants

The Institutional Ethics Committee of our hospital approved this prospective study, and written informed consent was obtained from each participant before the study.

From July 2014 to February 2015, 50 patients with endoscopic biopsy-proven ESCCs were enrolled in our study according to the following inclusion criteria: 1) patients had adequate cardiac and pulmonary functions, and could perform breath holding during the GRE T₂*WI scans, 2) patients did not receive any tumor-related treatments, such as radiation therapy or chemotherapy, prior to the MRI scans, and 3) patients desired to undergo surgical resection. The initial number of patients with biopsy-confirmed ESCCs was 50. Two of these were excluded from the study because: 1) the tumor was unable to be resected because of the contraindication for surgery (n = 1); or 2) the MR images were of poor quality, or tumors were too small to draw the region of interest (ROI) of 35–45 mm² when we reviewed the T₂*WI data (n = 1). Ultimately, 48 patients (31 males and 17 females; age range, 48–78 years; mean age, 62.5 years) were enrolled in our study.

Additionally, a group of 20 randomly selected, consecutive healthy volunteers (13 males and 7 females; age range, 49–73 years; mean age, 60.9 years) were included in this study. These served as the reference group from which benchmarks were obtained according to the following inclusion criteria: the volunteers had no esophageal diseases, no acute infections, and no histories of malignant cancer. In addition, the patients with ESCCs and the normal volunteers were from the same area where our hospital was located.

All the patients with ESCCs underwent magnetic resonance scans one week before the surgery. The ESCC patients did not receive any tumor-related treatments during the interval between the MRI and their surgery. The healthy volunteers also underwent magnetic resonance scans. Immediately after the ESCC resection surgery, the surgically removed tumor tissues were sent to the pathology department for histological examination. The TNM staging was based on surgical and postoperative pathological staging. According to the current revised TNM system (the depth of primary

tumor invasion, the regional lymph node involvement number and distant metastasis), the American Joint Committee on Cancer (AJCC) in 2010 (23), and the seventh edition of the AJCC/Union for International Cancer Control, cancer staging of the esophagus (24) was introduced as the criterion for staging ESCC. The corresponding patient distributions are illustrated in Table 1. All the 10 patients with T1-staged ESCCs plus one case of T2-staged cancer were determined as anatomic stage I as the standard control group to distinguish the anatomic stages. Additionally, the T3-staged ESCCs received adjuvant radiation therapy or chemotherapy after surgery.

Magnetic Resonance Imaging Protocol

T₂*-weighted imaging of ESCCs and normal esophagi was performed with a GE Signal 3T scanner (Discovery MR 750, GE Medical Systems, Milwaukee, WI, USA). To maintain the ratio of the scanning segments of the normal esophagi in the reference group to the anatomic distribution of the

Table 1. Patient Distributions of Esophageal Squamous Cell Carcinoma

Carcinoma	n (%)
Primary tumor (T)	
Tx	0
T1	10 (20.8)
T2	8 (16.7)
T3	30 (62.5)
Regional lymph nodes (N)	
Nx	0
N0	34 (70.8)
N1	8 (16.7)
N2	5 (10.4)
N3	1 (2.1)
Distant metastasis (M)	
M0	48 (100)
M1	0
Histologic grade (G)	
Gx	0
G1	21 (43.8)
G2	22 (45.8)
G3	5 (10.4)
Location of primary cancer site	
Upper esophagus	6 (12.5)
Middle esophagus	41 (85.4)
Lower esophagus	1 (2.1)
Anatomic stage	
I	11 (22.9)
II	26 (54.1)
III	11 (23)

ESCCs, 3 healthy participants randomly underwent T₂*WI of the upper thoracic portion of the esophagus, 16 healthy participants randomly received T₂*WI of the mid-thoracic portion, and the remaining 1 healthy participant underwent T₂*WI of lower thoracic portion. MRI was performed on each participant after overnight fasting. The scanning sequences included GRE T₂*WI and conventional T1- and T2-weighted imaging. Subsequently, 15 mL gadolinium diethylenetriamine-pentaacetic acid (Gd-DTPA; Magnevist, Bayer Healthcare, Berlin, Germany) was intravenously injected at a dose of 2.5 mL/s for a total of 0.2 mmol per kg of body weight via a pressure injector (Spectris MR Injection System, Medrad, Warrendale, PA, USA). This was followed by a 20-mL saline solution flush for the axial T1WI triphasic dynamic contrast-enhanced scans. The GRE T₂*WI sequence was completed with respiratory gating according to the following scanning parameters: repetition time of 41.8 ms, echo time of 1.5–36 ms, flip angle of 30°, acquisition matrix of 256 x 192 mm, pixel size of 1.6 x 1.6 mm, field of view of 420 x 360 mm, slice thickness of 5 mm, and sampling bandwidth of 83.3 kHz. Additionally, conventional T1- and T2-weighted scans were performed to localize the ESCCs to plan for the T₂*WI of the tumors, and axial T1-weighted triphasic dynamic contrast-enhanced scans were performed for the subsequent image analysis.

Image Analysis

The original MRI data were used to measure the T₂* values of the ESCCs or the normal esophageal walls on the workstation (GE Advantage Workstation Version 4.4–09, Sun Microsystems, Palo Alto, CA, USA). The contrast-enhanced T1WI was analyzed first to identify the hemorrhagic and necrotic regions of the ESCCs. Subsequently, R₂* maps were constructed, and the T₂* values of ESCCs and the normal esophageal walls were automatically determined by the software. Two experienced radiologists, including an experienced radiologic professor (the corresponding author, who has more than 17 years of experience in abdominal radiology) and a radiology resident (the first author, who has 2 years of experience in radiology), were blinded to the subjects' information and analyzed the MRI images. Three circular ROIs with approximately equal areas were independently and manually outlined in one maximal slice of the ESCC until three consecutive maximal slices of this tumor were covered (3 ROIs per slice, 9 ROIs per patient), and the T₂* values of each ROI were recorded independently by the two radiologists. Each ROI of approximately 35–45

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mm² in area was drawn by avoiding the hemorrhagic and necrotic regions as much as possible (Fig. 1). When the tumor was too small to draw a ROI of approximately 35–45 mm², a ROI was manually drawn as large as possible within the tumor on the magnified image, including images of T1 stage esophageal cancer. The estimate of the T₂* value for each slice was obtained from the averaged T₂* values of the three ROIs in each slice. The representative T₂* values of the three slices were then averaged to obtain a final estimate of the ESCC T₂* value for the data analysis. The T₂* values of the normal esophageal wall were obtained from the healthy volunteers in a similar manner via the acquisition of the T₂* values of the ESCCs except that each ROI drawn on the magnified image was approximately 3–5 mm² in area.

Statistical Analysis

All statistical analyses were performed with the SPSS software (version 13.0 for Windows, SPSS Inc., Chicago, IL, USA). Descriptive statistics included the means and standard deviations of the T₂* parameters. Differences were considered significant when the *p* values were below 0.05.

The agreement of each T₂* parameter from the two independent observers' measurements was assessed

with Bland-Altman statistics. The intraclass correlation coefficients and their 95% confidence intervals were used to assess the levels of agreement. When the intraclass correlation coefficients were greater than 0.99, and the mean differences of the replicated measurements were close to zero, good agreement between the replicated measurements was considered to have been obtained (25). If the intraclass correlation coefficient was less than 0.99 for any participant, the measurement of the T₂* parameter was repeated by the observers, and the mean of the four measurements was used as the final result for the further analysis.

Because the T₂* parameters were normally distributed, the independent samples Student's *t* test was used to compare the T₂* values between the ESCCs and the normal esophageal walls and between the grouped T-stages. The one-way ANOVA test and the Student-Newman-Keuls test for pairwise multiple comparisons were conducted to determine the associations between the T₂* values of the ESCCs and all clinical factors, such as the T and N stages and the anatomic stage of the ESCC. If a significant difference in the T₂* values between any two stages was demonstrated based on the results of the one-way ANOVA test together with the Student-Newman-Keuls test for pairwise multiple

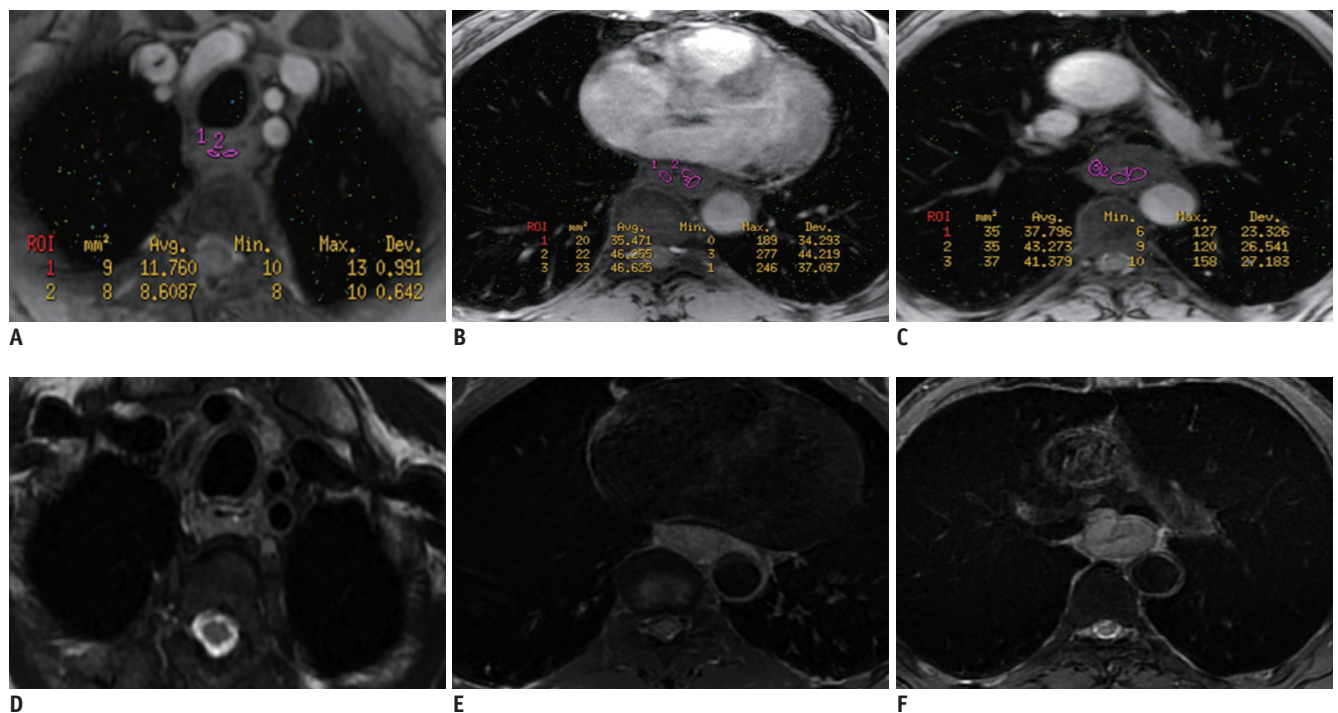


Fig. 1. Representative T₂* and T2-weighted images of esophageal squamous cell carcinoma.

T₂* weighted imaging (T₂*WI) (A-C) and T2-weighted imaging (D-F) of stages T1, T2, and T3 esophageal squamous cell carcinoma in 62-year-old male, 67-year-old female and 57-year-old male, respectively. Regions of interest are drawn on T₂*WI within each tumor to obtain T₂* value.

comparisons, and the independent samples Student's *t* test, the receiver operating characteristic (ROC) analysis of the T_2^* value was performed using the MedCalc statistical software (version 13.0 for Windows, SPSS Inc.) for the detection and staging of the ESCCs. In detail, ROC analyses of the T_2^* parameters with significant differences were performed between the normal esophageal walls and the ESCCs to detect these tumors, between the stages T0–1 and stages T2–3, and between the stages T0–2 and stage T3 to determine the grouped stages, and between stages T1 and T2, and between stages T1 and T3, to aid in the T staging of the ESCCs. Using the anatomic staging system, the significant differences in the T_2^* parameters between stages I and II or III were also examined by ROC analyses.

RESULTS

The Inter-Observer Agreements of the T_2^* Value Measurements

There were good agreements between the two independent observers in terms of the T_2^* values for the ESCCs and for normal esophagi (Table 2). The intraclass correlation coefficients were greater than 0.99 in 43 patients with ESCCs and in 18 healthy participants, and the first radiologist's measurements were used as the final results for the data analysis. Additionally, the intraclass correlation coefficient was less than 0.99 in 5 patients with ESCCs and in 2 healthy participants. The measurements of

the T_2^* parameters were repeated by the two observers, and the means of the four measurements were used as the final results for the further analysis.

Analysis of the T_2^* Values Associated with the T, N and Anatomic Stages

The averaged T_2^* values of the normal esophageal walls and ESCCs were 17.0 ± 2.9 ms and 25.2 ± 6.2 ms, respectively. There was a significant difference between the normal esophageal walls and the ESCCs (i.e., between stage T0 and stages T1–3, $p < 0.001$).

The averaged T_2^* values of the stage T1, T2, and T3 ESCCs were 17.7 ± 3.3 ms, 24.6 ± 2.7 ms, and 27.8 ± 5.6 ms, respectively. Multiple pairwise comparisons revealed that the T_2^* value aided the differentiation of stage T1 disease from stage T2, and of stage T1 from stage T3 (all $p_s < 0.001$). However, no difference in the T_2^* values was observed between stages T2 and T3 ($p > 0.05$). Regarding the grouped T-stages of the ESCCs, there were significance differences in the T_2^* values between stages T0–1 and T2–3 (17.3 ± 3.0 ms vs. 27.1 ± 5.3 ms, $p < 0.001$) and between stages T0–2 and T3 (18.8 ± 4.2 ms vs. 27.8 ± 5.6 ms, $p < 0.001$). In the patients with stage N0–2 ESCC, the averaged T_2^* values of the stages N0, N1, and N2 of ESCCs were 24.7 ± 6.9 ms, 25.4 ± 4.5 ms, and 26.8 ± 3.9 ms, respectively. The T_2^* values of N stages were not significantly different (all $p_s > 0.05$).

For the ESCC patients in different anatomic stages, the averaged T_2^* values of the stage I, II, and III tumors

Table 2. Inter-Observer Agreements of T_2^* Value Measurements

T_2^* Value	Mean Difference of Replicated Measurements (Mean \pm SD)			95% Inter-Observer Correlation Coefficient
	Differences between Two Measurements	95% CI	95% Limits of Agreement	
Normal Esophagi	0.01 ± 0.40	-0.774–0.794	-1.094–1.114	0.991 (0.976–0.996)
ESCCs	0.04 ± 0.84	-1.605–1.688	-2.021–2.104	0.993 (0.987–0.996)

CI = confidence interval, ESCCs = esophageal squamous cell carcinomas, SD = standard deviation

Table 3. Receiver Operating Characteristic Analysis of T_2^* for Detecting and Staging of Esophageal Squamous Cell Carcinoma

T_2^* Cutoff (ms)	Differentiation	AUC	Sensitivity	Specificity
T stage				
20	T0 vs. T1-3	0.897	0.833	0.900
21.3	T1 vs. T2	0.950	0.875	1.00
21.3	T1 vs. T3	0.947	0.833	1.00
21.3	T0–1 vs. T2–3	0.966	0.842	0.967
20.4	T0–2 vs. T3	0.903	0.967	0.684
Anatomic stage				
21.3	I vs. II	0.867	0.769	0.909
21.3	I vs. III	0.926	1.00	0.909

AUC = area under receiver operating characteristic curve, Stage T0 = the normal esophageal wall

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were 18.8 ± 4.8 ms, 26.9 ± 5.9 ms, and 27.3 ± 3.6 ms, respectively. The T_2^* value aided the differentiations of stage I from stage II and of stage I from stage III (all $p_s < 0.001$). However, the T_2^* value did not aid the differentiation of stage II from stage III disease ($p > 0.05$).

ROC Analysis of the T_2^* Value for the Detection and Staging of ESCCs

Based on the ROC analysis, the sensitivity, specificity, area under the ROC curve (AUC), and the cutoff value of T_2^* for detecting and staging ESCC are summarized in Table 3. As illustrated in Table 3, the T_2^* parameters were reliable indicators for detecting ESCCs and aided the ESCC staging.

DISCUSSION

In clinical settings, T1- or T2-staged ESCCs can be treated with endoscopic therapy or with esophagectomy, whereas higher stage lesions require neoadjuvant chemoradiation before or after esophagectomy (26). This study was conducted to explore the associations of the T_2^* values of resectable ESCCs with the stages to determine whether the T_2^* value can be used to detect and accurately stage esophageal cancer before treatment.

The study found that the averaged T_2^* value exhibited increasing trends from stage T0 to T1 and from stage T2 to T3. The potential mechanism for this finding might be the blood oxygenation level. Several previous studies reported that angiogenesis, together with rich oxygen (O_2) and nutrient supplies play vital roles in tumorigenesis, development and metastasis (27-30). The cyclooxygenase-2 (COX-2) protein is over-expressed in esophageal cancer. The microvascular density in COX-2-positive cases might be significantly higher than in COX-2-negative cases, and follow an ascending order from carcinomas *in situ*, to tumors invading the lamina propria mucosae, and tumors invading the muscularis mucosa or deeper cancers (31, 32). The increased number of blood vessels can lead to increased blood flow and blood O_2 content, whereas the content of deoxyhemoglobin is decreased. This could cause the phase of local magnetic fields to decrease, which ultimately results in the T_2^* value increasing with the progress of the T stage (33).

However, there was no significant difference in the T_2^* values between stages T0 and T1 of the ESCCs due to the overlap of this parameter. The potential mechanism for this finding might be a mechanism similar to that of tumor

angiogenesis in early-stage colon cancer (34). During the early stage of tumor angiogenesis, the rich vasculature of the lamina propria is able to cope with the initial transformation because the tumor's organization remains similar to that of the normal esophageal wall. This study revealed that there was no significant difference in the T_2^* values between stages T2 and T3 of the ESCCs due to the overlap of this parameter. With the progress of an ESCC from stage T2 to T3, the rapid proliferation of malignant tumor cells and abnormal hemodynamics can significantly increase O_2 consumption. The above-mentioned increase in O_2 content is due to the increased number of blood vessels, and the decrease in O_2 content is due to the rapid proliferation of malignant tumor cells. This leads to a significant decrease in deoxyhemoglobin content, which ultimately results in no significant difference between the T_2^* values of stages T2 and T3 (35-38).

Clinically, the blood oxygenation parameter (T_2^*) helped to differentiate ESCC stage T1 from T2 or T3, and the grouped T stages between T0-1 and T2-3, and stages between T0-2 and T3. The T_2^* value was also able to distinguish anatomic stage I disease from stage II or III disease. As demonstrated by the ROC analysis, the same cutoff T_2^* value (21.3 ms) aided the differentiation between the T1 stage and the T2 or T3 stages, and between the anatomic stages I and II or III. A possible reason for the same cutoff T_2^* value being reached might be related to the sample size in the standard control group that was used to obtain the threshold T_2^* value for the previous discrimination. All the 10 patients with T1-staged ESCCs were used as the standard control group to discriminate the above-mentioned T stages of the ESCCs. The same 10 patients with T1-staged ESCCs plus one case of T2-staged cancer were used as the standard control group to distinguish the above anatomic stages. The similar sample sizes of the standard control groups resulted in the same cutoff for the differentiation. However, the AUC, sensitivity and specificity were different for the corresponding differentiations.

This study has a limitation of relatively small sample size. However, in spite of the small sample size, some useful information about the associations of T_2^* values with the occurrences and stages of ESCCs was obtained. Future studies will expand the sample size to confirm these results.

In conclusion, the T_2^* values of ESCCs can help detect this cancer and can be an additional quantitative indicator for the preoperative stage of this tumor. The cutoff T_2^* value

of 20 ms aided the detection of ESCCs. The cutoff T_2^* value of 21.3 ms aided the differentiation of T stages between T1 and T2 or T3, and between the anatomic stages of I and II or III. Regarding the determination of the grouped T-stages of the ESCCs, the cutoff T_2^* values of 21.3 ms and 20.4 ms aided the discriminations of stage T0–1 from stage T2–3 and of stage T0–2 from stage T3, respectively. This study will be helpful in detecting ESCCs and in staging these tumors for therapeutic decision-making.

REFERENCES

- Enzinger PC, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003;349:2241-2252
- van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012;366:2074-2084
- Cao LY, Yin Y, Li H, Jiang Y, Zhang HF. Expression and clinical significance of S100A2 and p63 in esophageal carcinoma. *World J Gastroenterol* 2009;15:4183-4188
- Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. *CA Cancer J Clin* 2011;61:69-90
- Fitzgerald RC. Review article: Barrett's oesophagus and associated adenocarcinoma--a UK perspective. *Aliment Pharmacol Ther* 2004;20 Suppl 8:45-49
- Nomura M, Oze I, Kodaira T, Abe T, Komori A, Narita Y, et al. Comparison between surgery and definitive chemoradiotherapy for patients with resectable esophageal squamous cell carcinoma: a propensity score analysis. *Int J Clin Oncol* 2016;21:890-898
- Kitagawa Y. [Therapeutic strategies for advanced respectable esophageal cancer]. *Nihon Geka Gakkai Zasshi* 2008;109:333-337
- Fokas E, Rödel C. Definitive, preoperative, and palliative radiation therapy of esophageal cancer. *Viszeralmedizin* 2015;31:347-353
- Ripley RT, Sarkaria IS, Grosser R, Sima CS, Bains MS, Jones DR, et al. Pretreatment dysphagia in esophageal cancer patients may eliminate the need for staging by endoscopic ultrasonography. *Ann Thorac Surg* 2016;101:226-230
- Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. *World J Gastroenterol* 2008;14:1479-1490
- Rice TW. Clinical staging of esophageal carcinoma. CT, EUS, and PET. *Chest Surg Clin N Am* 2000;10:471-485
- Riddell AM, Allum WH, Thompson JN, Wotherspoon AC, Richardson C, Brown G. The appearances of oesophageal carcinoma demonstrated on high-resolution, T2-weighted MRI, with histopathological correlation. *Eur Radiol* 2007;17:391-399
- Riddell AM, Hillier J, Brown G, King DM, Wotherspoon AC, Thompson JN, et al. Potential of surface-coil MRI for staging of esophageal cancer. *AJR Am J Roentgenol* 2006;187:1280-1287
- Tang MY, Chen TW, Zhang XM, Huang XH. GRE T2*-weighted MRI: principles and clinical applications. *Biomed Res Int* 2014;2014:312142
- Li Y, Song QW, Sun MY, Wang HQ, Wang S, Wei Q, et al. Use of enhanced T2 star-weighted angiography (ESWAN) and R2* values to distinguish ovarian cysts due to endometriosis from other causes. *Abdom Imaging* 2015;40:1733-1741
- Howe FA, Robinson SP, Rodrigues LM, Stubbs M, Griffiths JR. Issues in GRE & SE magnetic resonance imaging to probe tumor oxygenation. *Adv Exp Med Biol* 2003;530:441-448
- Chavhan GB, Babyn PS, Thomas B, Shroff MM, Haacke EM. Principles, techniques, and applications of T2*-based MR imaging and its special applications. *Radiographics* 2009;29:1433-1449
- Rodrigues LM, Howe FA, Griffiths JR, Robinson SP. Tumor R2* is a prognostic indicator of acute radiotherapeutic response in rodent tumors. *J Magn Reson Imaging* 2004;19:482-488
- Zhang LJ, Zhang Z, Xu J, Jin N, Luo S, Larson AC, et al. Carbogen gas-challenge blood oxygen level-dependent magnetic resonance imaging in hepatocellular carcinoma: initial results. *Oncol Lett* 2015;10:2009-2014
- Li D, Wang X, Wang S, Cheng J. Correlation between BOLD-MRI and HIF expression level in renal carcinoma. *Int J Clin Exp Pathol* 2015;8:13759-13763
- Rakow-Penner R, Daniel B, Glover GH. Detecting blood oxygen level-dependent (BOLD) contrast in the breast. *J Magn Reson Imaging* 2010;32:120-129
- Alonzi R, Padhani AR, Maxwell RJ, Taylor NJ, Stirling JJ, Wilson JI, et al. Carbogen breathing increases prostate cancer oxygenation: a translational MRI study in murine xenografts and humans. *Br J Cancer* 2009;100:644-648
- Pennathur A, Gibson MK, Jobe BA, Luketich JD. Oesophageal carcinoma. *Lancet* 2013;381:400-412
- Li Z, Rice TW. Diagnosis and staging of cancer of the esophagus and esophagogastric junction. *Surg Clin North Am* 2012;92:1105-1126
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307-310
- Quint LE, Bogot NR. Staging esophageal cancer. *Cancer Imaging* 2008;8:S33-S42
- Butler JM, Kobayashi H, Rafii S. Instructive role of the vascular niche in promoting tumour growth and tissue repair by angiocrine factors. *Nat Rev Cancer* 2010;10:138-146
- Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011;144:646-674
- Gholamin M, Moaven O, Memar B, Farshchian M, Naseh H, Malekzadeh R, et al. Overexpression and interactions of interleukin-10, transforming growth factor beta, and vascular endothelial growth factor in esophageal squamous cell carcinoma. *World J Surg* 2009;33:1439-1445
- Wang W, Sun QK, He YF, Ma DC, Xie MR, Ji CS, et al.

- Overexpression of periostin is significantly correlated to the tumor angiogenesis and poor prognosis in patients with esophageal squamous cell carcinoma. *Int J Clin Exp Pathol* 2014;7:593-601
31. Koga T, Shibahara K, Kabashima A, Sumiyoshi Y, Kimura Y, Takahashi I, et al. Overexpression of cyclooxygenase-2 and tumor angiogenesis in human gastric cancer. *Hepatogastroenterology* 2004;51:1626-1630
 32. Kumagai Y, Sobajima J, Higashi M, Ishiguro T, Fukuchi M, Ishibashi K, et al. Coexpression of COX-2 and iNOS in angiogenesis of superficial esophageal squamous cell carcinoma. *Int Surg* 2015;100:733-743
 33. Pedersen M, Dissing TH, Mørkenborg J, Stødkilde-Jørgensen H, Hansen LH, Pedersen LB, et al. Validation of quantitative BOLD MRI measurements in kidney: application to unilateral ureteral obstruction. *Kidney Int* 2005;67:2305-2312
 34. Van Meir E. Hypoxia-mediated selection of cells with diminished apoptotic potential to solid tumours. *Neurosurgery* 1996;39:878-879
 35. He Q, Xu RZ, Shkarin P, Pizzorno G, Lee-French CH, Rothman DL, et al. Magnetic resonance spectroscopic imaging of tumor metabolic markers for cancer diagnosis, metabolic phenotyping, and characterization of tumor microenvironment. *Dis Markers* 2003-2004;19:69-94
 36. Arakelyan L, Vainstein V, Agur Z. A computer algorithm describing the process of vessel formation and maturation, and its use for predicting the effects of anti-angiogenic and anti-maturation therapy on vascular tumor growth. *Angiogenesis* 2002;5:203-214
 37. Boucher Y, Jain RK. Microvascular pressure is the principal driving force for interstitial hypertension in solid tumors: implications for vascular collapse. *Cancer Res* 1992;52:5110-5114
 38. Horsman MR, Overgaard J. The impact of hypoxia and its modification of the outcome of radiotherapy. *J Radiat Res* 2016;57 Suppl 1:i90-i98