



Potential use of high-resolution T2-weighted MRI with histopathologic findings in staging esophageal cancer

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Background: Magnetic resonance imaging (MRI) has shown promising capabilities in diagnosing local esophageal carcinoma. This study investigated the clinical value of high resolution (HR; small field of view and continuous thin section) axial T2-weighted MRI (HR-T2WI) as a noninvasive method for esophageal carcinoma tumor staging (T staging).

Methods: Forty-two patients with biopsy-proven esophageal cancer were investigated using HR-T2WI. The discrepancies between the esophageal wall layers and tumor tissue were assessed for MRI T staging using a visual MRI signal intensity scale (low, intermediate, and high intensities). The computed tomography (CT) and MRI T staging was compared with whole-mount histopathological sections in all patients who underwent resection.

Results: HR-T2WI provided a thorough view of the esophageal wall and the tumor's anatomic layers. Of the 42 patients with histological tumors (HTs), there were 6 cases with tumors classified as HT-1a, 5 cases with HT-1b, 14 cases with HT-2, and 17 cases with HT-3/4, and their MRI T stages were 5 MRI-T1a, 6 MRI-T1b, 14 MRI-T2, and 17 MRI-T3/4, respectively. After analyzing the imaging presentation at different HT staginess, we found that HR-T2WI enabled a more accurate classification than was possible with CT. The difference in accuracy between CT and T2WI was statistically significant ($P < 0.05$) in the entire sample and in HT₁₋₂ tumors and HT₃₋₄ tumors.

Conclusions: HR-T2WI clearly identified normal esophageal wall layers; it had high diagnostic accuracy when evaluating tumor invasion and in MRI-T staging for esophageal carcinoma. This study established staging criteria of esophageal carcinoma using HR-T2WI and indicated that this approach could be used as a supplemental noninvasive method for the local T staging of esophageal carcinoma.

Keywords: Esophageal cancer (EC); high-resolution magnetic resonance imaging (MRI); T staging

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Introduction

As one of the most common malignancies worldwide, esophageal cancer (EC) is on the rise globally (1,2). Patients with EC have a poor prognosis because early-stage EC is typically asymptomatic (1,2). As a result, the treatment options are significantly influenced by accurate and timely preoperative staging. Computed tomography (CT), endoscopic ultrasonography (EUS), and positron emission tomography (PET)/CT are used to stage EC (1-4). However, these imaging modalities have limitations in measuring the degree of tumor invasion. Tightly stenotic tumors, strong operator reliance with a well-defined learning curve, and difficulties in distinguishing ulcer-associated inflammation from infiltration all limit EUS (5-7). While the introduction of multidetector CT (MDCT) has contributed to the recently reported increase in local staging accuracy (8,9), it is still difficult to determine the degree of invasion of EC due to inadequate soft tissue contrast. PET/CT has been widely used in the diagnosis of distant metastatic disease. However, very little data exist evaluating PET/CT in EC staging, due to its limitation (3).

Magnetic resonance imaging (MRI) has been used as a potential means for local EC staging. Riddell *et al.* (10) compared MRI images of 33 patients with EC with histological whole-mount sections and found that high-resolution T2-weighted MRI accurately confirmed 4 T1, 12 T2, and 17 T3 tumors. Although the sample size of this study was relatively small, the results still suggest that this technique may be an alternative noninvasive method for the local staging of EC (10). However, the spatial resolution of the technique limits its ability to resolve the various layers of the esophageal wall (11-14). We thus developed an innovative, noninvasive technique for tumor staging (T staging) of EC by measuring the signal intensity (SI) of high resolution (HR, small field of view, and continuous thin section) axial T2-weighted MRI (HR-T2WI), and further compared the advantages and disadvantages of HR-T2WI and CT for T staging of EC.

Methods

Study population

This study employed a prospective design and was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of Shanghai Jiao Tong University affiliated Sixth People's Hospital South Campus (IRB #2021-KY-28-01),

and informed consent was obtained from all the patients.

Patients were included if they had pathologically confirmed EC, had not received radiotherapy and chemotherapy, did not have a severe cardiac or pulmonary impairment, did not have a contraindication to MRI, did not have an iodine contrast allergy, were fit for operation according to endoscopy and CT, and had HR-T2WI of the primary tumor performed the day before surgery. Patients with serious liver, kidney, heart, lung, or other serious chronic diseases and those with poor mental status who could not cooperate with the examination were excluded from the study.

Anatomic classification

The histologic tumor (HT) classification was used to indicate the degree of primary tumor invasion (15,16). The seventh edition of the tumor-node-metastasis (TNM) staging system for EC is depicted in *Figure 1A* (15). The HT classification is shown in *Figure 1A* (17).

Imaging technique

Prior to sequence acquisition, patients were taught breath-holding and free-breathing strategies. The images were all captured using a 3.0-T MRI machine (Ingenia; Philips Healthcare, Best, The Netherlands). The scanning range included the entire esophagus, with respiratory gating and respiratory triggering techniques being used. The scanning sequence included the sagittal T2W and axial T2W, high-resolution axial T2-weighted MRI, and a dynamic enhanced scan (mDIXON, Philips Healthcare). The injection of gadolinium-diethylene triamine pentaacetate (Beilu, Beijing, China) as the contrast agent was at a dose of 0.1 mmol/kg and an injection rate of 2.5 mL/s. The HR-T2WI sequence parameters were as follows: time of repetition/echo time, 1,203/90 ms; matrix size, 232×215; field of view, 140×140; voxel, 0.6×0.62×4; number of excitations, 2; section of thickness, 4 mm; and section gap, 1 mm. The T2W sequence had an average scan time of 7 to 8 minutes.

To compare the value of high-resolution T2WI and CT in EC staging, we performed a 64-slice CT (Discovery HD750; GE Healthcare, Chicago, IL, USA) on all patients at the same time. Contrast-enhanced multi detector computed tomography (MDCT) images were acquired at 28 and 40 s (arterial and venous phases) after intravenous injection of Iopamiro (Bracco, Shanghai, China) at a dose of 90 ml and an injection rate of 3.0 mL/s. Image data were

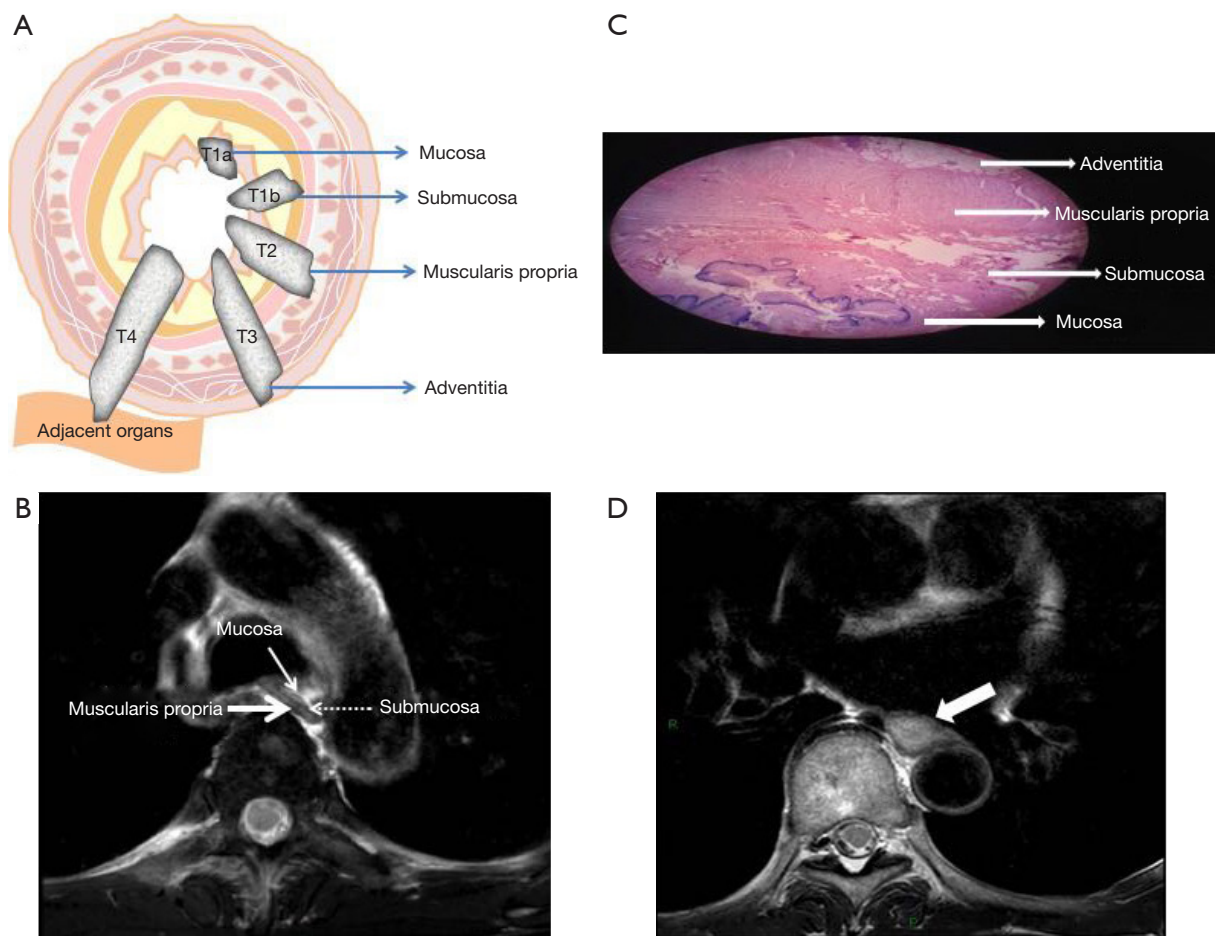


Figure 1 A schematic view of the tumor–node–metastasis staging system for esophageal cancer. (A) Representation of the mucosa, submucosa, muscularis propria, and the adventitia of the esophageal wall. (B) Layers of the normal esophageal wall on high-resolution (small field of view and continuous thin section) axial T2-weighted magnetic resonance imaging: mucosa (thin arrow), submucosa (dotted arrow), muscularis propria (thick arrow). (C) Comparison of histological sections with recorded magnetic resonance imaging observations. HE staining, $\times 40$. (D) Thickening of the esophageal wall with a slightly higher signal intensity observed in the presence of esophageal cancer (arrow).

obtained as follows: slice, 5 mm; rotation time, 600 ms; beam pitch, 0.83; and voltage, 120 kVp.

Image analysis

Two highly trained radiologists with 10 years of expertise in diagnostic abdominal radiology analyzed all the images. They were unaware of the patients' clinical results, with the exception of 1 case of EC. The 2 readers rated the MR image quality for the 3 sequences on a 5-point Likert scale (1= poor, 2= acceptable, 3= average, 4= good, 5= superb). Kappa statistics were used to determine the interobserver agreement between the 2 radiologists. The final score for visual quality was the lowest of the 3 sequences.

MRI SI of EC wall

MR images were reviewed for SI, homogeneity, and thickness of the esophagus lining layers. In our study, the normal esophageal wall had 4 main layers of different signal intensities. The SI of the layers of the normal esophageal wall on high-resolution T2W MR images are shown in *Table 1* and *Figure 1B*, which shows the mucosa (intermediate SI), submucosa (high SI), muscularis propria (low SI), and adventitia (high SI). These 4 layers were found to correspond well to the histologic layers of the esophageal wall (*Figure 1C*). The esophagus wall was separated into 4 layers, and the MRI-based T staging (MRI-T) was classified as MRI-T1a for mucosal or MRI-T1b for

submucosal lesions, MRI-T2 for muscularis lesions, MRI-T3 for adventitia lesions, and MRI-T4 for adjacent lesions. The depth of cancer cell invasion into the esophageal wall was assessed using visual SI on MR images, and each MRI-T had a different SI.

T2WI was used to analyze the SI, homogeneity, and thickness of each layer of the esophagus wall. To determine the level of involvement, the observers used the following T2WI criteria: (I) a distinct mass inside the layers, (II) a localized aberrant SI within layers, and (III) mucosal ulceration in the presence of a surrounding or underlying mass (18,19).

Histologic preparations and examination

Following T2WI, whole-mount sections were longitudinally sliced so that the orientation of the slices matched the orientation of the T2WI. These whole-mount sections captured an entire cross-section of a surgical tissue specimen, and we improved the sampling by preserving the spatial arrangement of the tissue to achieve a more accurate margin assessment as compared to a traditional section. Paraffin-embedded samples were sectioned to a thickness of 6 mm, stained with hematoxylin and eosin (HE), and analyzed for HT.

Table 1 SI of the esophageal wall layers on high-resolution T2WI

Structure	Resolution on T2WI
Mucosa	Intermediate
Submucosa	High
Muscularis propria	Low
Adventitia	High

SI, signal intensity; T2WI, axial T2-weighted magnetic resonance imaging.

Table 2 Evaluating the depth of carcinoma invasion compared to the T2WI signals

High-resolution T2WI findings (MRI-T staging)	Histopathologic findings			
	Mucosa (T1a; n=6)	Submucosa (T1b; n=5)	Muscularis propria (T2; n=14)	Adventitia (T3/T4; n=17)
Mucosa (T1a; n=5)	5	0	0	0
Submucosa (T1b; n=6)	1	3	2	0
Muscularis propria (T2; n=14)	0	2	12	0
Adventitia (T3/T4; n=17)	0	0	0	17

T2WI, axial T2-weighted magnetic resonance imaging; MRI-T staging, magnetic resonance imaging-tumor staging.

Statistical analysis

The accuracy, sensitivity, and specificity of CT and MRI were assessed using HT as a gold standard. To determine the consistency of outcomes between readers, the Cohen kappa coefficient was used. Kappa values of less than 0.40 were regarded as poor agreement, 0.41–0.75 indicated moderate to fair agreement, and those over 0.75 indicated excellent agreement. All statistical analyses were evaluated using commercial software (SPSS 16.0, IBM Corp, Armonk, NY, USA). To analyze the differences in staging accuracy between EC in the early stage (T1 or T2) and advanced stage (T3 or T4) across different approaches, a chi-squared test was performed. Statistical significance was set at a $P < 0.05$.

Results

A total of 42 patients with histologically confirmed EC (2 adenocarcinomas, 39 squamous cell carcinomas, and 1 neuroendocrine carcinoma), including 37 men and 5 women with a median age of 63 years (range 45–80 years), underwent surgical resection from December 1, 2019, to December 31, 2021, at Shanghai Jiao Tong University affiliated Sixth People's Hospital South Campus, Shanghai, China. According to HT classification, patients included 6 HT1a, 5 HT1b, 14 HT2, and 17 HT3/4 (Table 2). Moreover, 25 patients (11 with HT1 and 14 with HT2 EC tumors) were to undergo surgery, while 17 patients with HT3/4 EC tumors were to undergo neoadjuvant therapy and surgery because of poor outcomes with surgery alone.

SI of the normal esophageal wall on high-resolution T2WI

Figure 1 provides a schematic view of the TNM staging system for EC. The HT classification is shown in Figure 1A, and the equivalent histologic sections compared to the

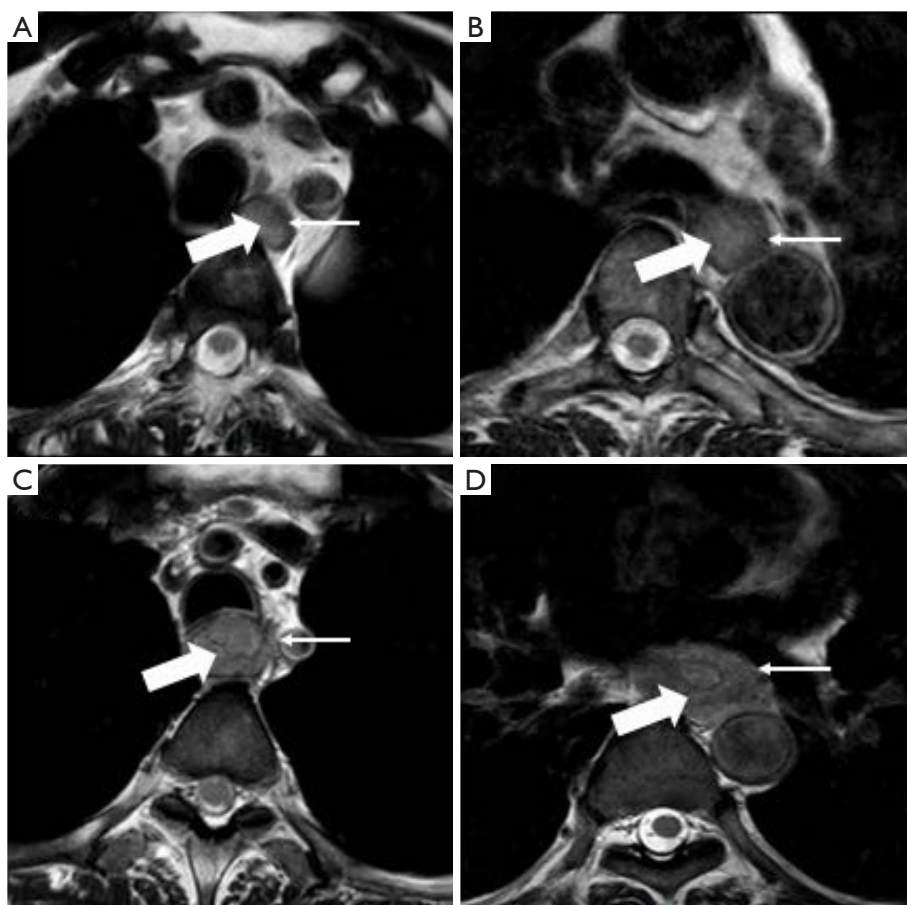


Figure 2 Assessment of tumor invasion into the esophageal wall by high-resolution (small field of view and continuous thin section) axial T2-weighted magnetic resonance imaging. (A) Magnetic resonance imaging–T1: axial T2-weighted magnetic resonance imaging showed an intermediate-signal intensity tumor involving the high-signal intensity submucosa (thick arrow), with the linear low-signal intensity muscularis propria being intact (thin arrow). (B) Magnetic resonance imaging–T2: axial T2-weighted magnetic resonance imaging showed that the muscularis propria appeared thinned because of invasion of tumor (thick arrow), with the linear low-SI muscularis propria being interrupted (thin arrow). (C) Magnetic resonance imaging–T3: axial T2-weighted magnetic resonance imaging showed that the tumor-invaded adventitia tended to have significant thickening of the esophageal wall (thick arrow), and on the resonance imaging, the esophageal wall was irregular and less well defined (thin arrow). (D) Magnetic resonance imaging–T4: axial T2-weighted magnetic resonance imaging showed that the tumor had a high signal (thick arrow) and that the normal fat line between the esophagus and the aorta had disappeared (thin arrow).

documented MRI observations are shown in *Figure 1C*.

Based on different MR signal intensities, *Figure 1B* shows the clear anatomical structures of the normal esophageal wall. The median single wall thickness measured by MRI was 5 mm (range, 3–10 mm). The esophagus was surrounded by high-signal periesophageal fat. HR-T2WI provided excellent contrast between the structures close to the esophagus, such as the tracheobronchial tree, descending thoracic aorta, and triangular fat space, which were clearly visible (*Figure 1B*). These 4 layers corresponded well with the histologic layers of the esophageal wall (*Figure 1C*). In

the presence of a tumor, thickening of the esophageal wall was observed (arrows, *Figure 1D*). In addition, a slightly higher SI was observed at the tumor site compared to the normal esophageal wall (arrows, *Figure 1D*).

Evaluation of EC invasion

The T2WI showed its evaluation on tumor invasion into the esophageal wall (*Figure 2*). On T2WI, carcinomas confined within the high-SI submucosa had discontinuous thickening of the mucosal layer with intermediate SI (thick

Table 3 Diagnostic accuracy of HR-T2WI for evaluating the depth of EC invasion

Depth of invasion	Sensitivity	Specificity	Accuracy
Mucosa (n, %)	5/6 (83.3)	0/0 (NA)	41/42 (97.6)
Submucosa (n, %)	3/5 (60.0)	34/37 (91.9)	37/42 (88.1)
Muscularis propria (n, %)	12/14 (85.7)	26/28 (92.9)	38/42 (90.5)
Adventitia (n, %)	17/17 (100.0)	25/25 (100.0)	42/42 (100.0)

HR, high-resolution, small field of view and continuous thin section; T2WI, axial T2-weighted magnetic resonance imaging; EC, esophageal cancer.

Table 4 Accuracy of the HT classification in ECs: spiral CT and HR-T2WI compared with histopathologic findings

Histopathology	n	Accuracy (n, %)	
		Spiral CT	T2WI*
HT ₁₋₂	11	33/42 (78.6)	34/42 (81.0)
HT ₃₋₄	31	33/42 (78.6)	38/42 (90.5)
HT ₁₋₄	42	33/42 (78.6)	37/42 (88.1)

*, P<0.05 for each result statistically significant compared to spiral CT. HT, histological tumor; EC, esophageal cancer; CT, computed tomography; HR, high-resolution, small field of view and continuous thin section; T2WI, axial T2-weighted magnetic resonance imaging.

arrow, *Figure 2A*); however, in these mucosa or submucosal tumors, the low-SI muscularis mucosae were shown to be intact (thin arrow, *Figure 2A*). Tumors limited to the mucosa and submucosa had a minimal mass effect on the esophageal wall, making the tumors difficult to distinguish from the surrounding normal wall. Carcinomas that invaded the submucosa appeared as irregular low-SI or intermediate-SI masses in contrast to the high-SI submucosa on T2WI. Tumors involving the muscularis propria appeared thinned because of invasion of the tumor (thick arrow, *Figure 2B*), and on the MRI, the esophageal wall was irregular and less well defined (thin arrow, *Figure 2B*). T2WI showed that the tumor-invaded adventitia tended to have significant thickening of the esophageal wall (thick arrow, *Figure 2C*), and on the MRI, the esophageal wall was irregular and less well defined (thin arrow, *Figure 2C*). Finally, carcinomas that extended into the adventitia were shown to be tumors that had fully destroyed the superficial and muscularis propria layers and had infiltrated the high-SI adventitia (thick arrow, *Figure 2D*); moreover, the normal fat line between the esophagus and the aorta had disappeared (thin arrow, *Figure 2D*).

Evaluation of the depth of EC invasion on high-resolution T2WI

MRI was performed on 42 patients to determine the depth of EC invasion, with interobserver agreement at excellent levels (intraobserver agreement =94.2%; Kapa =0.930; P<0.001). According to the worldwide TNM classification, the 42 esophageal malignancies in our series were evaluated; classifications of the depth of carcinoma invasion are shown in *Table 2*.

Table 3 shows the diagnostic accuracy of HR-T2WI in assessing the depth of EC invasion. The accuracy and sensitivity of assessing mucosal invasion were 97.6% and 83.3%, respectively, but the specificity was not determined. In all 3 lesions, T2WI was used to identify submucosal infiltration. One lesion was incorrectly staged as mucosal invasion, while the other two lesions were incorrectly staged as muscularis propria invasion. As a result, measuring submucosal invasion had a sensitivity, specificity, and accuracy of 60.0%, 91.9%, and 88.1%, respectively. All 12 lesions with muscularis propria invasion were diagnosed by T2WI, and 2 cancers were incorrectly staged as submucosa invasion. As a result, measuring muscularis propria invasion had a sensitivity, specificity, and accuracy of 85.7%, 92.9%, and 90.5%, respectively. T2WI had 100% sensitivity, specificity, and accuracy in identifying all 17 lesions with adventitia invasion.

Table 4 shows a comparison of CT and HR-T2WI with pathological criteria in all 42 patients. On HR-T2WI and CT, the primary tumor was correctly staged in 37 (88.1%) and 33 (78.6%) patients, respectively. Our primary data showed that HR-T2WI had a higher accuracy than did CT because the difference in accuracy between CT and T2WI in the overall sample and in the HT₁₋₂ tumors and HT₃₋₄ tumors was statistically significant ($\chi^2=1.0005534$, $\chi^2_{0.05,2}=0.975$, $\chi^2>0.975$; P<0.05 chi-square test). For HR-T2WI and CT, the accuracy of differentiating HT₁₋₂ lesions

was 81.0% and 78.6%, respectively, and the accuracy of differentiating HT₃₋₄ lesions was 90.5% and 78.6%, respectively.

Discussion

Our study revealed that the detailed depth of ECs can be obtained using HR-T2WI. T2W sequences, unlike those of T1W, which were not clearly delineated, showed discrete layers of the esophageal wall and allowed for the possibility of local tumor staging (13,18,20). The study also accurately indicated that the T2W signal properties of the normal esophageal wall had a median value of 5 mm, and the normal esophageal wall thickness was shown to be equivalent to previous research results (10,21).

Our findings also showed that HR-T2WI of the esophagus wall clearly exhibited 4 primary layers with varying SIs. Although the SI of the tumor described in this work was also consistent with the studies conducted by Yamada and Guo (14,22), our findings also provide important new information. In the study, rigorous radiologic and pathologic correlation was possible, and the esophagus wall was separated into 4 layers; we thus tested a new technique, MRI-T, that was found to correspond well to histologic layers of the esophageal wall of differing SI. The depth of carcinoma invasion into the esophagus wall was accurately identified using T2WI in the 42 ECs investigated. For measuring invasion into the mucosa, submucosa, muscularis propria, and adventitia, the sensitivity, specificity, and accuracy were 60–100%, 91.9–100%, and 88.1–100%, respectively, despite 3 false-negative and 2 false-positive identifications. As a result, we propose that HR-T2WI has a high degree of diagnostic accuracy for evaluating wall infiltration in EC. Early studies using conventional MRI (0.35–1.5-T without fast sequences) reported accuracy rates of 56–72% (7,21,23,24) and 64–77% (25,26). Yamada *et al.* (18) reported an MRI accuracy of 96–100% for 66 of 70 ECs using 1.5-T 3D constructive interference in steady state (CISS) MRI and 92–100% using 4.7-T MRI in 22 of 24 ECs. The slightly higher or lower diagnostic accuracies of HR-T2WI than the previous results were due to the increase in intensity (from the previous 0.35-T standard to the current 1.5-T and 3-T standard, and the 4.7-T and 7-T for the experimental systems) and because the development of faster sequences and cardiac and respiratory gating over time yielded better imaging qualities (27,28).

In earlier studies, the MRI appearance of the tumor *in*

in vivo was linked to the histology specimen (10). HT1 and HT2 tumors are early stages of EC that do not respond to neoadjuvant chemoradiotherapy (nCRT) (28). As a result, there is no discernible difference in staging between HT1 and HT2; however, when the tumor progresses to the HT3 or HT4 stage, nCRT or postoperative therapy alternatives may be required (29–31). Because of the differences in the management and prognosis situation for early and advanced EC, we chose patients grouped in the HT₁₋₂ and HT₃₋₄ stages in the study. The results indicated that the wall infiltration level shown by HR-T2WI did connect well with the HT stage in most cases. Our primary data indicated that HR-T2WI had a higher accuracy than did CT because the difference in accuracy between CT and T2WI was statistically significant in the overall sample of HT₁₋₂ and HT₃₋₄ tumors. The staging accuracy of MRI and CT for differentiating T1–2 lesions was 81.0% and 78.6%, respectively; the accuracy of differentiating T3–4 lesions was 90.5% and 78.6%, respectively (Table 4). Existing data (32–35) show that the accuracy of CT or MRI in staging local tumor infiltration varies from 45% to 73%. Our findings revealed that spiral CT was not optimal and that T2WI was more accurate than was spiral CT in the EC T staging, especially in early and advanced tumors. Although CT remains the most-used noninvasive technique in the preoperative T staging of EC, because of poor soft tissue resolution, CT may not differentiate between early-stage tumors (HT1 and HT2 lesions) (16).

Despite the small size of the present sample, the results still suggest that HR-T2WI is accurate in staging EC. This study demonstrated that staging EC using surface coil MRI scans of the esophagus is feasible when using HR-T2WI. The esophageal wall layers were accurately depicted, and the tumor could be identified separately from the surrounding tissue. Overall, the diagnostic value of T2WI for determining the exact depth of cancer invasion into the esophageal wall has improved over the past few years. The T2WI criteria for preoperative EC staging warrant prospective verification. However, we only looked at the clinical impact of the HR-T2WI signal on EC T staging based on pathological histology, and we did not look at the HR-T2WI signal in EC tumors at different sites (e.g., upper thoracic esophagus, middle thoracic esophagus, lower thoracic esophagus, abdominal esophagus, and cervical esophagus). Further, the MRI-T staging was observer dependent, and the accuracy of tumor diagnosis was affected in clinical application. Due to the limitations of MRI, such as it being time-consuming, its small field of view, and its

inability to diagnose distant metastasis, it is not the first choice in clinical diagnosis. In recent years, PET/MRI has received increasing attention for its potential to improve the accuracy of tumor diagnosis. It has advantages over MRI, such as the ability to combine multiple parameters, high soft tissue resolution, a lack of ionizing radiation, and the means to access the molecular information provided by PET (36,37). This is an avenue of research that will be pursued in the future.

Conclusions

This work revealed the promise of HR-T2WI as a noninvasive approach for local EC T staging. It also showed the spectrum of appearances that EC can have depending on the technology and method used to evaluate the depth of EC invasion.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://qims.amegroups.com/article/view/10.21037/qims-22-376/coif>). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Jiao Tong University affiliated Sixth People's Hospital South Campus (IRB #2021-KY-28-01), and informed consent was obtained from all the patients.

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