

Preoperative TN staging of esophageal cancer: Comparison of miniprobe ultrasonography, spiral CT and MRI

Ling-Fei Wu, Bing-Zhou Wang, Jia-Lin Feng, Wei-Rong Cheng, Guo-Re Liu, Xiao-Hua Xu, Zhi-Chao Zheng

Ling-Fei Wu, Bing-Zhou Wang, Department of Gastroenterology, **Jia-Lin Feng**, Department of Information, **Guo-Rui Liu**, Department of Medical Imaging, **Wei-Rong Cheng**, **Xiao-Hua Xu**, Department of Surgery, **Zhi-Chao Zheng**, Department of Pathology, Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province China

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Correspondence to: Dr. Ling-Fei Wu, Department of Gastroenterology, Second Affiliated Hospital, Shantou University Medical College, Shantou 515041, Guangdong Province China. lingfeiwu@21cn.com

Telephone: +86-754-8355461 **Fax:** +86-754-8346543

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Abstract

AIM: To evaluate the value of miniprobe sonography (MPS), spiral CT and MR imaging (MRI) in the tumor and regional lymph node staging of esophageal cancer.

METHODS: Eight-six patients (56 men and 30 women; age range of 39-73 years, mean 62 years) with esophageal carcinoma were staged preoperatively with imaging modalities. Of them, 81 (94 %) had squamous cell carcinoma, 4(5 %) adenocarcinoma, and 1(1 %) adenoacanthoma. Eleven patients (12 %) had malignancy of the upper one third, 41 (48 %) of the mid-esophagus and 34 (40 %) of the distal one third. Forty-one were examined by spiral CT in whom 13 were co-examined by MPS, and forty-five by MRI in whom 18 were also co-examined by MPS. These imaging results were compared with the findings of the histopathologic examination for resected specimens.

RESULTS: In staging the depth of tumor growth, MPS was significantly more accurate (84 %) than spiral CT and MRI (68 % and 60 %, respectively, $P < 0.05$). The specificity and sensitivity were 82 % and 85 % for MPS; 60 % and 69 % for spiral CT; and 40 % and 63 % for MRI, respectively. In staging regional lymph nodes, spiral CT was more accurate (78 %) than MPS and MRI (71 % and 64 %, respectively), but the difference was not statistically significant. The specificity and sensitivity were 79 % and 77 % for spiral CT; 75 % and 68 % for MPS; and 68 % and 62 % for MRI, respectively.

CONCLUSION: MPS is superior to spiral CT or MRI for T staging, especially in early esophageal cancer. However, the three modalities have the similar accuracy in N staging. Spiral CT or MRI is helpful for the detection of far-distance metastasis in esophageal cancer.

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INTRODUCTION

Patients with esophageal cancer have a poor prognosis because

on the onset of symptoms and the final diagnosis, most tumors have reached an advanced stage^[1-5]. Resection of esophageal cancers is the only curative method, but is limited to the early stages of the disease^[6-10]. Therefore, the early diagnosis and an accurate staging are very important for the surgery.

Esophageal tumor is a common disease in China^[11-17]. Shantou is a high-risk region. The incidence of the disease ranges from 60-150 per 100 000 population and the mortality is as high as 90-134 per 100 000 population^[18,19]. Currently, several cross sectional imaging techniques, such as endoscopic ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI) have been widely used to provide preoperative staging and follow-up information in these patients^[1, 20-26]. Unfortunately, all these techniques have their limitations.

Miniprobe endosonography (MPS) is a new intracavitary technique^[27], especially in China^[28,29]. In staging esophageal tumors, previously most studies used the 1987 TNM classification system^[30]. In this study, we adopted the new (1997) TNM classification standard^[31]. The purpose of our study is to compare the accuracy of the three different modalities in preoperative TN staging in patients with esophageal tumors and to analyze their advantages and limitations.

MATERIALS AND METHODS

Patients

From February 1997 to May 2001, 86 patients (56 men and 30 women; age range of 39-73 years, mean 62 years) with esophageal carcinoma were staged preoperatively with imaging modalities. All patients were operated on and staging was done either by histopathological assessment of the resected specimens, or by intraoperative findings, or both. The findings of histopathologic examination were as a gold standard and compared with the results of MPS, spiral CT, and MRI. Of the 86 patients, 81 (94 %) had squamous cell carcinoma, 4(5 %) adenocarcinoma, and 1(1 %) had adenoacanthoma. Eleven patients (12 %) had malignancy of the upper one third, forty-one (48 %) of the mid-esophagus and thirty-four (40 %) of the distal one third. Forty-one patients were examined by spiral CT in which 13 were co-examined by MPS, and 45 patients were examined by MRI in whom 18 were also co-examined by MPS. Of the 22 stenotic tumors in this group, 12 were examined by MPS and the others by spiral CT or MRI.

Imaging procedure

Miniprobe sonography system (Sp-501, Fujinon Co. Ltd, Japan) was used to obtain ultrasound images. A miniprobe (2.6 mm in diameter, 2.05 m in length, 12 MHz or 15 MHz in frequency) was passed through the biopsy channel of a video-endoscope (Olympus XQ-200) during routine endoscopy. Examinations were performed by one endoscopist using the following technique. Premedication with 5 mg midazolam was administered intravenously to 31 patients. First, a standard endoscopy was performed to determine the exact location and size of the tumor. Then the tip of the endoscope was placed 2 to 3 cm proximally to the tumor. The lumen was filled with 50-300 ml of deaerated water to achieve acoustic coupling

between transducer and wall. The normal esophageal wall is known to be visualized by MPS as a five-layer structure: (1) mucosa (hyperechoic), (2) muscularis mucosa (hypoechoic), (3) submucosa (hyperechoic), (4) muscularis propria (hypoechoic), and (5) adventitia (hyperechoic). TN staging of MPS was modified according to the 1997 standard of TNM classification^[31]. Depth of invasion of the primary tumor was assessed as follows: T1, tumor invading the lamina propria or submucosa; T2, tumor invading the muscularis propria and leading to complete or nearly complete loss of the layer structure, but with a smooth outer margin; T3, tumor invading the adventitia and surrounding fat tissues; and T4, tumor invading adjacent structures. The criteria for the assessment of lymph node metastasis were used according to our previous standard^[28]. In short, the hypoechoic pattern, clearly defined boundaries, especially the direct extension from the primary tumor were considered malignant nodes. In contrast, the hyperechoic pattern and fuzzy borders were considered benign nodes.

Spiral CT scans were obtained by means of a commercially available unit (Tomoscan AV EP-Plus, Phillip) with 10-mm thick contiguous sections from the pulmonary apices to the adrenal region. Enhanced CT scan was performed in a biphasic mode with a rapid intravenous injection of 50 ml iohalamate meglumine (Ultravist) in 38 patients. Three hundred ml of water was administered to the patients with distal neoplasms before the CT scanning in order to assess gastric extension. Spiral CT images were reviewed by an experienced radiologist, and TN stages were evaluated using the same criteria described below for MR examinations.

MR imaging was performed with a permanent magnet operating at 0.15T (ASP-015, Annke) with a 128×256 acquisition matrix. Multiple spin-echo pulse sequences were obtained in the transaxial plane at repetition times (TR) of 500, 1 800, or 2 500 msec and echo times (TE) of 35, 90 or 120 msec. In some patients, the sagittal and coronal images were obtained. T₁-weighted images were obtained at repetition times (TR) of 500msec and echo times (TE) of 30 msec, and T₂-weighted images were obtained at TR of 1 500-1 800 msec and TE of 90-120msec. Transaxial images with contiguous 8-10 mm sections were obtained from the pulmonary apices, including supra clavicular fossas to the upper abdomen, including the entire liver. Coronal and sagittal images with contiguous 8-10 mm sections were obtained in 37 patients, and 0.5 % Gd-DTPA was orally administered to distend the stomach before the MR examination. ECG-gated scans were not used in all patients. Five mm esophageal thickness was used as the upper limits of normal esophageal wall. Any increase beyond this was considered abnormal. Since CT or MRI cannot differentiate each layer of the esophageal wall, according to Botet *et al* standard^[32], thickening of the wall greater than 5 mm and less than 15 mm was diagnosed as modified T2, thickening of the wall greater than 15 mm with irregularity of the outer margin as T3, and tumor invasion of adjacent structures such as the trachea, aortic pericardium, or vertebral body as T4. Lymph nodes greater than 10 mm in shortaxis diameter were considered abnormal. In contrast, lymph nodes less than 10 mm in diameter were considered benign nodes.

Statistics

The accuracy, sensitivity and specificity of MPS, spiral CT and MRI were calculated using histopathologic staging as a gold standard. For T stage, the sensitivity is a measure of the ability of the three modalities to correctly stage T1/T2 and not overstage tumors as T3/T4, and conversely the specificity is a measure of the ability of the three modalities to correctly stage T3/T4 and not understage tumors as T1/T2^[30]. A Chi-squared test was performed to assess the differences in staging accuracy

by different methods. A *P* value of less than 0.05 was considered to be statistically significant.

RESULTS

Evaluation of tumor growth (T stage)

Tables 1 shows the accuracy of the three modalities for predicting the T category. Of the 86 patients, 4 patients had T1 tumor, 8 T2, 34 T3 and 40 T4 by final histopathologic examination.

Thirty-one patients were examined by MPS. It correctly diagnosed all 4 (100 %) T1 tumors, 5 of 7 (71 %) T2, 8 of 9 (89 %) T3, and 9 of 11 (82 %) T4. In stage T2, one was understaged and another was overstaged. In stage T3, only one tumor was misdiagnosed as T2. In stage T4, two tumors were understaged. The sensitivity and specificity were 82 % and 85 %, respectively. The overall accuracy of MPS was 84 %.

Spiral CT was performed in 41 patients. Among them, 2 had T1 tumor, 3 T2, 14 T3 and 22 T4 by final histopathologic examination. In 5 T1/T2 tumors, 2 were overstaged, and 3 were staged as modified T2 correctly (75 %). In stage T3, 2 tumors were understaged as T2 and 1 was overstaged, 11 of 14 were staged correctly (79 %). In stage T4, 8 were misdiagnosed, and only 14 of 22 were staged correctly (64 %). The sensitivity and specificity of T staging by spiral CT were 60 % and 69 %, respectively. The overall accuracy was 68 %.

MRI was performed in 45 patients. Among them, 5 had T2 tumor, 20 T3 and 20 T4 by final histopathologic examination. No T1 tumor was examined by MRI. In stage T2, one was understaged and 2 were overstaged, only 2 T2 were staged correctly (40 %). In stage T3, 2 tumors were understaged as T2 and 4 were overstaged, 14 of 20 were staged correctly (70 %). In stage T4, 9 were misdiagnosed, and only 11 of 20 were staged correctly (55 %). The sensitivity and specificity were 40 % and 63 %. The overall accuracy of MRI was 60 %.

Table 1 Accuracy of T classification in esophageal cancers: MPS, spiral CT, MRI compared with histopathologic staging

Histopathology	n	Accuracy (%)		
		MPS	Spiral CT	MRI
T1	4	4/4 (100)		
T2	8	5/7 (71)	3/5 (75)	2/5 (40)
T3	34	8/9 (89)	11/14 (79)	14/20 (70)
T4	40	9/11 (82)	14/22 (64)	11/20 (55)
Total	86	26/31 (84)	28/41 (68)	27/45 (60)

Evaluation of lymph node involvement (N stage)

Tables 2 shows the accuracy of the three modalities for predicting the overall N category differentiated as N0 or N1. Among the 86 patients, 47 had histopathologically proved lymph node involvement.

In 31 patients investigated by MPS, 19 had lymph node involvement and 12 had not by histopathologic examination. MPS correctly diagnosed 13 patients in 19 positive nodes. In 12 patients without lymph node involvement, MPS diagnosed 9 patients correctly. There were 3 false-positive and 6 false-negative. The sensitivity, specificity and accuracy were 68 %, 75 %, and 71 %, respectively.

Of 41 patients examined by spiral CT, 22 had lymph node involvement. Spiral CT showed 17 patients had regional lymph node metastasis in 22 positive patients. In 19 patients without lymph node involvement, spiral CT diagnosed 15 patients correctly. There were 4 false-positive and 5 false-negative.

The sensitivity, specificity and accuracy were 77 %, 79 %, and 78 %, respectively.

Among 45 patients examined by MRI, 26 had lymph node involvement. MRI showed 16 had regional lymph node metastasis in 26 positive patients. In 19 patients without lymph node involvement, MRI diagnosed 13 patients correctly. There were 6 false-positive and 10 false-negative. The sensitivity, specificity and accuracy were 62 %, 68 %, and 64 %, respectively.

Table 2 Accuracy of N classification in esophageal cancers: MPS, spiral CT, MRI compared to histopathologic staging

Histopathology	n	Accuracy (%)		
		MPS	Spiral CT	MRI
N0	39	9/12 (75)	15/19 (79)	13/19 (68)
N1	47	13/19 (68)	17/22 (77)	16/26 (62)
Total	86	22/31 (71)	32/41 (78)	29/45 (64)

DISCUSSION

It was reported that accuracy rates of EUS were approximately 52-92 % in the assessment of the infiltration depth of esophageal cancer^[33-39]. In our study, the overall accuracy of T staging was 84 %. We think that the high resolution of MPS contributes the good results, 12MHz translator made it possible to differentiate esophageal histological structures and delineate the entire margins of tumors, especially in the superficial esophageal cancer. The penetration depth of good resolution ultrasound was about 6-8 cm, which could clearly visualize the tumor and the adjacent organs^[40]. In some reports, T1 tumors were often overstaged as T2 because of the resultant obliteration of the submucosa and the muscularis propria^[33]. Although one study reported no benefit of miniprbes in esophageal cancers^[41], Menzel *et al* carefully compared the effects of higher frequency miniprbes with conventional probes and concluded that MPS had a higher accuracy for T staging and similar accuracy for N staging in esophageal tumors^[42]. Akahoshi *et al* also demonstrated the benefit of MPS in early gastric cancers^[43]. In this series, 4 T1 tumors (including one superficial mucosal carcinoma) were all correctly diagnosed because the tact border of muscularis propria was clearly visualized. In T2 tumor, the accuracy was 71 %. One T2 tumor was overstaged as T3 because the inflammation and fibrosis were mistakenly interpreted as tumor extension through the muscularis propria. Another T2 tumor was understaged because the microscopic invasion beyond the submucosa was not discerned. For T3 tumors, only one was understaged due to inexperience. The tumor was larger and the invasion outside the muscularis propria was interpreted as an irregular outer margin of the muscularis propria. In T4 stage, two tumors were understaged because the adjacent malignant stricture (tracheal or bronchial invasion) was not discerned in a limited field of view. We thought that endosonographic wall penetration was a critical factor. Richards *et al* also observed that ultrasound attenuation was a commonest reason which led to the error of diagnosis in the advanced tumor^[44], in particular in stenotic tumors^[45]. In addition, artifacts due to oblique scanning may also give rise to misrepresentation of the true depth of penetration, which was another deficient of MPS.

CT or MRI has been widely used in staging tumors of the upper intestinal tract. However, their diagnostic accuracy in evaluating esophageal carcinoma is controversial. Both of them have the same limitations, i.e. unable to discriminate the layer of the esophageal wall and to detect tumor spread through the muscular wall into adjacent tissues^[32]. Evaluation of direct invasion by CT or MRI is based on two criteria: mass effect

and loss of fat planes. When the trachea or bronchial wall is indented or displaced away by a tumor mass, the mass effect is present and invasion is presumed. The loss of fat plane between tumor and adjacent tissues is commonly used to predict aortic and pericardial invasion. According to the reports, the accuracy of CT or MRI in staging the local tumor infiltration ranged from 45 % to 73 %^[46-51]. Quint *et al* compared MRI with CT in the staging of esophageal tumors^[52]. In 12 patients evaluated, they found that both CT and MRI were 100 % accurate in prediction of tracheobronchial invasion with an accuracy rate of 75 % for aortic invasion and 88 % for pericardial invasion. In a late review, Kelly *et al* reported that the sensitivity of CT ranged from 40 % to 80 % and the specificity from 14 % to 97 %^[30]. In present study, the sensitivity of the three modalities ranged from 40 % to 82 % and the specificity from 63 % to 85 %. Three patients misdiagnosed by spiral CT and five patients by MRI were staged correctly by MPS, especially in T1-T2 tumors, which demonstrated the superiority of MPS. Spiral CT is an inspiring new technique. Our primary data showed that spiral CT was not optimistic, although spiral CT had a higher accuracy than MRI, no significant difference was found ($P>0.05$). MPS appeared more accurate (84 %) than spiral CT or MRI (68 % or 60 %, respectively, $P<0.05$). Although strictly blinded approach was not taken in this study, our results continue to support the hypothesis that endosonography is superior to CT or MRI in the T staging of esophageal cancer^[53-55].

MPS can only visualize lymph nodes close to the esophageal wall whereas CT and MRI can demonstrate both regional and distant lymph node metastases. For MPS, the differentiation of malignant lymph nodes from benign nodes could be made according to its size, distance from tumor and echo features. The round hypoechoic lymph nodes with a smoothly demarcated border and size greater than 5 mm had the greatest probability of malignancy^[56]. Murata *et al*^[57] used MPS to evaluate lymph nodes in different periesophageal areas and the accuracy being 88 %. Other reported that the accuracy of EUS ranged from 68 % to 92 %^[29,58-60]. In this study, the overall accuracy of MPS for diagnosing the N category was 71 %, with a sensitivity of 75 % and a specificity of 68 %. Our results were consistent with these reports.

We think that the lack of reliable criteria in N staging may be the main reason of low accuracy for MPS. The judging value of node size is still controversial. Some authors reported that nodes larger than 5 mm were not inflammatory in the resection specimens^[33, 61-64]. Tio *et al* thought that enlarged lymph nodes were not necessarily cancerous and small nodes might be involved by tumors^[33]. We also observed that lymph nodes larger than 5 mm were inflammatory by pathological examination^[28]. However, we believed that nodes greater than 10 mm, especially close to the primary tumor, rounder, darker, and more homogeneous had much more possibility of malignancy^[20]. In addition, the morphology of tumors would also be another important factor affecting these results.

Holscher *et al*^[65] thought that MPS was more accurate than CT or MRI in the diagnosis of lymph node metastases. Tio *et al*^[33], however, pointed out that CT was superior to EUS for evaluating celiac lymph nodes due to nontraversable stenoses. In this series, the accuracy of spiral CT (78 %) was higher than that of MPS or MRI (68 %, 64 %, respectively), but without significant difference ($P>0.05$). The cause was not clear. We think that methodologies of study designs are related to these results, because different assessment conditions, such as technical parameters, anatomical location of tumors and patient characteristics could lead to different results^[66]. For example, stenotic tumors were not included or accounted for different percentages in some studies^[65]. Hordijk *et al* assessed the influence of tumor stenosis on T staging accuracy of

miniprbes. A lower accuracy (46 %) was obtained with stenotic tumors than those with nontraversable tumors (82 %). They postulated that the main reason lay in the short focal distance between the ultrasonic transducer and tumor hampered clear visualization of the wall layers and tumor penetration depth^[45]. On the other hand, Kallimanis *et al*^[66] reported that the degree of esophageal stenosis was an important criteria for lymph node involvement. Brugge *et al* pointed out that T3 and T4 tumors were significantly thicker than T1 and T2 tumors^[67]. In our previous reports, about half of severe stenotic tumors were T3 and the other half T4^[18]. Tio *et al* indicated that the incidence of positive lymph nodes in the advanced tumors (T3/T4) was higher than the intramural tumors (T1/T2)^[33]. In this study, 23 (27 %) patients had stenotic tumors, in whom 10 patients had T3 and 13 had T4 and all had the lymph node involvement. No one had T2 or T1 stage. In other words, stenotic tumors had more possibilities of advanced stage and lymph node metastasis^[18, 68-72]. Our results strongly supported Brugge's view^[67]. However, in 12 stenotic tumors examined by MPS, only 5 (42 %) were correctly diagnosed. In another 10 stenotic tumors, 5 (5/6) were correctly diagnosed by Spiral CT and 3(3/4) by MRI. Spiral CT and MRI appeared more accurate than MPS in stenotic tumors^[30,71].

In clinical practice, two methods are commonly used to improve the accuracy of diagnosis. One is the use of contrast material, such as Ultravist on spiral CT or Gd-TDPA on MR imaging. Enhanced imaging can provide useful information of the blood supply of the lesions, which is helpful to distinguishing the malignant from the benign mass. The other one is the regulation of the section thickness. A section gap of 1-2 mm can help discover micro-lesions. However, Gd-DTPA has several disadvantages, such as non-specific distribution and slightly nephrotic toxicity^[73]. To develop new tissue-specific contrast material would further improve the accuracy of spiral CT and MRI in TNM staging of gastroesophageal carcinoma. In addition, it should be taken into consideration that in our study the MR equipment was of (first generation), which was also a reason for its low accuracy.

We think that the experience is an important factor to improve the accuracy of diagnosis^[28]. Some problems such as the lack of training facilities, EUS courses and EUS laboratories limit the wider use of MPS. No atlas of endosonography for different diseases has been published in the world so far. The interpretation of endosonographic images is dependent on the ultrasound knowledge or the results of animal experiments. The lack of experience in transabdominal ultrasonography hinders the reasonable interpretation for some complex image patterns. The ultrasound images are also unsteady. We observed that the esophageal wall can be visualized as a five-layer structure, but sometimes as a three-layer structure^[28]. Other authors also reported the similar results^[35,57]. The reason remains to be demonstrated. Many hospitals diagnosed the disease in cooperation between endoscopists and ultrasoundists. In addition, many surgeons have still doubted the role of endosonography. They would rather believe the results of spiral CT or MRI. In fact, CT or MRI plays an increasing role in ruling out the intra-abdominal metastasis so as to avoid unnecessary surgery^[74]. We also think it unnecessary to make MPS examination for those patients who have lost the operation chance. To our knowledge, surgeons in our hospital make the therapeutic plans for the patients with advanced tumors mainly relying on the results of spiral CT or MRI. As a matter of contrast, they select the surgical procedures for the patients with stage T1 and T2 much more depending on the results of MPS. As a matter of fact, MPS appears superior to CT or MRI mainly in staging early tumors and the latter have much higher accuracy in determining the presence or extent of more distant metastases. A combination of endoscopic ultrasound including

computer-assisted analysis and spiral CT or MRI are expected to provide a higher TNM accuracy^[75].

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