Usefulness of endoscopic ultrasonography (EUS) in diagnosing esophageal infiltration of thyroid cancer

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ABSTRACT. Pre-operative evaluation of esophageal infiltration is sometimes difficult in patients with advanced thyroid cancer even with recent imaging modalities. We evaluated the accuracy of endoscopic ultrasonography (EUS) in diagnosing esophageal infiltration of thyroid cancer. Twenty-nine patients with advanced thyroid cancer underwent EUS and other imaging examinations before surgery. The diagnostic accuracy of EUS was compared with that of magnetic resonance imaging (MRI) and esophagography based on pathologic findings in 27 of the 29 cases. EUS clearly demonstrated the 5-layer structure of the esophageal wall. EUS detected cancer invasion into the *muscularis propria* of the esophagus correctly in 8 of 10 patients diagnosed pathologically with muscular infiltration. EUS was significantly more accurate than MRI and esophagography (88.9% *vs* 63.0% and 66.7%, respectively). The specificity of EUS was also significantly better than the specificities of MRI or esophagography (94.1% *vs* 58.8% and 64.7%, respectively). The sensitivity, positive predictive value and negative predictive value of EUS tended to be better than those of MRI and esophagography. EUS is useful in evaluating the esophageal infiltration of thyroid cancer. This method has the further advantage of detecting the exact depth of cancer invasion into the esophageal wall.

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INTRODUCTION

In general, patients with thyroid cancer have an excellent prognosis, and excised differentiated thyroid cancers have decreased in size over the last few decades (1). However, advanced cancer still exists, though at a relatively low rate. Patients in whom the thyroid cancer has invaded adjacent tissue have a poor prognosis (2-4). Surgery with a curative intent improves the prognosis of patients with advanced thyroid cancer (5-7). It is important to know the precise local spread of the cancer in planning a successful surgical strategy. There are some imaging methods available for evaluation of esophageal infiltration. Although conventional computed tomography (CT), magnetic resonance imaging (MRI), esophagography, and esophagoscopy are able to detect esophageal invasion, these modalities are insufficient for a precise diagnosis and determination of the exact depth of invasion. The depth of cancer invasion is often clarified for the first time in surgery.

Endoscopic ultrasonography (EUS) has been used successfully for diagnosing depth or extension of gastrointestinal cancers (8-12), and its accuracy in the evaluation of esophageal cancer infiltration is greater than 80% (8, 9, 11). EUS is also useful in diagnosing pancreatic or biliary tract disease (13-15). In such cases, EUS examination is performed via the gastric or duodenal wall to detect the pancreas or biliary tract tumor and invasion into surrounding organs. Nakaizumi *et al*. showed EUS is more accurate than transabdominal ultrasonography (US) or CT in detecting pancreas cancer invasion into the blood vessels and stomach (16). Mukai *et al.* showed the usefulness of EUS in detecting invasion of extrahepatic bile duct cancer to adjacent tissue (17).

Since the thyroid is near the esophagus, the gland can be detected by EUS through the esophageal wall. There has been no report concerning the use of EUS for pre-operative examination of thyroid cancer other than our reported preliminary findings in 5 cases (18). In the present study, we evaluated the utility of EUS in diagnosing esophageal infiltration of thyroid cancer by comparing it with other imaging examination methods.

Key-words: Endoscopic ultrasonography, thyroid cancer, esophageal invasion.

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PATIENTS AND METHODS

Patients

Three hundred and eighty-one patients with thyroid cancer were treated at our institution between December 1998 and November 1999. Of the 381 patients, 29 with advanced thyroid cancer and suspected esophageal infiltration based on other imaging findings were evaluated by EUS before surgery. Two were excluded from the present study since they underwent only reduction surgery because of severe local invasion of the cancer. Thus, 27 patients (6 men and 21 women) were included as subjects for this study. The median age of these study patients was 66 years; the range was 35 to 82 years. The chief complaints were swelling or tumor of the neck (18 cases) and hoarseness (5 cases). No patient showed dysphagia or dyspnea. Seven had recurrent nerve paralysis. All 27 patients underwent thyroidectomy and lymph node dissection with a curative intent. Ten of the 27 showed invasion into the *muscularis propria* of the esophagus. There was no case of esophageal infiltration beyond the submucosal layer. Four of the 7 patients with recurrent nerve paralysis had esophageal infiltration; 4 of the 7 patients with tracheal invasion had simultaneous esophageal infiltration. The mean maximum tumor diameter was 38.6 mm, the range being 12 to 98 mm. Histology revealed papillary carcinoma in 23 patients, follicular carcinoma in 3, and carcinoma showing thymus-like differentiation (CASTLE) in 1 (19).

Imaging examinations

We generally use conventional US, MRI, and ^{201}Tl scintigraphy to examine thyroid cancer. When physical findings and/or MRI imaging suggest esophageal infiltration, esophagography and esophagoscopy are performed. EUS was performed in this series as a further examination when esophageal infiltration was suspected based on other imaging findings but mucosal infiltration was not detected esophagoscopically. The diagnostic criterion for esophageal infiltration based on MRI is lack of a clear border between the tumor and the esophagus. The criterion for esophageal infiltration based on esophagography is irregular compression of the esophagus.

EUS procedure

EUS was carried out via the balloon contact method at frequencies of 7.5 and 20 MHz (GFIUMQ200, radial type, Olympus Co. Ltd., Tokyo, Japan) (18). Preparation is the same as that for gastrofiberscopy, with adequate sedation. In the normal esophageal wall, 5 layers were recognized by EUS at 20 MHz (Fig. 1) (20). When continuity of any layer of the esophageal wall was interrupted by the tumor or the border between the layer and the tumor became unclear, esophageal invasion into the layer was considered positive. Since *adventitia* is not a membraneous structure but a loose connective tissue, respective esophageal infiltration means cancer invasion beyond the *muscularis propria*.

Statistical analysis

EUS findings were compared with those of MRI and esophagography in light of histopathologic findings, and differences were analyzed by χ^2 test. A p value <0.05 was considered significant.

RESULTS

At frequencies of 7.5 MHz, EUS showed structures adjacent to the esophagus, the vertebrae, trachea, common carotid artery, internal jugular vein, sternocleidomastoid muscle, and both lobes of the thyroid (Fig. 2). A frequency of 20 MHz showed the esophageal wall in detail (Fig. 1). In most cases, EUS detected all 5 layers of the esophageal wall, but in a few cases, only 3 layers were detected. In such cases, the hypo-echoic second layer was considered to be the *muscularis propria*. The cancers in all cases were detected by EUS as hypo-echoic or

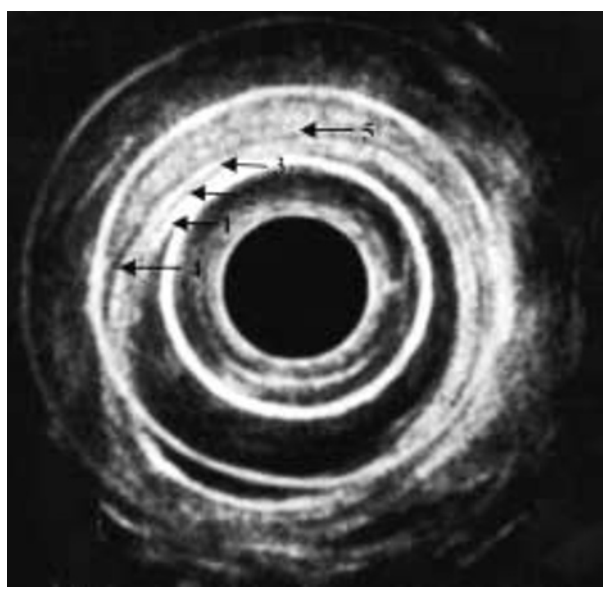

Fig. 1 - *Endoscopic ultrasonography (EUS, 20 MHz) showing the five-layered structure of the normal esophageal wall. 1-2) mucosa (hyper-echoic and hypo-echoic layers); 3) submucosa (hyper-echoic layer); 4)* muscularis propria *(hypo-echoic layer); 5)* adventitia *(hyper-echoic layer).*

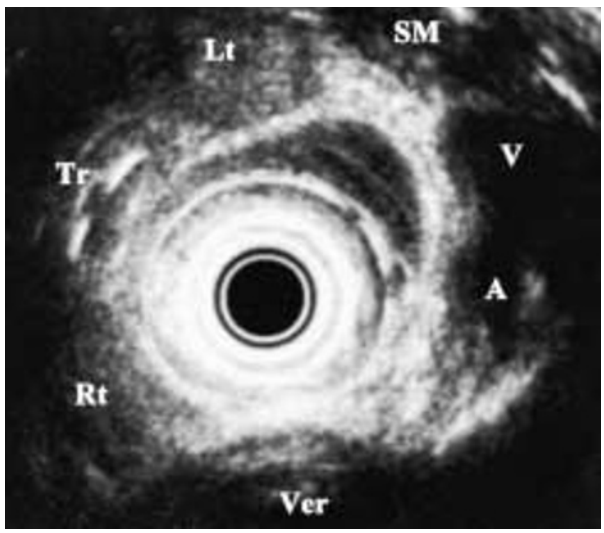

Fig. 2 - *Endoscopic ultrasonography (EUS, 7.5 MHz) showing structures adjacent to the esophagus. Ver: vertebra; Tr: trachea; A: common carotid artery; V: internal jugular vein; SM: sternocleidomastoid muscle; Rt: right lobe of the thyroid; Lt: left lobe of the thyroid.*

iso-echoic irregular masses. In some cases, the tumor showed cystic parts or small calcifications, as with conventional US. In 9 patients, EUS demonstrated cancer invasion into the fourth layer of the esophagus (muscularis propria), and 8 of these patients demonstrated muscular invasion pathologically. EUS showed no esophageal infiltration in 18 patients. Sixteen of these patients had no esophageal infiltration, but muscular invasion was detected pathologically in 2. No patient demonstrated esophageal invasion beyond the submucosa based on both EUS and pathologic findings. In 8 cases in which MRI or esophagography indicated esophageal infiltration, EUS revealed no invasion, a finding that was matched surgically and pathologically. The accuracies of EUS, MRI, and esophagography in demonstrating esophageal infiltration in light of the pathologic findings are shown in Table 1. The accuracy of EUS (88.9%) was significantly better than that of MRI (63.0%) and esophagography (66.7%) (EUS *vs* MRI, p=0.026, and EUS *vs* esophagography, p=0.049). The specificity of EUS (94.1%) was significantly better than that of MRI (58.8%) and esophagography (64.7%) (EUS *vs* MRI, p=0.015, and EUS *vs* esophagography, p=0.034, respectively). The sensitivity, positive predictive value, and negative predictive value of EUS were better than those of MRI and esophagography but not significantly.

A typical esophageal infiltration of papillary thyroid carcinoma is shown in Figure 3. In this case, both MRI and esophagography indicated esophageal infiltration (Fig. 3, A). EUS showed a mass in the left thyroid lobe (Fig. 3B) and discontinuity of the fourth layer of the esophagus close to the tumor (Fig. 3C). Paratracheal lymph node metastasis was also detected by EUS (Fig. 3D). During surgery, we observed cancer invasion into the esophageal muscle and performed thyroidectomy with modified radical neck dissection and partial resection of the esophageal muscle, preserving the mucosa. Massive infiltration of papillary carcinoma into the muscularis propria was confirmed in the pathologic specimen (Fig. 3E and F). The surgical margin was microscopically cancer-free. This patient started oral intake of food the day after surgery, and the postoperative course was uneventful.

An esophageal infiltration detected only by EUS is shown in Figure 4. Although MRI and esophagography showed no esophageal infiltration of papillary thyroid carcinoma in the right lobe (Fig. 4A), EUS demonstrated an absence of continuity of the fourth layer (Fig. 4B). Partial resection of the esophageal muscle was performed. The pathologic specimen showed papillary carcinoma invasion into the muscularis propria (Fig. 4C).

A tumor without esophageal infiltration is shown in

Table 1 - *Diagnostic accuracy of endoscopic ultrasonography (EUS), magnetic resonance imaging (MRI), and esophagography for esophageal infiltration of thyroid carcinoma.*

	EUS	MRI	Esophagography
Accuracy	88.9% (24/27)*,**	63.0% (17/27)	66.7% (18/27)
Sensitivity	80.0% (8/10)	70.0% (7/10)	70.0% (7/10)
Specificity	94.1% (16/17)°,°°	58.8% (10/17)	64.7% (11/17)
Positive predictive value	88.9% (8/9)	50.0% (7/14)	53.8% (7/13)
Negative predictive value	88.9% (16/18)	76.9% (10/13)	78.6% (11/14)

*p=0.026 between EUS and MRI; **p=0.049 between EUS and esophagography; °p=0.015 between EUS and MRI; °°p=0.034 between EUS and esophagography.

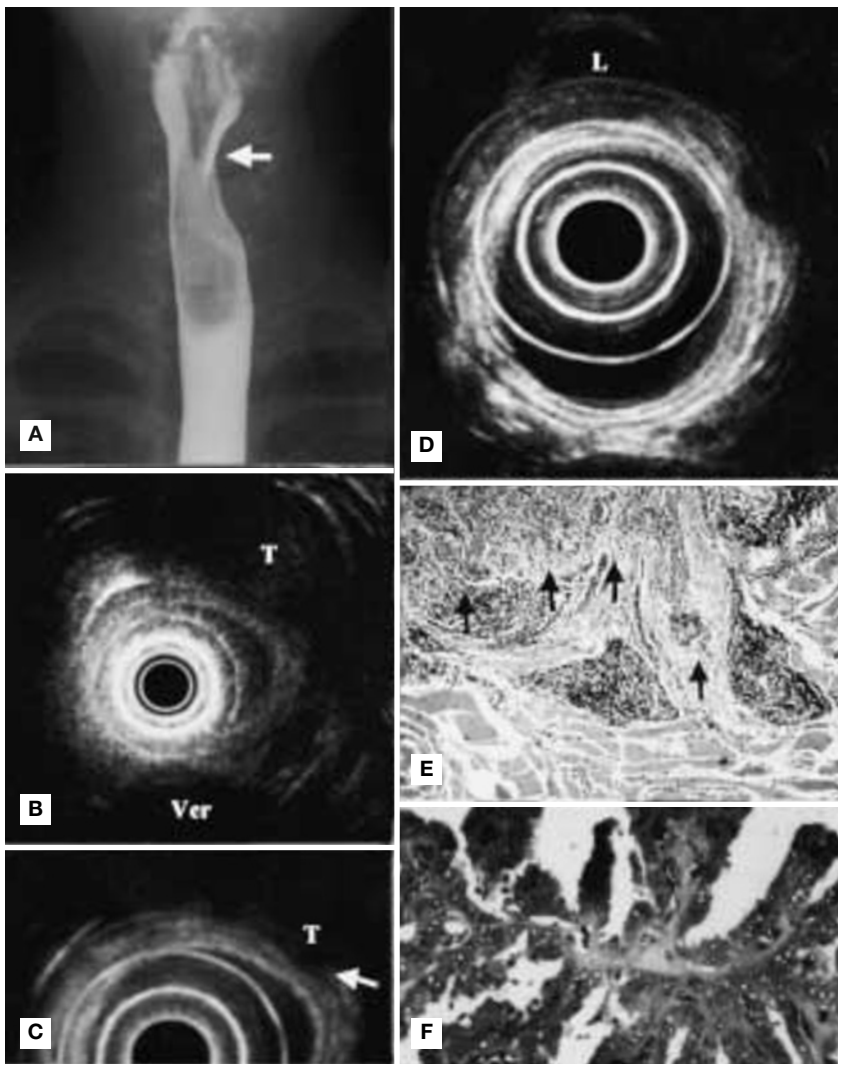

Fig. 3 - *A) Esophagography revealing irregular compression (arrow). B) Endoscopic ultrasonography (EUS, 7.5 MHz) showing a hypo-echoic tumor of the thyroid left lobe (T) and vertebrae (Ver). C), EUS (20 MHz) showing discontinuity of the fourth layer (arrow) by thyroid cancer infiltration (T). D) EUS (20 MHz) showing a metastatic paratracheal lymph node (L). E)* Muscularis propria *of the esophagus invaded by papillary carcinoma demonstrated in a predominantly solid pattern (arrow). F) Branching configuration of the papillae in the well-differentiated part of the papillary carcinoma.*

Figure 5. Cancer infiltration was suspected in the esophagus based on MRI and esophagography (Fig. 5A). EUS showed normal continuity of all layers of the esophagus (Fig. 5B). No esophageal infiltration of follicular carcinoma was noted during surgery or pathologically (Fig. 5C).

DISCUSSION

In spite of recent advances in imaging modalities, determining the exact depth of thyroid cancer invasion into the esophagus remains difficult. EUS is a safe and established diagnostic tool used for diseases of the digestive system. We used this technique to assess the esophageal spread of thyroid cancer and found the results to be satisfactory.

We used a frequency of 7.5 MHz for detecting tumors and adjacent organs such as vertebrae and trachea. Because 20 MHz has a higher resolution than 7.5 MHz, we used 20 MHz to distinguish the layers of the esophagus. Since 20 MHz showed only the esophageal wall, it was important to confirm the tumor at 7.5 MHz. With EUS, we were able to confirm the tumor in all cases as an irregular hypo-echoic or iso-echoic mass. Referring to the EUS features of pancreas or biliary duct cancer invasion into surrounding structures (16, 17), we considered the diagnostic criteria of esophageal infiltration for EUS to be discontinuity of the esophageal layer adjacent to the tumor or an unclear border between the tumor and the esophageal layer (18).

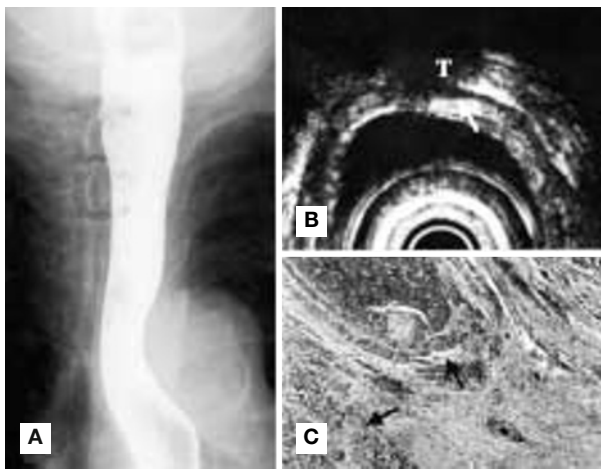

Fig. 4 - *A) Esophagography revealing no change in the esophagus. B) Endoscopic ultrasonography (EUS, 20 MHz) showing interruption of the fourth layer (arrow) by thyroid cancer (T). C)* Muscularis propria *of the esophagus invaded by papillary carcinoma demonstrating a follicular pattern (arrow).*

We performed EUS in 7.6% of thyroid cancer patients who underwent surgery during the study period. There were 211 patients with tumors larger than 10 mm who did not undergo EUS. The median age of these patients was 53 years, and the mean maximum tumor diameter was 20.2 mm. The patients examined by EUS were significantly older and had larger tumors than the patients who did not undergo EUS. Thyroid cancer with suspected esophageal infiltration is usually advanced. Not all patients with thyroid cancer require EUS. At the present time, we consider physical, CT, MRI, or esophagography findings of esophageal infiltration to be an indication for EUS study. Absence of mucosal invasion should be confirmed by esophagoscopy before EUS study.

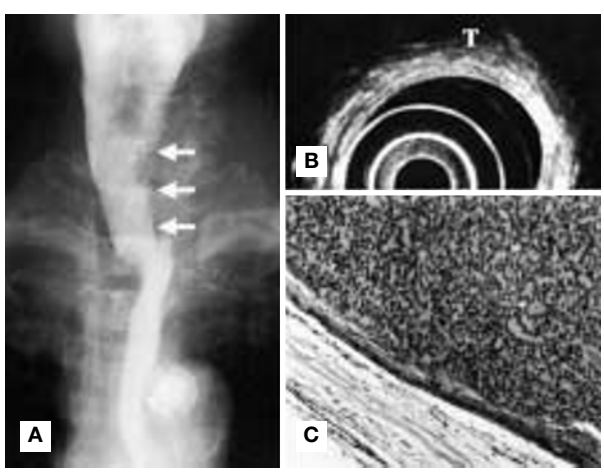

Fig. 5 - *A) Esophagography revealing irregular compression (arrow). B) Endoscopic ultrasonography (EUS, 20 MHz) showing the esophageal wall layers close to the tumor to be intact (T). C) No capsular invasion of follicular carcinoma close to the esophagus was observed.*

In the present series, EUS showed greater accuracy for detection of cancer invasion into the esophagus than did MRI or esophagography. In cases where EUS detected muscular infiltration with an intact submucosal layer, we were able to perform thyroidectomy with partial resection of the esophageal muscle, confidently leaving the mucosal layer. There were no instances of thyroid cancer showing esophageal infiltration beyond the submucosa. However, if thyroid cancer were to invade the submucosal layer, EUS could detect the exact depth of invasion.

EUS had a higher specificity than MRI or esophagography. Although there were 8 false positive MRI or esophagography findings, EUS correctly revealed no invasion. In such cases, knowing the exact depth of cancer invasion before surgery, we were able to avoid unnecessary esophageal resection. There were 2 false negative EUS findings. One was an absence of the fifth layer and tumor adjacent to the fourth layer. Since the fourth layer was clear and showed no irregularity, we assumed there was no muscular infiltration. MRI and esophago-graphy also failed to show esophageal infiltration. Surgical and pathologic findings revealed superficial infiltration of cancer cells into the muscularis propria. In the second false negative case, MRI indicated esophageal infiltration, but esophagography detected no infiltration. Surgical and pathological findings showed a small area of infiltration into the muscularis propria. Detecting cancer infiltration into superficial or small areas of the muscularis propria by EUS remains difficult. EUS findings were false positive in 1 case; MRI and esophago-graphy also revealed esophageal infiltration. Since the tumor was in the upper part of the thyroid gland near the cricoid cartilage and the pharynx, we had to place an EUS balloon close to the entrance of the esophagus. The false finding could have been due to the difficulty in performing EUS because of the swallowing reflex.

In conclusion, the diagnostic accuracy of EUS exceeded that of MRI and esophagography. EUS is useful in evaluating esophageal infiltration, and a distinctive and important feature of EUS is its ability to detect the exact depth of cancer invasion into the esophagus.

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