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# Endoscopic Ultrasound-Guided Fine Needle Aspiration in Hollow Viscus Cancer

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Accurate cancer staging is essential in patients with hollow viscus malignancy to decide therapeutic modalities. Endoscopic ultrasound (EUS) is considered as the best modality for local staging of hollow viscus cancer. EUS-guided fine needle aspiration (FNA) is a minimally invasive and effective sampling method. EUS-FNA should be applied when positive diagnosis of malignancy can possibly change the choice of therapeutic options. EUS in conjunction with EUS-FNA can optimize stage-directed therapy which is helpful in selecting minimally invasive treatment option including endoscopic treatment and avoiding unnecessary surgery in advanced cases.

**Key Words:** Endosonography; Fine needle biopsy; Staging; Neoplasms

## INTRODUCTION

Accurate diagnosis of tumor, node, metastasis (TNM) staging and stage-based therapy is essential for the management of hollow viscus malignancy. Endoscopic ultrasound (EUS) is the best modality for the delineation of gut wall layers and adjacent structures.<sup>1</sup> For that reason, EUS is well utilized for the evaluation of invasion depth of hollow viscus cancer (T staging). In addition, EUS-guided fine needle aspiration (EUS-FNA) is a minimally invasive, highly accurate, and safe procedure for the diagnosis of lymph node (LN) metastasis (N staging). EUS in combination with EUS-FNA has been already proved for its uncountable value on patient management with hollow viscus cancer.<sup>2</sup>

Guiding role of EUS, especially of EUS-FNA, on the process of selecting treatment strategy for esophageal, gastric and rectal cancers are reviewed in this paper.

## EUS AND EUS-FNA IN ESOPHAGEAL CANCER

Currently, EUS is considered to be the most accurate loco-regional staging technique for patients with esophageal cancer. The diagnostic sensitivities of EUS in esophageal T staging and N staging were reported as 85% to 95% and 70% to 80%, respectively, which are superior to those of computed tomography (CT).<sup>3</sup> When performed before treatment, EUS T staging is not only a guide for therapy but also a good prognostic tool and a predictive measure to determine whether complete resection would be feasible.<sup>4</sup>

EUS and EUS-FNA have important position in esophageal cancer staging. In fact, they may reveal an advanced stage cancer and perhaps enable physicians to change the treatment plan to avoid unnecessary surgery. A study aimed at demonstrating the impact of EUS on the esophageal cancer staging and finally on patient management and survival has demonstrated over 24% to 29% of change in patient management strategies after the EUS staging.<sup>5</sup> Another study estimated the occurrence of management change after the EUS and EUS-FNA in patients with esophageal cancer to find similar results. While the initial management recommendations were based on history, physical examination, upper endoscopy, and CT scan results, EUS prompted a change of management in 24% (95% confidence interval [CI], 12% to 36%) of the studied cases. Findings from EUS-FNA have changed the manage-

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ment strategy an additional 8% (95% CI, 6% to 15%) of the cases.<sup>6</sup> It was shown, in another study, that EUS-FNA has altered the management strategy in as high as 67% of patients.<sup>7</sup> Addition of EUS-FNA to EUS is generally recommended when the histopathologic result of EUS-FNA can influence the diagnosis or choice of therapeutic options. In a study, EUS-FNA was performed in cases where abdominal ultrasound or CT guided biopsy was not capable of providing definite diagnosis. EUS-FNA was also used when metastatic lesion was suspected during EUS and malignant finding of biopsy could possibly change the subsequent treatment options. EUS-FNA had clinical impact in 14 out of 108 patients (13%).<sup>8</sup> EUS with EUS-FNA may reduce the total expenses of esophageal cancer patients in advanced stage by preventing unnecessary surgery. When 60 consecutive patients with esophageal cancer were examined with EUS, the accuracies of EUS with EUS-FNA in T and N staging were 83% and 89%, respectively. This study suggested EUS guided therapy can potentially decrease the cost of care by \$740,424 (\$12,340/patient) by reducing the number of thoracotomies.<sup>9</sup>

The 7th edition of American Joint Committee on Cancer (AJCC) TNM Staging System was released recently.<sup>10</sup> There are several changes in the new edition on the staging of esophageal cancer. T4 is subdivided into T4A (resectable cancer invasion) and T4B (unresectable cancer invasion). N is subclassified based on the number of positive regional LNs (N1, 1 to 2 nodes; N2, 3 to 6 nodes; N3,  $\geq 7$  nodes). M staging is redefined based on the presence of distant metastasis, and the term nonregional LN is eliminated. As a result, celiac axis LN metastasis, which was regarded as M1a stage previously, is now scored as a regional nodal disease. This change may reduce the value of EUS-FNA in the management of esophageal cancer patients with celiac axis LN metastasis which was not detected by CT but only by EUS. Nevertheless, poor prognosis of such cases still preserves diagnostic usefulness of EUS-FNA.

In conclusion, EUS is recommended in all cases with potentially curable esophageal cancer diagnosed with helical CT. Also EUS-FNA should be recommended for suspicious nodes as required to optimize treatment strategy and to assess prognosis.

## EUS AND EUS-FNA IN GASTRIC CANCER

A meta-analysis reported that pooled sensitivities of EUS for staging of gastric T1, T2, T3, T4, N1, and N2 cancers were 88.1%, 82.3%, 89.7%, 99.2%, 58.2%, and 64.9%, respectively. These results suggest that EUS is highly accurate in gastric TNM staging, especially of advanced stage.<sup>11</sup> In a study comparing helical CT and EUS for preoperative diagnosis of gas-

tric cancer, accuracies of CT in T and N staging were 76% and 70%, respectively. In comparison, EUS provided accuracies of 86% and 90% in T and N staging, respectively, in another study.<sup>12</sup> We should keep in mind, however, that the presence of ulcer, fibrosis, inflammation and microinvasion can cause over-staging or under-staging with EUS. Over-staging of T2 cancer is usually considered as a major problem of gastric cancer staging by EUS. These misdiagnoses may cause incorrect assignment to neoadjuvant treatments. In addition, because a cancer located in the upper third of the stomach, with depressed morphology and the size of larger than 3 cm in diameter has a tendency of lowering diagnostic accuracy of EUS, these factors should be taken account when therapeutic options are weighed.<sup>13</sup>

Since endoscopic therapy is considered as an appropriate alternative therapeutic modality for early stage gastric cancer, the importance of EUS in superficial gastric cancer staging is attracting more attention recently. Kim et al.<sup>14</sup> reported high accuracy in diagnosing mucosal gastric cancer by using high-frequency catheter EUS, which was suitable for endoscopic submucosal dissection with 97.6% of diagnostic accuracy.

In one of the above mentioned studies,<sup>8</sup> further evaluation with EUS after abdominal US and CT staging of gastric cancer showed additional evidence of metastasis such as mediastinal or para-aortic LNs, ascites, and hepatic lesion. Clinical impact of EUS-FNA was 8% when EUS-FNA was performed for these lesions. Another study also revealed huge impact of EUS-FNA in the diagnosis of gastric cancer metastasis.<sup>15</sup> Mediastinal LNs, hepatic lesion, adrenal gland, and ascites were targeted by EUS-FNA and treatment strategy was adjusted as a result in 15% of the cases.<sup>15</sup>

One of the major revisions in the 7th edition of AJCC TNM Staging System for gastric cancer is on N staging. N is subclassified, as with the esophageal cancer, based on the number of positive regional LNs (N1, 1 to 2 nodes; N2, 3 to 6 nodes; N3,  $\geq 7$  nodes). Another notable change is that positive peritoneal cytology is classified as metastatic disease (M1). EUS could detect ascites missed by CT scan.<sup>16,17</sup> In a study, when EUS-FNA was performed for detected ascites, the sensitivity, specificity, positive predictive value and negative predictive value of EUS-FNA for diagnosing malignant ascites was 94%, 100%, 100%, and 89%, respectively.<sup>18</sup> Further studies are needed to define the clinical impact of EUS-FNA in detection of malignant ascites missed by CT.

## EUS AND EUS-FNA IN RECTAL CANCER

TNM staging guides treatment decision and is a strong prognostic tool in rectal cancers. Accurate staging and stage-based adequate selection of multidisciplinary management

options is essential to maximize the chance of cure and minimize tumor recurrence or treatment complications. As with esophageal and gastric malignancies, EUS is the method of choice in T staging of rectal cancers. According to a meta-analysis, pooled sensitivities of EUS for staging of rectal T1, T2, T3, and T4 were 87.8%, 80.5%, 96.4%, and 95.4%, respectively, and pooled specificities were 98.3%, 95.6%, 90.6%, and 98.3%, respectively.<sup>19</sup> In N staging, a meta-analysis showed pooled sensitivity of 73.2% and specificity of 75.8%.<sup>20</sup> In comparison, previous studies reported 65% to 75% and 55% to 65%, respectively for T and N staging accuracies of CT and 75% to 85% and 60% to 65%, respectively for those of magnetic resonance imaging. Identification of locally advanced stage such as T3-4N0 or TxN1-2 is important because such patients can benefit from preoperative chemoradiation therapy. High diagnostic sensitivities and specificities of EUS demonstrated by the meta-analyses strongly suggest that EUS should be considered for T and N staging of rectal cancer preoperatively.

The number of nodes involved with metastasis influences prognosis. N staging was revised in the 7th edition of AJCC TNM Staging System for colorectal cancer. N is subclassified as N1a (metastasis in 1 regional node), N1b (metastasis in 2

to 3 nodes), N2a (metastasis in 4 to 6 nodes), and N2b (metastasis in 7 or more nodes). The echo features and the size of nodes are often inadequate for differentiating between benign and metastatic nodes. EUS-FNA can add accuracy in the diagnosis of locoregional metastatic disease. When EUS-FNA was performed in 77 patients for colorectal cancer staging or for the evaluation of rectal or peri-rectal masses, sensitivity and specificity of EUS-FNA were reported as 89% and 79%, respectively.<sup>21</sup>

In addition, detection of extramesenteric LN metastases (M1 disease in the 7th edition of AJCC TNM Staging System) by EUS-FNA can affect therapeutic decisions for the rectal cancer. In a 6-year retrospective cohort study, EUS-FNA of extramesenteric LN resulted in tumor upstaging in 48% of patients with negative findings by CT. Extramesenteric LN metastases outside of standard radiation fields or total mesorectal excision resection margins were detected by EUS-FNA in 41 of 316 patients (13%) with primary rectal cancer.<sup>22</sup>

EUS-FNA also allows early detection of local recurrence. About 15% to 25% of patients experience local recurrence after the resection of rectal cancer, and majority of them are peri-anastomotic or pelvic recurrence. EUS-FNA is more sensitive than CT in diagnosing these cases. In the follow-up

**Table 1.** Accuracy of EUS with 95% Confidence Intervals for T and N Staging of Hollow Viscus Cancer

	Pooled sensitivity (%)	Pooled specificity (%)	Pooled positive likelihood ratio	Pooled negative likelihood ratio	Pooled DOR
<b>Esophageal cancer<sup>3</sup></b>					
T1	81.6 (77.8-84.9)	99.4 (99.0-99.7)	44.4 (15.5-127.4)	0.2 (0.2-0.4)	221.5 (118.5-413.9)
T2	81.4 (77.5-84.8)	96.3 (95.4-97.1)	16.6 (9.3-29.7)	0.2 (0.2-0.3)	90.7 (48.3-170.5)
T3	91.4 (89.5-93.0)	94.4 (93.1-95.5)	12.5 (7.7-20.3)	0.1 (0.1-0.2)	145.2 (90.3-233.4)
T4	92.4 (89.2-95.0)	97.4 (96.6-98.0)	25.4 (13.7-47.0)	0.1 (0.1-0.2)	250.0 (145.2-430.5)
N	84.7 (82.9-86.4) <sup>a)</sup>	84.6 (83.2-85.9) <sup>a)</sup>	3.3 (2.6-4.3) <sup>a)</sup>	0.24 (0.9-0.3) <sup>a)</sup>	19.1 (12.7-28.5) <sup>a)</sup>
	96.7 (92.4-98.9) <sup>b)</sup>	95.5 (91.0-98.2) <sup>b)</sup>	7.3 (0.9-54.3) <sup>b)</sup>	0.05 (0.01-0.64) <sup>b)</sup>	164.5 (4.5-6027.7) <sup>b)</sup>
<b>Gastric cancer<sup>11</sup></b>					
T1	88.1 (84.5-91.1)	100.0 (99.7-100.0)	90.1 (48.9-165.7)	0.17 (0.10-0.28)	605.6 (296.8-1235.6)
T2	82.3 (78.2-86.0)	95.6 (94.4-96.6)	17.3 (10.9-27.5)	0.23 (0.17-0.29)	108.6 (56.6-208.1)
T3	89.7 (87.1-92.0)	94.7 (93.3-95.9)	14.3 (10.3-19.8)	0.13 (0.08-0.19)	144.4 (95.4-218.7)
T4	99.2 (97.1-99.9)	96.7 (95.7-97.6)	19.6 (14.1-27.2)	0.07 (0.04-0.12)	507.8 (247.5-1042.1)
N1	58.2 (53.5-62.8)	87.2 (84.4-89.7)	4.1 (2.4-7.1)	0.49 (0.41-0.58)	9.5 (5.3-16.9)
N2	64.9 (60.8-68.8)	92.4 (89.9-94.4)	6.7 (4.1-10.9)	0.39 (0.31-0.49)	26.6 (13.9-50.7)
<b>Rectal cancer<sup>19,20</sup></b>					
T1	87.8 (85.3-90.0)	98.3 (97.8-98.7)	44.0 (22.7-85.5)	0.16 (0.13-0.23)	333.9 (161.4-690.4)
T2	80.5 (77.9-82.9)	95.6 (94.9-96.3)	17.3 (11.9-24.9)	0.22 (0.17-0.29)	92.1 (64.2-132.2)
T3	96.4 (95.4-97.2)	90.6 (89.5-91.7)	8.9 (6.8-11.8)	0.06 (0.04-0.09)	204.9 (124.9-336.6)
T4	95.4 (92.4-97.5)	98.3 (97.8-98.7)	37.6 (19.9-71.0)	0.14 (0.09-0.23)	367.6 (170.9-790.6)
N	73.2 (70.6-75.6)	75.8 (73.5-78.0)	2.84 (2.16-3.72)	0.42 (0.33-0.52)	7.9 (5.3-11.7)

DOR, diagnostic odds ratio.

<sup>a)</sup>Results of endoscopic ultrasound alone; <sup>b)</sup>Results of endoscopic ultrasound with fine needle aspiration.

of post-operative rectal cancer patients, findings from EUS-FNA had a considerable impact on the management in 26% of patients.<sup>23</sup>

## CONCLUSIONS

EUS is one of the powerful methods to observe gastrointestinal wall layers and LNs in its vicinity. Staging with EUS in combination with EUS-FNA, if necessary, is essential for patients with hollow viscus malignancy in deciding therapeutic modalities. Reported diagnostic accuracy of EUS in the staging of hollow viscus cancer is summarized in Table 1. EUS-FNA is a minimally invasive and effective sampling method. EUS-FNA should be applied when positive diagnosis of malignancy can possibly change the choice of therapeutic options. Many studies have been performed to evaluate the clinical impact of EUS-FNA in patient with hollow viscus cancer. The researchers demonstrated the importance of EUS-FNA on confirming metastasis in patient with hollow viscus malignancy. Frequent targets included mediastinal LNs, left hepatic lobe, adrenal gland and ascites. In summary, EUS and EUS-FNA have important roles in clinical settings, especially for hollow viscus malignancy, with their ability to obtain cytologic or histologic materials to avoid unnecessary surgeries. EUS-FNA should be performed when the cytopathological or histopathological results can influence the diagnosis or therapeutic strategy.

## Conflicts of Interest

The author has no financial conflicts of interest.

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