State of the art review 2005-2006:
EUS in esophago-gastric disease

Jan-Werner Poley
Erasmus MC, Rotterdam, the Netherlands
Introduction

• esophageal cancer (EC) and EUS
  – staging accuracy
  – restaging after neo-adjuvant treatment
  – impact on patient management
  – quality

• gastric cancer
EUS & esophago-gastric disease 2005-2006

• EC & EGJ cancer
  – approximately 40 papers published
  – 8 reviews
  – majority original contributions
number of papers on EC & EUS
T3- and T3+?


- **hypothesis:** the extent of invasion beyond the proper muscle layer is predictive of survival and tumor recurrence
T3- and T3+?

- retrospective analysis of 39 patients with T3 N1 disease (out of 165 patients with EC)
- all patients underwent surgery after neoadjuvant chemoradiation
- n=17 had “minimally invasive disease” (extent beyond MP < 3 mm) vs n= 22 with advanced disease
- no difference in either mortality or recurrence-free survival
nodes & survival (Clin Gastro Hep 2006)

Influence of the Number of Malignant Regional Lymph Nodes Detected by Endoscopic Ultrasonography on Survival Stratification in Esophageal Adenocarcinoma

JAIME CHEN,* RONGHUI XU,† GORDON C. HUNT,* MARY LEE KRINSKY,*.§ and THOMAS J. SAVIDES*  

**background**: surgical data suggest relationship between number of malignant lymph nodes and survival in EC, it is not known whether this relationship holds true when staging with pre-operative EUS
nodes & survival

- retrospective analysis of 85 patients with esophageal adenocarcinoma without obvious distant metastases
- no routine dilation in stenotic tumors
- classification (0, 1 – 2, or more than 2) of malignant appearing lymph nodes based on morphology
- no routine use of FNA
Figure 1. Kaplan-Meier curve showing survival for esophageal adenocarcinoma based on the number of malignant-appearing periesophageal lymph nodes (LM) detected by EUS.
nodes & survival

- Survival also correlated with U-TNM classification, malignant appearing celiac nodes and tumor length (cut-off 2.9 cm).

- The TNM classification should be modified to accommodate for the number of malignant lymph nodes in EC.
Routine vs. selective EUS-guided FNA approach for preoperative nodal staging of esophageal carcinoma

Enrique Vazquez-Sequeiros, MD, PhD, Michael J. Levy, MD, Jonathan E. Clain, MD, David A. Schwartz, MD, Gavin C. Harewood, MD, PhD, Diva Salomao, MD, Maurits J. Wiersema, MD

Rochester, Minnesota, USA
When to FNA?

- in most centers patients with node-positive disease are treated with neo-adjuvant therapy
- FNA of lymph nodes is not always possible due to non-traversable stenosis or peritumoral localization
- FNA increases procedure time, costs and chance of complications
When to FNA?

- prospective inclusion of 144 patients (AC / SCC) without distant metastasis
- patients with prior chemoradiation or without peritumoral nodes were excluded
- N-classification was given on classical morphological criteria (size, border, shape and echogenicity) and then followed by EUS-FNA
- 3 new criteria were defined: location in celiac trunc region, total number of nodes > 5 and T stage 3 or 4
- definite classification based on either surgical specimen or results of EUS-FNA
When to FNA?

### TABLE 3. Patient demographics at baseline and tumor characteristics in the study group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>65.4 ± 10.3 (35, 85)</td>
</tr>
<tr>
<td>Gender f/m</td>
<td>16/128 (11/89)</td>
</tr>
<tr>
<td>Tumor location</td>
<td></td>
</tr>
<tr>
<td>Upper third esophagus</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Mid third esophagus</td>
<td>28 (20)</td>
</tr>
<tr>
<td>Lower third esophagus</td>
<td>114 (79)</td>
</tr>
<tr>
<td>Barrett’s esophagus</td>
<td>83 (58)</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>126 (88)</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>18 (12)</td>
</tr>
<tr>
<td>Smoker</td>
<td>45 (31)</td>
</tr>
<tr>
<td>T stage†</td>
<td></td>
</tr>
<tr>
<td>T1/T2/T3/T4</td>
<td>8/6/17/1 (25/19/53/3)</td>
</tr>
<tr>
<td>T stage‡</td>
<td></td>
</tr>
<tr>
<td>T1/T2/T3/T4</td>
<td>17/21/97/9 (12/15/67/6)</td>
</tr>
<tr>
<td>N stage§</td>
<td></td>
</tr>
<tr>
<td>(N0/N1)§</td>
<td>23/121 (16/84)</td>
</tr>
</tbody>
</table>

*Mean ± standard deviation; (minimum, maximum).
†Pathology T stage for patients who underwent direct surgical resection (n = 32).
‡T stage as assessed by EUS examination with radial echoendoscope.
§N stage as per criterion standard.

### TABLE 4. N staging accuracy: modified EUS LN criteria; univariate and multivariate (multiple logistic regression) analysis of diagnostic criteria used to differentiate between benign and malignant LN

<table>
<thead>
<tr>
<th>EUS LN criteria</th>
<th>Benign LN (n = 23), n (%)</th>
<th>Malignant LN (n = 121), n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width &gt; 5 mm</td>
<td>10 (43)</td>
<td>102 (84)</td>
</tr>
<tr>
<td>Roundness</td>
<td>5 (22)</td>
<td>67 (55)</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>5 (22)</td>
<td>64 (53)</td>
</tr>
<tr>
<td>Sharp border</td>
<td>9 (39)</td>
<td>83 (69)</td>
</tr>
<tr>
<td>Celiac lymph nodes on EUS</td>
<td>0 (0)</td>
<td>17 (14)</td>
</tr>
<tr>
<td>Number of LN on EUS &gt; 5</td>
<td>1 (4)</td>
<td>65 (54)</td>
</tr>
<tr>
<td>EUS T3/4</td>
<td>6 (26)</td>
<td>100 (83)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>EUS LN criteria</th>
<th>Univariate analysis, p value</th>
<th>Multivariate analysis, p value, OR (95% CI OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width &gt; 5 mm</td>
<td>&lt;0.0001</td>
<td>0.008; 5.90 (1.65, 24.20)</td>
</tr>
<tr>
<td>Roundness</td>
<td>0.005</td>
<td>0.047; 4.29 (1.07, 20.21)</td>
</tr>
<tr>
<td>Hypoechoic</td>
<td>0.011</td>
<td>0.283; 0.38 (0.05, 2.08)</td>
</tr>
<tr>
<td>Sharp border</td>
<td>0.009</td>
<td>0.239; 2.25 (0.58, 9.18)</td>
</tr>
<tr>
<td>Celiac LN on EUS</td>
<td>0.074</td>
<td>0.89; 79,966.58 (1.43, &gt; 100,000)</td>
</tr>
<tr>
<td>No. LN on EUS &gt; 5</td>
<td>&lt;0.0001</td>
<td>0.014; 29.32 (3.24, 947.854)</td>
</tr>
<tr>
<td>EUS T3/4</td>
<td>&lt;0.0001</td>
<td>0.0005; 12.29 (3.30, 60.30)</td>
</tr>
</tbody>
</table>

LN, Lymph node; OR, odds ratio.
When to FNA?

**Figure 1.** N staging accuracy comparisons. Standard vs. modified EUS lymph node criteria: ROC (receiver operating characteristic) curves. (AUC, Area under the curve.) ROC curve shows that 2 positive standard criteria is the cutoff point with the highest accuracy (78%).

**Figure 2.** N staging accuracy comparisons. Standard vs. modified EUS lymph node criteria: ROC curves. (AUC, Area under the curve.) ROC curve shows that 3 positive modified criteria is the cutoff point with the highest accuracy (86%).
When to FNA?

- When 6 or more criteria were met PPV was 100% whereas in patients with 0 or 1 positive criterion the NPV for the presence of malignant LN was 100%

- These modified criteria for N-status have better accuracy in predicting N status

- EUS-FNA might be avoided in selected patients
To dilate or not to dilate (Dig Dis Sci 2007)

Through-the-Scope Balloon Dilation for Endoscopic Ultrasound Staging of Stenosing Esophageal Cancer

Brian C. Jacobson · Vanessa M. Shami · Douglas O. Faigel · Alberto Larghi · Michel Kahaleh · Charles Dye · Marcos Pedrosa · Irving Waxman

Background:

conflicting data exist with regard to safety of dilating stenotic tumors in patients with EC to complete EUS staging
To dilate or not to dilate

- 272 patients of 5 high-volume centers were analysed.
- Dilation necessary to complete EUS staging in 77 patients (28%) and successful in 73
- Mean balloon size 15 mm
- Perforation in 1 patient (T3 N1)
- Routine balloon dilation seems safe with a complication risk comparable to standard EUS without dilation
Restaging esophageal cancer

• with the increasing use of neoadjuvant regimens in patients with EC selecting patients that might benefit from surgical resection after chemoradiation becomes more important

• EUS (as any other modality) has relatively poor accuracy under these circumstances
EUS-FNA in restaging
(J Thor Cardiovasc Surg 2005)

The accuracy of endoscopic ultrasonography with fine-needle aspiration, integrated positron emission tomography with computed tomography, and computed tomography in restaging patients with esophageal cancer after neoadjuvant chemoradiotherapy

Robert James Corfolio, MD, FACS, FCCP,
Ayesha S. Bryant, MSPH, Buddhiwardhan Ohja, MD, MPH,
Alfred A. Bartolucci, PhD, and Mohamad A. Eloubeidi, MD, MHS, FACP

- prospective trial; 48 patients were restaged after chemoradiation with CT, EUS-FNA and PET-CT
- 41 patients underwent surgical resection
- accuracy with regard to T stage (T1-3 vs T4) was comparable for all modalities (76 – 80%)
- PET-CT was better in determining N-status: accuracy 93% vs 78% for both CT and EUS-FNA
- PET-CT was better in predicting complete response
- no modality can rule out T4 disease
- PET-CT is the best modality to predict nodal status and complete response when restaging after neoadjuvant therapy
Quality and outcome

- more and more papers are published dealing with effect of EUS on outcome, quality and its implementation in daily practice, as opposed to the setting of clinical trials
use of EUS (GI Endoscopy 2005)

ORIGINAL ARTICLE

Do physician attitudes and practices limit use of EUS in the staging and the treatment of esophageal carcinoma?

Stephen A. McClave, MD, Whitney F. Jones, MD, William B. Evans, MD
Louisville, Kentucky, USA

• although the superiority of EUS in locoregional staging of EC has been proven, its use, at least in the USA, seems less than to be expected
use of EUS

- questionnaire was sent to 114 surgeons, oncologists, internists and gastroenterologists
- 53% of respondents would not routinely use EUS in the work-up of patients with EC
- physicians in academic practice and those with a high “knowledge base” were more likely to use EUS
- EUS, especially in a primary care setting, seems to be grossly underused in staging of patients with EC
Endoscopic Ultrasonography and Prognosis of Esophageal Cancer

ANANYA DAS, * AMITABH CHAK, † MICHAEL V. SIVAK, JR, ‡ JONATHAN PAYES, † and GREGORY S. COOPER †,§

*Division of Gastroenterology, Mayo Clinic Scottsdale, Scottsdale, Arizona; †Division of Gastroenterology, University Hospitals of Cleveland, and §Department of Epidemiology & Biostatistics, Case Western Reserve University, Cleveland, Ohio

• to evaluate the effect of EUS on outcome for patients an epidemiological study was undertaken
EUS and patient outcome

- 2380 patients diagnosed with EC aged 65 and older were selected from the SEER database
- only 10.7% had undergone EUS at the time of diagnosis!
- EUS was more likely in white patients (11.4 vs 7.8%), adenocarcinoma (12.5 vs 8.5%) and in younger (<75) patients (12.4 vs 8.5%)
- In the EUS group patients were more likely to undergo surgical resection (21.1 vs 14.7%) and adjuvant therapy (11.2 vs 6.7%)
- Furthermore receipt of EUS was associated with a reduced risk of death (RR 0.594; CI 0.52-0.68)
- Evaluation of EC with EUS is associated with better outcome, possibly due to better patient selection
Quality of EUS in EC (Endoscopy 2007)

Quality control of endoscopic ultrasound in preoperative staging of esophageal cancer

- although EUS is widely regarded as the best tool for locoregional staging of patients with EC most data is available from clinical trials. Accuracy is probably lower in a routine setting
Quality of EUS in EC

- 214 patients without neo-adjuvant treatment were analyzed
- all patients underwent complete (radial) EUS staging
- AC 37% - SCC 63%
- standard morphologic criteria were used in N-staging (3 out of 4 positive)
## Quality of EUS in EC

### Table 2: Depth of tumor invasion (T status): correlation between EUS (uT status) and pathological (pT stage) results

<table>
<thead>
<tr>
<th>uT Status</th>
<th>pT Stage</th>
<th>n</th>
<th>% Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pT1</td>
<td>pT2</td>
<td>pT3</td>
</tr>
<tr>
<td>uT1</td>
<td>27</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>uT2</td>
<td>11</td>
<td>27</td>
<td>15</td>
</tr>
<tr>
<td>uT3</td>
<td>1</td>
<td>33</td>
<td>86</td>
</tr>
<tr>
<td>uT4</td>
<td>-</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>39</td>
<td>66</td>
<td>102</td>
</tr>
</tbody>
</table>

Overstaged: 12 (30.8%) 36 (54.5%) 1 (0.9%) -
Understaged: - 3 (4.5%) 15 (14.7%) 6 (85.7%)

### Table 3: Depth of lymph node invasion (N status): correlation between EUS (uN status) and pathological (pN stage) results

<table>
<thead>
<tr>
<th>uN Status</th>
<th>pN Stage</th>
<th>n</th>
<th>% Correct</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>pN0</td>
<td>pN1</td>
<td></td>
</tr>
<tr>
<td>uN0</td>
<td>17</td>
<td>8</td>
<td>25</td>
</tr>
<tr>
<td>uN1</td>
<td>68</td>
<td>121</td>
<td>189</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>85</td>
<td>129</td>
<td>214</td>
</tr>
</tbody>
</table>

Overstaged: 68 (80%)
Understaged: - 8 (6.2%)
Quality of EUS in EC

• diagnostic accuracy of routine radial EUS is limited; both in T and N staging
• potential over- and undertreatment
• take care in translating published accuracies to your own practice
• EUS-FNA will partially improve results
numbers and quality  (GI Endoscopy 2006)

Staging of esophageal carcinoma in a low-volume EUS center compared with reported results from high-volume centers

Evelyn P. M. van Vliet, MSc, Marinus J. C. Eijkemans, PhD, Jan-Werner Poley, MD, Ewout W. Steyerberg, PhD, Ernst J. Kuipers, MD, PhD, Peter D. Siersema, MD, PhD

Rotterdam, The Netherlands

- from the very early days of EUS it is clear a definite learning curve exists
- It is not known whether the number of annual procedures influences quality of EUS
numbers and quality

- results from a high-volume center with a large number of echoendoscopists were compared with the data from the literature
- 244 patients underwent EUS followed by surgical resection; these data were compared with 670 published cases
- dilatation or EUS-FNA was not performed routinely
- both sensitivity (58 vs 75 – 90%) and specificity (87 vs 95%) was lower for detecting T1 or T2 stages
numbers and quality

• For nodal staging no differences were found with regard to specificity but sensitivity for both locoregional (45 vs 63 – 89%) and celiac nodes (19 vs 72 – 83%) was much lower

• EUS should probably be performed by experienced and dedicated echoendoscopists that are able to maintain an adequate volume

• In another study the same authors ruled out publication bias as a possible cause of these unfavourable results
Gastric cancer (GC)

- less publications on GC and EUS:
  - 23 relevant papers:
    - 3 case reports
    - 3 about ESD for early GC
    - 4 review articles
Peritoneal metastasis and EUS

Accuracy of endoscopic ultrasonography in diagnosing ascites and predicting peritoneal metastases in gastric cancer patients

Y T Lee, E K W Ng, L C T Hung, S C S Chung, J Y L Ching, W Y Chan, W C Chu, J J Sung

Background: presence of peritoneal metastases in GC is difficult to ascertain using conventional imaging modalities
Peritoneal metastasis and EUS

- 241 patients were evaluated with radial EUS, CT and surgical staging
- EUS T-stage accuracy was between 80% and 94%
- EUS N-stage accuracy was between 68% (N0) and 86% (N3)
- Sensitivity in predicting peritoneal metastases (n=71) by diagnosing ascites (n=93) was 73% with EUS vs. 18% for combined CT / US
- EUS is very sensitive in detecting, sometimes minute amounts of ascites and this finding seems to correlate well with the presence of peritoneal metastases
Staging accuracy in GC (Ann Surg Oncol 2007)

Clinical Correlation of Endoscopic Ultrasonography with Pathologic Stage and Outcome in Patients Undergoing Curative Resection for Gastric Cancer

David Bentrem, MD,¹ Hans Gerdes, MD,² Laura Tang, MD,³ Murray Brennan, MD,¹ and Daniel Coit, MD¹

- evidence is increasing for the use of neo-adjuvant therapy in patients with GC.
- adequate staging is necessary to select those patients that might benefit most from neo-adjuvant treatment
Staging accuracy in GC

- 225 patients were analyzed with regards to EUS performance
- all had GC (124 proximal), had no neo-adjuvant therapy and underwent R0 resections
- overall accuracy of T stage was rather low (57%), mainly due to understaging of pT2 cancers and overstaging of T2 and T3 cancers
staging accuracy in GC

- accuracy for N-staging was only 50% with equal occurrence of under- and overstaging
- accuracy improved to 71% when nodal staging was limited to identify only node-positive and node-negative patients
- EUS tends to overstage low-risk patients but is capable of identifying most high-risk patients with node-positive and/or serosal disease
Conclusions

• EUS is still the most accurate method in staging EC and GC
• restaging after neo-adjuvant chemoradiotherapy is still problematic
• attention is shifting towards quality and influence on outcome of EUS
• maximum effort should be made to ensure and maintain quality of EUS in daily practice