How to stage gastric cancer? The endoscopist’s point of view

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Gastric cancer staging: why is it important?

Give some indication of prognosis for cancer patients

Aid the clinician in treatment planning
Endoscopy / Surgery ± chemo(radio)therapy / Palliation

The main goal of staging is to identify patients who are eligible for endoscopic therapy and to select those patients who require surgical management as curative treatment.
Staging: determination of the therapeutic approach

Superficial cancer
(invasion is limited to the mucosa and submucosa)

Advanced cancer
(invasion is reached to the muscularis propria or deeper)

- T1a
- T1b
- T2
- T3
- T4a
- T4b

Endoscopic resection/ Surgery

Surgery ± Chemo(radio)therapy
(more advanced, LN+) / Palliation

N+
0%
100%

Mucosal layer
Muscularis mucosae
Submucosal layer
Muscularis propria
Subserous layer
Serous membranae
Adjacent organ

Endoscopic classification review group, Endoscopy 2005;37:570-8
Sobin LH TNM Classification of Malignant Tumours Seventh Edition, 2009
T1 gastric cancer: risk of lymph node metastasis

Endoscopic resection and could be curative only in selected cases of mucosal (m1-m3) and minimally submucosal cancers (sm1)

Accurate determination of the depth of gastric cancer invasion is absolutely necessary in order to establish the feasibility of endoscopic resection

ESGE recommends a high quality endoscopy, ideally with contrast or digital chromoendoscopy, by an experienced endoscopist in order to establish the feasibility of gastric endoscopic resection (strong recommendation, moderate quality evidence).
STAGING:
High quality endoscopy evaluation

- Paris classification
- Surface, margins, folds
- Delineation and size
Paris Classification of superficial neoplastic lesions

<table>
<thead>
<tr>
<th>Paris type</th>
<th>Depth of invasion</th>
<th>Lymph node metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mucosa</td>
<td>submucosa</td>
</tr>
<tr>
<td>I/II</td>
<td>67.2%</td>
<td>32.8%</td>
</tr>
<tr>
<td>III/Mixed</td>
<td>34.3%</td>
<td>65.7%</td>
</tr>
</tbody>
</table>

Endoscopic resection feasible

LN metastasis risk (RR, 95% CI) - 3.165 (1.758–5.696)

Endoscopic classification review group. Endoscopy 2005;37:570-8
Zheng Z et al. BMC Cancer 2016, 16:92
Chromoendoscopy is essential for accurate typing of gastric lesions!

What kind the lesion is?

Type 0-IIa?

Type 0-IIa+IIc!

Chromoendoscopy is essential for accurate typing of gastric lesions!
What lesion is feasible for endoscopic resection?

Type 0-IIc  Endoscopic resection feasible

PostESD specimen: intramucosal cancer, pT1a (m2)

Type 0-III  Endoscopic resection NOT feasible

Postgastrectomy specimen: deep submucosal invasion, pT1b (sm3)
Surface, margins, folds

Mucosal lesion (T1m)
- smooth surface protrusion or depression
- slight marginal elevation
- smooth tapering of converging folds

Endoscopic resection feasible

Submucosal invasion (T1sm)
- Irregular / nodular surface
- marked marginal elevation
- clubbing/abrupt cutting/fusion of converging folds

Endoscopic resection NOT feasible

Overall accuracy of endoscopic staging was 78.0%

Choi J et al. Gastrointest Endosc 2011 May;73(5):917-27
“Non-extension sign”

“Non-extension sign” is determined as “positive” when massive surround elevation or mucosal convergence with elevation are detected by the conventional endoscopic observation with insufflation of a large volume of air into the stomach.

Mild extension

Strong extension

Insufflation of a large volume of air into the stomach

Relate to the increased thickness and rigidity caused by massive submucosal invasion (sm2 or deeper)

Adopted from Iwashita A et al. 2015

“Non-extension sign” demonstrated superior diagnostic performance compared to EUS (diagnostic accuracy of “non-extension sign “ vs. EUS 98.4% (96–99.3%) vs. 80.9% (76.8–85.1%), p<0.0001)

Conventional endoscopy using “non-extension sign” is an effective diagnostic marker for discriminating submucosal massively invasive cancer (SM2 and over) from mucosal/submucosal micro-invasive cancer (m/sm1)

Iwashita A et al. United European Gastroenterology Journal; 2015: 2 (Supplement 1)
Otsu K et al. United European Gastroenterology Journal; 2014: 2 (Supplement 1)
Size: delineation of the lateral margin

**Chromoendoscopy with indigocarmine** is a basic technique for delineation (overall accuracy 80%-85%)

**Chromoendoscopy with acetic acid–indigocarmine mixture** can enhance the diagnostic yield in terms of delineation (overall accuracy 90.7%)

**Autofluorecence imaging (AFI)** could be helpful for the determination of the lateral margin, but so far weak evidence
Kuvaev R, Kashin S et al., Endoscopy 2012; 44 (Suppl 1) A130

**Narrow band imaging endoscopy with magnification** provides reliable delineation of the lesions, especially when the margins are unclear using chromoendoscopy
Uchita K et al. BMC Gastroenterol. 2015 Nov 2;15:155
Narrow band imaging: microscopic appearance

The association between the diameter of microvessels and depth of tumor invasion has been reported in superficial esophageal lesions, colorectal neoplasia, and recently – in early gastric cancers.

Dilated vessels (D vessels) are defined as those vessels with a diameter 3 times larger than that of the irregular microvessels that are observed in the lesions.

Dilated vessels are associated with submucosal infiltration

Diagnostic accuracy: 81.5%
Sensitivity: 37.5%
Specificity: 88.3%

<table>
<thead>
<tr>
<th>Comparison of histopathological features of the lesions</th>
<th>D vessels and depth of tumor invasion</th>
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<tbody>
<tr>
<td>Group V</td>
<td>Group N</td>
</tr>
<tr>
<td>Undifferentiated cancer</td>
<td>16.7% (3/18)</td>
</tr>
<tr>
<td>Cancer with ulcer scar</td>
<td>16.7% (3/18)</td>
</tr>
<tr>
<td><strong>Submucosal cancer</strong></td>
<td><strong>33.3% (6/18)</strong></td>
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<table>
<thead>
<tr>
<th>Mucosal cancer</th>
<th>Submucosal cancer</th>
</tr>
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<tbody>
<tr>
<td>D vessel (−)</td>
<td>91</td>
</tr>
<tr>
<td>D vessel (+)</td>
<td>12</td>
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</table>

STAGING:
Endoscopic ultrasound

...BUT BE AWARE
T-staging of gastric tumors by EUS might be incorrect because of overstaging due to ulceration, peritumoral inflammatory changes or fibrosis mimicking deeper invasion

EUS: diagnostic accuracy in T-staging

EUS can distinguish between superficial and advanced cancers (T1-T2 vs. T3-T4 and T1 vs. T2) with a sensitivity and a specificity greater than 85%.

However, when the tumor has invaded the SM or deeper layer, the standard therapeutic option is surgical resection. EUS does not substantially impact the management of these patients.

However, EUS diagnostic accuracy is lower when it comes to differentiating between mucosal and submucosal cancers (T1a vs. T1b), which is crucial in the selection of patients for ESD/EMR.
Conventional endoscopy has a higher level of overall accuracy for T staging of early gastric cancer in comparison with EUS (79.5% vs. 59.6%, p< 0.001), and its accuracy was similar to that of miniprobe EUS (79.0%).

In one ESD series that systematically used EUS before endoscopic resection, the feasibility of ESD was comparable and even slightly inferior to that in another ESD series where EUS was not performed (93% vs. 97%).
EUS: predicting resectability

ESGE suggests that a strategy of precise endoscopic evaluation of these lesions is sufficient for predicting resectability, with EUS reserved only for selected cases.

STAGING: Endoscopic ultrasound

...BUT BE AWARE

N-staging by EUS might be incorrect because of **understaging** due to micrometastases present in the lymph nodes, or **overstaging** due to the presence of large reactive lymph nodes.
EUS: lymph node metastasis (N0 vs. N+)

**Cochrane Database of Systematic Reviews 2015, Issue 2. Art. No.: CD009944**

### Table: N0 versus N+ tumors

<table>
<thead>
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<th>Studies</th>
<th>44 (patients enrolled: 3573)</th>
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<tbody>
<tr>
<td>Summary results</td>
<td>Sensitivity: 0.83 (95% CI: 0.79 to 0.87). Specificity: 0.67 (95% CI: 0.61 to 0.72)</td>
</tr>
</tbody>
</table>

EUS diagnostic accuracy is low when it comes to distinguishing between tumors with versus those without lymph node disease.

Ultimately, the best method for assessment of the risk of lymph node involvement may be not EUS but a diagnostic endoscopic resection with assessment of the infiltration depth of the lesion.
What do we need to know?

**Tumor characteristics:**

1. Infiltration depth (m1-m3, sm1-sm3)
2. Histological grading (G1-G3)
3. Lymph vessel infiltration (l)
4. Blood vessel infiltration (v)

Based on Oliver Pech “How to treat early esophageal SCC after detection. We only need endoscopy for staging”, Quality in Endoscopy Symposium on Upper GI Endoscopy & Neoplasia, April 15, 2016
STAGING:
Endoscopic resection
(EMR/ESD)
Patients with endoscopically visible dysplasia or cancer should undergo staging and endoscopic resection for adequate management


Endoscopic resection is vital for staging of an early gastric cancer because it provide
• an objective and accurate histological T–staging of the resected lesion
• evaluation of other prognostic factors such as differentiation grade and lymphatic and vascular involvement
Clinical case: early gastric cancer

White light endoscopy

Chromoendoscopy with indigocarmine
Early gastric cancer: delineation

White light endoscopy

Narrow band imaging endoscopy with magnification
EUS (miniprobe 20MHz) didn’t reveal any signs of deep submucosal invasion
Post ESD histology

0-IIa, 60x35mm, UL-, pT1a (m3)
Moderate-differentiated adenocarcinoma (G2) with minimal invasion into muscularis mucosa
Post ESD histology

Lymphovascular invasion (+)

Endoscopic resection was not curative

…but it was appeared as an important diagnostic step

Additional surgery was necessary
Take home messages

Is endoscopic resection feasible?

High quality endoscopy, ideally with contrast or digital chromoendoscopy, by an experienced endoscopist:
- Paris classification, surface, margins, folds, size ± EUS (in selected cases)

EMR/ESD

Histology

Follow up

Is EMR/ESD curative?

Surgery

Histology

Yes

No

Yes

No