Modern Stage-Specific Management of Esophageal Cancer

8th Masters of Minimally Invasive Thoracic Surgery
Orlando
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Chief Thoracic Surgery, Chief Medical Officer
Duke Cancer Institute
Disclosure

Consultant: Scanlan

No conflicts related to this presentation
Case 1

- 73 year old man with GERD undergoes surveillance EGD for Barrett’s esophagus
- Previous biopsies: low-grade dysplasia
- PMH: GERD
- Current biopsy: HGD and focal adenocarcinoma
Question 1

The most appropriate option is:

a. Observation
b. Endoscopic resection
c. Photodynamic therapy
d. Esophagogastrectomy
e. Induction therapy followed by esophagogastrectomy
Question 1

The most appropriate option is:

a. Observation
b. Endoscopic resection
c. Photodynamic therapy
d. Esophagogastrectomy
e. Induction therapy followed by esophagogastrectomy
Question 2

Endoscopic resection is performed with a positive lateral margin. The best option is:

a. Repeat endoscopic resection
b. Esophagogastrectomy

c. Induction therapy followed by esophagogastrectomy
d. Definitive chemoradiotherapy
Question 2

Endoscopic resection is performed with a positive lateral margin. The best option is:

a. Repeat endoscopic resection
b. Esophagogastrectomy
c. Induction therapy followed by esophagogastrectomy
d. Definitive chemoradiotherapy
Question 3

Endoscopic resection is performed with a positive deep margin. The best option is:

a. Repeat endoscopic resection
b. Esophagogastrectomy
c. Induction therapy followed by esophagogastrectomy
d. Definitive chemoradiotherapy
Question 3

Endoscopic resection is performed with a positive deep margin. The best option is:

a. Repeat endoscopic resection
b. Esophagogastrectomy
c. Induction therapy followed by esophagogastrectomy
d. Definitive chemoradiotherapy
Case 2

- 68 year old man presents with dysphagia
- Upper endoscopy demonstrates long distal esophageal mass
- Biopsy demonstrates adenocarcinoma
- Next steps?
Case 2

- 68 year old man presents with dysphagia
- Upper endoscopy demonstrates long distal esophageal mass
- Biopsy demonstrates adenocarcinoma
- PET/CT performed
- EUS: T3N1
Endoscopic ultrasound
Case

- 68 year old man with GERD presents with dysphagia
- Upper endoscopy demonstrates long distal esophageal mass
- Biopsy demonstrates adenocarcinoma

- PET = T3N0
- EUS = T3N1
Question 4

The most appropriate option is:

a. Esophagogastrectomy

b. Induction chemotherapy and esophagogastrectomy

c. Induction chemoradiotherapy and esophagogastrectomy

d. Definitive chemoradiotherapy
Question 4

The most appropriate option is:

a. Esophagogastrectomy
b. Induction chemotherapy and esophagogastrectomy
c. Induction chemoradiotherapy and esophagogastrectomy
d. Definitive chemoradiotherapy
Question 5

Regarding esophagogastrectomy, the least important factor regarding prognosis is:

a. The number of lymph nodes resected
b. The surgical margins
c. Postoperative anastomotic leak
d. Postoperative pneumonia
Question 5

Regarding esophagogastrectomy, the least important factor regarding prognosis is:

a. The number of lymph nodes resected
b. The surgical margins
c. Postoperative anastomotic leak
d. Postoperative pneumonia
T Status

T1a: Lamina propria or muscularis mucosa
T1b: Submucosa
T2: Muscularis propria
T3: Adventia
T4a: Pleura, pericardium, diaphragm (resectable)
T4b: Aorta, vertebral body, trachea (unresectable)
T Status
N Status

N1: 1-2 regional nodes
N2: 3-6 regional nodes
N3: 7 or more regional nodes
<table>
<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
</tr>
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<tbody>
<tr>
<td>N0</td>
<td>IA</td>
<td>IB</td>
<td>IIA</td>
<td></td>
</tr>
<tr>
<td>N1</td>
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</tr>
<tr>
<td>N3</td>
<td>IIIC</td>
<td>IIIC</td>
<td>IIIC</td>
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</tr>
</tbody>
</table>

Legend:
- G1-2: Green
- G3: Purple

Adenocarcinoma staging classification.
Squamous Cell Carcinoma T1-3N0

<table>
<thead>
<tr>
<th>G1</th>
<th>T1</th>
<th>T2 - T3</th>
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<tbody>
<tr>
<td></td>
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<table>
<thead>
<tr>
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<th>T2 - T3</th>
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<td>IB</td>
</tr>
<tr>
<td></td>
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Grade/Location
- Lower
- Upper Middle
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<thead>
<tr>
<th></th>
<th>T1</th>
<th>T2</th>
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<th>T4a</th>
<th>T4b</th>
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<td></td>
<td></td>
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<tr>
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<td>IIIA</td>
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</tr>
<tr>
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<td>IIIB</td>
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<td>IIIIC</td>
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<tr>
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<tr>
<td>B</td>
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<tr>
<td>Stage</td>
<td>T</td>
<td>N</td>
<td>M</td>
<td>Grade</td>
<td></td>
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<td>Stage 0</td>
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<td>M0</td>
<td>1-2, X</td>
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<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
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<tr>
<td>Stage IIA</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>3</td>
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</tr>
<tr>
<td>Stage IIB</td>
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<td>N0</td>
<td>M0</td>
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<tr>
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<td>T1~2</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
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<tr>
<td>Stage IIIA</td>
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<td>N2</td>
<td>M0</td>
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<tr>
<td></td>
<td>T3</td>
<td>N1</td>
<td>M0</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
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<tr>
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<tr>
<td>Stage IIIC</td>
<td>T4a</td>
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<td>M0</td>
<td>Any</td>
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</tr>
<tr>
<td></td>
<td>T4b</td>
<td>Any</td>
<td>M0</td>
<td>Any</td>
<td></td>
</tr>
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<td>Any</td>
<td>N3</td>
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<tr>
<td>Stage IV</td>
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<td>Any</td>
<td>M1</td>
<td>Any</td>
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</tr>
</tbody>
</table>

**Histologic Grade (G)**

GX  Grade cannot be assessed – stage grouping as G1
G1  Well differentiated
G2  Moderately differentiated
G3  Poorly differentiated
G4  Undifferentiated – stage grouping as G3 squamous
**Staging: WECC/AJCC 7**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor (T)</th>
<th>Node (N)</th>
<th>Metastasis (M)</th>
<th>Grade</th>
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<tr>
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<td>Grade 1-2</td>
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<tr>
<td>IB</td>
<td>T1N0M0</td>
<td>Grade 3-4</td>
<td>T2N0M0</td>
<td>1-2</td>
</tr>
<tr>
<td>IIA</td>
<td>T2N0M0</td>
<td>Grade 3-4</td>
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<td></td>
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<tr>
<td>IIB</td>
<td>T3N0M0</td>
<td>Any Grade</td>
<td>T0-2N1M0</td>
<td>Any Grade</td>
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<td>Any Grade</td>
<td>T3N1M0</td>
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<td>IIIB</td>
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<td>Any Grade</td>
<td>T4aN0M0</td>
<td>Any Grade</td>
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<td></td>
<td></td>
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<td>Any TN3M0</td>
<td>Any Grade</td>
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<tr>
<td>IV</td>
<td>AnyT</td>
<td>AnyNM1</td>
<td></td>
<td>Any Grade</td>
</tr>
</tbody>
</table>

*Esophageal Cancer: Improving Outcomes*
Esophageal Cancer: Improving Outcomes by AJCC staging

Survival by AJCC staging


Risk-Adjusted Survival (%) vs Years

Adenocarcinoma
The Effect of a Multidisciplinary Thoracic Conference (MTC) on Treatment of Patients With Esophageal Carcinoma

<table>
<thead>
<tr>
<th>2001-2007</th>
<th>Before MTC (n=117)</th>
<th>MTC (n=138)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Staging Evaluation</td>
<td>67%</td>
<td>97%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mult-D evaluation prior to Tx</td>
<td>72%</td>
<td>98%</td>
<td>0.0001</td>
</tr>
<tr>
<td>NCCN Guidelines adherence</td>
<td>83%</td>
<td>98%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Days from Dx to Tx (mean)</td>
<td>27</td>
<td>16</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Endoscopic Resection

![Endoscopic Resection Diagram]

Endoscopic Resection

1. Diagnostic

2. Therapeutic – for tumors at low risk of lymphatic metastasis
   - T1a, superficial T1b
   - Part of multimodality endoscopic therapy (combined with ablation of dysplasia with RFA)
   - Positive lateral margins: repeat endoscopic resection
   - Positive deep margins= esophagectomy
Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett’s oesophagus

O Pech¹, A Behrens¹, A May¹, L Nachbar¹, L Gossner¹, T Rabenstein¹, H Manner¹, E Guenter¹, J Huijsmans¹, M Veith², M Stolte², C Ell¹

¹Department of Internal Medicine II, HSK Wiesbaden, Wiesbaden, Germany;
²Institute of Pathology, Bayreuth Hospital, Bayreuth, Germany
Wiesbaden Experience

- 349 patients; 96.6% completely resected
- Surgery necessary in 3.7% (n=13) after failed EMR
- Metachronous subsequent lesions in 21.5%
- Long-term surveillance required
- 5-yr survival = 84% (no esophageal CA-related deaths)

Gut 2008;57:1200-1206
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer


- Pts with resectable (T2-3N0-1M0) tumors
- Preop CRT (carboplatin/paclitaxel) + RT (41.4 Gy) followed by surgery vs. surgery alone
- 366 pts enrolled (2004-8); male 284, adeno 273
- Toxicities (grade ≥ 3) in the CRT arm: <5%
## CROSS Study

<table>
<thead>
<tr>
<th></th>
<th>CRT+Surgery</th>
<th>Surgery Alone</th>
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</thead>
<tbody>
<tr>
<td>Resection Rate</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>R0 Resection Rate</td>
<td>92%*</td>
<td>69%</td>
</tr>
<tr>
<td>pCR</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Median OS</td>
<td>49 months*</td>
<td>24 months</td>
</tr>
<tr>
<td>1, 2, 3, 5 yr survival</td>
<td>82, 67, 58, 47%*</td>
<td>70, 50, 44 34%</td>
</tr>
</tbody>
</table>
A  Survival According to Treatment Group

Proportion Surviving

Follow-up (mo)
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value for Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.657 (0.495–0.871)</td>
<td>0.665 (0.500–0.884)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.913 (0.482–1.729)</td>
<td>0.928 (0.487–1.766)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male</td>
<td>0.612 (0.446–0.841)</td>
<td>0.614 (0.447–0.845)</td>
<td>0.003</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.627 (0.056–6.970)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.732 (0.524–0.998)</td>
<td>0.741 (0.536–1.024)</td>
<td>0.07</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>0.453 (0.243–0.844)</td>
<td>0.422 (0.226–0.788)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>0.414 (0.234–0.732)</td>
<td>0.422 (0.239–0.747)</td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>0.793 (0.567–1.108)</td>
<td>0.807 (0.576–1.130)</td>
<td>0.21</td>
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<tr>
<td>Could not be determined</td>
<td></td>
<td>0.552 (0.066–4.602)</td>
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<tr>
<td>WHO performance score</td>
<td></td>
<td></td>
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<tr>
<td>0</td>
<td>0.617 (0.452–0.844)</td>
<td>0.625 (0.456–0.857)</td>
<td>0.004</td>
</tr>
<tr>
<td>1</td>
<td>0.864 (0.433–1.726)</td>
<td>0.898 (0.753–1.631)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Esophagogastrectomy: Standard Resections

- **Standard**
  - Ivor Lewis
  - 3-incision (McKeown)
  - Thoracoabdominal
  - Transhiatal

- **Minimally Invasive Esophagectomies (MIE)**
  - VATS + laparoscopic/laparotomy + cervical
  - Laparoscopic + thoracotomy/VATS
Lymph Node Dissection

1. All thoracic nodes
2. Left gastric pedicle nodes
3. Celiac axis nodes
4. Gastro-hepatic ligament nodes

Target: At least 16

Surgical Mortality: Esophagectomy

Birkmeyer JD et al. *NEJM* 2002;346:1128

Adjusted Mortality (%) by Hospital Volume (procedures/year):
- <2: 20.3%
- 2-4: 17.8%
- 5-7: 16.2%
- 8-19: 11.4%
- >19: 8.4%

*Esophageal Cancer: Improving Outcomes*
Surgical Mortality: Esophagectomy

Birkmeyer JD et al. *NEJM* 2004;349:2117

Adjusted Mortality (%)

<table>
<thead>
<tr>
<th>Surgeon Volume (procedures/year)</th>
<th>Adjusted Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2</td>
<td>18.8</td>
</tr>
<tr>
<td>2-6</td>
<td>13.1</td>
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<tr>
<td>&gt;6</td>
<td>9.2</td>
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</tbody>
</table>

*Esophageal Cancer: Improving Outcomes*
## Surgical Mortality: Esophagectomy

Birkmeyer JD et al. *NEJM* 2004;349:2117

<table>
<thead>
<tr>
<th>Hospital Volume (procedures/year)</th>
<th>&lt;2</th>
<th>2-5</th>
<th>&gt;5</th>
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<tr>
<td>&lt;5 cases</td>
<td>21.7</td>
<td>14.7</td>
<td>14.6</td>
</tr>
<tr>
<td>5-13 cases</td>
<td>13.3</td>
<td>9.8</td>
<td>9.8</td>
</tr>
<tr>
<td>&gt;13 cases</td>
<td>8</td>
<td>8</td>
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</table>

*Adjusted Mortality (%)*

---

*Esophageal Cancer: Improving Outcomes*
Trends in Hospital Volume and Operative Mortality for High-Risk Surgery

Finks JF, et al. NEJM 2011; 364:2128-2137

- Median hospital volumes of 4 cancer resections analyzed using Medicare database 1999-2008
- Lung, esophagus, pancreas, and bladder
- Operative mortality declined for all procedures
- Higher volumes explained a large portion of the decline in mortality for pancreatectomy (67%), cystectomy (37%), and esophagectomy (32%), but not for the other procedures

Esophageal Cancer: Improving Outcomes
Risk-Adjusted Mortality Associated with Cancer Resections among Medicare Patients, 1999–2008


*Esophageal Cancer: Improving Outcomes*
Esophageal Cancer: Improving Outcomes
Comprehensive Evaluation for Aspiration After Esophagectomy Reduces the Incidence of Post-Operative Pneumonia

Berry et al, J Thorac Cardiovasc Surg 2010; 140: 1266-72

• We started a comprehensive evaluation prior to oral feedings following esophagectomy after demonstrating that pneumonia strongly predicts mortality: HR for death=20

• Rigorous swallowing evaluation with clinical observation, cineradiography, and fiberoptic endoscopy was used prior to oral feedings

Comprehensive Evaluation for Aspiration After Esophagectomy Reduces the Incidence of Post-Operative Pneumonia  
Berry et al, J Thorac Cardiovasc Surg 2010; 140: 1266-72

• 799 patients (379 early era, 420 later era)
• 30-day mortality = 3%
• Postop aspiration 12%; pneumonia 14%
• Age (p<0.0001), cervical anastomosis (p=0.0009) predicted aspiration (multivariable model)
• Incidence of postop pneumonia was significantly decreased (10% vs 18%, p=0.002) in the later era
Endoscopic Resection

1. High grade dysplasia (Carcinoma in situ)

2. T1aN0, superficial T1bN0
Esophageal Cancer: Improving Outcomes

Radio Frequency Ablation

1. High-grade dysplasia, <10 cm

2. Low-grade dysplasia

3. ? Metaplasia
Photodynamic Therapy

1. T1a tumors not amenable to EMR in marginally operable patients

2. HGD in RFA failures

3. Advanced endoluminal disease, symptomatic, after radiation
Esophagectomy without Induction Therapy

1. High grade dysplasia, T1
   Extensive, failed mucosal ablation, patient choice

2. Selected T2N0 (dose reduction=no Rx)

3. Medical contraindications to tri-modality therapy
   Age, performance status, perforation, bleeding
Induction CRT + Surgery

Standard of care based on selected studies and meta-analyses

1. Most patients with T3 or N1 disease

2. Selected patients with T2N0
Surgery + Adjuvant Therapy

1. Patients with unexpected N1 or M1a disease

2. Patients who refused induction therapy
Modern Esophageal Resection

- Multidisciplinary evaluation is essential
- Induction therapy esophagogastrectomy is the best option for most patients with $\geq$T2N0
- Centers with experience have the best outcomes
- Approaches that avoid thoracotomy are preferable
- Perioperative mortality $\leq 2 \%$
- Best predictor of post-operative outcome: pneumonia

*Esophageal Cancer: Improving Outcomes*