ARROCase
Esophageal Cancer

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Case: Clinical Presentation

• 58 y/o male with 3 month history of dysphagia initially to solids, progressing to liquids
• Odynophagia
• Vague mid-chest discomfort
• 15 pound weight loss over the past 3 months
• Denies vomiting or regurgitation of food
• Denies cough/SOB
• KPS 80
Work-Up: Upper Endoscopy

- Large, friable, malignant-appearing mass noted spanning 25-31 cm from the incisors
- Occupying 50-60% of the lumen
- Remainder of endoscopic exam including stomach and duodenum were normal
- Biopsy was obtained, revealing moderately differentiated squamous cell carcinoma
Work-Up: PET/CT Scan

- Large area of FDG avid wall thickening seen in mid esophagus, with a maximal SUV of 12.7
- No FDG avid lymphadenopathy is identified to suggest metastatic disease
- The distribution of the FDG is otherwise within physiological limits
Work-Up: Endoscopic Ultrasound

- Hypoechoic lesion extending through the muscularis propria
- No abnormal lymphadenopathy was noted, confirming the lesion to be T3 N0
- No frank invasion into the surrounding structures was noted
Epidemiology

• Two distinct histopathologic types: squamous cell carcinoma and adenocarcinoma
• Relatively uncommon in the US
• Lifetime risk of being diagnosed with the disease is less than 1%
• 18,170 new cases in 2014
• 15,450 patients expected to die of the disease

3 American Cancer Society
Risk Factors

• Tylosis
• Plummer-Vinson Syndrome
• Caustic injury
• HPV (SCC)
• Tobacco
• Alcohol
  – 90% of SCC in Western Europe and North America can be attributed to tobacco and alcohol use
• Obesity, GERD, Barrett’s Esophagus (adenocarcinoma)
• Raw fruits and vegetables are protective

Anatomy

• Cervical esophagus
  – Cricopharyngeus to the thoracic inlet
  – 15-18 cm from the incisors
• Upper third
  – Thoracic inlet to the carina
  – 18-24 cm from the incisors
• Middle third
  – Carina to the inferior pulmonary veins
  – 24-32 cm from the incisors
• Lower third
  – Traversing the remaining distance to the GE junction
  – 32-40 cm from the incisors

Lymphatic Drainage

• Rich mucosal and submucosal lymphatic system which may extend long distances (reason why proximal/distal margins used for radiation planning have traditionally been a minimum of 5 cm)

• Submucosal plexus drains into internal jugular, peritracheal, hilar, subcarinal, periesophageal, periaortic, and pericardial lesser curvature lymph nodes

• Left gastric and celiac nodes for lower third lesions

Minsky, Bruce D., MD, Goodman, Karyn, MD, MS, Warren, Robert, MD - Leibl and Phillips Textbook of Radiation Oncology, 772-787.
Histology

• Squamous cell carcinomas
  – Majority of cases throughout the world
  – 40% of esophageal cancer in the US
  – 70% in the proximal and middle third

• Adenocarcinoma
  – Frequently arise in the context of Barrett’s esophagus
  – Mainly occur in the distal third of the esophagus
  – Rate of adenocarcinoma rising in US (obesity & GERD)

• No significant survival differences have been noted between various histologies

Clinical Presentation

• **Dysphagia**
  – Most common
  – Initially to solids, then progressing to liquids
  – Large impact on QOL
• **Odynophagia**
• **Weight loss (Anorexia)**
• **Pain**
• **Cough/Hoarseness (Recurrent laryngeal nerve)**
• **Vomiting**
Diagnosis/Work-Up

- Upper endoscopy - allows for biopsy and diagnosis
- Bronchoscopy in patients with tumors above the level of the carina
- Barium esophagram (optional) – can identify a tracheoesophageal fistula
- CT chest and abdomen – can identify extension beyond the esophageal wall, enlarged lymph nodes, and visceral metastases
- For cervical primaries, a neck CT should be performed to evaluate for cervical lymph node involvement
- Endoscopic ultrasound – highly accurate in determining depth of invasion as well as lymph node involvement
- FDG-PET scan for staging and response to pre-operative treatment

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2Minsky, Bruce D., MD, Goodman, Karyn, MD, MS, Warren, Robert, MD - Leibel and Phillips Textbook of Radiation Oncology, 772-787.
## TNM Staging, AJCC 7th Edition

### Primary Tumor

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>High-grade dysplasia</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor invades lamina propria, muscularis mucosae, or submucosa</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor invades lamina propria or muscularis mucosae</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invades submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invades muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invades adventitia</td>
</tr>
<tr>
<td>T4</td>
<td>Tumor invades adjacent structures</td>
</tr>
<tr>
<td>T4a</td>
<td>Resectable tumor invading pleura, pericardium, or diaphragm</td>
</tr>
<tr>
<td>T4b</td>
<td>Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea</td>
</tr>
</tbody>
</table>

### Regional Lymph Nodes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional nodes not assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Metastasis in 1-2 regional lymph nodes*</td>
</tr>
<tr>
<td>N2</td>
<td>Metastasis in 3-6 regional lymph nodes*</td>
</tr>
<tr>
<td>N3</td>
<td>Metastasis in 7 or more regional lymph nodes*</td>
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</table>

### Distant Metastasis

<table>
<thead>
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<th>Code</th>
<th>Description</th>
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<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

*Regional lymph nodes extend from cervical nodes to celiac nodes.
## Group Staging, AJCC 7th Edition

### Adenocarcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T, N, M, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>Tis, N0, M0, grade 1 or X</td>
</tr>
<tr>
<td><strong>Stage IA</strong></td>
<td>T1, N0, M0, grade 1-2 or X</td>
</tr>
<tr>
<td><strong>Stage IB</strong></td>
<td>T1, N0, M0, grade 3</td>
</tr>
<tr>
<td></td>
<td>T2, N0, M0, grade 1-2 or X</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td>T2, N0, M0, grade 3</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>T3, N0, M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T1-2, N1, M0, any grade</td>
</tr>
<tr>
<td><strong>Stage IIIA</strong></td>
<td>T1-2, N2, M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T4a, N0, M0, any grade</td>
</tr>
<tr>
<td><strong>Stage IIIB</strong></td>
<td>T3, N2, M0, any grade</td>
</tr>
<tr>
<td><strong>Stage IIIC</strong></td>
<td>T4a, N1-2, M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T4b, any N, M0, any grade</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T, N3, M0, any grade</td>
</tr>
</tbody>
</table>

### Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Stage</th>
<th>T, N, M, Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stage 0</strong></td>
<td>Tis, N0, M0, grade 1 or X, any location</td>
</tr>
<tr>
<td><strong>Stage IA</strong></td>
<td>T1, N0, M0, grade 1 or X, any location</td>
</tr>
<tr>
<td><strong>Stage IB</strong></td>
<td>T1, N0, M0, grade 2 or 3, any location</td>
</tr>
<tr>
<td></td>
<td>T2-3, N0, M0, grade 1 or X, lower esophagus or X</td>
</tr>
<tr>
<td><strong>Stage IIA</strong></td>
<td>T2-3, N0, M0, grade 1 or X, upper and middle esophagus</td>
</tr>
<tr>
<td></td>
<td>T2-3, N0, M0, grade 2 or 3, lower esophagus or X</td>
</tr>
<tr>
<td><strong>Stage IIB</strong></td>
<td>T2-3, N0, M0, grade 2 or 3, upper and middle esophagus</td>
</tr>
<tr>
<td></td>
<td>T1-2, N1, M0, any grade, any location</td>
</tr>
<tr>
<td><strong>Stage IIIA</strong></td>
<td>T1-2, N2, M0, any grade, any location</td>
</tr>
<tr>
<td></td>
<td>T3, N1, M0, any grade, any location</td>
</tr>
<tr>
<td></td>
<td>T4a, N0, M0, any grade, any location</td>
</tr>
<tr>
<td><strong>Stage IIIB</strong></td>
<td>T3, N2, M0, any grade, any location</td>
</tr>
<tr>
<td><strong>Stage IIIC</strong></td>
<td>T4a, N1-2, M0, any grade, any location</td>
</tr>
<tr>
<td></td>
<td>T4b, any N, M0, any grade, any location</td>
</tr>
<tr>
<td><strong>Stage IV</strong></td>
<td>Any T, N3, M0, any grade, any location</td>
</tr>
<tr>
<td></td>
<td>Any T, any N, M1, any grade, any location</td>
</tr>
</tbody>
</table>
Treatment: T1 Disease (Localized to the Mucosa)

- Little or no risk of lymph node metastases

- T1a (lamina propria or muscularis mucosa)
  - Endoscopic mucosal resection followed by ablation (preferred)
  - Esophagectomy

- T1b (Invades submucosa)
  - Esophagectomy

NCCN. Esophageal and Esophagogastric Junction Cancers (Version 1.2014)
Treatment: Locally Advanced Disease (Resectable)

- **T1bN+, T2-T4aN0-N+**
  - Trimodality therapy with neoadjuvant chemoradiotherapy (CRT) followed by surgical resection

- **RT dose 41.4 - 50.4 Gy in 1.8 Gy daily fractions**
  - No utility in dose escalation
    - RTOG 94-05 (Minsky et al) 50.4 v. 64.8 Gy (w/ cis/5-FU)
    - Closed after interim analysis showed no probability of superiority in the high-dose arm

- Multiagent chemotherapy with cisplatin and 5-FU or paclitaxel and carboplatin typically used
CROSS Trial

• Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer
• 366 patients w/ T1N1 or T2-3N0 GE junction or esophageal cancer
• Randomized
  – Preoperative CRT (41.4 Gy & Carboplatin/Paclitaxel) followed surgery
  – Surgery alone
CROSS Trial Results

• R0 resection
  – 92% in CRT v. 69% in surgery arm (p<0.001)

• pCR (ypT0N0)
  – 29% CRT arm
  – 28% in adenoca v. 49% in SCC (p=0.008)

• +LN in resection specimen
  – 31% (CRT) v. 75% (p<0.001)

• Median OS
  – 49 months (CRT) v. 24 months (p=0.003)

• Overall Survival (5-year)
  – 47% (CRT) v. 34%
Treatment Planning

• CT Simulation
  – IV and/or esophageal contrast may be used to aid in target localization
  – Arms above head to maximize number of beam arrangements
  – Immobilization cradle
  – Consider 4D-CT for GE junction tumors
Target Volumes (RTOG 1010)

- GTVp: primary tumor in the esophagus
- GTVn: grossly involved regional lymph nodes
- CTV = GTVp with a 4 cm expansion sup/inf along the length of the esophagus and gastric cardia and a 1.0-1.5 cm radial expansion plus the GTVn with a 1.0-1.5 cm expansion in all dimensions
- The celiac axis should be covered for tumors of the distal esophagus or GE junction
- PTV (45Gy) expansion should be 0.5 to 1.0 cm and does not need to be uniform in all dimensions
- Boost PTV (50.4Gy) = GTVp and GTVn with an expansion of 0.5 to 1.0 cm
Target Volumes

- **GTV**
- **CTV**
  - Cropped off anatomic structures in which invasion is not likely (i.e. vertebrae, trachea/bronchi, aorta, lung)
- **PTV**
Target Volumes

- GTV
- CTV
- PTV (45Gy)
Boost Volumes

- Boost PTV (50.4Gy) = GTV with an expansion of 0.5 to 1.0 cm
Treatment Plan

- 3D-CRT with daily CBCT
- AP/PA to 36 Gy followed by 3-field boost to 45 Gy
- Additional cone down (Boost PTV) to 50.4 Gy
- Concurrent chemotherapy with carbo/taxol
Plan Sum
# Dose Constraints (RTOG 1010)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Metric</th>
<th>Per Protocol</th>
<th>Acceptable Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs (- PTV)</td>
<td>Max Dose (0.03 cc)</td>
<td>\leq 110% Rx Dose</td>
<td>\leq 113% Rx Dose</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
<td>\leq 20 Gy</td>
<td>\leq 21 Gy</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>\leq 20%</td>
<td>\leq 25%</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>\leq 25%</td>
<td>\leq 30%</td>
</tr>
<tr>
<td></td>
<td>V10</td>
<td>\leq 40%</td>
<td>\leq 50%</td>
</tr>
<tr>
<td></td>
<td>V5</td>
<td>\leq 50%</td>
<td>\leq 55%</td>
</tr>
<tr>
<td>Heart (&amp; pericardium)</td>
<td>Max Dose (0.03 cc)</td>
<td>\leq 52 Gy</td>
<td>\leq 54 Gy</td>
</tr>
<tr>
<td></td>
<td>Mean Dose</td>
<td>\leq 32 Gy</td>
<td>\leq 34 Gy</td>
</tr>
<tr>
<td></td>
<td>V40</td>
<td>\leq 50%</td>
<td>\leq 55%</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Max Dose (0.03 cc)</td>
<td>\leq 45 Gy</td>
<td>\leq 50 Gy</td>
</tr>
<tr>
<td></td>
<td>V20</td>
<td>\leq 30%</td>
<td>\leq 40%</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Max Dose (0.03 cc)</td>
<td>\leq 45 Gy</td>
<td>\leq 50 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean Dose</td>
<td>\leq 21 Gy</td>
<td>\leq 25 Gy</td>
</tr>
<tr>
<td></td>
<td>V30</td>
<td>\leq 30%</td>
<td>\leq 40%</td>
</tr>
</tbody>
</table>
Cumulative DVH
Including dose to PTV1 and Boost PTV2


