Introduction to ACRODeck

- The goal of ACRODeck is to introduce standard treatments of oncologic malignancies for early radiation oncology residents.

- Please note that there is often considerable variation in standard treatment recommendations.

- Moreover, the landscape of oncology is ever-changing; for practice changing landmark studies and feedback, please email: resident@acro.org.
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Clinical Presentation and Differential Diagnosis

- Patients often present with progressive dysphagia and weight loss
  - Chest pain, odynophagia, cough, and hoarseness are sometimes seen as well

- Differential Diagnosis:
  - GERD
  - Barrett’s esophagus
  - Esophageal stricture
  - Achalasia
  - Esophageal infections (candidiasis)
  - Esophageal cancer
  - Gastric cancer

For patients with severe dysphagia, a jejunostomy tube is preferred (to a gastrostomy)
Initial Workup

- H/P with labs
  - Emphasis on nutritional assessment and smoking cessation
  - CBC and CMP

- Imaging
  - CT CAP (with oral and IV contrast)
  - PET CT

- Procedures
  - Upper GI endoscopy (with biopsy)
  - EUS
  - Bronchoscopy (if tumor is at or above the carina)

Endoscopic resection is recommended for T1a or Tb tumors
Staging

Group staging is dependent on grade as well as histology

Table 32.3: AJCC 8th Edition (2017) Staging for Esophageal Cancer

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Node</th>
<th>Distant Metastasis</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>N0</td>
<td>No regional LNs</td>
<td>G1</td>
</tr>
<tr>
<td></td>
<td>M0</td>
<td>No distant metastasis</td>
<td></td>
</tr>
<tr>
<td>T1a</td>
<td>b. Invades submucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1b</td>
<td>a. Invades lamina propria or muscularis mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>N1</td>
<td>1 to 2 regional LNs</td>
<td>M1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distant metastasis</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>N2</td>
<td>3 to 6 regional LNs</td>
<td>G3</td>
</tr>
<tr>
<td>T4</td>
<td>N3</td>
<td>7 regional LNs</td>
<td></td>
</tr>
</tbody>
</table>

Notes: Resectable = invades pleura, pericardium, diaphragm, esophagus vein, or peritoneum. Unresectable = invades aorta, vertebral body, narium. AJCC suggests ≥10 nodes removed for pT1 tumors, ≥20 for pT2, and ≥30 for pT3-4.

ACRODeck: Esophageal Cancer
GEJ Tumors and the Siewert System

- GEJ tumors are between 5 cm proximal and 5 cm distal to the GEJ

- These tumors are classified via the Siewert System:
  - Type 1: adenocarcinoma of the distal esophagus
  - Type 2: true carcinoma of the cardia arising immediately at the GEJ
  - Type 3: subcardial gastric carcinoma that infiltrates the GEJ and distal esophagus from below
    - These are considered gastric cancers per NCCN (and are treated as such)
Stage II - IVA

- Stage I disease (no muscularis propria involvement) can often be treated definitively with resection alone
- T4b disease (unresectable) and surgically unfit patients can be treated with definitive chemoRT
- Disease with invasion into significant OARs (heart, trachea, great vessels) can be treated with chemotherapy alone
Systemic Therapy

- The mainstay of esophageal cancer treatment is neoadjuvant chemoRT followed by surgery
  - However: chemotherapy may be utilized in the neoadjuvant, perioperative, adjuvant, or definitive settings

- NCCN category 1 recommendations include:
  - Carboplatin and Paclitaxel (5 cycles delivered weekly)
  - Oxaliplatin and Fluorouracil (3 cycles delivered q2 weeks)

If a pathologic complete response is not seen on surgical pathology, nivolumab is recommended (PMID: 33789008)
Radiotherapy

- The mainstay of esophageal cancer treatment is neoadjuvant chemoradiation (chemoRT) followed by surgery
  - However, radiotherapy may be utilized in the neoadjuvant, adjuvant, or definitive settings

- Radiotherapy volumes and dosing are quite variable, however:
  - A dose of around 50 Gy (with conventional fractionation) is commonly utilized for both neoadjuvant and definitive therapy
    - Lower doses (41.4 Gy as used in CROSS) are also acceptable for neoadjuvant therapy
  - Volumes include the gross tumor with a wide margin
    - See contouring atlas for details, PMID: 26104943

- Some institutions will dose escalate for tumors (i.e.: squamous cell carcinomas) in the cervical esophagus up to 74 Gy

Dose escalation had no benefit in the ARTDECO and INT 0123 trials
Radiation Simulation

- 4DCT (with oral and IV contrast)
  - Other techniques of motion management are also acceptable
  - NPO 3 hours prior

- Fuse PET-CT

- Use of immobilization device is strongly recommended
# Dose Constraints

<table>
<thead>
<tr>
<th>OAR</th>
<th>Dose Constraint (Per NCCN)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Mean &lt; 20 Gy</td>
</tr>
<tr>
<td></td>
<td>V20 Gy ≤ 20%</td>
</tr>
<tr>
<td>Heart</td>
<td>Mean &lt; 30 Gy</td>
</tr>
<tr>
<td></td>
<td>V30 Gy ≤ 30%</td>
</tr>
<tr>
<td>Kidneys (individual)</td>
<td>Mean &lt; 18 Gy</td>
</tr>
<tr>
<td>Liver</td>
<td>Mean &lt; 25 Gy</td>
</tr>
<tr>
<td>Stomach</td>
<td>Mean &lt; 45 Gy</td>
</tr>
<tr>
<td></td>
<td>Max &lt; 54 Gy</td>
</tr>
<tr>
<td>Spinal Cord</td>
<td>Max ≤ 45 Gy</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>Max ≤ 54 Gy</td>
</tr>
<tr>
<td></td>
<td>V45 Gy ≤ 195 cc</td>
</tr>
</tbody>
</table>

Dose constraints to critical OARs (i.e.: heart) may sometimes lead to the prescription of a lower neoadjuvant dose (41.4 Gy)
Radiation Toxicities

- **Acute:**
  - Fatigue
  - Esophagitis and weight loss
    - Often, the tumor will shrink and dysphagia will improve; then, esophagitis sets in later in the treatment course
  - Pneumonitis

- **Late:**
  - Esophageal strictures (can develop 4 – 12 weeks after therapy)
    - Dilations are helpful to alleviate symptoms
  - Esophageal fistulas
  - Pulmonary fibrosis
  - Pericarditis and coronary artery disease
A Word on Adjuvant Treatment

- While neoadjuvant chemoRT is typically the mainstay of esophageal cancer treatment, adjuvant chemoRT can be considered in cases of:
  - Positive margins
  - Tumor upstaging after surgery and/or nodal positivity
PET CT is performed 5-8 weeks after completion of neoadjuvant therapy to assess for surgical candidacy.
- Cervical and cervicothoracic tumors < 5 cm from the cricopharyngeus muscle are typically treated nonoperatively given the morbidity of surgery.

Surgery (esophagectomy/esophagogastrectomy) is typically done 8-12 weeks after neoadjuvant therapy.
- For most distal lesions, mediastinal and upper abdominal lymphadenectomy is also performed.

If a pathologic complete response is not seen on the surgical specimen, adjuvant nivolumab is prescribed (for a treatment duration of 1 year).

Radiopaedia: Image shows the radiological landmarks in the esophagus and their distance (in cm) from the upper incisors on endoscopy.
Per the 2012 CROSS trial (PMID 22646630):
- Median overall survival for SCC was 6.8 years (with a 49% pCR)
- Median overall survival for ACA was 4.1 years (with a 23% pCR)

Follow-up after surgery is typically q3-6 months initially with imaging and endoscopy as clinically indicated

Survival by clinical T category: A) Squamous Cell Carcinoma B) Adenocarcinoma
Review
Review #1: The CROSS Regimen

In the CROSS study, what was the neoadjuvant chemoradiation treatment regimen for resectable disease?

(A) 41.4 Gy with FLOT
(B) 61.6 Gy with FLOT
(C) 41.4 Gy with carboplatin/paclitaxel
(D) 61.6 Gy with carboplatin/paclitaxel

Adenocarcinoma (75%) was the more common histology seen on the CROSS trial.
Review #2: Modern Radiation

The use of IMRT in esophageal cancer has been showed to reduce toxicity of what OAR?

(A) Lung
(B) Heart
(C) Stomach

NRG GI006 is a phase 3 RCT comparing proton therapy to IMRT
Review #3: Wu Contouring Atlas

What is a recommended superior CTV expansion (on the primary) for a cT3N1 GEJ adenocarcinoma?

(A) 1.5 cm
(B) 3.5 cm
(C) 5.5 cm
Review #4: Checkmate 577

In the Checkmate 577 trial, which of the following was statistically improved with the addition of adjuvant Nivolumab?

(A) Disease Free Survival
(B) Overall Survival
(C) All of the above
Review #5: NEO-AGIS

In the NEO-AGIS study, which of the following was significantly improved in the chemoRT arm?

(A) R0 resection rate
(B) pCR rate
(C) ypN0 rate
(D) Tumor regression (grades 1 and 2)
(E) All of the above

The rate of neutropenia (grade 3 and 4) was 5x greater in the chemotherapy alone arm vs. the chemoRT arm (14.1% vs. 2.8%)
The ESOPEC trial is comparing perioperative CHT (with FLOT) with the CROSS regimen (chemoRT)