Management of Stage I Esophageal Cancer

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Case Presentation

• 52 y/o Female
• CC: 15 lbs weight loss in 3 mo.
• HPI: denies chest or abdominal pain, dysphagia, SOB or fevers. Normal BMs.
• PMH: HTN, Emphysema
• Meds: atenolol, amlodipine, valsartan, HCTZ, flovent, albuterol
• PSH: denied
• Soc hx: smoking ½ pack/day x 30 yrs. Quit 1 mo ago. ETOH occasional
• Fam Hx: non-contributory
Case Presentation

- V/S- afebrile, BP 163/93, HR 79  RR 18, O2sat 98%
- PE- NAD
  - Neck- no lymphadenopathy
  - Chest- CTA x 2
  - Abdomen- soft, nontender, nondistended
- Labs- unremarkable. Hct 37
- Pt referred to GI
  - EGD- erosive gastritis and nodular mucosa at mid esophagus (at 24 cm).
    - Esophageal biopsy- moderate to poorly differenciated Squamous Cell Carcinoma.
  - Colonoscopy- negative
Esophageal Cancer Work-up

- CXR - unremarkable
- Double contrast Barium Esophagram
  - Negative, no obstruction, no narrowing or filling defects
- Chest, Abdomen, Pelvis CT scan – unremarkable.
- EUS - esophageal lesion at mucosa, not through wall, no suspicious LN → T1
- Test for cardiopulmonary status:
  - PFT - moderate obstructive lung disease.
  - Echo - EF 65%
  - Stress test - no ischemia
**OR - Esophagogastrectomy**

- **Exploratory laparotomy**
  - Mobilization of stomach and duodenum.
  - Preservation of right gastroepiploic artery.
  - Pyloroplasty. Feeding jejunostomy.

- **Right posterolateral thoracotomy over 4\textsuperscript{th} ICS.**
  - EGD- localization of lesion at upper mid esophagus
  - Paraesophageal LN- negative on frozen section.
  - Division of stomach distal to GE junction along lesser curve with stapling device.
  - Division upper esophagus with scalpel.
  - Specimen margins - negative on frozen section.
  - Anastomosis- stomach fundus to upper esophagus
    - 1 layer interrupted 2-oEthibond sutures.
  - NGT. Chest tubes x 2. EBL – 500 ml. Crystalloid- 6 L
Post-op Course

- POD #2 - Transferred to floor from PACU
- POD#5 - Barium Esophagram - Negative
- POD#6 - TF via jejunostomy
- POD#7 - Clear liquid diet
- POD#10 - Chest tubes removed
- POD#13 - Discharged home
Pathology

- Esophagus and proximal stomach
  - Moderately to poorly differentiated squamous cell carcinoma – Grade 3.
  - Invasive into submucosa.
  - Tumor 2.8 x 2.2 x 0.3 cm
  - Negative margins
    - 3cm proximal margin
    - 7.5cm distal margin
  - Negative lymphovascular invasion
    - 11 LN, all negative
- Celiac, paraesophageal, paratracheal LN- negative

- Stage I B
  - pT1b → tumor invades submucosa
  - pNo → 16 neg LN
  - pM0 → no mets
  - Grade 3
Management of Stage I Esophageal Cancer
Esophageal Cancer

- Squamous cell carcinoma
  - Majority of esophageal carcinomas worldwide.
  - Incidence is highly variable
    - 20 per 100,000 in the United States and Britain
    - 160 per 100,000 in certain parts of South Africa and China
    - African American males
- Environmental factors
  - Smoking and alcohol consumption (in Western societies)
  - Nitroso compounds in pickled vegetables and smoked meats
  - Mineral deficiencies (zinc and molybdenum)
- Long-standing achalasia
- Lye strictures
- Tylosis- autosomal dominant disorder, hyperkeratosis
Esophageal Cancer

• Adenocarcinoma
  • Increasing frequency
    • > 50% of esophageal cancer in most Western countries.
    • White males
  • Association with GERD and Barrett’s esophagus (BE).
  • BE – replacement of squamous epithelium in the distal esophagus with columnar epithelium.
    • Occurs in approximately 10 - 15% of patients with GERD.
    • The most important etiologic factor in the development of esophageal adenocarcinoma
  • Incidence of adenocarcinoma in a patient with BE
    • 1 in 100 to 200 patient-years of follow-up
    • Risk it is at least 40 to 50 times that expected for a similar population without BE.
Signs and Symptoms - Esophageal Ca

- Dysphagia
  - Late presentation
    - Lack of a serosal layer on the esophagus allows the smooth muscle to dilate with ease.
    - Dysphagia → 60% of the esophageal circumference is infiltrated with cancer.
- Tracheoesophageal fistula
  - coughing, choking, and aspiration pneumonia
  - >40% will have evidence of distant metastases
- Hoarseness
  - Vocal cord paralysis caused by invasion of the left recurrent laryngeal nerve by the primary tumor or LN metastasis.
- Severe bleeding
  - from the primary tumor or from erosion into the aorta or pulmonary vessels
- Weight loss
- Nonspecific upper GI symptoms
  - that results in patient having an upper endoscopy.
Work-up for Esophageal Cancer

- Confirmation of diagnosis
  - Esophagram
  - Upper endoscopy
    - Location of tumor
    - Biopsy
- Determination of extent of disease → Staging
  - CT scan of the chest, abdomen, and pelvis
    - Identify metastatic disease: lung and liver.
    - May underestimate tumor depth
  - PET scan or PET-CT scan - identify metastasis
  - Endoscopic ultrasound (EUS)
    - Determines depth of the wall penetration by the tumor and the presence of LN metastases with 80% accuracy.
    - Limited accuracy in differentiating between intamucosal and submucosal tumor invasion.
Primary tumor \((T)\)

- **TX** – cannot be assessed
- **T0** - No evidence of primary tumor
- **Tis** - High-grade dysplasia
- **T1** - Tumor invades lamina propria or submucosa
- **T2** - Tumor invades muscularis propria
- **T3** - Tumor invades adventitia
- **T4a** - **Resectable** tumor invades adjacent structures
  - pleura, pericardium, diaphragm
- **T4b** - **Unresectable** tumor invades adjacent structures
  - aorta, vertebral body, trachea
American Joint Committee on Cancer (AJCC) tumor node metastasis (TNM) staging system

**Regional lymph nodes (N)**
- **N**0- No regional LN mets
- **N**1- 1 to 2 positive LN
- **N**2- 3 to 6 positive LN
- **N**3- 7 or more positive LN

**Distant metastases (M)**
- **M**0- No distant metastases
- **M**1- Distant metastases
### TABLE 2 -- AJCC Definitions of TNM classifications for esophageal cancer

<table>
<thead>
<tr>
<th><strong>Primary tumor (T)</strong></th>
<th><strong>Definition of TNM</strong></th>
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<tbody>
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### Regional lymph nodes (N)

*Regional lymph node* is defined as any periesophageal lymph node from cervical periesophageal lymph nodes to celiac lymph nodes.

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<thead>
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<td>N0</td>
<td>No regional lymph node metastases</td>
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<td>1 to 2 positive regional lymph nodes</td>
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<td>7 or more positive regional lymph nodes</td>
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<th><strong>M</strong></th>
<th><strong>Definition</strong></th>
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<tr>
<td>M0</td>
<td>No distant metastases</td>
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<tr>
<td>M1</td>
<td>Distant metastases</td>
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### Definition of Histologic Grade

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<th><strong>G</strong></th>
<th><strong>Definition</strong></th>
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<tr>
<td>G1</td>
<td>Well differentiated</td>
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<tr>
<td>G2</td>
<td>Moderately differentiated</td>
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<tr>
<td>G3</td>
<td>Poorly differentiated</td>
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<td>G4</td>
<td>Undifferentiated</td>
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### Definition of Cancer Location

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<thead>
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<tr>
<td>Upper thoracic</td>
<td>Proximal tumor margin is 20 to 25 cm from incisors</td>
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<tr>
<td>Middle thoracic</td>
<td>Proximal tumor margin is &gt;25 to 30 cm from incisors</td>
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<tr>
<td>Lower thoracic</td>
<td>Proximal tumor margin is &gt;30 to 40 cm from incisors</td>
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<tr>
<td>Gastroesophageal junction</td>
<td>Includes tumors whose epicenter is in the distal thoracic esophagus, gastroesophageal junction, or within the proximal 5 cm of the stomach that extend into the gastroesophageal junction or esophagus</td>
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<td>HISTOLOGY</td>
<td>ADENOCARCINOMA</td>
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Esophageal Cancer

- Early stage ~ mucosal based cancer
- Locally advanced cancer
- Metastatic cancer
Esophagectomy

- **Morbidity**
  - 30% of patients develop at least one serious postoperative complication such as pneumonia, myocardial infarction, and wound infection. *

- **Mortality**
  - Dutch National Medical Registry**
    - Mortality rates for esophagectomy were 12.1%, 7.5%, and 4.9% at centers performing 1 to 10, 11 to 20, and > 50 esophagectomies per year, respectively.


Are there any treatment alternatives to esophagectomy?
Endoscopic Treatment

- Literature - treatment for Barrett’s esophagus (BE).
  - Removal of metaplastic epithelium and repopulation with normal squamous cells.

- Techniques
  - Mucosal ablation
    - Muscularis mucosa
  - Mucosal resection
    - Submucosa

- Depth of ablation
  - Subsquamous islands of BE.
  - Ablating deeper may result in stricture formation.
Endoscopic Ablation

- **Thermal energy**
  - Laser, electrocoagulation, argon plasma coagulation.

- **Radiofrequency ablation (RFA)**
  - Delivery of bipolar energy through electrodes
  - Controlled and precise duration, intensity and depth of ablation.
    - deep injury to the esophagus is avoided → decreasing esophageal stricture and other complications.
  - HALO – electrodes wrapped around a balloon.
Endoscopic Ablation

- Photodynamic therapy (PDT)
  - Porfimer sodium (PORPDT).
  - Endoscopic light $\rightarrow$ activation of the photosensitizer $\rightarrow$ O$_2$ free radicals

- Overholt (2006)
- Prospective, randomized, controlled trial comparing PDT and omeprazole vs omeprazole alone in the treatment of BE with HGD in 208 pts
- Treatment arm underwent 1-3 PDT sessions.
- Complete ablation of HGD - 77% of patients who had PDT
- 13% of patients in the PDT group progressed to adenocarcinoma compared with 28% in the control group.
- SE: Photosensitivity reactions (69%), esophageal strictures (36%), vomiting (32%), and chest pain (20%).
- Recurrence of subsquamous intestinal metaplasia 30% in most studies.

Overholt BF. Porfimer sodium photodynamic therapy for management of Barrett’s esophagus with high-grade dysplasia. Center of Excellence for Treatment of Barrett’s Esophagus, Thompson Cancer Survival Center, Knoxville, Tennessee
Endoscopic Ablation

- Less invasive, less morbidity and mortality than esophagectomy.
- Ablation destroys metaplastic tissue, but do not provide a pathology specimen by which to judge the depth of neoplastic invasion and the completeness of the ablation.
- Subsquamous islands of dysplastic tissue.
- PPI tx
- Repeat treatments, surveillance with EGD.
Endoscopic mucosal resection (EMR)

With single channel scope

A

Injection needle

Injected submucosal saline

snare

With dual channel scope

B

Grasping forceps

Cap method

C

Suction and snaring

cap
Figure 5: Endoscopic Mucosal Resection—(A) Focal nodular lesion composed of Barrett's epithelium with high-grade dysplasia. (B) The focal lesion has been completely excised via endoscopic mucosal resection. (C) Circumferential long-segment Barrett's esophagus. (D) Circumferential mucosal resection can achieve complete excision of more extensive Barrett’s involvement.
Endoscopic Mucosal Resection

- Specimen - mucosa and submucosa
  - Provides pathologic information about depth of invasion by tumor
- Most series are nonrandomized
  - Treatment arms are combination of various ablative therapies.
  - EMR - high stricture rate (70%) due to extensive resection of the submucosa.
  - Localized and more limited EMR - short-term recurrence rates of 11% to 30%.
- Combination tx - EMR followed by ablation.
Retrospective review of pts treated 2001-2010
40 pts – endotherapy (HDG-22, Adenoca-18)
  • EMR and ablation ~3 interventions per pt
61 pts- esophagectomy (HDG-13, Adenoca-48)
Endotherapy
  • Intramucosal adenocarcinoma resected in all pts
  • Esophagectomy for persistent HGD-2pts
  • Lap Nissen Fundoplication-8 pts
Esophagectomy with neg margins – all pts
Endotherapy had lower morbidity than Esophagectomy
  • 39% vs 0 (P < .0001)
Similar survival
  • 94% at 3 years in both groups
  • Median follow-up 34 months after esophagectomy vs 17 months after endotherapy (P = .0026).
Retrospective review of records of all patients who underwent esophagectomy without preoperative therapy for pT1 esophageal cancer.

75 consecutive patients (58 men, 17 women), median age was 68 years.

30 patients had T1a and 45 had T1b. 60 patients had adenocarcinoma.

Nodal metastases in 2 of 30 (6%) T1a and 8 of 45 (17.5%) T1b tumors.

MFN was present in 30% (9 of 30) of T1a tumors and 29% (13 of 45) of T1b tumors.

10 of 30 (33.3%) patients with T1a and 25 of 45 (58%) with T1b had MFN, LVI, or nodal metastases.

Four patients with squamous carcinoma had nodal metastases and 5 had MFN.

Overall 5-year survival was 78%.

High incidence of MFN, LVI, and occult nodal metastases does not support the use of ET in patients with T1 esophageal cancer.
Prevalence of nodal metastasis at various depths of mucosal and submucosal invasion.

Retrospective review of 54 T1 adenocarcinomas from 258 esophagectomy specimens.

Tumors were classified as:
- intramucosal
- submucosal
  - SM1 (upper third), SM2 (middle third), or SM3 (lower third)

Nodal metastases were present in:
- 0% of intramucosal
- 21% of SM1, 36% of SM2, and 50% of SM3 tumors.
- The differences were significant between intramucosal and submucosal tumors (p < 0.0001), but not between the various subclassifications of submucosal tumors (p = 0.503).

High prevalence of nodal metastases at all depths of submucosal invasion.
Conclusion

- Endoscopic treatment for esophageal cancer
  - May be limited to intramucosal tumors
  - Alternative to patients with prohibitive risk for esophagectomy
  - Patients need surveillance with EGD.
    - Risks of recurrence and stenosis
- Esophagectomy is still standard of care for treatment esophageal cancer, specially with submucosal invasion.
References