ESOPHAGEAL CANCER

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Disclosures
Nothing to disclose.

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Geographic distribution</th>
<th>Risk factors</th>
<th>Precursor lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell carcinoma (SCC)</td>
<td>Asia, Africa, South America, African American in North America</td>
<td>Alcohol, tobacco</td>
<td>Esophageal squamous dysplasia</td>
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<tr>
<td>Adenocarcinoma (EAC)</td>
<td>North America, Europe</td>
<td>GERD, Obesity</td>
<td>Barrett’s esophagus</td>
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Esophageal Carcinoma: subtypes

Esophageal Adenocarcinoma (EAC)

- Epidemiology
- Risk factors
- Staging and therapy
  - Early stage disease & endoscopic therapy
- Prognoses
- Future developments

Epidemiology

- In 2014, 18,000 new cases of esophageal ca, 60% of which were EAC
- The incidence of EAC in the US was 2.5 per 100,000 people in 2011
- The incidence of EAC has continued to increase in the US but may be reaching a plateau

Trend of incidence of EAC in US

SEER cancer registry, US
Risk factors of EAC

- Male sex
- Advancing age
- White race
- GERD
- Obesity
- Tobacco use
- Barrett’s esophagus

Risk Factors of EAC

- Risk of EAC is 8-fold greater in patients with recurrent GERD symptoms
- Patients with long standing symptoms, nocturnal symptoms, or more frequent symptoms are at increased risk
- Severity of symptoms is not associated with increased risk of EAC
- GERD \(\rightarrow\) erosive esophagitis \(\rightarrow\) aberrant healing process \(\rightarrow\) BE \(\rightarrow\) EAC
- Approximately 50-60% patients with EAC do not have GERD

Risk factors of EAC

- Obesity increases risk by x2.4 to 2.8
- Abdominal obesity increases risk of BE & EAC
- Mechanical effect of obesity \(\rightarrow\) hiatal hernia \(\rightarrow\) increased risk of GERD
- Hormonal effects of obesity (IGF) \(\rightarrow\) alterations of adipokines \(\rightarrow\) BE \(\rightarrow\) EAC

Risk Factors of EAC

- Infection with H pylori appears to protect against EAC
- EAC risk is reduced in population with H pylori prevalence; meta-analysis of 15 studies showed EAC risk decreased by 41% among those with H pylori
- However, HPE neither cause or worsens GERD

Endoscopic screening & surveillance (EAC)

- BE is precursor of EAC
- 6-12% of patient with long standing GERD have BE on endoscopic screening
- 40% patients with BE do not have GERD
- Annual cancer risk of EAC is 0.12 to 0.40% in non-dysplastic BE
- Dysplasia in BE signals increased risk:
  - 1% for LGD and >5% for HGD
Endoscopic screening and surveillance

- Endoscopic surveillance every 3 years is recommended for non-dysplastic BE
- 80-90 percent EAC diagnosed in patient with no BE
- EAC detected during endoscopic surveillance for BE is more likely to be early stage, amenable to curative therapy & survival is longer compared to those with symptoms in whom EAC is diagnosed

Clinical presentation

- Progressive dysphagia, weight loss, refractory GERD, GIB
- Less common symptoms: Fe def anemia, oropharyngeal dysphagia
- Asymptomatic: discovered during screening or surveillance endoscopy (<15% cases of EAC)
- Only 25% of patients with EAC present with localized disease

Diagnosis

- CT doesn’t accurately identify localized EAC
- Barium esophagogram
- Endoscopy: diagnosis and plan of therapy
  - Stricture, mass, ulcer, nodule, subtle irregularity in the mucosa
  - Size, location and morphology
- EAC occur in distal esophagus or GE junction in 75% of patients

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>AJCC Staging Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage T</td>
<td>N</td>
</tr>
<tr>
<td>T1</td>
<td>N0</td>
</tr>
<tr>
<td>T2</td>
<td>N0</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
</tr>
<tr>
<td>T4</td>
<td>Any</td>
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</tbody>
</table>

- Regional LN cannot be assessed: T4a
- N0 Regional LN cannot be assessed: T4b
- N1 Metastasis: T1a, T1b, T2
- N2 Metastasis: T3, T4a
- N3 Metastasis: T4b

- Distant metastasis: X
- MI: distant metastasis

- Stage grouping: Stage grouping or TNM

- Note: Based on the 2010 American Joint Committee on Cancer staging system.
Staging and LN metastasis


Management: Staging

• Endoscopy with or without mucosal resection (EMR)
• CT chest/abdomen
• Endoscopic ultrasound (EUS)
• PET scan

Role of EUS in staging

• Highly accurate for T, N staging
• Not reliable for T1a vs T1b
  – endoscopic appearance — size, diameter, failure to rise with submucosal injection, multifocality, mucosectomy/large biopsy
• Lymph node >10 mm, round, smooth, hypoechoic
  – Accuracy 80%; FNA increases accuracy to 92-98%
• Restaging after chemo-radiation
  – EUS accuracy for T (30-60%), N (40-70%)
  – PET /CT better accuracy than EUS

Qumaseya B, et al. GIE 2015;81:865

Management: Mucosal Tumors

(Stage 0 or 1a)

• Stage 0 or 1a: HGD or EAC limited to the mucosa
• Risk of LN metastasis is 0
• Esophagectomy
• Endoscopic therapy
  – Visible lesions, <2 cm in size
  – Small resectable areas of dysplastic BE
  – Moderate or well differentiated grade EAC
  – Lack of lymphovascular invasion

Gastroenterology 2011;141:42

Endoscopic therapy

• Endoscopic resection
  – EMR, ESD
  – Provides histologic data: depth of invasion, grade, LVI
  – Staging and treatment
• Endoscopic ablation
  – RFA, Cryoablation, Argon, PDT
  – Doesn’t provide histologic data
  – Buried glands
• Hybrid (resection+ ablation)

Endoscopic therapy

• Endoscopic eradication of residual BE
  – 30% recurrence of EAC without adjuvant BE eradication
• Stepwise radical endoscopic resection of residual BE
  – High rate of stricture formation compared to ablation therapy
• Most reported modality is RFA
  – 80% success in complete remission of dysplasia in patients with T1a EAC
  – Recurrence of BE in 33% within 2 years after complete eradication of BE (cohort without cancer at baseline)
  – Aggressive surveillance is recommended: q 3 months for 1 year, q 6 months during 2nd year, and annually thereafter


Management: Mucosal Tumors

Stage 1b

• Stage 1b: tumors that have penetrated muscular mucosae and have invaded submucosa
• sm1, sm2, sm3
• Risk of LN metastasis is up to 13-56%
  – ESD for selected sm1/sm2 (<2 cm, no lymphovascular invasion, <500mminction invasion)
  – Radical esophagectomy

Management: locally advanced tumors

- Neo-adjuvant CRT
- Esophagectomy
- Surgical outcome better in high-volume centers
- Minimally invasive esophagectomy may have similar outcomes but is technically challenging
- Overall 3-year survival is 30-60%
- Poor outcome in residual, node+, completely resected disease
  - adjuvant CRT benefits SCC, ?EAC

Surgical Outcomes

Stage IIA: T2N0M0
Stage IIB: T3N0M0; T1-2N1M0


Management: Advanced Tumors

- 5 yr survival is <15%
- Endoscopic placement of SEMS
- High dose intraluminal brachytherapy
- Endoscopic dilation or ablation, placement of plastic stents, bypass surgery or chemoradiotherapy are NOT recommended
  - Low efficacy & high complications
- Palliative chemotherapy
  - Unresectable, metastatic, recurrent disease

Palliative Treatment of Malignant Esophageal Stricture

- FC or PC SEMS equally effective & safe
- Stents with anti-reflux features may have decreased GER & complications
- Special features (niti-S) to reduce migration rate can cause traumatic injury & major adverse events
- Insufficient evidence to recommend one type of SEMS over other type
- SEPS conforms less easily to stricture, high complication rate including migrations, & increased failure rate of stent placement because of wider diameter of delivery system

Palliative Treatment of Malignant Esophageal Fistula

- Fistula result from invasion of respiratory tract or pleural cavity, mediastinal or lung cancer invasion of esophagus
- Closure rate 73-100% with covered SEMS
- FC or PC SEMS can be used as long as covering completely seals the fistula
- Treatment of choice for malignant fistula

Shin JH. Radiology 2004;232:252

Stent Placement as a Bridge to Surgery

- Neo-adjuvant CRT used in regionally localized esophageal cancer
- Stent could serve as bridge to surgery during neo-adjuvant CRT by maintaining nutrition
- Stent-related complications can be avoided by performing esophagectomy shortly after neo-adj CRT is completed
- Several studies reported benefit in improving dysphagia & maintaining nutrition; however, complications such as perforation, migration leading SB perforation & obstruction have been reported


Irradiation Stents

- SEMS loaded with I125 combines the advantages of stents & brachytherapy into a single treatment modality
- Prolongs survival, sustained relief of dysphagia in advanced or non-resectable esophageal cancer
- No difference in complications compared to SEMS
- Non FDA device in Asian populations, no data from US
- Not recommended in US

Lancet 2014:15:546

Stent-related Complications: Early

- Immediately or within 2-4 weeks
- Chest pain
  - up to 60%, moderate to severe lasting 10 days, requiring analgesics in 90%, rarely need to remove stent
- Fever
- GERD
  - mixed data on effectiveness of stent with reflux valve
- Globus sensation
- Perforation
- Stent migration 7-75%
- Bleeding: 1%
Stent-related Complications: Delayed

- Recurrent dysphagia rate 53-65% requiring re-intervention in 50%
  - Tumor over- or ingrowth: 2nd stents restores luminal patency
  - Migration in 7-75%: Endoscopic repositioning or exchange for new stent
  - Food impaction: endoscopy
  - Recurrence of stricture: 50%
- Spontaneous stent fracture & collapse
  - Endoscopic stent in stent technique
- Fistula formation
  - Due to radial force causing pressure necrosis, next to proximal or distal margin, managed by covered stent
- Death: 0.5-2%

Ramirez FC, et al. Gastrointest Endosc 1997;45:360

Prognosis

- The overall 5-year survival rate of EAC in US is 17%
- Patients are diagnosed when regional (30%) or distant (40%) metastasis has already occurred
- 5-year survival for localized disease is 39% and 4% when distant metastasis is present
- 60-70% have not been receiving guidelines concordant therapy
- Management appear to improve by discussion with multidisciplinary tumor board

Summary

- The main risk factors for EAC are GERD, obesity, cigarette smoking; cigarette smoking & alcohol consumption are main risk factors for SCC
- Endoscopic screening detects BE & periodic surveillance of BE detects dysplasia and early EAC
- Endoscopic hybrid therapy (EMR+RFA) is effective & safe for mucosal tumors
- Esophagectomy preceded by neoadjuvant CRT is the treatment of choice for localized tumors
- Endoscopic placement of SEMS is first line palliative options for dysphagia due to advanced or recurrent tumors