FWCC guidelines
Esophageal Cancers

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**Diagnosis and work up:**

1. H&P
2. EGD
3. Pathological evaluation including Her2neu status
4. CT Chest/Abdomen
5. PET/CT scan
6. EUS (where needed)
7. Nutritional evaluation (Amanda Milligan Ext: 55642)
9. Multi-disciplinary decision making
10. Her2+ve testing using IHC (3+) or FISH

5. **PET/CT scan:**

95% of primary esophageal cancers are FDG-avid. Meta-analysis shows that PET is 67% sensitive and 97% specific in detecting distant metastasis as opposed to CT scan which is 37% sensitive and 66% specific to detect distant metastasis.

For loco-regional cancer spread PET is 51% sensitive and 84% specific.

PET can also be used to assess response in adenocarcinoma after 14 days of chemotherapy and help guide further treatment.

Medicare covers for PET during initial evaluation and subsequent treatment evaluation.

(Ref 1-3)
**Staging:**

New WECC (World esophageal cancer consortium)/AJCC 8: Staging system for esophageal cancer (Ref 4):

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>GX</td>
<td>Grade cannot be assessed</td>
</tr>
<tr>
<td>G1</td>
<td>Well differentiated</td>
</tr>
<tr>
<td>G2</td>
<td>Moderately differentiated</td>
</tr>
<tr>
<td>G3</td>
<td>Poorly differentiated</td>
</tr>
<tr>
<td>G4</td>
<td>Undifferentiated</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>T stage</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>T1a</td>
<td>Tumor invading lamina propria or muscularis mucosa</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor invading submucosa</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor invading muscularis propria</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor invading adventitia</td>
</tr>
<tr>
<td>T4a</td>
<td>Tumor invading pleura, pericardium, or diaphragm</td>
</tr>
<tr>
<td>T4b</td>
<td>Tumor invading adjacent structures</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>N stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nx</td>
<td>Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>N0</td>
<td>No regional lymph node metastasis</td>
</tr>
<tr>
<td>N1</td>
<td>Regional lymph node metastasis involving 1-2 nodes*</td>
</tr>
<tr>
<td>N2</td>
<td>Regional lymph node metastasis involving 3-6 nodes*</td>
</tr>
<tr>
<td>N3</td>
<td>Regional lymph node metastasis involving 7 or more nodes*</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>M stage</th>
<th>Description</th>
</tr>
</thead>
<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>Nonregional lymph node metastasis or distant metastasis</td>
</tr>
</tbody>
</table>

*Regional lymph nodes extend from peri-esophageal cervical to celiac nodes.*
**NEW WECC/AJCC 8: Staging system for esophageal cancer:**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T0N0M0, any grade</td>
</tr>
<tr>
<td></td>
<td>TisN0M0, any grade</td>
</tr>
<tr>
<td>Stage 1A</td>
<td>T1N0M0, grade 1/2</td>
</tr>
<tr>
<td>Stage 1B</td>
<td>T1N0M0, grade 3</td>
</tr>
<tr>
<td></td>
<td>T1N0M0, grade 4</td>
</tr>
<tr>
<td></td>
<td>T2N0M0, grade 1/2</td>
</tr>
<tr>
<td>Stage IIA</td>
<td>T2N0M0, grade 3/4</td>
</tr>
<tr>
<td>Stage IIB</td>
<td>T3N0M0</td>
</tr>
<tr>
<td></td>
<td>T0-2N1M0, any grade</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>T0-2N2M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T3N1M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T4aN0M0, any grade</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>T3N2M0, any grade</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>T4aN1-2M0, any grade</td>
</tr>
<tr>
<td></td>
<td>T4banyNM0, any grade</td>
</tr>
<tr>
<td></td>
<td>Any TN3M0, any grade</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T, any N, M1, any grade</td>
</tr>
</tbody>
</table>
Treatment:

1. Medically fit localized or locally advanced resectable cancer: (T1a-T4a N0-N1 M0)
   Cervical or cervical thoracic <5cm from cricopharyngeus or +ve Cervical lymph nodes are considered unresectable

   a) Adenocarcinoma:
      i. Clinical trial (ACOSOG Z4051) Adenocarcinoma distal esophagus.
      ii. Neo-adjuvant chemo-radiotherapy followed by surgery
      iii. Peri-operative chemotherapy and surgery
      iv. Tis and T1a may be treated with EMR or ablation
      v. T1a-T4a treated with Esophagectomy

   b) Squamous cell cancer:
      i. Neo-adjuvant chemoradiotherapy followed by surgery though survival advantage has been inconsistent. Latest Danish trial shows survival advantage with neo-adjuvant chemo-radiotherapy in both squamous and adenocarcinoma.
2. Locally advanced unresectable or patient not medically fit to undergo surgery

a) Adenocarcinoma:

i. Clinical trial (CTSU/RTOG 0436)
ii. Definitive chemo-radiotherapy
iii. Palliative XRT and/or stent placement

b) Squamous cell cancer:

i. Clinical trial (CTSU/RTOG 0436)
ii. Definitive chemo-radiotherapy
iii. Palliative XRT and/or stent placement
3. **Adjuvant treatment:**

i. R0 resection: Only indicated if patient did not receive Neo-adjuvant treatment.

ii. R0 resection (squamous cell N0 or N+ve= no treatment indicated)

iii. R0 resection (Adenocarcinoma, Post-op chemo-radiotherapy for T2N0 high risk and T3N0 if not received pre-operatively.

iv. R1 resection: Consider adjuvant chemotherapy or chemoradiotherapy
4) Stage IVC or metastatic disease

Palliative chemotherapy + best supportive care
Follow up:

1. Every 3-6 months or as clinically indicated
2. Use of CT or PET/CT or EGD as indicated
Treatment regimens:

1) **ACOSOG Z4051** - A Phase II Study of Neoadjuvant Therapy with Cisplatin, Docetaxel, Panitumumab Plus Radiation Therapy Followed by Surgery in Patients with Locally Advanced Adenocarcinoma of the Distal Esophagus

Criteria: Histologic proof of resectable primary adenocarcinoma of the distal esophagus or GE junction, Siewert Type I or II. TNM stages T3NOMOm T2-3N1, M0, or T2-3N0-1M1a

2) **Neo-adjuvant chemo-radiotherapy**

   A) Cisplatin 100mg/m2 on day 1 and 29
      5FU 1000mg/m2 continuous infusion for 4 days on day 1-4 and 29-32
      XRT 54 Gy for 5.5 weeks  (Ref 5)

   B) Paclitaxel 50mg/m2 and Carboplatin AUC=2 on days 1, 8, 15, 22 and 29 with 41.4 Gy radiation (Weekly carbo/taxol for 5 weeks with XRT) (Ref 11)

   C) Cisplatin 30mg/m2 and Irinotecan 50mg/m2 days 1,8,22,29 with 45 Gy XRT
      Post-op
      Cisplatin 30mg/m2 and Irinotecan 65mg/m2 days 1,8 q 21 days for 3 cycles
      (Ref 8)

      OR

      Cisplatin 30mg/m2 and Paclitaxel 50mg/m2 days 1,8,15,22,29 with 45Gy XRT
      Post op
      Cisplatin 75mg/m2 and Paclitaxel 175mg/m2 day 1 q 21 days for 3 cycles

   D) Oxaliplatin 85mg/m2 IV on days 1,15, and 29 for 3 doses
      Capecitabine 625-825mg/m2 PO BID on days 1-5 for 5 weeks with XRT

3) **Definitive chemo-radiotherapy**

   A) **CTSU/ROTG 0436**: A Phase III Trial Evaluating the Addition of Cetuximab to Paclitaxel, Cisplatin, and Radiation for patients with Esophageal cancer who are treated without surgery.
      Criteria: T1N1M0; T2-4, Any N, M0; or Any T, Any N, M1; Must be treated with Chemo/XRTonly.
      PS = Zubrod 0-2
B) Cisplatin 75mg/m² + 5FU 1,000mg/m² continuous infusion days 1-4. Each cycles repeated every 28 days during XRT (50.4 Gy).

Following XRT 4 weeks rest followed by 2 more cycles of Cisplatin/5FU (Days 1, 29) (Ref 10)

C) Paclitaxel 50mg/m² and Caroaplant AUC 2 on days weekly for 5 weeks with 50.4 Gy of XRT

D) Oxaliplatin 85mg/m² IV on days 1,15 and 29 for 3 doses
   Capecitabine 625-825mg/m² PO BID on days 1-5 for 5 weeks with XRT

E) FOLFOX 4 3 cycles with XRT and 3 after XRT
   Oxaliplatin 85 on day 1 and leucovorin 200, fluorouracil 400 followed by fluorouracil 600 in 22-h infusions on days 1 and 2. (Ref 18)

4) Peri-operative chemotherapy:

A) ECF or EOX
   Epirubicin 50mg/m²
   Cisplatin 60mg/m² Or Oxaliplatin 130mg/m³
   5FU 200mg/m² continuous infusion for 21 days Or capecitabine 625mg/m²

   Total of 3 pre-operative and 3 post-operative cycles (Ref 6)

5) Palliative chemotherapy:

A) DCF
   Docetaxel 75mg/m²
   Cisplatin 75mg/m²
   5FU 750mg/m² days 1-5 every 28 days
   (Ref 14)

B) ECF or EOX
   Epirubicin 50mg/m²
   Cisplatin 60mg/m² Or Oxaliplatin 130mg/m³
   5FU 200mg/m² continuous infusion for 21 days Or Capecitabine 625mg/m²
   (Ref 7)
C) Cisplatin 75mg/m²  
   Or  
   Irinotecan 250mg/m²  
   Capecitabine 1000mg/m² for 14 days  
   Repeat cycle every 3 weeks (Ref 15)

D) FLO regimen  
   5FU 2600mg/m² for 24 hrs  
   Leucovorin 200mg/m²  
   Oxaliplatin 85mg/m² repeat q 2 weeks. (Ref 16)

E) ToGA trial  
   5FU 800mg/m² IV q daily for days 1-5 every 3 weeks  OR 
   Capecitabine 1000mg/m² PO BID for 14 days on and 7 days off q 21 days  
   Cisplatin 80mg/m² IV q 3 weeks.  
   Herceptin 8mg/kg IV loading dose on cycle 1 and then 6mg/kg IV every 21 days in  
   patients with Her2 +ve GE junction cancer (20% of the population) (Ref 17)
References:

1) NCCN task force: Clinical utility of PET in a variety of tumors. JNCCN Volume 7, supplement 2 2009.

2) Systemic review of the staging performance of FDG PET in Esophageal Cancer JCO (22):18 2004:3805-12

3) PET to assess early metabolic response and to guide treatment of adenocarcinoma of the esophagogastric junction: the MUNICON phase II trial Lancet Oncology 8(9):797-805 2007


11)(Neo-adjuvant chemo-radiotherapy carbo/paclitaxel) A v. Gaast et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with
resectable esophageal or esophagogastric junction cancer: Results from a multi-center randomized phase III trial. ASCO 2010 abstract 4004. (Both squamous and adenocarcinomas)

12) **Definitive chemo-radiotherapy carbo/paclitaxel** E V Meerten et al. ASCO 2010
Definitive concurrent chemoradiation (CRT) with weekly paclitaxel and carboplatin for patients with irresectable esophageal cancer: A phase II study

13) **Meta-analysis (Survival benefit from neo-adjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma :).** Lancet Oncol. 8, 226-234

14) Van Cutsem et al. Phase III study of Docetaxel and Cisplatin plus Fluorouracil compared with cisplatin and fluorouracil as first line therapy for advanced gastric cancer: A report of V325 study group. JCO, 2006;4991-4997


