Induction Therapy for Esophageal Cancer

9th Annual Masters in Minimally Invasive Thoracic Surgery
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Disclosure

Consultant: Scanlan

No conflicts related to this presentation
Improving Outcomes for Patients with EC

1. More effective systemic therapy
2. Optimizing surgical outcomes
3. Minimizing practice variation
Educational Objectives

1. Discuss the staging system for esophageal cancer
2. Demonstrate details of NCCN Treatment Guidelines for esophageal cancer
3. Improve the understanding of multidisciplinary management of locally advanced disease
4. Comprehend the surgical options as part of multidisciplinary therapy

Esophageal Cancer: Induction Therapy
Esophageal Cancer:
Induction Therapy
Survival by AJCC staging

Esophageal and Esophagogastroduodenal Cancer


NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients
Esophageal Cancer

4 How to use this book

5 Part 1 Esophageal cancer basics
Explains how esophageal cancer starts and how it spreads.

9 Part 2 Cancer staging
Describes how doctors rate the growth of esophageal cancer.

15 Part 3 Preparing for treatment
Presents the steps of care needed before starting treatment.

23 Part 4 Overview of cancer treatments
Describes the treatments used to cure or control esophageal cancer.

33 Part 5 Treatment guide: Squamous cell carcinomas
Presents which treatments are options for this type of esophageal cancer.

51 Part 6 Treatment guide: Adenocarcinomas
Presents which treatments are options for this type of esophageal cancer.

69 Part 7 Making treatment decisions
Offers tips for choosing the best treatment.

79 Glossary:
80 Dictionary
84 Acronyms

87 NCCN Panel Members
88 NCCN Member Institutions
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NCCN Evidence Block

- Use consistent methodology and display to inform decision-making
- Measures
  - Efficacy
  - Safety
  - Quality of Evidence
  - Consistency of Evidence
  - Affordability
- More shading is better
<table>
<thead>
<tr>
<th>Score</th>
<th>Summary</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Highly effective</td>
<td>Often provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>4</td>
<td>Very effective</td>
<td>Sometimes provides long-term survival advantage or curative potential</td>
</tr>
<tr>
<td>3</td>
<td>Moderately effective</td>
<td>Modest, no, or unknown impact on survival but often provides control of disease</td>
</tr>
<tr>
<td>2</td>
<td>Minimally effective</td>
<td>Modest, no, or unknown impact on survival and sometimes provides control of disease</td>
</tr>
<tr>
<td>1</td>
<td>Palliative only</td>
<td>Symptomatic benefit only</td>
</tr>
</tbody>
</table>
**NCCN Evidence Blocks Categories and Definitions**

- **E** = Efficacy of Regimen/Agent
- **S** = Safety of Regimen/Agent
- **Q** = Quality of Evidence
- **C** = Consistency of Evidence
- **A** = Affordability of Regimen/Agent

**Example Evidence Block**

```
 | 5 | 4 | 3 | 2 | 1 |
---|---|---|---|---|---|
 E |   |   |   |   |   |
 S |   |   |   |   |   |
 Q |   |   |   |   |   |
 C |   |   |   |   |   |
 A |   |   |   |   |   |
```

```
 | 5 | 4 |
---|---|
 E | 4 |
 S | 4 |
 Q | 3 |
 C | 4 |
 A | 3 |
```

**NCCN Guidelines Version 2.2016**

**Multiple Myeloma**

**NCCN Guidelines Index**

Multiple Myeloma TOC

Discussion
Multiple Myeloma
NCCN Evidence Blocks™

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS

**Efficacy of Regimen/Agent**

5 Highly effective: Often provides long-term survival advantage or has curative potential
4 Very effective: Sometimes provides long-term survival advantage or has curative potential
3 Moderately effective: Modest, no, or unknown impact on survival but often provides control of disease
2 Minimally effective: Modest, no, or unknown impact on survival and sometimes provides control of disease
1 Palliative: Provides symptomatic benefit only

**Quality of Evidence**

5 High quality: Multiple well-designed randomized trials and/or meta-analyses
4 Good quality: Several well-designed randomized trials
3 Average quality: Low quality randomized trials or well-designed non-randomized trials
2 Low quality: Case reports or clinical experience only
1 Poor quality: Little or no evidence

**Safety of Regimen/Agent**

5 Usually no meaningful toxicity: Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4 Occasionally toxic: Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3 Mildly toxic: Mild toxicity that interferes with ADLs is uncommon
2 Moderately toxic: Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1 Highly toxic: Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

**Consistency of Evidence**

5 Highly consistent: Multiple trials with similar outcomes
4 Mainly consistent: Multiple trials with some variability in outcome
3 May be consistent: Few trials or only trials with few patients; lower quality trials whether randomized or not
2 Inconsistent: Meaningful differences in direction of outcome between quality trials
1 Anecdotal evidence only: Evidence in humans based upon anecdotal experience

**Affordability of Regimen/Agent** (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

6 Very inexpensive
4 Inexpensive
3 Moderately expensive
2 Expensive
1 Very expensive

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## Esophageal Cancer: Induction Therapy

This page from the NCCN Guidelines Version 2.2016 Multiple Myeloma section includes a table titled "MYELOMA THERAPY". The table outlines preferred and other regimens for primary therapy for non-transplant candidates, assessing for response after 2 cycles.

### Primary Therapy for Non-Transplant Candidates

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bortezomib/dexamethasone</td>
<td>• Dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td>• Melphalan/prednisone (MP)</td>
</tr>
<tr>
<td>• Lenalidomide/low-dose dexamethasone (category 1)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>• Thalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>• Melphalan/prednisone/bortezomib (MPB) (category 1)</td>
<td>• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)</td>
</tr>
<tr>
<td>• Melphalan/prednisone/lenalidomide (MPL) (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Melphalan/prednisone/thalidomide (MPT) (category 1)</td>
<td></td>
</tr>
</tbody>
</table>

### Maintenance Therapy

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Bortezomib</td>
<td>• Bortezomib + prednisone (category 2B)</td>
</tr>
<tr>
<td>• Lenalidomide&lt;sup&gt;6&lt;/sup&gt; (category 1)</td>
<td>• Bortezomib + thalidomide (category 2B)</td>
</tr>
<tr>
<td>• Thalidomide (category 1)</td>
<td>• Interferon (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Steroids (category 2B)</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide + prednisone (category 2B)</td>
</tr>
</tbody>
</table>
57% of cancer and 65% of cancer deaths happen in low- to mid-level resource regions of the world

To extend the use of NCCN Guidelines in regions with limited resources

To provide treatment recommendations applicable to different levels of health-care resources preserving the context of the full NCCN Guidelines

To provide a framework for adding health-care resources to efficiently improve patient outcomes
Level of Resources

- **Basic:** Core resources necessary for any cancer care system to treat a specific cancer
- **Limited:** Second-tier resources to provide cancer care that improve outcome in a major way but is not cost prohibitive
- **Enhanced:** Third-tier resources that make some optional treatments available, some cost-prohibitive therapies become available
- **Maximal:** Resources applied in a modern cancer care practice, typical of a country with high-level resources that improve outcome in a minor way compared with the enhanced level
Esophageal Cancer: Induction Therapy
NCCN Guidelines Version 3.2015
Invasive Breast Cancer
NCCN Framework™: Basic Level (Preliminary)

CLINICAL STAGE

WORKUP

- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram; ultrasound as necessary
- Pathology review
- Determination of tumor ER/PR status* and HER2 status
- Genetic counseling if patient is high risk for hereditary breast cancer
- Breast MRI (optional), with special consideration for mammographically occult tumors
- Fertility counseling if premenopausal
- Assess for distress (See NCCN Guidelines for Distress Management)

For clinical stage I-IIIB, consider additional studies only if directed by signs or symptoms:
- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT (if pulmonary symptoms present)
  - Chest x-ray (if pulmonary symptoms present)

For clinical stage IIIA (T3, N1, M0) consider:
- Chest diagnostic CT
- Abdominal ± pelvic diagnostic CT or MRI
- Bone scan or sodium fluoride PET/CT (category 2B)
- FDG PET/CT (optional, category 2B)
  - Chest x-ray (if pulmonary symptoms present)

*While treatment can be provided in the absence of ER/PR status, it is important to determine ER/PR status for proper drug utilization. Therefore, the NCCN panel believes that ER/PR testing should be available in all treatment centers.
**Esophageal Cancer:** Induction Therapy

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**NCCN Guidelines Version 3.2015**

**Invasive Breast Cancer**

**NCCN Framework™: Limited Level (Preliminary)**

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**CLINICAL STAGE WORKUP**

- History and physical exam
- CBC, platelets
- Liver function tests and alkaline phosphatase
- Diagnostic bilateral mammogram; ultrasound as necessary
- Pathology review
- Determination of tumor ER/PR status and HER2 status
- Genetic counseling if patient is high risk for hereditary breast cancer
- Breast MRI (optional), with special consideration for mammographically occult tumors
- Fertility counseling if premenopausal
- Assess for distress (See NCCN Guidelines for Distress Management)

For clinical stage I-IIB, consider additional studies only if directed by signs or symptoms:

- Bone scan indicated if localized bone pain or elevated alkaline phosphatase
- Abdominal ± pelvic diagnostic CT or MRI indicated if elevated alkaline phosphatase, abnormal liver function tests, abdominal symptoms, or abnormal physical examination of the abdomen or pelvis
- Chest diagnostic CT (if pulmonary symptoms present)
  - **Chest x-ray (if pulmonary symptoms present)**

For clinical stage IIIA (T3, N1, M0) consider:

- Chest diagnostic CT
- Abdominal ± pelvic diagnostic CT or MRI
- Bone scan or sodium fluoride PET/CT (category 2B)
- FDG PET/CT (optional, category 2B)
- **Chest x-ray (if pulmonary symptoms present)**
• Radiation Therapy
  – Content under development by an MS Radiation Therapy dosimetrist
  – Information has been extracted for all 38 guidelines that contain radiation therapy, with greater than 700 recommendations in total
  – Radiation therapy content for all guidelines has been sent for review and is complete for 34

Note: all compendium content is reviewed by NCCN guideline panel members
PRINCIPLES OF SURGERY

- Prior to surgery, clinical staging should be performed to assess resectability with CT scan of the chest and abdomen, whole body PET (integrated PET/CT is preferred), and endoscopic ultrasound.
- Prior to starting therapy all patients should be assessed by an esophageal surgeon for physiologic ability to undergo esophageal resection. Esophageal resection should be considered for all physiologically fit patients with resectable esophageal cancer (> 5 cm from cricopharyngeus).

Siewert Classification

- Siewert tumor type should be assessed in all patients with adenocarcinomas involving the esophagogastric junction (EGJ).2,3
  - Siewert Type I: adenocarcinoma of the lower esophagus with the center located within 1 cm to 5 cm above the anatomic EGJ.
  - Siewert Type II: true carcinoma of the cardia with the tumor center within 1 cm above and 2 cm below the EGJ.
  - Siewert Type III: subcardial carcinoma with the tumor center between 2 and 5 cm below EGJ, which infiltrates the EGJ and lower esophagus from below.
- The treatment of Siewert types I and II is as described in the NCCN Guidelines for Esophageal and EGJ Cancers, and a variety of surgical approaches may be employed.
- Siewert type III lesions are considered gastric cancers, and thus the NCCN Guidelines for Gastric Cancer should be followed. In some cases additional esophageal resection may be needed in order to obtain adequate margins.2,4,5
- Laparoscopy may be useful in select patients in detecting radiographically occult metastatic disease, especially in patients with Siewert II and III tumors.1
- Positive peritoneal cytology (performed in the absence of visible peritoneal implants) is associated with poor prognosis and is defined as M1 disease. Patients with advanced tumors, clinical T3 or N+ disease should be considered for laparoscopic staging with peritoneal washings.
- Cervical or cervicothoracic esophageal carcinomas < 5 cm from the cricopharyngeus should be treated with definitive chemoradiation.

Resectable esophageal or EGJ cancer:

- T1a tumors, defined as tumors involving the mucosa but not invading the submucosa, may be considered for EMR + ablation or esophagostomy in experienced centers.6-10
- Tumors in the submucosa (T1b) or deeper may be treated with esophagectomy.
- T1-T3 tumors are resectable even with regional nodal metastases (N+), although bulky, multi-station lymphatic involvement is a relative contraindication to surgery, to be considered in conjunction with age and performance status.
- T4a tumors with involvement of pericardium, pleura, or diaphragm are resectable.

Unresectable esophageal cancer:

- T4b tumors with involvement of the heart, great vessels, trachea, or adjacent organs including liver, pancreas, lung, and spleen are unresectable.
- Most patients with multi-station, bulky lymphadenopathy should be considered unresectable, although lymph node involvement should be considered in conjunction with other factors, including age and performance status and response to therapy.
- Patients with EGJ and supraclavicular lymph node involvement should be considered unresectable.
- Patients with distant (including nonregional lymph nodes) metastases (stage IV) are unresectable.

Continued on next page
PRINCIPLES OF SURGERY

- The type of esophageal resection is dictated by the location of the tumor, the available choices for conduit, as well as by the surgeon's experience and preference and the patient's preference.
- In patients who are unable to swallow well enough to maintain nutrition during induction therapy, esophageal dilatation, or a feeding jejunostomy tube are preferred to a gastrostomy (which may compromise the integrity of gastric conduit for reconstruction).

Acceptable operative approaches for resectable esophageal or EGJ cancer:
- Ivor Lewis esophagogastrectomy (laparotomy + right thoracotomy)
- McKeown esophagogastrectomy (right thoracotomy + laparotomy + cervical anastomosis)
- Minimally invasive Ivor Lewis esophagogastrectomy (laparoscopy + limited right thoracotomy)\textsuperscript{11,12}
- Minimally invasive McKeown esophagogastrectomy (right thoracoscopy + limited laparotomy/laparoscopy + cervical anastomosis)
- Transhiatal esophagogastrectomy (laparotomy + cervical anastomosis)
- Robotic minimally invasive esophagogastrectomy
- Left transthoracic or thoracoabdominal approaches with anastomosis in chest or neck

Acceptable conduits:
- Gastric (preferred)
- Colon
- Jejunum

Acceptable lymph node dissections:\textsuperscript{13}
- Standard
- Extended (En-Bloc)

In patients undergoing esophagectomy without induction chemoradiation, at least 15 lymph nodes should be removed to achieve adequate nodal staging. The optimum number of nodes after preoperative chemoradiation is unknown, although similar lymph node resection is recommended.\textsuperscript{14}

Patients who develop localized, resectable esophageal cancer after definitive chemoradiation can be considered for salvage esophagectomy if they do not have distant recurrence.\textsuperscript{15}

Patients with potentially resectable esophageal cancer should undergo multidisciplinary review. Esophageal resection, endoscopic mucosal resection, and other ablative techniques should be performed in high-volume esophageal centers by experienced surgeons and endoscopists.\textsuperscript{16}
<table>
<thead>
<tr>
<th>2001-2007</th>
<th>Before MTC (n=117)</th>
<th>MTC (n=138)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Staging Evaluation</td>
<td>67%</td>
<td>97%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Mult-D evaluation prior to Tx</td>
<td>72%</td>
<td>98%</td>
<td>0.0001</td>
</tr>
<tr>
<td>NCCN Guidelines adherence</td>
<td>83%</td>
<td>98%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Days from Dx to Tx (mean)</td>
<td>27</td>
<td>16</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
Esophageal Cancer: Induction Therapy

### Workup
- H&P
- Upper GI endoscopy and biopsy
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT with contrast as clinically indicated
- PET-CT evaluation if no evidence of M1 disease
- CBC and comprehensive chemistry profile
- Endoscopic ultrasound (EUS), if no evidence of M1 disease
- Endoscopic resection (ER) is essential for the accurate staging of early-stage cancers (T1a or T1b)
- Biopsy of metastatic disease as clinically indicated
- HER2-neu testing if metastatic adenocarcinoma is documented/suspected
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated
- Screen for family history

### Clinical Stage
- Stage I–III (locoregional disease)
  - Squamous cell carcinoma → See ESOPH-2
  - Adenocarcinoma → See ESOPH-11

- Stage IV (metastatic disease)
  - Squamous cell carcinoma → See ESOPH-10
  - Adenocarcinoma → See ESOPH-19
Esophageal Cancer: Induction Therapy

Esophageal and Esophagogastric Junction Cancers

TUMOR CLASSIFICATION

cT1b, N+, cT2-T4a, N0-N1

PRIMARY TREATMENT OPTIONS FOR MEDICALLY FIT PATIENTS

- Preoperative chemoradiation\(^{v,w,i,j}\) (preferred)
  - (RT, 41.4–50.4 Gy + concurrent chemotherapy)
  - or
- Definitive chemoradiation\(^{v,w}\)
  - (only for patients who decline surgery)
  - (RT, 50–50.4 Gy + concurrent chemotherapy)
  - or
- Esophagectomy\(^{c,d,t,u}\)
  - (T1b-T2 low-risk lesions: <2 cm, well differentiated)
  - or
- Perioperative chemotherapy\(^{v}\)
  - or
- Preoperative chemotherapy\(^{v}\)
  - or
- Definitive chemoradiation\(^{v,w}\)
  - (RT, 50–50.4 Gy + concurrent chemotherapy)

See Response Assessment (ESOPH-14)
See Surgical Outcomes After Esophagectomy (ESOPH-15)
See Surgical Outcomes After Esophagectomy (ESOPH-16)
See Response Assessment (ESOPH-14)
Preoperative Chemoradiation
Infusional fluorouracil can be replaced with capecitabine
- Preferred Regimens:
  - Paclitaxel and carboplatin (category 1)\(^1\)
  - Fluorouracil and cisplatin (category 1)\(^2,3\)
  - Fluorouracil\(^\dagger\) and oxaliplatin (category 1)\(^4,5\)
- Other Regimens:
  - Irinotecan and cisplatin (category 2B)\(^6\)
  - Paclitaxel and fluoropyrimidine
    (fluorouracil or capecitabine) (category 2B)\(^7\)

Perioperative Chemotherapy
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
(3 cycles preoperative and 3 cycle postoperative):
- Fluorouracil and cisplatin (category 1)\(^8\)
- ECF (epirubicin, cisplatin, and fluorouracil) (category 3)\(^9\)
- ECF modifications (category 3 for all modifications)\(^10,11\)
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capcitabine
  - Epirubicin, oxaliplatin, and capcitabine

Definitive Chemoradiation
Infusional fluorouracil can be replaced with capecitabine
- Preferred Regimens:
  - Fluorouracil and cisplatin (category 1)\(^13\)
  - Fluorouracil\(^\dagger\) and oxaliplatin (category 1)\(^4,5\)
  - Paclitaxel and carboplatin\(^1\)
- Other Regimens:
  - Cisplatin with docetaxel or paclitaxel\(^14-16\)
  - Irinotecan and cisplatin (category 2B)\(^6\)
  - Paclitaxel and fluoropyrimidine
    (fluorouracil or capecitabine) (category 2B)\(^7\)

Postoperative Chemoradiation
- Fluoropyrimidine (infusional fluorouracil\(^\dagger\) or capecitabine) before and after fluoropyrimidine-based chemoradiation\(^17\)

Preoperative chemotherapy (2 cycles)
(Only for adenocarcinoma of the thoracic esophagus or EGJ)
- Fluorouracil and cisplatin (category 2B)\(^12\)
Esophageal and Esophagogastric Junction Cancers


**Esophageal Cancer: Induction Therapy**

**Primary Treatment for Medically Fit Patients with Adenocarcinomas**

- **Preoperative Chemoradiation**
  - Chest/abdominal CT scan with contrast (not required if PET/CT is done)
  - PET/CT or PET\(^x\) (category 2B)
  - Upper GI endoscopy and biopsy (optional if surgery is planned)

- **Definitive Chemoradiation**
  - Chest/abdominal CT scan with contrast (not required if PET/CT is done)
  - PET/CT or PET\(^x\) (category 2B)
  - Upper GI endoscopy and biopsy

**Response Assessment**

- **No Evidence of Disease**
  - Esophagectomy\(^c,d,t,u\) (preferred)
  - Surveillance\(^2\) (category 2B)

- **Persistent Local Disease**
  - Esophagectomy\(^c,d,t,u\) (preferred)

- **Unresectable or Metastatic Disease**
  - Surveillance\(^2\)

**Additional Management**

- **See Surgical Outcomes After Esophagectomy**
  - (ESOPH-16)

- **See Palliative Management**
  - (ESOPH-19)

**Outcome**

- Follow-up (See ESOPH-18)

**Summary**

- NCCN Guidelines Index
- Esophageal/EGJ Table of Contents
- Discussion
SURGICAL OUTCOMES/CLINICAL PATHOLOGIC FINDINGS FOR ADENOCARCINOMAS (Patients Have Not Received Preoperative Chemoradiation or Chemotherapy)

R0 resection

Node negative

- pTis and pT1 → Surveillance
- pT2 → Surveillance or Consider chemoradiation (category 2B) for select patients
- pT3, pT4a → Surveillance or Chemoradiation (Fluoropyrimidine-based)

Node positive (pTis, pT1, pT2, pT3, pT4a)
- pTis and pT1 → Surveillance
- pT2 → Surveillance or Consider chemoradiation (category 2B) for select patients
- pT3, pT4a → Chemoradiation (Fluoropyrimidine-based)

R1 resection

→ Chemoradiation (Fluoropyrimidine-based)

R2 resection

→ Chemoradiation (Fluoropyrimidine-based) or Palliative Management (See ESOPH-19)

Follow-up (See ESOPH-18)
Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer


- Pts with resectable (T2-3N0-1M0) tumors
- Preop CRT (carboplatin/paclitaxel) + RT (41.4 Gy) followed by surgery vs. surgery alone
- 366 pts enrolled (2004-8); male 284, adeno 273
- Toxicities (grade ≥ 3) in the CRT arm: <5%
## CROSS Study

<table>
<thead>
<tr>
<th></th>
<th>CRT+Surgery</th>
<th>Surgery Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resection Rate</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>R0 Resection Rate</td>
<td>92%*</td>
<td>69%</td>
</tr>
<tr>
<td>pCR</td>
<td>29%</td>
<td>NR</td>
</tr>
<tr>
<td>In-hospital Mortality</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Median OS</td>
<td>49 months*</td>
<td>24 months</td>
</tr>
<tr>
<td>1, 2, 3, 5 yr survival</td>
<td>82, 67, 58, 47%*</td>
<td>70, 50, 44 34%</td>
</tr>
</tbody>
</table>
A Survival According to Treatment Group

Proportion Surviving vs. Follow-up (mo)

- CRT+surgery
- Surgery alone

P = 0.003
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P Value for Adjusted Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>0.657 (0.495–0.871)</td>
<td>0.665 (0.500–0.884)</td>
<td>0.005</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.913 (0.482–1.729)</td>
<td>0.928 (0.487–1.766)</td>
<td>0.82</td>
</tr>
<tr>
<td>Male</td>
<td>0.612 (0.446–0.841)</td>
<td>0.614 (0.447–0.845)</td>
<td>0.003</td>
</tr>
<tr>
<td>Histologic type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.627 (0.056–6.970)</td>
<td></td>
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</tr>
<tr>
<td>Adenocarcinoma</td>
<td>0.732 (0.524–0.998)</td>
<td>0.741 (0.536–1.024)</td>
<td>0.07</td>
</tr>
<tr>
<td>Squamous-cell carcinoma</td>
<td>0.453 (0.243–0.844)</td>
<td>0.422 (0.226–0.788)</td>
<td>0.007</td>
</tr>
<tr>
<td>Clinical N stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.414 (0.234–0.732)</td>
<td>0.422 (0.239–0.747)</td>
<td>0.003</td>
</tr>
<tr>
<td>1</td>
<td>0.793 (0.567–1.108)</td>
<td>0.807 (0.576–1.130)</td>
<td>0.21</td>
</tr>
<tr>
<td>Could not be determined</td>
<td></td>
<td>0.552 (0.066–4.602)</td>
<td></td>
</tr>
<tr>
<td>WHO performance score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.617 (0.452–0.844)</td>
<td>0.625 (0.456–0.857)</td>
<td>0.004</td>
</tr>
<tr>
<td>1</td>
<td>0.864 (0.433–1.726)</td>
<td>0.898 (0.753–1.631)</td>
<td>0.77</td>
</tr>
</tbody>
</table>
Improved Long-Term Outcome With Chemoradiotherapy Strategies in Esophageal Cancer

- 157 patients preop chemo vs chemoRT + surgery
- Preop Chemo (76) vs preop C/RT (81)
- Preoperative C/RT
  - Higher pathologic complete response rate
    (28% vs 4%, \( p < 0.001 \))
  - Better 3-year survival (48% versus 29%, \( p = 0.04 \))
Overall Survival

p = 0.046

Percent Alive

Months

Pre C: 76 57 34 24 21 18
Pre C/RT: 81 63 50 40 36 29
Disease-free Survival

p = 0.038

<table>
<thead>
<tr>
<th>Pre C:</th>
<th>76</th>
<th>41</th>
<th>25</th>
<th>24</th>
<th>18</th>
<th>17</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre C/RT:</td>
<td>81</td>
<td>56</td>
<td>41</td>
<td>37</td>
<td>32</td>
<td>27</td>
</tr>
</tbody>
</table>
Preoperative Chemoradiation Therapy Versus Chemotherapy in Patients Undergoing Modified En Bloc Esophagectomy for Locally Advanced Esophageal Adenocarcinoma: Is Radiotherapy Beneficial?


<table>
<thead>
<tr>
<th>214 patients cT3 N1 EC</th>
<th>ChT (n=114)</th>
<th>ChRT (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>31.2 m</td>
<td>39.2 m</td>
<td>0.665</td>
</tr>
<tr>
<td>Disease free survival</td>
<td>23.9 m</td>
<td>26.4 m</td>
<td>0.582</td>
</tr>
<tr>
<td>90 day mortality</td>
<td>5.3%</td>
<td>4%</td>
<td>0.754</td>
</tr>
</tbody>
</table>
Esophageal Cancer: Induction Therapy
Trends and Outcomes in the Use of Surgery and Radiation for the Treatment of Locally Advanced Esophageal Cancer: A propensity score adjusted analysis of the Surveillance, Epidemiology, and End Results Registry from 1998 to 2008

Mathias Worni, MD, MHS\textsuperscript{1,2}, Anthony W. Castleberry, MD, MMCi\textsuperscript{1}, Beat Gloor, MD\textsuperscript{2}, Ricardo Pietrobon, MD, PhD\textsuperscript{1}, John C. Haney, MD\textsuperscript{1}, Thomas A. D’Amico, MD\textsuperscript{1}, Igor Akushevich, PhD\textsuperscript{3}, and Mark F. Berry, MD\textsuperscript{1}


Trends in surgery and radiation for patients with T1-T3N1M0 squamous cell or adenocarcinoma of the mid or distal esophagus in the SEER database from 1998–2008 were analyzed

Esophageal Cancer: Induction Therapy
Surgery and RT for Esophageal Cancer

- 3,295 patients: Overall 5-year survival 18.9%
- 1,325 (40%) RT alone; 696 (21%) surgery alone
- Bimodal therapy (32.8%-42.5%, p=0.01) increased significantly from 1998 to 2008
- Bimodal therapy predicted improved CSS (HR:0.68, p<0.001) and OS (HR:0.58, p<0.001) compared to unimodal therapy
Surgery and RT for Esophageal Cancer

![Graph showing survival rates for bimodal and unimodal therapy.](image)
Induction Therapy: Summary

• Despite inadequate randomized trials and conflicting meta-analyses, induction chemoradiotherapy + surgery probably represents the best treatment in operable esophageal adenocarcinoma

• Randomized trials comparing induction chemotherapy to induction chemoradiotherapy are needed
Esophagogastrectomy: Standard Resections

- **Standard**
  - Ivor Lewis
  - 3-incision (McKeown)
  - Thoracoabdominal
  - Transhiatal

- **Minimally Invasive Esophagectomies (MIE)**
  - VATS + laparoscopic/laparotomy + cervical
  - Laparoscopic + thoracotomy/VATS
Lymph Node Dissection

1. All thoracic nodes
2. Left gastric pedicle nodes
3. Celiac axis nodes
4. Gastro-hepatic ligament nodes

Target: At least 16

Minimally Invasive McKeown

- Thoracoscopic mobilization
- Lymph node dissection
- Ligation of thoracic duct
- Gastric mobilization and lymph node dissection
- No pyloroplasty
- Feeding jejunostomy
- Stapled cervical anastomosis

*Esophageal Cancer: Induction Therapy*
Trends in Hospital Volume and Operative Mortality for High-Risk Surgery
Finks JF, et al. NEJM 2011; 364:2128-2137

- Median hospital volumes of 4 cancer resections analyzed using Medicare database 1999-2008
- Lung, esophagus, pancreas, and bladder
- Operative mortality declined for all procedures
- Higher volumes explained a large portion of the decline in mortality for pancreatectomy (67%), cystectomy (37%), and esophagectomy (32%), but not for the other procedures

Esophageal Cancer: Induction Therapy
Risk-Adjusted Mortality Associated with Cancer Resections among Medicare Patients, 1999 -2008


Esophageal Cancer: Induction Therapy
Esophageal Cancer: Induction Therapy
Radio Frequency Ablation

1. High-grade dysplasia, <10 cm

2. Low-grade dysplasia

3. ? Metaplasia
Endoscopic Resection + Ablation

1. High grade dysplasia (Carcinoma in situ)

2. T1aN0, superficial T1bN0
Photodynamic Therapy

1. T1a tumors not amenable to EMR in marginally operable patients

2. HGD in RFA failures

3. Advanced endoluminal disease, symptomatic, after radiation
Esophagectomy without Induction Therapy

1. High grade dysplasia, T1
   Extensive, failed mucosal ablation, patient choice

2. Selected T2N0 (dose reduction=no Rx)

3. Medical contraindications to tri-modality therapy
   Age, performance status, perforation, bleeding
Induction CRT + Surgery

Standard of care based on selected studies and meta-analyses

1. Most patients with T3 or N1 disease

2. Selected patients with T2N0

Esophageal Cancer: Induction Therapy
Surgery + Adjuvant Therapy

1. Patients with unexpected T3, N1 or M1a disease

2. Patients who refused induction therapy
Modern Esophageal Resection

- Multidisciplinary evaluation is essential
- Induction therapy + esophagogastrectomy is the best option for most patients with $\geq$T2N0
- Centers with experience have the best outcomes
- Approaches that avoid thoracotomy are preferable
- Perioperative mortality $\leq 2\%$
- Best predictor of post-operative outcome: pneumonia