Esophageal Cancer

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Esophageal cancer

- **In the US (2012):**
  - **17,460 new cases, 15,070 deaths**
- **Worldwide (2008)**
  - **482,300 new cases, 406,800 deaths**
  - **6th leading cause of cancer deaths**
- **Median age of diagnosis: 67 years**
- **Male predominance**

Esophageal cancer

Histology	Squamous cell	Adenocarcinoma
Anatomic location	Proximal and mid-portion	Distal third and gastroesophageal junction
Incidence	Decreasing	Increasing
	African American > Caucasian	Caucasian > African American
Risk factors	Tobacco and alcohol	Tobacco
	HPV	Obesity
	Ingestion of corrosives	GERD
	Plummer-Vinson Syndrome	Barrett's esophagus

Barrett's esophagus

- **Replacement of squamous epithelium with intestinal columnar epithelium**
- **Incidence:**
  - **10-15% of endoscopies evaluating GERD**
  - **40% patients with esophageal strictures**
- **2% risk of adenocarcinoma over 10 yrs**
- **No therapy reverts (antacids, surgery, laser)**

Barrett's esophagus

- **Consider screening if with risk factors for esophageal cancer:**
  - **>50 years, Caucasian**
  - **chronic GERD**
  - **hiatal hernia**
  - **high body mass index**

Wang et al. Am J Gastroenterol 2008;103:788

Barrett's esophagus

Dysplasia	Repeat endoscopy
No dysplasia	3 years
Low-grade	6-12 months
High-grade	Every 3 months or local therapy

Chemoprevention for Barrett's Esophagus Trial

- ↑COX-2 in Barrett'sesophagus
- U.S. trial with celecoxib
  - 100 pts with Barrett's esophagus: low or high grade dysplasia
  - Placebo vs Celecoxib 200 mg BID
  - No change in EGD findings at 48 weeks
  - No change in COX 1/2 mRNA

Heath et al JNCI 2007;99:545

Esophageal cancer

- <u>Signs and symptoms:</u>
  - Dysphagia and odynophagia (solids before liquid)
  - Weight loss
  - Abdominal pain
  - Cough and hoarseness
  - Supraclavicular adenopathy

Diagnostic work-up

- CBC and chemistry
- Esophagogastroduodenoscopy
- CT chest/abdomen/pelvis with IV and PO contrast

- PET/CT
- Endoscopy with ultrasound
- Bronchoscopy (if above and at level of carina)

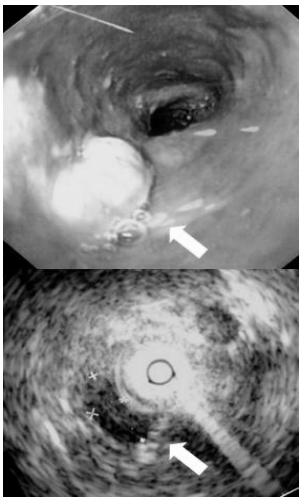


Image from: en.wikipedia

PET/CT

- Utilized for preoperative staging
  - Correlate with EUS and CT scans
  - Upstages tumor to avoid surgery
- Prognostic
  - PET/CT responders after induction chemotherapy have improved survival

Staging

Tumor

- **Tis – High grade dysplasia**
- **T1 – Tumor invades lamina propria, muscularis mucosae or submucosa**
- **T2 – Tumor invades muscularis propria**
- **T3 – Tumor invades adventitia**
- **T4 – Tumor invades adjacent structures**
  - **T4a – Resectable tumor invading pleura, pericardium or diaphragm**
  - **T4b – Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc**

Staging

Node

- **N0 – No regional LN involvement**
- **N1 – Metastasis in 1-2 regional nodes**
- **N2 – Metastasis in 3-6 regional nodes**
- **N3 – Metastasis in more than 7 regional nodes**

Metastasis

- **M0 – No distant metastasis**
- **M1 – Distant metastasis**

5 Year Survival by Stage

Stage	TNM	5-year Survival
Stage 0	TisN0M0	
Stage I	T1N0M0	80-90%
Stage IIA	T2-T3N0M0	50%
Stage IIB	T1-2N1M0	20%
Stage III	T3N1M0 T4N0-1M0	10-15%
Stage IVA	M1a	10%
Stage IVB	M1b	Anecdotal

Treatment Options

- **Resectable cancer**
  - **Surgery**
  - **Radiation**
  - **Chemotherapy**
- **Unresectable cancer**
  - **Radiation**
  - **Chemotherapy**
- **Metastatic cancer**
  - **Chemotherapy**
  - **Radiation therapy**
  - **Photodynamic Therapy**
  - **Laser Ablation**
  - **Stents**
  - **Nutrition (PEG, TPN)**

Resectable cancer

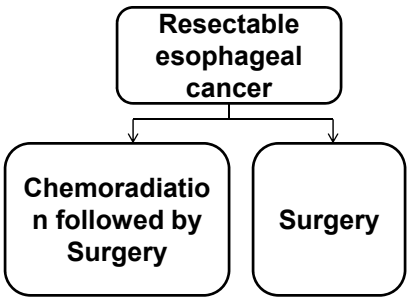
- **Tumor location**
- **Tumor stage (nodal involvement, metastasis)**
- **Patient medically fit for esophagectomy**

Meta-analysis: Survival benefit from neoadjuvant chemoradiation vs. chemotherapy

	Neoadjuvant chemoradiation	Neoadjuvant chemotherapy
Number	10 studies, total n = 1209	8 studies, total n = 1724
HR for all-cause mortality	0.81 (p=0.002)	0.90 (p=0.05)
Absolute survival difference at 2 years	13%	7%
Comments	Similar results for SCC and AC	Benefit only in AC, not SCC

Gebski et al, Lancet Oncol 2007; 8:226-34.

CALGB 9871 trial

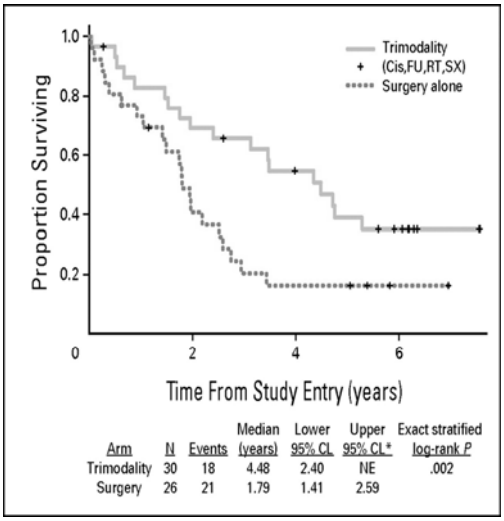


Trimodality vs surgery:

Median OS :4.5 vs 1.8 years

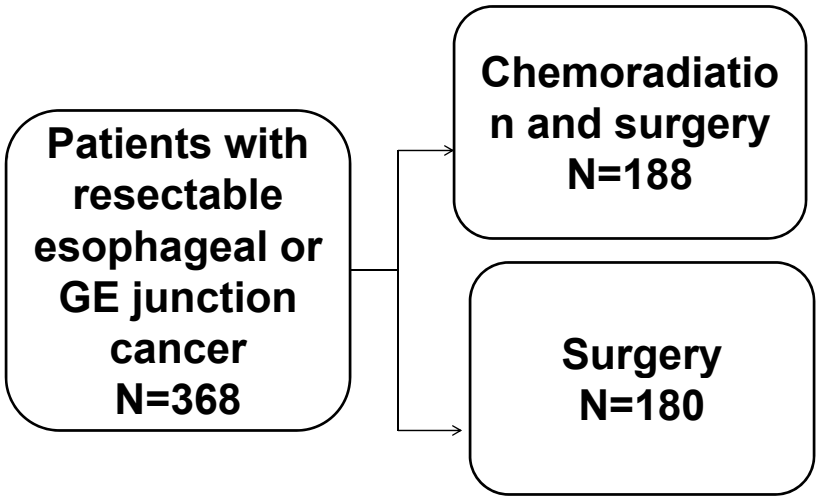
5-yr survival: 39% vs. 16%

Median PFS: 3.5 vs. 1 yr



Tepper et al. J Clin Oncol 2008; 26:1086

CROSS trial



Van Hagen et al, NEJM 2012;366:2074

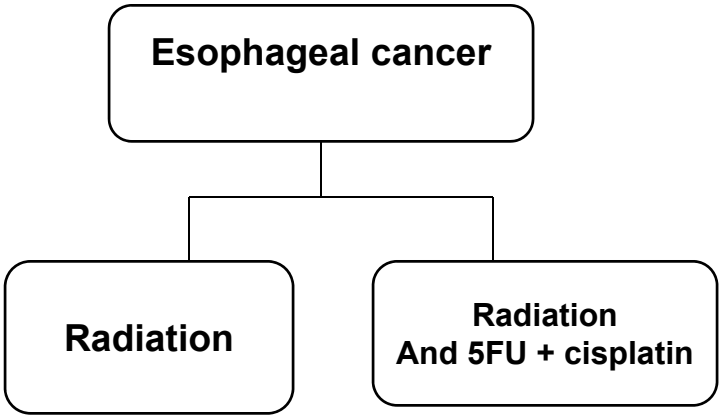
CROSS trial results

Surgery		Trimodality
67%	R0 resection	92.3%
3.8%	In hospital mortality	3.4%
26 months	Median survival	49 months
70%	1 year survival	82%
52%	2 year survival	67%
48%	3 year survival (HR 0.67, p=0.011)	59%

Van Hagen et al, NEJM 2012;366:2074

Unresectable tumor

Non-operative trial: RTOG 85-01



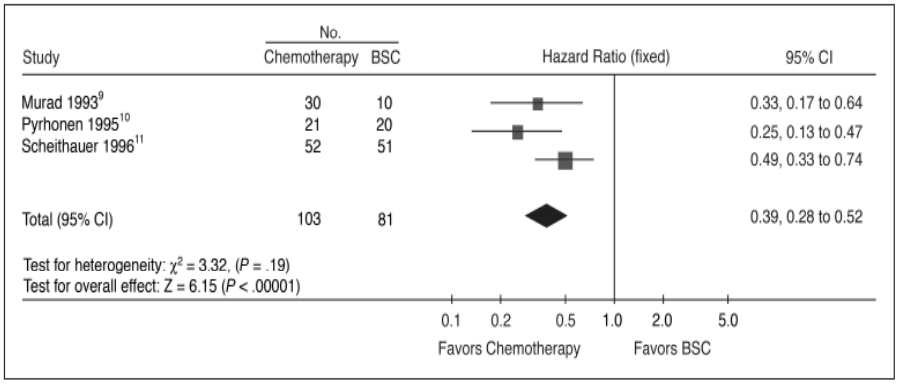
Cooper et al. JAMA 1999;281:1623.

Definitive Chemoradiation or Radiation for Esophageal Cancer

	Chemoradiation	Radiation
Median survival	12.5 months	8.9 months
1- year survival	52%	34%
2-year survival	36%	10%
5-year survival	26%	0%

Cooper et al. JAMA 1999;281:1623.

Metastatic esophageal cancer: Best Supportive Care vs Chemotherapy

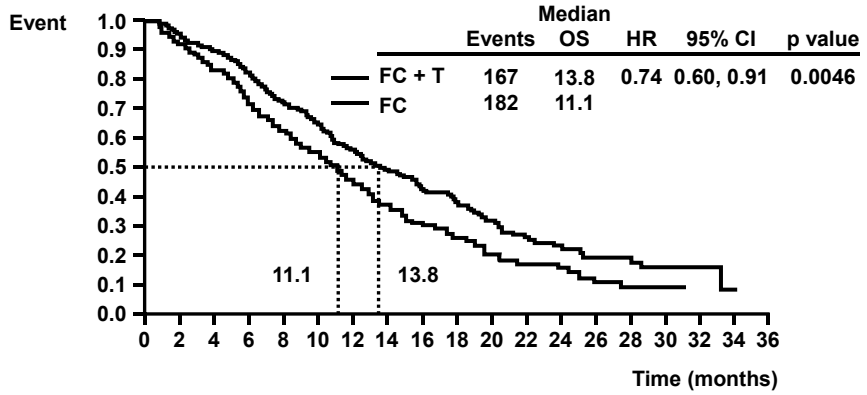


Wagner et al. JCO 2006;24:2903.

Targeted therapy-HER2

- Human epidermal growth factor receptor-2
- HER2 is over-expressed in 20% gastro-esophageal and gastric cancers
- Antibody to HER2- trastuzumab

Primary end point: OS



Bang et al, Lancet 2010;376:687.

In summary

- Incidence: Adenocarcinoma ↑, squamous cell ↓ carcinoma
- Risk factors:
  - Adenocarcinoma: tobacco, obesity, GERD, Barrett's esophagus
  - Squamous cell carcinoma: tobacco, alcohol, HPV, corrosive ingestion
- Signs and symptoms:
  - Dysphagia/odynophagia, weight loss, pain, and cough
- Work-up: CBC + CMP, EGD, CT chest/abdomen/pelvis
- Treatment: Multi-modality- surgery, radiation, chemotherapy
- Prognosis:
  - Poor prognosis (1/3 patients have metastatic disease at diagnosis)
  - Improved prognosis if localized, resectable cancer

Surgical Intervention for Esophageal Cancer

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Overview

- **OSU approach to esophageal cancer**
- **Morbidity and mortality after esophagectomy**
- **Approaches to esophageal resection**

Using evidence-based medicine, has the ideal operative approach been determined?

Answer: No

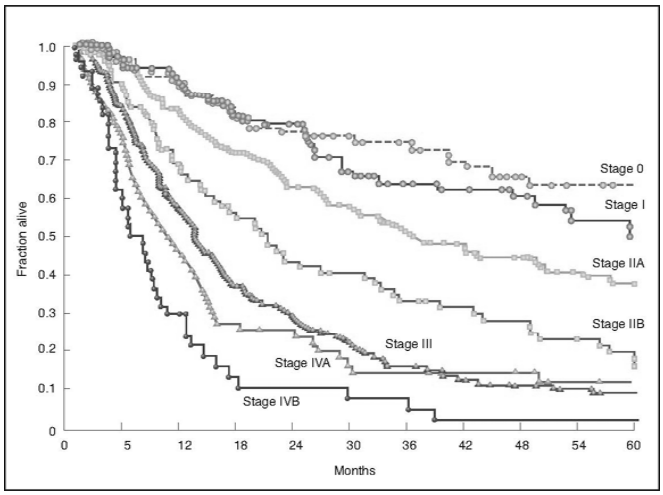
Algorithm for Esophageal Cancer: OSU Approach

CT C/A/P, PET/CT, EUS

T4 or Metastases → Photodynamic therapy
Esophageal stenting
Palliative CTX/XRT

T1N0 → Esophagectomy
T2-T3 → Chemo/XRT, esophagectomy
N1 → Chemo/XRT, esophagectomy

Survival by Stage



Esophagectomy and Survival

Author (year)	N	Approach	1 year survival	5-year survival
Swanson (2001)	250	Three hole	44	NR
Bailey (2003)	1777	Varied	NR	NR
Rizk (2004)	510	Varied	44	NR
Lerut (2005)	394	Varied	63	30
Portale (2006)	263	Varied	NR	46.5
Orringer (2007)	2007	THE	70	29
Mathisen (1998)	104	Varied	NR	15%

Esophagectomy and Mortality

- **Open esophagectomy mortality rates range from 8% at high volume centers to 23% in low volume centers (NEJM 2002)**
- **Published series from experienced centers report a mortality rate of 5%**

High Volume Centers for Esophagectomy: Number needed to achieve low post-operative mortality

ROL in last 10 years w/13 papers:

- Reduction in post-op mortality with increasing case volumes per year
- Post-op complication rates are lower in high-volume hospitals

Metzger, R. et al. Dis of the Esophagus, Vol17(4)310,Dec, 2004

High Volume Centers: What is the number needed to achieve low post-operative mortality

- Management of complications is more successful in high-volume hospitals
- Long-term prognosis is also correlated to case-volume
- With the experience of > 20 esophagectomies/yr mortality <5% can be achieved

Metzger, R. et al. Dis of the Esophagus, Vol17(4)310,Dec, 2004

High Volume Centers for Esophagectomy: What is the number needed to achieve low post-operative

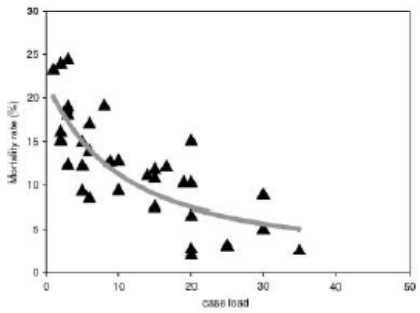


Fig. 2 Correlation between number of esophagectomies and hospital mortality rate.

Metzger, R. et al. Dis of the Esophagus, Vol17(4)310,Dec, 2004

Hospital Volume and Mortality

Author	Study period	Low volume	High volume
Begg (1998)	1984-1993	17.3 (<5)	3.4 (>11)
Patti (1998)	1990-1994	16 (<8)	4.8 (>30)
Swisher (2000)	1994-1996	12.2 (<5)	3 (>5)
Dimick (2001)	1989-1999	16 (<3)	2.7 (>15)
Von Lanachot (2001)	1993-1998	12.1 (<10)	4.9 (>50)
Birkmeyer (2002)	1994-1999	23% (<2)	8.1 (>19)
Dimick (2003)	1994-1998	15.4	2.5%
Finlayson (2003)	1995-1997	15 (<4)	6.5 (>9)
Dimick (2005)	1998-1999	24.3 (<5)	11.4 (>12)

Esophagectomy and Periopertive Mortality

Author (year)	N	Approach	LOS	Mortality
Swanson (2001)	250	Three hole	13	3.6
Bailey (2003)	1777	Varied	NR	9.8
Rizk (2004)	510	Varied	11	6.1
Lerut (2005)	394	Varied	NR	2.1
Portale (2006)	263	Varied	NR	4.5
Orringer (2007)	2007	THE	10	3.0
Mathisen (1998)	104	Varied	NR	2.9

Esophagectomy Morbidity

	Michigan	VA	MSKCC	Duke
Leak	12%	NR	21%	14%
Pneumonia	2%	21%	21%	16%
RLN Injury	4.5%	NR	4%	NR
Conduit Necrosis	2%	NR	NR	NR
Chylothorax	1%	0.02%	NR	NR
MI	NR	1.2%	NR	NR
Tracheal Injury	0.4%	NR	NR	NR
Splenectomy	2%	NR	NR	NR
Diaphragm Hernia	NR	NR	1.2%	NR

Lowering the Morbidity of Esophagectomy

- Limit rib spreading to 5 cm during transthoracic esophagectomy (Skinner 1967)
- Avoid thoracotomy and perform transhiatal approach (Orringer 1980)
- Perform only in high volume centers (Birkmeier 2002)
- Perform minimally invasive esophagectomy in high volume center (Luketich 1996)

Surgical Options

Approach

- Transhiatal
- Transthoracic
- Three Field
- Minimally Invasive
- En Bloc

Anastomosis

- Neck
- Chest
- Abdomen

Conduit

- Stomach
- Colon
- Jejunum
- Skin Tube

Route

- Post. Mediast.
- Retrosternal
- Subcutaneous

Transhiatal Esophagectomy

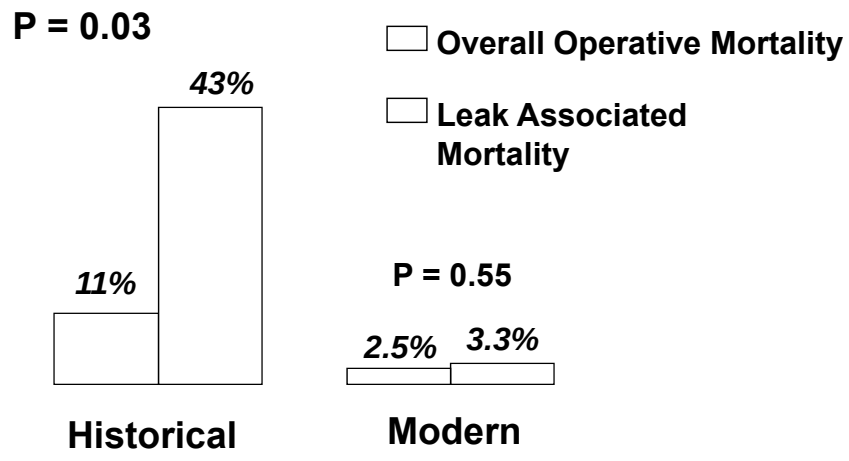
- Experienced centers report <5% mortality
- Overall survival: 20-25%
- Stage I: 60-70%
- Stage III: 5%
- 40% rate of local recurrence
- Major complication rate of 30-40%

Comparison of Approach
Transhiatal vs. Transthoracic

- No difference in operative time, blood loss, morbidity or mortality
- Survival similar
- Anastomotic Leak rate
  - Cervical 11%
  - Thoracic 6%

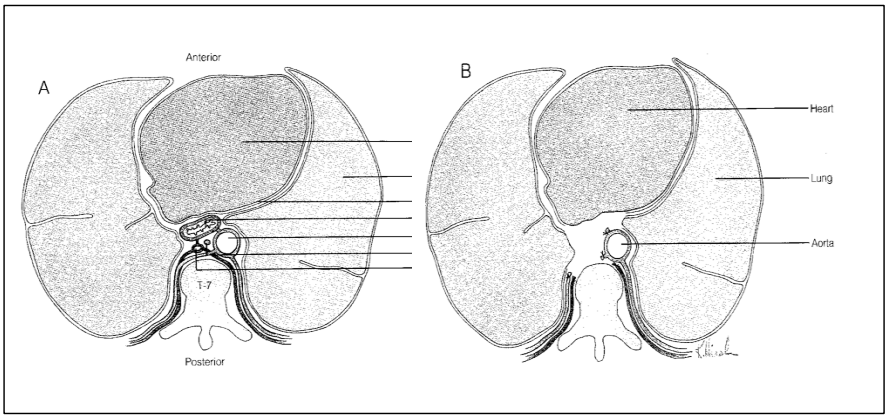
Putnam et al., Annal Thor Surg, 1994

Perioperative Mortality After Intrathoracic Leak



Martin et al., Ann Surg, 2006

En-Bloc Esophagectomy



Extended Surgical Resection

Transhiatal vs. Transthoracic "En Bloc"

	THE	TT "En Bloc"	
No. Pts.	106 pts	114 pts	
Pulm Cxns	29 (27%)	65 (57%)	< 0.001
ICU Days	2 (0-38)	6 (0-79)	<0.001
Op Mort	2 (2%)	5 (4%)	0.45
Relapse	62 (58%)	57 (50%)	0.60
5-yr Surv.	27%	39%	0.12

Hulscher et al., NEJM, 2002

Radical Three Field Esophagectomy

- Thoracic, abdominal and cervical incisions
- Three field lymphadenectomy
- Increased complications:
  - RLN Injury: 56 vs 30%
  - Tracheostomy: 53 vs 10%
  - Phrenic nerve injury: 13 vs 0%
  - No difference in 5-year survival
- Significant increase in morbidity with no improvement in survival

MIE Techniques

- Thoracoscopic; laparotomy
- Laparoscopic; thoracotomy
- Laparoscopic; transhiatal
- Thoracoscopic; laparoscopic

MIE vs Open

	MIE	Transthoracic	Transhiatal
Operative time	364	437	391
Blood Loss	297	1046	1142
Intraop Transfusion	0.3	1.8	2.9
ICU Stay	6.1	9.9	11.1
Hospital Stay	11.3	23.0	22.3
No. LN's Removed	10.8	6.3	6.9

MIE

- Luketich, 2003
- 222 patients
- High grade dysplasia 47 pts
- Esophageal cancer 175 pts
  - Neoadjuvant chemotherapy 78 pts
  - Neoadjuvant radiotherapy 36 pts

MIE

- MIE completed in 206 (92.8%) pts
- Conversion to open
  - Thoracotomy 12 pts
  - Laparotomy 4 pts

MIE

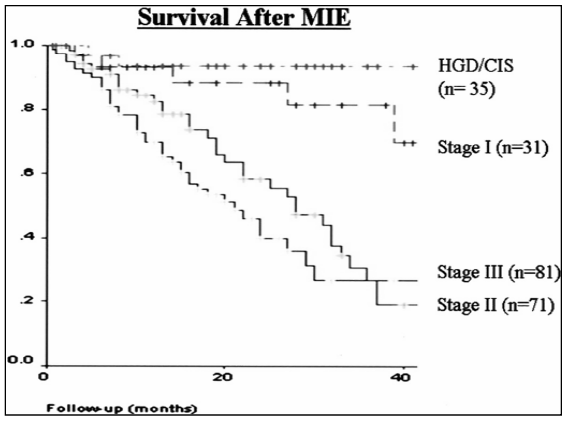
- ICU stay 1 day (1 – 30)
- Time to oral intake 4 days (1 – 40)
- Hospital stay 7 days (3 – 75)
- Median follow-up 9 months

MIE

- Minor complications 53 (24%)
- Major complications 71 (32%)

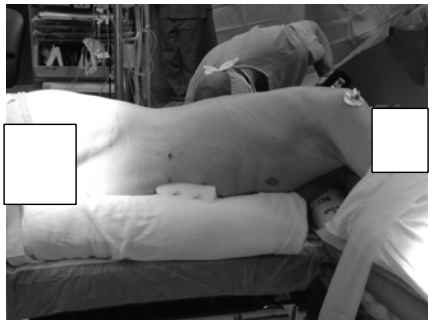
Complication	N (%)	Complication	N (%)
Death	3 (1.4)	Chylothorax	7 (3.2)
Leak	26 (11.7)	Gastric necrosis	7 (3.2)
Pneumonia	17 (7.7)	Delayed gastric empying	4 (1.8)
Pleural effusion	14 (6.3)	Tracheal injury	4 (1.8)
Recurrent nerve palsy	8 (3.6)	ARDS	4 (1.8)

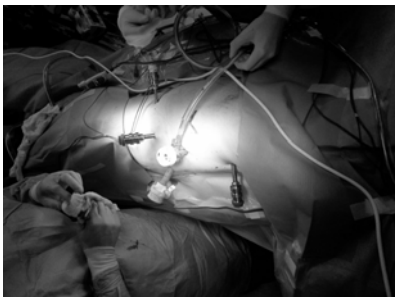
MIE Survival



Totally Robotic Ivor Lewis Esophagectomy

Totally Robotic Ivor Lewis Esophagectomy





Totally Robotic Ivor Lewis Esophagectomy

- Two patients completed thus far
- Mean age 59 years
- Mean operative time 10 hours
- Mean blood loss <100 cc
- Mean LOS 7 days
- No anastomotic leak

Summary

- Debate continues as to optimal approach
  - Transhiatal
    - Pros: Avoid thoracotomy
      Technically easier operation
    - Cons: Increase rate of anastomotic leak
      Recurrent laryngeal nerve injury (aspiration)
      Limited thoracic lymphadenectomy

Summary

- Transthoracic (Ivor Lewis)
  - Pros: Lower rate of leaks, More extensive lymphadenectomy, decreased stricture rate, no risk to recurrent laryngeal nerve
  - Cons: Increased pain (thoracotomy)
- Intrathoracic leak not associated with increased mortality

Summary

- **Three field esophagectomy and 'en-bloc' esophagectomy increase morbidity without improving survival**
- **MIE**
  - **? Decrease in peri-operative complications**
  - **Not proven to be superior to open approach**
  - **Long term outcomes similar to open approach**

Esophagectomy

Techniques

	Transhiatal	Ivor Lewis	Three field
Advantages	Shorter operation ↓ Pulm Comp ↓ Pain	↓ Neck morbidity Lower leak rate Increased lymph node yield ? Increased complete resection	↓ Chest Leak
Disadvantages	↓ Node dissection Double the leak rate Recurrent nerve injury Injury to thoracic structures Neck morbidity		Increased pulmonary comp Increased pain

Summary

- Overall survival still poor in patients with esophageal cancer
- Surgery remains mainstay of treatment
- In order for surgery to have an impact on survival peri-operative mortality and morbidity must be low

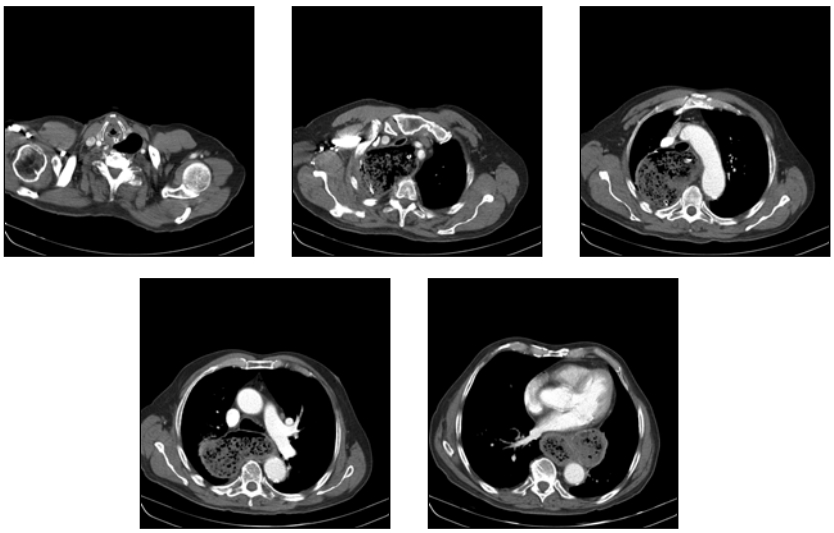
Summary

- There is no ideal approach to esophagectomy
- Outcomes are best when performed in high volume centers

Jejunal Interposition

- 79 year old male with esophageal cancer in the setting of end stage achalasia
- History of multiple dilations and Botox injections
- History of subtotal gastrectomy
- New onset dysphagia and dyspnea

CT Chest



Jejunal Interposition for Esophageal Replacement

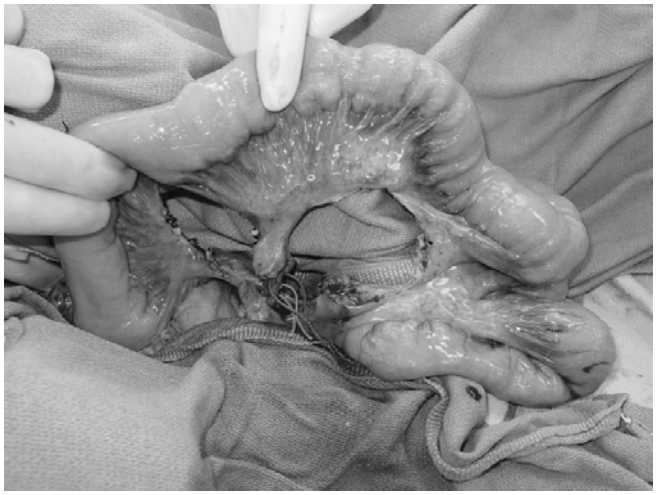
- Advantages
  - Readily available
  - Limited physiologic impact
  - Sterile conduit
  - Generally free of intrinsic disease
  - Approximates diameter of esophagus
  - Maintains intrinsic peristalsis

Jejunal Interposition for Esophageal Replacement

- Disadvantages
  - Anatomic limitations of mesenteric arcades
- Limited to short segment interpositions
- Longer segment risks ischemia

Technique

Technique



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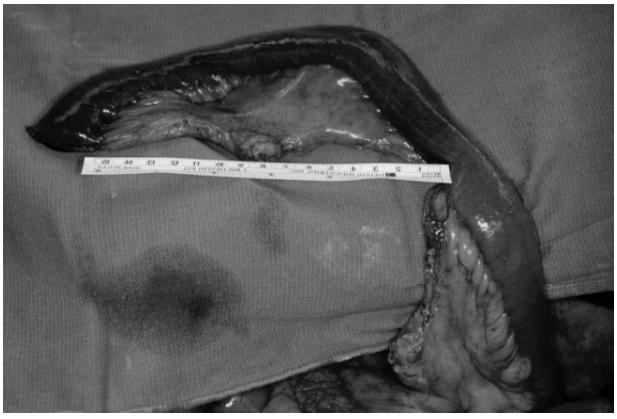

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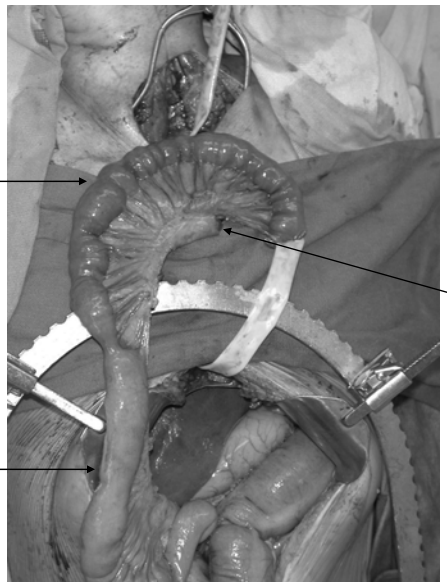

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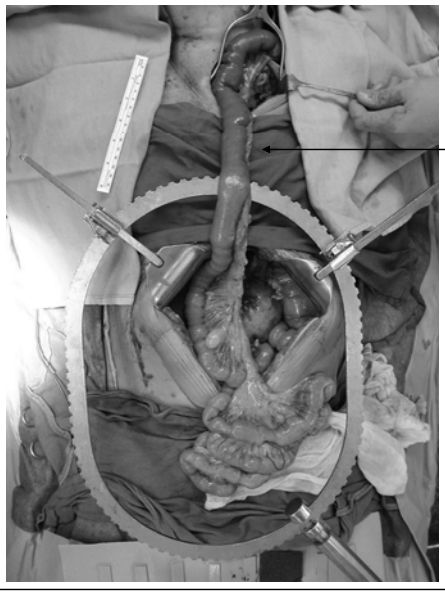

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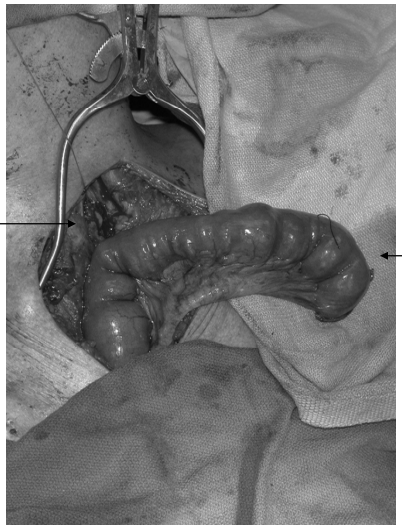

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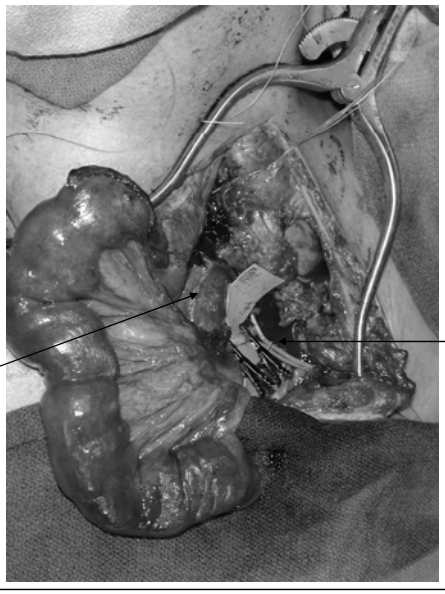
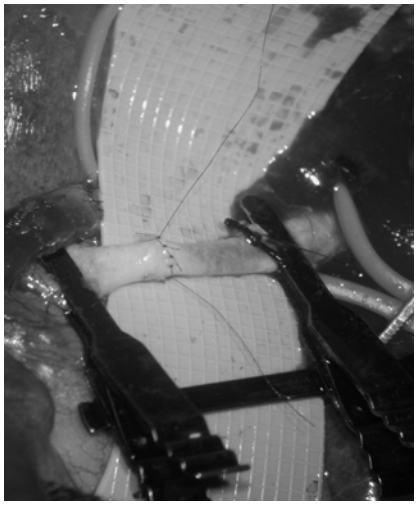


“Supercharging”

- Microvascular augmentation
- Internal thoracic or cervical vessels



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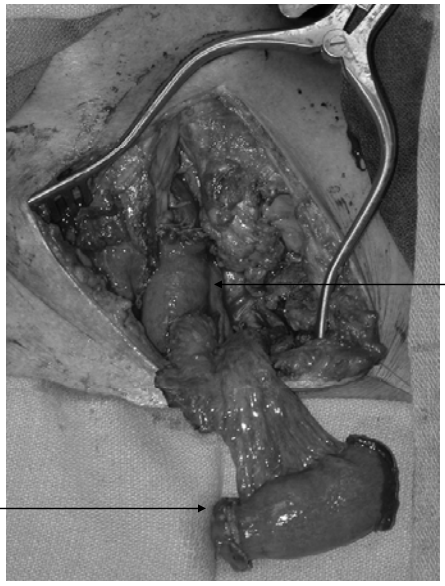

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