

Esophageal Cancer Cases

Quiz Questions:

Relationship between proto-oncogene and oncogene?

Examples:

Ras

HER2/neu

MYC

Tumor Suppressor Genes

FAP Prophylactic Surgery

- Total proctocolectomy with ileal pouch
- Total colectomy with ileorectal anastomosis
- Proctocolectomy with end ileostomy

Lynch Syndrome Prophylactic Surgery

- No role for prophylactic colon surgery
- Prophylactic hysterectomy with BSO

BRCA 1/2 Prophylactic Surgery

- Bilateral mastectomy reduces lifetime risk 90%
- Surveillance is a reasonable option
 - Yearly mammogram
 - Yearly breast MRI

BRAC 1/2 Prophylactic Surgery

- Prophylactic BOS age 35-40 or after childbearing
- Reduces risk of ovarian cancer 80%
- Surveillance not as effective
 - Transvaginal ultrasound
 - CA-125 screening

MEN 2A/2B or FMTC Prophylactic surgery

- Timing of thyroidectomy depends upon risk category
- Highest risk: Throidectomy within first year of life
- High risk: Thyroidectomy by age 5 or if calcitonin elevated
- Moderate risk: surveillance starting age 5
 - physical exam
 - neck ultrasound
 - serum calcitonin

FAP

Median age of dx 39

- Duodenal and ampullary tumors
- Gastric polyps
- Thyroid tumors
- Desmoid tumors

FAP screening

Colonoscopy age 10-12 EGD for duodenal polyps at age 20-30
CT 1-3 years after colectomy and q5 yrs in those with family hx of desmoids

Lynch

Amdterdam Criteria

(Bethesda Criteria)

Mean age dx colon cancer 44-61 Predominant right side colon cancer Lifetime penetrance 82%

Lynch Other Cancers

- Endometrial
- Stomach
- Ovarian
- Urinary tract
- Biliary Tract
- Small bowel
- CNS

Lynch Screening

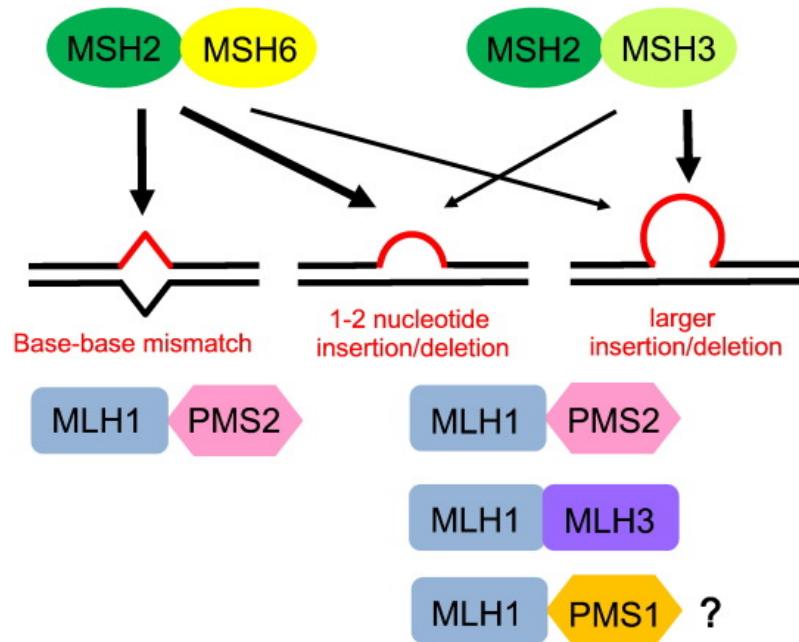
Colonoscopy q1-2 years staring age 20-25

Women with Lymch have 25-60% lifetime risk of endometrial cancer 45-12% lifetime risk of ovarian cancer Male: 1.2% risk of breast cancer (0.1% in general populations)

MMR and MSI

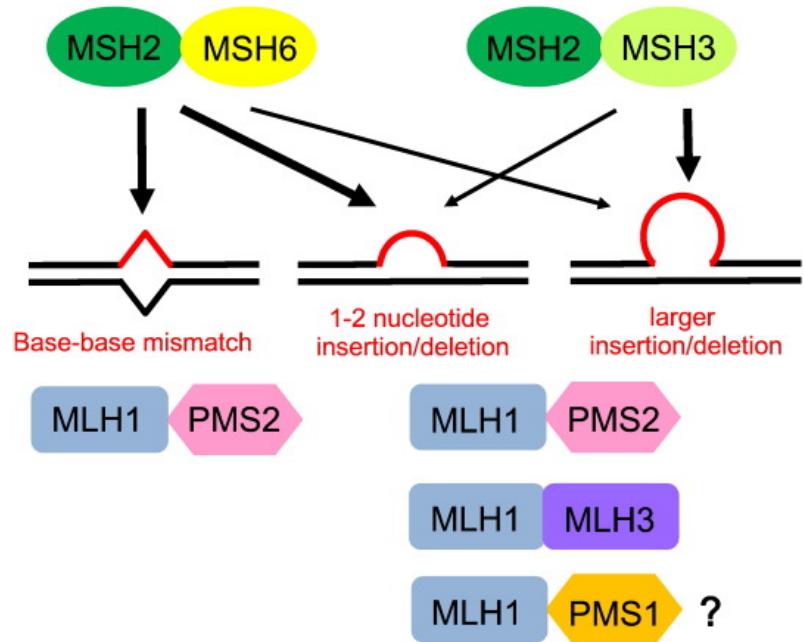
Greater than 90% of LS tumors are MSI-high (MSI-H) and/or lack expression of at least one of the MMR proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H most often due to abnormal methylation of the MLH1 gene promoter, rather than due to LS. Mutant BRAF V600E is found in many sporadic MSI-H CRCs and is rarely found in LS-related CRCs. There are some tumors that will have MLH1 methylation but lack a BRAF PV.

DNA Mismatch Repair Proteins

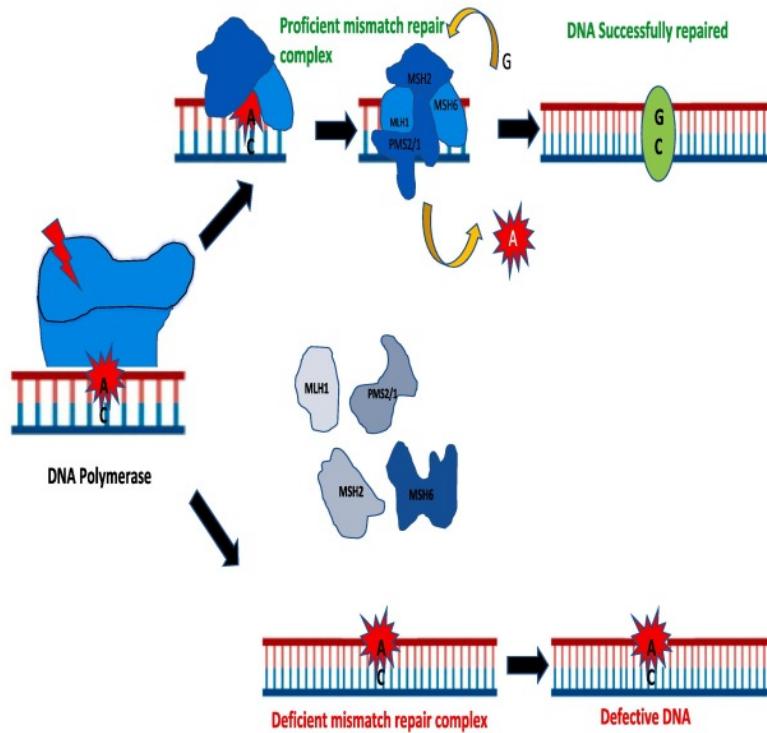


DNA Mismatch Repair Proteins

MLH1 PMS1 MSH6 MSH2 MSH5



DNA Mismatch Repair Proteins



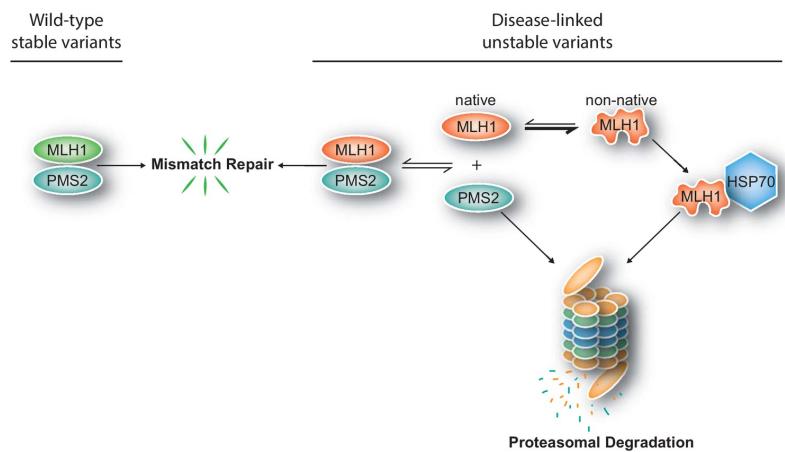
Mismatch Repair Proteins in Lynch Syndrome

Lynch Syndrome can be caused by loss of expression of:

- MLH1
- PMS1
- MSH6
- MSH2
- MSH5

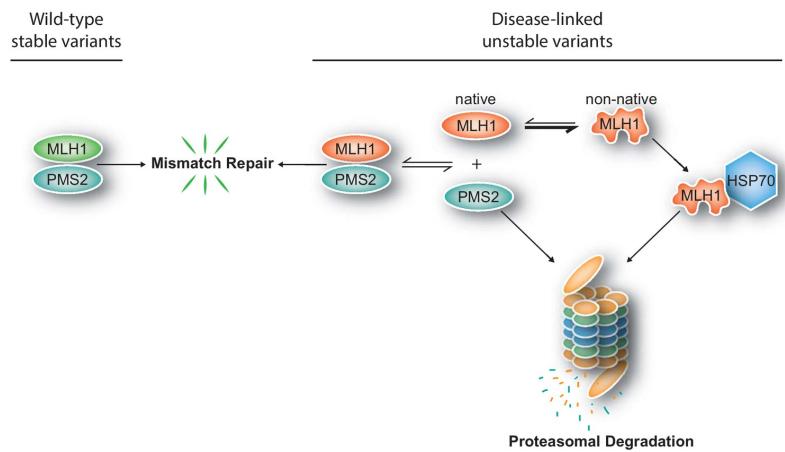
MLH1 and PMS Dimer in Mismatch Repair

wild-type MLH1 and PMS2 form a stable heterodimer



MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer



MLH1 and PMS Dimer in Mismatch Repair

Mutant MLH1 fails to form a stable heterodimer → PMS2 is degraded



MLH1 and PMS Dimer in Mismatch Repair

If MLH1 is mutated → PMS2 protein is *not* detected



Colon Polyposis: >10 adenomatous polyps

- Classical FAP
- Attenuated FAP (AFAP)
- MUTYH-associated polyposis (MAP)
- Colonic adenomatous polyposis of unknown etiology (CPUE)

Colon Polyposis: >4 hamartomatous polyps

- Puetz-Jaggers
- Juvenile Polyposis Syndrome
- Cowden Syndrome/PTEN Hamartoma Tumor Syndrome

Serrated Colon Polyps

5 serrated polyps/lesions proximal to the rectum, all being 5 mm in size, with 2 being 10 mm in size OR >20 serrated polyps/lesions of any size distributed throughout the large bowel, with 5 being proximal to the rectum

Muir-Torre Syndrome

Muir-Torre syndrome refers to individuals with LS who have LS-associated skin findings of sebaceous adenomas/carcinomas or keratoacanthomas.

BRCA 1/2

BRCA1: 87% lifetime risk of breast cancer and 40-60% risk of ovarian cancer

BRCA2: 80% lifetime breast cancer and 15-27% ovarian cancer
- Elevated risk of prostate, pancreas, melanoma

Male carriers of BRCA2: 8.9% lifetime risk of breast cancer

BRCA risk factors:

- Breast cancer dx before age 40
- Bilateral breast cancer
- Breast and ovarian cancer
- 2 family members with breast cancer < age 50
- Family history of breast and ovarian
- Family history of male breast cancer

Attenuated FAP

~30 polyps 70% penetrance by age 80 - mean age at dx 50-55

Li-Fraumeni

Mutation of TP53 tumor suppressor gene

- Breast cancer 90% by age 50
- Sarcoma
- Leukemia
- Brain tumors
- Andrenocortical carcinoma

Breast cancer in Li-Fraumeni

Mastectomy favored to avoid radiation therapy

Bilateral prophylactic mastectomy recommended

p16 = CDKN2A mutation

- Increased risk of melanoma
 - Familial Atypical Multiple Mole Melanoma (FAMMM)
 - Familiar Atypical Multiple Mole-Pancreatic Carcinoma (FAMMMPC)
- Melanoma penetrance 58-92% by 80
- Pancreatic cancer penetrance 17% by age 75

FAMMM

- Malignant melanoma in one or more first degree or second-degree relatives
- High total body nevus count
- Nevi with certain features on microscopy

Genetic testing not performed as only 50% of FAMMM harbor a mutation in CDKN2A

Neurofibromatosis 1

Mutation in NF1 tumor suppressor gene

- Multiple neurofibromas
- Cafe au lait spots
- Lisch nodules (hamartoma of the iris)

Risk of - NPNST - Pheochromocytoma - Astrocytoma - Leukemia

NF1 diagnosis

Two or more of the following 6 criteria:

- Six or more café-au-lait macules
- Two or more neurofibromas or one plexiform neurofibroma
- Axillary or inguinal freckling
- Optic glioma
- Two or more Lisch nodules
- Characteristic osseous lesions
- A first degree relative with NF1

Neurofibromatosis 2

NF2 gene

- Multiple neurofibromas
- Cafe au lait spots
- Bilateral vestibular schwannomas
- CNS tumors

Most affected develop bilateral schwannomas by age 30 with average age of death 26

Annual surveillance MRI starting age 10-12 and hearing evaluation

PTEN

Cowden Syndrome Mutation in *PTEN* tumor suppressor gene

- Mucocutaneous facial lesions
- Macrocephaly
- Bilateral breast cancer
- Thyroid and endometrial tumors
- Hamartomatous polyposis of the GI tract

MEN1

- Mutation of MENIN tumor suppressor
- Parathyroid
- Pituitary
- Pancreatic islet cells

Hyperparathyroidism usually first presentation Most common pancreatic tumor is non-functional

Dx by 2/3 of following:

- Parathyroid adenoma/hyperplasia
- Pancreatic islet cell tumors
- Pituitary tumors

MEN1 screening

Surveillance with serum prolactin, IGF-1, folic acid and insulin starting age 5 Calcium, chormogranin A, pancreatic polypeptide glucagon AP age 8 Serum gastrin starting age 20 Brain MRI starting age 5 Abdominal CT/MRI starting age 20

MEN1 surgical treatment

Parathyroidectomy 3.5 gland or 4 glands with autotransplantation

Pancreatic tumor resection if >2cm

Pituitary tumors resected via transsphenoidal

MEN2 Family of Syndromes

- RET proto-oncogene
- Medullary thyroid cancer in almost 100%
- MEN2A
 - pheochromocytoma in 50%
 - Parathyroid hyperplasia in 20-30%

-MEN2B - pheochromocytoma in 50% - Megacolon - Marfanoid habitus - Ganglioneromas - Mucosal neuromas

MEN 2 Prophylactic surgery

Prophylactic total thyroidectomy

Testing for pheochromocytoma prior with adrenalectomy prior

Monitor calcitonin and CEA after thyroidectomy

Case 1

Pathology shows Barrett's metaplasia without dysplasia

What is appropriate follow up?

Biopsy strategy?

Case 1 Barrett's metaplasia without dysplasia

What is appropriate follow up?

AGA Guidelines

- No dysplasia: 3-5 years
- Low grade dysplasia: 6-12 months
- High grade dysplasia 3 months
 - (in the absence of ablation)

Case 1 Barrett's metaplasia without dysplasia

Biopsy strategy?

AGA Guidelines

- White light endoscopy
- 4-quadrant biopsy every 2cm
- Mucosal irregularity biopsied separately
- 4-quadrant biopsy every 1cm if dysplasia)

Case 2

Pathology shows high-grade dysplasia

Treatment Options:

- Observation
- Esophagectomy
- Cryotherapy
- Irreversible Electroporation
- Radio-frequency Ablation

Observation

You receive a hand-written note from the family
inviting you to the funeral of the patient
who passed after a heroic battle with esophageal cancer

[Case 2](#)

Esophagectomy

Correct answer, wrong century (not the 20th)

[Case 2](#)

Cryotherapy

Correct answer, wrong century (not the 22nd)

[Case 2](#)

Irreversible Electroporation



[Case 2](#)

Radio-frequency Ablation

Radiofrequency Ablation results in eradication of Barrett's in 75% at 1 year



Case 3

(Shaheen et al. 2009)

Case 3

EGD shows a nodule in the Barrett's esophagus

Treatment Options:

- Surveillance
- Minimally Invasive Esophagectomy
- Endoscopic Mucosal Resection
- Radio-frequency Ablation Barxx

Surveillance

You receive a hand-written note from the family
inviting you the patient's 70th birthday

after being treated at a competing medical center
for esophageal cancer

Case 3

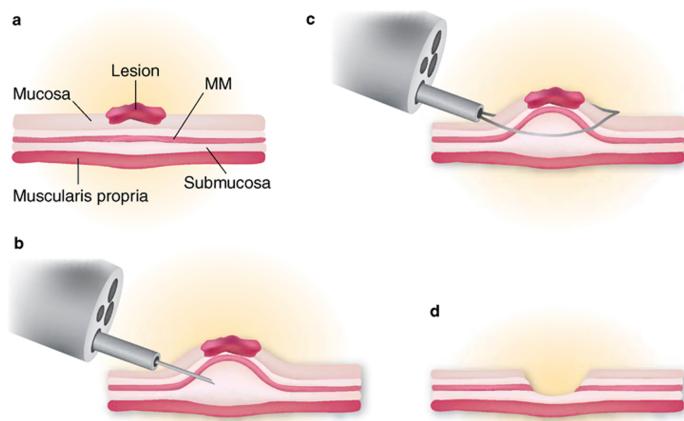
Minimally Invasive Esophagectomy

Correct answer, wrong patient

Case 3

Endoscopic Mucosal Resection

Endoscopic procedure resects mucosal tumor



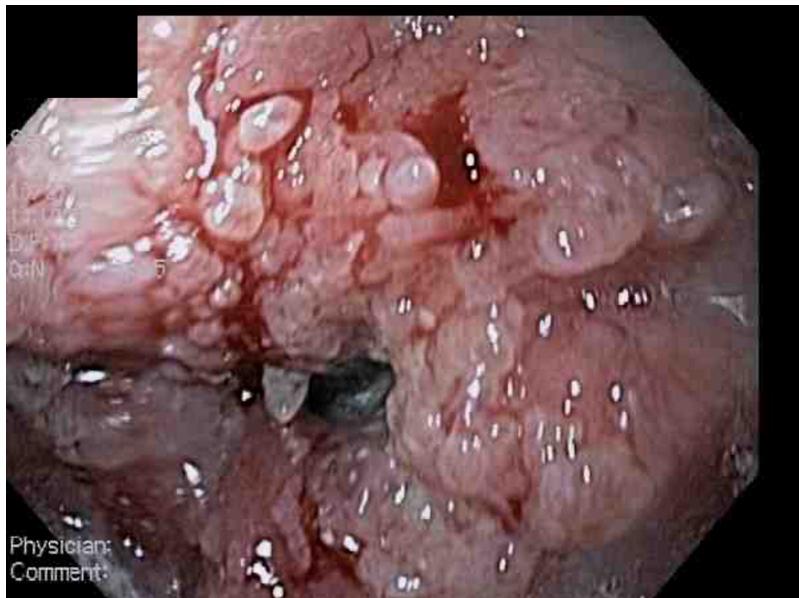
Case 4

Radio-frequency Ablation Barxx

Correct answer, wrong question

Case 4

Your patient from Case 2 returns with dysphagia and weight loss



Case 4 Adenocarcinoma

Pathology shows adenocarcinoma

Workup?

Case 4 Adenocarcinoma

Workup?

- Barium Swallow
- Endoscopic Ultrasound
- [CT Chest/Abdomen/Pelvis]

Barium Swallow

Correct answer, wrong century

[Case 4](#)

Endoscopic Ultrasound

You receive a hand-written note from the family
inviting you the patient's funeral
after they died from an esophageal perforation
which occurred during EUS

Autopsy showed T3 adenocarcinoma

[EUS in Patients with Dysphagia](#)

[Case 4](#)

MLH1 and PMS Dimer in Mismatch Repair

What test do you order next?

T3 N0 M0 adenocarcinoma

Treatment Options - First Treatment Course

- [MI Esophagectomy](#)
- [Chemo + Radiation](#)
- [Chemotherapy](#)

MI Esophagectomy

Correct answer, wrong timing

Why?

[T3 N0 M0 adenocarcinoma](#)

Chemo + Radiation

Concurrent chemotherapy and radiation followed by surgery =
Trimodality therapy

CROSS Trial

- 368 esophageal cancer patients randomized:
 - Surgery alone
 - Chemo+RT → Surgery
- 75% adenocarcinoma
- T3: 80%. T2: 17%
- age $\tilde{x}=60$
- longer survival with Chemo+RT → Surgery

CROSS Trial Details

Chemotherapy: Weekly carboplatin and paclitaxel
Radiation: 4140 cGy in 23 fractions (180cGy/fraction)

(Shapiro et al. 2015)

CROSS - Overall Survival

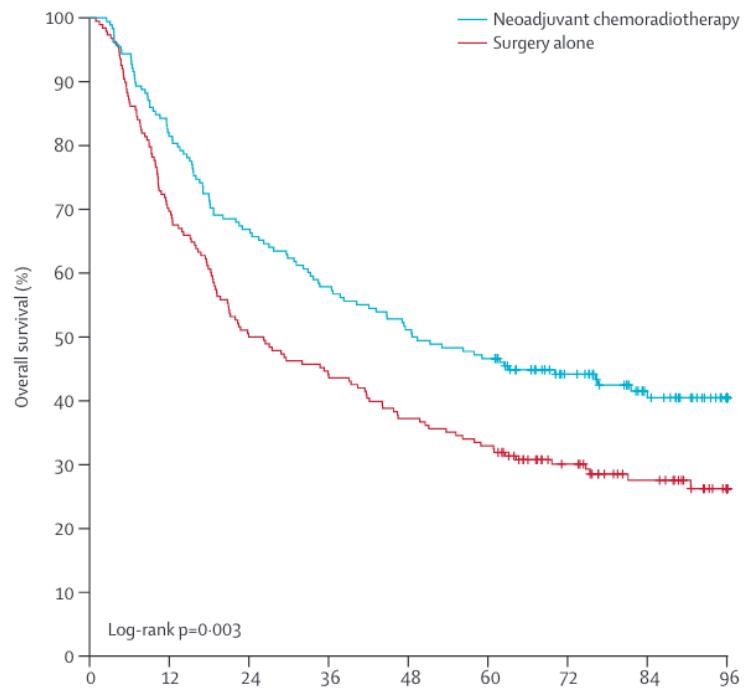


Figure 1: Surgery vs ChemoRT → Surgery

(Shapiro et al. 2015)

CROSS - Survival by Histology

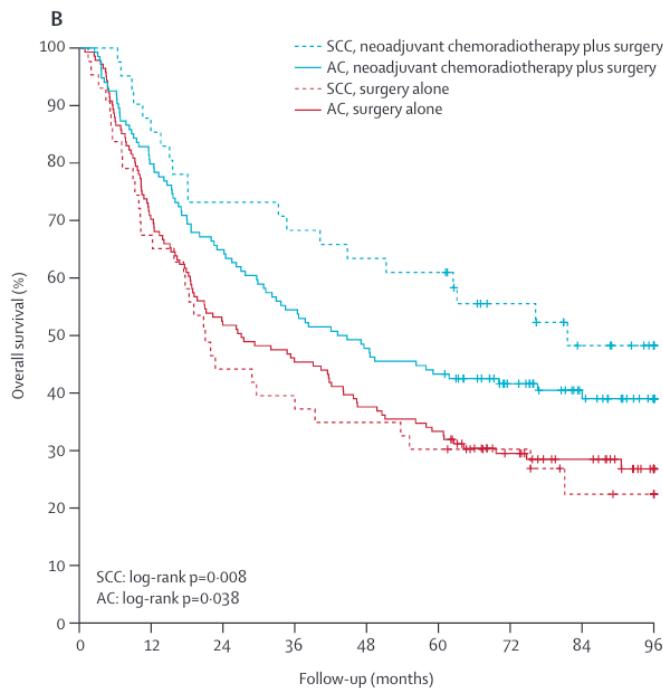


Figure 2: Surgery vs ChemoRT → Surgery

CROSS - Adenocarcinoma

(Shapiro et al. 2015)

Median survival 43mo vs 27mo

Pathologic complete response in 23%

CROSS - Squamous cell carcinoma

Median survival 82mo vs 21mo

Pathologic complete response in 40%

(Shapiro et al. 2015)

T3 N0 M0 Adenocarcinoma

Family asks if there is a better treatment option than CROSS

Chemotherapy

“Sandwich” Chemotherapy may be superior to Trimodality therapy

EsoPEC Trial

- Adenocarcinoma esophagus - T1 N+ or T2-4a M0. Median age =63. 89% men
- Randomized to CROSS (n=217) vs FLOT chemotherapy (n=221) = 438
- CROSS: carboplatin/paclitaxel + 4140cGy → Surgery
- FLOT: FLOT → Surgery → FLOT
- Excluded: Squamous cell, gastric cancer, T1N0, T4b, M1

EsoPEC Trial Results

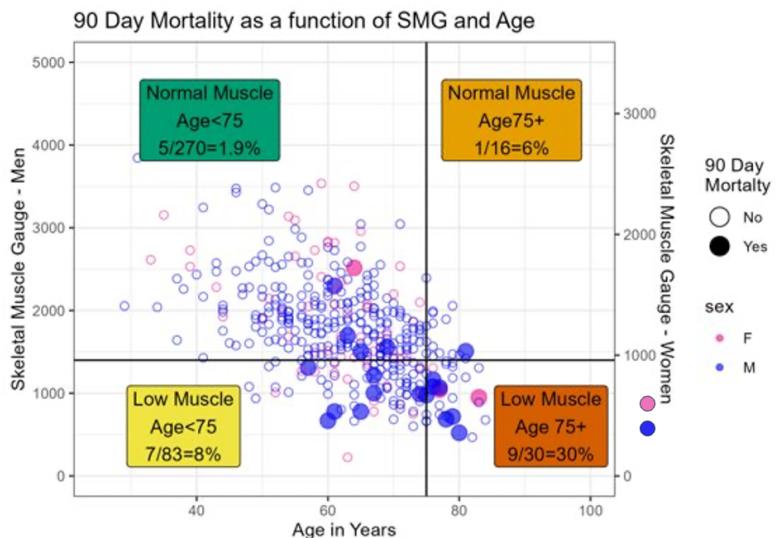
- Surgery performed in 371/438 patients
- 90-day mortality 4.3% (3.2% in FLOT and 5.6% CROSS)
- Median survival 66mo in FLOT arm and 37mo in Cross arm
- 3-year overall survival 57% FLOT vs 51% CROSS
- 5-year overall survival 51% FLOT vs 29% CROSS
- pCR 17% for FLOT and 10% CROSS

Case 7

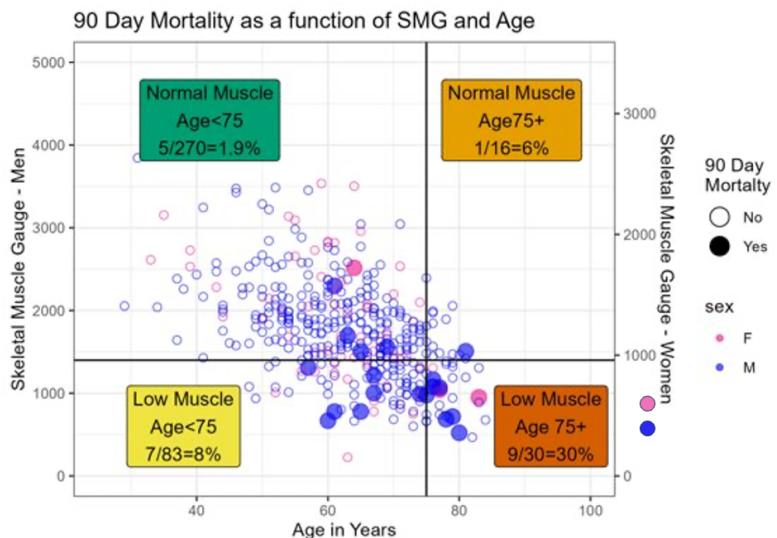
Patient returns after FLOT chemotherapy

What are risks of surgery?

Preoperative Evaluation



Preoperative Evaluation



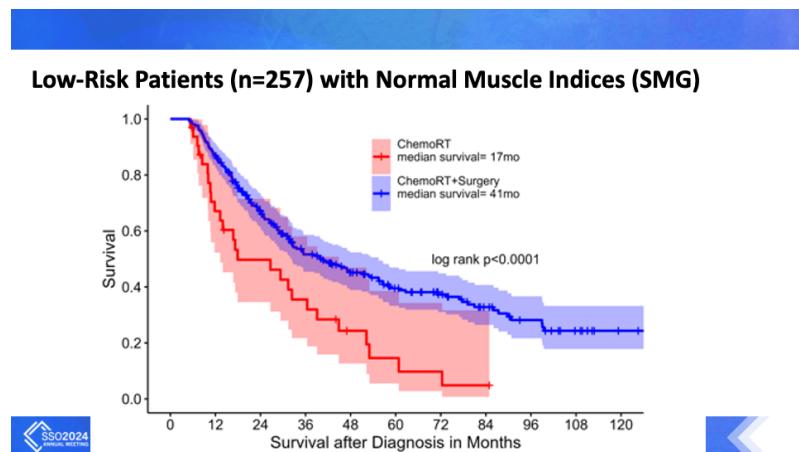
25th percentile: Grip Strength 26kg (men) / 16kg (women)

Case 7

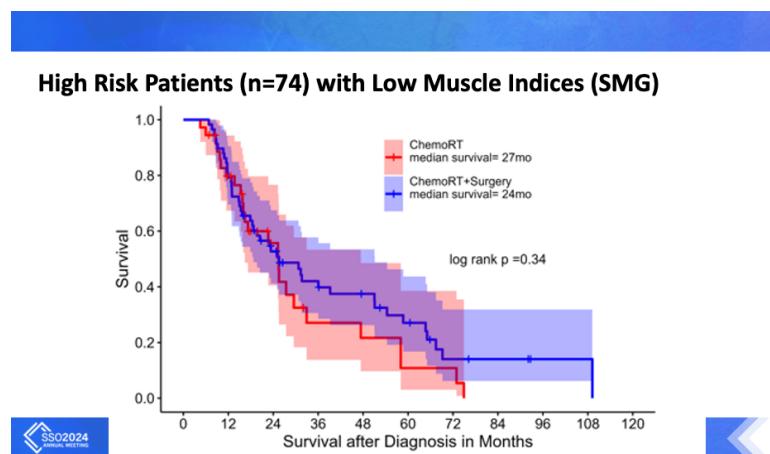
Patient returns after FLOT chemotherapy

What are surgical options?

Low Risk Adenocarcinoma



High Risk Adenocarcinoma



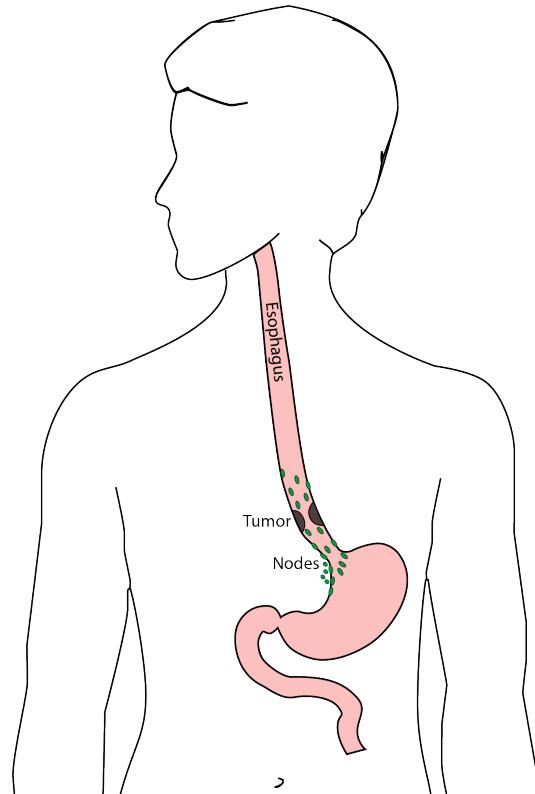
Surgery for Esophageal Cancer

Surgery for esophageal cancer is performed for:

- Superficial Tumors (T1) not completely removed by endoscopy
- Localized Tumors (T2N0)
- Locally Advanced (T3) after preoperative therapy.

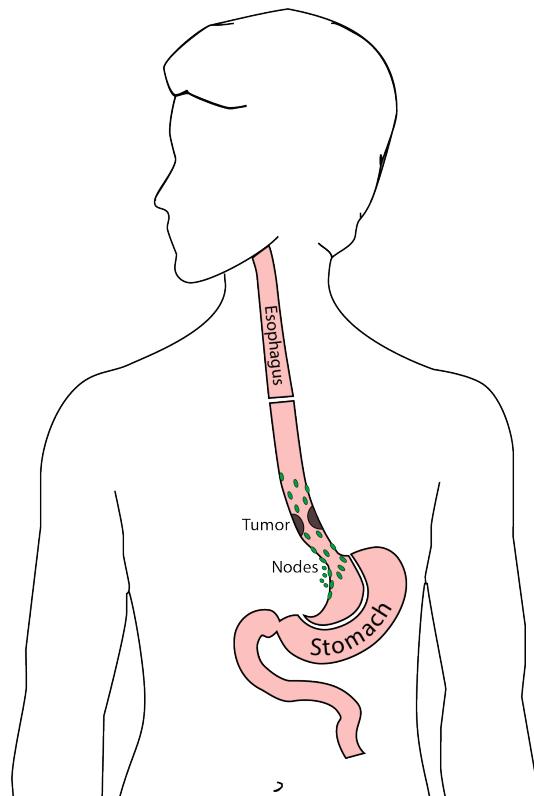
Goals of Surgery

- Remove tumor from esophagus
- Remove surrounding lymph nodes
- Create a new esophagus



Ivor Lewis (Transthoracic) Esophagectomy

- Removes tumor
- Removes lower 1/3 of esophagus
- Removes surrounding lymph nodes
- Reconstruction of GI tract



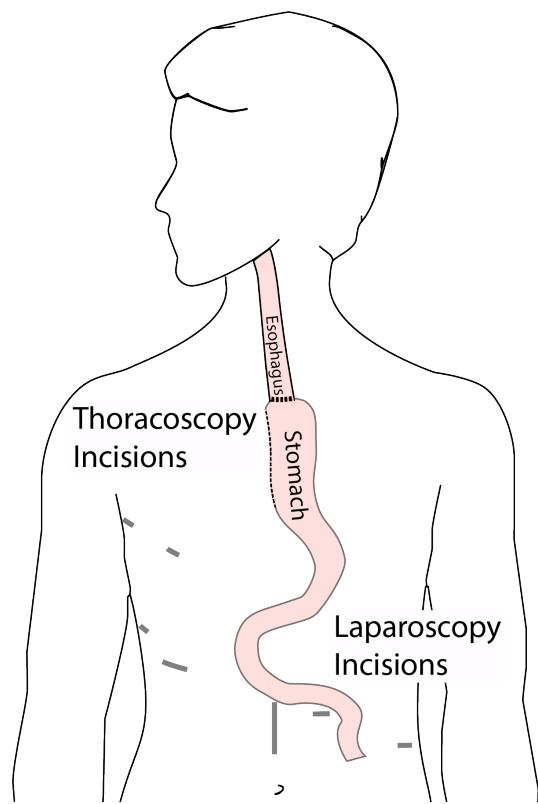
Reconstruction

A new esophagus is created from the stomach in the abdomen by fashioning it into a tube.

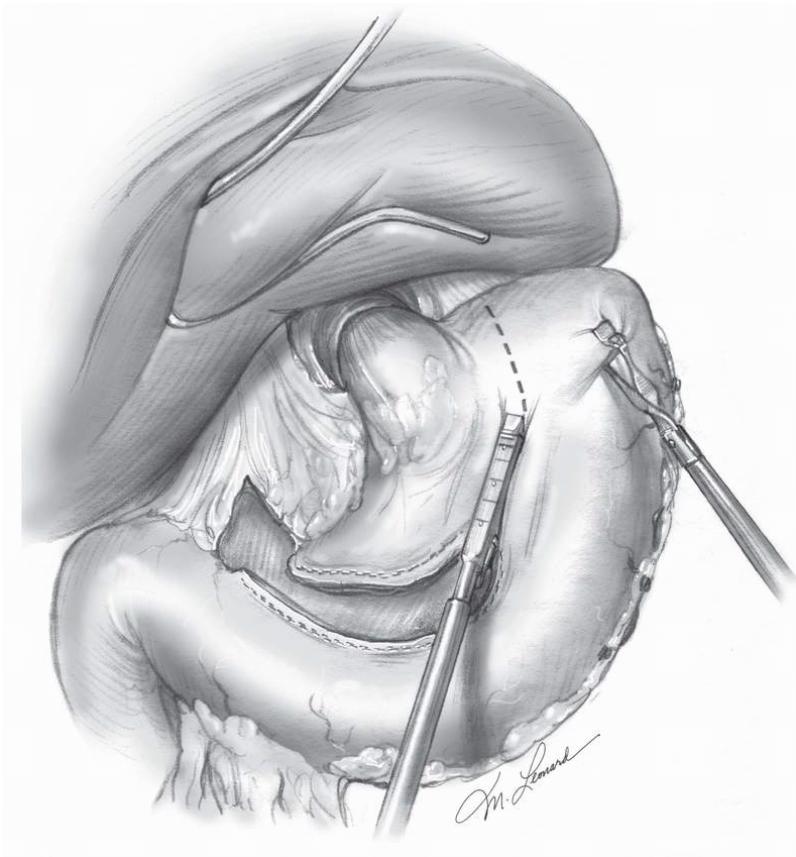


Minimally-invasive Ivor Lewis

- Laparoscopic mobilization of stomach
- Construction of gastric conduit
- Thoracic anastomosis



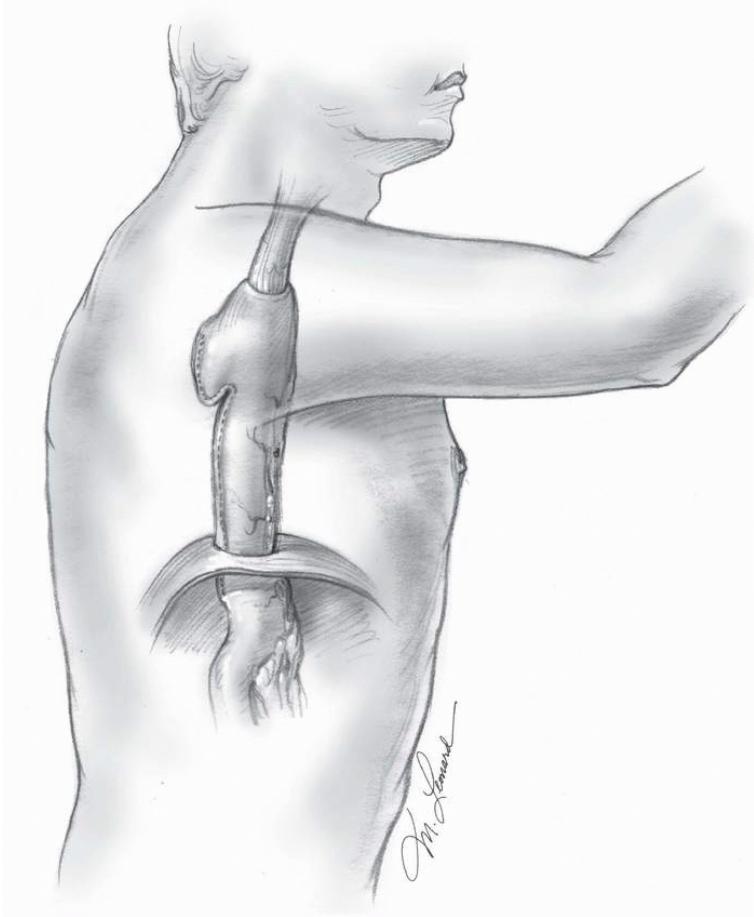
Ivor Lewis esophagectomy





Ivor Lewis esophagectomy





Thoracic Circular Stapled Anastomosis

Open Ivor Lewis

We use the minimally-invasive approach in 95% of cases

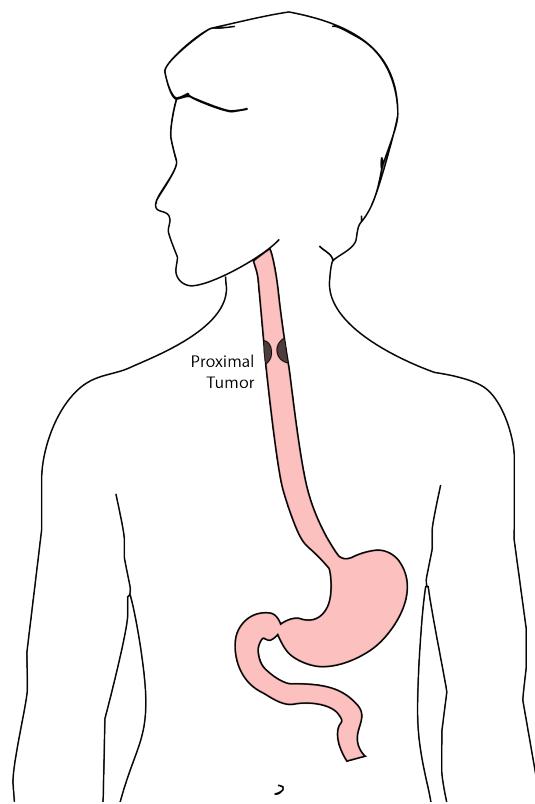
In some cases, an open approach is still necessary.



Total Esophagectomy

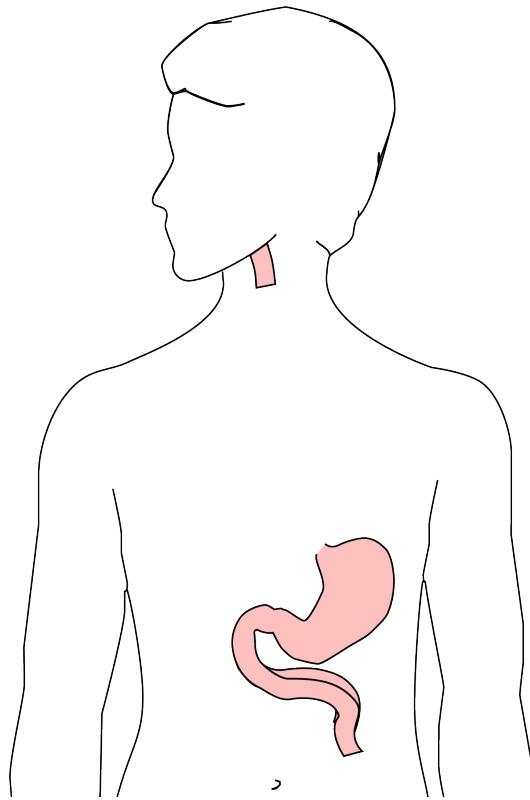
For patients with tumors in the upper esophagus, we need to remove more of the esophagus

We need to remove the whole esophagus, including the portion in the neck

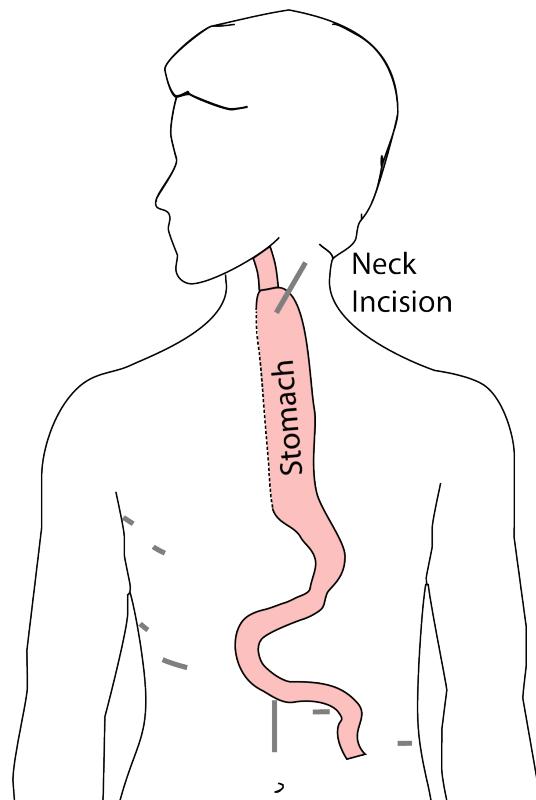


McKeown Esophagectomy

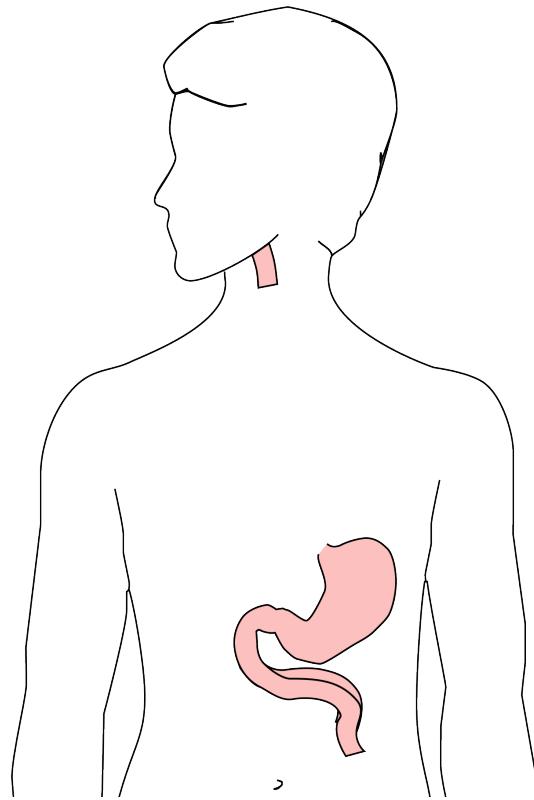
All of esophagus removed

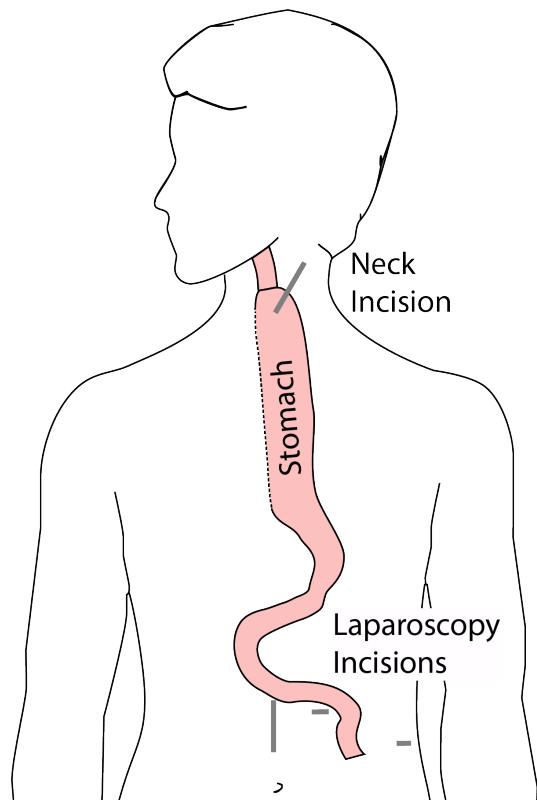


Connection made in the neck



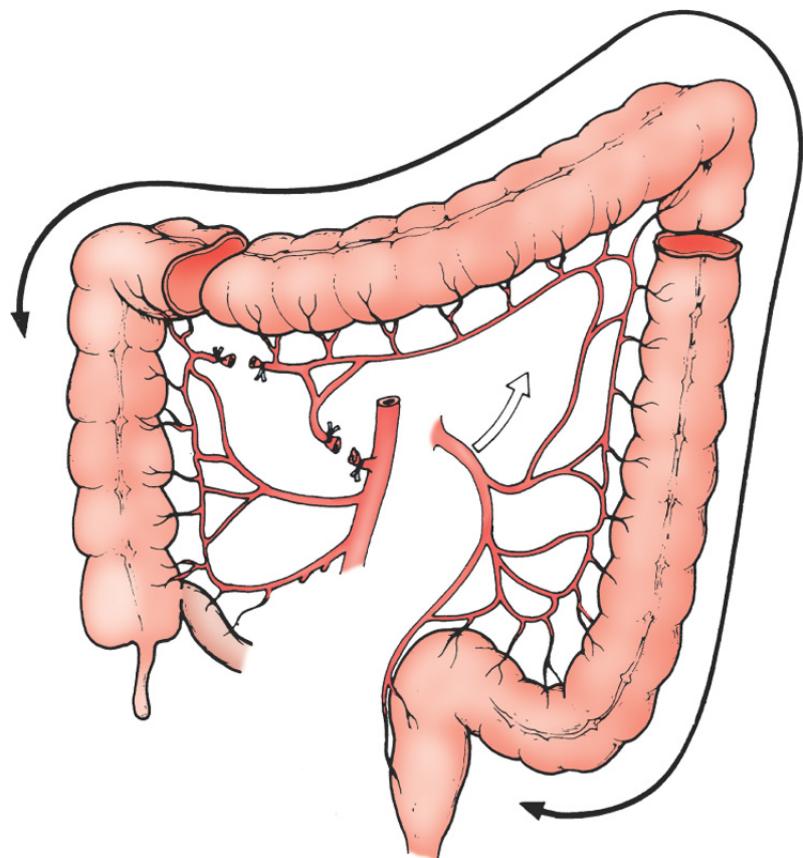
Transhiatal Esophagectomy





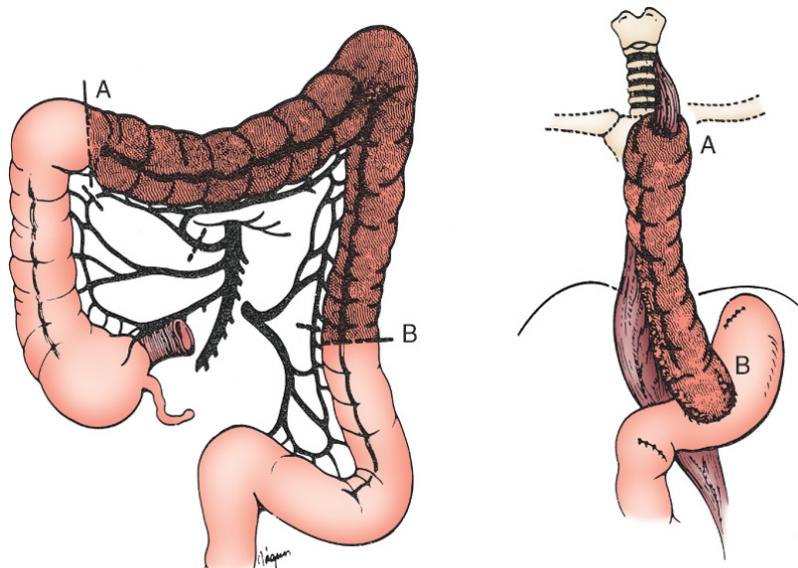
Colon Interposition

If the stomach is not suitable to make a new esophagus, the colon can be used to replace the esophagus



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Colon Interposition



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Esophageal Cancer Treatment Categories

Category	Stage	Treatment
Dysplasia	Tis	Radiofrequency Ablation
Superficial Tumors	T1a	Endoscopic Therapy
Localized Tumors	T1b T2	Surgery
Locally-advanced	T3 or N ⁺	Chemo or ChemoRT → Surgery
Metastatic	M1	Chemotherapy +/- Radiation

Dysplasia

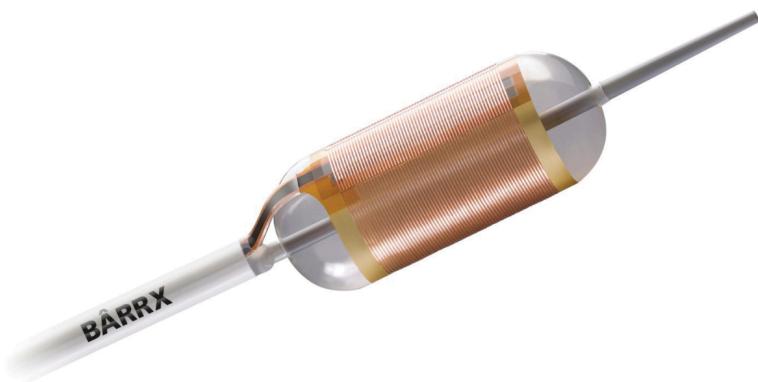
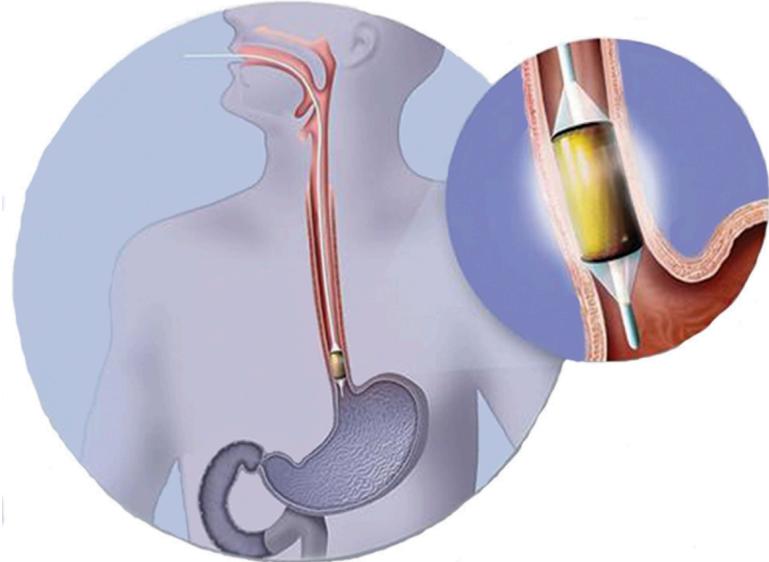
Radiofrequency Ablation for Dysplasia

127 patients with dysplasia randomized:

- Radio-frequency ablation
- Sham ablation

Low-grade dysplasia in 64

High-grade dysplasia in 63



(Shaheen et al. 2009)

Radiofrequency Ablation for Dysplasia

Radiofrequency Ablation results in eradication of Barrett's in 75% at 1 year



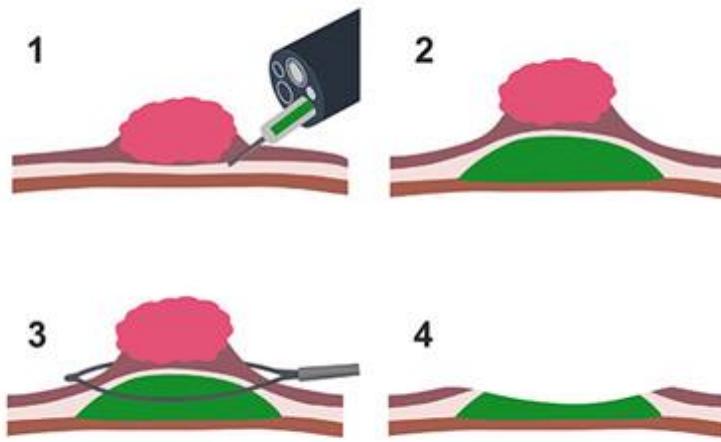
(Shaheen et al. 2009)

Superficial Tumors

Workup of nodular Barretts:

- Endoscopic Ultrasound
- Endoscopic Mucosal Resection
 - Diagnostic (T staging)
 - May be therapeutic for T1a tumors

Endoscopic Musocal Resection



Localized Tumors

Patients staged as uT2 N0 are candidates for primary surgery.

However:

- EUS has a 25% rate of understaging uT2 N0 tumors
- Understaged patients who undergo primary surgery would need chemo or chemoRT postop

Small Tumors (minimal dysphagia)

- EUS to distinguish T2 from T3 tumors
- If uT2 N0 → CT chest/abdomen/pelvis → Esophagectomy
- If uT3 or N1 → PET → neoadjuvant therapy

Patients with dysphagia almost always are T3 tumors (and don't need EUS)

Symptomatic Tumors (Dysphagia)

Patients with dysphagia to solids or weight loss or tumor length >3cm are unlikely to have T1-2 tumors and can be initially evaluated with PET Scan

- Disease confined to the esophagus and regional nodes → Locally-advanced
- Metastatic disease → Metastatic
- N3 → induction chemotherapy followed by chemoradiation and surgical evaluation.

EUS in Patients with Dysphagia

Memorial Sloan Kettering¹ patients with esophageal cancer:

- 61 with dysphagia, 54 (89%) were found on EUS to have uT3-4 tumors.
- 53 without dysphagia, 25 (47%) were uT1-2 → candidates for primary surgery.

EUS can be omitted for patients with dysphagia, but is useful in patients *without* dysphagia.

PET Scan

PET has more specificity and sensitivity than CT in detecting regional lymph node and distal metastasis²

Locally-advanced

For patients with locally-advanced esophageal cancer, improved survival with adjunctive therapy. There are two options:

- ChemoRT → Surgery (CROSS Trial)
- Chemo → Surgery → Chemo (EsoPEC Trial)

¹Ripley et al. (2016)

²Block et al. (1997)

Surgery for Squamous Cell Carcinoma

Squamous Cell Carcinoma of the esophagus

- responds well to chemo+RT
- more difficult to get a surgical margin on the airway
- additional benefit of surgery on top of chemoRT is uncertain

FFCD 9102 2007 (Bedenne)

All patients received 4500cGy RT + 2 cycles of cisplatin + 5FU

Patients with a clinical response were randomized:

- Surgery -> 2 year survival 34% Median 17.7mo
- 3 cycles of chemo + 2000 cGy RT -> 2 year survival 40% Median 19.3mo

No difference in overall survival

German Trial (Stahl)

4000 cGY RT + Chemo → Surgery. 64% 2-year PFS. Mortality 12.8%

6500cGy RT + Chemo: 41% 2-year PFS. Mortality 3.5%

No difference in overall survival

Metastatic

FOLFOX is first-line systemic therapy for metastatic GI cancers

- Dose-limiting toxicity is frequently peripheral neuropathy

Orientation Handbook



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