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Locally Advanced Esophageal and Gastric Cancer

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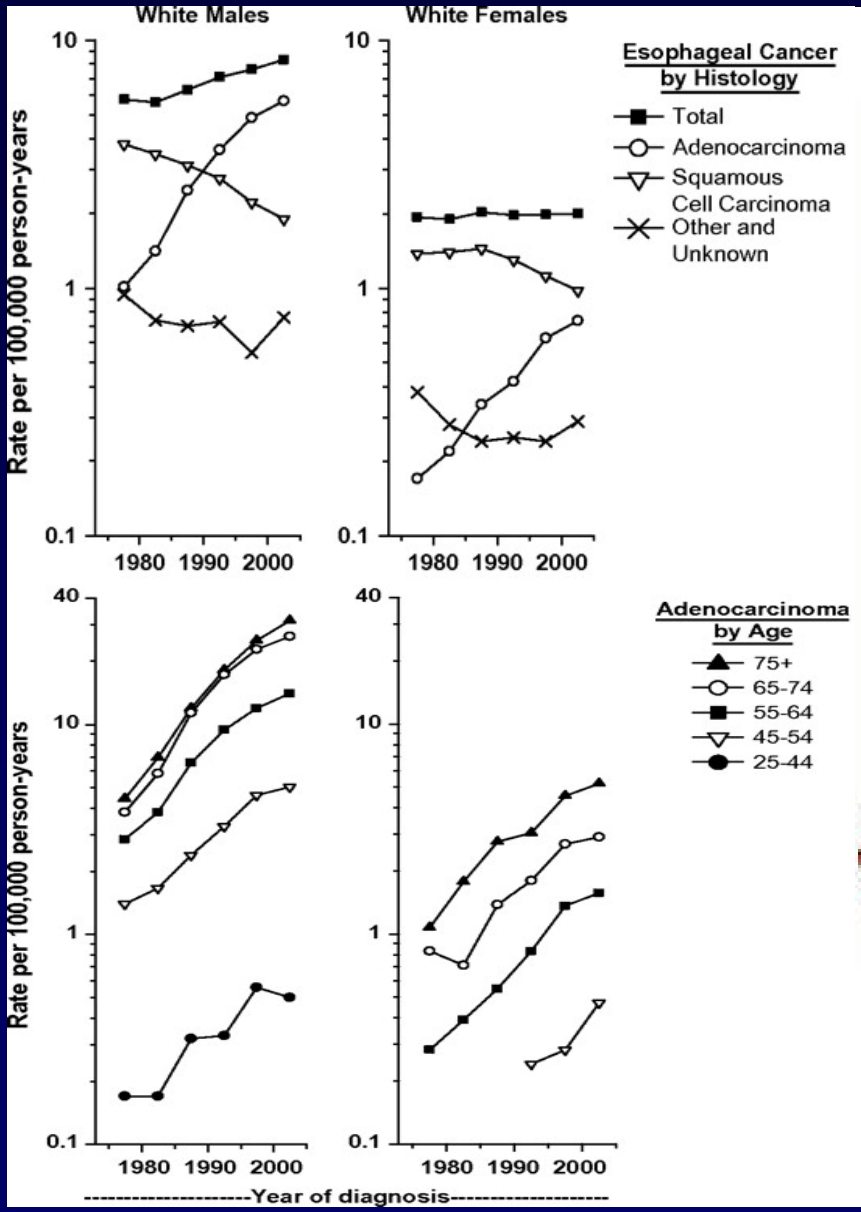
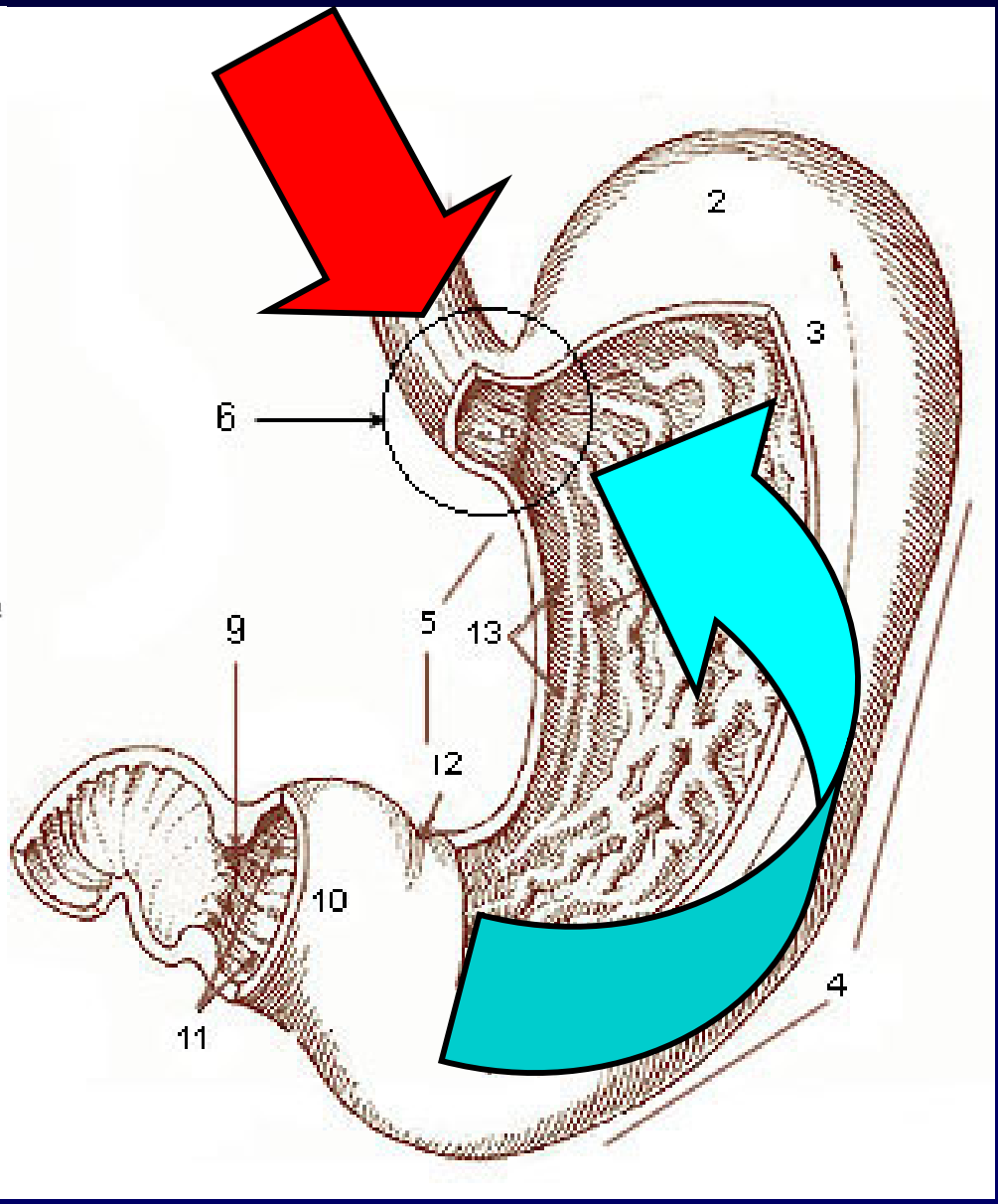
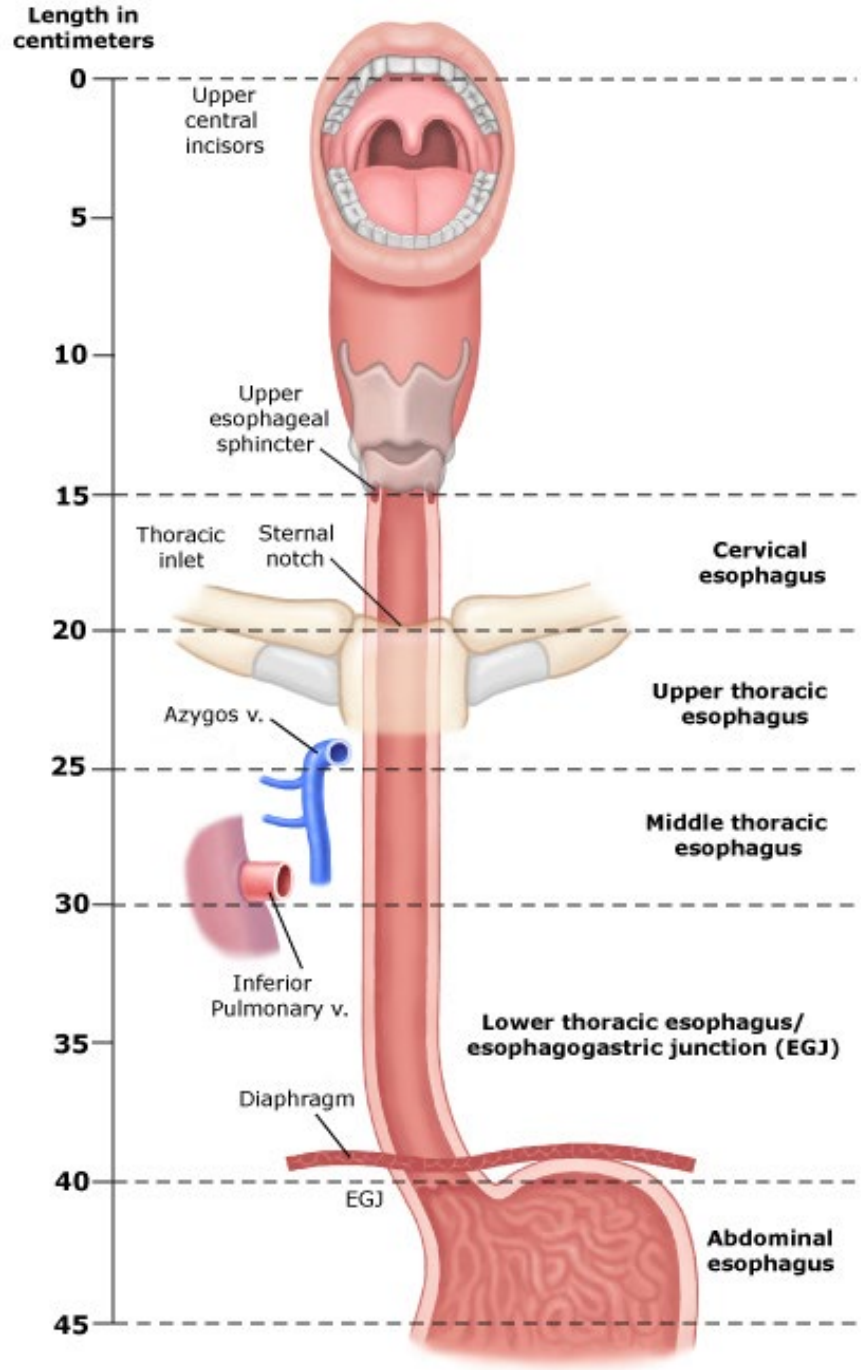
Trends in Esophagogastric Cancer:



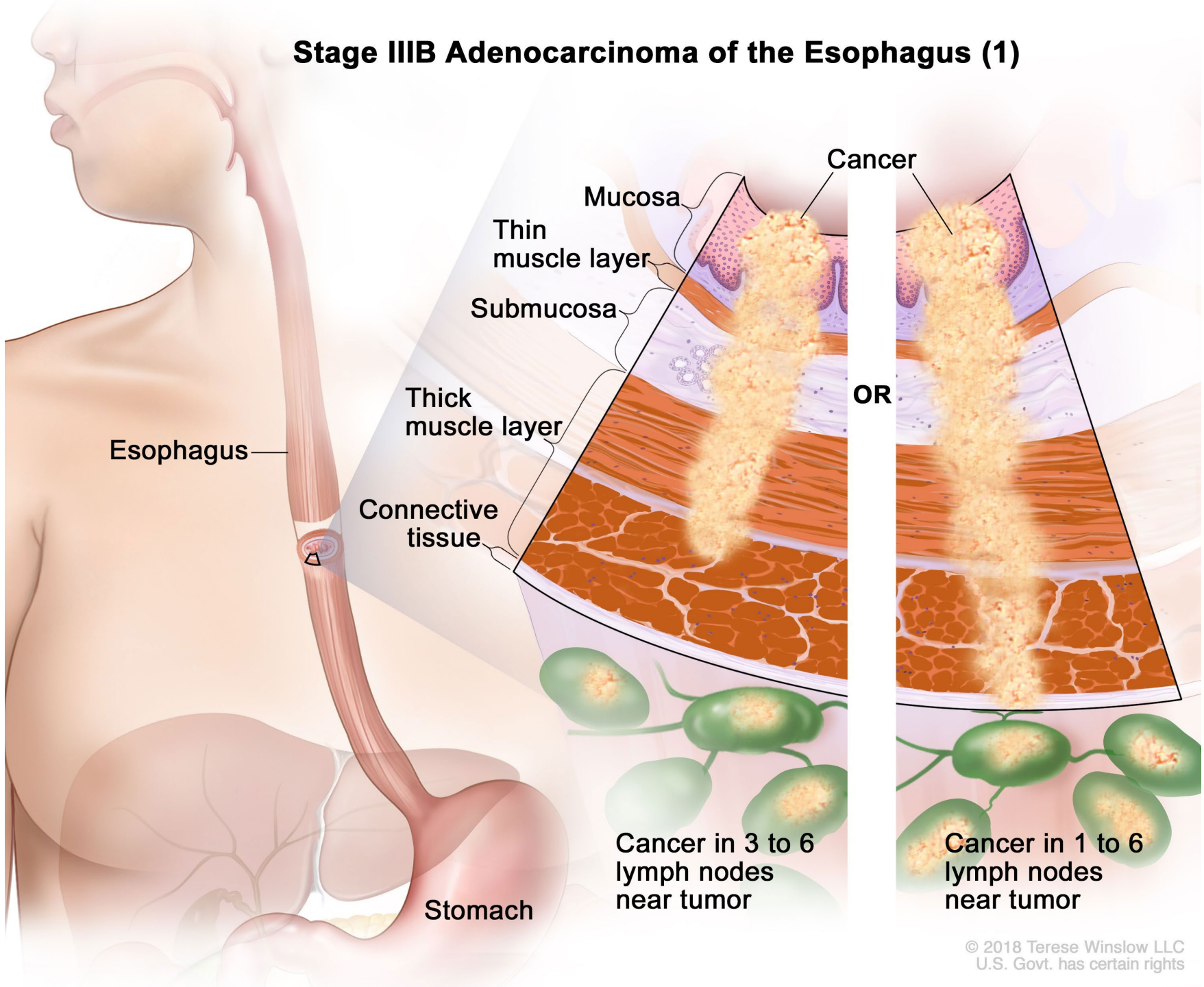


Brown. J. Natl. Cancer Inst. 2008

Esophageal Cancer


Length in centimeters
0
5
10
15
20
25
30
35
40
45
Upper central incisors
Upper esophageal sphincter
Thoracic inlet
Sternal notch
Azygos v.
Inferior Pulmonary v.
Diaphragm
EGJ
Cervical esophagus
Upper thoracic esophagus
Middle thoracic esophagus
Lower thoracic esophagus/ esophagogastric junction (EGJ)
Abdominal esophagus

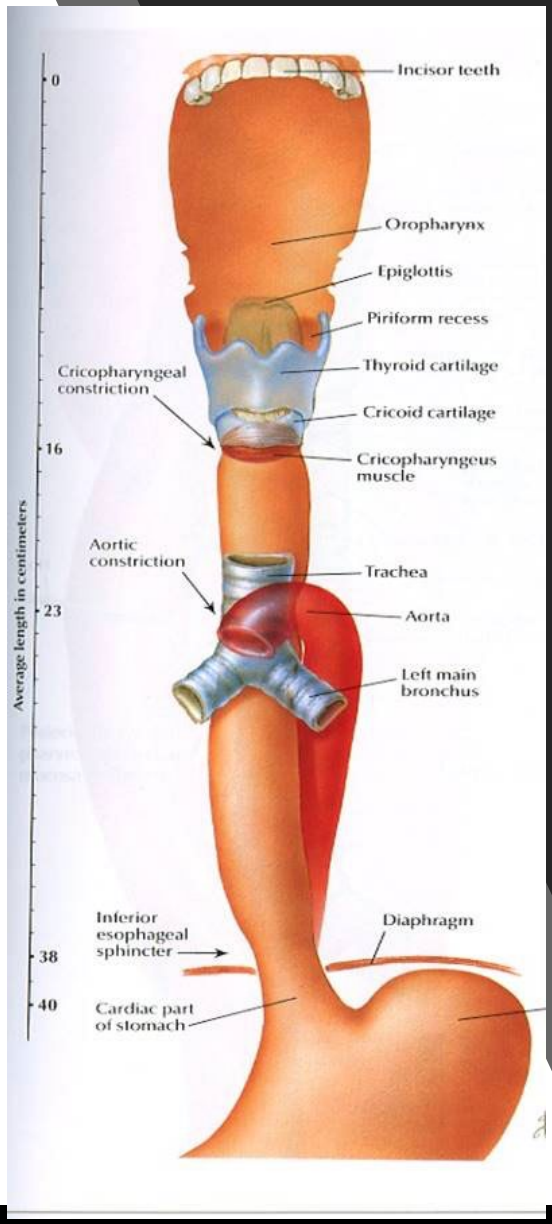
Stage IIIB Adenocarcinoma of the Esophagus (1)



What are the treatment modalities for locally advanced esophageal cancer?

- Surgery
  - Ivor-Lewis
  - 3-hole
  - Transhiatal
  - Minimally invasive
  - Robotic
- Radiation Therapy
  - External Beam Radiation Therapy
    - Conventional
    - IMRT
    - Protons
- Chemotherapy
- Immunotherapy
  - Checkmate 577 – nivolumab vs placebo

Surgery



What is an Esophagectomy

- The esophagus is the conduit between the mouth and the stomach
- It traverses the chest next to the spine
- It extends 2-4 cm into the abdomen before becoming the stomach

- An esophagectomy is removal of MOST of the esophagus.
- A gastrectomy is removal of the stomach

ESOPHAGECTOMY

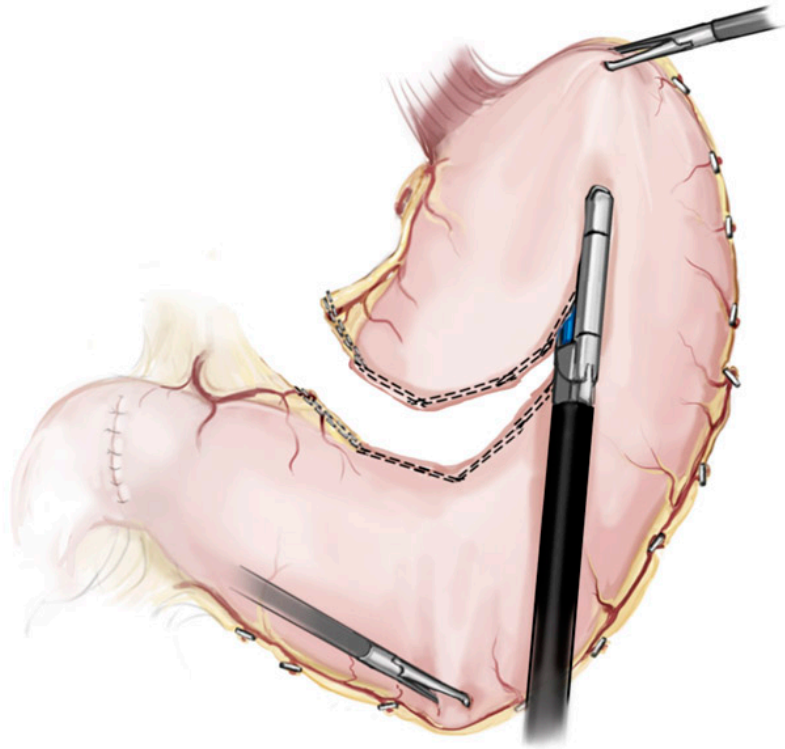
- Best approach remains controversial
- Chosen technique depends on multiple factors
- Historically was one of the highest incidences of mortality and morbidity

Miller et al. Surg Clin North Am. 1997

ESOPHAGECTOMY

- As better surgical techniques developed, safer more reliable options came about
- Multiple different approaches
  - Thoracotomy/Laparotomy (Ivor Lewis)
  - 3-Hole (Thoracotomy, Laparotomy, neck)
  - Left Thoracoabdominal
  - Transhiatal

Laparoscopic Steps: Gastric Tubularization, Celiac node dissection, stapling of left gastric vessels

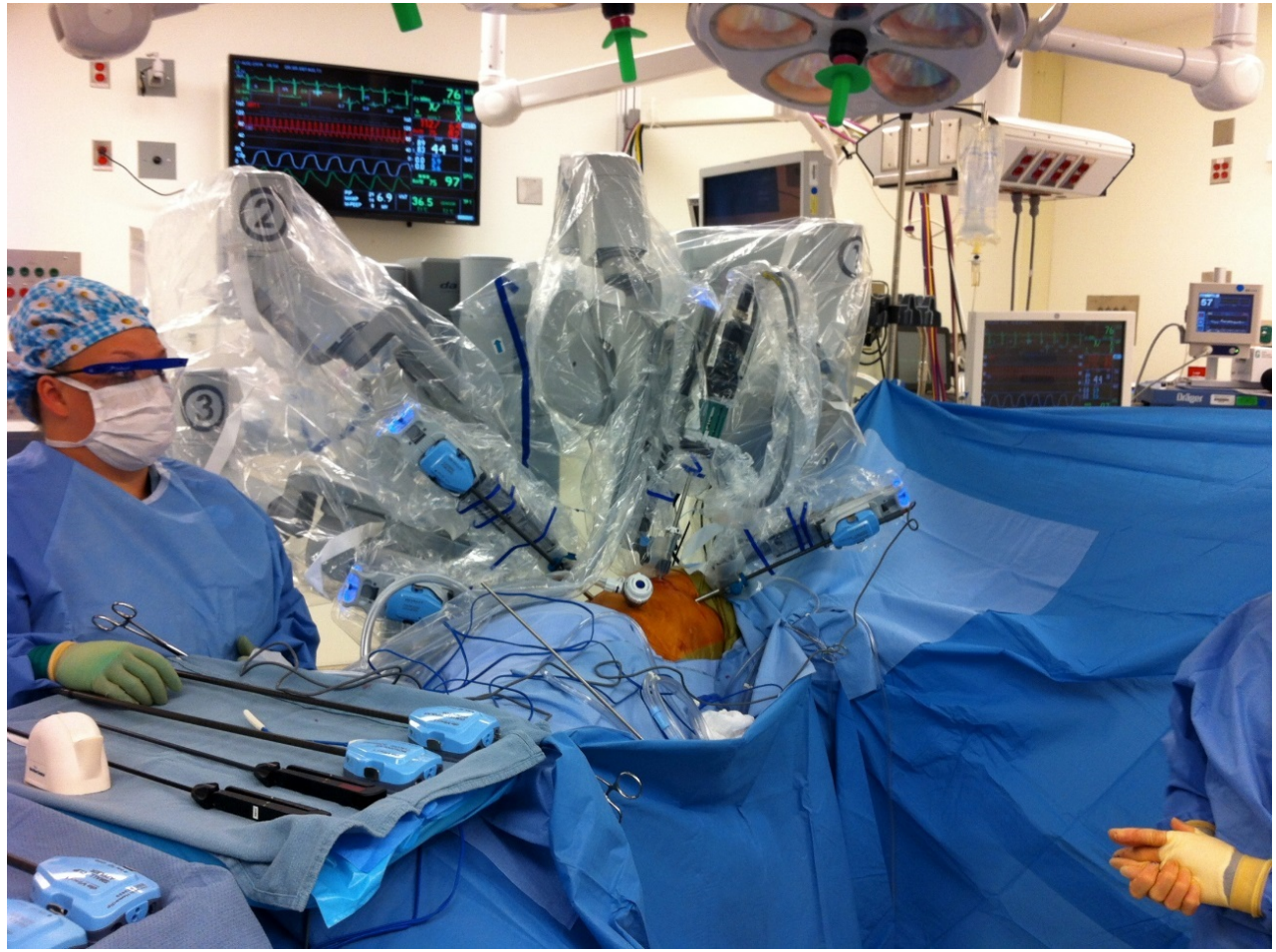


ESOPHAGECTOMY

- Minimally invasive approaches are feasible and safe
- Reduced mortality and morbidity rates
- Less Blood loss
- Less respiratory complications
- Similar oncologic results

Luketich et al. J Soc Laparoendosc Surg. 1998
Nguyen et al. J Am Coll Surg. 1999
Patty et al. World J Gastroenterol 2010

Robotic Esophagectomy

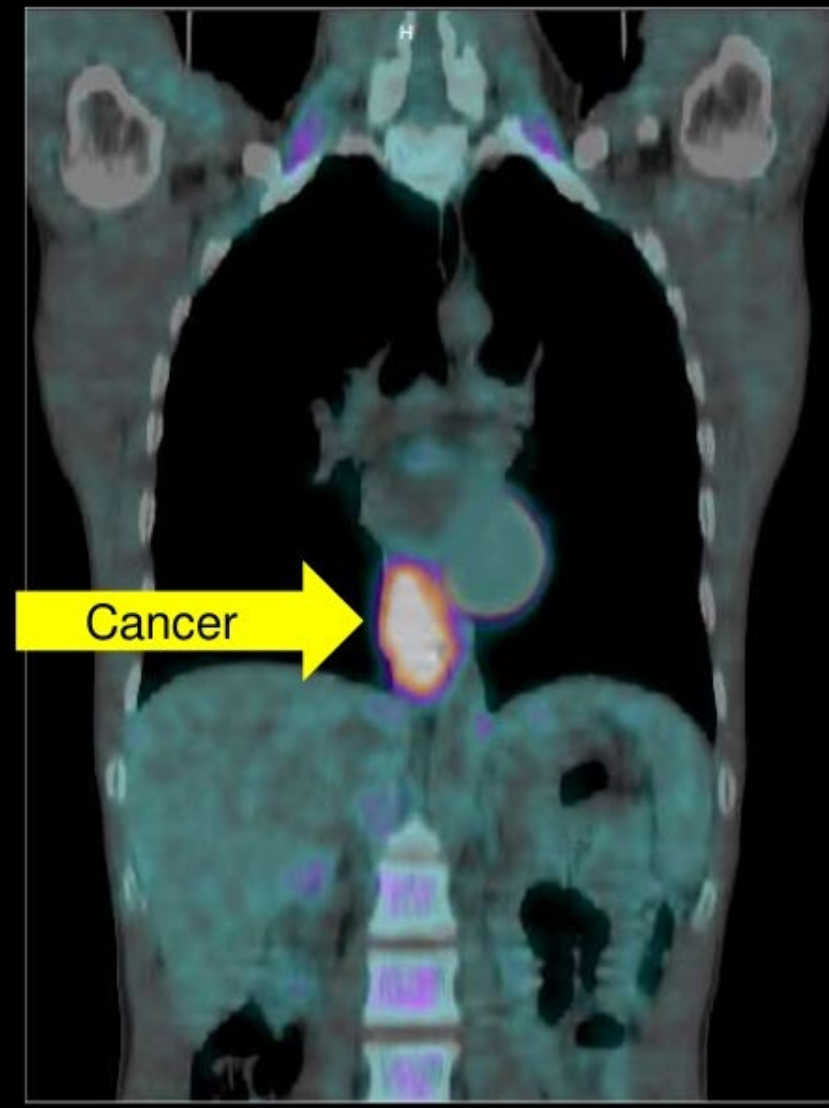


Postoperative Complications

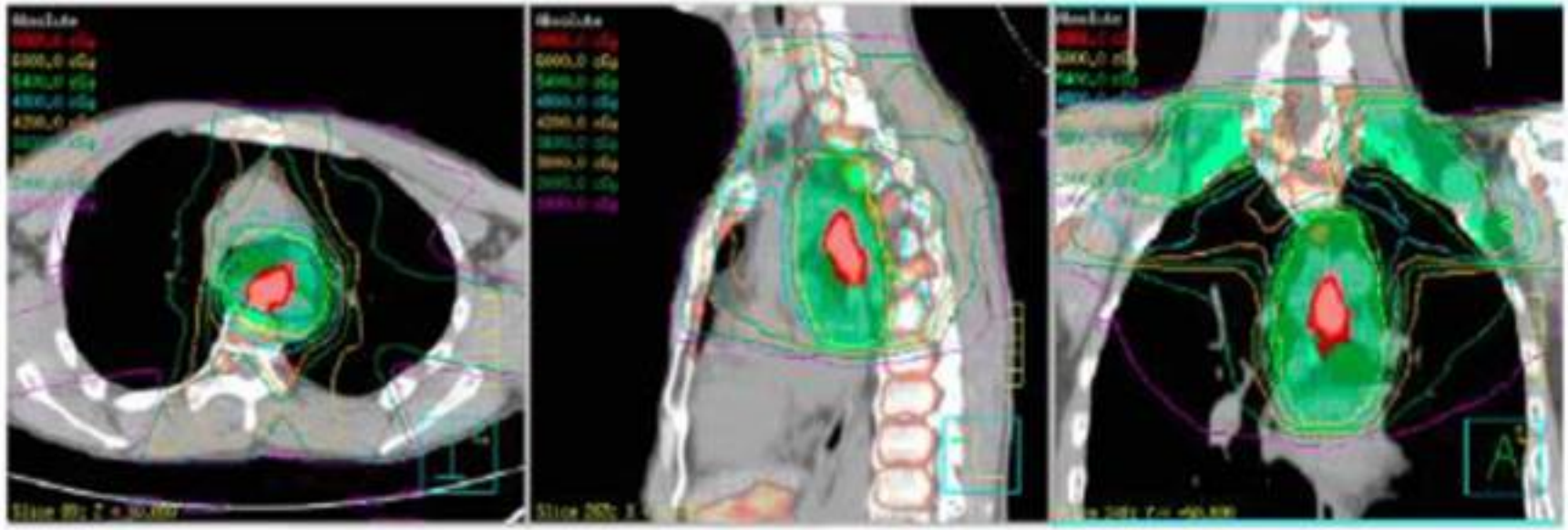
	Hybrid (103) (N)	Converted (51) (N)	MIE (200) (N)
Patients with Postoperative Complications	77 (74.8%)	34 (66.7%)	147 (73.5%)
Cardiac	27 (26.2%)	7 (13.7%)	53 (26.5%)
Pulmonary	26 (25.2%)	12 (23.5%)	58 (29.0%)
Gastrointestinal	11 (10.7%)	3 (5.9%)	20 (10.0%)
Bleeding	2 (1.9%)	0 (0.0%)	4 (2.0%)
Vocal Cord Paralysis/Paresis	17 (16.5%)	5 (9.8%)	9 (4.5%)
Chylothorax	11 (10.7%)	2 (3.9%)	12 (6.0%)
Wound Infection	9 (8.7%)	9 (17.6%)	29 (14.5%)
Anastomotic and Conduit Complications	13 (12.6%)	9 (17.6%)	36 (18.0%)
Deep Vein Thrombosis	6 (5.8%)	3 (5.9%)	9 (4.5%)
30 Day Mortality (N)	1 (1.0%)	1 (2.0%)	1 (0.5%)
90 Day Mortality (N)	6 (5.8%)	3 (5.9%)	5 (2.5%)

Radiation Therapy

Start with PET – CT images of Cancer Target

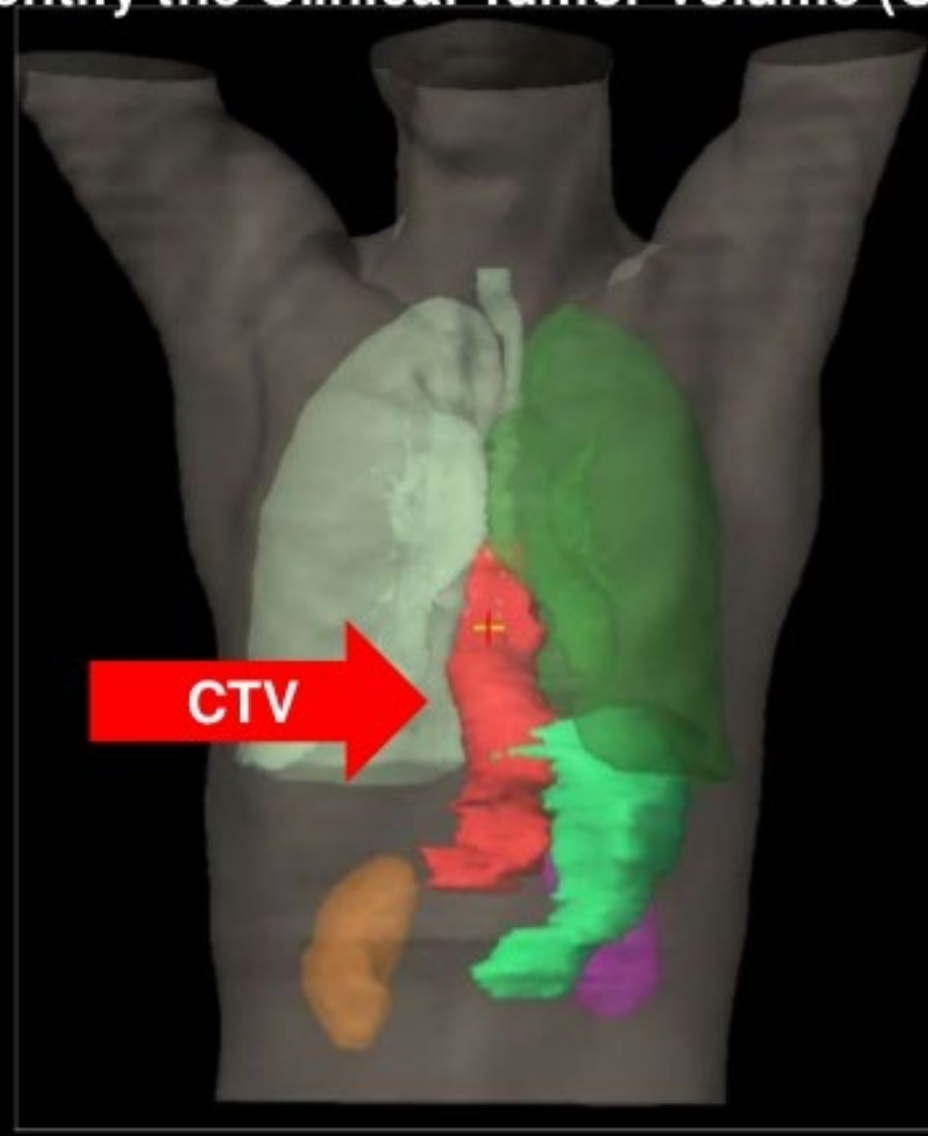


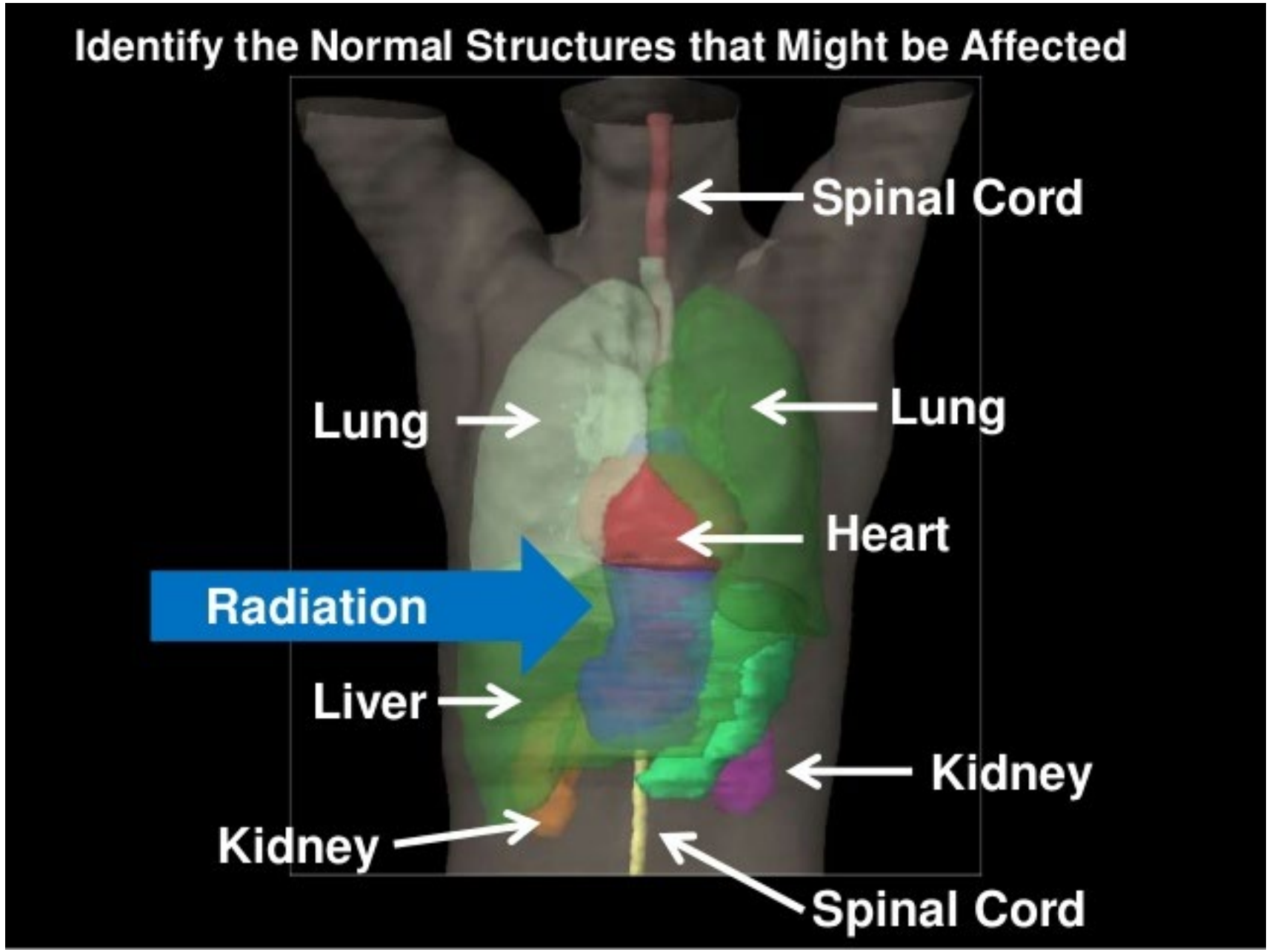
(a)

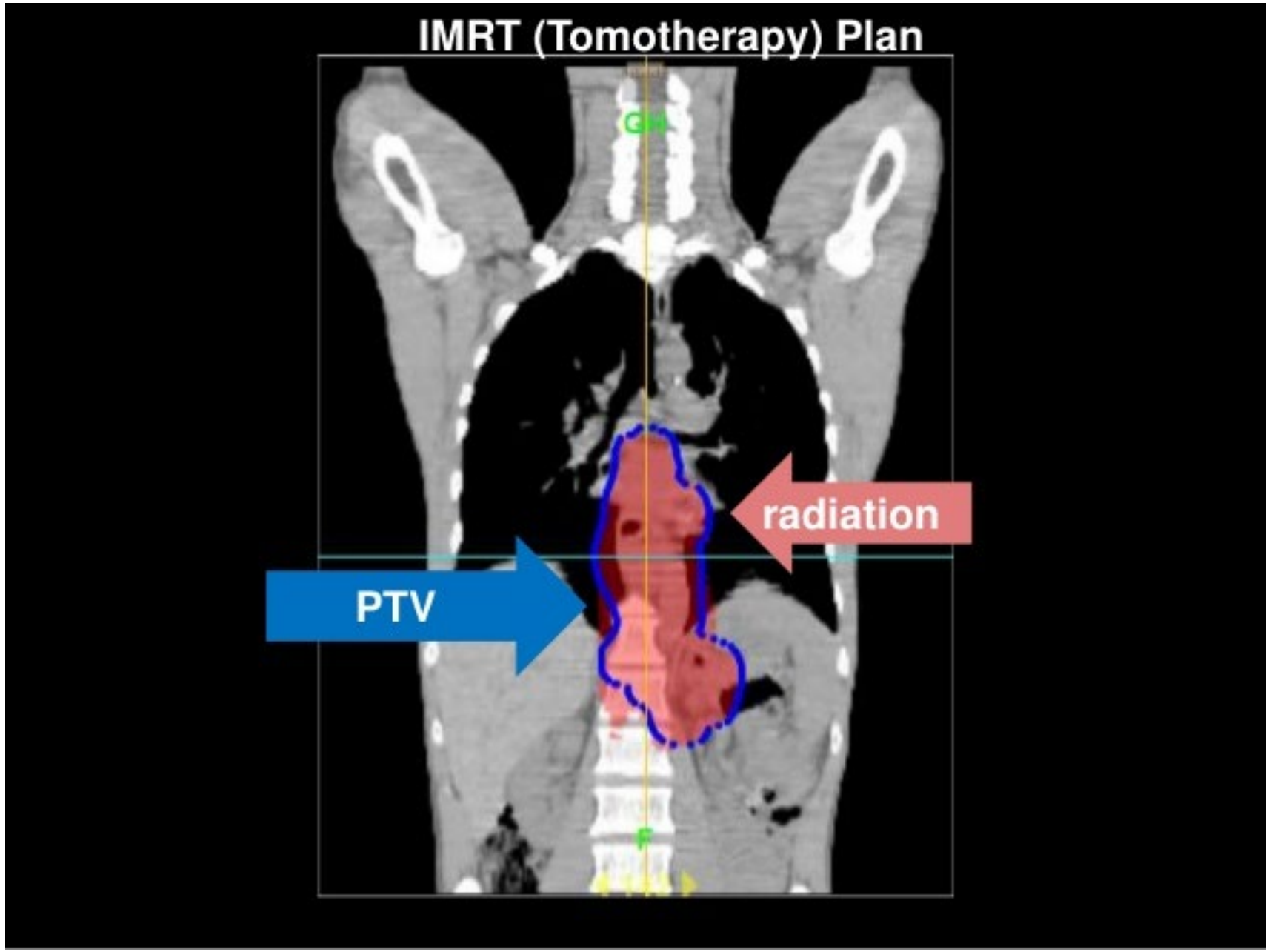


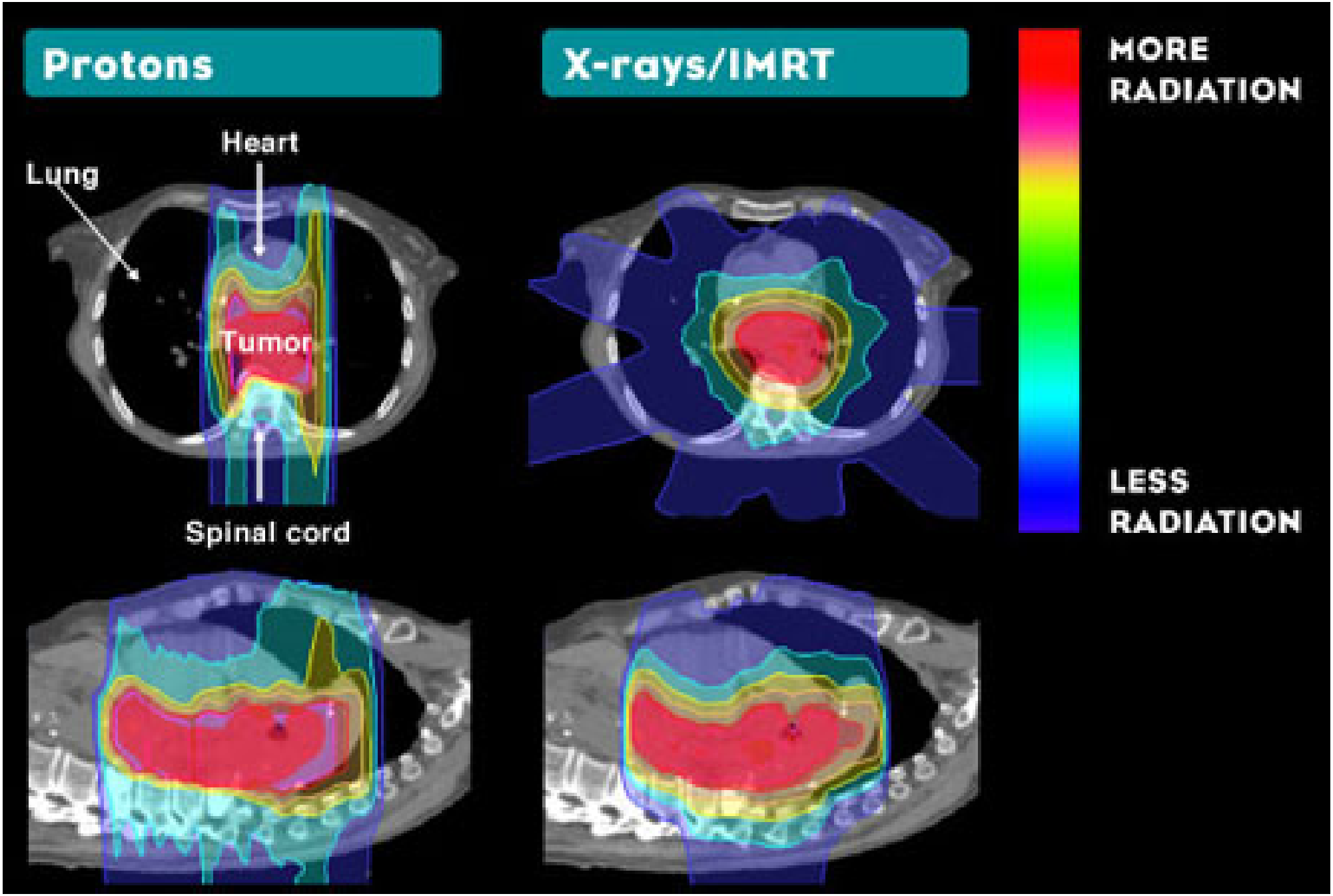
(b)

Identify the Clinical Tumor Volume (CTV)




Identify the Normal Structures that Might be Affected
Spinal Cord
Lung
Lung
Heart
Radiation
Liver
Kidney
Kidney
Spinal Cord

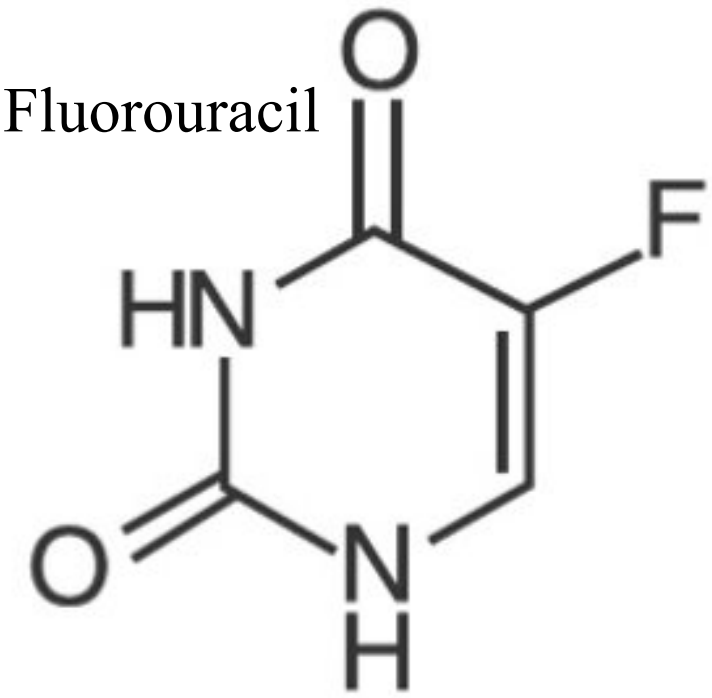

IMRT (Tomotherapy) Plan
radiation
PTV

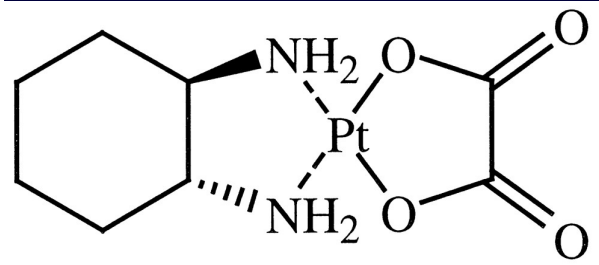

Protons
X-rays/IMRT
MORE RADIATION
LESS RADIATION
Heart
Lung
Tumor
Spinal cord


VARIAN

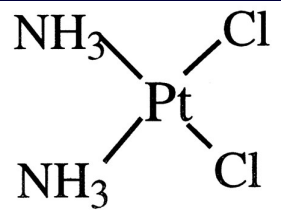
Chemotherapy

Fluorouracil



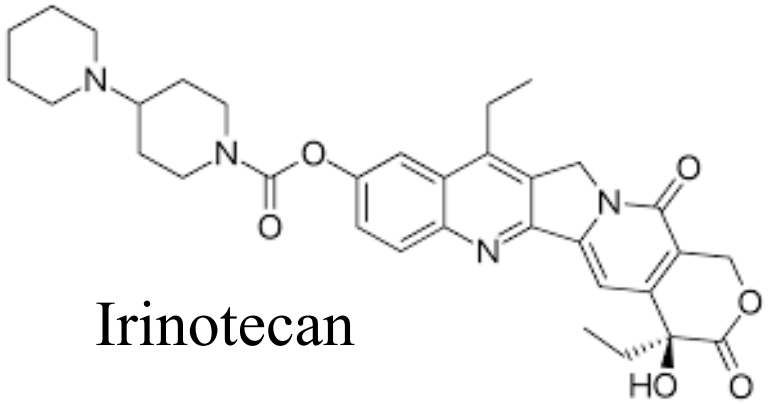


Oxaliplatin

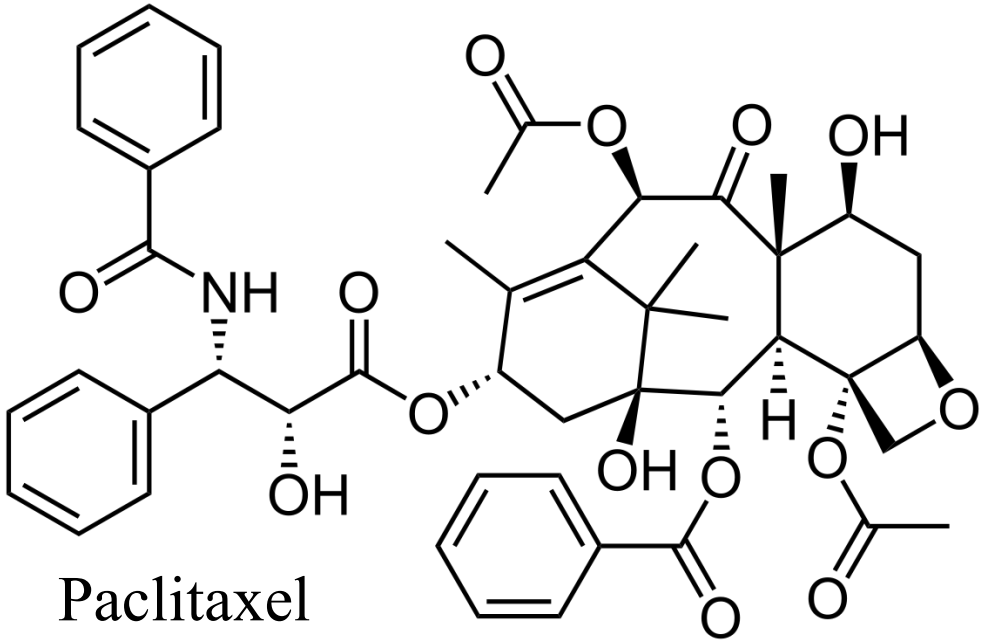


Cisplatin

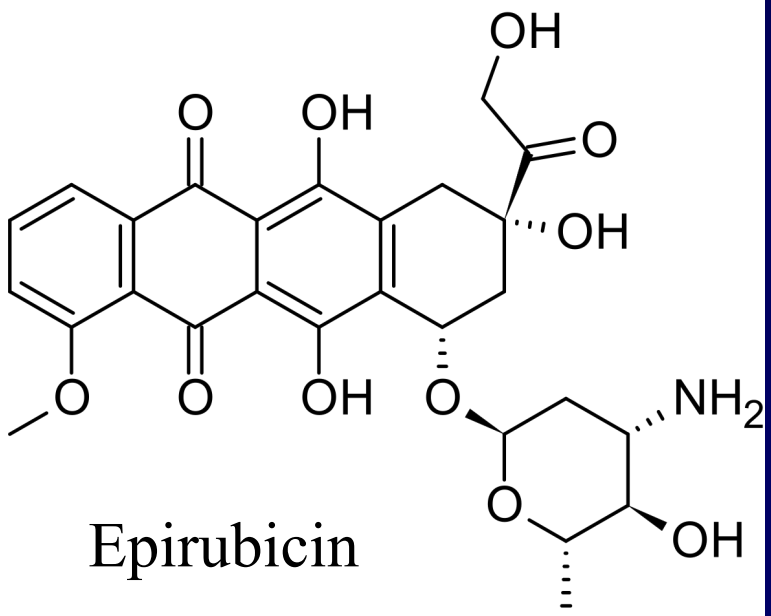
Chemo



Irinotecan



Paclitaxel



Epirubicin

Alkylating agents keep the cell from reproducing by damaging its DNA. These drugs work in all phases of the cell cycle and are used to treat many different cancers

Anthracyclines: Anthracyclines are anti-tumor antibiotics that interfere with enzymes involved in copying DNA during the cell cycle. (Enzymes are proteins that start, help, or speed up the rate of chemical reactions in cells.)

Antimetabolites interfere with DNA and RNA growth by substituting for the normal building blocks of RNA and DNA. These agents damage cells during the phase when the cell's chromosomes are being copied.

These drugs interfere with enzymes called topoisomerases, which help separate the strands of DNA so they can be copied.

Mitotic inhibitors are compounds derived from natural products, such as plants. They work by stopping cells from dividing to form new cells

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Does (Neo)Adjuvant Chemotherapy Improve Surgical Outcomes?

Neoadjuvant Chemotherapy Compared with Surgery Alone for Localized Esophageal Cancer

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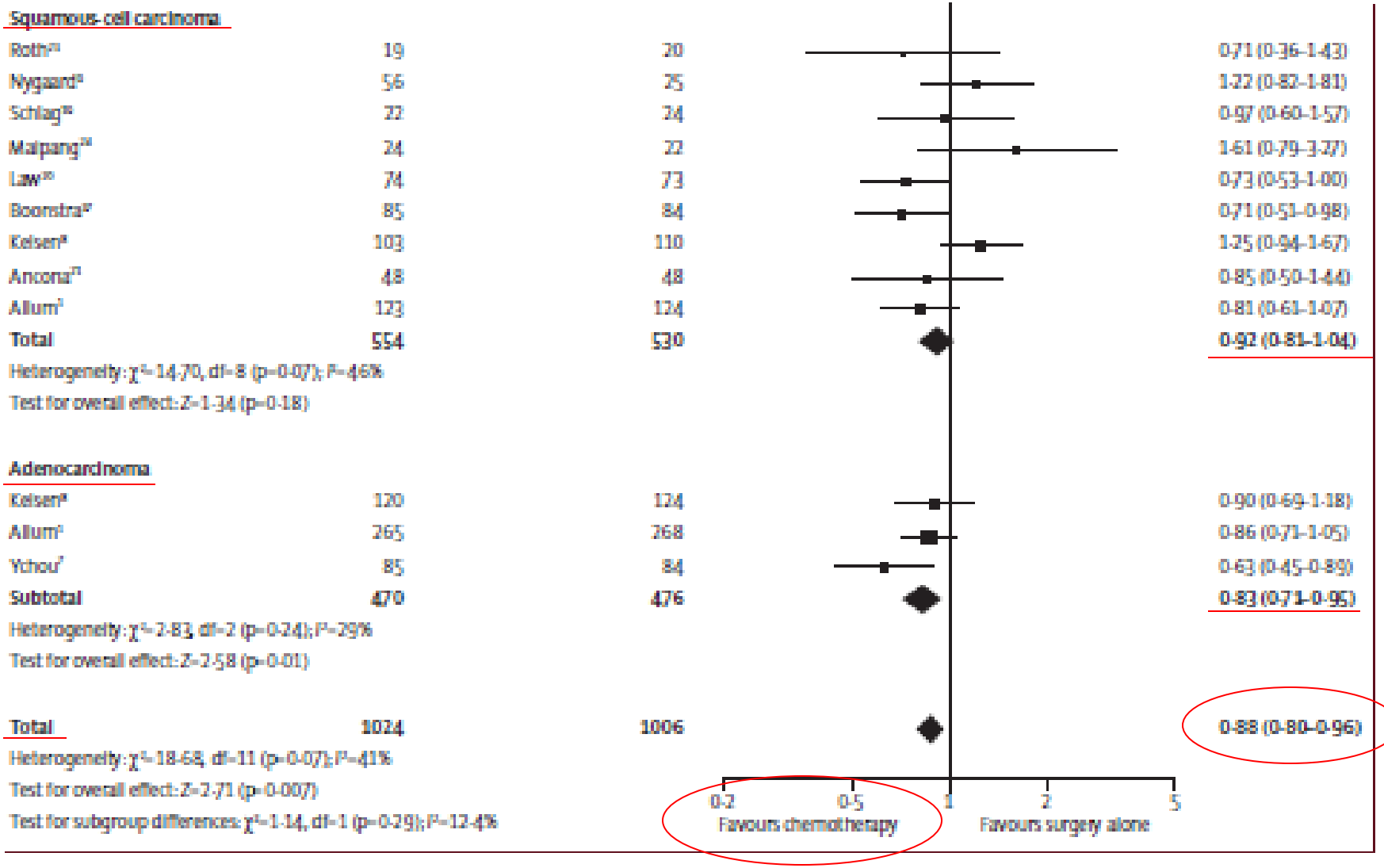
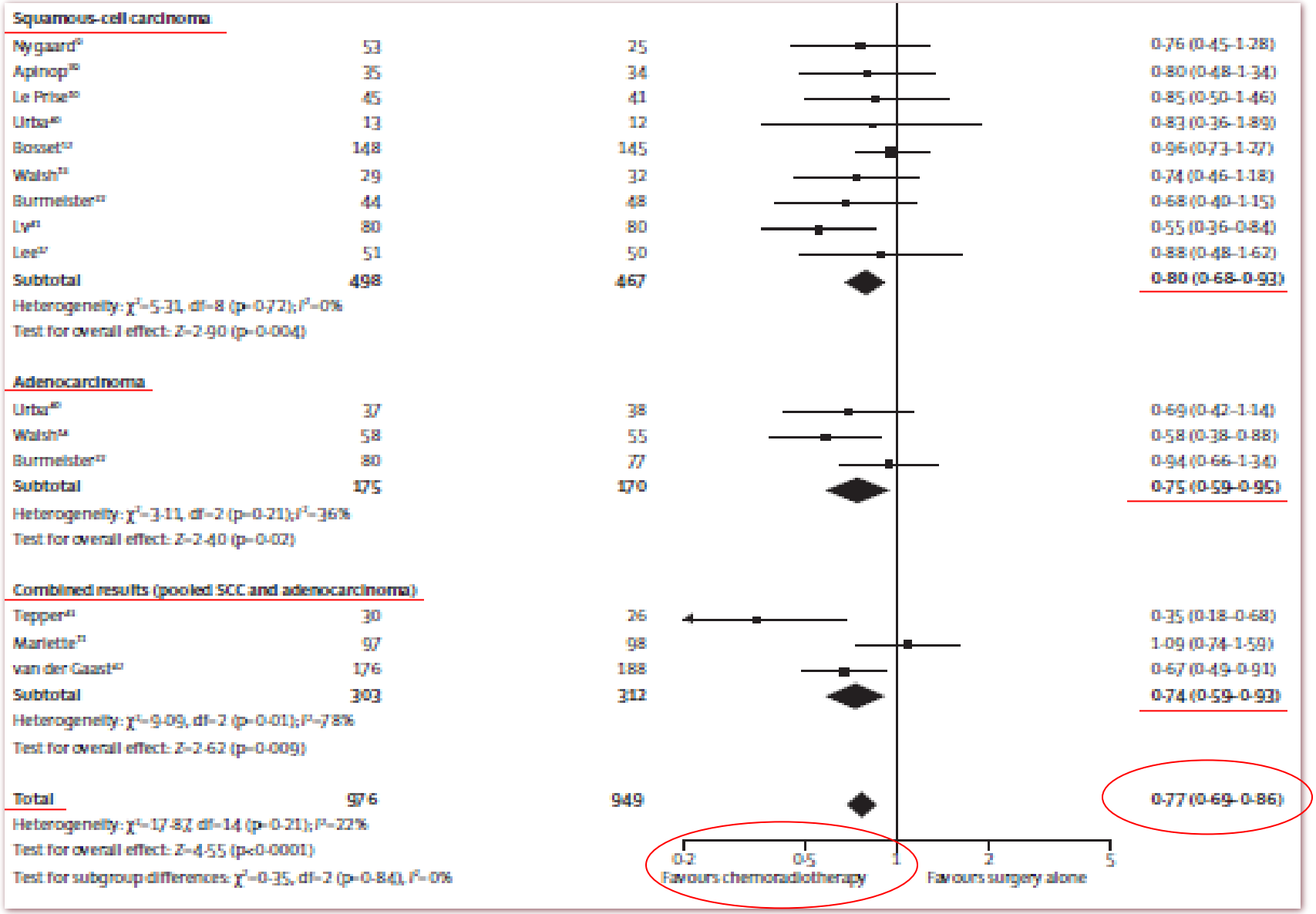


Sjoquist et al. Lancet Oncol 2011;12(7):681-92

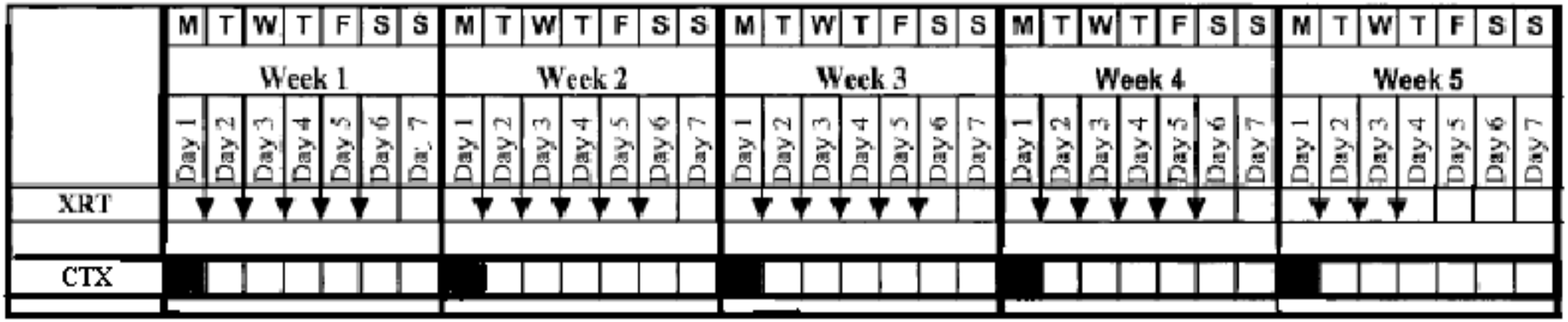
Does Neoadjuvant Chemoradiation Therapy Improve Surgery Outcomes?

All-Cause Mortality Estimates for Neoadjuvant C/RT Compared with Surgery Alone



Sjoquist et al. Lancet Oncol 2011; 12(7):681-92

CROSS Study: Schema



- **Chemoradiotherapy regimen:**
  - **Paclitaxel 50mg/m^2 + Carboplatin AUC=2 on days 1, 8, 15, 22 and 29**
  - **Concurrent radiotherapy of 41.4 Gy in 23 fractions of 1.8 Gy**

- **Surgery within 6 weeks after completion of chemoradiotherapy (THE/TTE)**

Van Hagen et al. N Engl J Med 2012;366:2074-84.

CROSS Study: Overall survival

No residual cancer after Chemo+RT: 29%.

Median Survival was doubled with Chemo+ RT over surgery alone.

Median Survival was nearly quadrupled for patients with squamous cell carcinoma.

Median Survival was improved by 66% in adenocarcinoma patients.

Van Hagen et al. N Engl J Med 2012;366:2074-84.
Shapiro et al. Lancet Oncol 2015; 16: 1090-98

CheckMate 577 study design

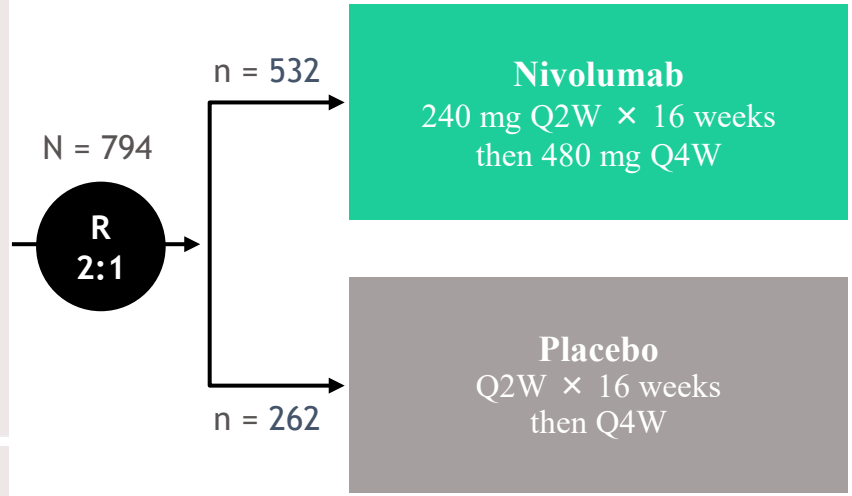
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

Key eligibility criteria

- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0–1

Stratification factors

- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])



Primary endpoint:

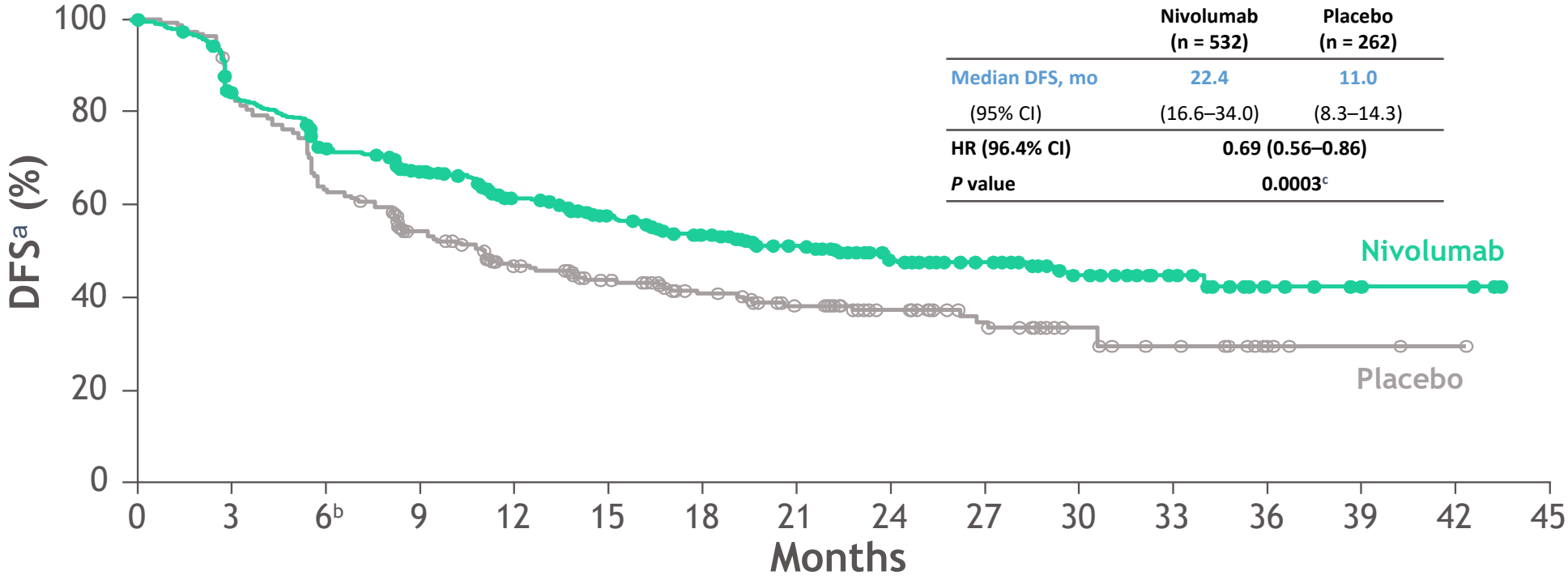
- DFS[e]

Secondary endpoints:

- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2–44.9)[g]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

Disease-free survival



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	0.69 (0.56–0.86)	
P value	0.0003[c]	

No. at risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

[a]Per investigator assessment; [b]6-month DFS rates were 72% (95% CI, 68-76) in the nivolumab arm and 63% (95% CI, 57-69) in the placebo arm; [c]The boundary for statistical significance at the pre-specified interim analysis required the *P* value to be less than 0.036.

Conclusions from these Studies

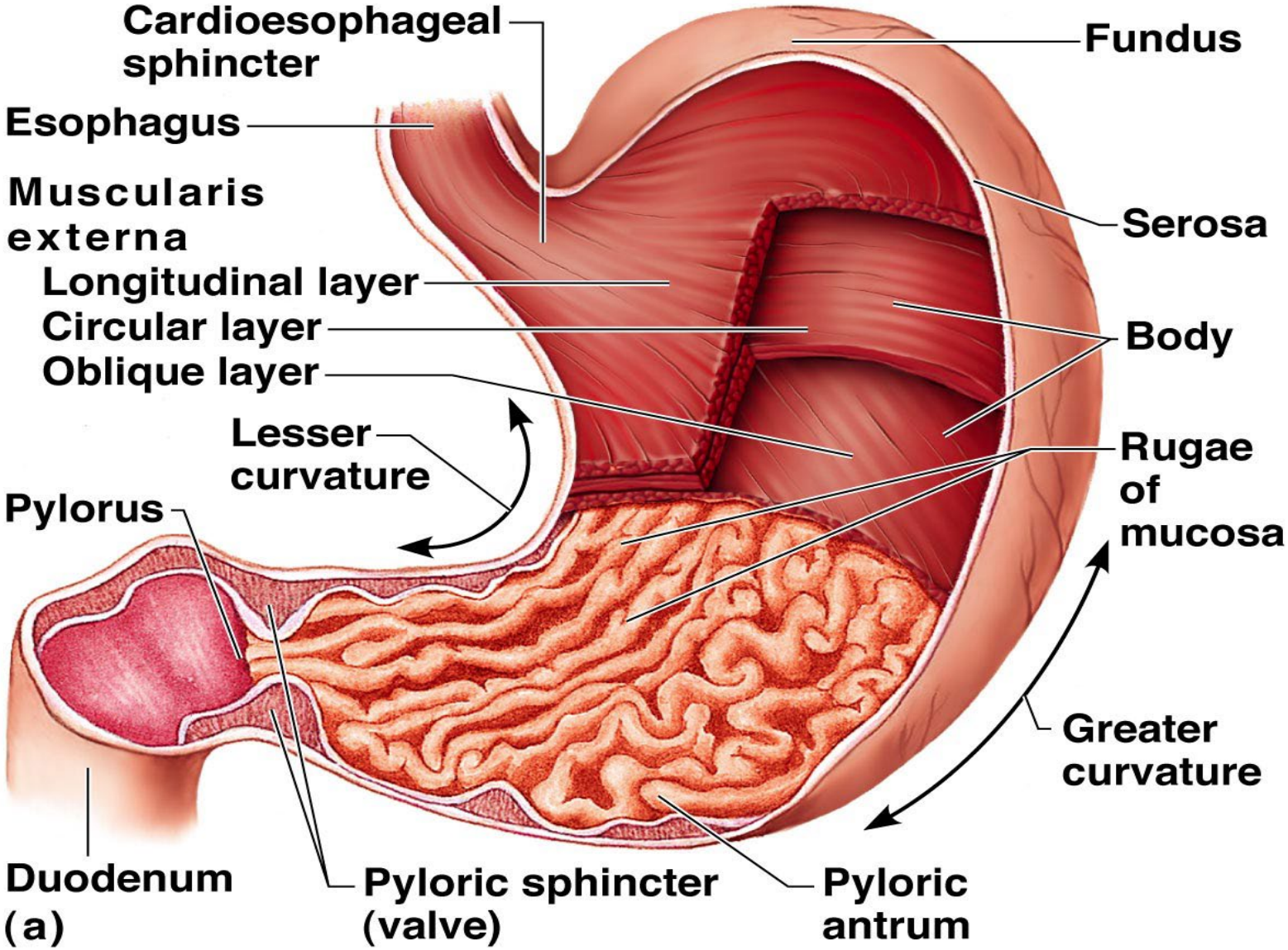
Localized Esophageal

Pre-operative cisplatin/5-FU chemotherapy offers a small survival advantage in distal esophageal and GE junction cancer.

Neoadjuvant platinum-based chemoradiation (esp. w. carbo/tax) offers a greater survival advantage with better local control but increased surgical morbidity.

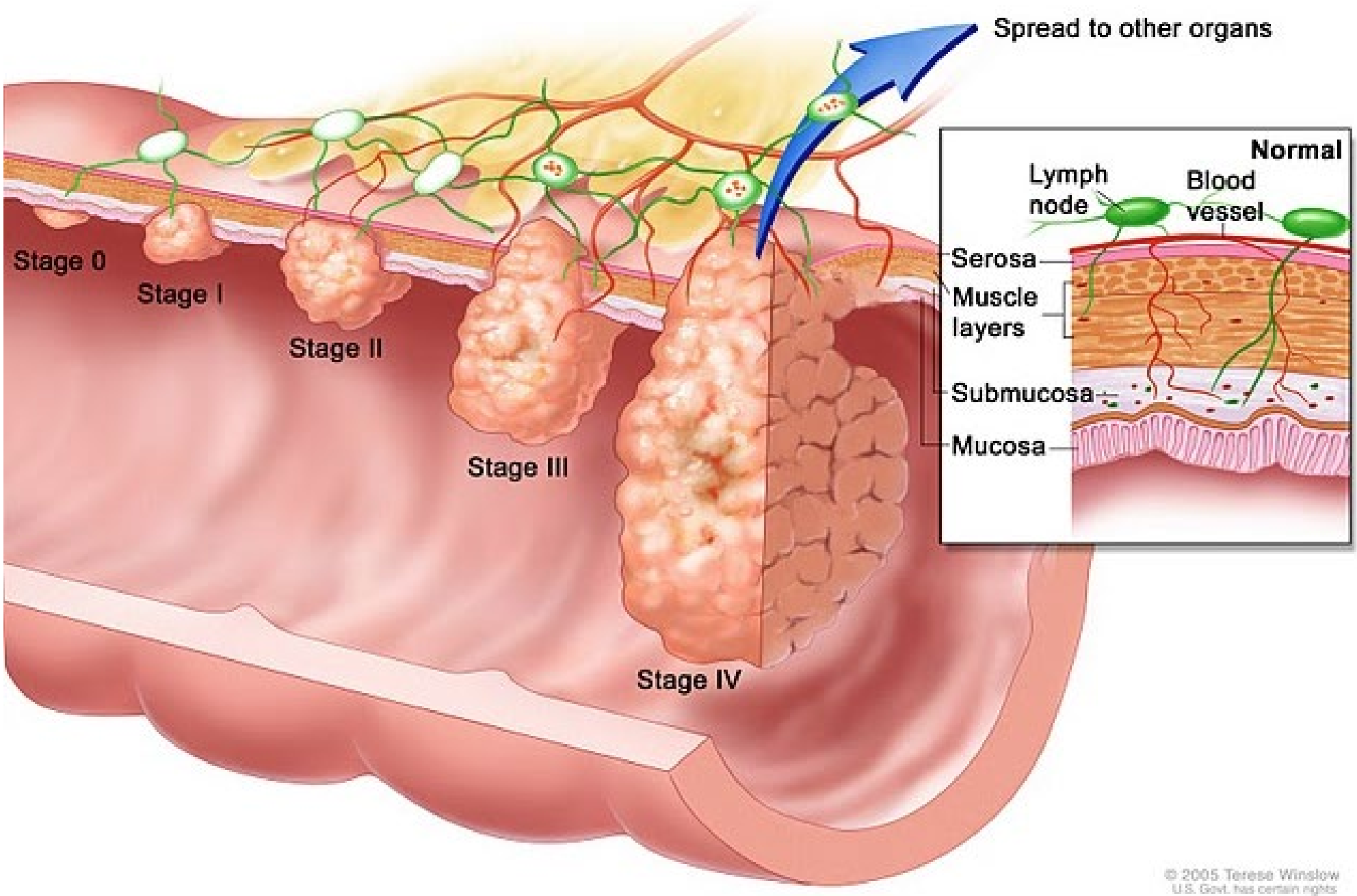
Post-operative therapy with nivolumab will likely get FDA approval next year and become standard of care.

Gastric Cancer



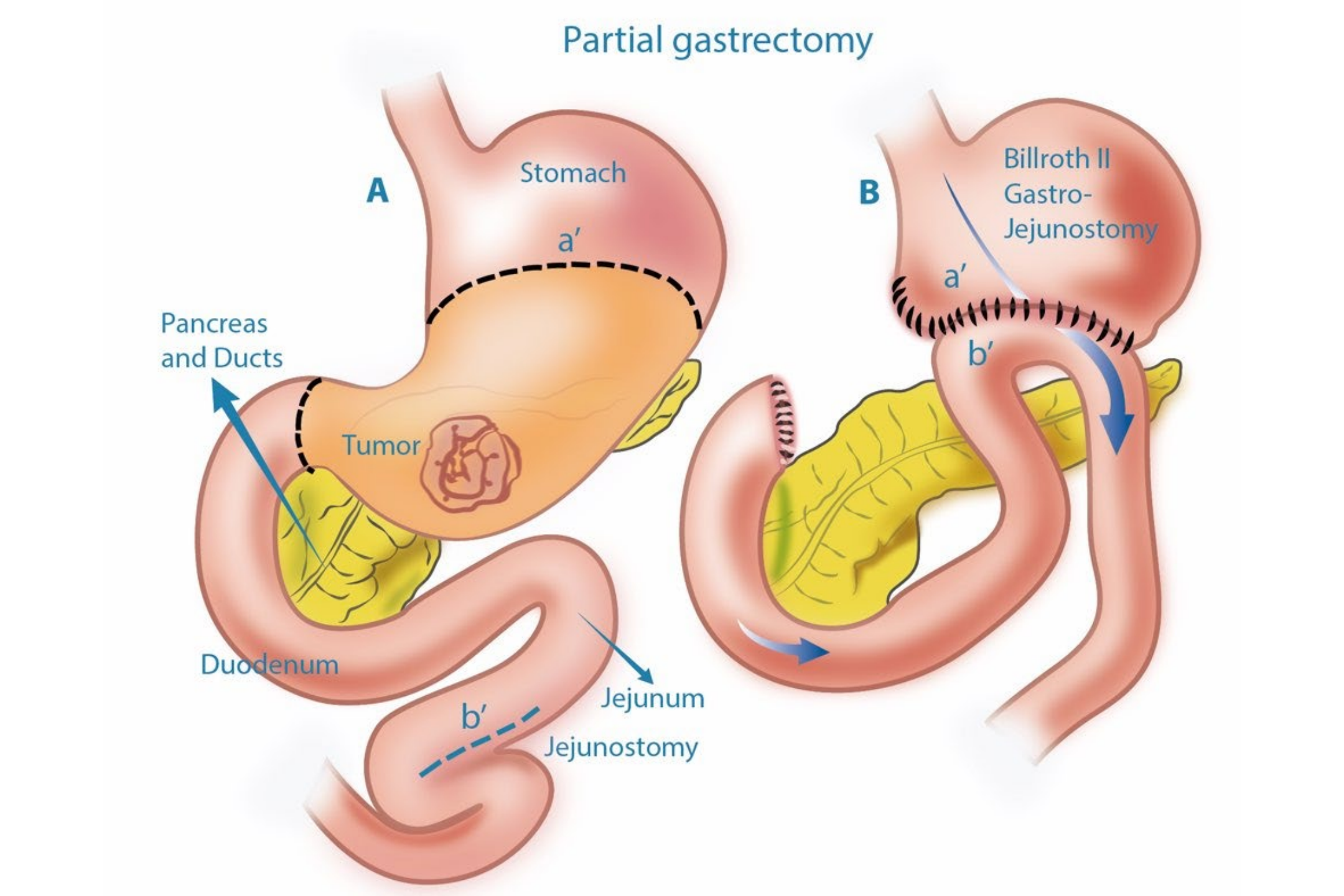
The stomach can be divided into 4 regions:

1. **Cardia**
2. **Fundus**
3. **Body**
4. **Pylorus**

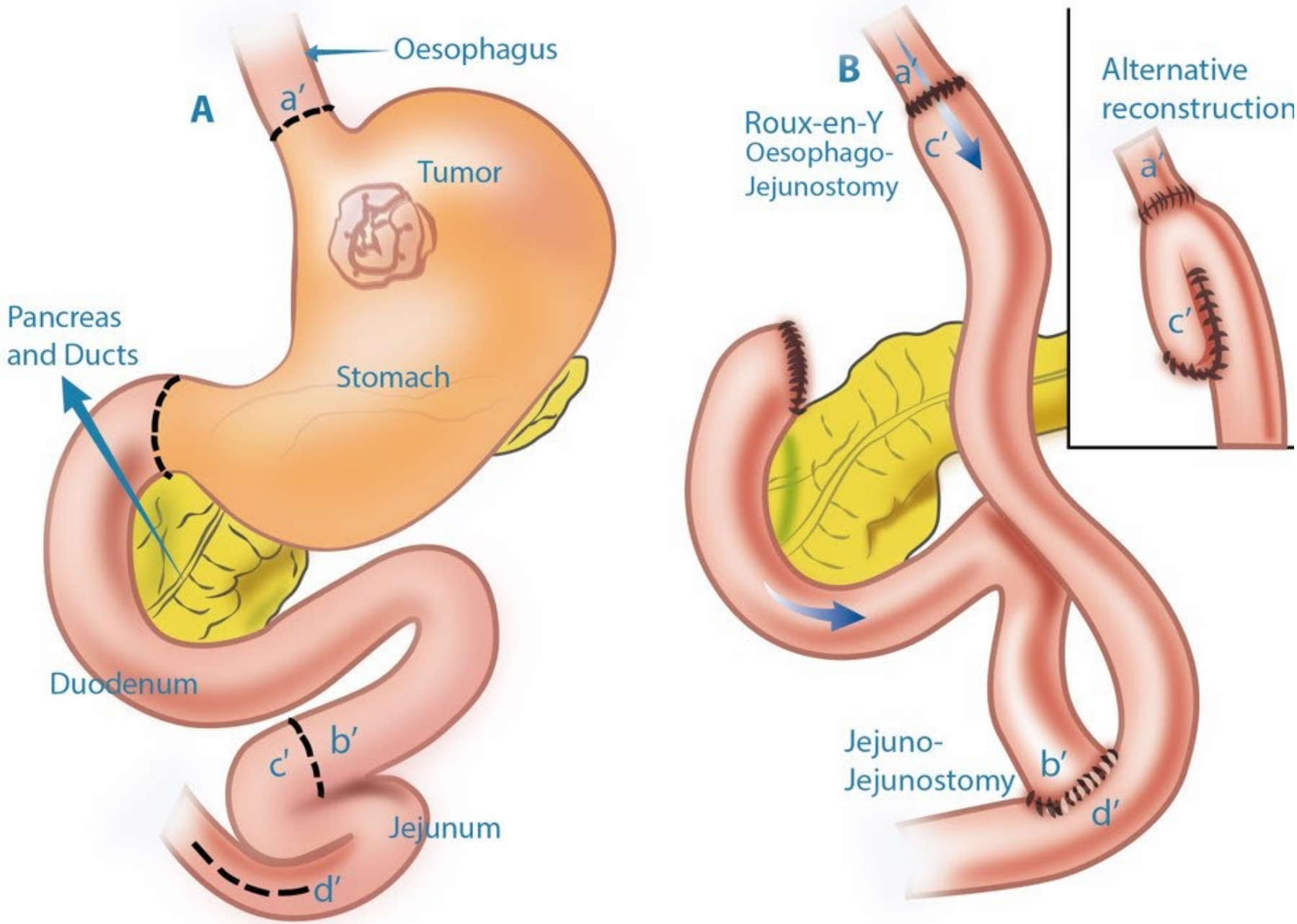


What are the treatment modalities for locally advanced gastric cancer?

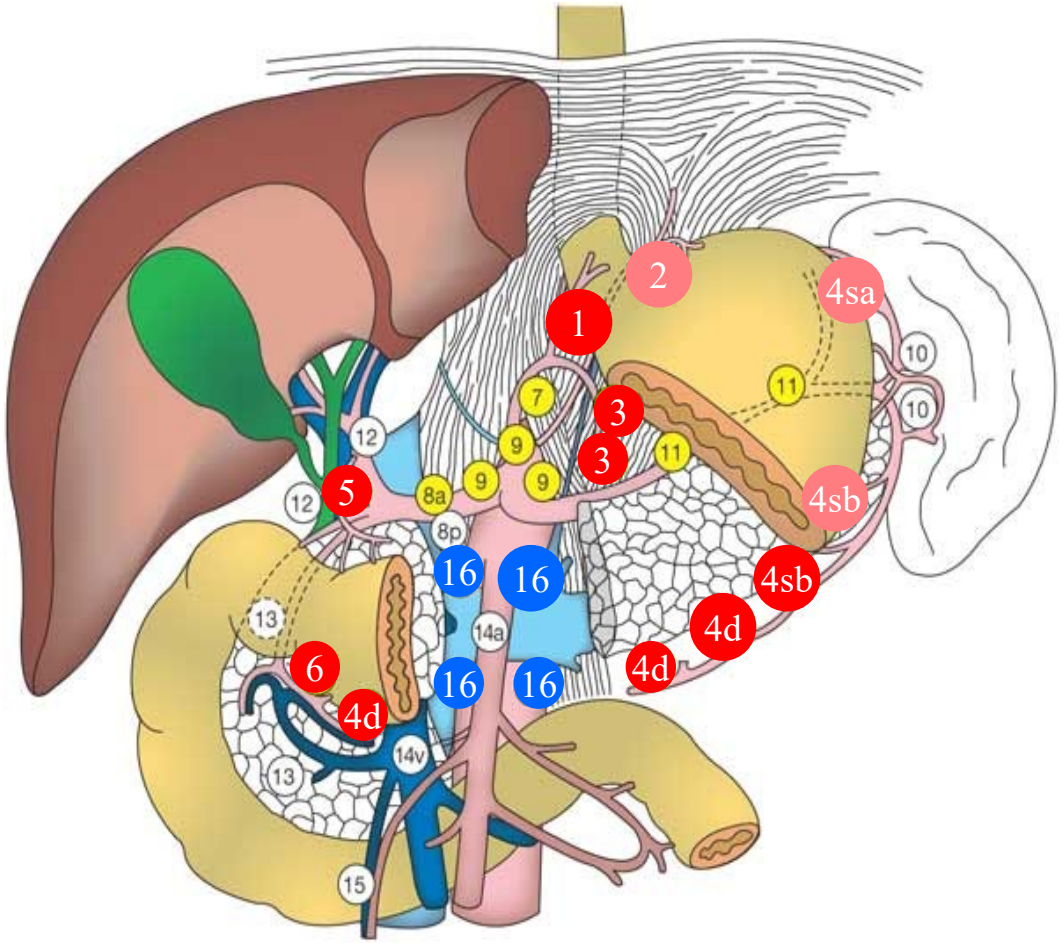
- Surgery
  - Subtotal gastrectomy
  - Total gastrectomy
  - Laparoscopic
  - Robotic
- Chemotherapy


Partial gastrectomy
A
Stomach
a′
Pancreas
and Ducts
Tumor
Duodenum
Jejunum
b′
Jejunostomy
B
Billroth II
Gastro-
Jejunostomy
a′
b′

Total gastrectomy



What Is the Ideal Extent of Lymphadenectomy?



D0 - removes <u>less than</u> all relevant N1 nodes

D1 - requires the dissection of the N1 nodes (1 - 6)*

D2 - includes the N1 <u>and</u> N2 nodes (7–11)

D3 – includes the N1, N2, <u>and</u> N3 nodes (12-15)

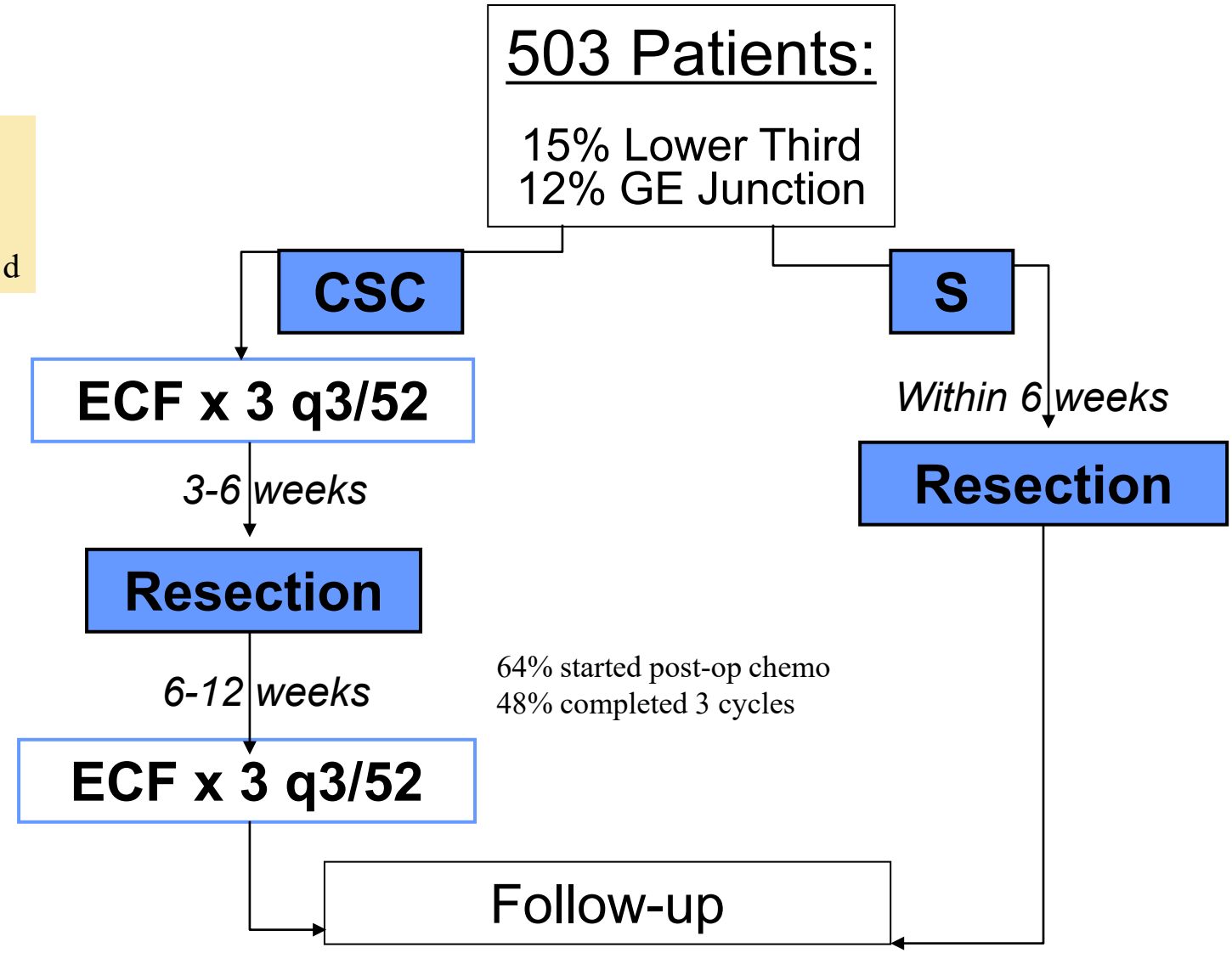
D4 – includes the N1, N2, N3 <u>and</u> N4 nodes (16)

***nodes 2, 4 remain if distal subtotal gastrectomy**

What are Proven Strategies to Enhance Outcomes for Surgical Resection?

MAGIC Trial: Schema

ECF q 3weeks:
Epirubicin 50/-/s1
Cisplatin 60/-/d1
CI 5-FU 200/-/d x 21d



Cunningham D, et al. *N Engl J Med.* 2006;355:11-20.

MAGIC: Survival

2-Year Survival: 23% improvement for peri-operative chemotherapy over surgery alone.

5-Year Survival: 57% improvement for peri-operative chemotherapy over surgery alone.

Median Survival: 9 month improvement for MAGIC over surgery alone.

Cunningham D, et al.
N Engl J Med. 2006;355:11-20.

FLOT4 Study Design

Randomized, multicenter, investigator-initiated, phase II/III study

- Gastric cancer or adenocarcinoma of the gastro-esophageal junction type I-III
- Medically and technically operable
- cT2-4/cN-any/cM0 or cT-any/cN+/cM0

STRATIFICATION

R

n=716

FLOT x4 - RESECTION - FLOT x4

FLOT: docetaxel 50mg/m2, d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

ECF/ECX x3 - RESECTION - ECF/ECX x3

ECF/ECX: Epirubicin 50 mg/m2, d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

Stratification: ECOG (0 or 1 vs. 2), location of primary (GEJ type I vs. type II/III vs. stomach), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

Presented by: Salah-Eddin Al-Batran

FLOT: Survival

2-Year Survival: 15% improvement for peri-operative FLOT over peri-operative MAGIC.

5-Year Survival: 25% improvement for peri-operative FLOT over peri-operative MAGIC.

Median Survival: 15 month improvement for FLOT over MAGIC

Cunningham D, et al.
N Engl J Med. 2006;355:11-20.

Conclusions from these Results

Localized Gastric:

The peri-operative FLOT4 regimen is the current standard of care and should be considered for patients of better performance status.

Perioperative chemotherapy likely has improved survival by 2 years over just surgery alone.

Thank You!