Pathophysiology and Decision Making of Esophageal cancer

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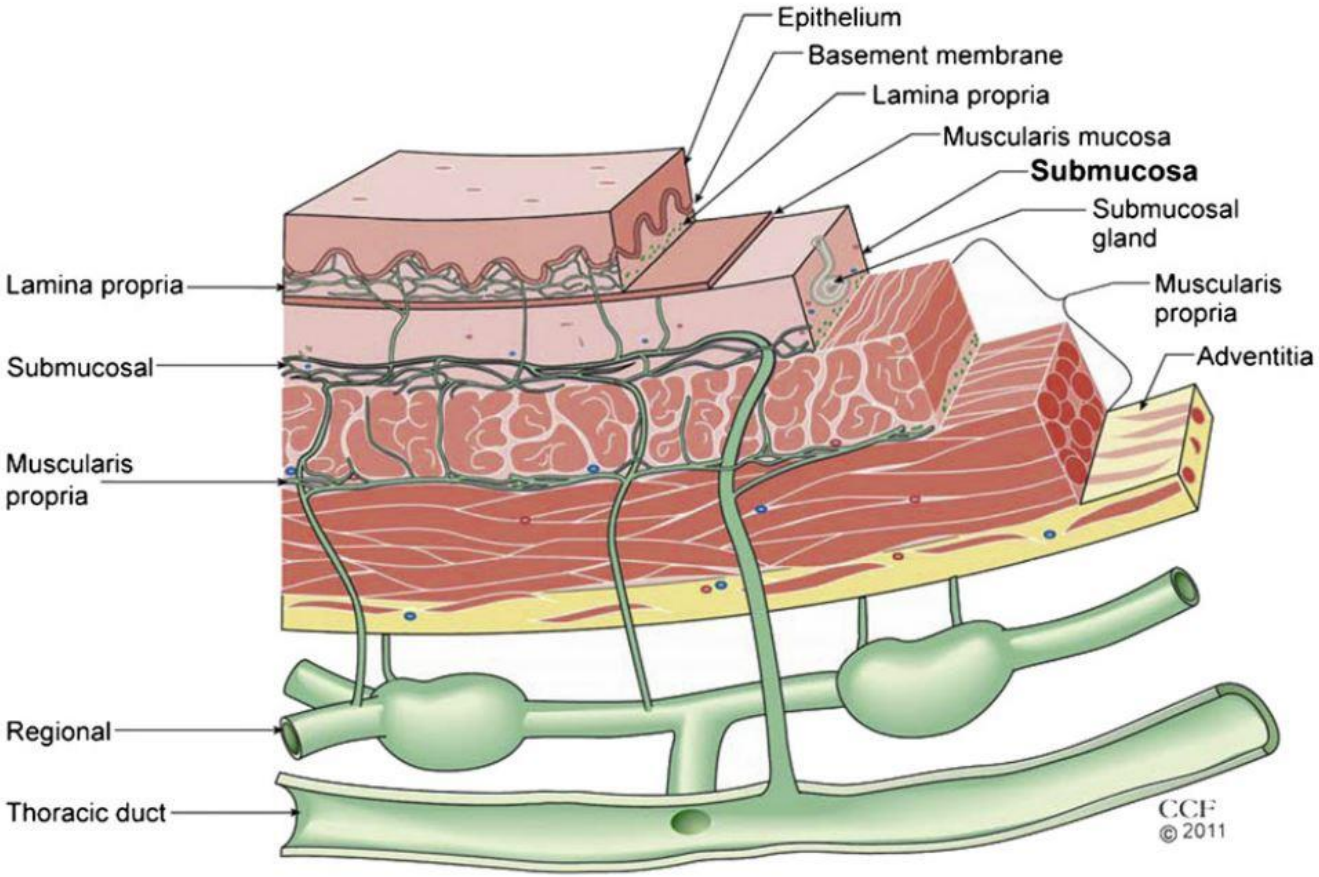
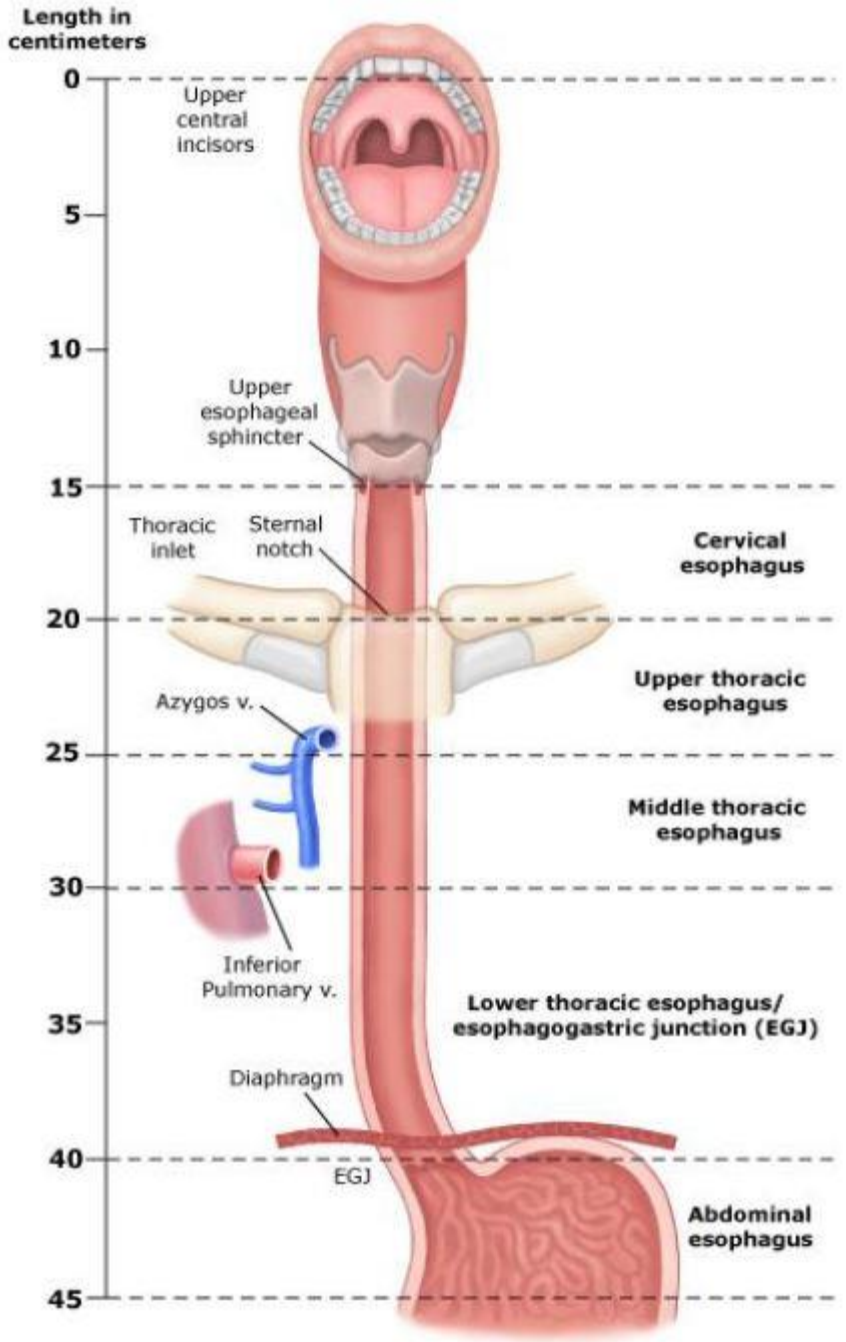
Anatomy of Esophagus

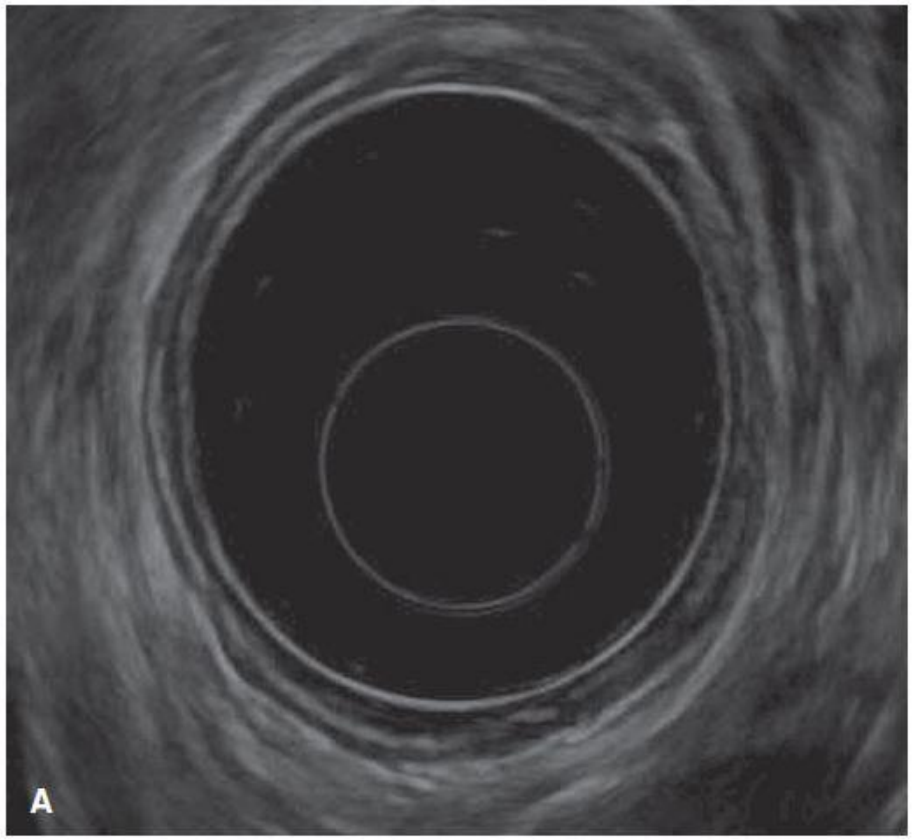
Anatomy of esophagus

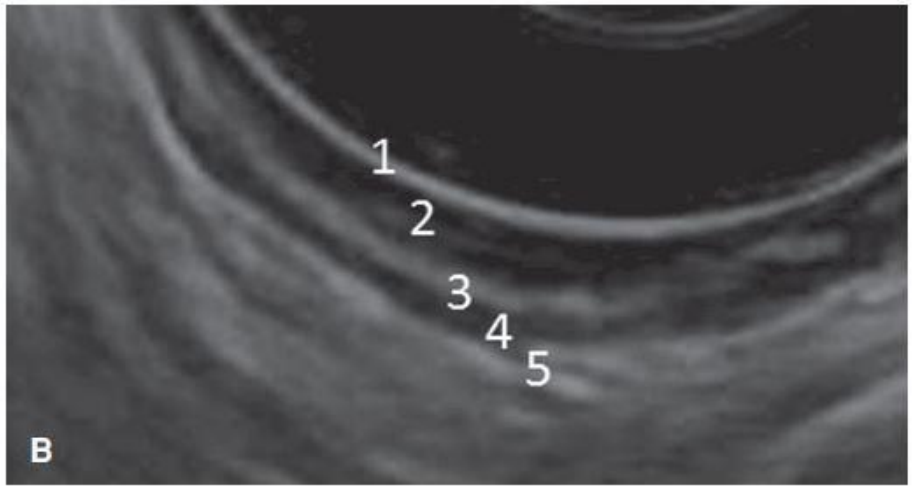


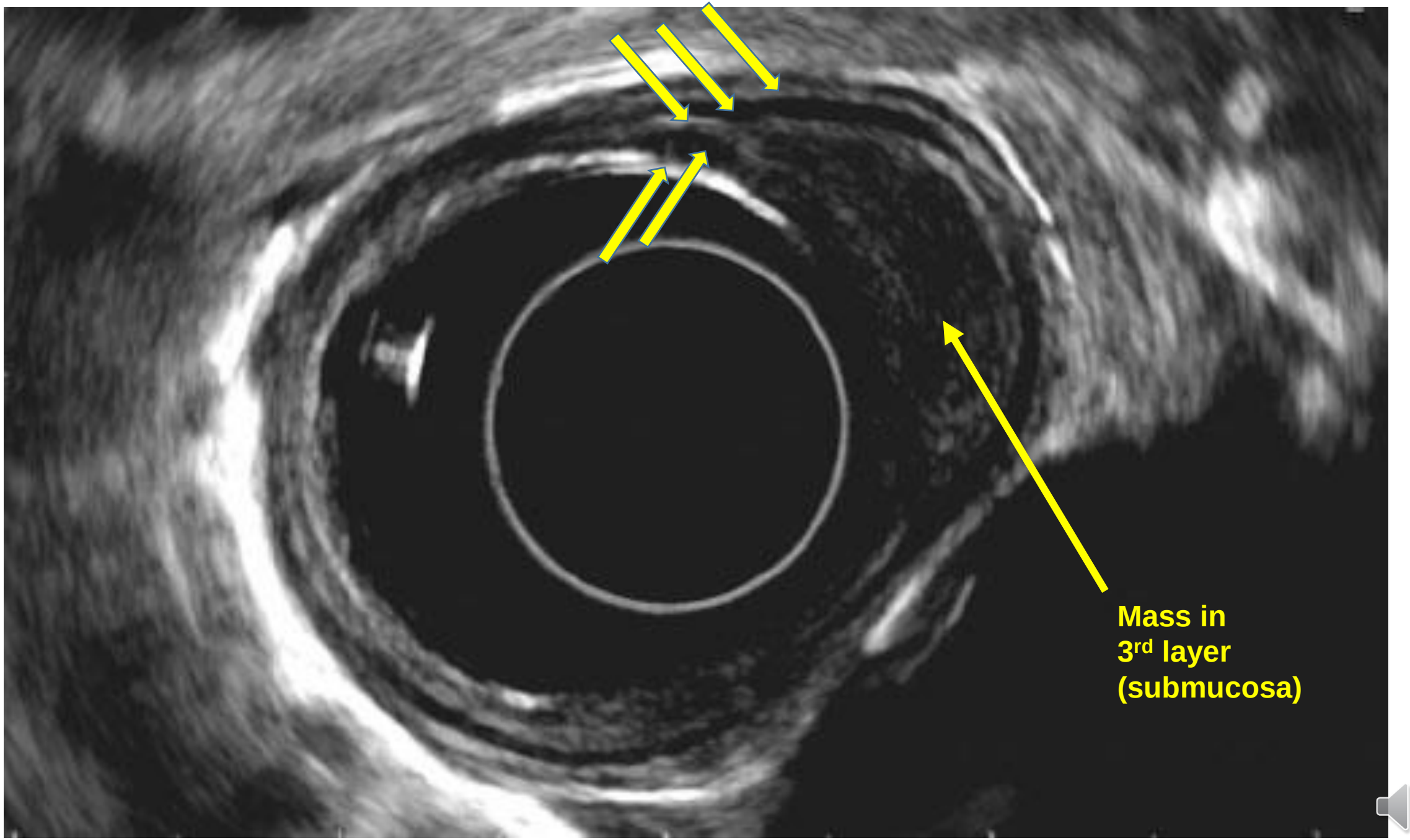


EUS anatomy

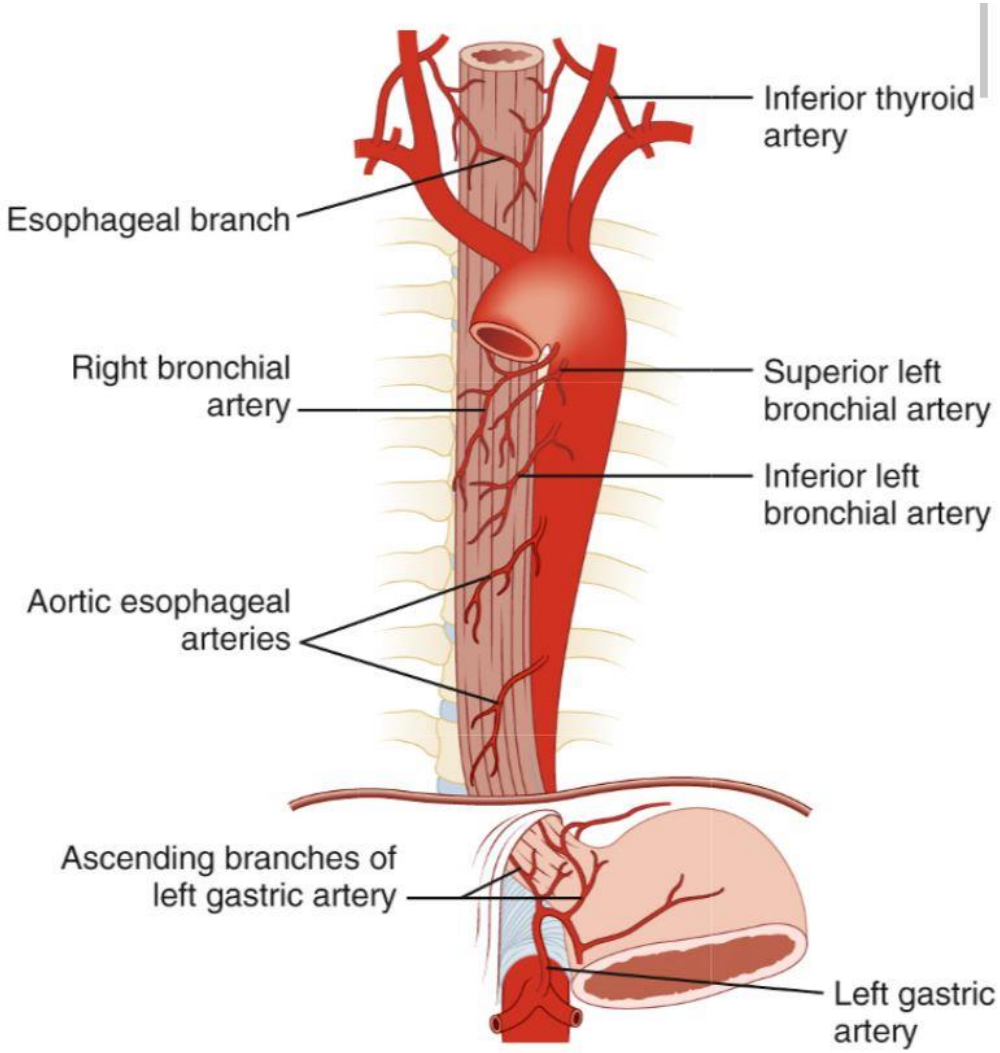
1. Interface between intraluminal fluid and the superficial mucosa (hyperechoic, white)
2. Deep mucosa including lamina propria and muscularis mucosae (hypoechoic, dark)
3. Submucosa (hyperechoic, white)
4. Muscularis propria (hypoechoic, dark)
5. Adventitia or interface with surrounding mediastinal structures (hyperechoic, white)

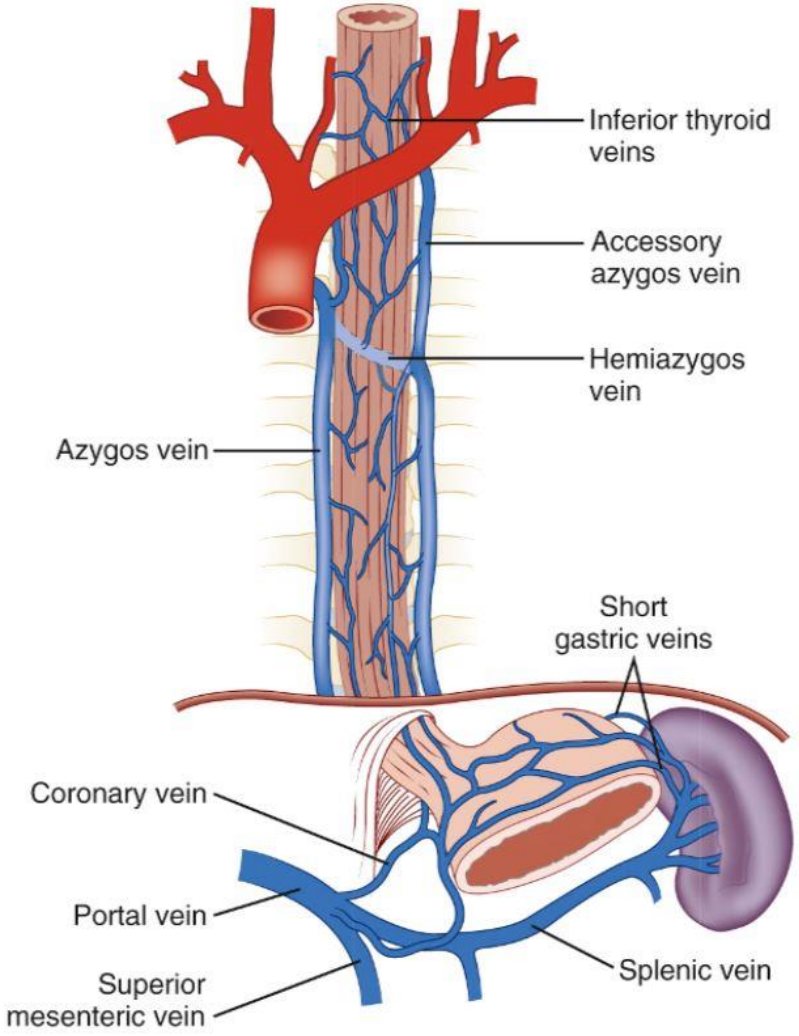




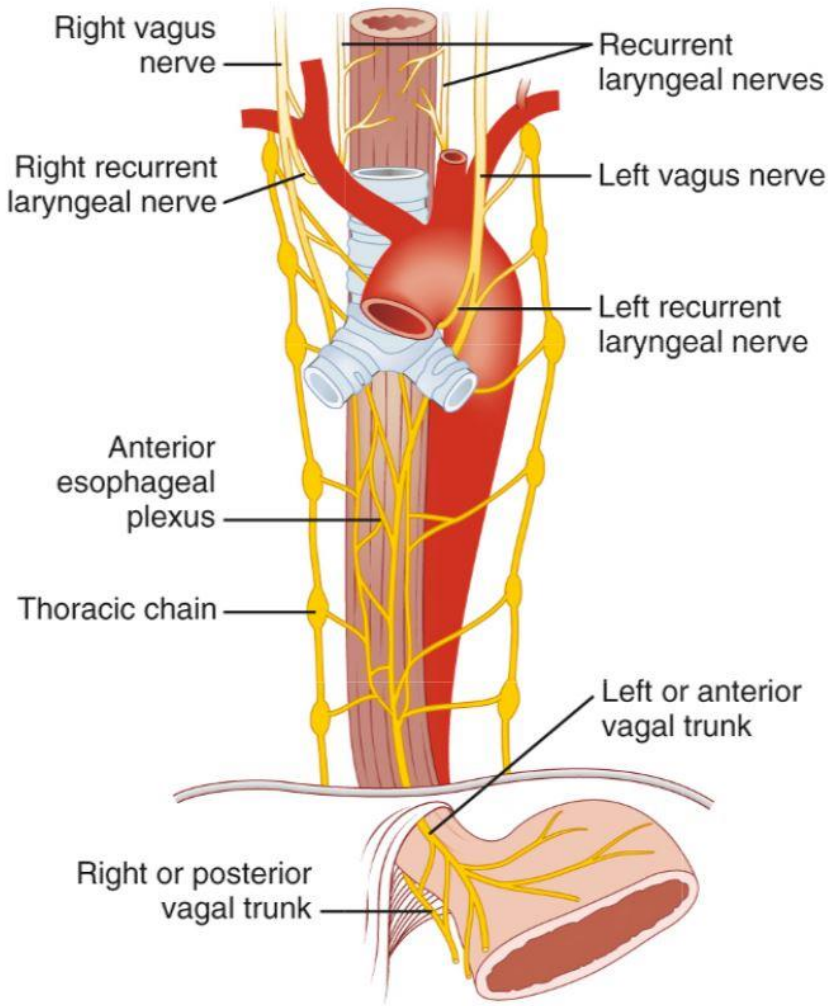

Mass in
3rd layer
(submucosa)

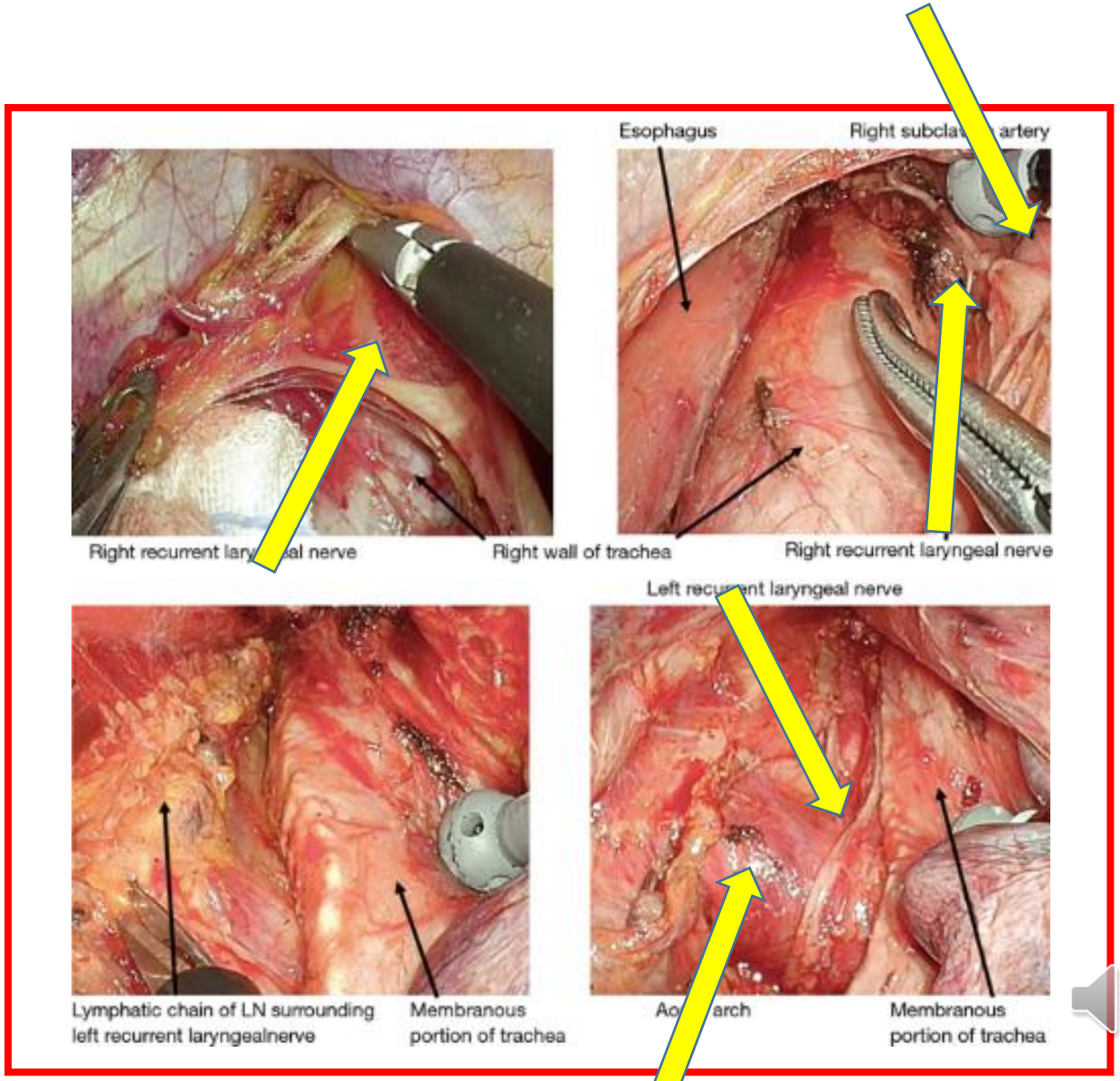
Vascular structures



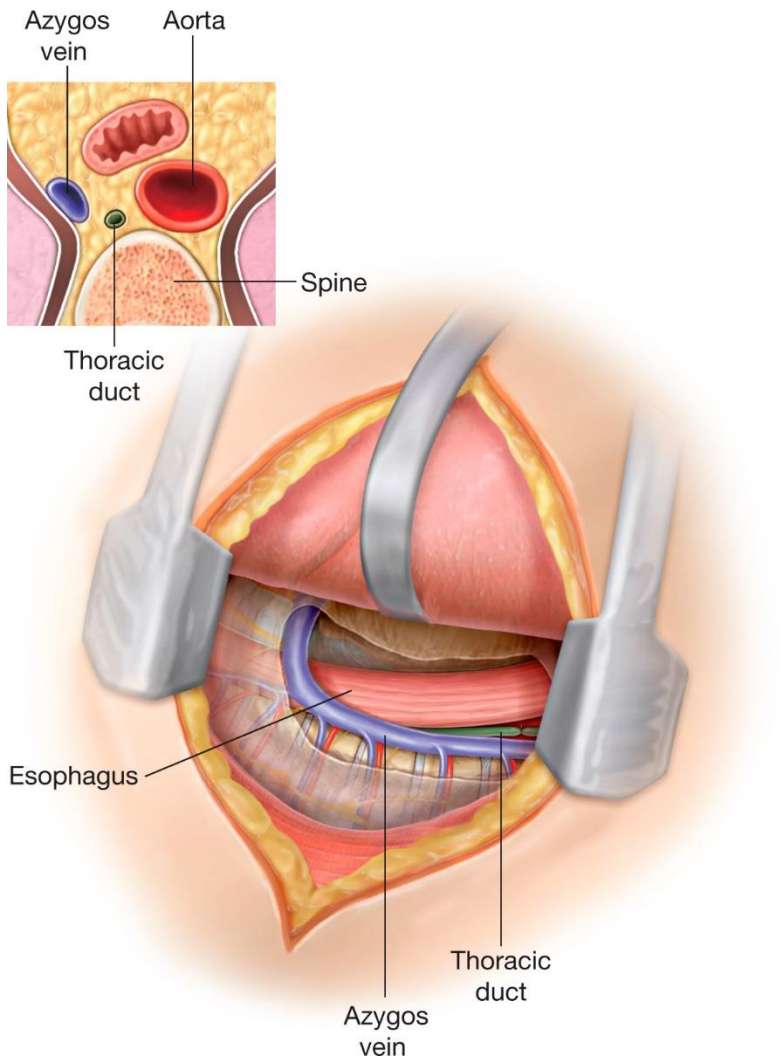


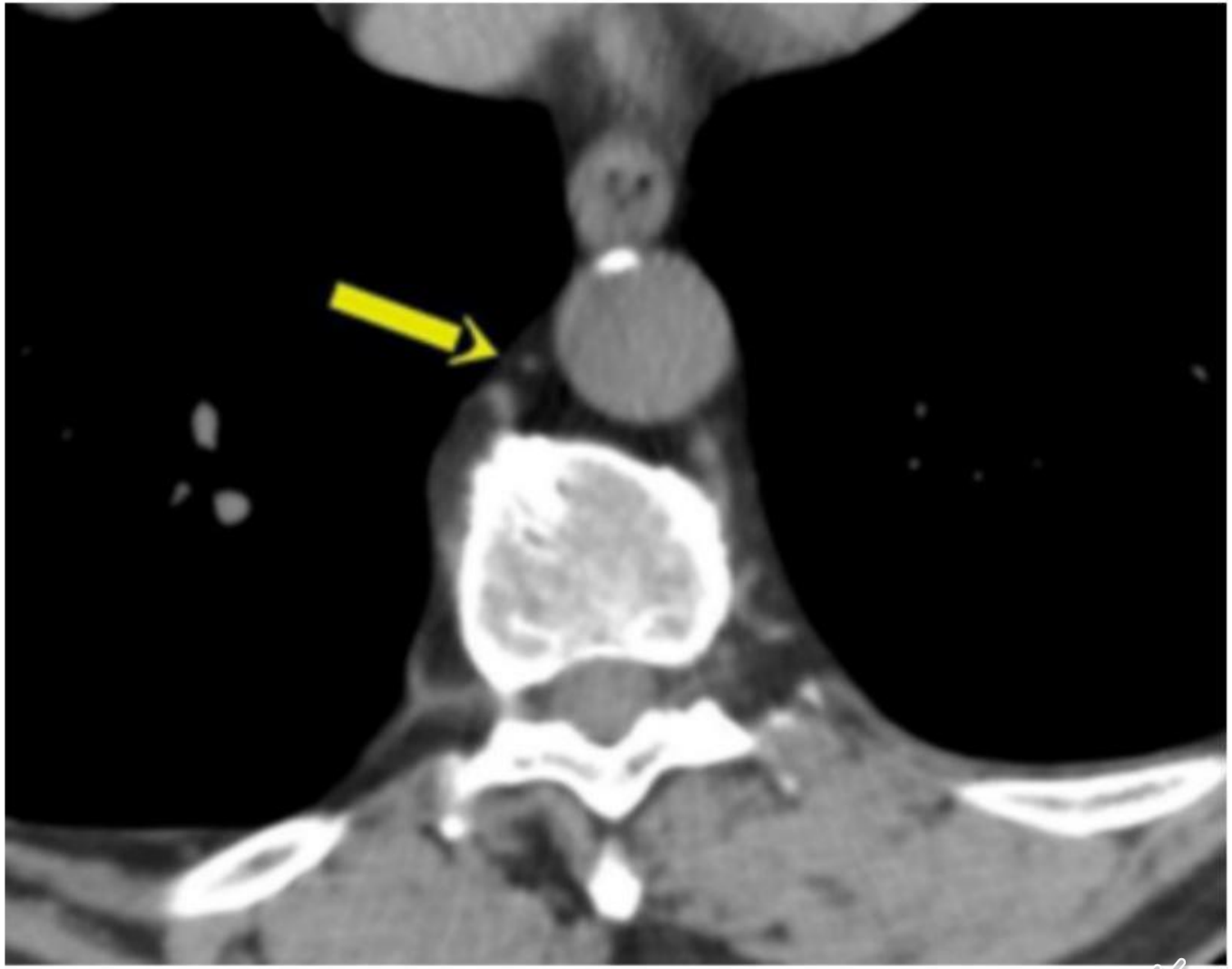
Nervous system



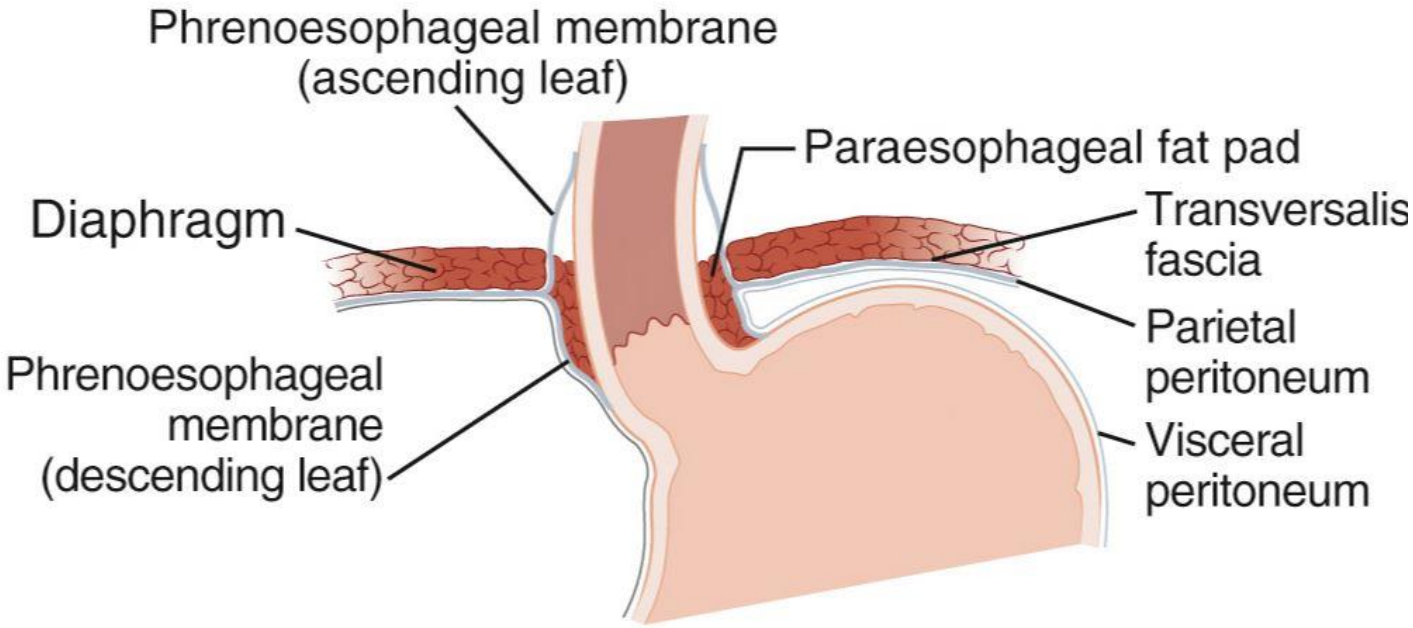


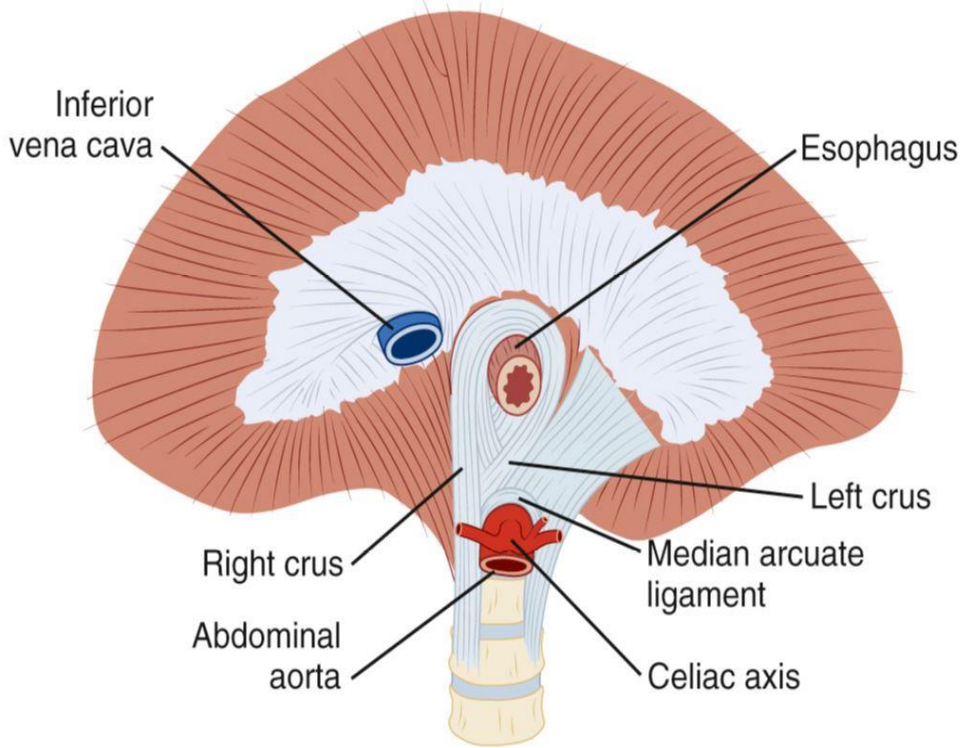
Thoracic Duct



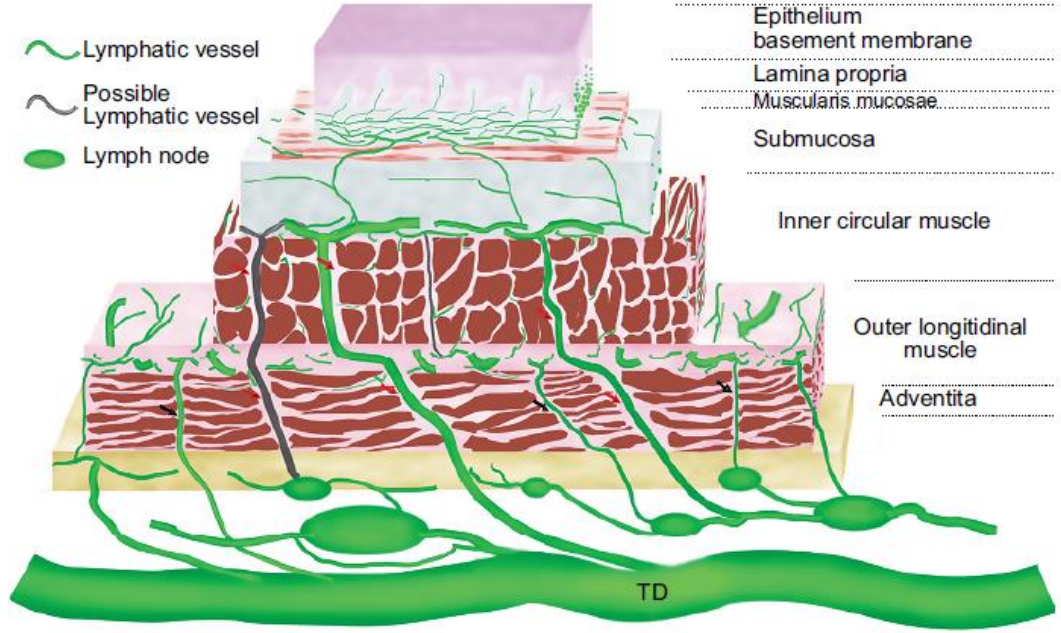


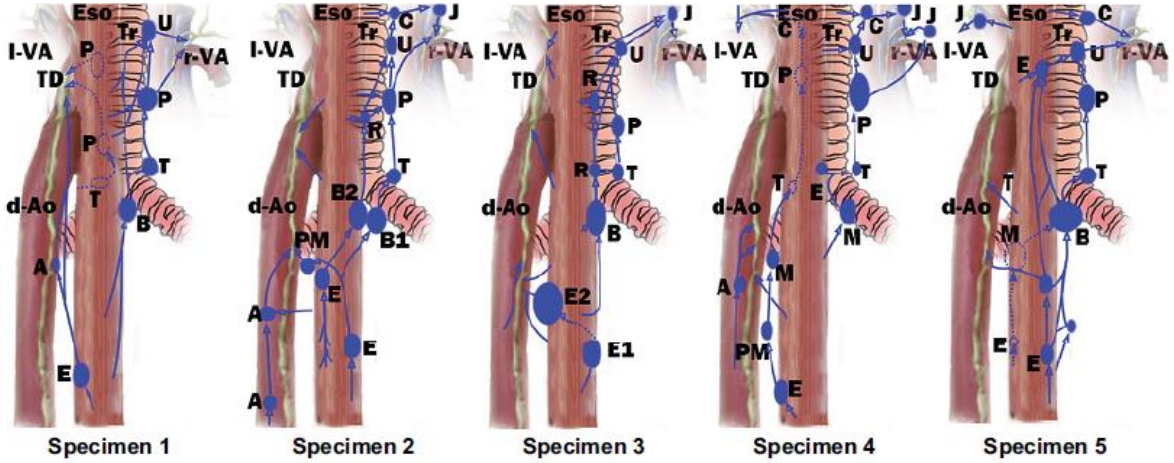
Diaphragm


Phrenoesophageal membrane
(ascending leaf)
Paraesophageal fat pad
Diaphragm
Transversalis
fascia
Parietal
peritoneum
Phrenoesophageal
membrane
(descending leaf)
Visceral
peritoneum

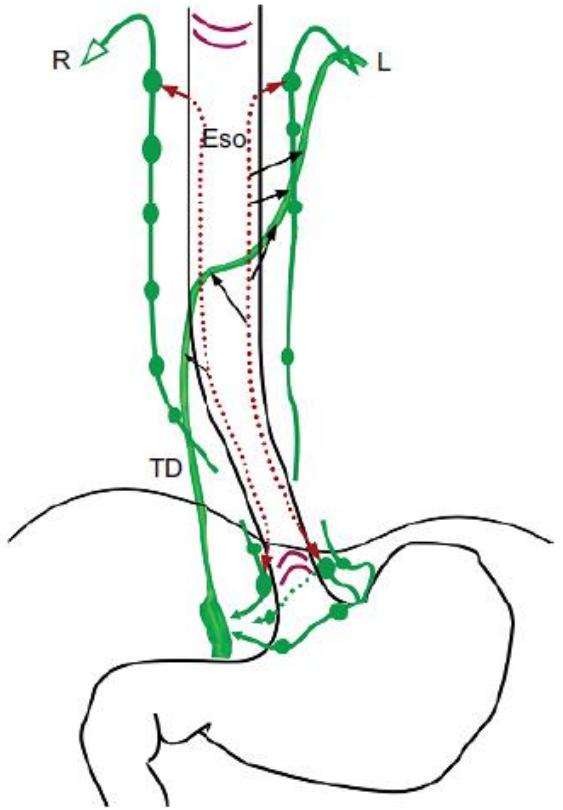

Inferior
vena cava
Esophagus
Left crus
Right crus
Median arcuate
ligament
Abdominal
aorta
Celiac axis

Lymphatic drainage of esophagus





- 2 routes of lymphatic drainage
  - Direct drainage to thoracic duct
  - Lymphatic drainage with nodal relay
- Bidirectional flow



Patterns of lymph node metastasis

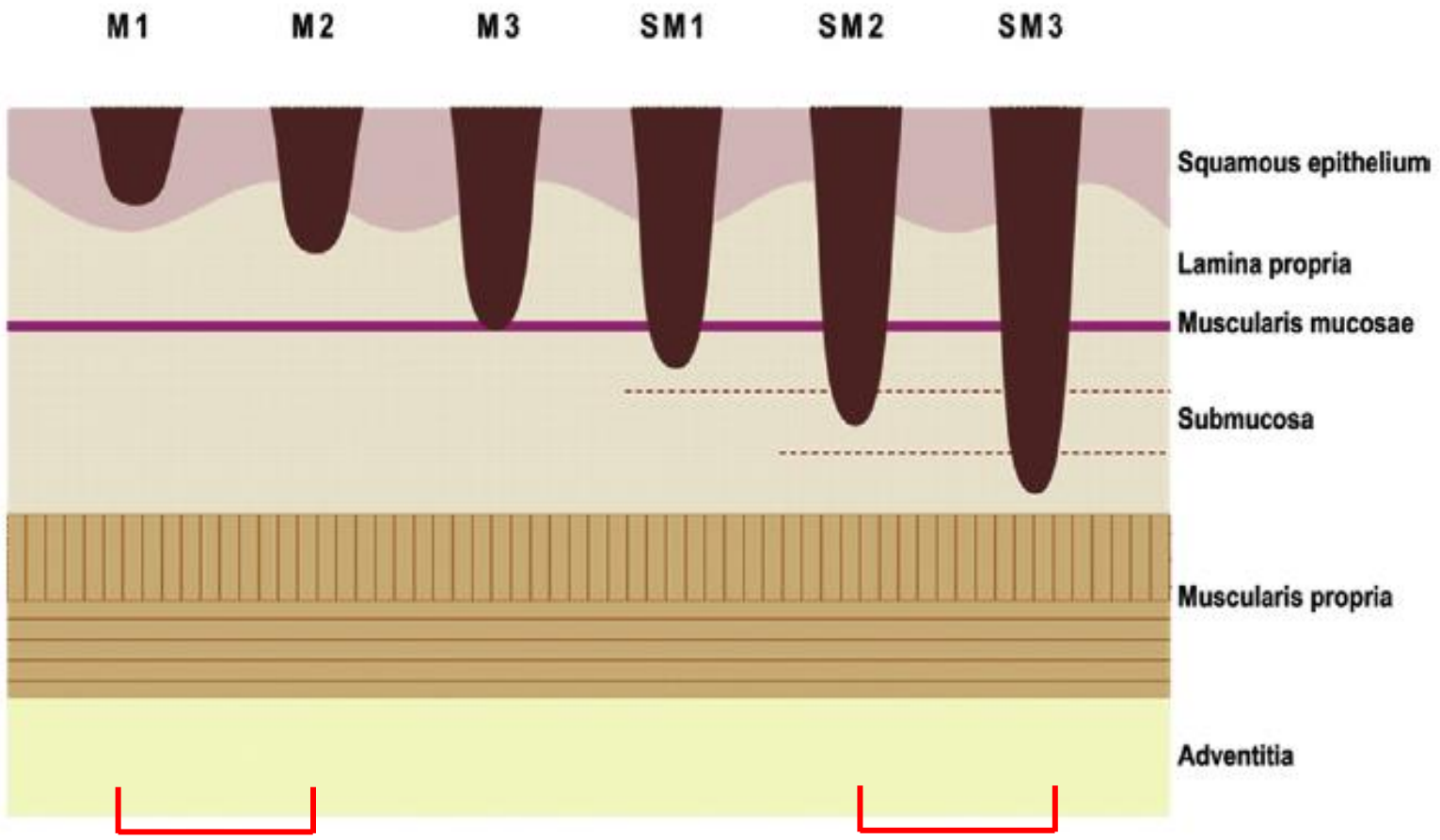
Esophageal SqCC vs Adenoca.

	Squamous cell carcinoma	**Adenocarcinoma**
Region	East Asia (most common type in worldwide)	Western
Location	Upper, middle	Lower, EGJ
Risk factors	Diet, Alcohol, Tobacco, Achalasia	Barrett esophagus, GERD, Obesity
Lymph node metastasis	Skip	Regional

Lymph node metastasis in superficial ESCC

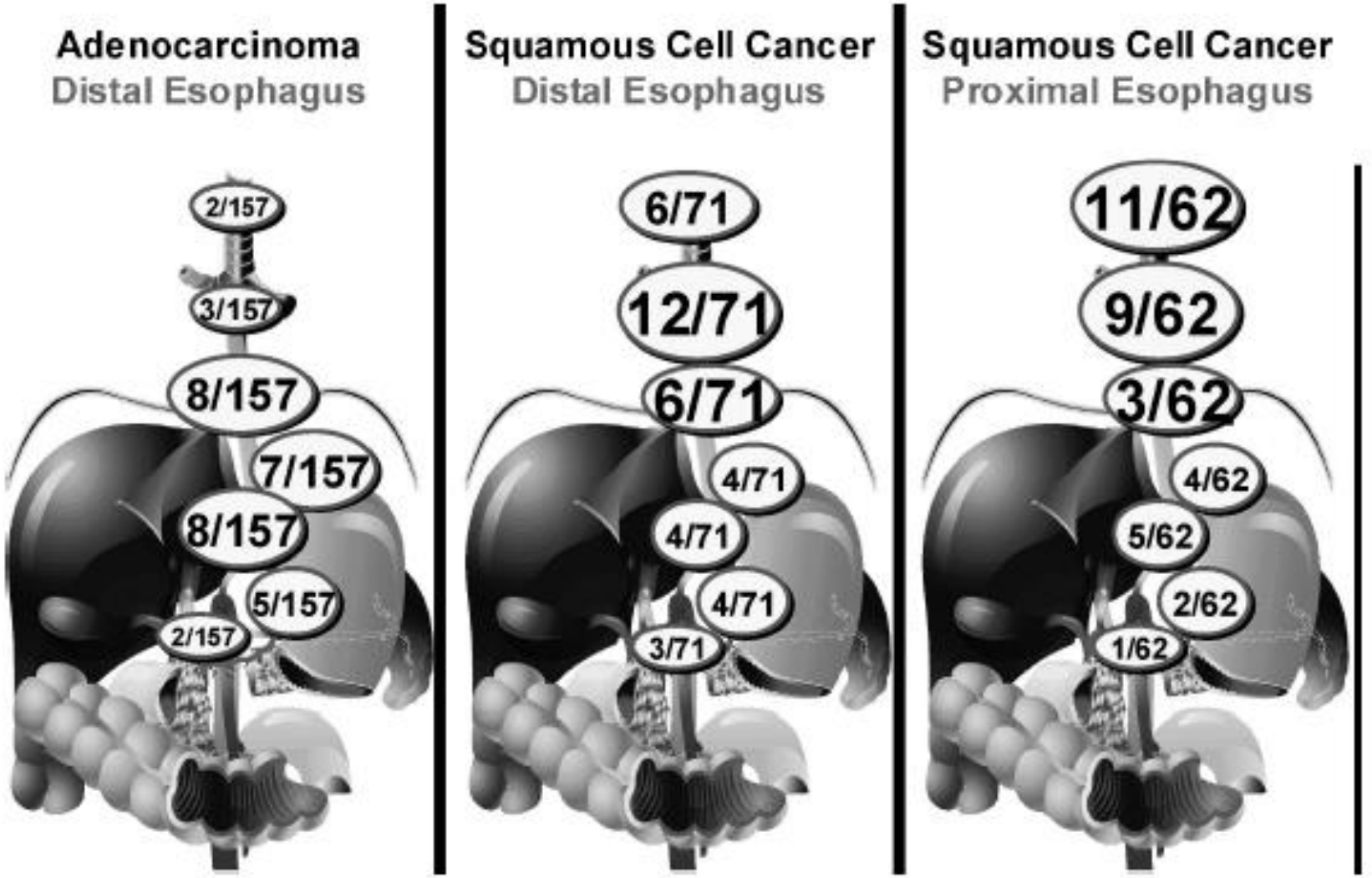
T1a
- M1: carcinoma in situ
- M2: invading lamina propria
- M3: invading muscularis mucosa

T1b
- SM1: invading upper 1/3 of submucosa
- SM2: invading middle 1/3 of submucosa
- SM3: invading lower 1/3 of submucosa



Maximal % of LN metastasis	0 – 4%	16%	53%	75%

Patterns of lymphatic spread of early esophageal cancer (ADC, Sqcc)



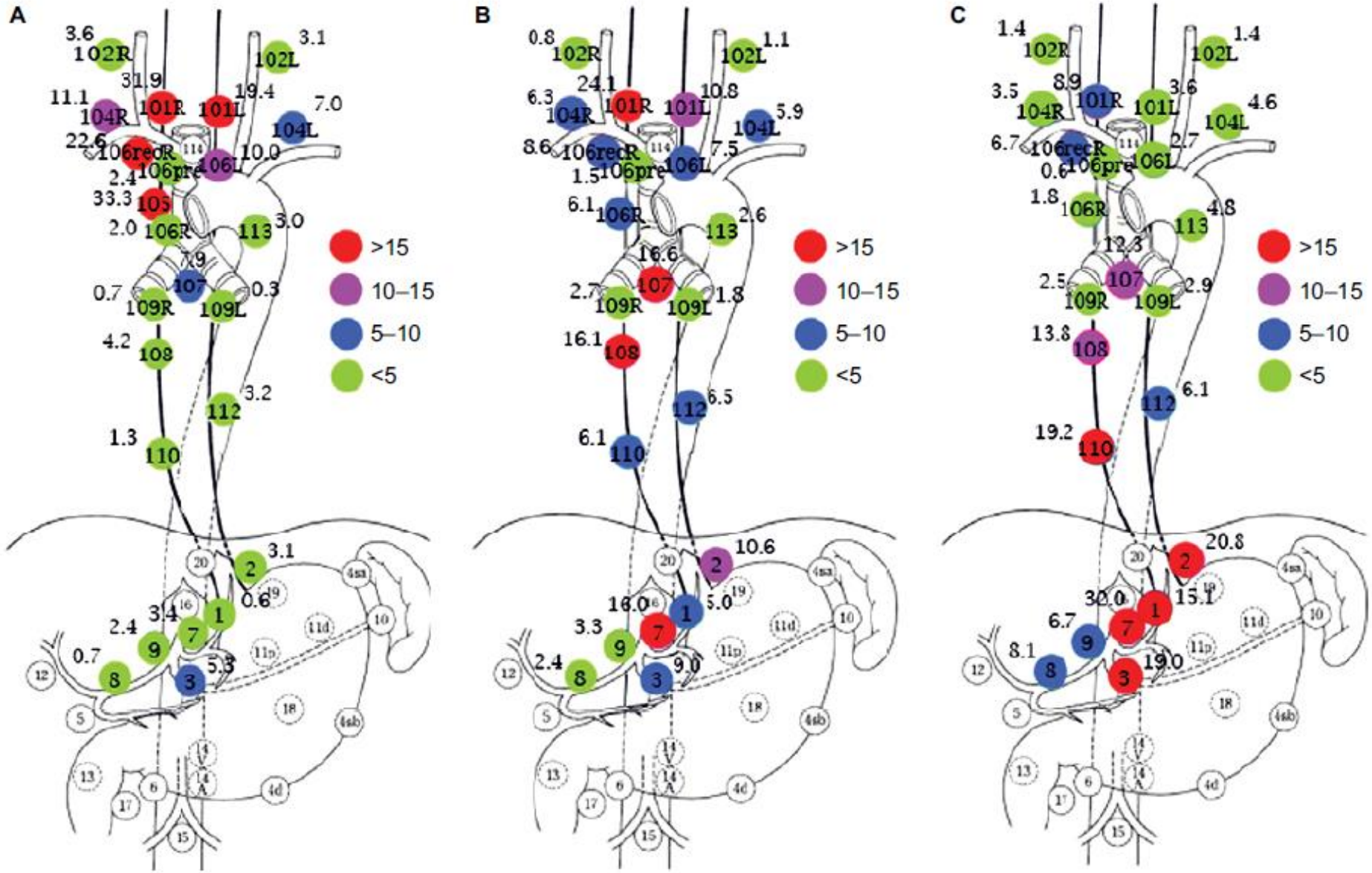


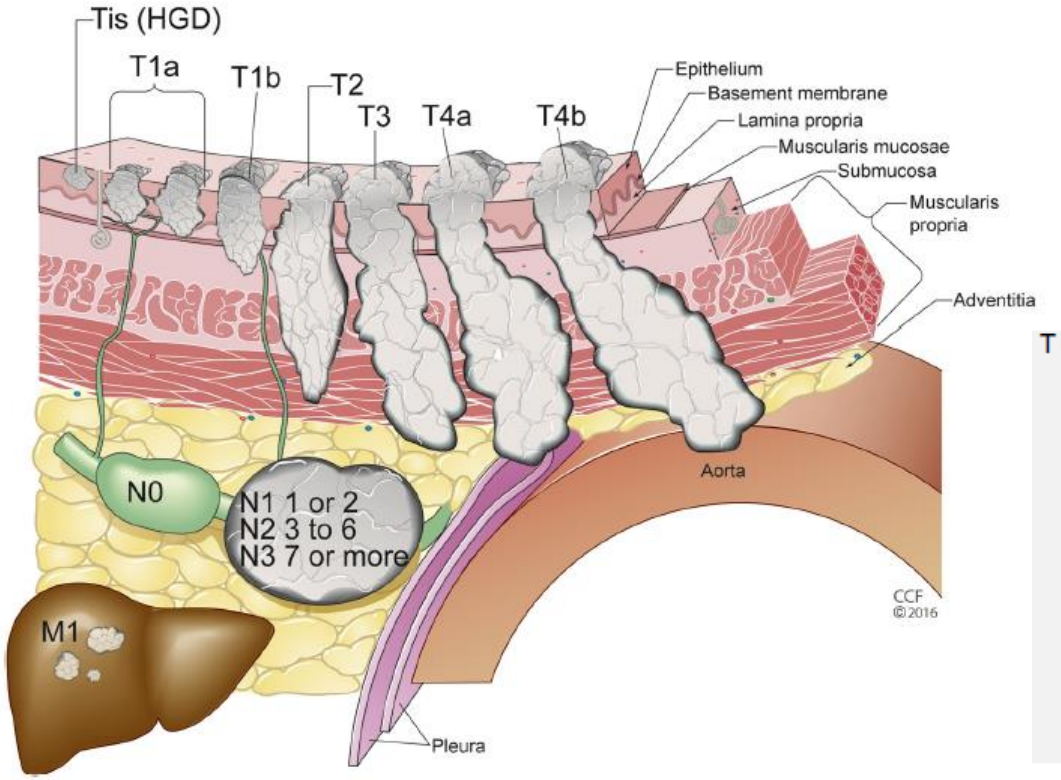
Figure 4 The LNMR of different stations in the upper TEC (A); the middle TEC (B); and the lower TEC (C) (%).

Notes: Numbers and naming of main regional LN. 101, cervical paraesophageal LN; 102, deep cervical LN; 104, supraclavicular LN; 105, upper thoracic paraesophageal LN; 106, thoracic paratracheal LN; 106rec, recurrent nerve LN; 106pre, pretracheal LN; 107, subcarinal LN; 108, middle thoracic paraesophageal LN; 109, main bronchus LN; 110, lower thoracic paraesophageal LN; 112, posterior mediastinal LN; 113, ligamentum arteriosum LN; 1, right paracardial LN; 2, left paracardial LN; 3, lesser curvature LN; 4, LN along the greater curvature; 5, suprapyloric LN; 6, infrapyloric LN; 7, LN along the left gastric artery; 8, LN along the common hepatic artery; 9, LN along the celiac artery.

Abbreviations: L, left; R, right; LN, lymph nodes; LNMR, lymph node metastasis rate; TEC, thoracic esophageal cancer.

Staging of Esophageal cancer

Staging of esophageal cancer (AJCC 8th edition)

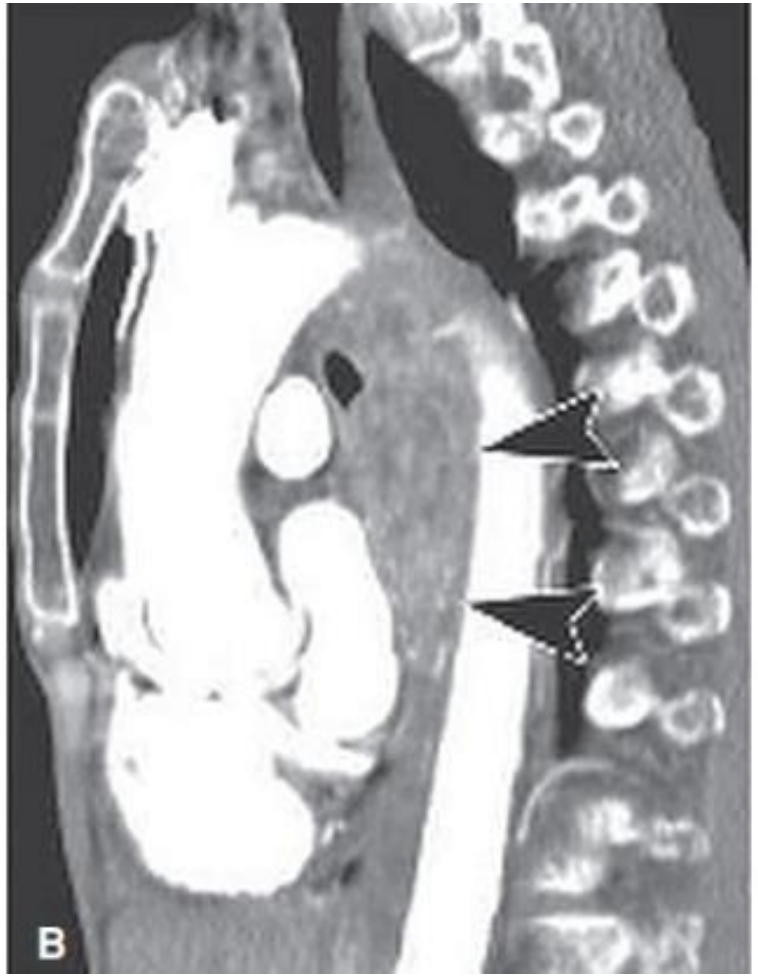


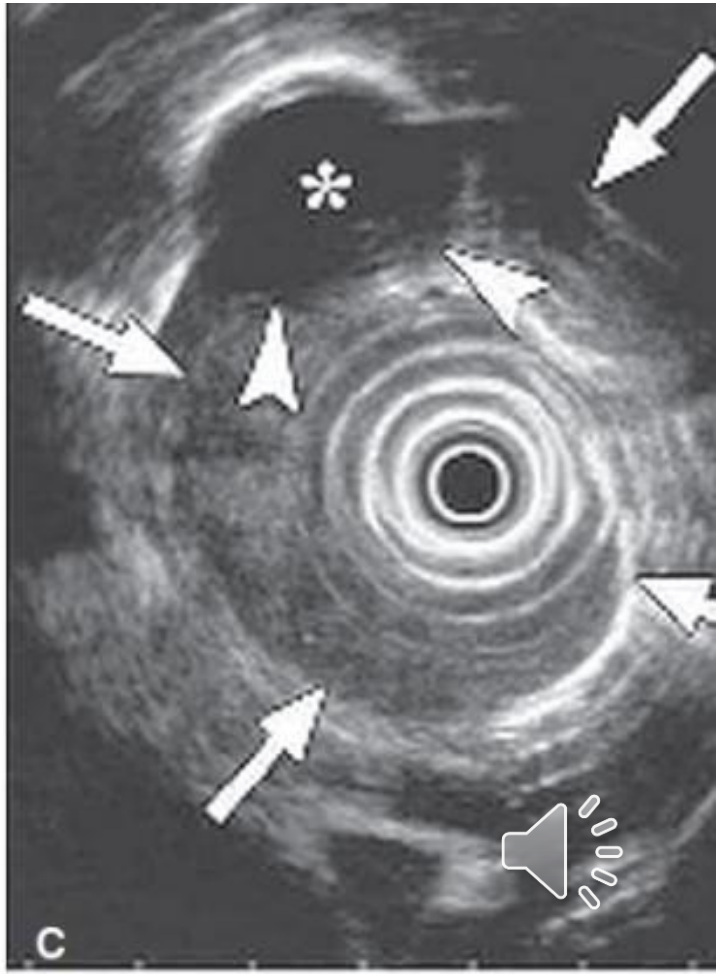
T category	
TX	Tumor cannot be assessed
T0	No evidence of primary tumor
Tis	High-grade dysplasia, defined as malignant cells confined by the basement membrane
T1	Tumor invades the lamina propria, muscularis mucosae, or submucosa
T1a[a]	Tumor invades the lamina propria or muscularis mucosae
T1b[a]	Tumor invades the submucosa
T2	Tumor invades the muscularis propria
T3	Tumor invades the adventitia
T4	Tumor invades adjacent structures
T4a[a]	Tumor invades the pleura, pericardium, azygos vein, diaphragm, or peritoneum
T4b[a]	Tumor invades other adjacent structures, such as the aorta, vertebral body, or trachea

Figure 1. Eighth edition TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); T2 is cancer that invades the muscularis propria; T3 is cancer that invades the adventitia; T4 is cancer that invades the local structures and is subcategorized as T4a (cancer that invades adjacent structures such as the pleura, pericardium, azygos vein, diaphragm, or peritoneum) and T4b (cancer that invades the major adjacent structures, such as the aorta, vertebral body, or trachea). N is categorized as N0 (no regional lymph node metastasis), N1 (regional lymph node metastases involving one to two nodes), N2 (regional lymph node metastases involving three to six nodes), and N3 (regional lymph node metastases involving seven or more nodes). M is categorized as M0 (no distant metastasis) and M1 (distant metastasis).

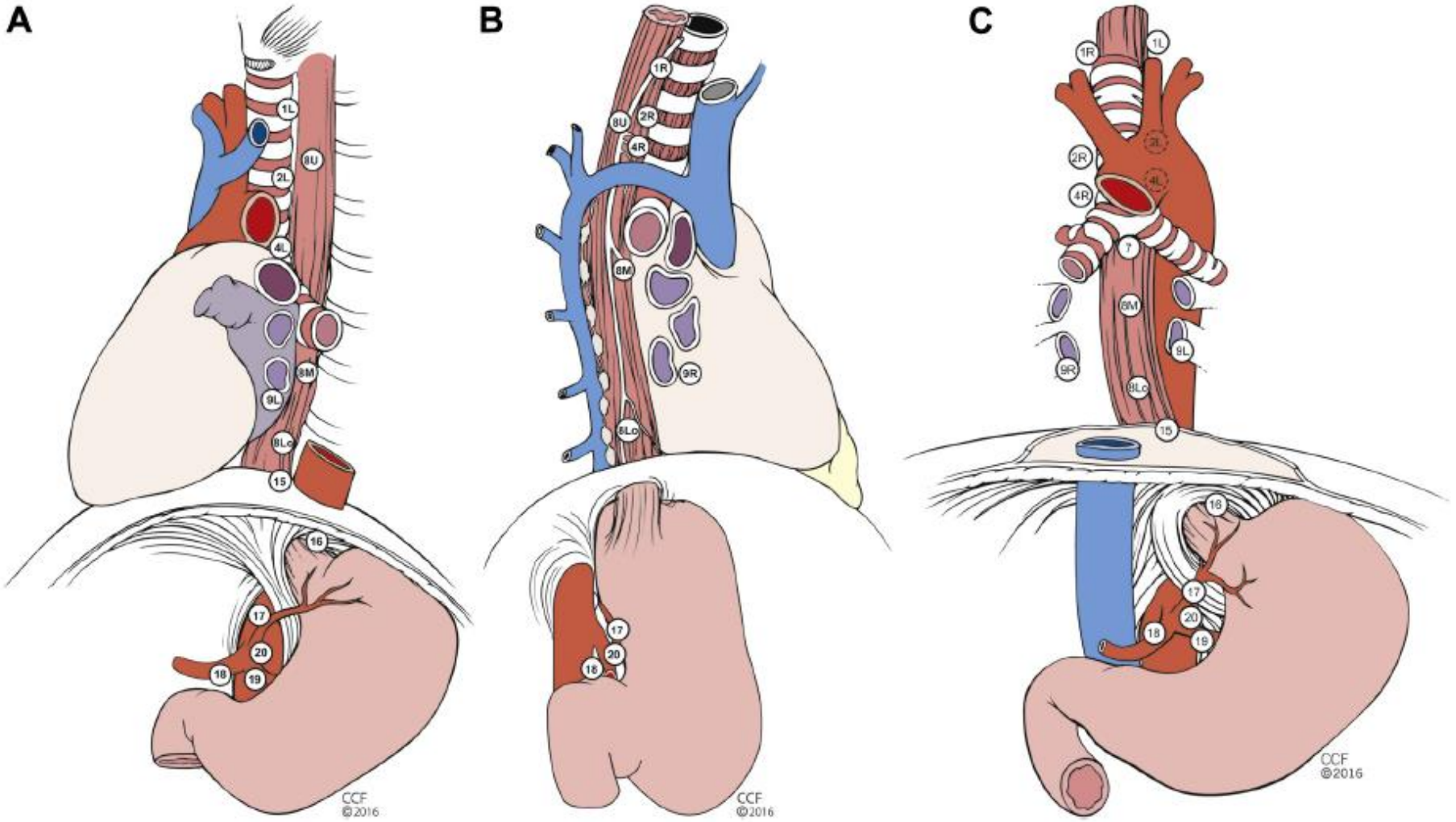
Endoscopy and Chromoendoscopy

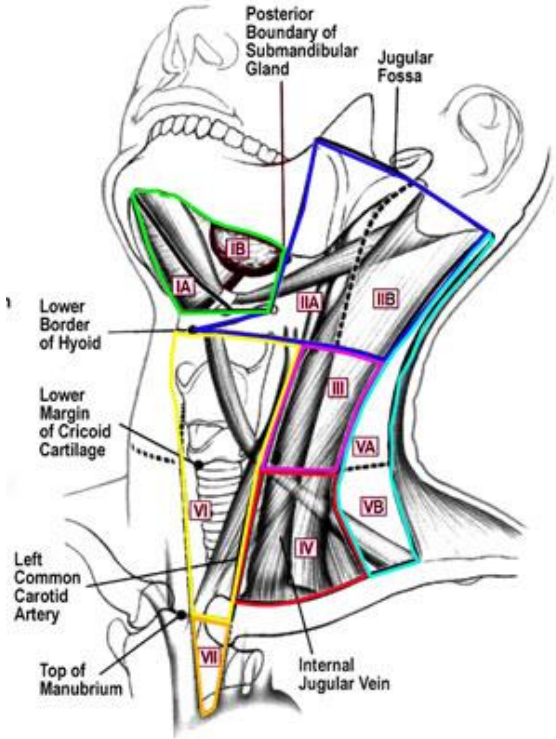
CT scan





Regional lymph node stations for esophageal cancer





1: lower cervical paratracheal
2: upper paratracheal
4: lower paratracheal
7: subcarinal
8: thoracic paraesophageal
9: pulmonary ligament
15: diaphragmatic
16: paracardial
17: left gastric
18: common hepatic
19: splenic
20: celiac

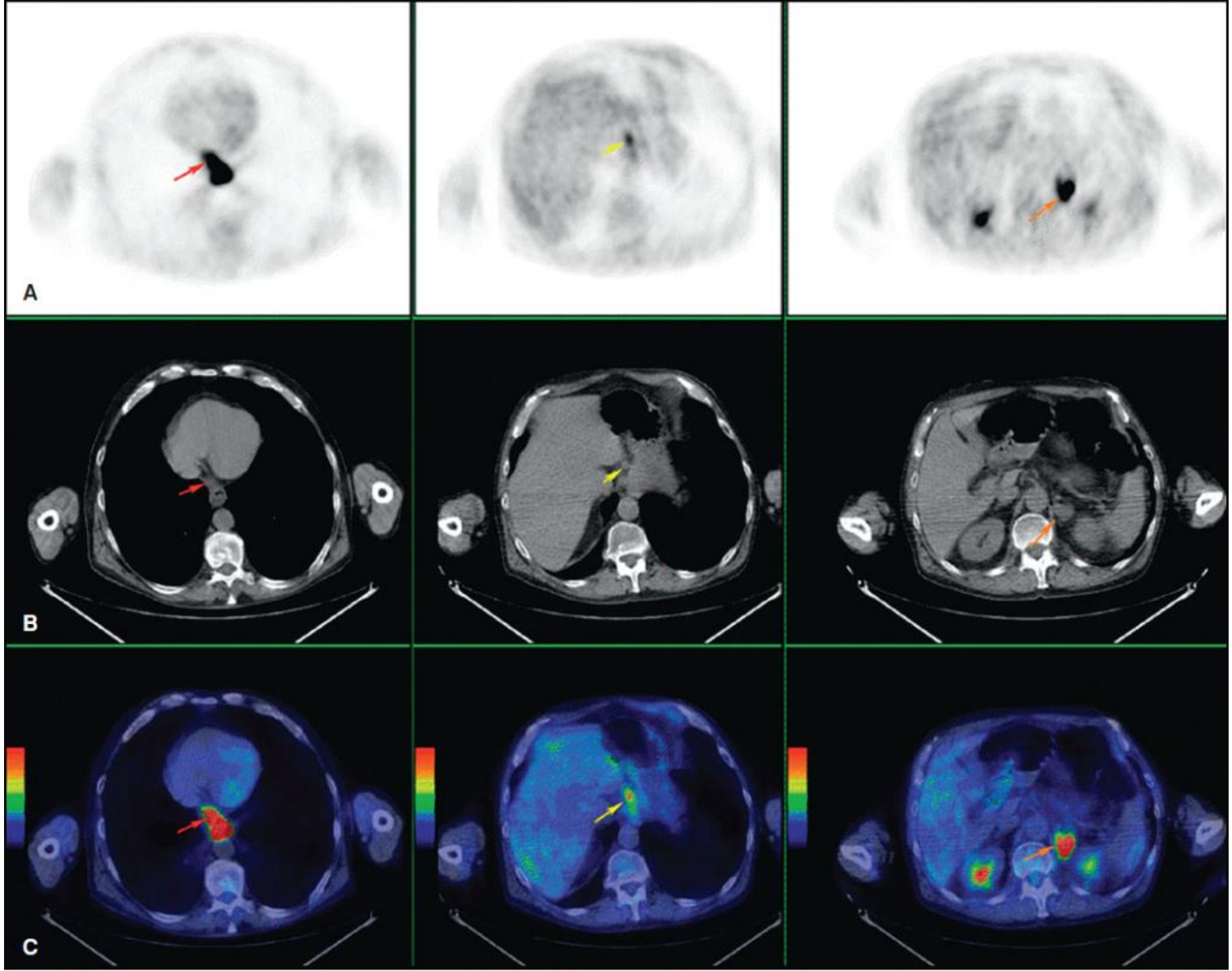
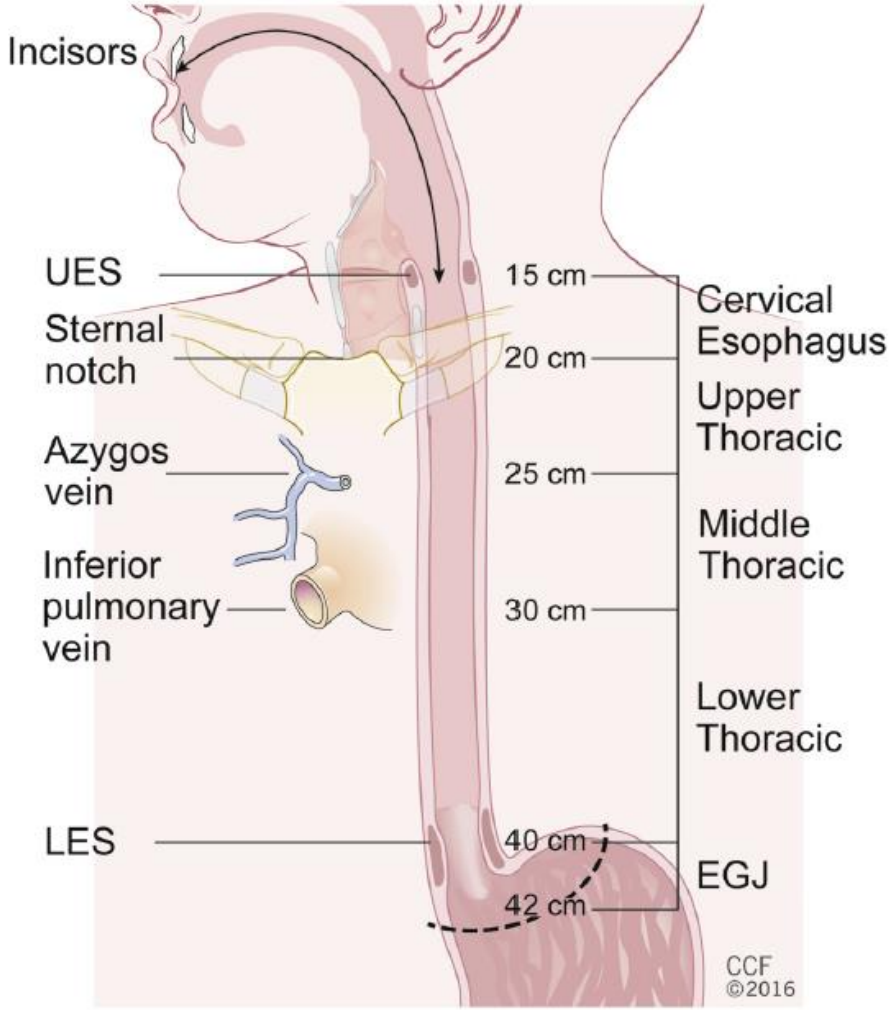

A
B
C

Table 1. General Information about FDG PET/CT and MSCT with Pathological Diagnosis in Lymph Nodes Metastasis of Esophageal Cancers

Detection methods		pathological examination +	pathological examination -	Total	sensitivity	specificity	accuracy
PET/CT	+	165	20	185	74.7%	97.2%	92.0%
	-	56	705	761			
MSCT	+	143	26	169	64.7%	96.4%	89.0%
	-	78	699	777			
P value					0.030	>0.05	>0.05

Cancer location and EG junction cancer



- Assessment of cancer location
  - Upper edge of the cancer (7th edition)
  - Epicenter of the cancer (8th edition)
- Definition of EGJ cancer
  - Epicenter within the proximal 2cm of the cardia

Grade of esophageal cancer

Table 1. Cancer Staging Categories for Cancer of the Esophagus and Esophagogastric Junction

Category	Criteria
Adenocarcinoma G category	
GX	Differentiation cannot be assessed
G1	Well differentiated, with >95% of the tumor composed of well-formed glands
G2	Moderately differentiated, with 50%-95% of the tumor showing gland formation
G3[b]	Poorly differentiated, with tumors composed of nest and sheets of cells with <50% of the tumor demonstrating glandular formation
Squamous cell carcinoma G category	
GX	Differentiation cannot be assessed
G1	Well-differentiated, with prominent keratinization with pearl formation and a minor component of nonkeratinizing basal-like cells, tumor cells arranged in sheets, and mitotic counts low
G2	Moderately differentiated, with variable histologic features ranging from parakeratotic to poorly keratinizing lesions and pearl formation generally absent
G3[c]	Poorly differentiated, consisting predominantly of basal-like cells forming large and small nests with frequent central necrosis and with the nests consisting of sheets or pavement-like arrangements of tumor cells that are occasionally punctuated by small numbers of parakeratotic or keratinizing cells

T (tumor) + N (regional lymph node) + M (distant metastasis) + G (grade) + L (location)

cTNM (clinical), pTNM (pathologic), ypTNM (postneoadjuvant pathologic)

Table 2 Clinical (cTNM) stage groups

cStage group	cT	cN	cM
Squamous cell carcinoma			
0	Tis	N0	M0
I	T1	N0–1	M0
II	T2	N0–1	M0
	T3	N0	M0
III	T3	N1	M0
	T1–3	N2	M0
IVA	T4	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1
Adenocarcinoma			
0	Tis	N0	M0
I	T1	N0	M0
IIA	T1	N1	M0
IIB	T2	N0	M0
III	T2	N1	M0
	T3–4a	N0–1	M0
IVA	T1–4a	N2	M0
	T4b	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1

Table 3 Pathologic (pTNM) stage groups

pStage group	pT	pN	pM	pGrade	pLocation
Squamous cell carcinoma					
0	Tis	N0	M0	N/A	Any
IA	T1a	N0	M0	G1, X	Any
IB	T1b	N0	M0	G1, X	Any
	T1	N0	M0	G2–3	Any
	T2	N0	M0	G1	Any
IIA	T2	N0	M0	G2–3, X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	G1	Upper/middle
IIB	T3	N0	M0	G2–3	Upper/middle
	T3	N0	M0	X	Any
	T3	N0	M0	Any	X
	T1	N1	M0	Any	Any
IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
IIIB	T4a	N0–1	M0	Any	Any
	T3	N1	M0	Any	Any
	T2–3	N2	M0	Any	Any
IVA	T4a	N2	M0	Any	Any
	T4b	N0–2	M0	Any	Any
	T1–4	N3	M0	Any	Any
IVB	T1–4	N0–3	M1	Any	Any

Table 3 Pathologic (pTNM) stage groups

pStage group	pT	pN	pM	pGrade	pLocation
Adenocarcinoma					
0	Tis	N0	M0	N/A	
IA	T1a	N0	M0	G1, X	
IB	T1a	N0	M0	G2	
	T1b	N0	M0	G1–2, X	
IC	T1	N0	M0	G3	
	T2	N0	M0	G1–2	
IIA	T2	N0	M0	G3, X	
IIB	T1	N1	M0	Any	
	T3	N0	M0	Any	
IIIA	T1	N2	M0	Any	
	T2	N1	M0	Any	
IIIB	T4a	N0–1	M0	Any	
	T3	N1	M0	Any	
	T2–3	N2	M0	Any	
IVA	T4a	N2	M0	Any	
	T4b	N0–2	M0	Any	
	T1–4	N3	M0	Any	
	T1–4	N0–3	M1	Any	

N/A, not applicable; X, not defined.

A cTNM Adenocarcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1	I	IIA	IVA	IVA	IVB
T2	IIB	III	IVA	IVA	IVB
T3	III	III	IVA	IVA	IVB
T4a	III	III	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

B cTNM Squamous Cell Carcinoma

	N0	N1	N2	N3	M1
Tis	0				
T1	I	I	III	IVA	IVB
T2	II	II	III	IVA	IVB
T3	II	III	III	IVA	IVB
T4a	IVA	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

A pTNM Adenocarcinoma

		N0	N1	N2	N3	M1
Tis		0				
T1a	G1	IA	IIB	IIIA	IVA	IVB
	G2	IB				
	G3	IC				
T1b	G1	IB	IIB	IIIA	IVA	IVB
	G2	IC				
	G3					
T2	G1	IC	IIIA	IIIB	IVA	IVB
	G2	IIA				
	G3					
T3		IIB	IIIB	IIIB	IVA	IVB
T4a		IIIB	IIIB	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

B pTNM Squamous Cell Carcinoma

		N0		N1	N2	N3	M1
		L	U/M				
Tis		0					
T1a	G1	IA	IA	IIB	IIIA	IVA	IVB
	G2-3	IB	IB				
T1b		IB		IIB	IIIA	IVA	IVB
T2	G1	IB	IB	IIIA	IIIB	IVA	IVB
	G2-3	IIA	IIA				
T3	G1	IIA	IIA	IIIB	IIIB	IVA	IVB
	G2-3	IIA	IIB				
T4a		IIIB		IIIB	IVA	IVA	IVB
T4b		IVA		IVA	IVA	IVA	IVB

Postneoadjuvant pathologic stage

Table 4 Postneoadjuvant therapy (ypTNM) stage groups

ypStage group	ypT	ypN	ypM
I	T0–2	N0	M0
II	T3	N0	M0
IIIA	T0–2	N1	M0
IIIB	T4a	N0	M0
	T3	N1–2	M0
	T0–3	N2	M0
IVA	T4a	N1–2, X	M0
	T4b	N0–2	M0
	T1–4	N3	M0
IVB	T1–4	N0–3	M1

X, not defined.

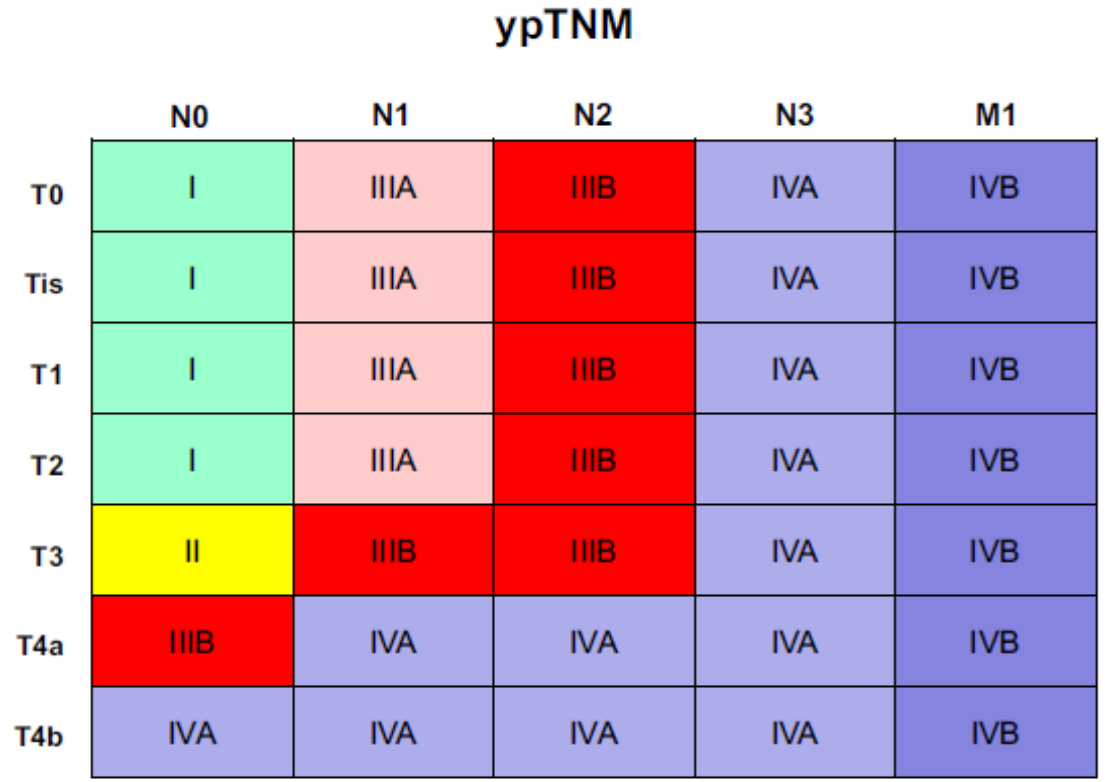


Figure 5. Postneoadjuvant pathologic stage groups (ypTNM): adenocarcinoma and squamous cell carcinoma.

Japanese Classification of Esophageal Cancer, 11th Edition

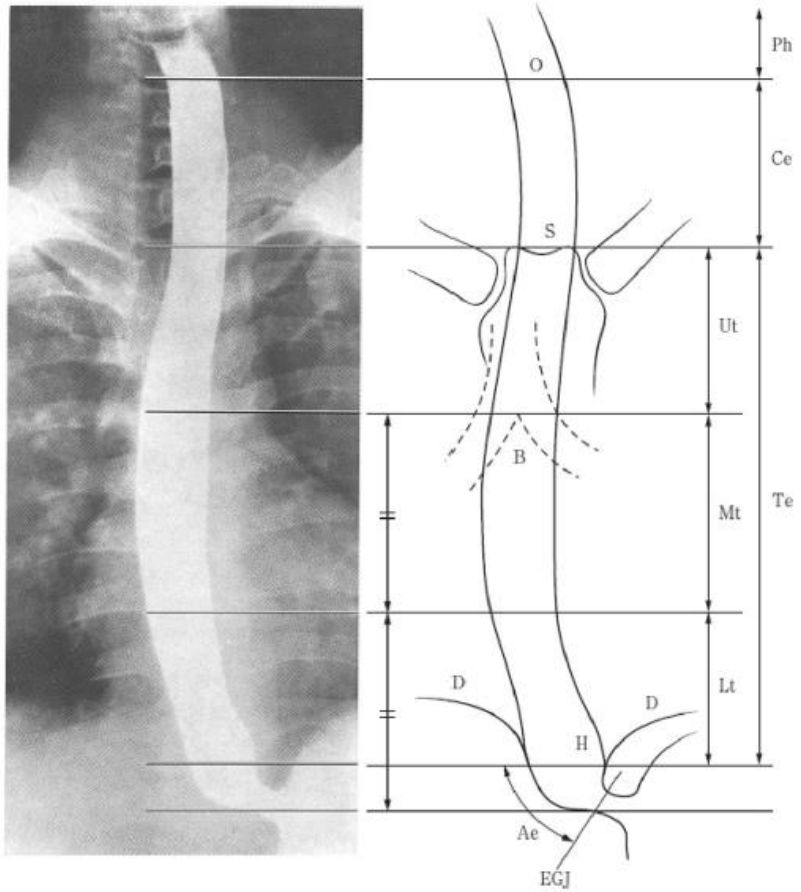


Fig. 1-1 Tumor location. *O* esophageal orifice, *S* superior margin of the sternum, *B* tracheal bifurcation, *D* diaphragm, *EGJ* esophagogastric junction, *H* esophageal hiatus

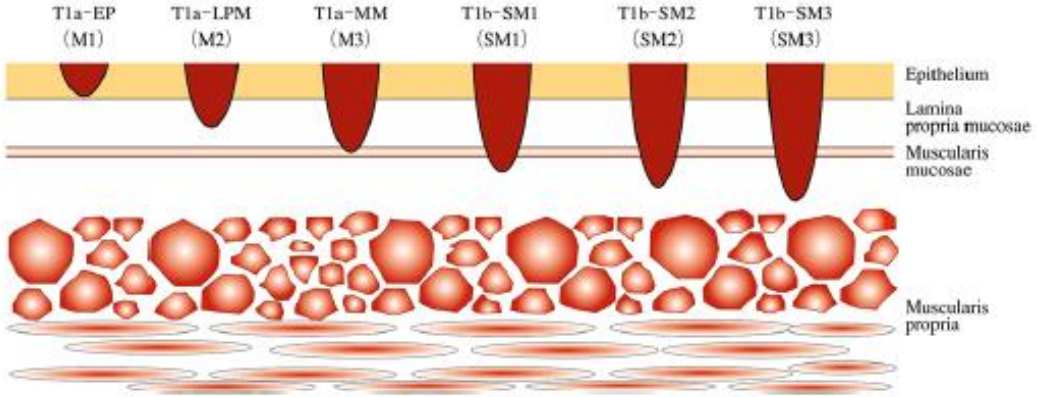


Fig. 1-3 Subclassification for superficial cancer (modified from the guidelines for esophageal cancer treatment)

Depth of tumor invasion \ Metastasis	N0	N1	N2	N3	N4	M1
T0, T1a	0	II	II	III	IVa	IVb
T1b	I	II	II	III	IVa	IVb
T2	II	II	III	III	IVa	IVb
T3	II	III	III	III	IVa	IVb
T4a	III	III	III	III	IVa	IVb
T4b	IVa	IVa	IVa	IVa	IVa	IVb

T4a pleura, pericardium, diaphragm, lung, thoracic duct, azygos vein, nerve

T4b aorta (large vessel), trachea, bronchus, pulmonary vein, pulmonary artery, vertebra

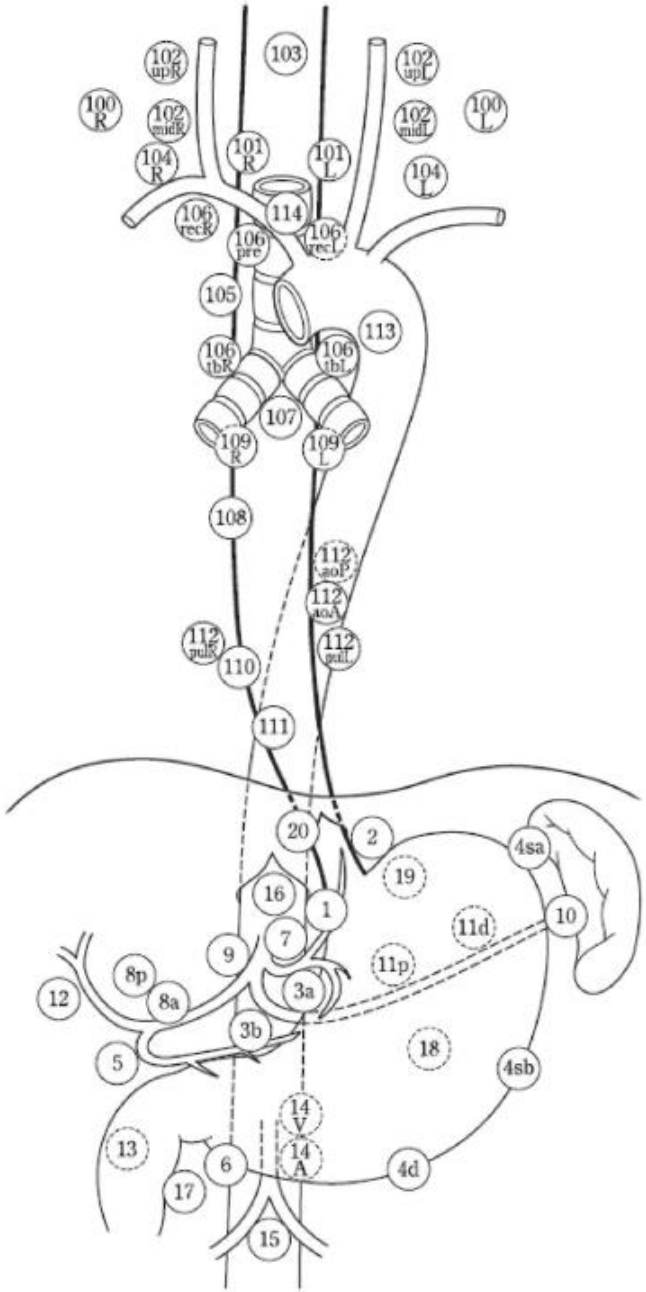


Fig. 1-4 Station numbers of regional lymph nodes

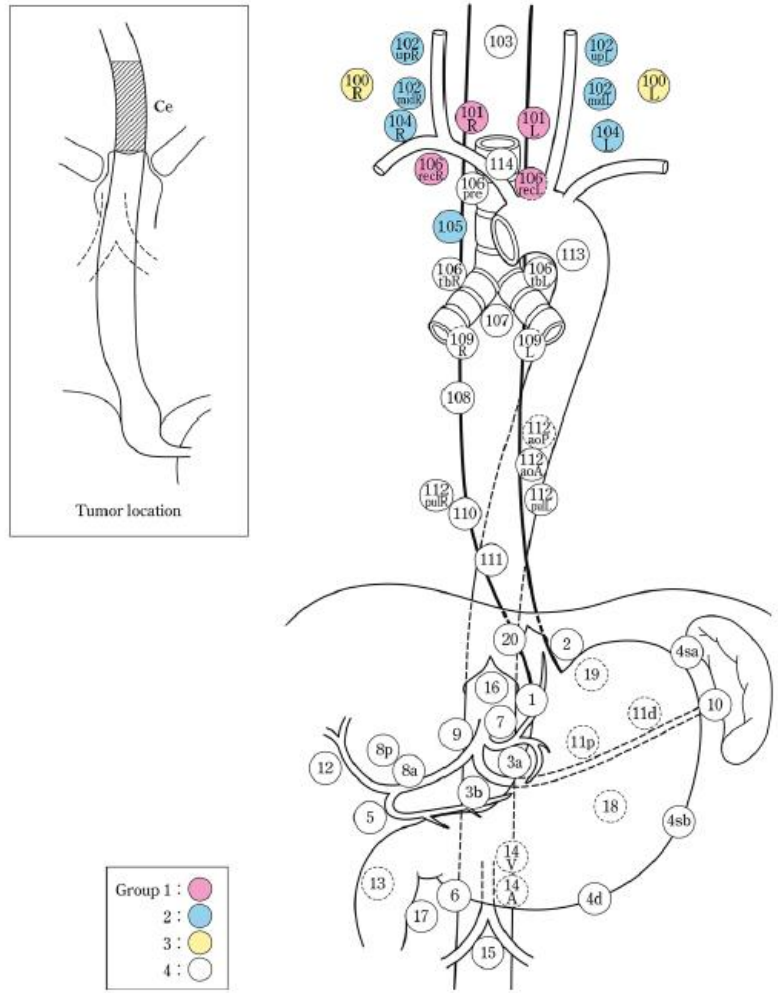


Fig. 1-8 Lymph node groups for tumors located in Ce

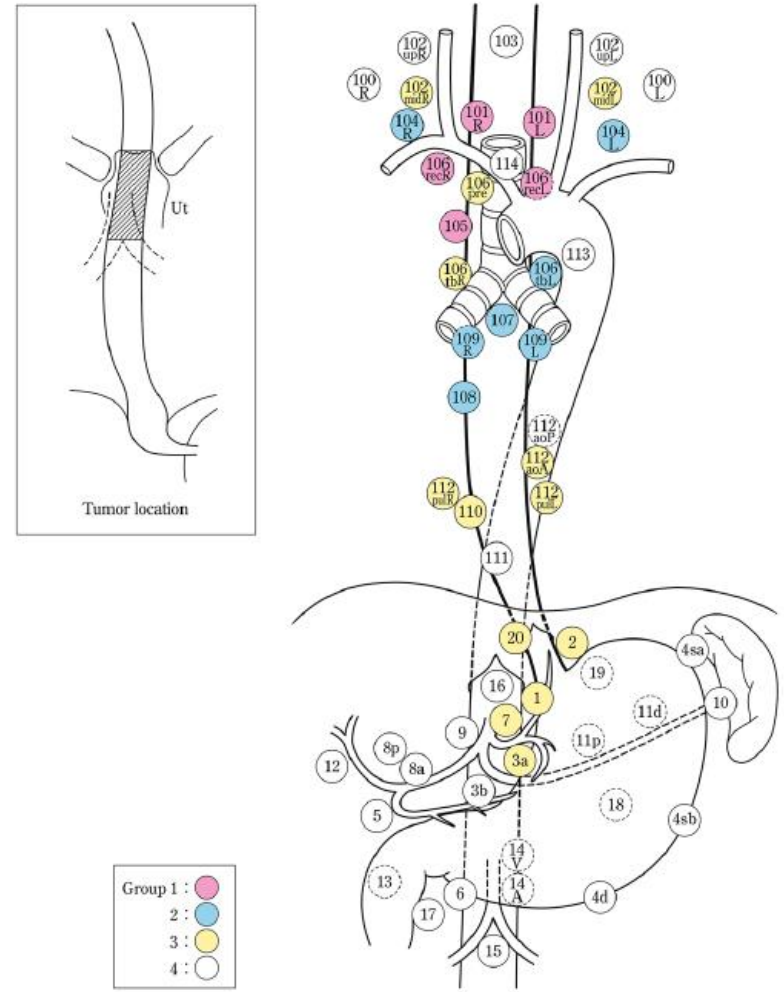


Fig. 1-9 Lymph node groups of tumors located in Ut

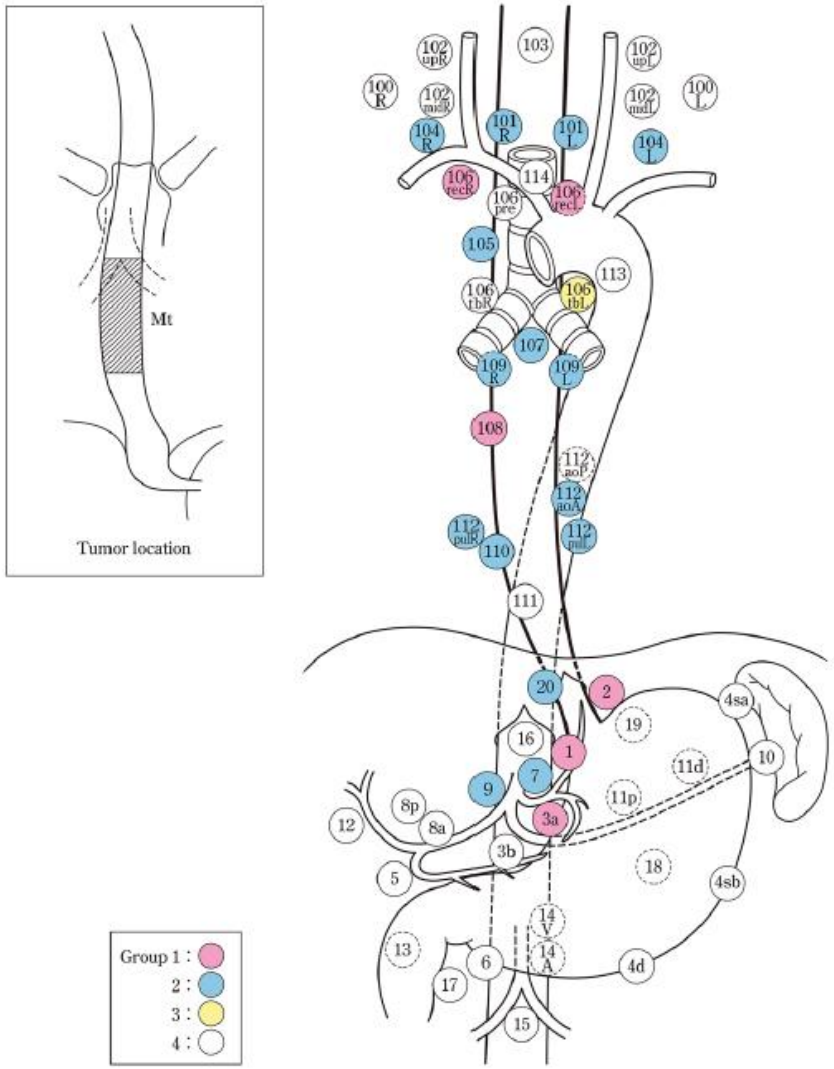


Fig. 1-10 Lymph node groups for tumors located in Mt

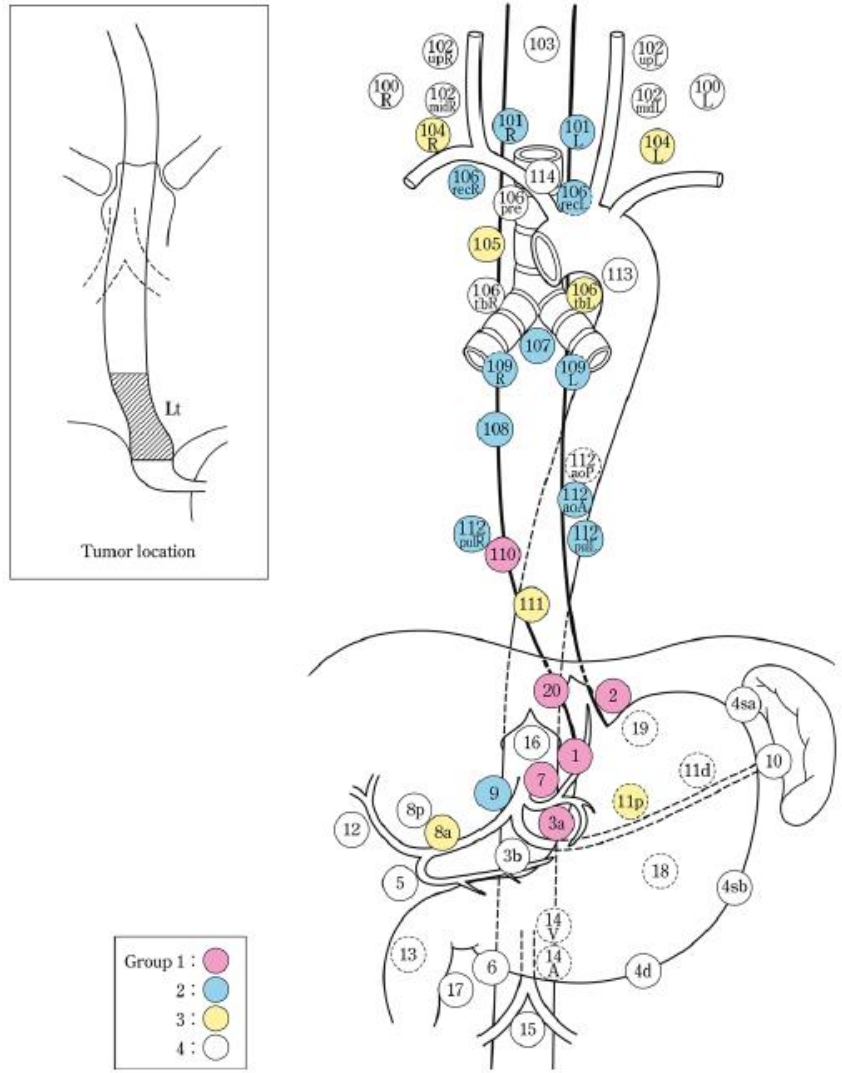


Fig. 1-11 Lymph node groups for tumors located in Lt

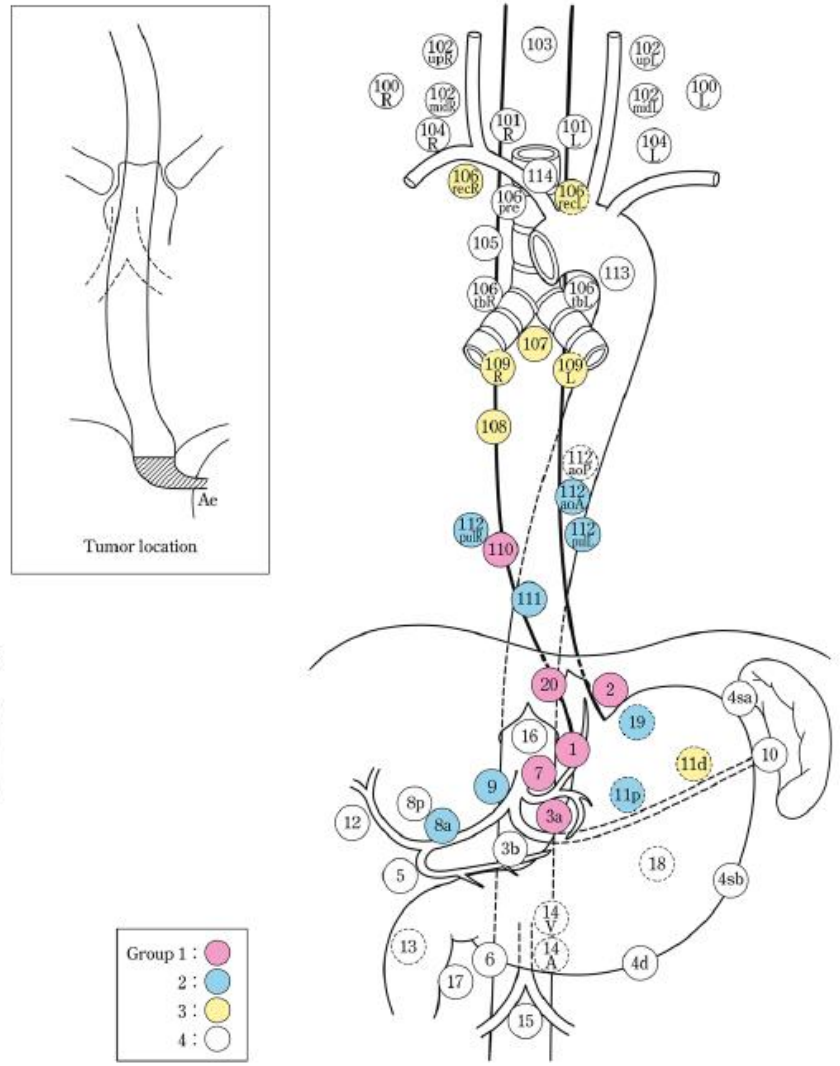


Fig. 1-12 Lymph node groups for tumors located in Ae (EG)

Decision making of Esophageal cancer

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WORKUP

- H&P
- Upper gastrointestinal (GI) endoscopy and biopsy[a]
- Chest/abdominal CT with oral and IV contrast
- Pelvic CT with contrast as clinically indicated
- FDG-PET/CT evaluation (skull base to mid-thigh) if no evidence of M1 disease
- Complete blood count (CBC) and comprehensive chemistry profile
- Endoscopic ultrasound (EUS), if no evidence of M1 unresectable disease
- Endoscopic resection (ER) is recommended for the accurate staging of early-stage cancers (T1a or T1b).[a,b] Early-stage cancers can best be diagnosed by ER
- Biopsy of metastatic disease as clinically indicated
- Microsatellite instability (MSI) and programmed death ligand 1 (PD-L1) testing if metastatic disease is documented/suspected[c]
- HER2 testing if metastatic adenocarcinoma is documented/suspected[c]
- Next-generation sequencing (NGS) may be considered[c]
- Bronchoscopy, if tumor is at or above the carina with no evidence of M1 disease
- Assign Siewert category[d]
- Nutritional assessment and counseling
- Smoking cessation advice, counseling, and pharmacotherapy as indicated[e]
- Screen for family history[f]

CLINICAL STAGE[g]

HISTOLOGIC CLASSIFICATION[c]

Stage I–IVA[g,h] (locoregional disease, except T4b or unresectable N3[h])

- Squamous cell carcinoma → See ESOPH-2
- Adenocarcinoma → See ESOPH-11

Stage IVA[g] (includes T4b or unresectable N3 only) and IVB (metastatic disease)

- Squamous cell carcinoma → See ESOPH-10
- Adenocarcinoma → See ESOPH-19

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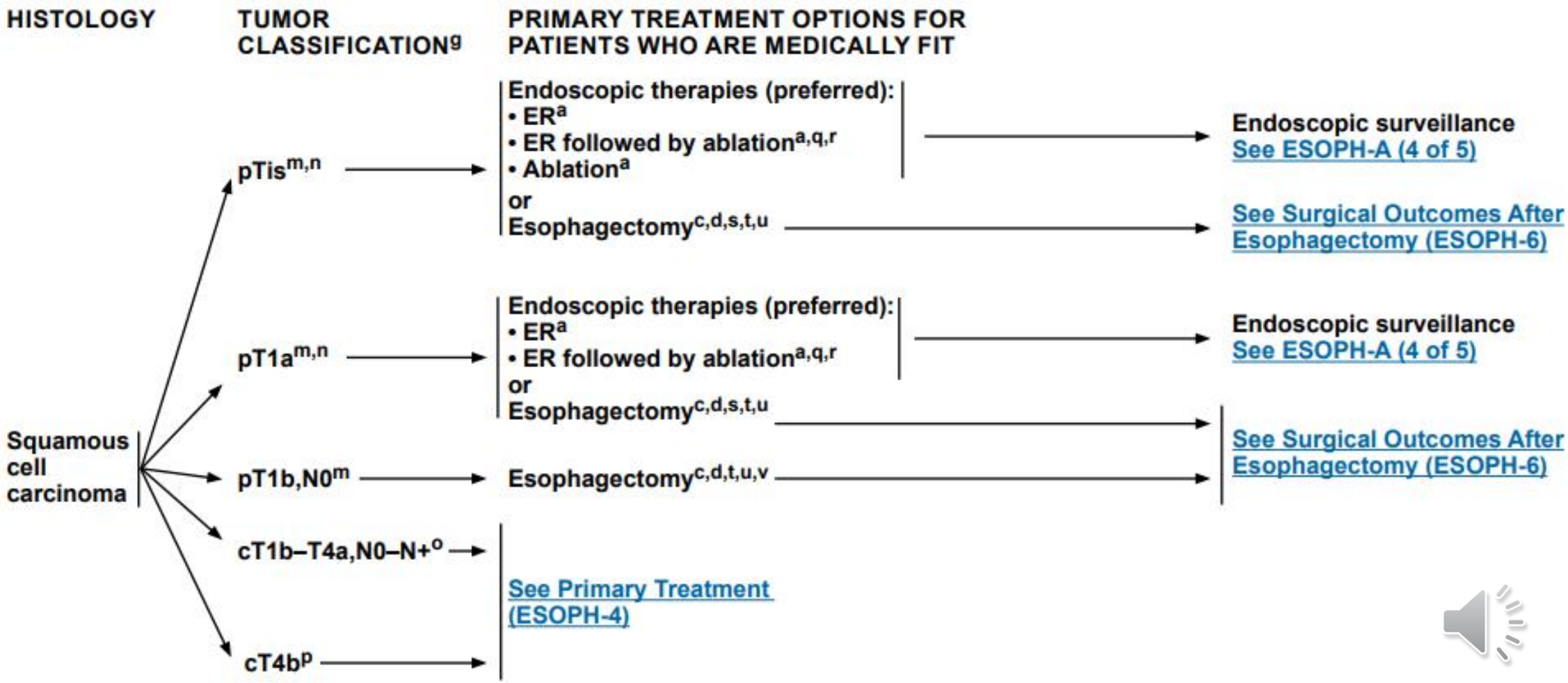

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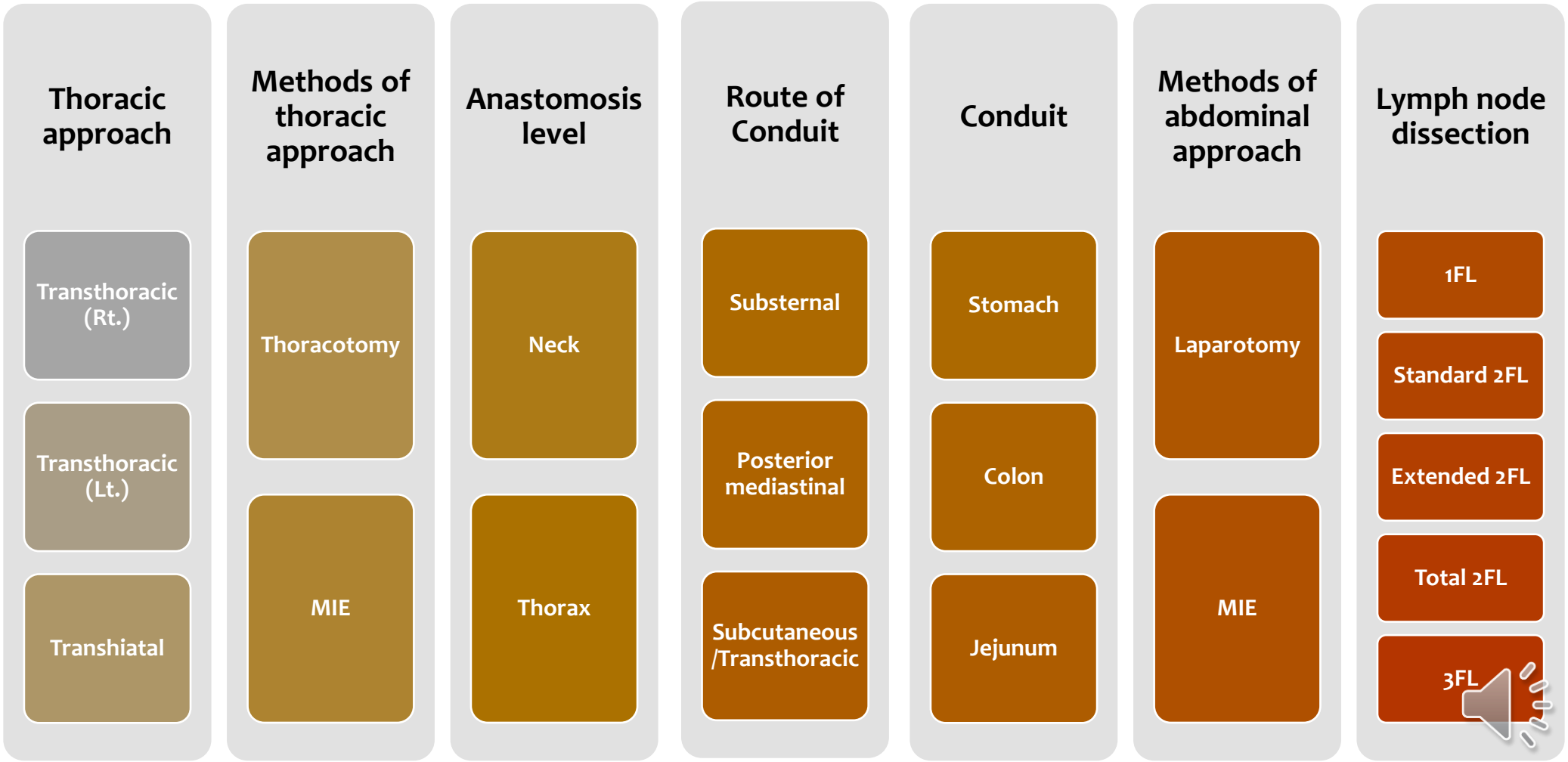
HISTOLOGY	TUMOR CLASSIFICATION[g]	PRIMARY TREATMENT OPTIONS FOR PATIENTS WHO ARE MEDICALLY FIT	
Squamous cell carcinoma	cT1b–cT2,N0 (low-risk lesions: <3 cm, well differentiated)[o]	Esophagectomy[c,d,t,u] (for non-cervical esophagus)	See Surgical Outcomes After Esophagectomy (ESOPH-6)
	cT2, N0 (high-risk lesions: LVI, ≥3 cm, poorly differentiated) cT1b–cT2, N+ or cT3–cT4a, Any N[w]	Preoperative chemoradiation[x,y]	See Response Assessment (ESOPH-5)
		or	
		Definitive chemoradiation[x,y]	Follow-up (See ESOPH-9)
	cT4b[p]	Definitive chemoradiation[x,y]	See Response Assessment (ESOPH-5)
		or	
		Consider chemotherapy alone in the setting of invasion of trachea, great vessels, vertebral body, or heart[x] See Palliative Management (ESOPH-10)	

Combinations of Operation



Take home messages

- Anatomy of esophagus
  - Location and pathway of recurrent laryngeal nerve
  - Submucosal lymphatic networks
- Patterns of lymph node metastasis
  - Reason of early distant metastasis
- Staging system of esophageal cancer
  - Factors of esophageal staging system
    - TNM + G + L

Thanks for Attention