Pathophysiology and clinical characteristics of Esophageal Cancer

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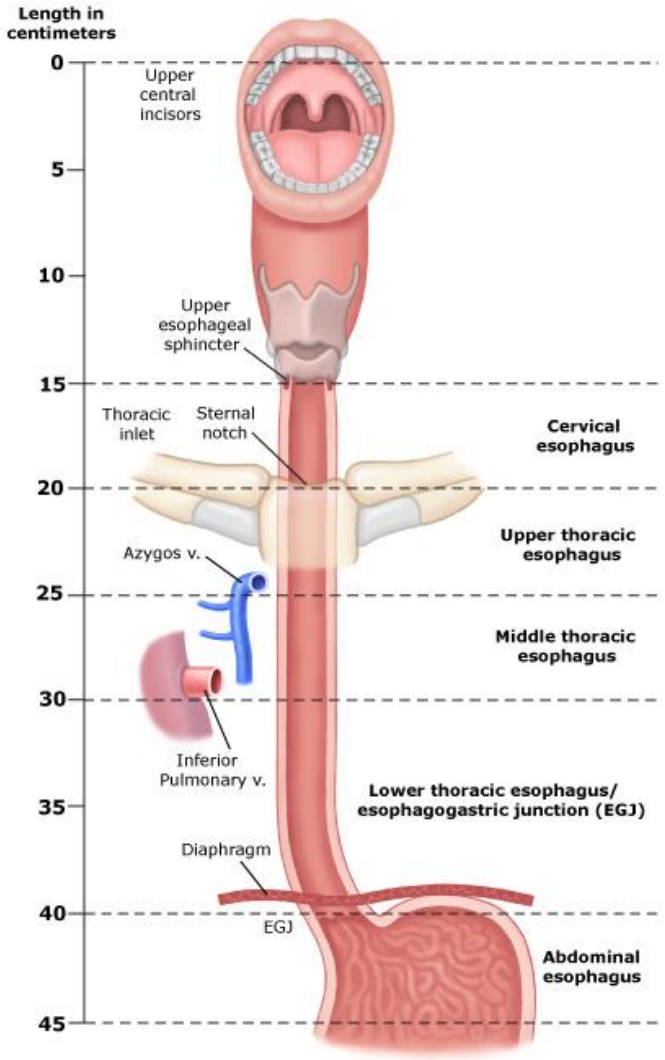
Agenda

- Anatomy of esophagus, related to esophageal cancer
- Clinical characteristics of esophageal cancer and patterns of lymph node metastasis
- Staging System of Esophageal Cancer

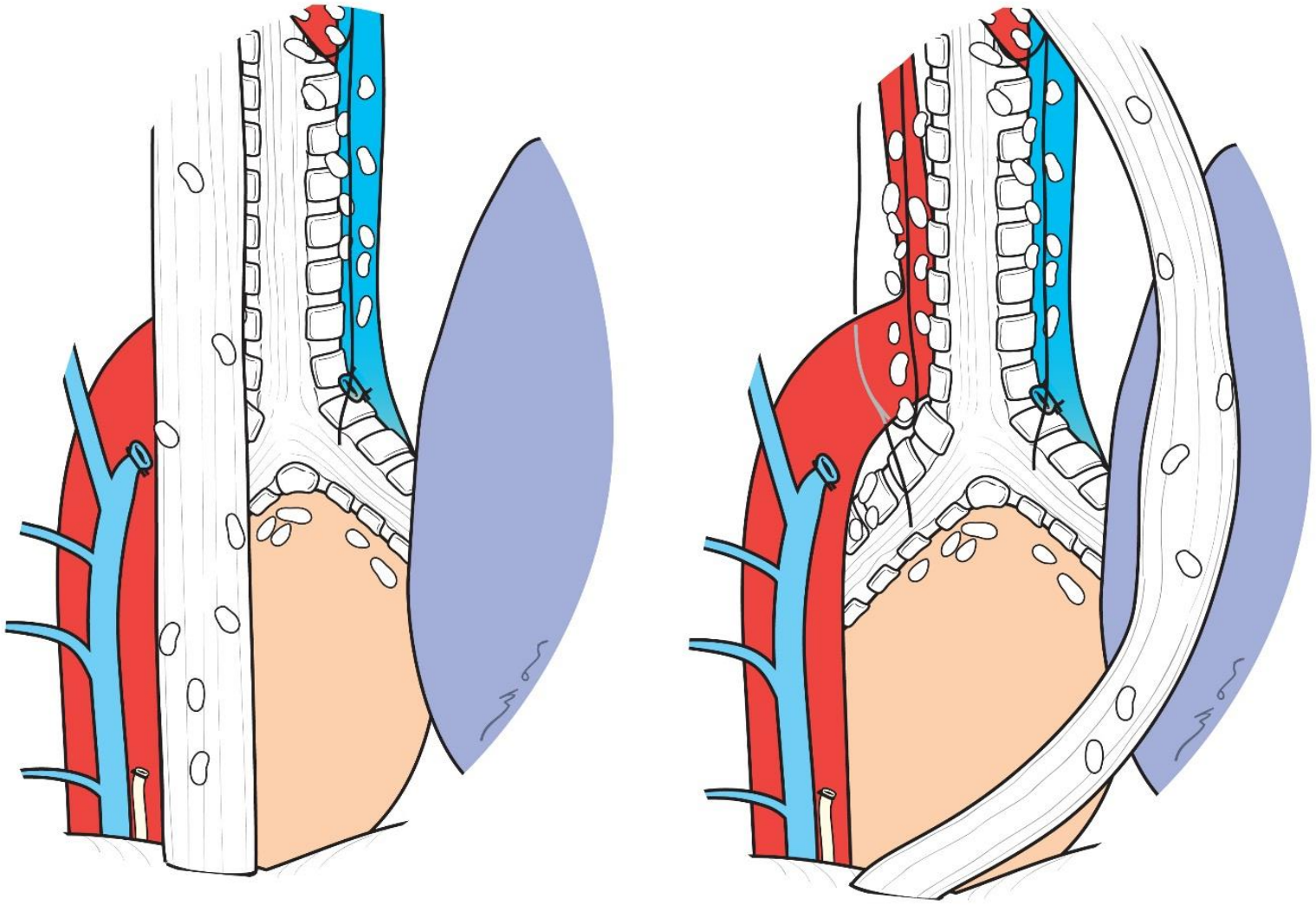
Anatomy of esophagus

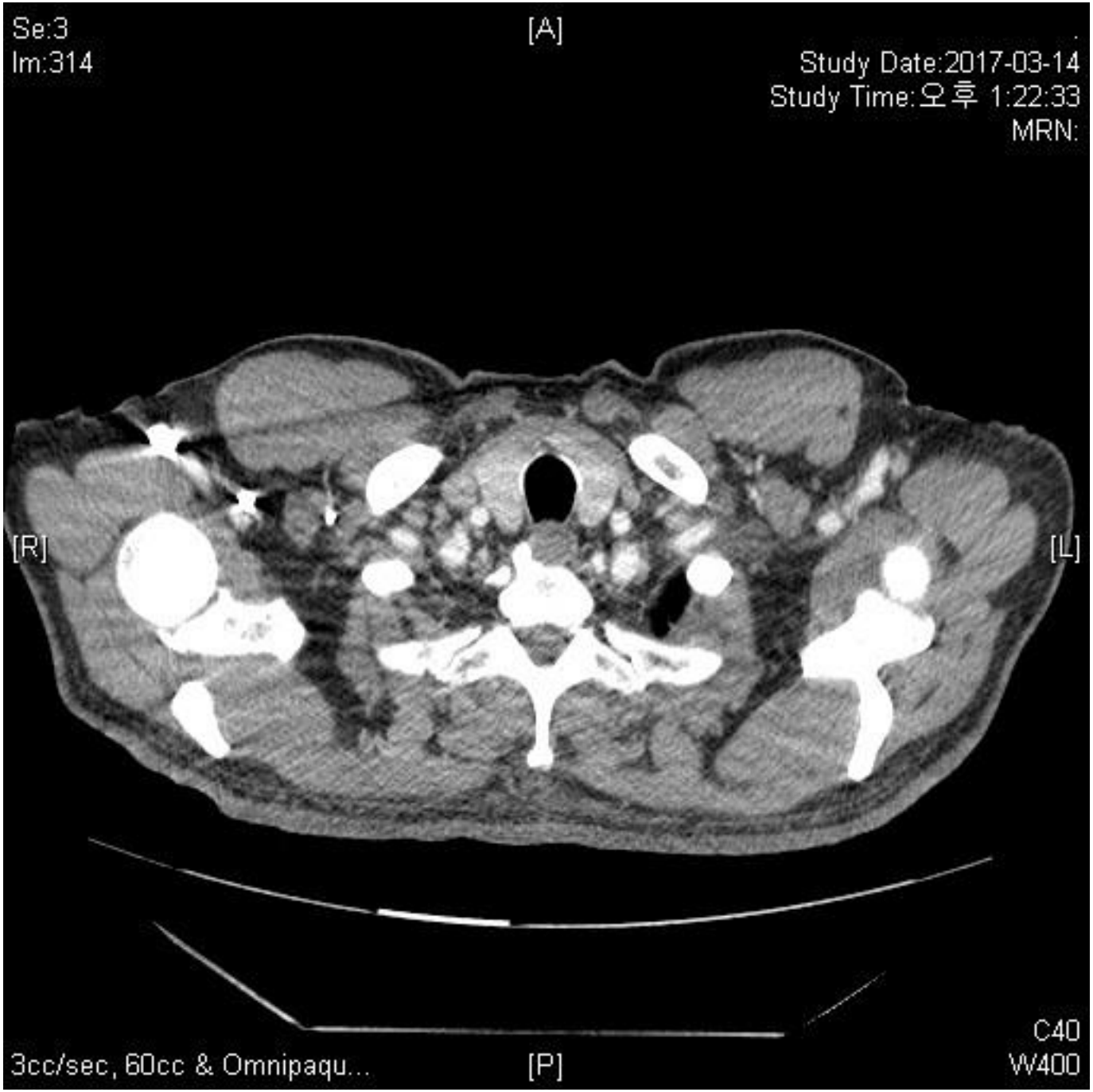
Anatomy of Esophagus



- Hollow viscus from neck to stomach
- 3 layers; mucosa, submucosa, muscle layer
- No serosa, no mesentery
- Abundant submucosal lymphatic network

Related Structures

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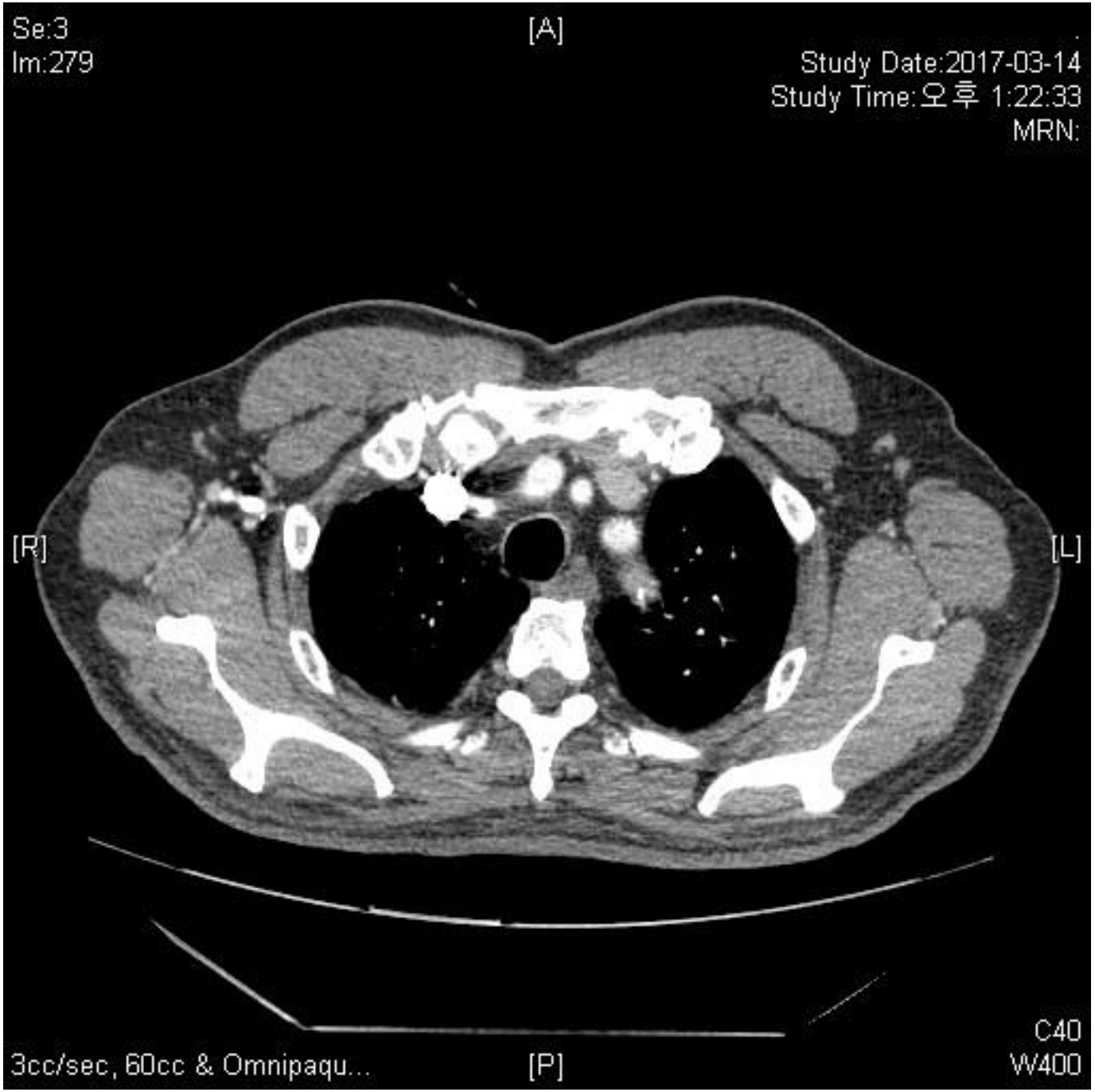
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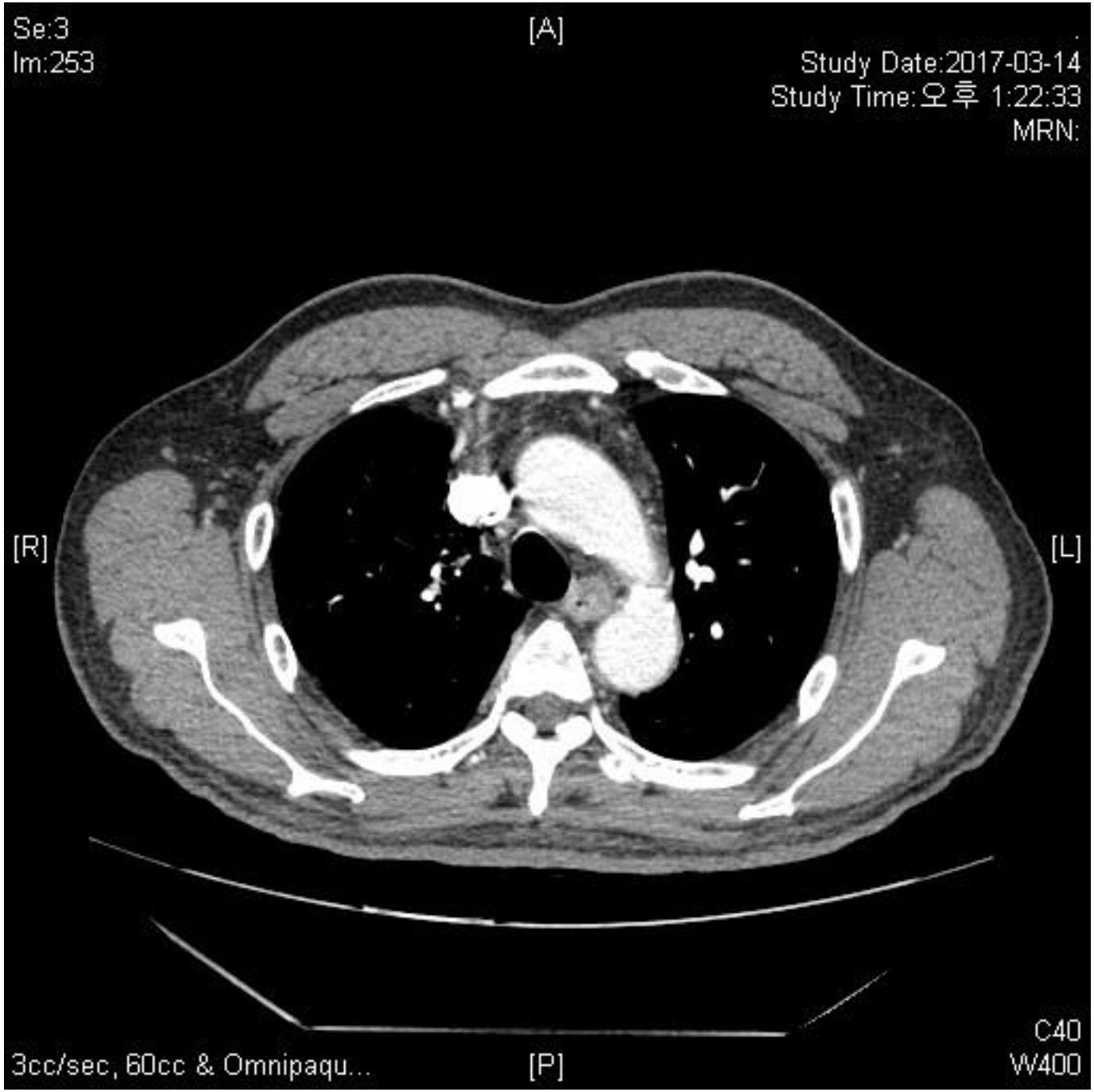
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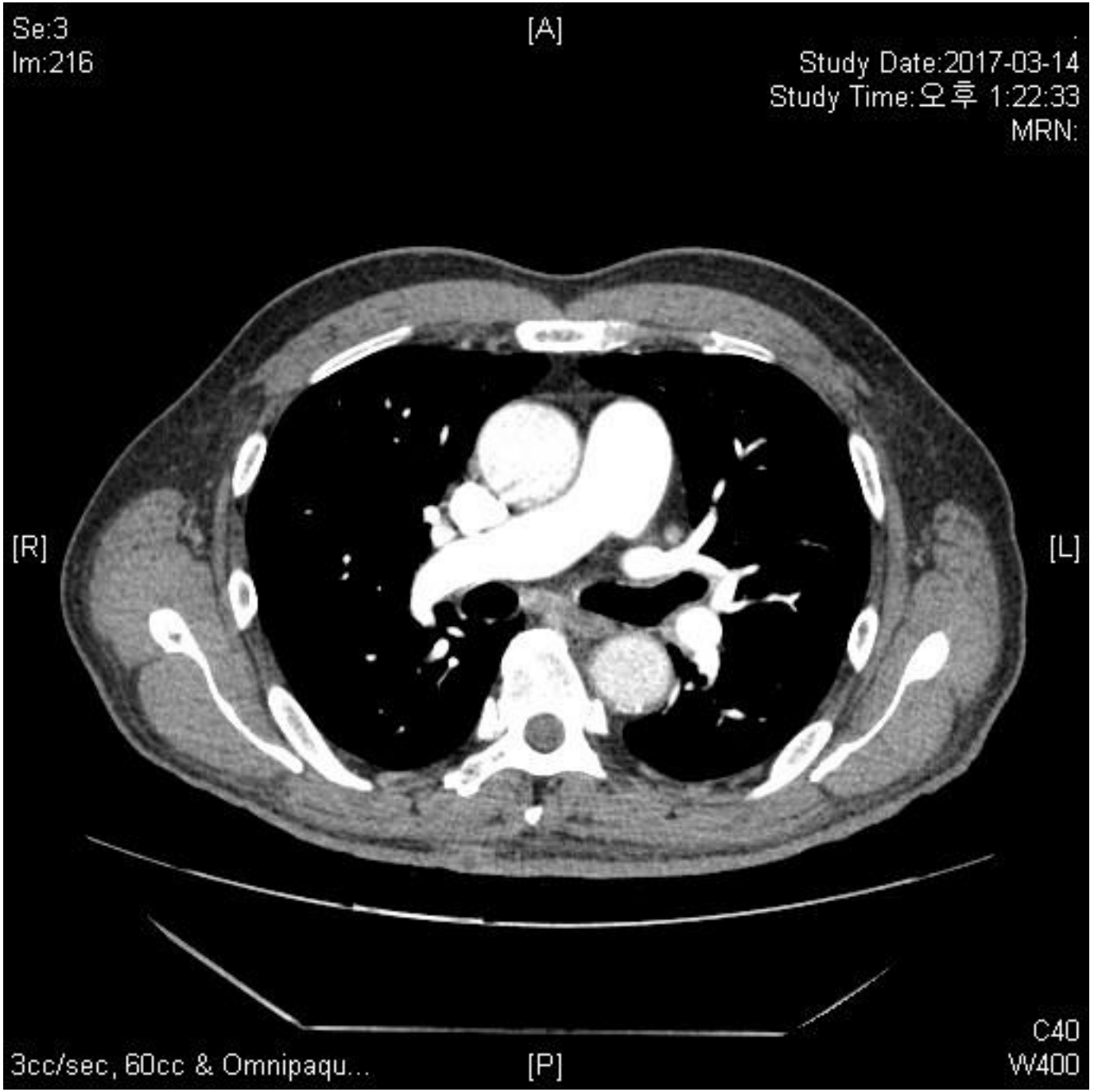
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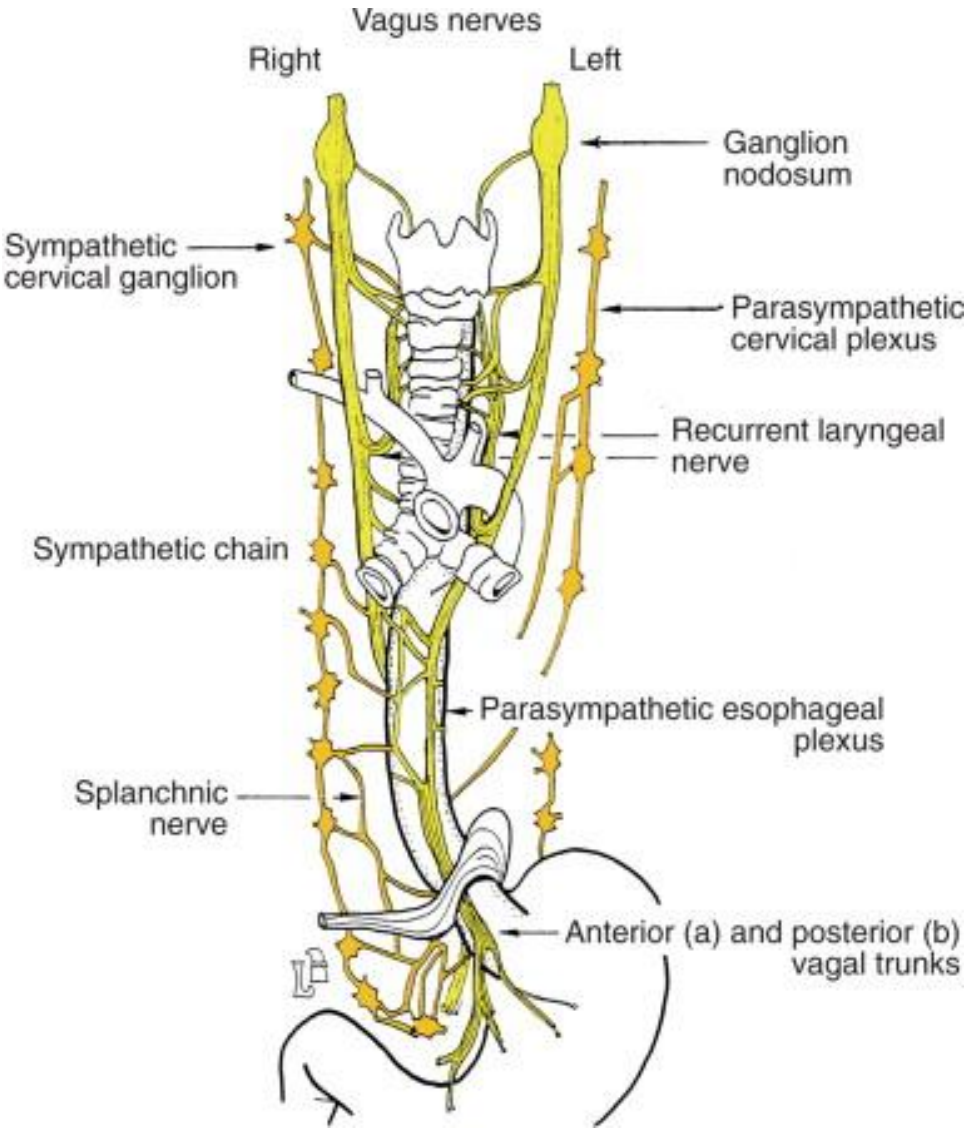
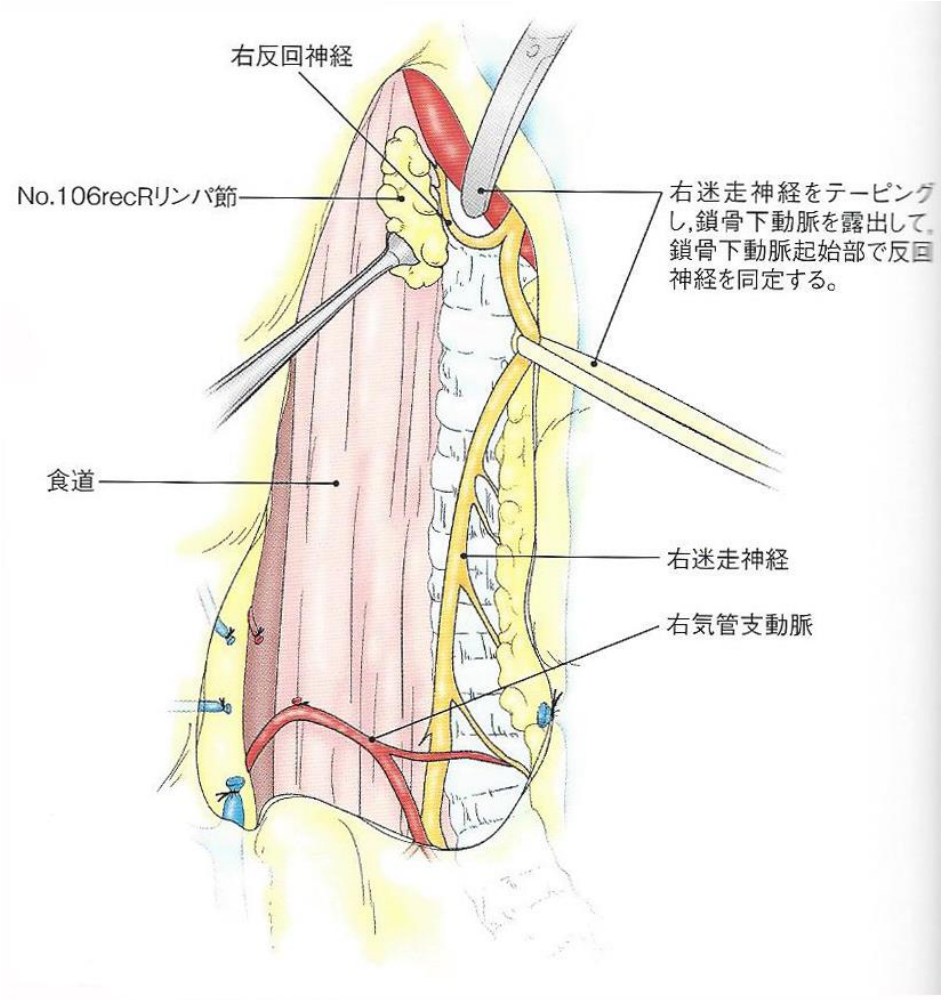
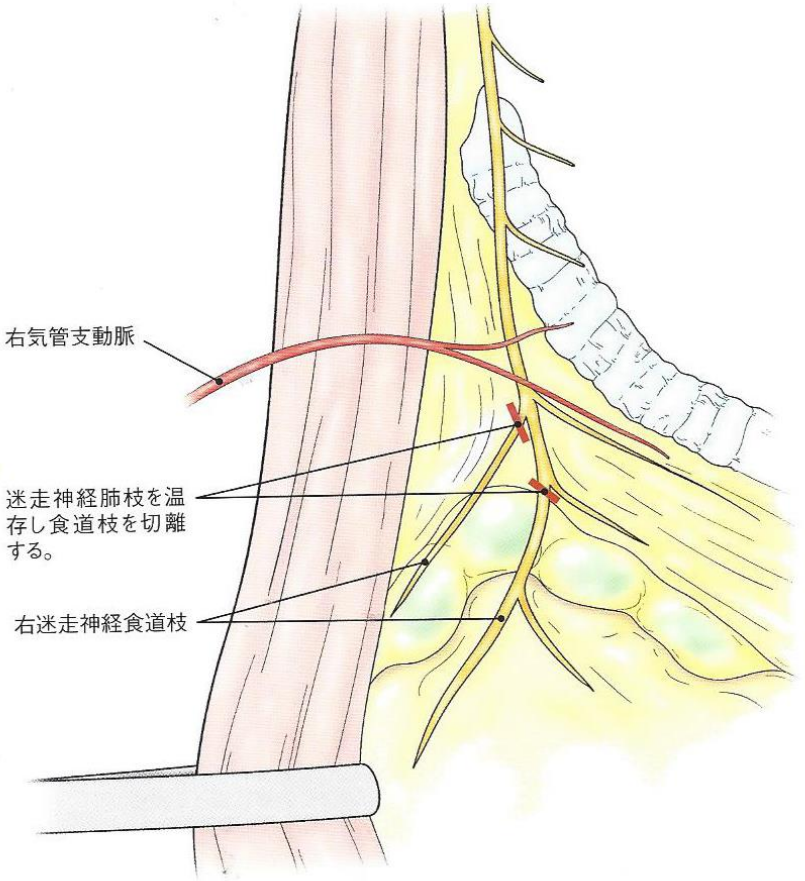
Nerve innervation

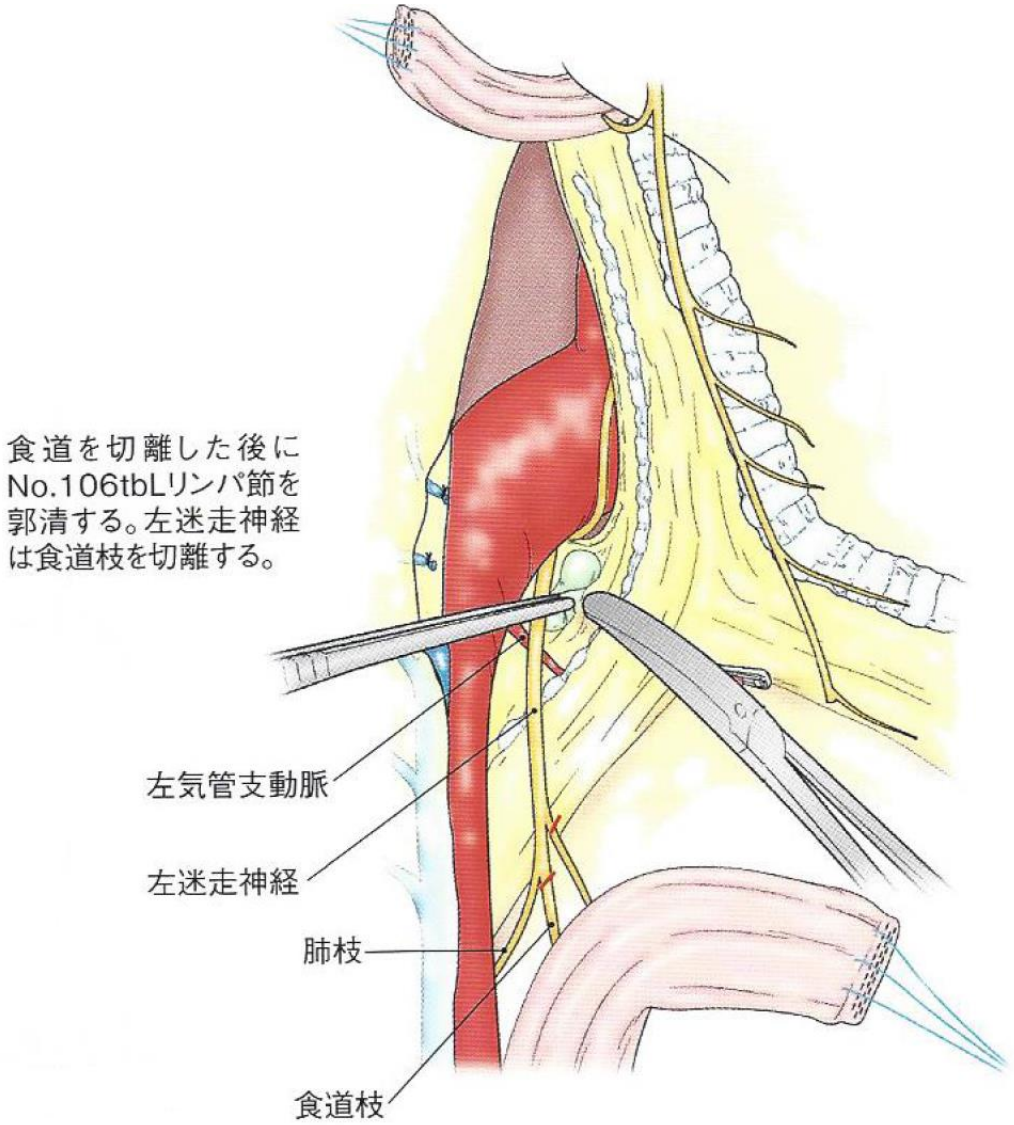


Right recurrent laryngeal nerve

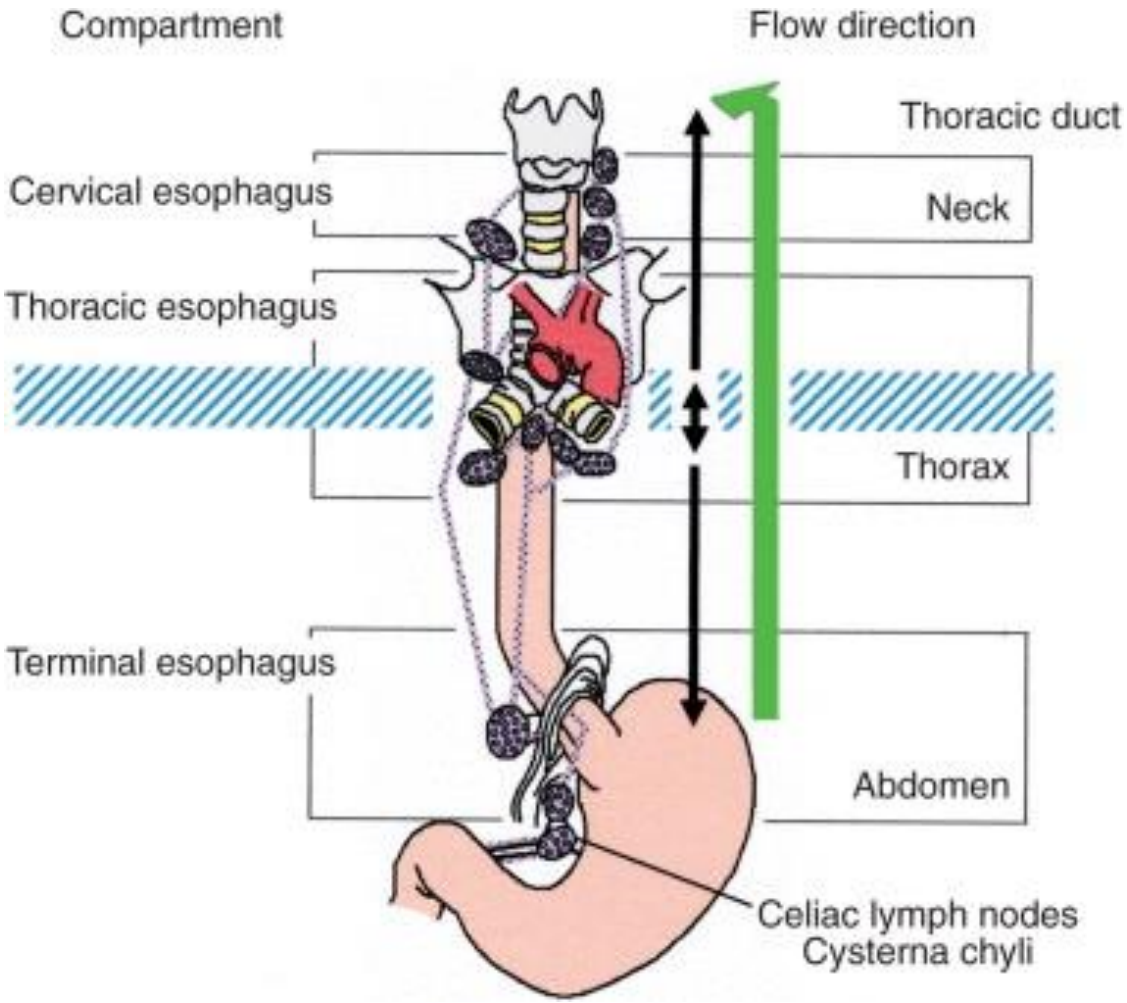




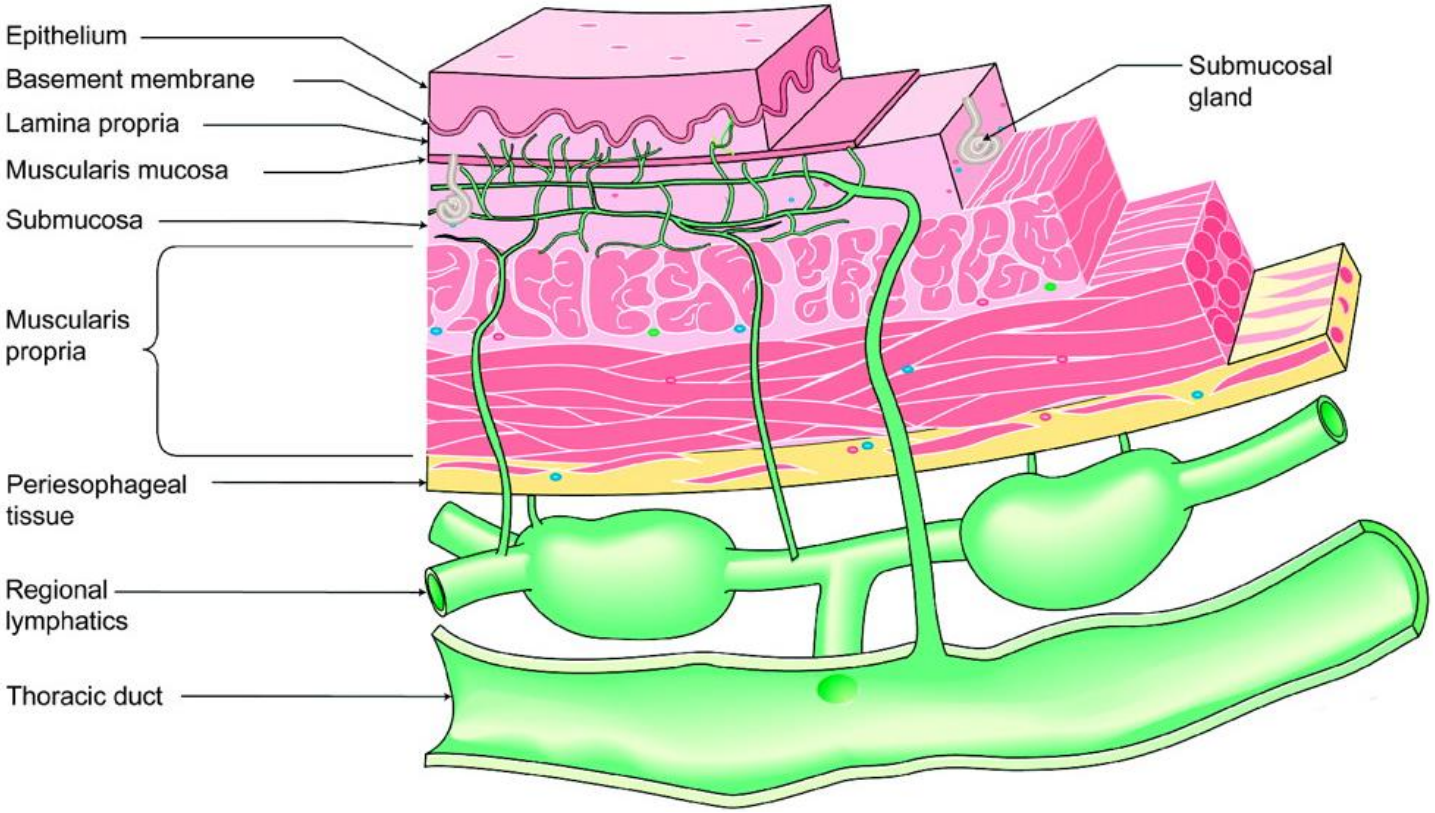
Left recurrent laryngeal nerve



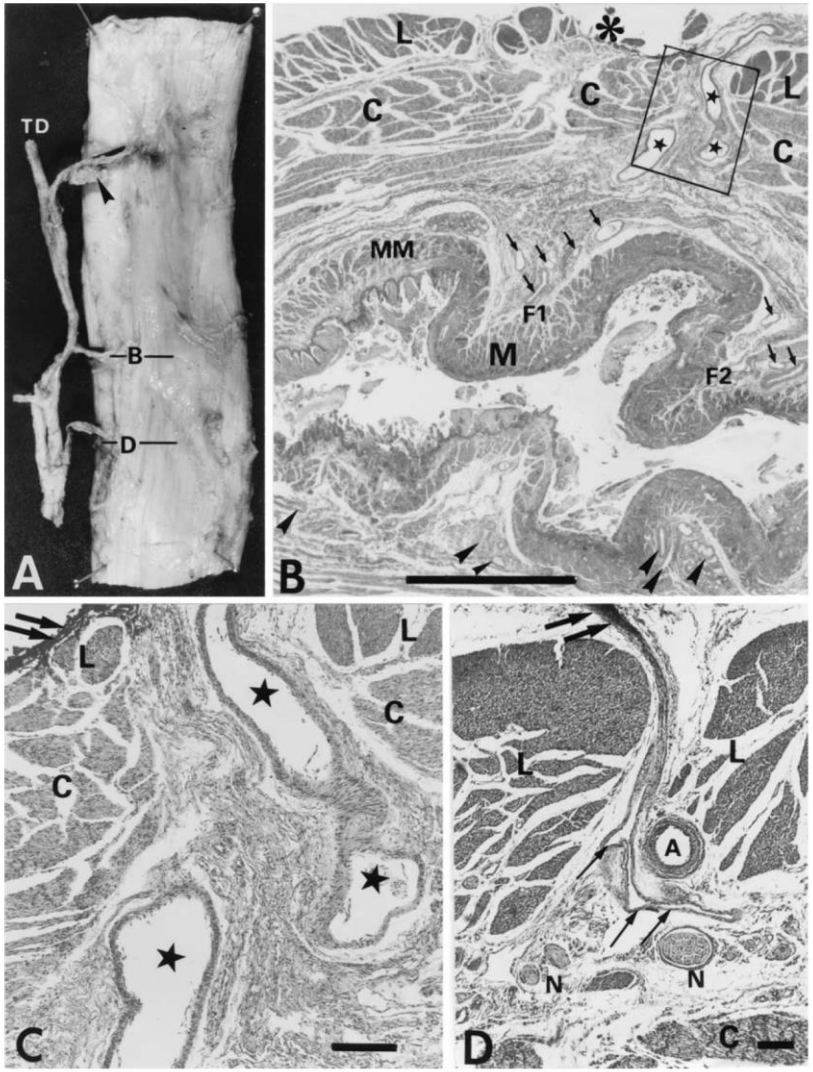
Bidirectional lymphatic drainage



Submucosal lymphatic plexus



Direct drainage to thoracic duct



Kuge et al. JTCVS 2003

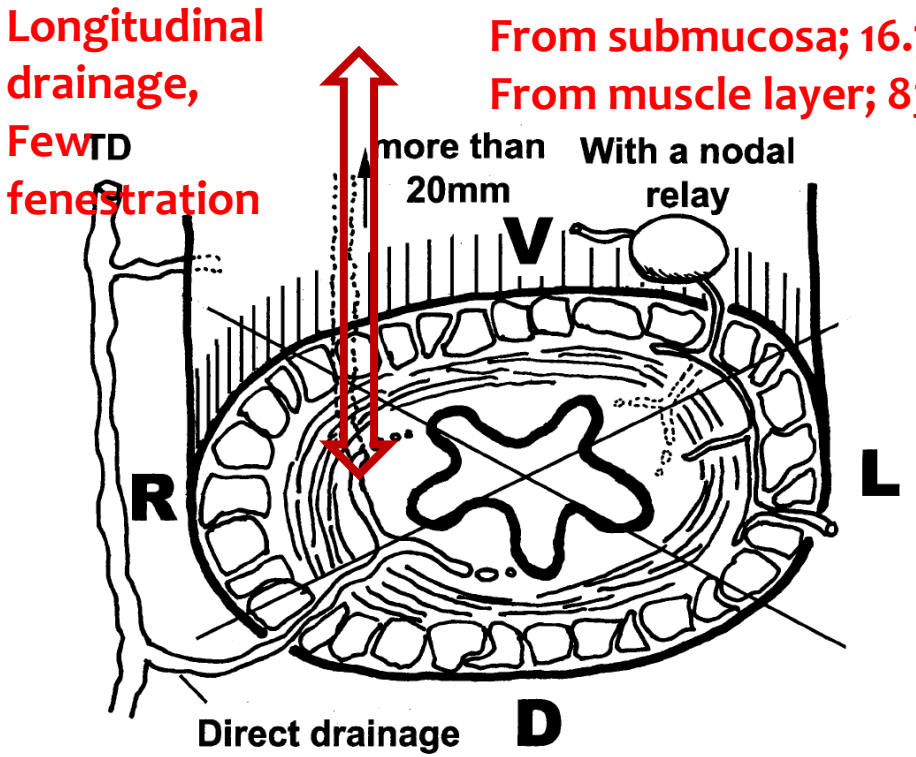
- Cadaver dissection; 75 cases
- Direct communication from submucosal lymphatic plexus to thoracic duct via complete muscle gap; 17 of 75 (22.7%)
- This communication might be related to early skip metastasis in some cases

Lymphatic drainage to the regional LN

- The lymphatic drainage from intermuscular layer to the regional LN (paraesophageal LN) was observed in 5/6 patients; 83.3%

- The lymphatic drainage from submucosal layer to regional LNs; 16.7%

Lymphatic drainage by Kuge

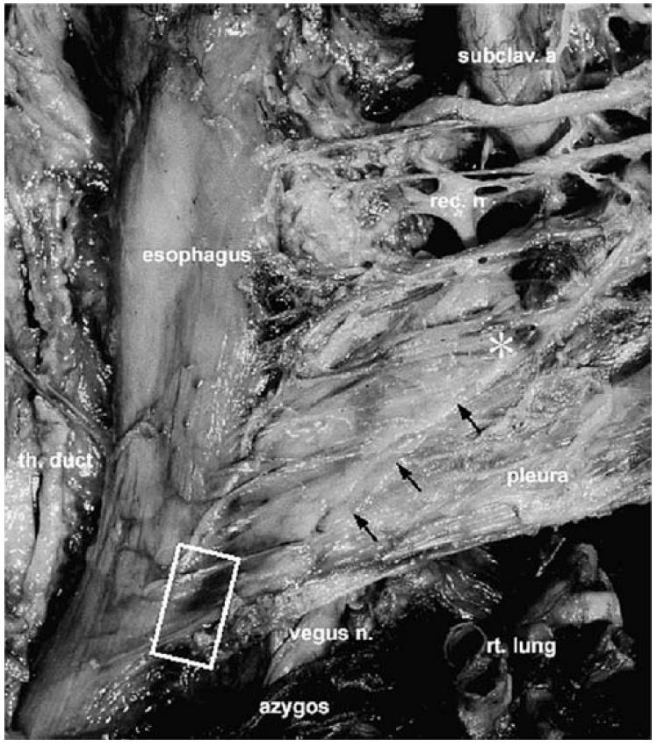


Direct drainage from submucosa to thoracic duct; 22.7%

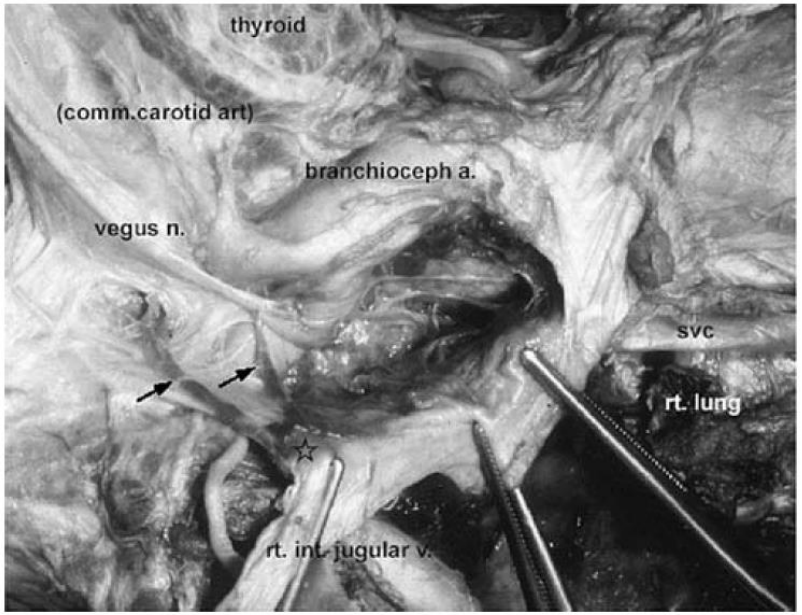
- Direct communication from submucosal lymphatic plexus to thoracic duct via complete muscle gap can be a source of skip, distant metastasis in early ESCC
- Regional LN metastasis could be developed usually in T2-3 ESCC, not in T1

Kuge et al. JTCVS 2003

Communication to RecLN



12/20; 60%

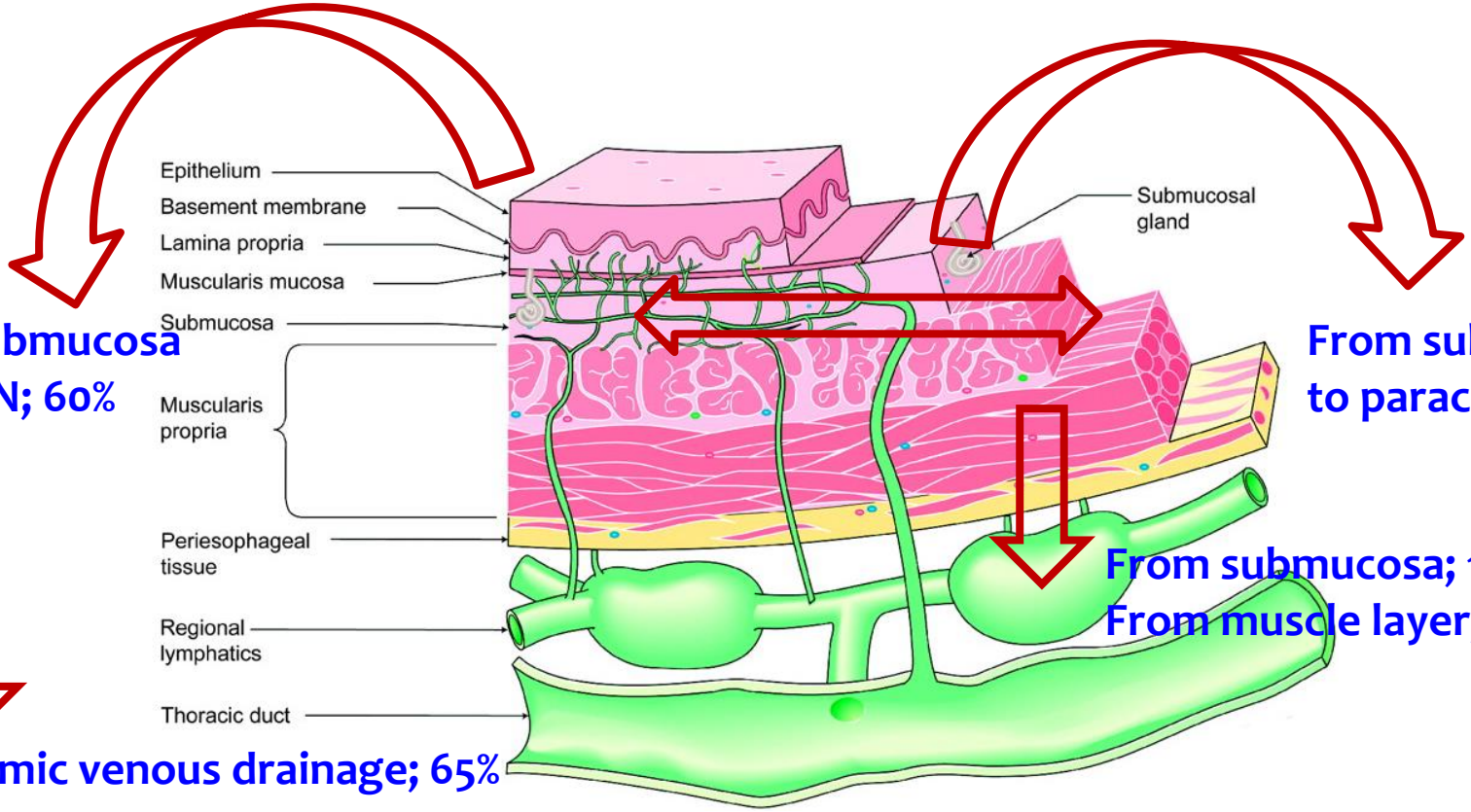


13/20; 65%

Mizutani et al. Surg Radiol Anat 2006

- Cadaver dissection; 20 cases
- Submucosal lympathic plexus to right RecLN (thorough TE groove); 60%
- Right RecLN to venous system (right subclavian vein); 65%

Schematic lymphatic drainage



From submucosa to RecLN; 60%

From submucosa to paracardial LN

From submucosa; 16.7%
From muscle layer; 83.3%

to systemic venous drainage; 65%

Direct drainage from submucosa to thoracic duct; 22.7%

Clinical characteristics of esophageal cancer and Patterns of lymph node metastasis

WHO classification of Esophageal Cancer

- Squamous
  - Squamous intraepithelial neoplasia
  - Squamous cell carcinoma
  - Basaloid squamous cell carcinoma
  - Adenosquamous cell carcinoma
  - Spindle cell squamous carcinoma
  - Verrocous squamous carcinoma
  - Undifferentiated carcinoma with squamous component
- Adenocarcinoma
  - Glandular dysplasia
  - Adenocarcinoma
  - Adenoid cystic carcinoma
  - Mucopidermoid carcinoma
  - Mixed adenoneuroendocrine carcinoma
  - Undifferentiated carcinoma with gladular component
- Others
  - Neuroendocrine tumor
  - NET G2
  - Large cell NEC
  - Small cell NEC

Squamous cell ca. vs. Adenocarcinoma

	Esophageal Squamous cell carcinoma	Esophageal adenocarcinoma
Region	East Asia	Western
Location	Upper, Mid	Distal, EG junction
Cause	Repeated expose to carcinogen Alcohol, smoking	Barrett's esophagus Acid reflux Obesity
Patterns of lymph node metastasis	Skip metastasis	Regional lymph node metastasis

LN metastasis patterns in ESCC

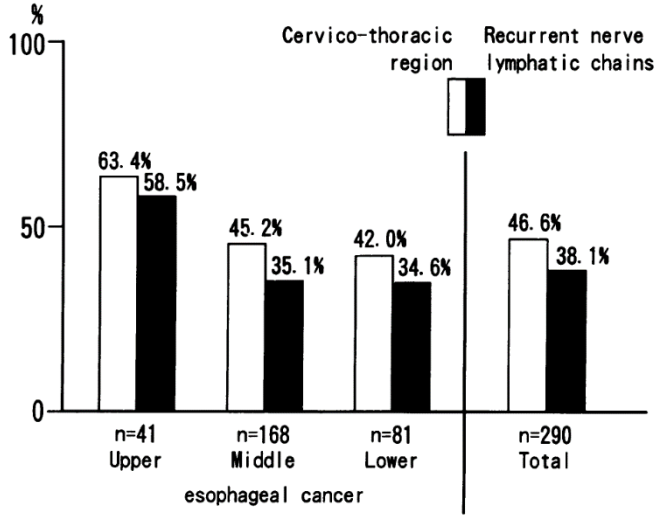
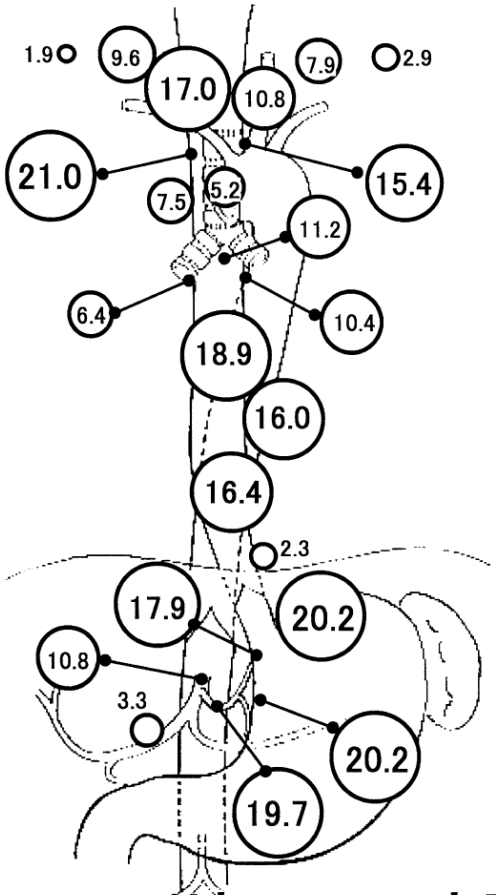


Figure 5. Frequency of lymph node metastases to the cervicothoracic region and specifically, recurrent nerve lymphatic chains (three-field dissection).

Akiyama et al. Ann Surg 1994



Udagawa et al. Dis Esoph 2001

Patterns of LN metastasis in ESCC

Table 2 Primary tumor location and areas of nodal metastases in 127 patients with tumor limited to within the submucosa (pT1)

	Tumor location			
Area	Upper (n = 22) (%)	Mid (n = 67) (%)	Lower (n = 38) (%)	Total (n = 127) (%)
Supraclavicular	3 (13.6)	8 (11.9)	–	11 (8.7)
Upper mediastinal	12 (54.5)	15 (22.4)	5 (13.2)	32 (25.2)
Mid-mediastinal	1 (4.5)	4 (6.0)	2 (5.3)	7 (5.5)
Lower mediastinal	–	6 (9.0)	2 (5.3)	8 (6.3)
Perigastric	–	16 (23.9)	15 (39.5)	31 (24.4)
Celiac	–	2 (3.0)	–	2 (1.6)

Table 3 Primary tumor location and areas of nodal metastases in 229 patients with tumor invading into or through the muscularis propria (pT2-4)

	Tumor location			
Area	Upper (n = 33) (%)	Mid (n = 106) (%)	Lower (n = 90) (%)	Total (n = 229) (%)
Supraclavicular	7 (21.2)	27 (25.5)	5 (5.6)	39 (17.0)
Upper mediastinal	28 (84.8)	65 (61.3)	24 (26.7)	117 (51.1)
Mid-mediastinal	2 (6.1)	52 (49.1)	21 (23.3)	75 (32.8)
Lower mediastinal	2 (6.1)	27 (25.5)	24 (26.7)	53 (23.1)
Perigastric	2 (6.1)	57 (53.8)	59 (65.6)	118 (51.5)
Celiac	–	5 (4.7)	8 (8.9)	13 (5.7)

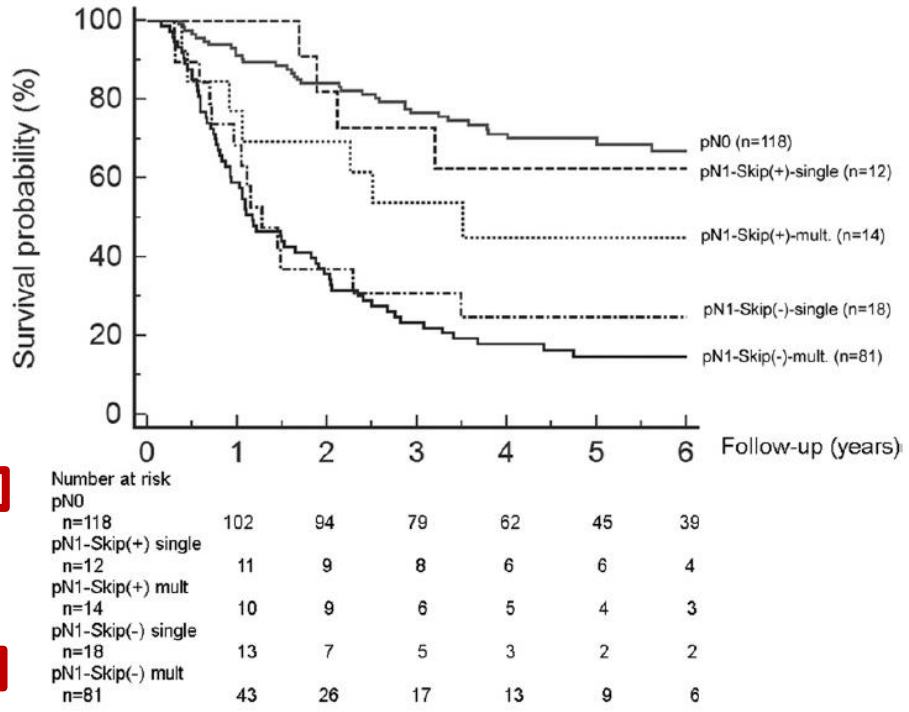
Tachimori et al. Dis Esoph 2010

Skip metastasis

Table 2. Incidence of Skip Metastasis of 128 Patients With Lymph Node Metastasis (pN1) Esophageal Cancer According to Clinical Variables

Variable	Skip(+), n = 26	Skip(−), n = 102	*p* Value
Sex			0.38
Female	6 (30%)	14 (70%)	
Male	20 (19%)	88 (81%)	
Histology			0.171
AC	10 (15%)	57 (85%)	
SCC	16 (20%)	45 (80%)	
T Status			0.032
pT1	9 (39%)	14 (61%)	
pT2	5 (22%)	17 (78%)	
pT3	12 (14%)	71 (86%)	
Tumor localization			0.022
Middle/upper third	11 (37%)	19 (63%)	
Lower third	15 (15%)	83 (85%)	

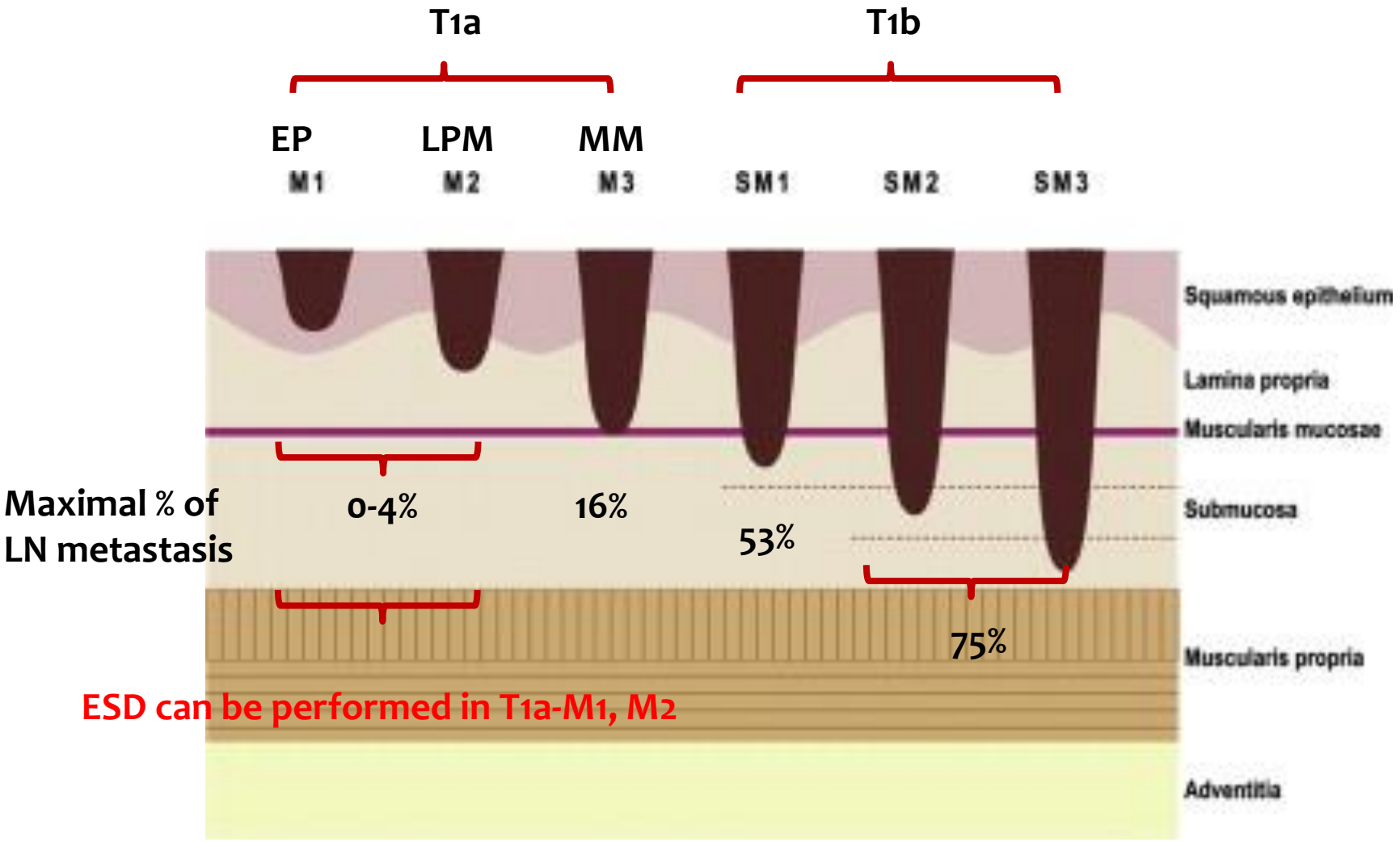
AC = adenocarcinoma; SCC = squamous cell carcinoma.



Prenzel et al. Ann Thorac Surg 2010

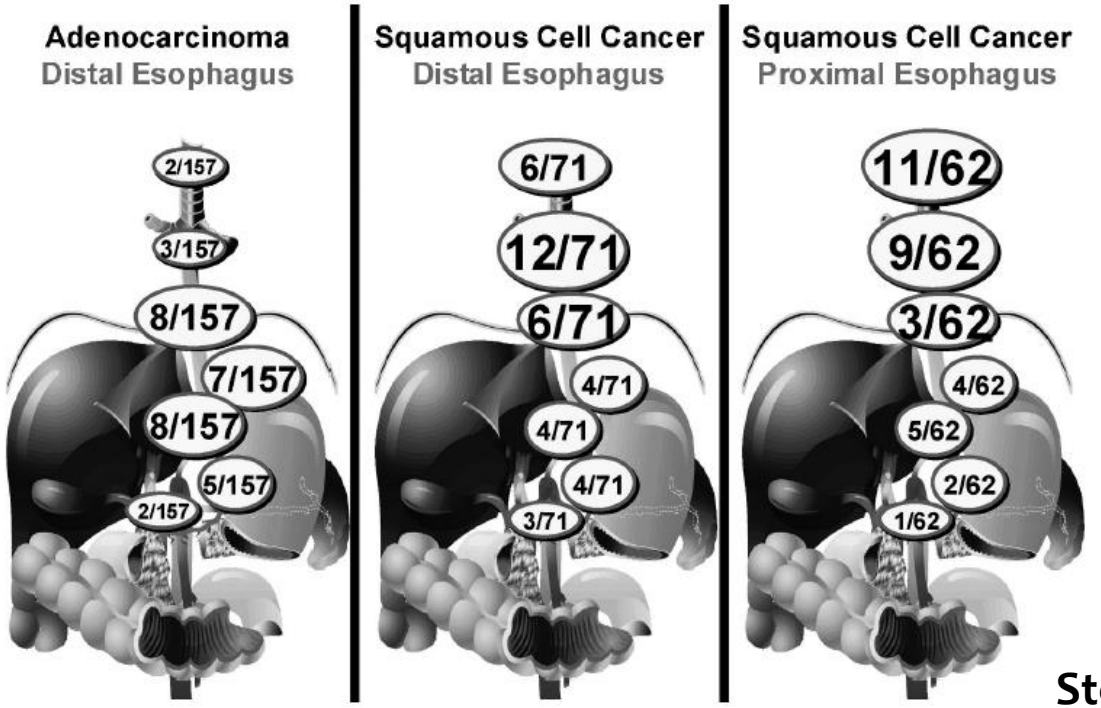
- 128 patients with node metastasis
- 20% skip metastasis among the all metastasis
- The skip metastasis is more frequent in pT1 and middle/upper

LN metastasis in superficial ESCC



Shimizu et al. Best Practice & Research Clinical Gastroenterology 2013

Early ESCC vs. Early EA



Stein et al. Ann Surg 2005

- Analyzed 290 patients with early esophageal cancer
- Frequent early distant metastasis in early ESCC, but rare early distant metastasis in esophageal adenocarcinoma
- Hypothesis; repeated inflammation and metaplasia in adenocarcinoma interrupts submucosal lymphatic networks

Staging of Esophageal Cancer

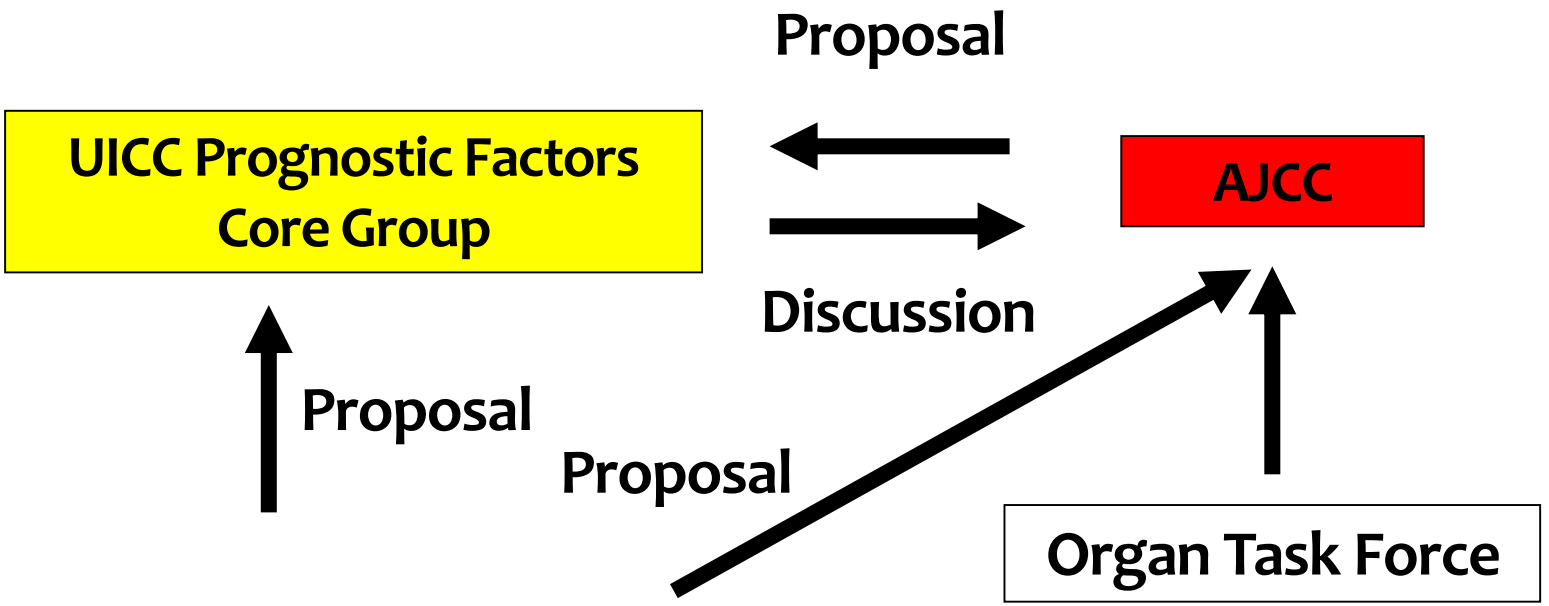
General Rules of the TNM System

- The TNM system for describing the anatomical extent of disease is based on the assessment of three components;
  - T; The extent of the primary tumor
  - N; The absence or presence and extent of regional lymph node metastasis
  - M; The absence or presence of distant metastasis

  - Stage grouping based on TNM

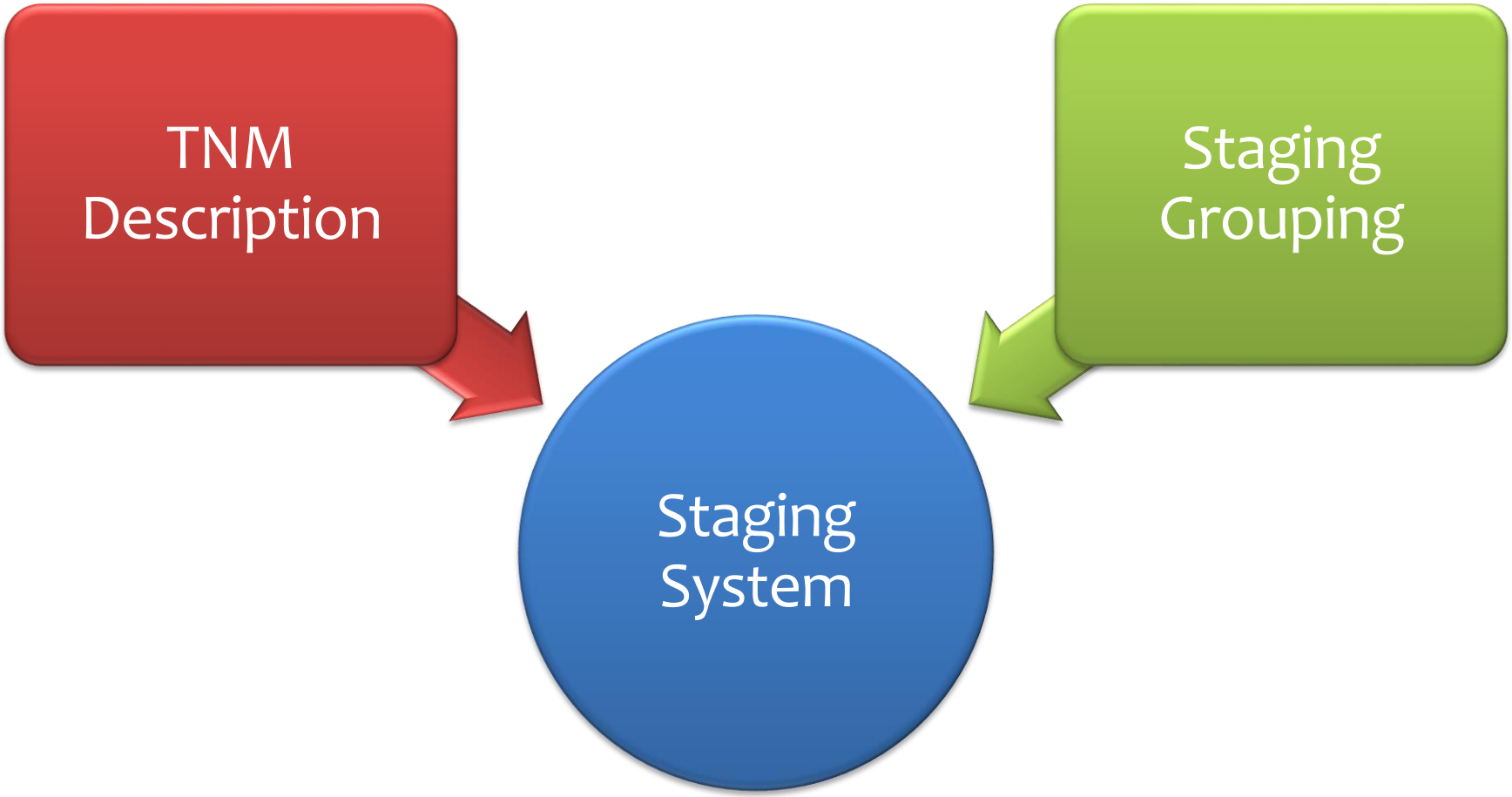
- Purpose of TNM system
  - To predict the prognosis
  - To establish the treatment plan
  - To communicate with other medical centers

Mechanism of revision: UICC and AJCC



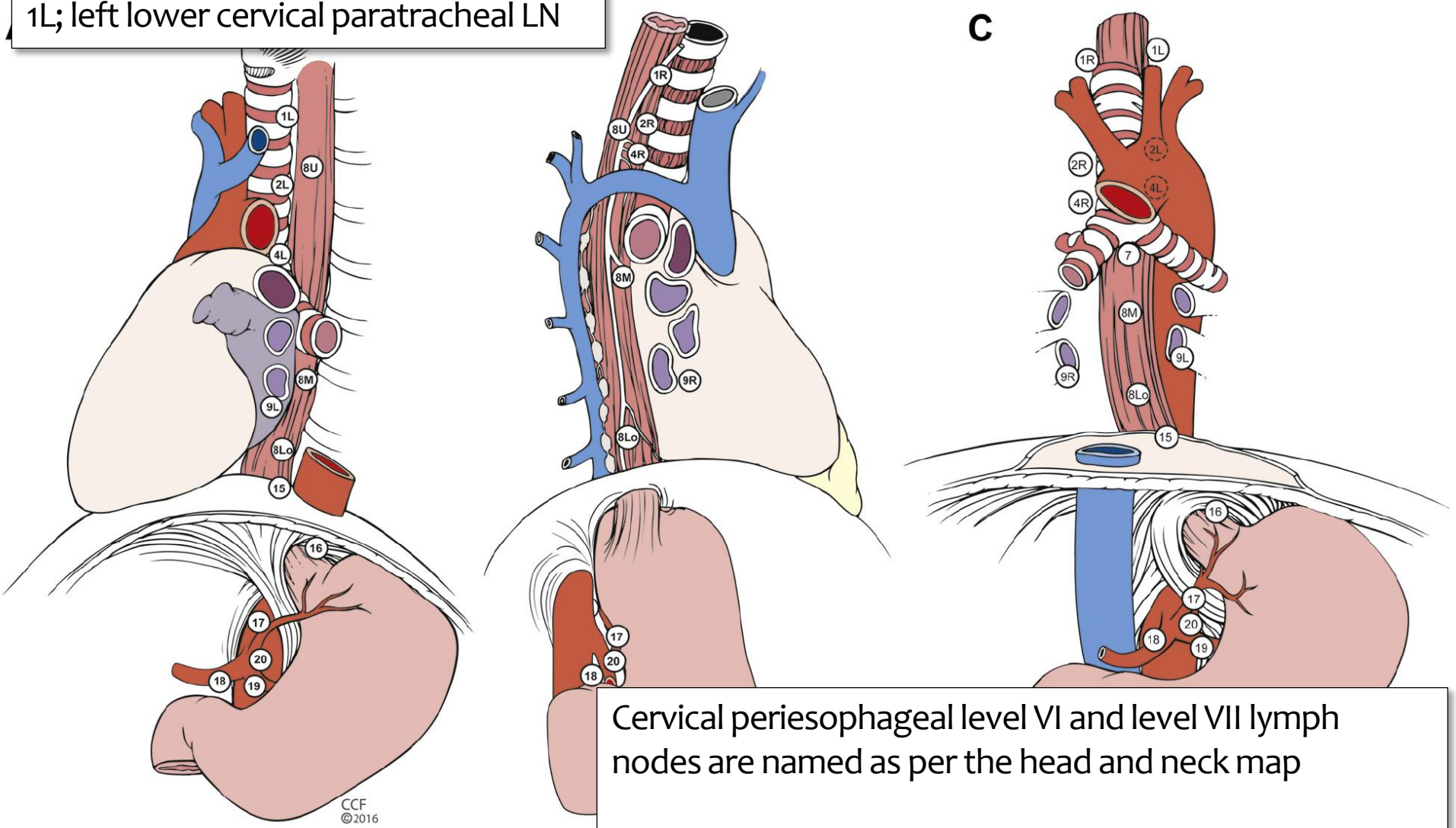
IASLC: International Association for the Study of Lung Cancer
FIGO: International Federation of Gynecology and Obstetrics
WECC: Worldwide Esophageal Cancer Collaboration

Staging System



8th AJCC Lymph Node Map

1R; right lower cervical paratracheal LN
1L; left lower cervical paratracheal LN



Cervical periesophageal level VI and level VII lymph nodes are named as per the head and neck map

Supraclavicular LN is not regional LN in AJCC 8th edition

Definition of EG Junction Cancer

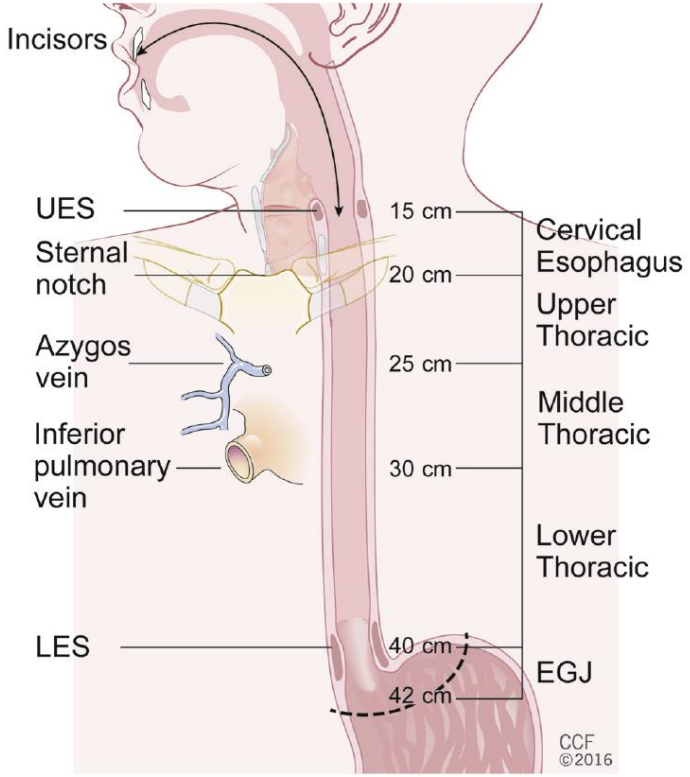


Figure 3. Location of esophageal cancer primary site, including typical endoscopic measurements of each region measured from the incisors. Exact measurements depend on body size and height. Location of cancer primary site is defined by cancer epicenter. Cancers involving the esophagogastric junction (EGJ) that have their epicenter within the proximal 2 cm of the cardia (Siewert types I/II) are to be staged as esophageal cancers. Cancers whose epicenter is more than 2 cm distal from the EGJ, even if the EGJ is involved, will be staged using the stomach cancer TNM and stage groups. LES, lower esophageal sphincter; UES, upper esophageal sphincter.

- 7th edition
  - Epicenter within the proximal 5cm of the cardia
  - Siewert type I / II / III
- 8th edition
  - Epicenter within the proximal 2cm of the cardia
  - Siewert type I / II

T staging

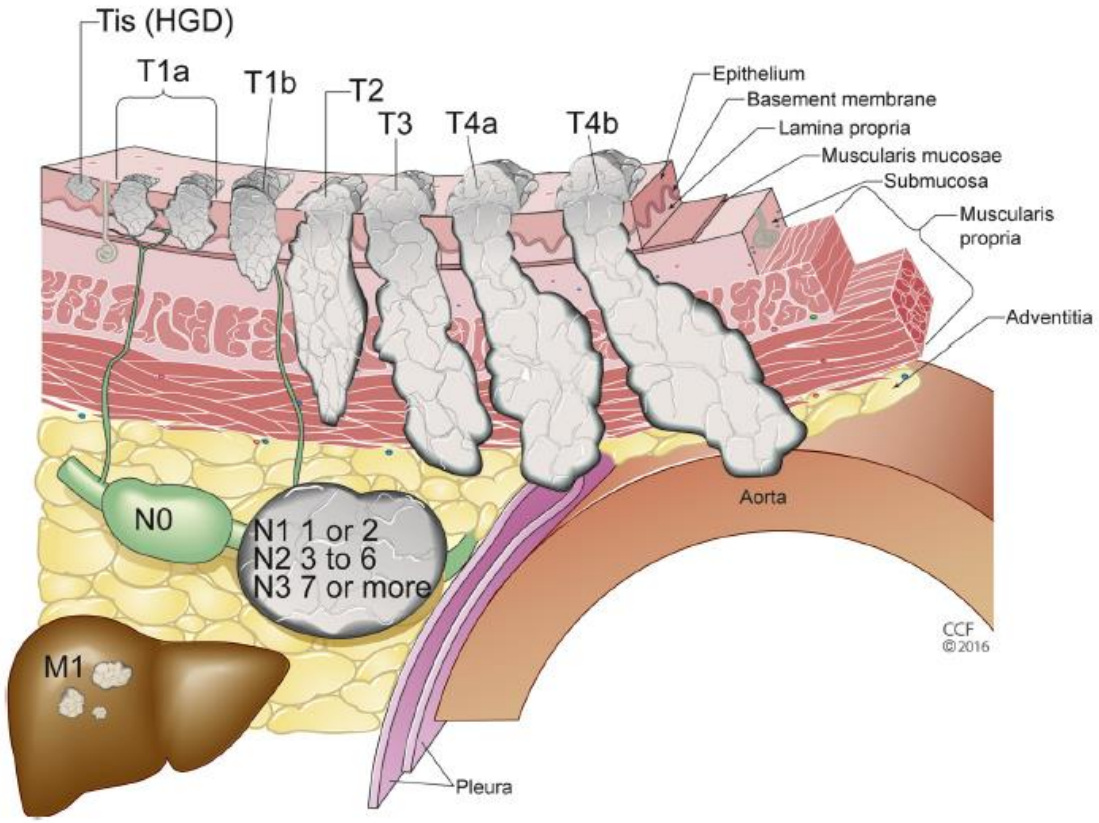


Figure 1. Eighth edition TNM categories. T is categorized as Tis: high-grade dysplasia (HGD). T1 is cancer that invades the lamina propria, muscularis mucosae, or submucosa and is subcategorized into T1a (cancer that invades the lamina propria or muscularis mucosae) and T1b (cancer that invades the submucosa); 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).

8th edition of AJCC / UICC staging

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

Category	Criteria
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
N category	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1-2 regional lymph nodes
N2	Metastasis in 3-6 regional lymph nodes
N3	Metastasis in $\geq$7 regional lymph nodes
M category	
M0	No distant metastasis
M1	Distant metastasis

[a]Subcategories.
[b]If further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3.
[c]If further testing of "undifferentiated" cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.
[d]Location is defined by epicenter of esophageal tumor.

8th edition of AJCC / UICC staging

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
Squamous cell carcinoma L category[d]	
LX	Location unknown
Upper	Cervical esophagus to lower border of the azygos vein
Middle	Lower border of the azygos vein to lower border of the inferior pulmonary vein
Lower	Lower border of the inferior pulmonary vein to the stomach, including the esophagogastric junction

[a]Subcategories.
[b]If further testing of "undifferentiated" cancers reveals a glandular component, categorize as adenocarcinoma G3.
[c]If further testing of "undifferentiated" cancers reveals a squamous cell component or if after further testing they remain undifferentiated, categorize as squamous cell carcinoma G3.
[d]Location is defined by epicenter of esophageal tumor.

Stage Grouping - pTNM

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	IIA				
T2	G1	IC	IIIA	IIIB	IVA	IVB
	G2	IIA				
	G3	IIB				
T3		IIB	IIIB	IIIB	IVA	IVB
T4a		IIIB	IIIB	IVA	IVA	IVB
T4b		IVA	IVA	IVA	IVA	IVB

Stage I; T1 sub-category analysis – IA-IC
Stage II; pG3T2N0M0 - IIA
pT1N1M0 meets pT3N0M0 – IIB
Stage III; regrouping and redistribution – no IIIC

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

Stage I; T1 sub-category analysis – IA-IB
Stage IB, IIA, IIB
pT2N0M0 (G1 - IB, IIA)
pT3N0M0 (IIA, IIB - G2-3 U/M)
Stage III ; regrouping and redistribution – no IIIC

Stage Grouping - cTNM

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

Stage 0; cTis
Stage I; cT1N0M0
Stage II; subgrouped IIA cT1N1M0 and IIB cT2N0M0
Stage III; cT2N1M0 and cT3-4aN0M0 unlike cStage SCCa but mirroring pStage III adenocarcinoma
Stage IVA; merging of cN2-3

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

Stage 0; cTis
Stage I ; cT1N0-1M0
Stage II; cT2N0-1M0 plus cT3N0M0 (cStage III adenocarcinomas)
Stage III; cT3N1M0 and cT1-3N2, mirroring pStage IIIA-B squamous cell ca.
Stage IVA; Most advanced cancers are subgrouped
Stage IVB; cM1

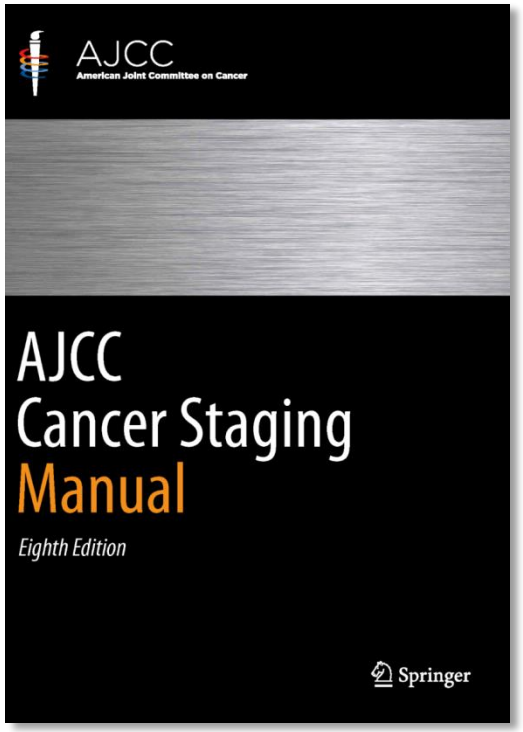
Stage Grouping - ypTNM

ypTNM

	N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB
Tis	I	IIIA	IIIB	IVA	IVB
T1	I	IIIA	IIIB	IVA	IVB
T2	I	IIIA	IIIB	IVA	IVB
T3	II	IIIB	IIIB	IVA	IVB
T4a	IIIB	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

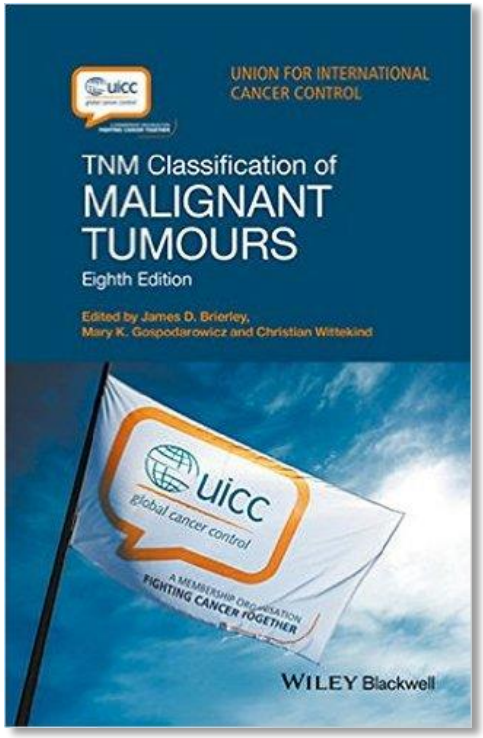
Identical for Adenocarcinoma and Squamous Cell Carcinoma

AJCC vs. UICC Staging System



AJCC
American Joint Committee on Cancer

uicc
global cancer control



WECC: Worldwide Esophageal Cancer Collaboration

UICC Stage Grouping – Squamous cell carcinoma

Clinical Staging

Stage 0	Tis	N0	M0
Stage I	T1	N0, N1	M0
Stage II	T2 T3	N0, N1 N0	M0
Stage III	T1,T2 T3	N2 N1, N2	M0
Stage IVA	T4a, T4b Any T	N0, N1, N2 N3	M0
Stage IVB	Any T	Any N	M1

Pathologic Staging

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T1 T3	N1 N0	M0 M0
Stage IIIA	T1 T2	N2 N1	M0 M0
Stage IIIB	T2 T3 T4a	N2 N1, N2 N0, N1	M0 M0 M0
Stage IVA	T4a T4b Any T	N2 Any N N3	M0 M0 M0
Stage IVB	Any T	Any N	M1

UICC Stage Grouping – Adenocarcinoma

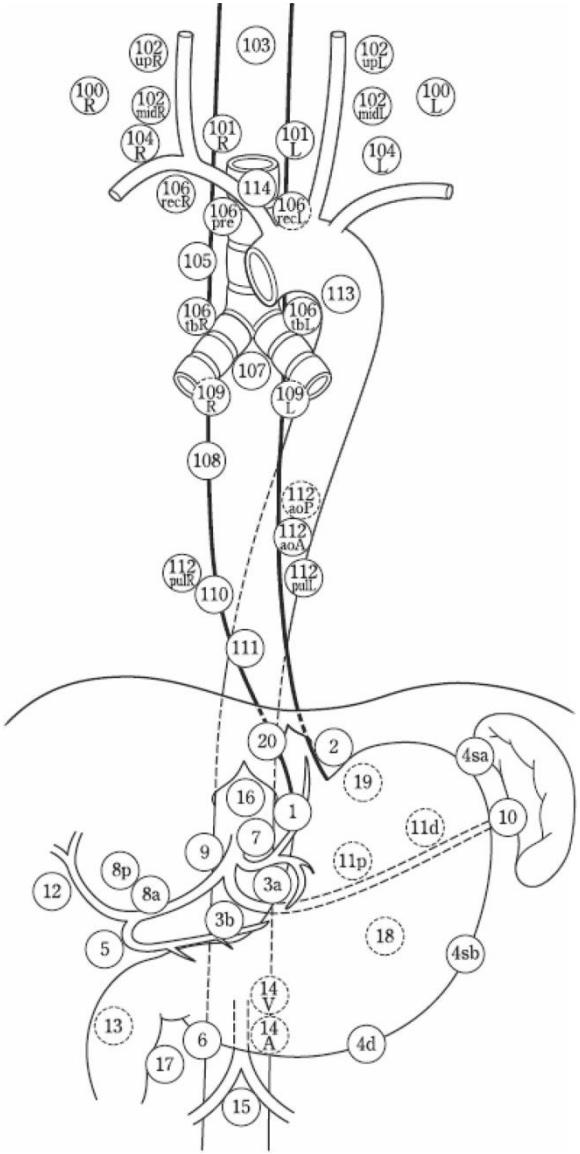
Clinical Staging

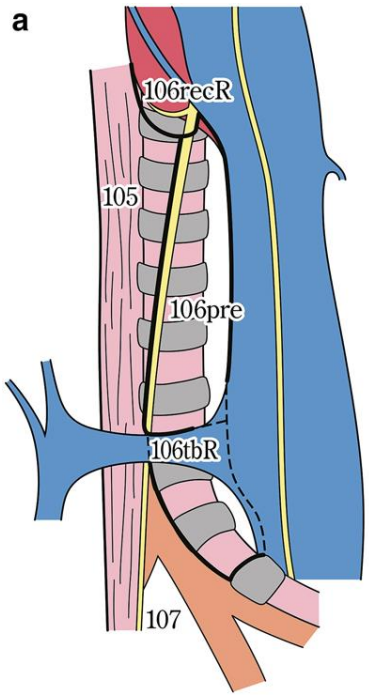
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage IIA	T2	N1	M0
Stage IIB	T2	N0	M0
Stage III	T2 T3, T4a	N1 N0, N1	M0 M0
Stage IVA	T1-T4a T4b Any T	N2 N0, N1, N2 N3	M0 M0 M0
Stage IVB	Any T	Any N	M1

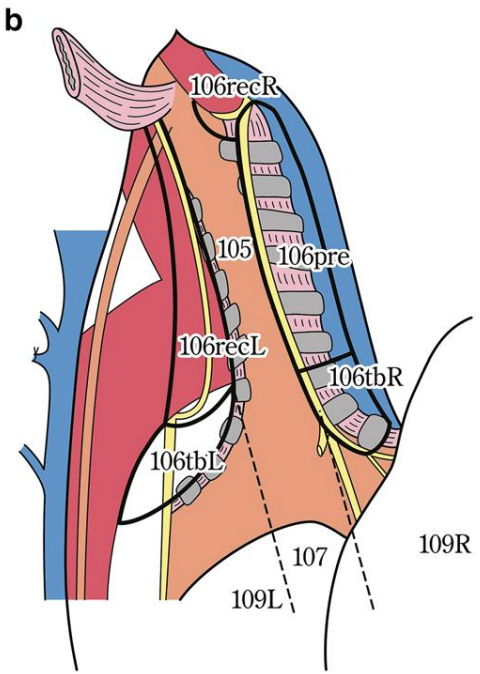
Pathologic Staging

Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
Stage IB	T1b	N0	M0
Stage IIA	T2	N0	M0
Stage IIB	T1 T3	N1 N0	M0 M0
Stage IIIA	T1 T2	N2 N1	M0 M0
Stage IIIB	T2 T3 T4a	N2 N1, N2 N0, N1	M0 M0 M0
Stage IVA	T4a T4b Any T	N2 Any N N3	M0 M0 M0
Stage IVB	Any T	Any N	M1

11th Japanese Classification







11th Japanese Staging

Table 1-6 Lymph node groups according to the location of the tumor

Tumor location	Group 1 (N1)	Group 2 (N2)	Group 3 (N3)
Cervical Ce	101, 106rec[a]	102, 104, 105[a]	100
Upper thoracic Ut	101, 105, 106rec	104, 106tbL, 107, 108, 109	102mid, 106pre, 106tbR, 110, 112aoA, 112pul, 1, 2, 3a, 7, 20
Middle thoracic Mt	106rec, 108, 1, 2, 3a	101, 104, 105, 107, 109, 110, 112aoA, 112pul, 7, 9, 20	106tbL
Lower thoracic Lt	110, 1, 2, 3a, 7, 20	101, 106rec, 107, 108, 109, 112aoA, 112pul, 9	104, 105, 106tbL, 111, 8a, 11p
Abdominal Ae	110, 1, 2, 3a, 7, 20	111, 112aoA, 112pul, 8a, 9, 11p, 19	106rec, 107, 108, 109, 11d

Nodes other than N1 through N3 are expressed as N4

[a] Limited to the area which can be dissected from the cervical incision

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

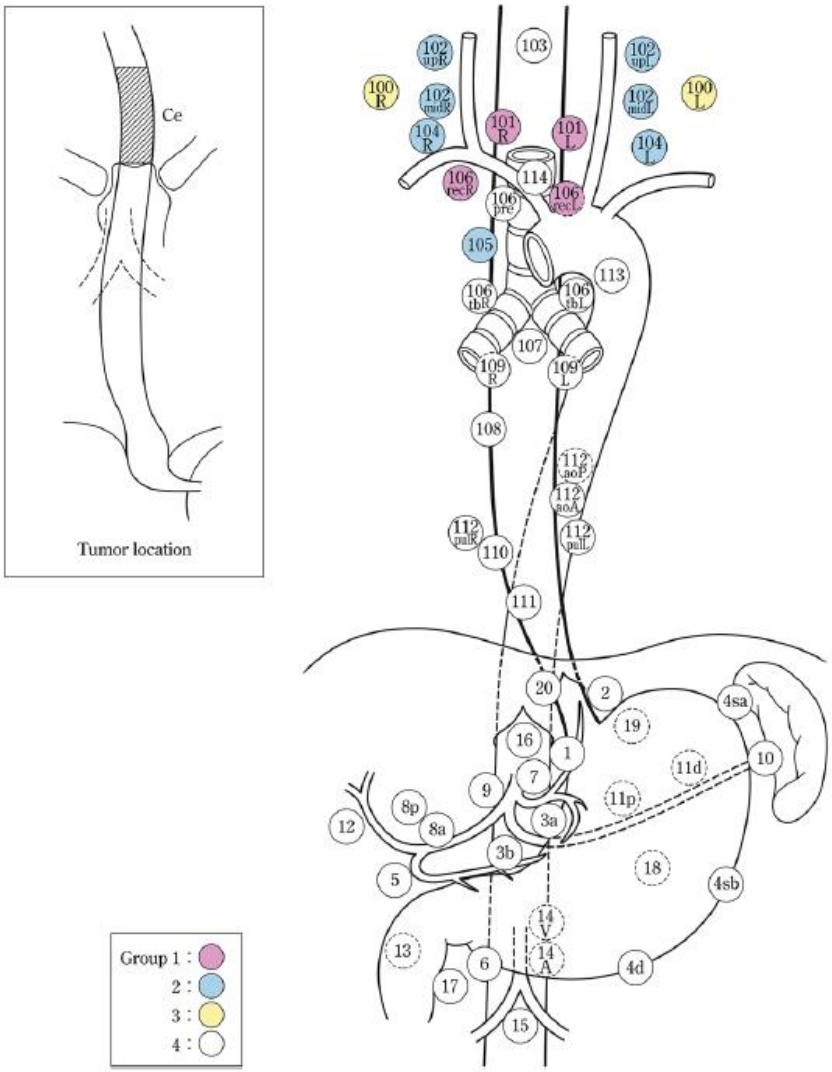


Fig. 1-8 Lymph node groups for tumors located in Ce

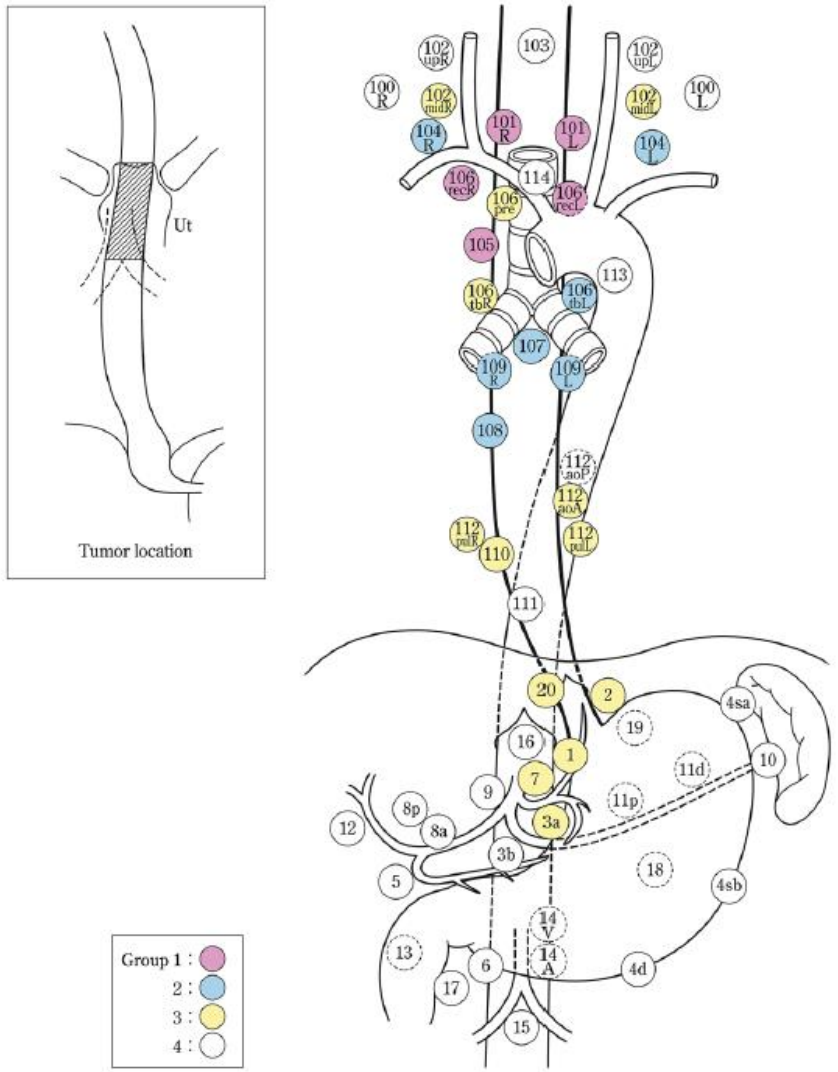


Fig. 1-9 Lymph node groups of tumors located in Ut

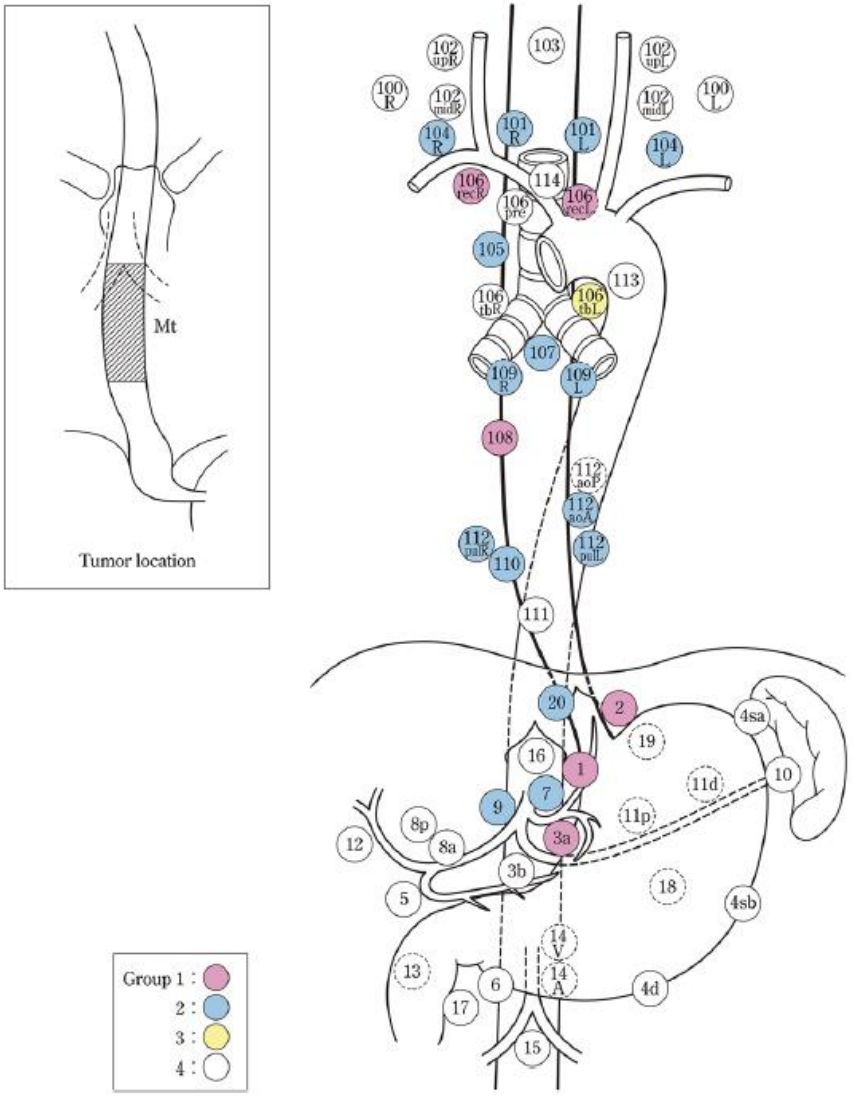


Fig. 1-10 Lymph node groups for tumors located in Mt

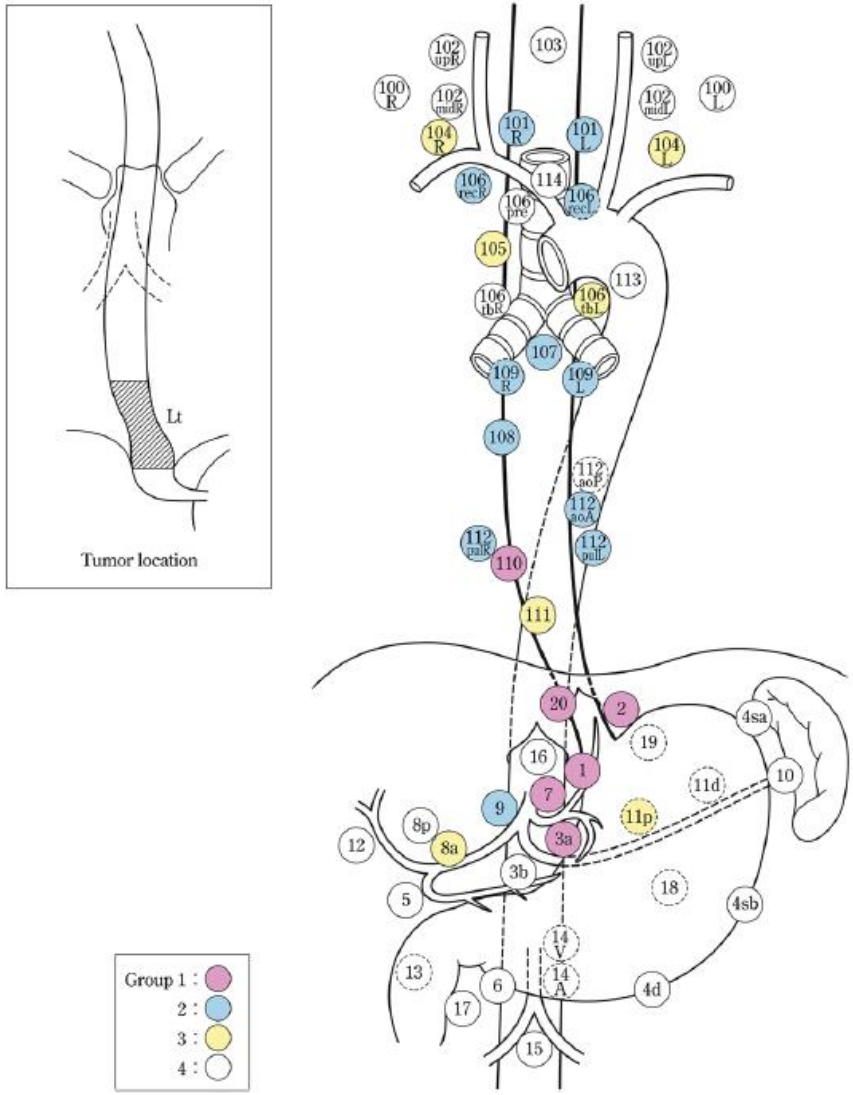


Fig. 1-11 Lymph node groups for tumors located in Lt

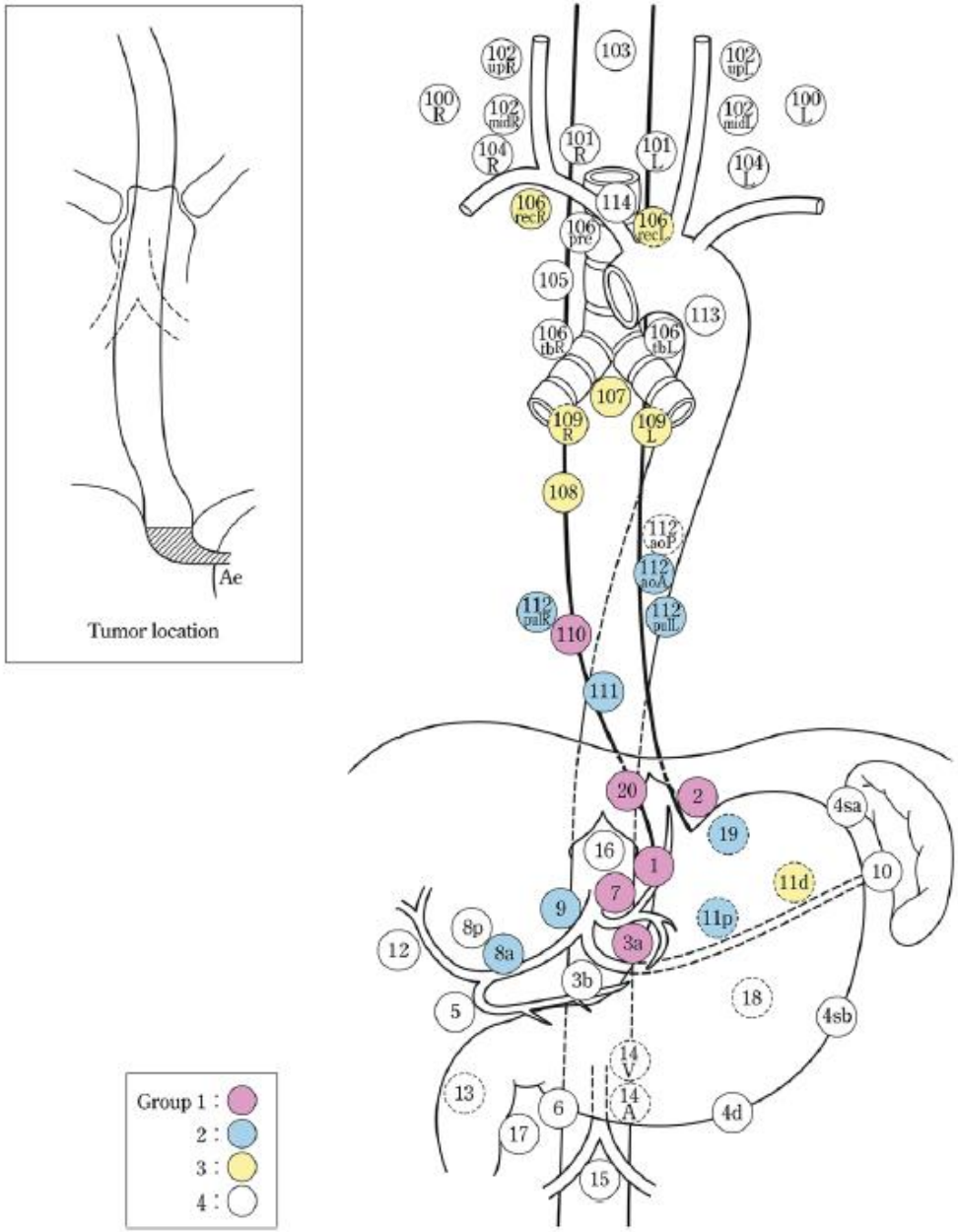


Fig. 1-12 Lymph node groups for tumors located in Ae (EG)