Orta ve Alt Özofagus Tümörlerinde Radyoterapiye Tam Cevapta İzlenecek Yol Nedir?

Lenf Diseksiyonu Nereye Kadar?

Ali GÜNER

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KTÜ Bioistatistik ve Tıbbi Bilişim ABD

V. Çukurova Gastrointestinal Hastalıklar ve Cerrahisi Kongresi
Adana / 4 Mart 2022

Herhangi bir biyomedikal firma ile sunumun içeriği ile ilgili bilimsel/etik ihlal oluşturacak çıkar çatışmam bulunmamaktadır.

Medtronic - Kurs eğitmeni honorarium (>3 yıl)
Bard - Kurs eğitmeni honorarium (>3 yıl)
Eczacıbaşı - Konuşmacı honorarium (>3 yıl)
Nutricia - Konuşmacı (>3 yıl)

Fresenius - Konuşmacı honorarium

Operative Versus Nonoperative Treatment for Stage 0 Distal Rectal Cancer Following Chemoradiation Therapy

Long-term Results

Angelita Habr-Gama, MD, Rodrigo Oliva Perez, MD,* Wladimir Nadalin, MD,†*
*Jorge Sabbaga, MD,† Ulysses Ribeiro Jr, MD,‡ Afonso Henrique Silva e Sousa Jr, MD,**
Fábio Guilherme Campos, MD, Desidério Roberto Kiss, MD,* and Joaquim Gama-Rodrigues, MD‡*

265 distal rectum
5040 cGy RT
5-FU + Folinic asit

Rektal Tuşe
Endoskopi + Bx
CEA

Clinical Response

Result	No. Patients (%)
Complete (group OB)	71 (26.8)
Incomplete	194 (73.2)
Total	265 (100)

Incomplete Clinical Response

Stage (Pathological)	No. Patients (%)
pT0N0M0 (group R)	22 (8.3)
p Stage I	61 (23)
p Stage II	70 (26.4)
p Stage III	41 (15.5)
Total	194 (73.2)

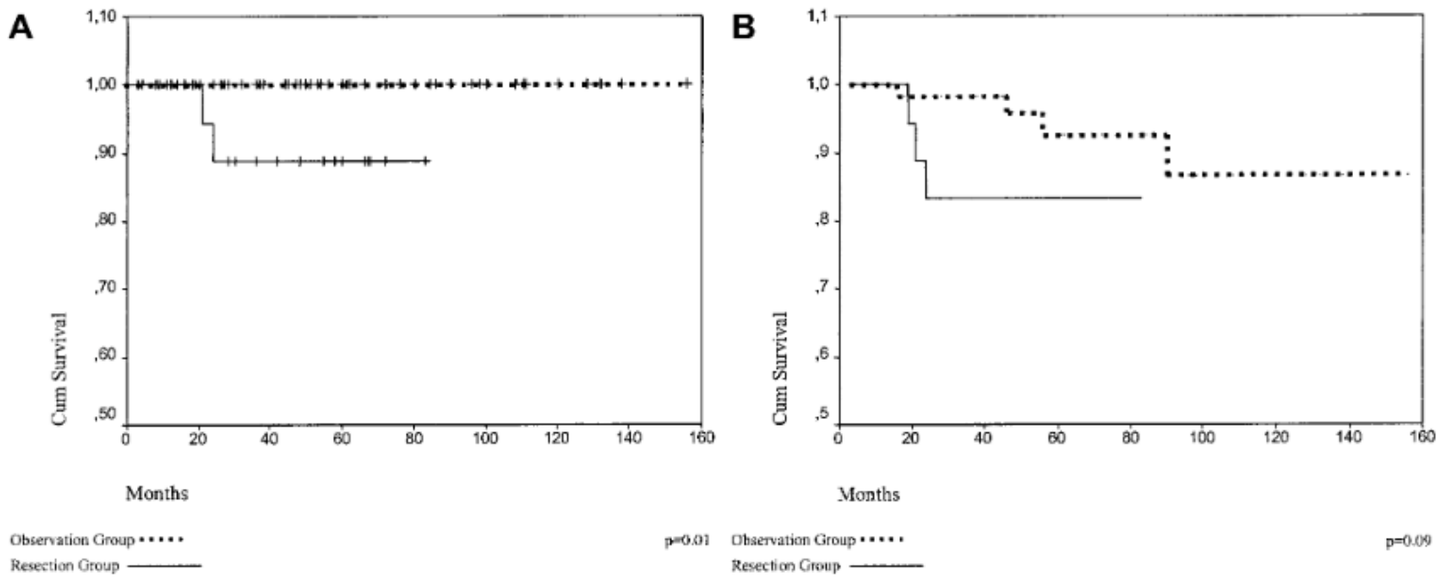


FIGURE 1. A, Overall survival. B, Disease-free survival.

Overall rekürrens: 7.0% (ortalama 57 ay takip)

2 endo-lüminal: full-thickness transanal eksizyon, brakiterapi

3 Sistemik metastaz: Sistemik kemoterapi

Habr-Gama A et al. Ann Surg 2004

Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study

*Maxime J M van der Valk, Denise E Hilling, Esther Bastiaannet, Elma Meershoek-Klein Kranenbarg, Geerard L Beets, Nuno L Figueiredo, Angelita Habr-Gama, Rodrigo O Perez, Andrew G Renehan, Cornelis J H van de Velde, and the IWWD Consortium**

1009 distal rectum

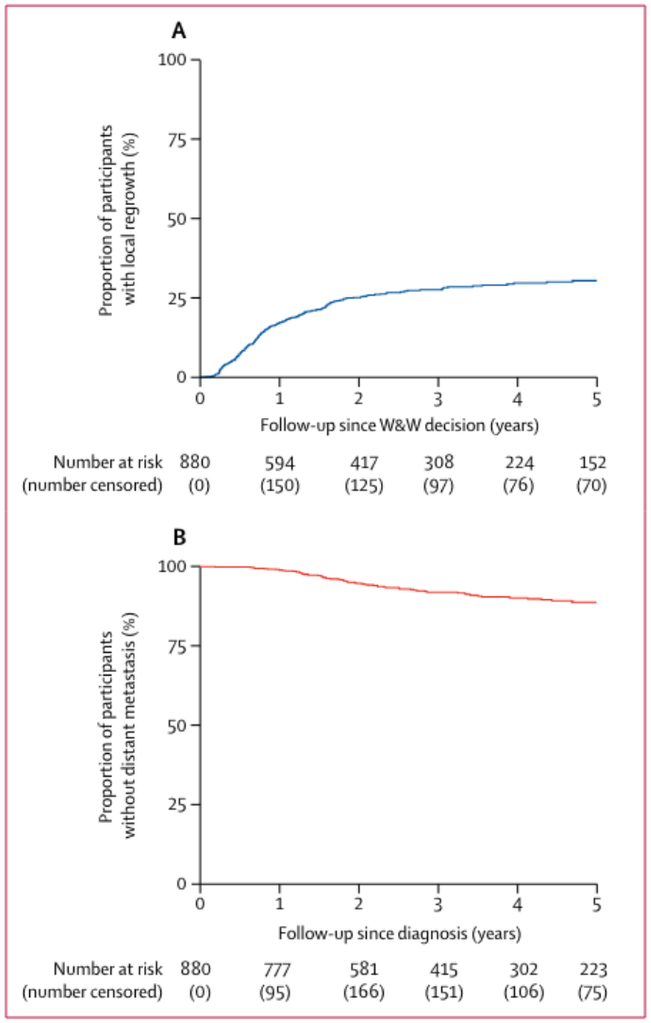
880 (87%) cCR

	Total number of patients (N=880)	Instituto Angelita e Joaquim Gama, São Paolo, Brazil (n=192)	Antoni van Leeuwenhoek and Maastricht University Medical Center, Netherlands (n=239)	OncoRe research database, UK (n=149)	Other participating institutes (n=300)
Country					
Argentina	46 (5%)	..	..	..	46 (15%)
Belgium	27 (3%)	..	..	..	27 (9%)
Brazil	201 (23%)	192 (100%)	..	..	9 (3%)
Germany	25 (3%)	..	..	..	25 (8%)
Denmark	40 (5%)	..	..	..	40 (13%)
France	42 (5%)	..	..	..	42 (14%)
UK	150 (17%)	..	..	149 (100%)	1 (0%)
Ireland	35 (4%)	..	..	..	35 (12%)
Netherlands	252 (29%)	..	239 (100%)	..	13 (4%)
Poland	15 (2%)	..	..	..	15 (5%)
Portugal	21 (2%)	..	..	..	21 (7%)
Russia	5 (1%)	..	..	..	5 (2%)
Sweden	15 (2%)	..	..	..	15 (5%)
Turkey	6 (1%)	..	..	..	6 (2%)

	Baseline (n=880)	Reassessment
Endoscopy	848 (96%)	779 (89%)
MRI pelvis	678 (77%)	620 (71%)
CT pelvis	378 (43%)	261 (30%)
Endorectal ultrasound	146 (17%)	67 (8%)
PET scane	116 (13%)	39 (4%)
CEA	540 (61%)	196 (22%)
Local excision	..	45 (5%)
ypT0	..	40 (4%)
ypT+	..	5 (1%)

Data are n (%). CEA=carcinoembryonic antigen.

Table 2: **Diagnostic procedures at baseline and at reassessment after induction therapy**



2-y lokal regrowth: 25.2%

Uzak metastaz: 71 (8%)

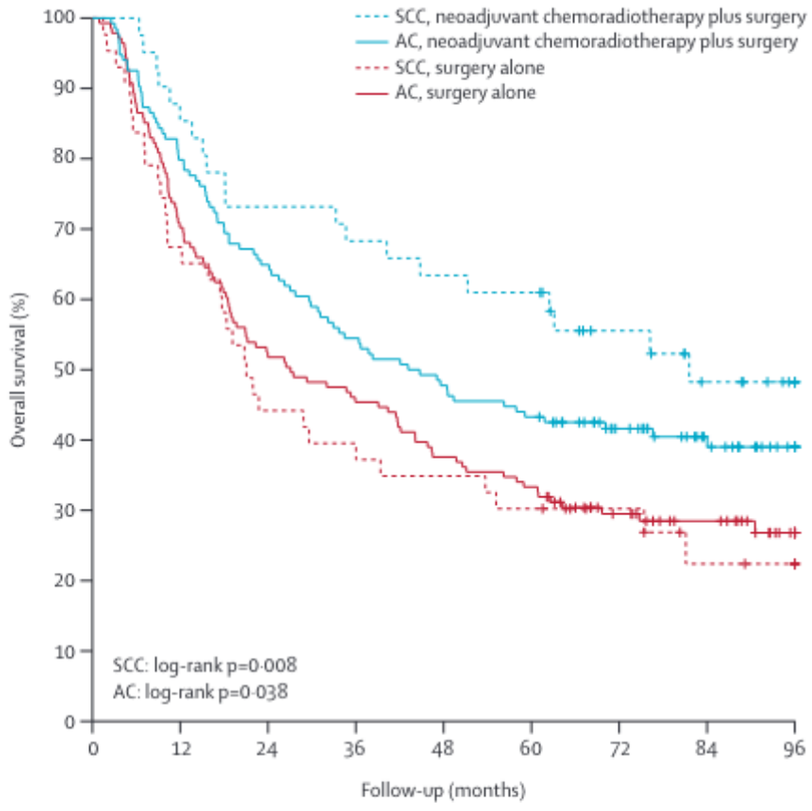
optimal selection?
follow-up protocol?
best approach for a near-complete clinical response?
best candidates to pursue organ preservation?
long-term quality-of-life outcomes?
effects of (chemo)radiotherapy on bowel function?

Van der Valk MJM et al. Lancet 2018

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer



Number at risk									
SCC, neoadjuvant chemo-radiotherapy plus surgery	41	35	30	28	26	25	17	11	6
SCC, surgery alone	43	29	19	17	16	13	9	5	4
AC, neoadjuvant chemo-radiotherapy plus surgery	134	107	87	73	64	58	42	29	16
AC, surgery alone	141	99	73	64	53	47	32	23	10
Total	359	270	209	182	158	143	100	68	36

41.4 Gy + carboplatin + paclitaxel

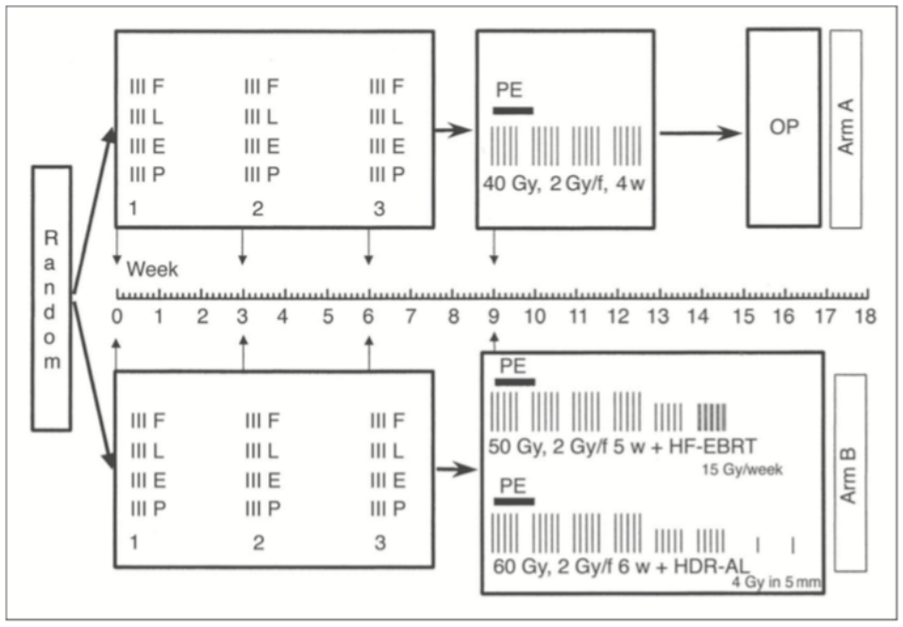
pCR: 47 of 161 patients (**29%**)

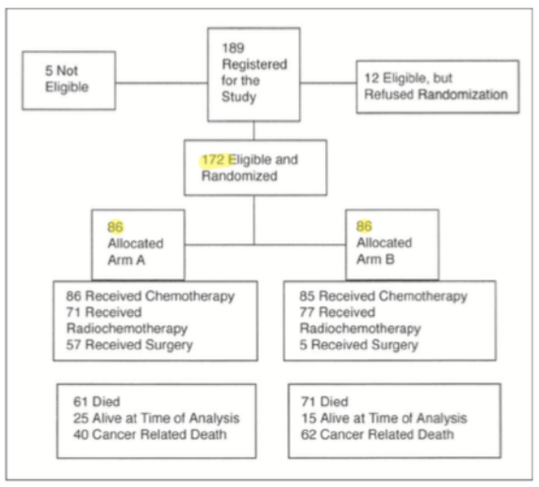
28 of 121 AdenoCa (23%)

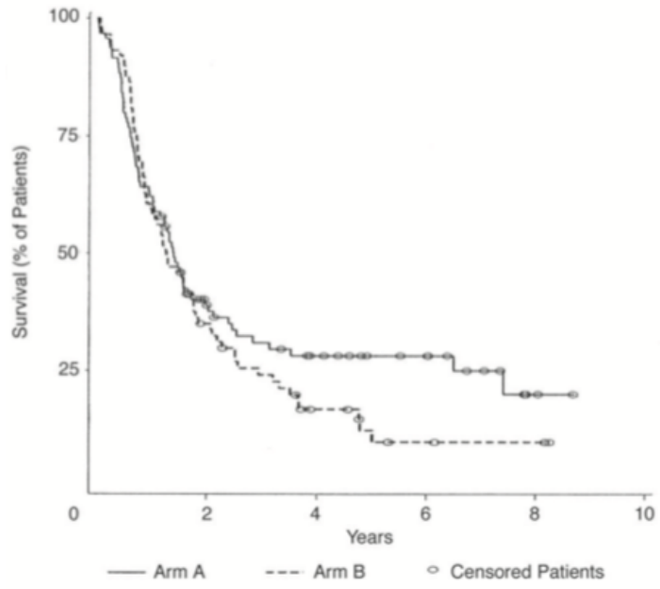
18 of 37 SCC (49%)

van Hagen P et al. NEJM 2012
Shapiro J et al. Lancet Oncol 2015

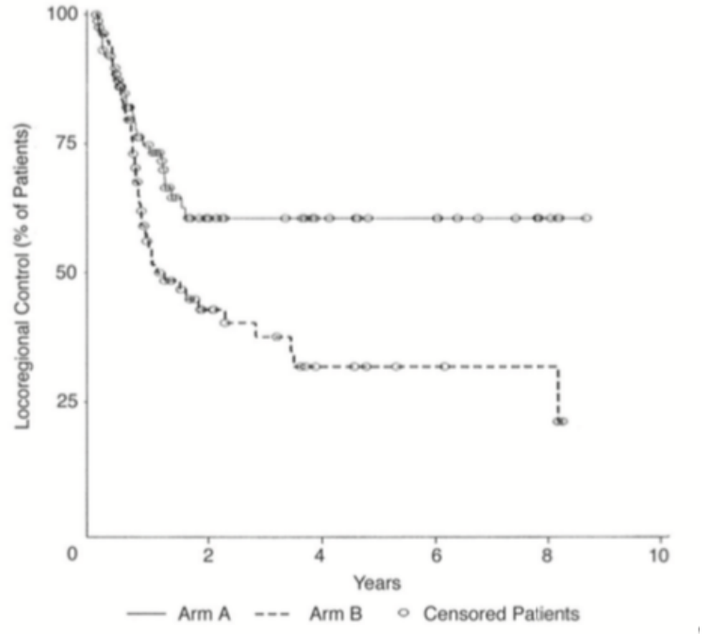
Chemoradiation With and Without Surgery in Patients With Locally Advanced Squamous Cell Carcinoma of the Esophagus







2y: 39.9% vs. 35.4%



2y: 64.3% vs. 40.7%

Surgery + chemoradiotherapy

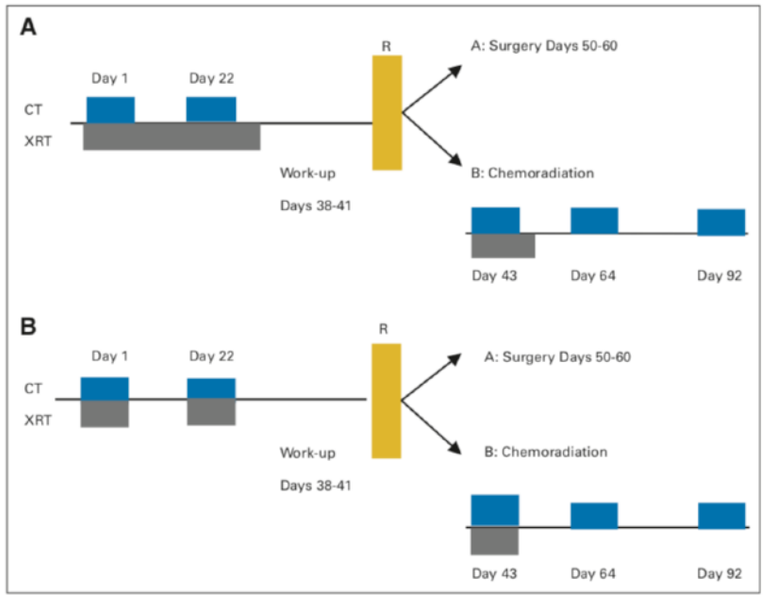
improves local tumor control, but **does not increase survival**

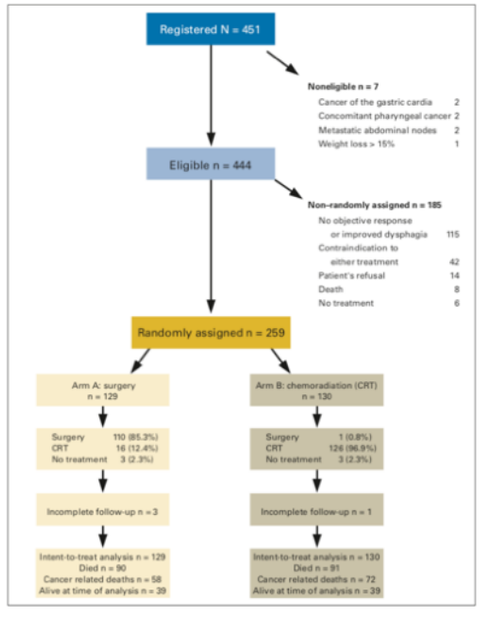
of patients with locally advanced esophageal SCC

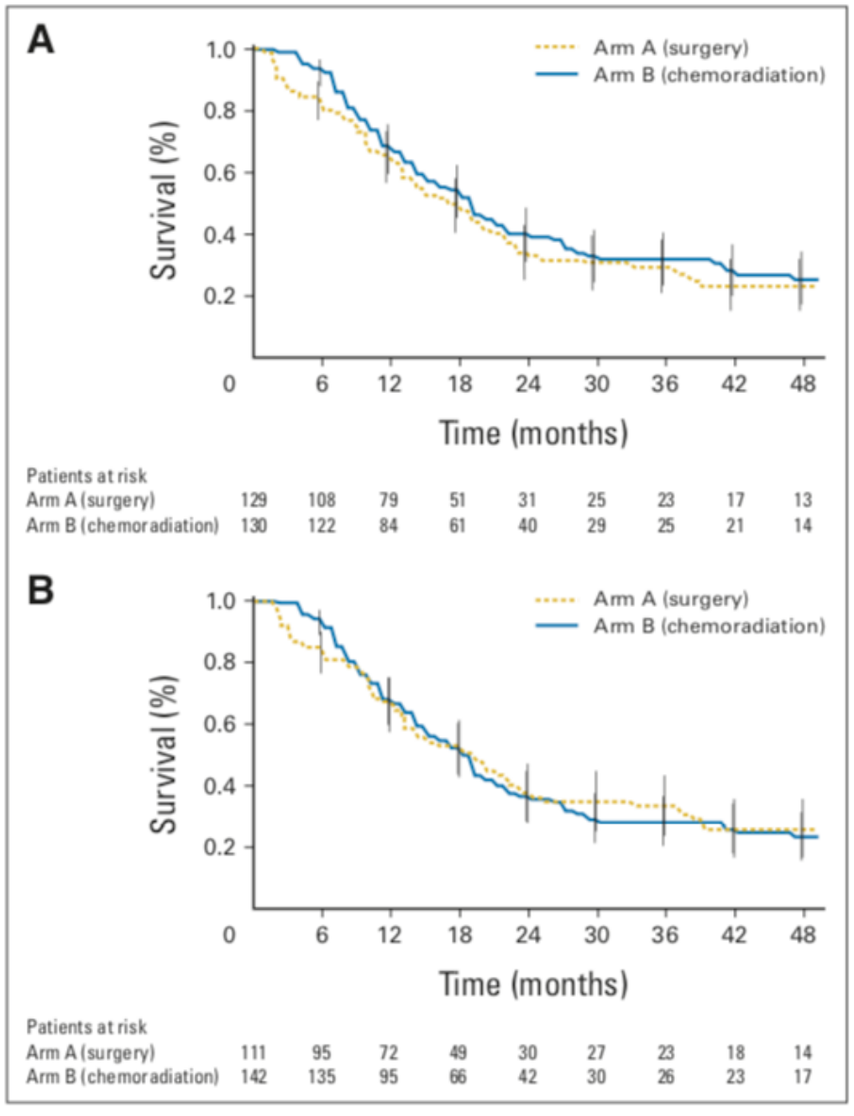
chemoradiotherapy alone offers **equivalent survival** to chemoradiotherapy followed by surgery **with less treatment-related mortality**

Stahl M et al. JCO 2004

Chemoradiation Followed by Surgery Compared With Chemoradiation Alone in Squamous Cancer of the Esophagus: FFCD 9102







2y: 34% vs. 40%

2y local control
66.4% vs. 57.0%

3m mortality
9.3% vs. 0.8%

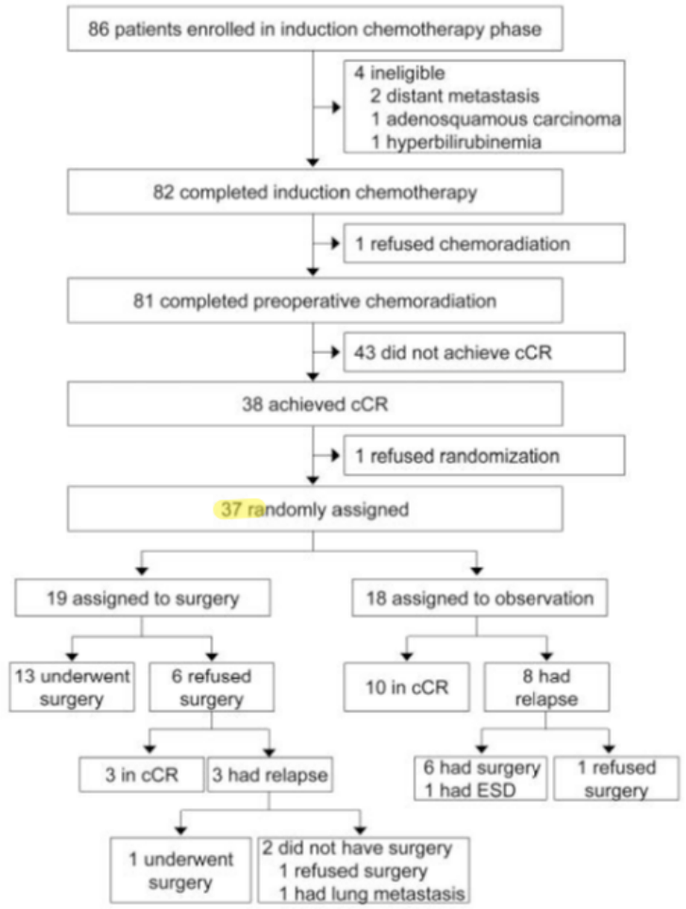
there is **no benefit** for the addition of surgery after chemoradiation compared with the continuation of additional chemoradiation.

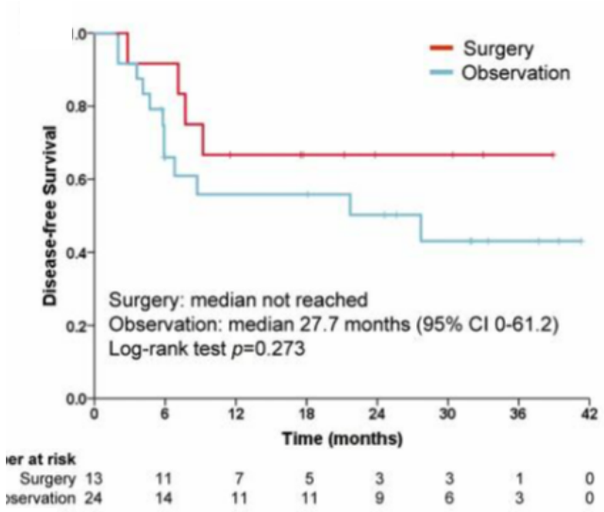
Bedenne L et al. JCO 2007

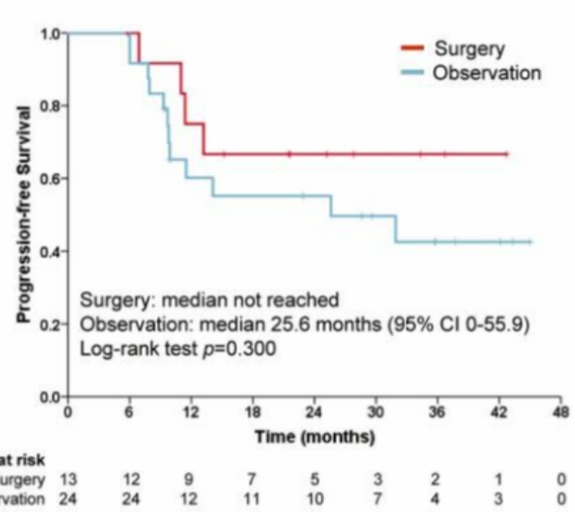
A Randomized Phase III Trial on the Role of Esophagectomy in Complete Responders to Preoperative Chemoradiotherapy for Esophageal Squamous Cell Carcinoma (ESOPRESSO)

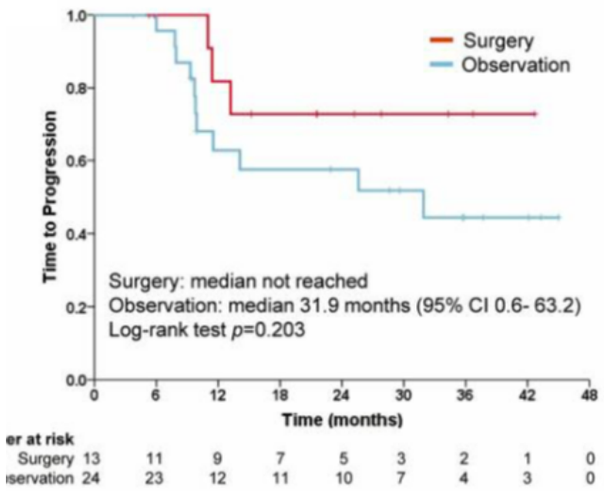
Complete responder
No radiologic/metabolic evidence
No tm on endoscopy+bx

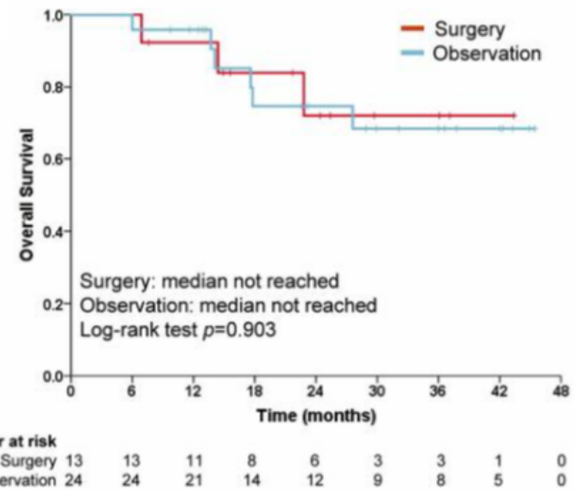
Sample size (Estimated): 486











Non-adherence --> Early closure

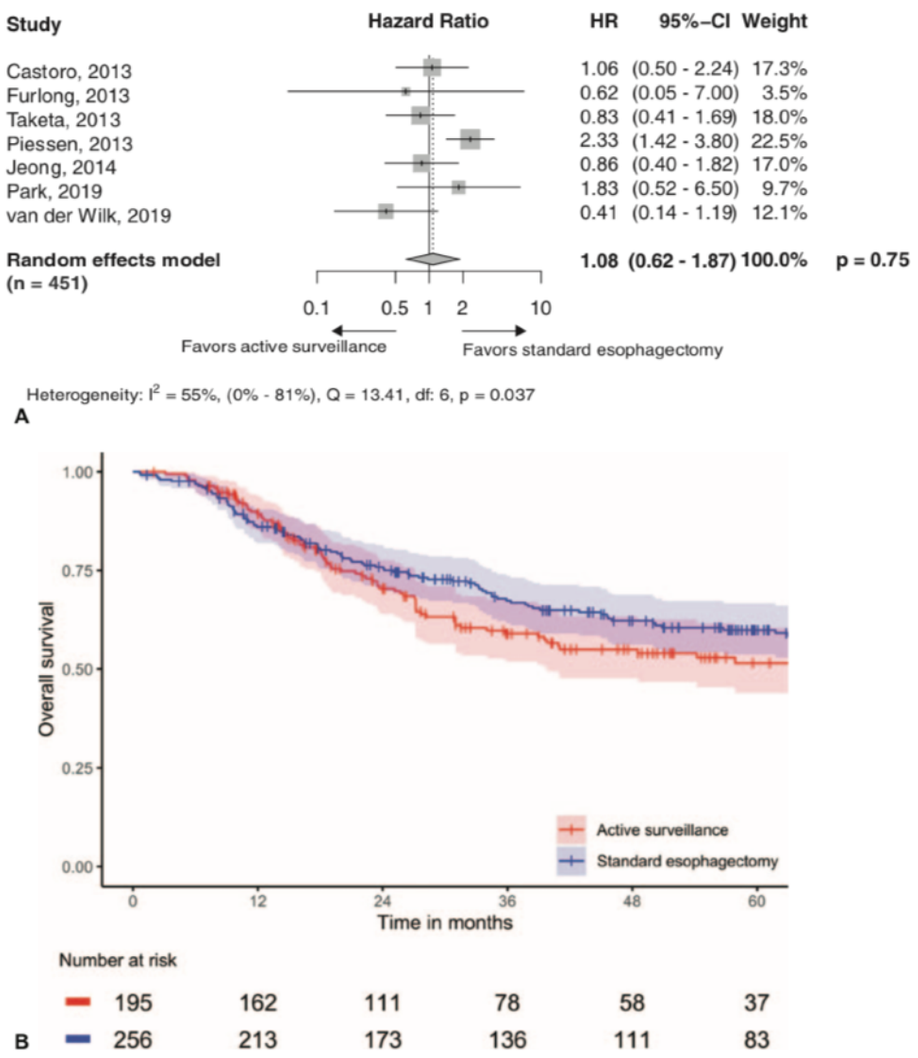
Close observation with salvage surgery **might be a reasonable option** in resectable ESCC patients achieving cCR after chemoradiation.

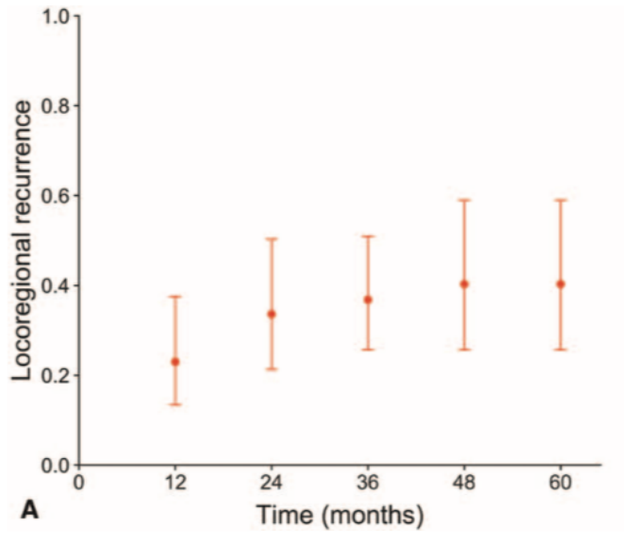
Park SR et al. Anticancer Res 2019

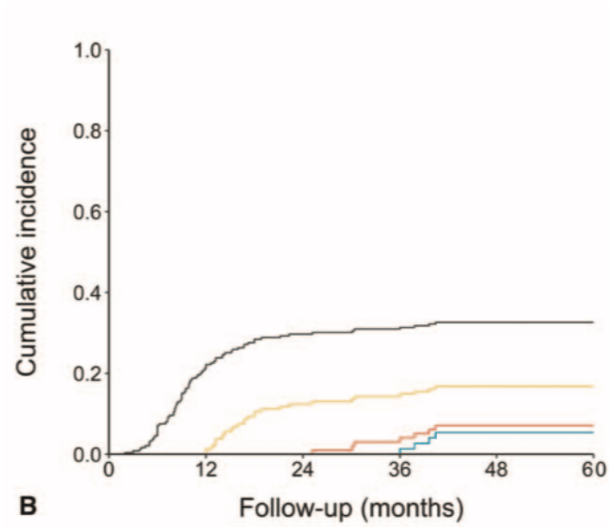
Chemoradiotherapy Followed by Active Surveillance Versus Standard Esophagectomy for Esophageal Cancer

A Systematic Review and Individual Patient Data Meta-analysis

196 active surveillance vs. 257 surgery







<u>Overall mortality</u>

1.08 (0.62–1.87, P = 0.75) ITT

0.93 (0.56–1.54, P = 0.75) per-protocol

<u>PFS</u>

1.14 (95% CI: 0.83–1.58, P = 0.36)

5y locoregional recurrence: 40% (7% in Surgery)

93/239 patients (+ 7 distant metastasis)

Recurrence (+) --> 95% of radical surgery option

Overall survival **was comparable**

Van der Wilk NJ et al. Ann Surg 2022

	Definition	Tests
Castoro, 2013	**Disappearance** of tumor lesion, ulceration and absence of cancer cells in biopsy specimens upon endoscopic observation of the esophagus.	Endoscopic biopsies and CT (PET-CT >2005)
Furlong, 2013	No tumor observed in post-treatment **endoscopic** evaluation, and a **negative CT** result.	Endoscopic biopsies CT
Taketa, 2013	A negative **endoscopic biopsy** for cancer and a physiologic range of the glucose uptake by **PET**.	Endoscopic biopsies PET-CT
Piessen, 2013	Absence of tumoral residue visible by **endoscopy**, negative endoscopic **biopsies**, and on **CT** scan, absence of the appearance of residual tumor, lymph nodes of more than 10-mm diameter, and metastases.	Endoscopic biopsies, Barium swallow CT
Jeong, 2014	**Decrease in FDG uptake of primary tumor and lymph nodes** to a level indistinguishable from that of the surrounding normal tissue. Diffuse accumulation of FDG in radiotherapy field without focal activity was considered radiotherapy induced oesophagitis and defined as PET-CR.	PET-CT
Park, 2019	No **radiographic** or **metabolic** evidence of disease without residual tumor on endoscopy with **biopsy**.	Endoscopic biopsies PET-CT
van der Wilk, 2019	No **cyto/histological** evidence of locoregional residual disease (at endoscopic biopsies or endoscopic ultrasonography with fine-needle aspiration (EUS-FNA)) and distant metastases (on **PET-CT**) was detected during 2 clinical response evaluations (CREs) 6 and 12 wk after completion of nCRT.	Endoscopic biopsies, EUS + FNA PET-CT

Preoperative prediction of a pathologic complete response of esophageal squamous cell carcinoma to neoadjuvant chemoradiotherapy

Primary tumor	ypT0, $n=55$	Non-ypT0, $n=75$	
Endoscopy			*P* value
Disappearance, $n=53$	30 (57)	23 (43)	.01
Non-disappearance, $n=77$	25 (33)	52 (68)	
PET			
Metabolic disappearance, $n=49$	30 (61)	19 (39)	.001
Nonmetabolic disappearance, $n=81$	25 (31)	56 (69)	
Endoscopy and PET			
ycT0, $n=33$	22 (67)	11 (33)	.001
Non-ycT0, $n=97$	33 (34)	64 (67)	
Lymph nodes	**ypN0 M (LYM) 0, n = 73**	**Non-ypN0 M (LYM) 0, n = 57**	
CT			
LN metastasis-negative, $n=110$	66 (60)	44 (40)	.04
LN metastasis-positive, $n=20$	7 (35)	13 (65)	
PET			
Metabolic LN metastasis-negative, $n=106$	65 (61)	41 (39)	.01
Metabolic LN metastasis positive, $n=24$	8 (33)	16 (67)	
CT and PET			
ycN0M (LYM) 0, $n=96$	61 (64)	35 (36)	.004
Non-ycN0M (LYM) 0, $n=34$	12 (35)	22 (65)	
Primary tumor and lymph nodes	**pCR: ypT0N0M (LYM) 0 Stage 0 n = 43**	**Non-pCR: non-ypT0N0M (LYM) 0 Stage 0 n = 87**	
Endoscopy, CT and PET			
cCR: ycT0N0M (LYM) 0 ycStage 0, $n=29$	17 (59)	12 (41)	.001
Non-cCR: ycT0N0M (LYM) 0 ycStage 0, $n=101$	26 (26)	75 (74)	

Primary tumor (ypT0)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Endoscopic disappearance	54.5	69.3	56.6	67.5	63.1
Metabolic disappearance on PET	54.5	74.7	61.2	69.1	66.2
ycT0	40.0	85.3	66.7	66.0	66.2
Lymph nodes (ypN0M [LYM] 0)					
LN metastasis-negative by CT	90.4	22.8	60.0	65.0	60.8
Metabolic LN metastasis-negative by PET	89.0	28.1	61.3	66.7	62.3
ycN0M (LYM) 0	83.6	38.6	63.5	64.7	63.8
Primary tumor and lymph nodes (pCR: ypT0N0M (LYM) 0 Stage 0)					
cCR: ycT0N0M (LYM) 0 ycStage 0	39.5	86.2	58.6	74.3	70.8

ycT0: clinical complete disappearance of primary tumor evaluated by endoscopy and PET after NCRT.
ycN0M (LYM) 0: clinical negative LN metastasis evaluated by CT and PET after NCRT.
ycT0N0M (LYM) 0 ycStage 0: cCR in primary tumor and lymph nodes evaluated by endoscopy, CT and PET after NCRT.
ypT0N0M [LYM] 0 Stage 0: pCR in primary tumor and lymph nodes.

Although pathologic complete response was **predictable** preoperatively to some extent, the accuracy was somewhat **low**
Considerable caution should be exercised when selecting.....

Hamai Y et al. Surgery 2018

Detection of residual disease after neoadjuvant chemoradiotherapy for oesophageal cancer (preSANO): a prospective multicentre, diagnostic cohort study

*Bo Jan Noordman, Manon C W Spaander, Roelf Valkema, Bas P L Wijnhoven, Mark I van Berge Henegouwen, Joël Shapiro, Katharina Biermann, Ate van der Gaast, Richard van Hillegersberg, Maarten C C M Hulshof, Kausilia K Krishnadath, Sjoerd M Lagarde, Grard A P Nieuwenhuijzen, Liekele E Oostenbrug, Peter D Siersema, Erik J Schoon, Meindert N Sosef, Ewout W Steyerberg, J Jan B van Lanschot, for the SANO study group**

STUDY PROTOCOL

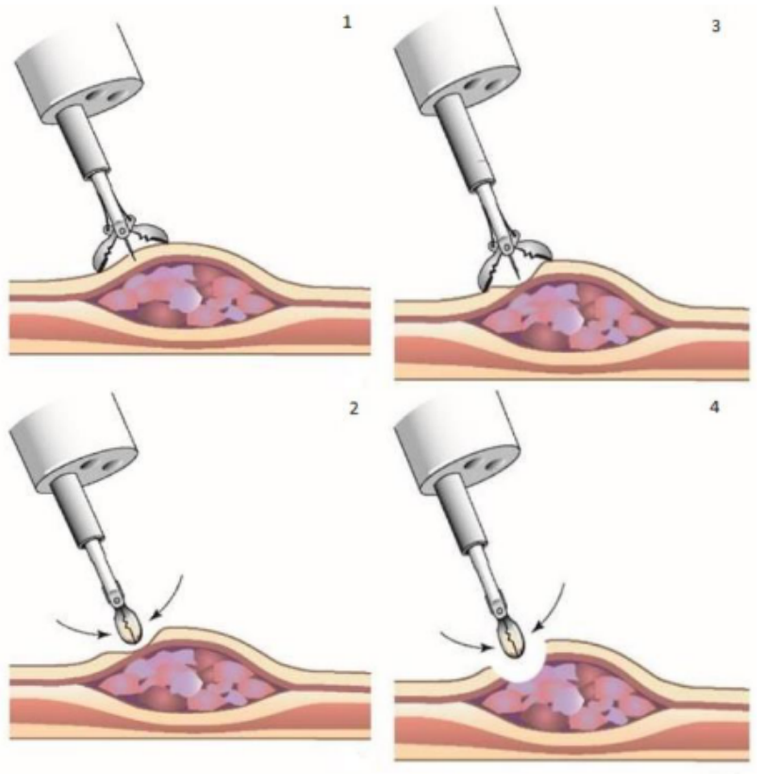
Neoadjuvant chemoradiotherapy plus surgery versus active surveillance for oesophageal cancer: a stepped-wedge cluster randomised trial

1. control

- nCRT sonrası 4-6 hafta
- Endoskopi + en az 8 random bx (en az 4 bite-on-bite)

2. control

- İlk kontrol sonrası 6-8 hafta
- PET-CT
- Endoskopi
- Radial EndoUSG
- Linear EndoUSG + FNA



Noordman BJ et al. Lancet Oncol 2018

Noordman BJ et al. BMC Cancer 2018

Surgery As Needed for Oesophageal Cancer - 2 (SANO-2)

ClinicalTrials.gov Identifier: NCT04886635

Primary Outcome Measures :

1. Safety of active surveillance (including delayed surgery), measured by the number of patients with adverse events [Time Frame: after the procedure/surgery and at least up to 2 years]

   Including:

   - Complications from OGD with bite-on-bite biopsies, EUS-FNA and PET-CT
   - Unresectable or incurable (T4b or R2) regrowth
   - Microscopically non-radical (R1) resection
   - Postoperative mortality (90 day- or in-hospital mortality)
   - Postoperative hospital stay of >60 days
   - Postoperative complications, defined by the Esophagectomy Complications Consensus Group (ECCG)
   - Development of distant metastases

Comparison of Systematic Surgery Versus Surveillance and Rescue Surgery in Operable Oesophageal Cancer With a Complete Clinical Response to Radiochemotherapy (Esostrate)

ClinicalTrials.gov Identifier: NCT02551458

Primary Outcome Measures :

1. Proportion of surviving patients [Time Frame: 1 year after randomisation]
2. Disease-free survival [Time Frame: Up to 5 years]

Kötü prognozlu - Yüksek morbidite/mortalite

Cerrah için UMUT VERİCİ

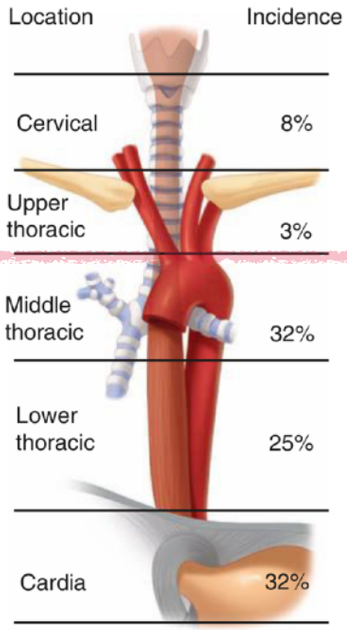
Hasta için UMUT VERİCİ (QoL)

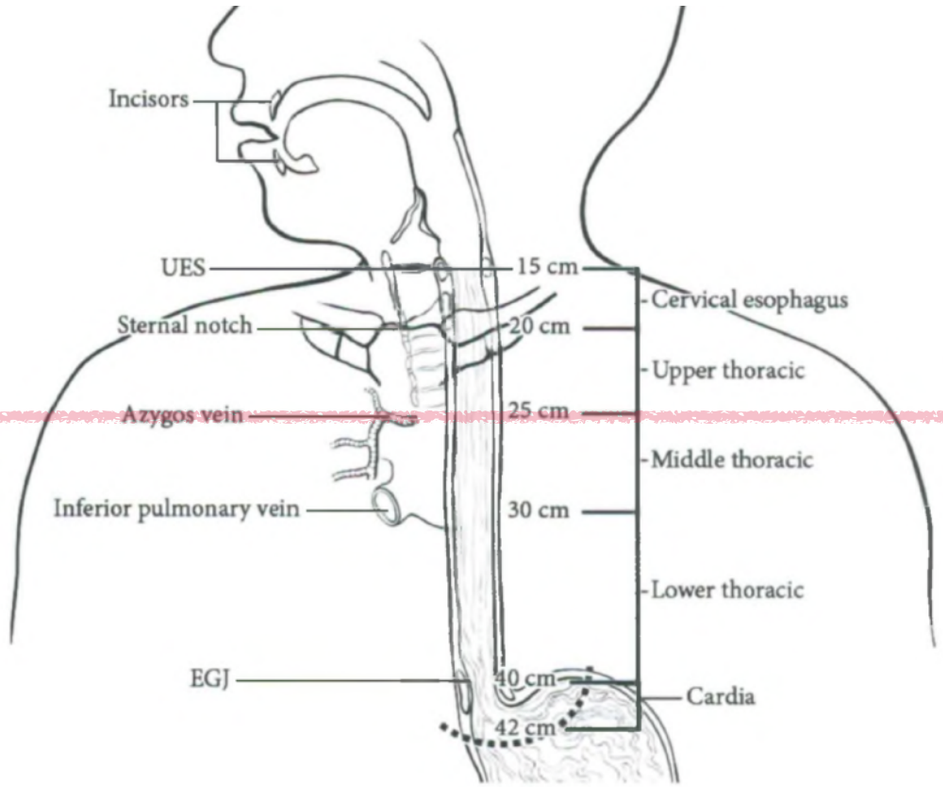
Morbidite (Salvage Özofajektomi) - no stoma

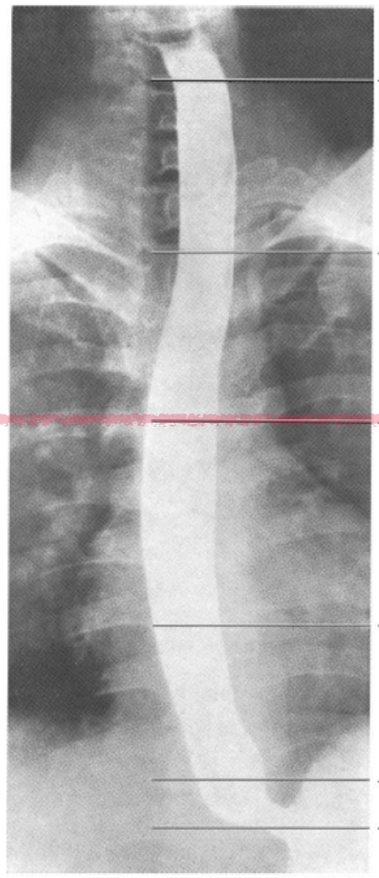
Uzak metastaz tedavisi - sistemik KT?

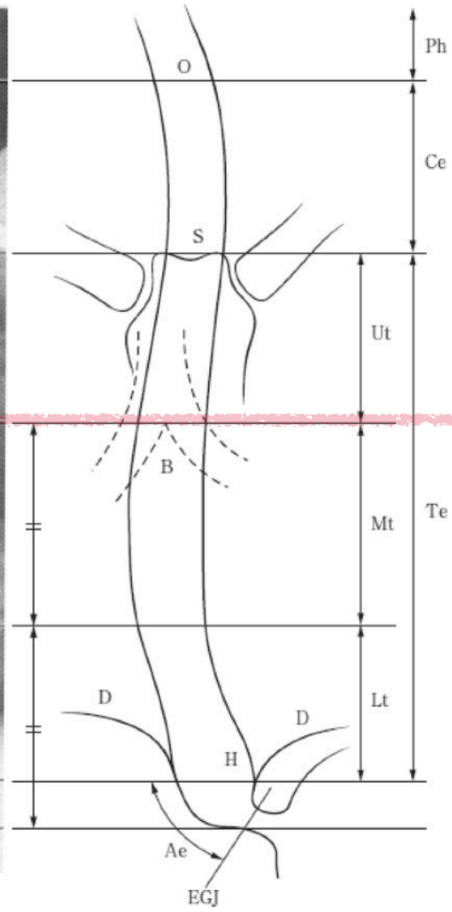
cCR tanısı (no direkt temas, no tuşe, no big bx)

Yakın takip

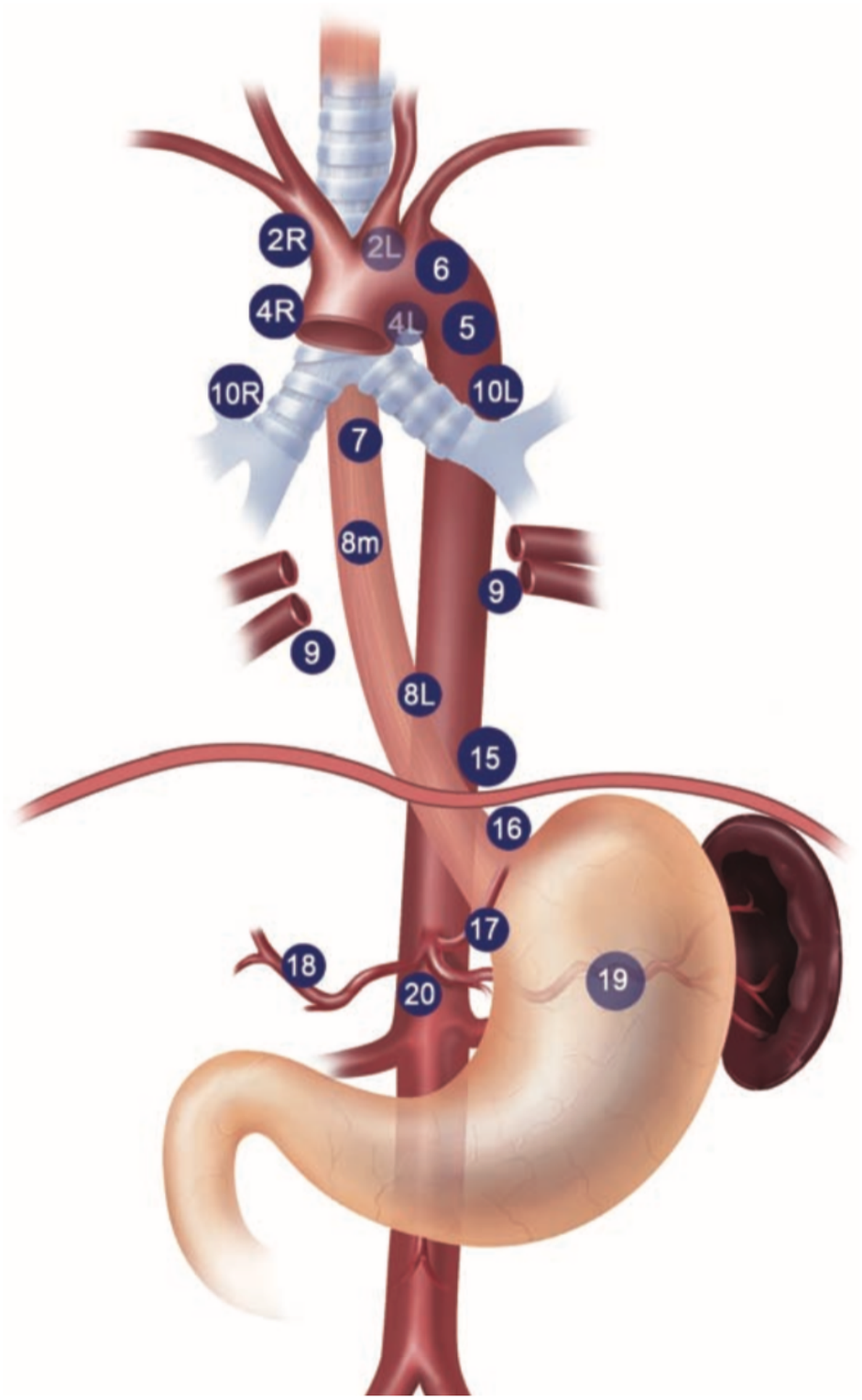








Orta-Alt Özofagus


2R
2L
6
4R
4L
5
10R
10L
7
8m
9
9
8L
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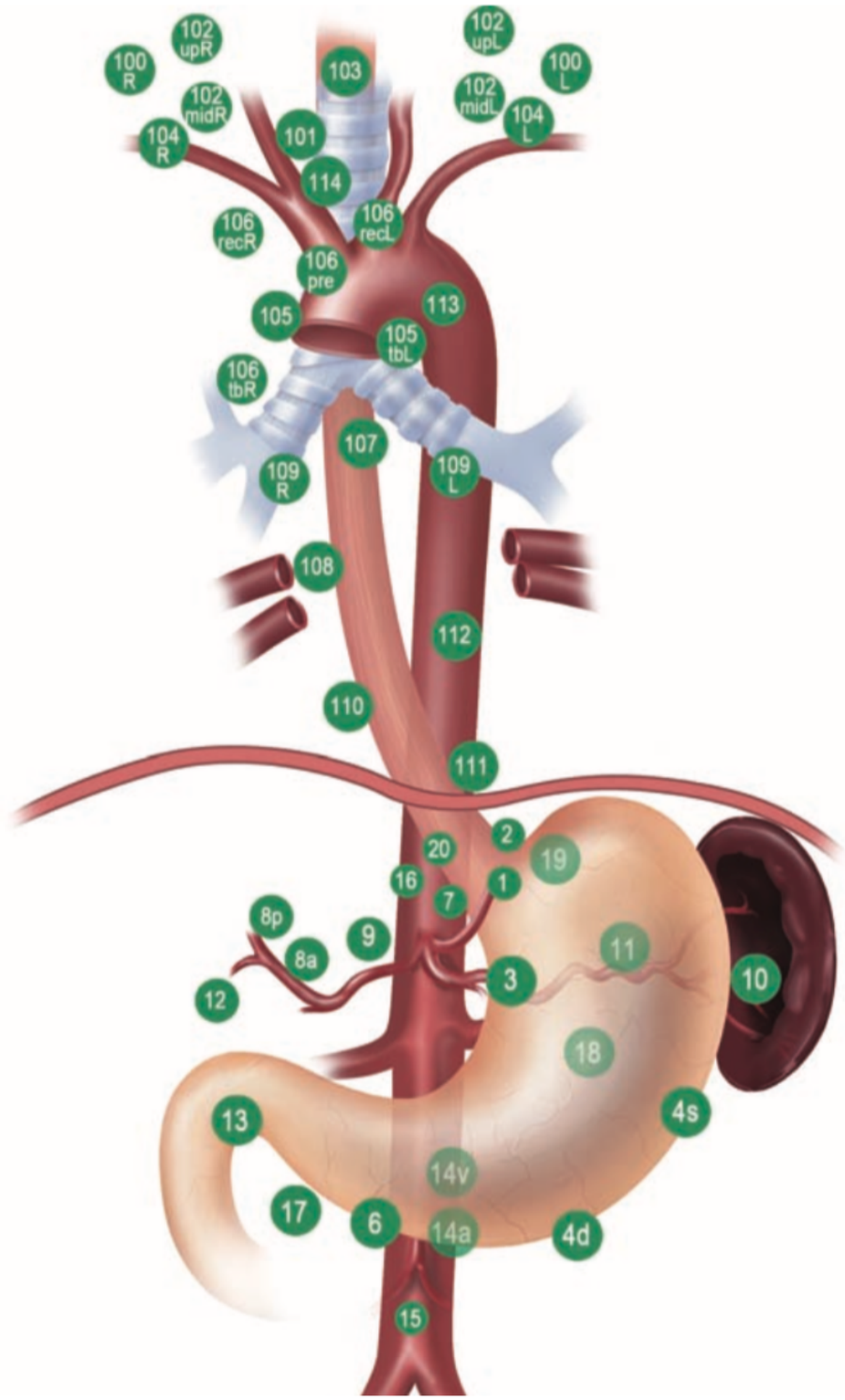
19

AJCC


102 upR
102 upL
100 R
100 L
103
102 midR
102 midL
104 L
104 R
101
114
106 recR
106 recL
106 pre
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113
105 tbL
106 tbR
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109 R
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7
8p
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8a
11
10
3
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18
13
4s
14v
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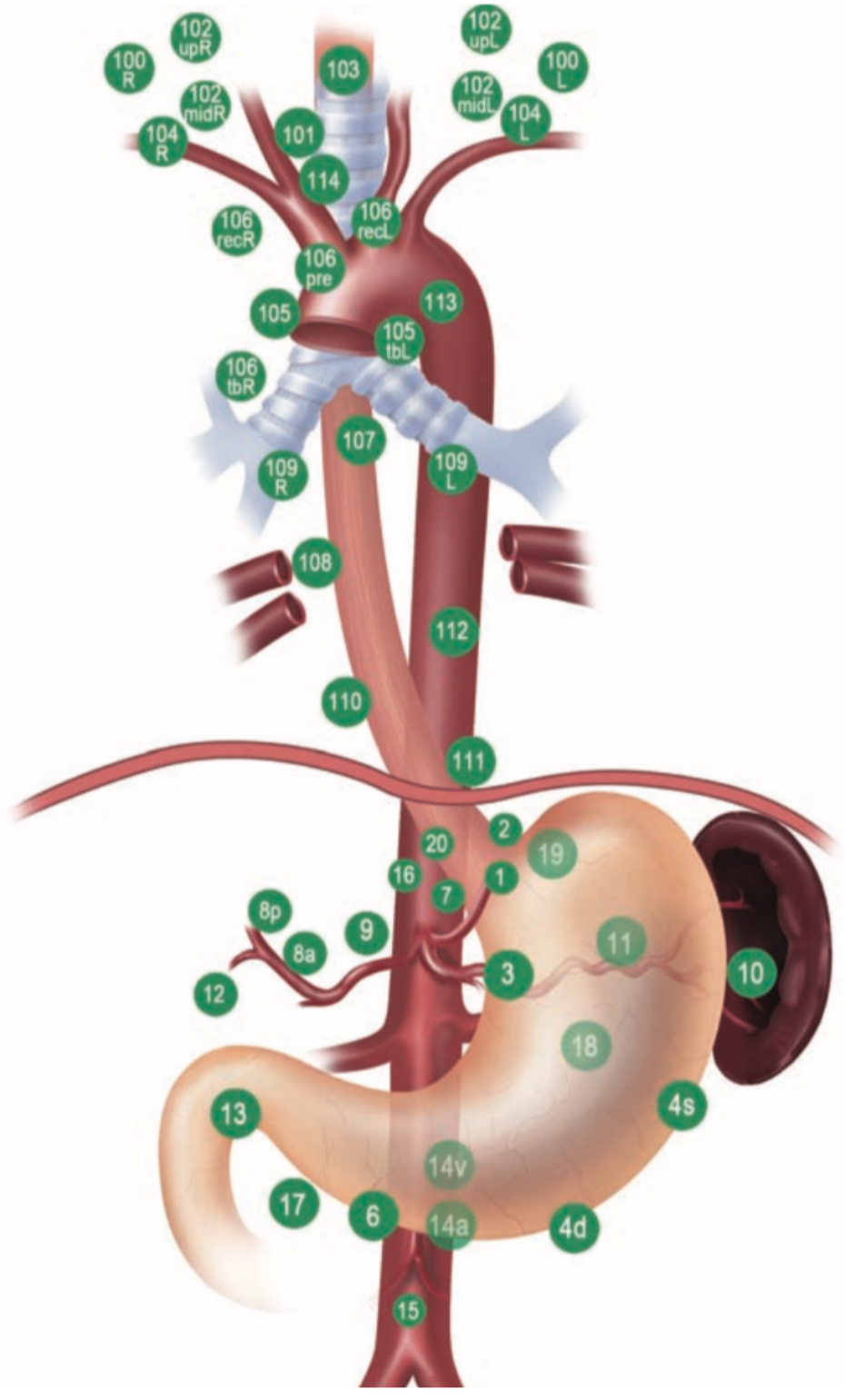
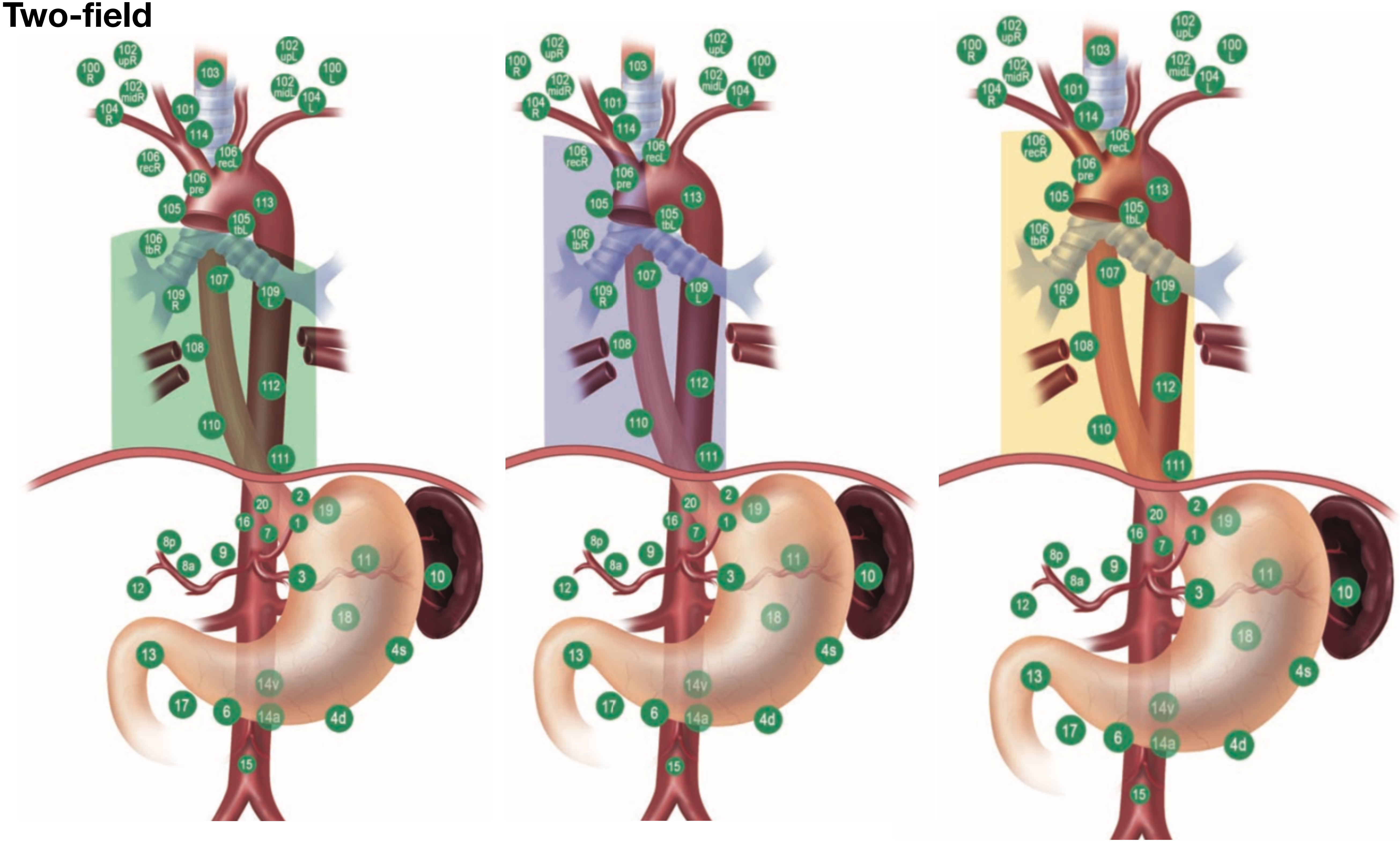
6
14a
4d
15

Japon

(1) Cervical lymph nodes	
No. 100	Superficial lymph nodes of the neck
No. 100spf	Superficial cervical lymph nodes
No. 100sm	Submandibular lymph nodes
No. 100tr	Cervical pretracheal lymph nodes
No. 100ac	Accessory nerve lymph nodes
No. 101	**Cervical paraesophageal lymph nodes**
No. 102	Deep cervical lymph nodes
No. 102up	Upper deep cervical lymph nodes
No. 102mid	Middle deep cervical lymph nodes
No. 103	Peripharyngeal lymph nodes
No. 104	**Supraclavicular lymph nodes**
(2) Thoracic lymph nodes	
No. 105	Upper thoracic paraesophageal lymph nodes
No. 106	Thoracic paratracheal lymph nodes
No. 106rec	**Recurrent nerve lymph nodes**
No. 106recL	Left recurrent nerve lymph nodes
No. 106recR	Right recurrent nerve lymph nodes
No. 106pre	Pretracheal lymph nodes
No. 106tb	Tracheobronchial lymph nodes
No. 106tbL	Left tracheobronchial lymph nodes
No. 106tbR	Right tracheobronchial lymph nodes
No. 107	Subcarinal lymph nodes
No. 108	Middle thoracic paraesophageal lymph nodes
No. 109	Main bronchus lymph nodes
No. 109L	Left main bronchus lymph nodes
No. 109R	Right main bronchus lymph nodes
No. 110	Lower thoracic paraesophageal lymph nodes
No. 111	Supradiaphragmatic lymph nodes
No. 112	Posterior mediastinal lymph nodes
No. 112aoA	Anterior thoracic paraaortic lymph nodes
No. 112aoP	Posterior thoracic paraaortic lymph nodes
No. 112pul	Pulmonary ligament lymph nodes
No. 113	Ligamentum arteriosum lymph nodes (Botallo lymph nodes)
No. 114	Anterior mediastinal lymph nodes

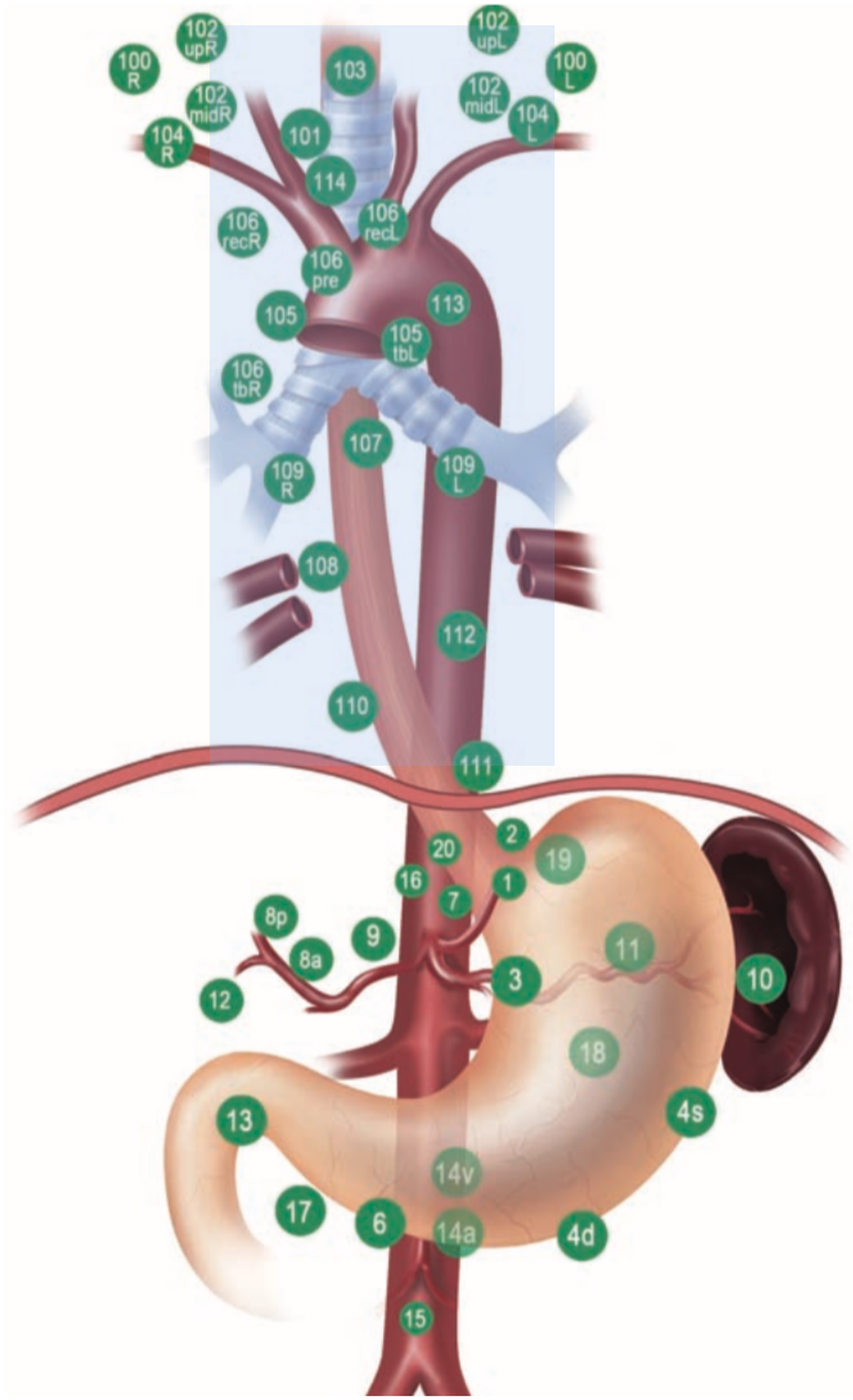


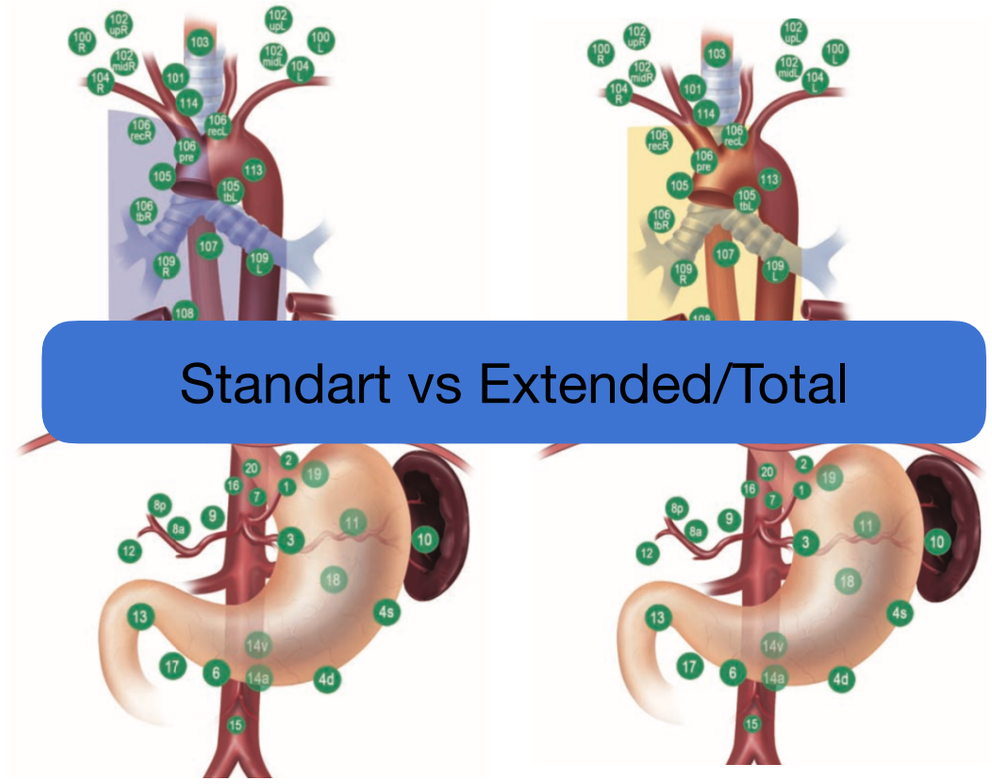
Two-field

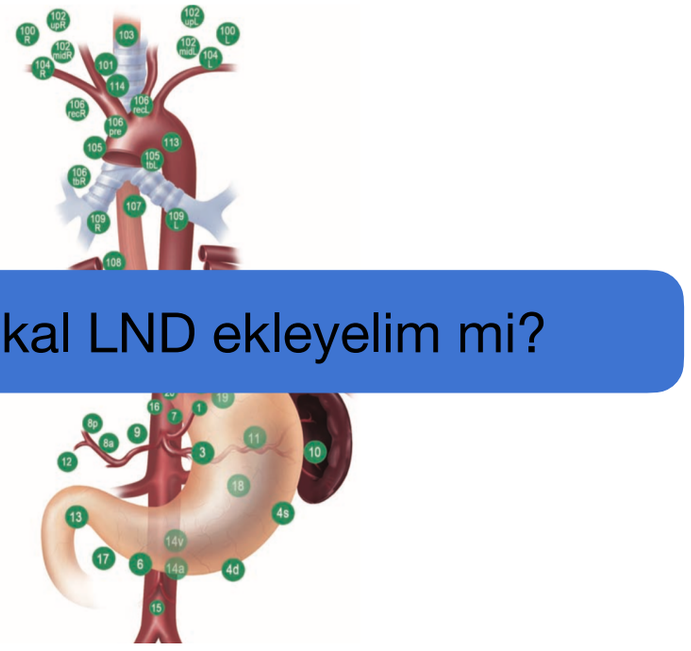


Standard mediastinal		**Extended** mediastinal		**Total** mediastinal
Paraözofageal Subkarinal Bronşial (R-L)	**+**	R Apikal nodlar R RLN R Paratrakeal	**+**	L RLN L Paratrakeal

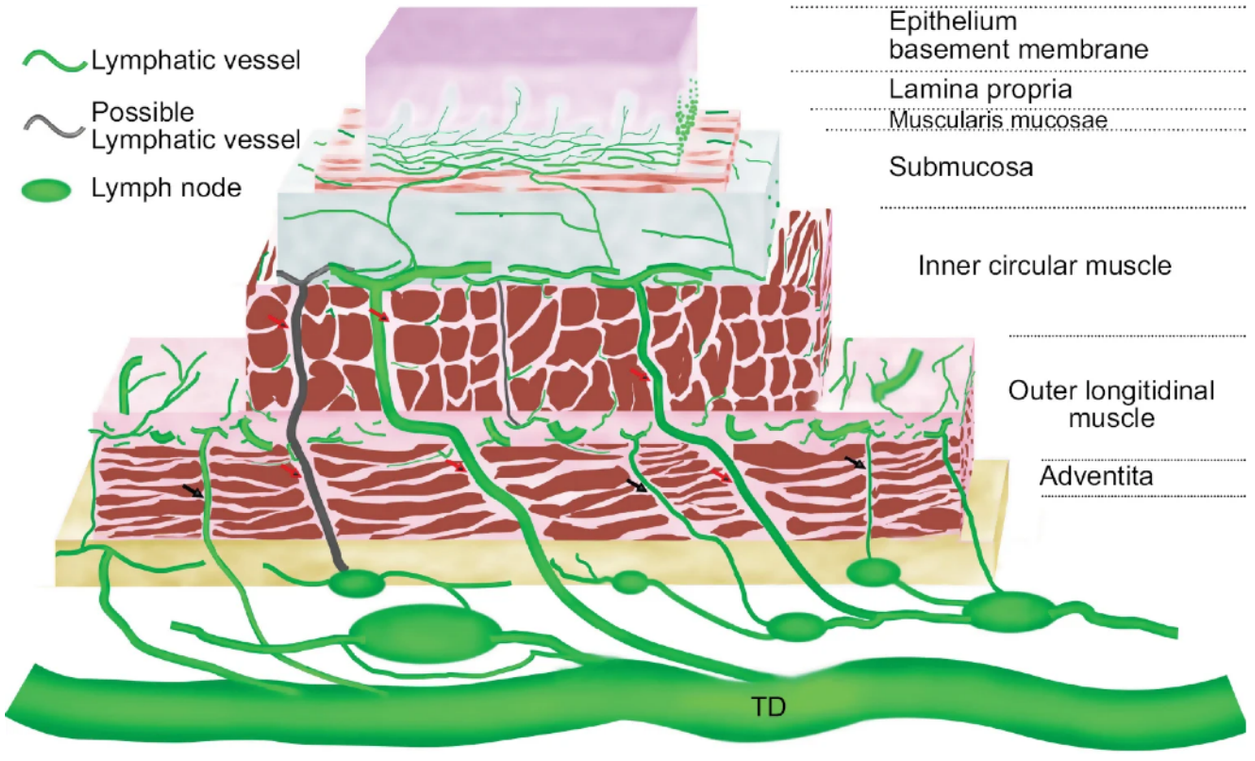
Three-field


102 upR
102 upL
100 R
100 L
103
102 midR
102 midL
104 L
104 R
101
114
106 recL
106 recR
106 pre
113
105
105 tbL
106 tbR
107
109 R
109 L
108
112
110
111
2
20
19
16
1
7
8p
9
8a
11
3
10
12
18
13
4s
14v
17
6
14a
4d
15


Standart vs Extended/Total


Servikal LND ekleyelim mi?

Lenf modu metastaz paterni?



ELSEVIER

The American Journal of Surgery
Volume 141, Issue 2, February 1981, Pages 216-218

Scientific paper

Lymph node metastases in cancer of the thoracic esophagus

Yasuo Sannohe MD [1], Ryuzoh Hiratsuka [1], Kiyoshi Doki [1]

“jumping metastasis”: Neck or the abdominal lymph nodes metastasis without intrathoracic involvement was observed in

27.8%.

Sannohe Y, Am J Surg 1981

Lenf modu metastaz paterni?

		Cervical Esophagus (n = 2)		Upper Thoracic Esophagus (n = 8)		Middle Thoracic Esophagus (n = 38)		Lower Thoracic Esophagus (n = 14)		Abdominal Esophagus to EGJ (n = 5)	
	Station	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis	SLN	Metastasis
Cervical nodes	101	1 (50)	1 (50)	2 (25)	0	2 (5)	1 (3)	0	0	0	0
	102R	0	0	0	0	2 (5)	0	0	0	0	0
	102L	0	0	0	0	2 (5)	0	0	0	0	0
	103	0	0	0	0	0	0	0	0	0	0
	104R	1 (50)	0	3 (38)	0	2 (5)	1 (3)	0	0	0	0
	104L	0	0	2 (25)	0	6 (16)	1 (3)	1 (7)	0	0	0
Thoracic nodes	105	0	0	2 (25)	0	0	0	2 (14)	0	0	0
	106recR	2 (100)	1 (50)	5 (63)	2 (25)	13 (34)	4 (11)	3 (21)	2 (14)	0	0
	106recL	0	0	6 (75)	2 (25)	8 (21)	3 (8)	0	0	0	0
	106pre	0	0	0	0	0	0	0	0	0	0
	106tbL	0	0	0	0	5 (13)	0	0	0	0	0
	107	0	0	4 (50)	0	12 (32)	1 (3)	2 (14)	0	1 (20)	0
	108	0	0	0	0	12 (32)	3 (8)	4 (28)	1 (7)	0	0
	109R	0	0	0	0	10 (26)	0	2 (14)	0	0	0
	109L	0	0	0	0	11 (29)	1 (3)	1 (7)	0	0	0
	110	0	0	0	0	8 (21)	0	5 (36)	2 (14)	2 (40)	1 (20)
	111	0	0	0	0	1 (3)	0	2 (14)	0	0	0
	112	0	0	0	0	3 (8)	1 (3)	1 (7)	1 (7)	0	0
Abdominal nodes	1	0	0	0	0	5 (13)	1 (3)	5 (36)	3 (21)	2 (40)	0
	2	0	0	0	0	3 (8)	1 (3)	3 (21)	2 (14)	2 (40)	0
	3	0	0	0	0	5 (13)	0	3 (21)	0	3 (60)	0
	4sa	0	0	0	0	0	0	0	0	0	0
	4sb	0	0	0	0	0	0	0	0	0	0
	4d	0	0	0	0	0	0	0	0	0	0
	5	0	0	0	0	0	0	0	0	0	0
	6	0	0	0	0	0	0	0	0	0	0
	7	0	0	2 (25)	0	4 (11)	1 (3)	5 (36)	2 (14)	3 (60)	0
	8a	0	0	0	0	0	0	0	0	0	0
	9	0	0	0	0	0	0	1 (7)	0	0	0
	10	0	0	0	0	0	0	0	0	0	0
	11p	0	0	0	0	0	0	0	0	0	0
	20	0	0	1 (13)	0	2 (5)	0	0	0	0	0

Takeuchi H, Ann Surg 2009

The Prevalence of Overall and Initial Lymph Node Metastases in Clinical T1N0 Thoracic Esophageal Cancer

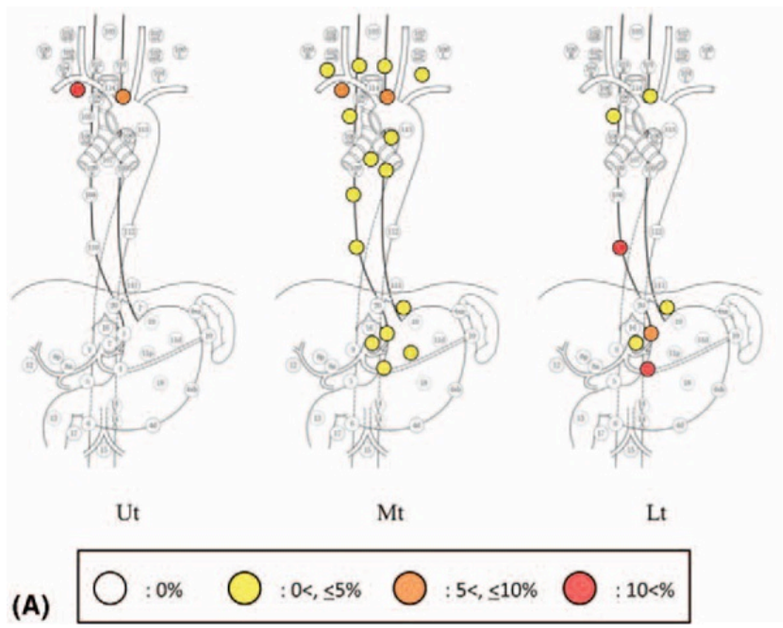
From the Results of JCOG0502, a Prospective Multicenter Study

	Pathologic Tumor Depth						
	pT0	**T1a**	**T1b**	**pT2**	**pT3**	**pT4**	**Total**
Clinical T1 case	0 (0)	64 (30.3)	140 (66.4)	5 (2.4)	2 (1.0)	0 (0)	211 (100)
Clinical T1a case (%)	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)	1 (100)
Clinical T1b case (%)	0 (0)	63 (30.0)	140 (66.7)	5 (2.4)	2 (1.0)	0 (0)	210 (100)

	Pathological N Status		
	Negative	**Positive**	**Total**
Clinical node negative cases (%)	154 (73.0)	57 (27.0)	211* (100)

			Tumor Location			
			Ut	**Mt**	**Lt**	**Total**
	Station number	Station name	Case (%), n = 22	Case (%), n = 118	Case (%), n = 45	n = 185
		Any	4 (18.2)	33 (28.0)	12 (26.7)	49 (26.5)
Neck region	101R	rt. cervical paraesophageal		4 (3.4)		
	101L	lt. cervical paraesophageal		4 (3.4)		
	102-midR	rt. middle deep cervical				
	102-midL	lt. middle deep cervical				
	104R	rt. supraclavicular		1 (0.8)		
	104L	lt. supraclavicular		1 (0.8)		
		Neck any N	0 (0.0)	9 (7.6)	0 (0.0)	Sub total
Mediastinal region	105	Upper thoracic paraesophageal		3 (2.5)	1 (2.2)	
	106recR	rt. recurrent nerve	3 (13.6)	9 (7.6)		
	106recL	lt. recurrent nerve	2 (9.1)	9 (7.6)	1 (2.2)	
	106pre	pretracheal				
	106tbR	rt. tracheobronchial				
	106tbL	lt. tracheobronchial		1 (0.8)		
	107	Subcarinal		2 (1.7)		
	108	Middle thoracic paraesophageal		2 (1.7)		
	109R	rt. main bronchus				
	109L	lt. main bronchus		1 (0.8)		
	110	Lower thoracic paraesophageal		4 (3.4)	5 (11.1)	
	111	Supradiaphragmatic				
	112	Posterior mediastinal				
		Mediastinal any N	4 (18.2)	21 (17.8)	7 (15.6)	Sub total
Abdominal region	1	rt. cardiac		5 (4.2)	4 (8.9)	
	2	lt. cardiac		5 (4.2)	2 (4.4)	
	3	Lesser curvature		1 (0.8)	5 (11.1)	
	7	lt. gastric artery		5 (4.2)	2 (4.4)	
	9	Celiac artery				
	11p	Proximal splenic artery		1 (0.8)		
	19	Infradiaphragmatic				
	20	Esophageal hiatus of the diaphragm				
		Abdominal any N	0 (0.0)	14 (11.9)	9 (20.0)	Sub total

Tumor Location	**Skip LNM (+)**	**Skip LNM Rate, %**	**95% CI, %**
Ut (n = 4)	0	0	0–60.2
Mt (n = 33)	15	45.5	28.1–63.7
Lt (n = 12)	3	25.0	5.5–57.2
Total (n = 49)	18	36.7	23.4–51.7



Akutsu Y, Ann Surg 2015

pT1 SCC

Area	Tumor location			Total (n = 127) (%)
	Upper (n = 22) (%)	Mid (n = 67) (%)	Lower (n = 38) (%)	
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)

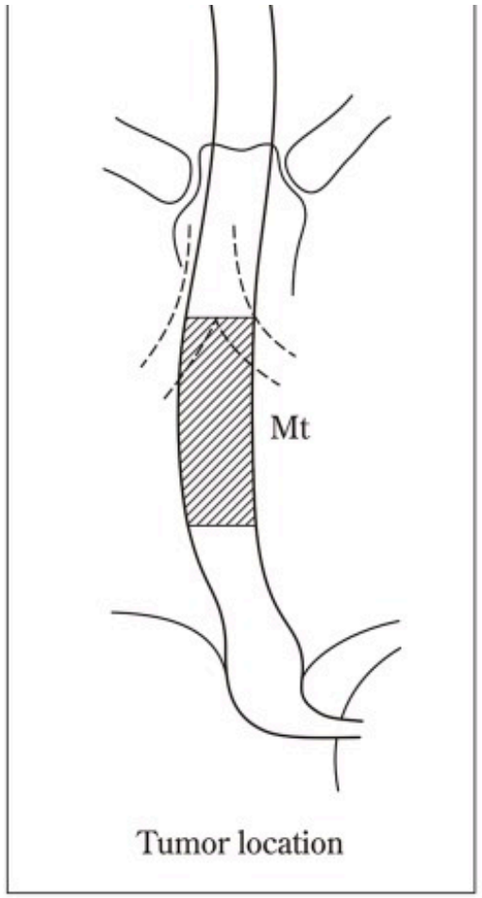
pT2-4 SCC

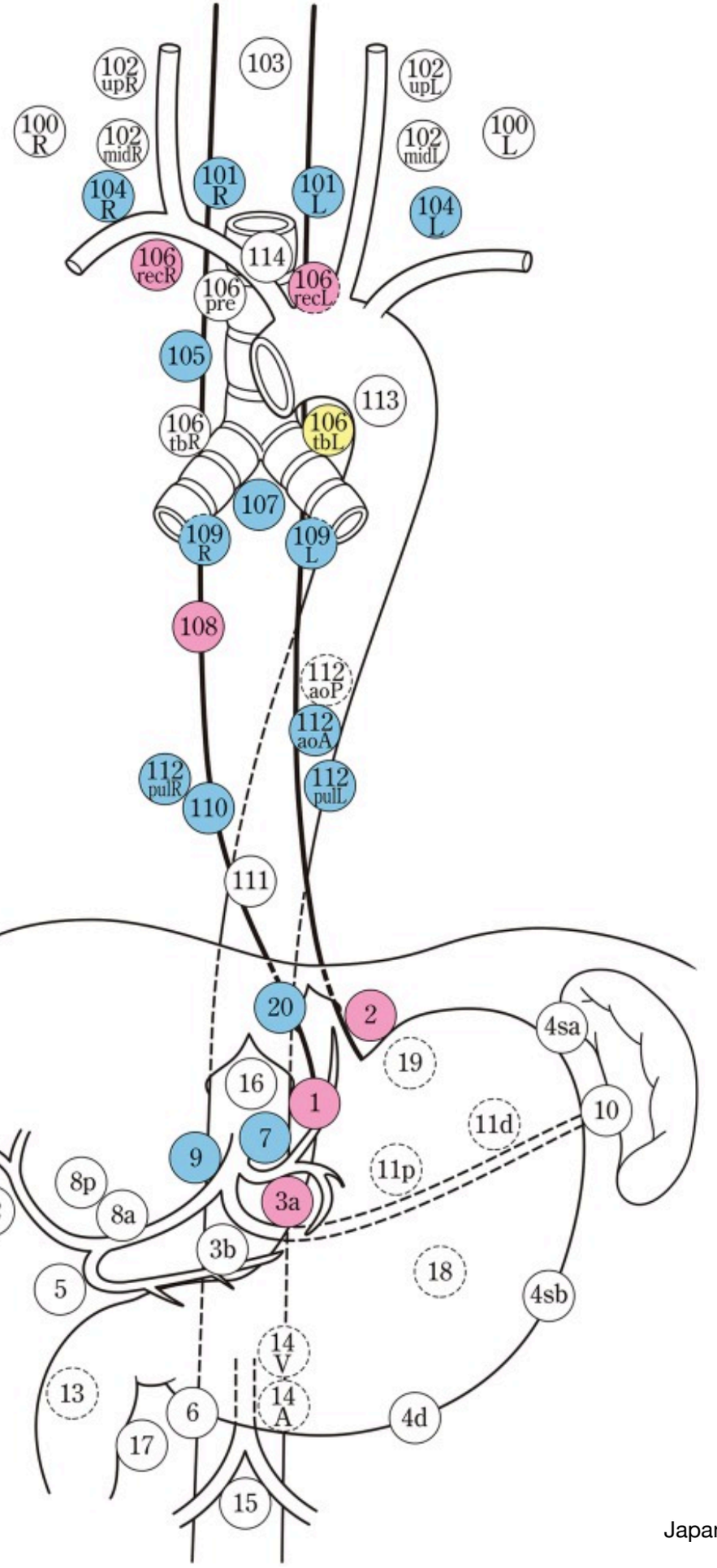
Area	Tumor location			Total (n = 229) (%)
	Upper (n = 33) (%)	Mid (n = 106) (%)	Lower (n = 90) (%)	
Supraclavicular	7 (21.2)	27 (25.5)	5 (5.6)	39 (17.0)
Upper mediastinal	28 (84.8)	65 (61.3)	24 (26.7)	117 (51.1)
Mid-mediastinal	2 (6.1)	52 (49.1)	21 (23.3)	75 (32.8)
Lower mediastinal	2 (6.1)	27 (25.5)	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 Y, Dis Esophagus 2011

Japanese Classification of Esophageal Cancer, 11th Edition: part I

Japan Esophageal Society[1]



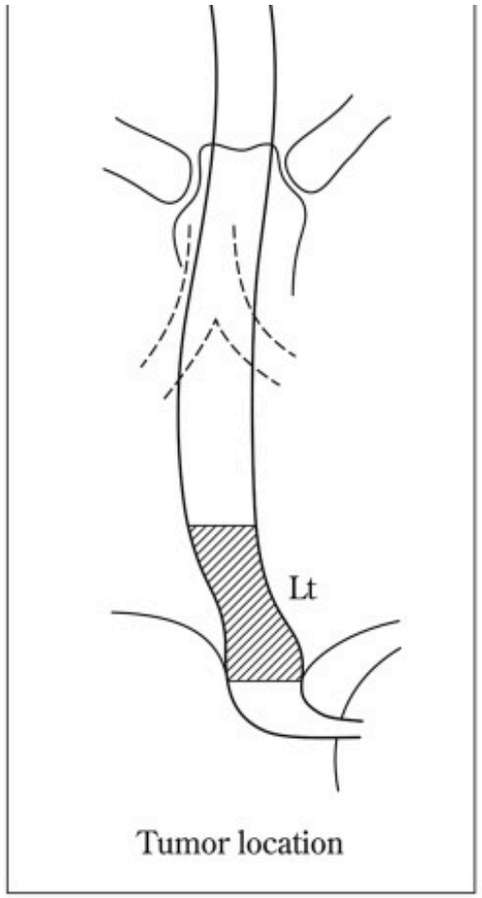


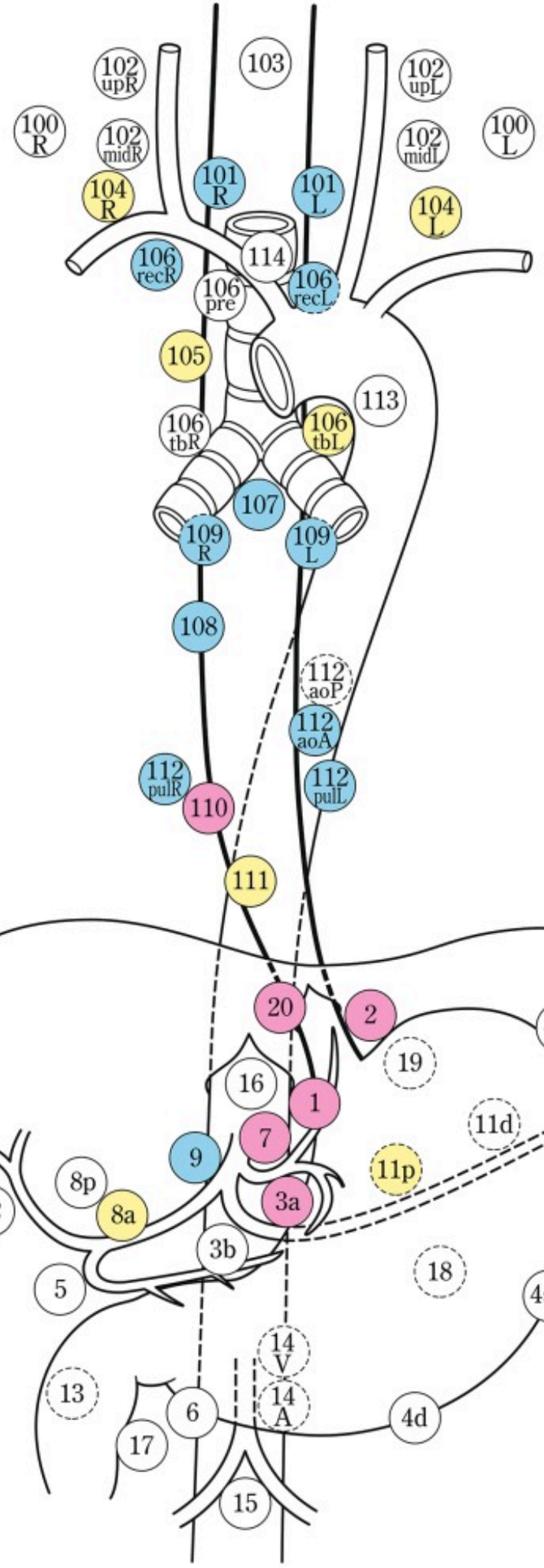
Group 1 :
2 :
3 :
4 :

Japan Esophageal Society, Esophagus 2017

Japanese Classification of Esophageal Cancer, 11th Edition: part I

Japan Esophageal Society[1]





Group 1 :
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Japan Esophageal Society, Esophagus 2017

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journal homepage: www.JournalofSurgicalResearch.com

Three-Field versus Two-Field Lymphadenectomy for Esophageal Squamous Cell Carcinoma: A Meta-analysis

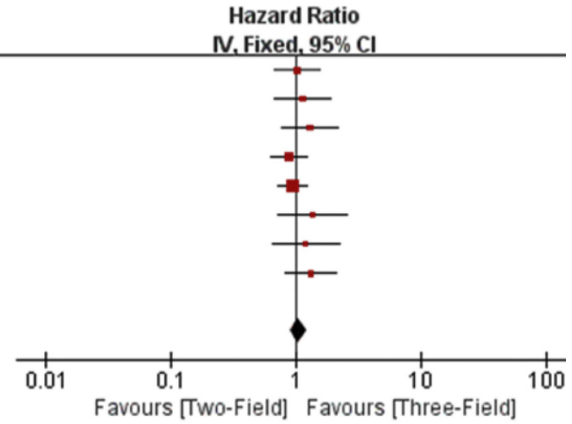
Jingpu Wang, MM,[a] Yang Yang, PhD,[a,] Mohammed Shafiulla Shaik, BM,[b] Jingfeng Hu, MD,[a] Kankan Wang, MN,[c] Chunzhi Gao, MD,[d] Tingting Shan, MM,[a] and Dongfei Yin, MM[e]*

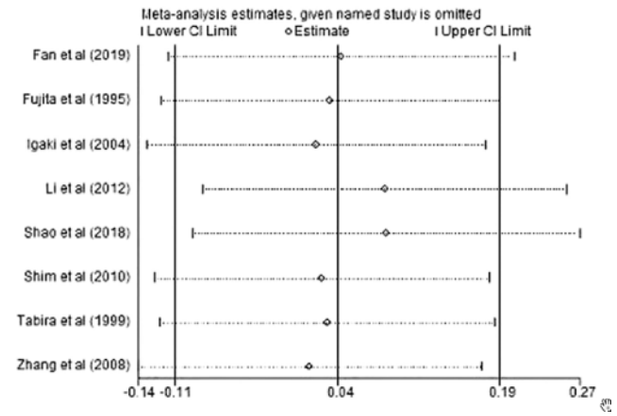
Study	Study interval	Study type	Country	Total cases	Adjuvant therapy	Neoadjuvant therapy	Location of cancer
Fan 2019	2008.03-2013.12	Retrospective cohort/propensity score matching	China	166	Part of all patients	NA	All thoracic segments
Shim 2010	1994.09-2007.12	Retrospective cohort	South Korea	91	Part of all patients	Part of all patients	Upper thoracic segment
Igaki 2004	1988.01-1997.12	Retrospective cohort	Japan	156	Part of all patients	Part of all patients	Lower thoracic segment
Tabira 1999	1983.01-1995.12	Retrospective cohort	Japan	86	All patients	All patients	All thoracic segments
Fujita 1995	1986-1991	Prospective cohort	Japan	128	Part of all patients	Part of all patients	All thoracic segments
Fujita 2003	1986-1998	Retrospective cohort	Japan	241	Part of all patients	Part of all patients	All thoracic segments
Koterazawa 2019	2010.04-2015.12	Retrospective cohort/propensity score matching	Japan	162	NA	Part of all patients	All thoracic segments
Akiyama 1994	1973.01-1993.06	Retrospective cohort	Japan	717	Part of all patients	NA	All thoracic segments
LI 2012	2000.01-2010.08	Retrospective cohort	China	363	NA	None	All thoracic segments
Shao 2018	2009.01-2013.12	Retrospective cohort/propensity score matching	China	564	NA	None	All thoracic segments
Noguchi 2004	1990-2001	Retrospective cohort	Japan	146	NA	None	All thoracic segments
Zhang 2008	2001.01-2006.12	Retrospective cohort	China	122	All patients	None	Middle thoracic segment

Overall Sağkalım

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Fan et al 2019	0.01980263	0.22	12.0%	1.02 [0.66, 1.57]
Fujita et al 1995	0.12221763	0.27	8.0%	1.13 [0.67, 1.92]
Igaki et al 2004	0.25464222	0.26	8.6%	1.29 [0.77, 2.15]
Li et al 2012	-0.12783337	0.17	20.1%	0.88 [0.63, 1.23]
Shao et al 2018	-0.0618754	0.14	29.7%	0.94 [0.71, 1.24]
Shim et al 2010	0.30010459	0.33	5.3%	1.35 [0.71, 2.58]
Tabira et al 1999	0.18232156	0.31	6.1%	1.20 [0.65, 2.20]
Zhang et al 2008	0.27002714	0.24	10.1%	1.31 [0.82, 2.10]
Total (95% CI)			**100.0%**	**1.05 [0.90, 1.21]**

Heterogeneity: Chi² = 4.03, df = 7 (P = 0.78); I² = 0%
Test for overall effect: Z = 0.58 (P = 0.56)

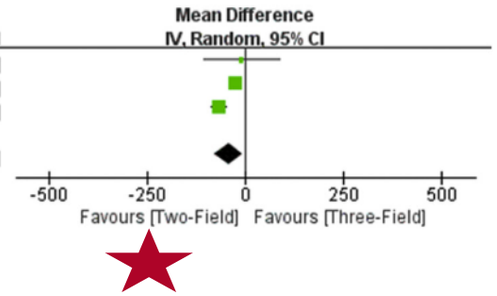




Kan kaybı

Study or Subgroup	Two-Field Mean	SD	Total	Three-Field Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Igaki et al 2004	530	247	55	540	356	101	11.1%	-10.00 [-105.30, 85.30]
Shao et al 2018	211	108	282	238	87	282	44.8%	-27.00 [-43.19, -10.81]
Zhang et al 2008	245.74	47.32	62	313.35	50.76	60	44.1%	-67.61 [-85.04, -50.18]
Total (95% CI)			**399**			**443**	**100.0%**	**-43.05 [-79.05, -7.05]**

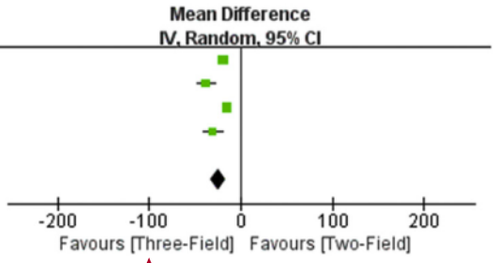
Heterogeneity: Tau² = 685.08; Chi² = 11.73, df = 2 (P = 0.003); I² = 83%
Test for overall effect: Z = 2.34 (P = 0.02)



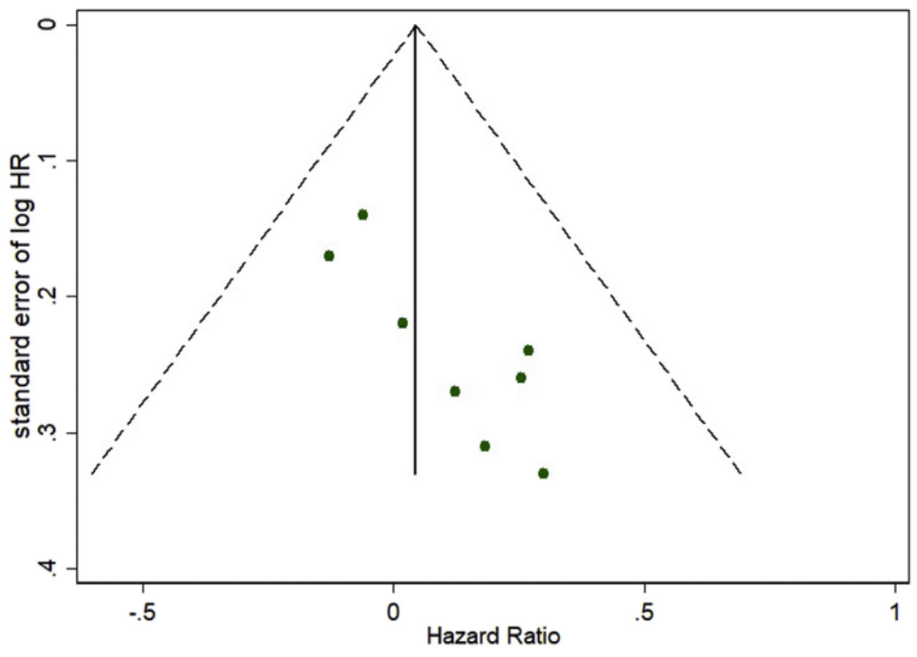
Çıkarılan lenf nodu

Study or Subgroup	Two-Field Mean	SD	Total	Three-Field Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fan et al 2019	35	14.07	83	54	14.81	83	28.0%	-19.00 [-23.39, -14.61]
Fujita et al 1995	46.7	26.1	65	85	28.7	63	21.6%	-38.30 [-47.81, -28.79]
Shao et al 2018	23.1	10.9	282	38.5	14.2	282	29.9%	-15.40 [-17.49, -13.31]
Shim et al 2010	37.8	20.8	34	68.7	29.5	57	20.5%	-30.90 [-41.27, -20.53]
Total (95% CI)			**464**			**485**	**100.0%**	**-24.54 [-32.76, -16.32]**

Heterogeneity: Tau² = 57.83; Chi² = 29.08, df = 3 (P < 0.00001); I² = 90%
Test for overall effect: Z = 5.85 (P < 0.00001)



Outcomes	No. of studies	No. of patients	WMD/OR (95% CI)	Heterogeneity	Test for overall effect	Favors group
Anastomotic leakage	6	1227	0.51 (0.28, 0.92)	$I^2 = 59\%$, $P = 0.03$	$Z = 2.24$, $P = 0.02$	Two-field
Anastomotic stricture	2	219	0.60 (0.22, 1.65)	$I^2 = 0\%$, $P = 0.46$	$Z = 0.99$, $P = 0.32$	-
RLN trauma	6	1227	0.51 (0.26, 1.01)	$I^2 = 62\%$, $P = 0.02$	$Z = 1.92$, $P = 0.05$	-
Chylothorax	5	1099	0.92 (0.48, 1.79)	$I^2 = 0\%$, $P = 0.56$	$Z = 0.23$, $P = 0.82$	-
Pneumonia	5	1105	1.15 (0.84, 1.57)	$I^2 = 0\%$, $P = 0.64$	$Z = 0.88$, $P = 0.38$	-
Ileus	3	375	1.09 (0.27, 4.41)	$I^2 = 0\%$, $P = 0.51$	$Z = 0.12$, $P = 0.91$	-
Cervical nodal recurrence	2	257	0.55 (0.18, 1.63)	$I^2 = 0\%$, $P = 0.86$	$Z = 1.08$, $P = 0.28$	-
Hospital mortality	3	783	1.99 (0.36, 10.97)	$I^2 = 0\%$, $P = 0.99$	$Z = 0.79$, $P = 0.43$	-



Wang J, JSR 2020

Morbidity

Randomized clinical trial

Three-field *versus* two-field lymphadenectomy in transthoracic oesophagectomy for oesophageal squamous cell carcinoma: short-term outcomes of a randomized clinical trial

B. Li[1,5], H. Hu[1,5], Y. Zhang[1,5], J. Zhang[1,5], L. Miao[1,5], L. Ma[1,5], X. Luo[1,5], Y. Zhang[1,5], T. Ye[1,5], H. Li[6], Y. Li[2,5], L. Shen[2,5], K. Zhao[3,5], M. Fan[3,5], Z. Zhu[3,5], J. Wang[4,5], J. Xu[1,2], Y. Deng[1,5], Q. Lu[1,5], H. Li[1,5], Y. Zhang[1,5], Y. Pan[1,5], S. Liu[7], H. Hu[1,5], L. Shao[1,5], Y. Sun[1,5], J. Xiang[1,5] and H. Chen[1,5]

400 SCC, RCT, no Neoadj

	Three-field lymphadenectomy (*n* = 200)	Two-field lymphadenectomy (*n* = 200)	*P*§
Duration of operation (min)*	183 (160–216)	168 (146–191)	< 0·001¶
Blood transfusion	4 (2·0)	5 (2·5)	1·000#
Anastomotic leak	4 (2·0)	10 (5·0)	0·103
Vocal cord paralysis	21 (10·5)	24 (12·0)	0·635
Pulmonary infection	20 (10·0)	14 (7·0)	0·282
Reintubation	6 (3·0)	0 (0)	0·030#
Arrhythmia	9 (4·5)	13 (6·5)	0·380
Chylothorax	7 (3·5)	7 (3·5)	1·000
Wound infection	2 (1·0)	6 (3·0)	0·284#
Intestinal obstruction	1 (0·5)	0 (0)	1·000#
Delayed gastric emptying	1 (0·5)	1 (0·5)	1·000#
90-day mortality	0 (0)	1 (0·5)	1·000#
Duration of hospital stay (days)*	13 (9–15)	12 (9–16)	0·872¶
Clavien–Dindo grade†			
No complication	144 (72·0)	139 (69·5)	0·583
I	19 (9·5)	21 (10·5)	0·739
II	24 (12·0)	32 (16·0)	0·249
III	3 (1·5)	3 (1·5)	1·000#
IV	10 (5·0)	4 (2·0)	0·103
V	0 (0)	1 (0·5)	1·000#
Clavien–Dindo grade III–IV complications†			
Anastomotic leak	0 (0)	2 (1·0)	0·499#
Pulmonary infection	9 (4·5)	3 (1·5)	0·079
Reoperation	4 (2·0)	3 (1·5)	1·000#
Bleeding	2 (1·0)	1 (0·5)	1·000#
Chylothorax	0 (0)	2 (1·0)‡	0·499#
Removal of chest tube	1 (0·5)	0 (0)	1·000#
Cystoscopy for uroschesis	1 (0·5)	0 (0)	1·000#

21.5% servival metastaz-stage migration

Li B, BJS 2020

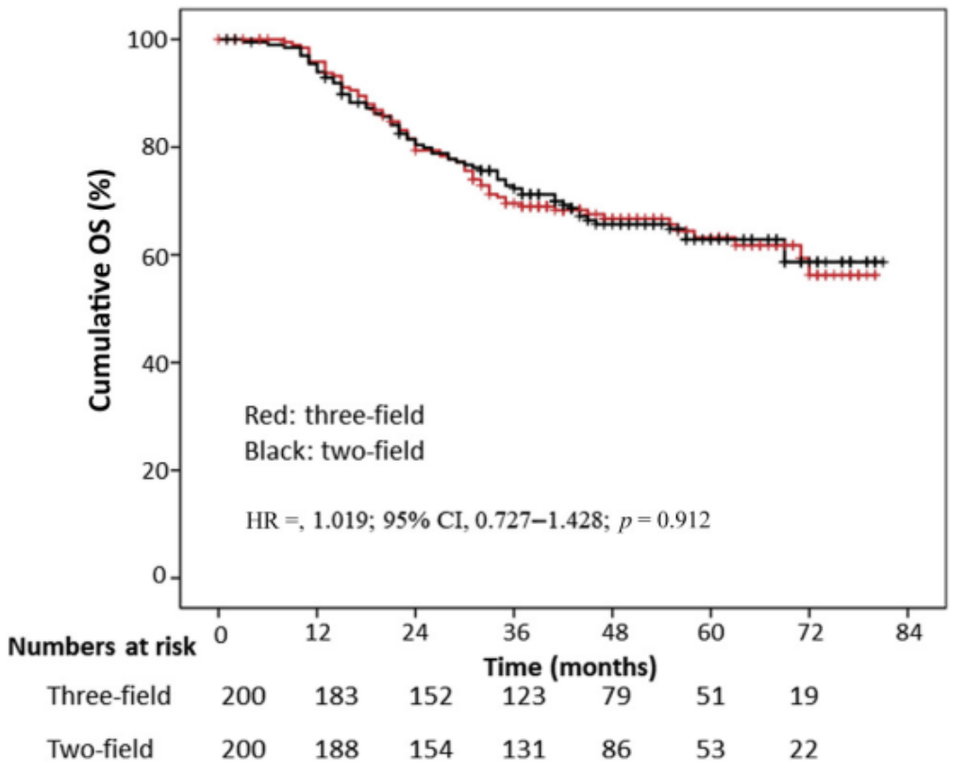
Sağkalım

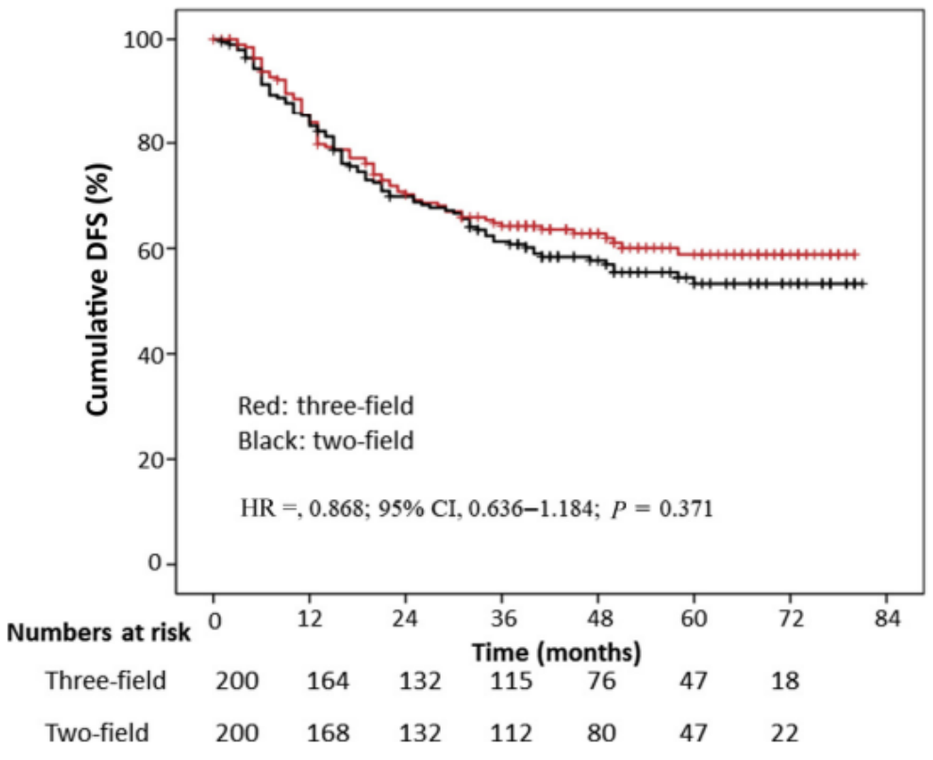
Randomized clinical trial

Three-field *versus* two-field lymphadenectomy in transthoracic oesophagectomy for oesophageal squamous cell carcinoma: short-term outcomes of a randomized clinical trial

B. Li[1,5], H. Hu[1,5], Y. Zhang[1,5], J. Zhang[1,5], L. Miao[1,5], L. Ma[1,5], X. Luo[1,5], Y. Zhang[1,5], T. Ye[1,5], H. Li[6], Y. Li[2,5], L. Shen[2,5], K. Zhao[3,5], M. Fan[3,5], Z. Zhu[3,5], J. Wang[4,5], J. Xu[1,2], Y. Deng[1,5], Q. Lu[1,5], H. Li[1,5], Y. Zhang[1,5], Y. Pan[1,5], S. Liu[7], H. Hu[1,5], L. Shao[1,5], Y. Sun[1,5], J. Xiang[1,5] and H. Chen[1,5]

400 SCC, RCT, no Neoadj





Characteristics	Three Fields (n = 200)	Two Fields (n = 200)
Recurrence type, no. (%)		
Locoregional recurrence	27 (13.5)	27 (13.5)
Distant metastasis	27 (13.5)	32 (16.0)
Mixed[a]	14 (7.0)	13 (6.5)
Unclear	2 (1.0)	5 (2.5)

three-field lymphadenectomy offered **more accurate tumor staging**

21.5% rate of unforeseen cervical lymphatic metastasis, most of which, however, occurred as **part of multiple lymph node metastases**

Compared with radical esophagectomy with two-field lymphadenectomy, esophagectomy with threefield lymphadenectomy **did not improve OS and DFS** for patients with middle and lower thoracic esophageal cancer.

Li B, J Thorac Oncol 2021

Lymph Node Retrieval During Esophagectomy With and Without Neoadjuvant Chemoradiotherapy

Prognostic and Therapeutic Impact on Survival

A. Koen Talsma, MD, Joel Shapiro, MD,* Caspar W. N. Looman, PhD,† Pieter van Hagen, MD,* Ewout W. Steyerberg, PhD,† Ate van der Gaast, MD, PhD,‡ Mark I. van Berge Henegouwen, MD, PhD,§ Bas P. L. Wijnhoven, MD, PhD,* and J. Jan B. van Lanschot, MD, PhD*; On behalf of CROSS Study Group*

		Univariable Analysis, HR (95% CI)		Multivariable Analysis, HR (95% CI)	
	Category	**Surgery Alone**	**nCRT + Surgery**	**Surgery Alone**	**nCRT + Surgery**
Age	Every 10 additional years	1.28 (1.03–1.60)	1.16 (0.90–1.51)	1.20 (0.94–1.52)	1.26 (0.93–1.70)
(y)pT stage	0/in situ	n/a	0.48 (0.29–0.81)	n/a	0.55 (0.32–0.95)
	ypT1	0.12 (0.03–0.50)	0.64 (0.28–1.44)	0.14 (0.03–0.59)	0.64 (0.28–1.51)
	ypT2	0.56 (0.30–1.06)	0.55 (0.31–1.01)	0.80 (0.42–1.54)	0.44 (0.23–0.85)
	ypT3	1 (ref)	–	–	–
	ypT4	0.28 (0.04–2.04)	7.11 (0.92–54.84)	0.25 (0.03–1.69)	5.44 (0.62–47.74)
Resection margin involvement	R0	1 (ref)	–	–	–
	R1	1.34 (0.90–2.00)	1.62 (0.78–3.38)	1.42 (0.93–2.10)	1.20 (0.53–2.73)
Number of resected nodes	Every 10 additionally resected nodes	0.95 (0.79–1.14)	1.02 (0.84–1.25)	0.76 (0.61–0.95)	1.00 (0.84–1.25)
Number of resected positive nodes	Every additionally resected positive node	1.11 (1.08–1.15)	1.15 (1.06–1.25)	1.12 (1.08–1.16)	1.18 (1.07–1.29)

- The **therapeutic value of extended lymphadenectomy**, remains questionable in this group.
- After nCRT, the number of resected nodes is not associated with survival.
- These data **question the indication for maximization of lymph node dissection after nCRT** for staging purposes as well as for therapeutic reasons.

Talsma AK, Ann Surg 2014

Neoadj CRT.....WWA

(SANO: Abdominal + at least the **right paratracheal, subcarinal and paraoesophageal lymph nodes** should be harvested.)

Neoadj CRT + Cerrahi

(CROSS: A transthoracic approach with **two-field lymph-node dissection** was performed for tumors extending <u>proximally to the bifurcation</u>.

For tumors involving the <u>esophagogastric junction</u>, a **transhiatal** resection was preferred.)

Neoadj CT + Cerrahi

(NExT: Regional lymph nodes for <u>upper</u> thoracic disease include both **cervical and thoracic** (paraesophageal, paratracheal, subcarinal and mediastinal) lymph nodes.

Those for <u>middle and lower</u> disease include **thoracic and perigastric** nodes)

Periop CT + Cerrahi (2-field) + Postop RT (for N+)