University of Verona
Department of Surgery
Division of Upper G.I. Surgery
Prof. G. de Manzoni

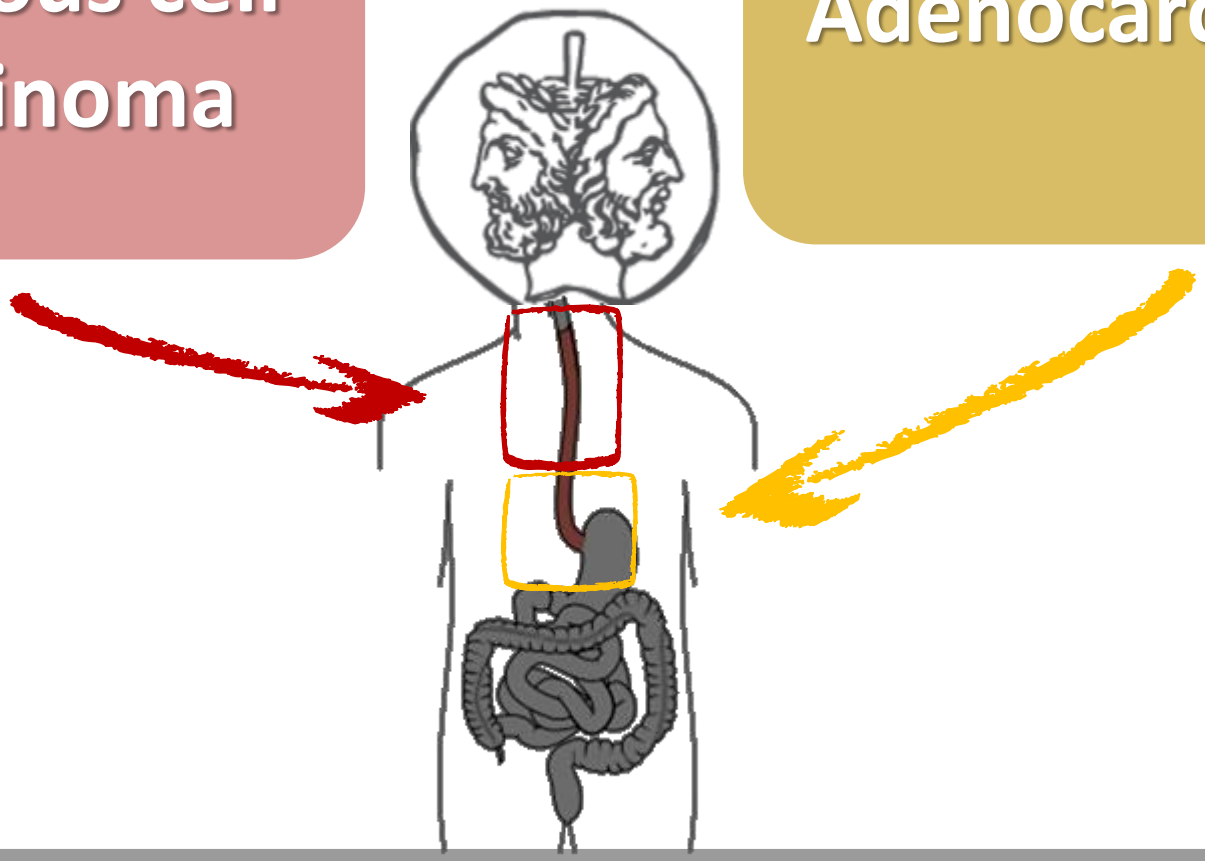
Tecniche chirurgiche nel carcinoma squamoso e nell'adenocarcinoma del cardias

Prof. Giovanni de Manzoni

Negrar, 13 dicembre 2016

Squamous cell carcinoma

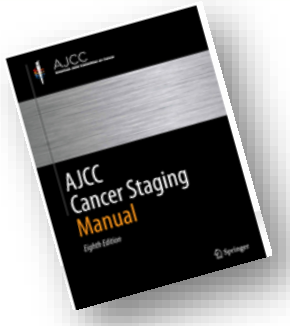
Adenocarcinoma



Two different diseases & Two different treatments

The new TNM classification

8th edition



What's new?

1 New clinical/pathological classification

2 New classification of EGJ adenocarcinoma

The new TNM classification

8th edition

What's new?

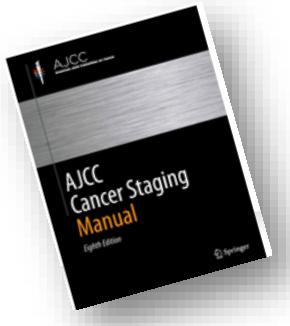
1

cTNM (Clinical Stage)

Neoadjuvant therapy	Neoadjuvant therapy + surgery	Surgery
cTNM	**ypTNM**	**pTNM**
Clinical stage	**AJCC y Stage**	**Pathological stage**

The new TNM classification

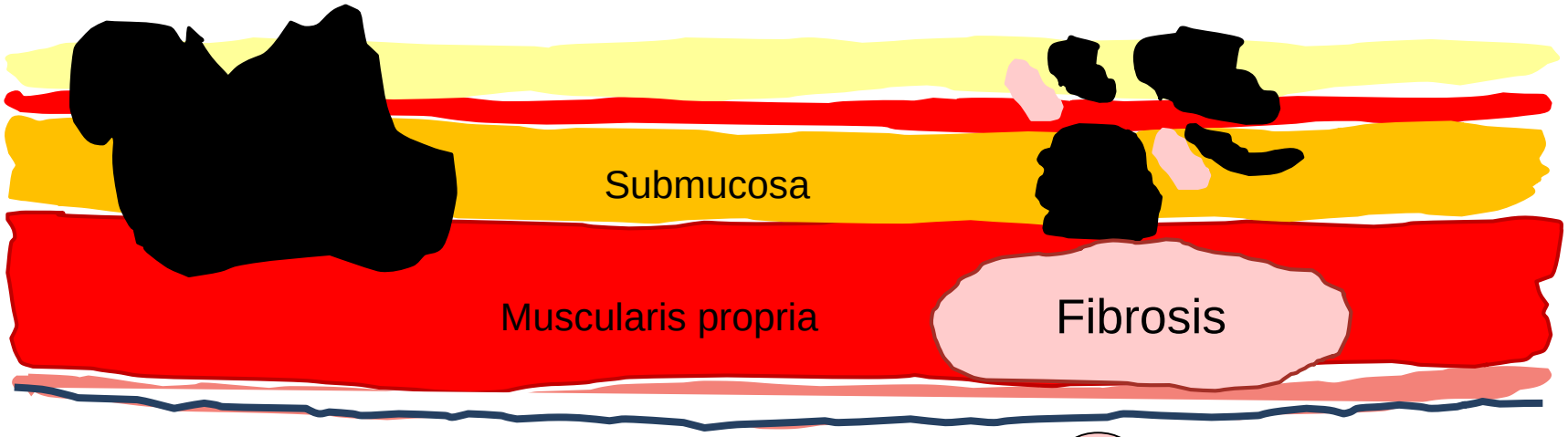
8th edition



What's new?

Changes due to neoadjuvant therapy = is the same TNM adequat?

1

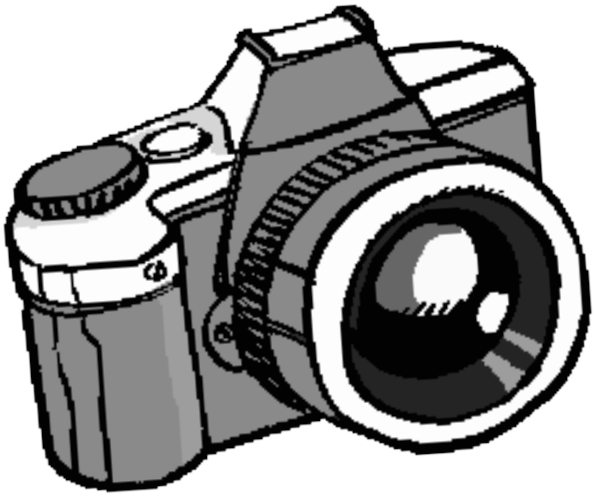


No neoadjuvant therapy
pT2N2

Subserosa

Comparable?

Neoadjuvant therapy
pT2N1



TNM

TRG

Tumor regression grade

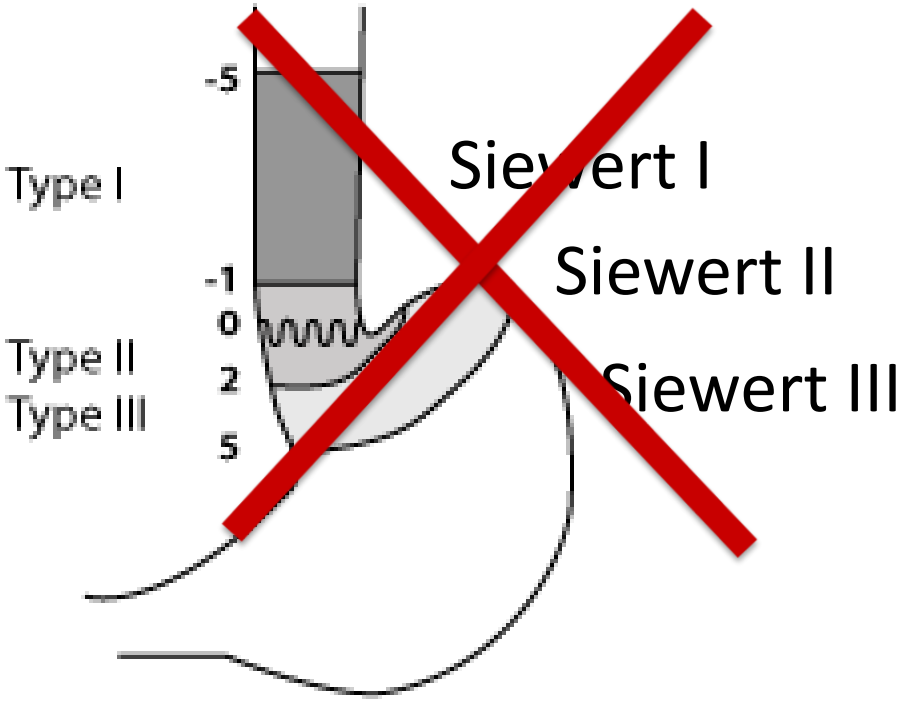
Mandard classification
Becker grading system
SPR (Size-Based Pathological Response)

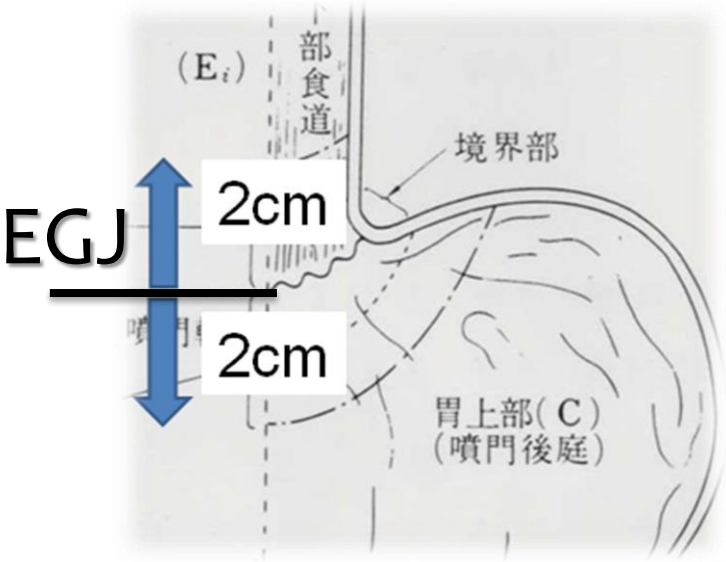
The new TNM classification

8th edition

What's new?

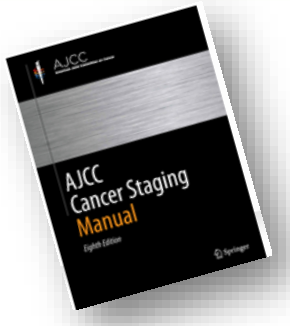
2 **EGJ adenocarcinoma**





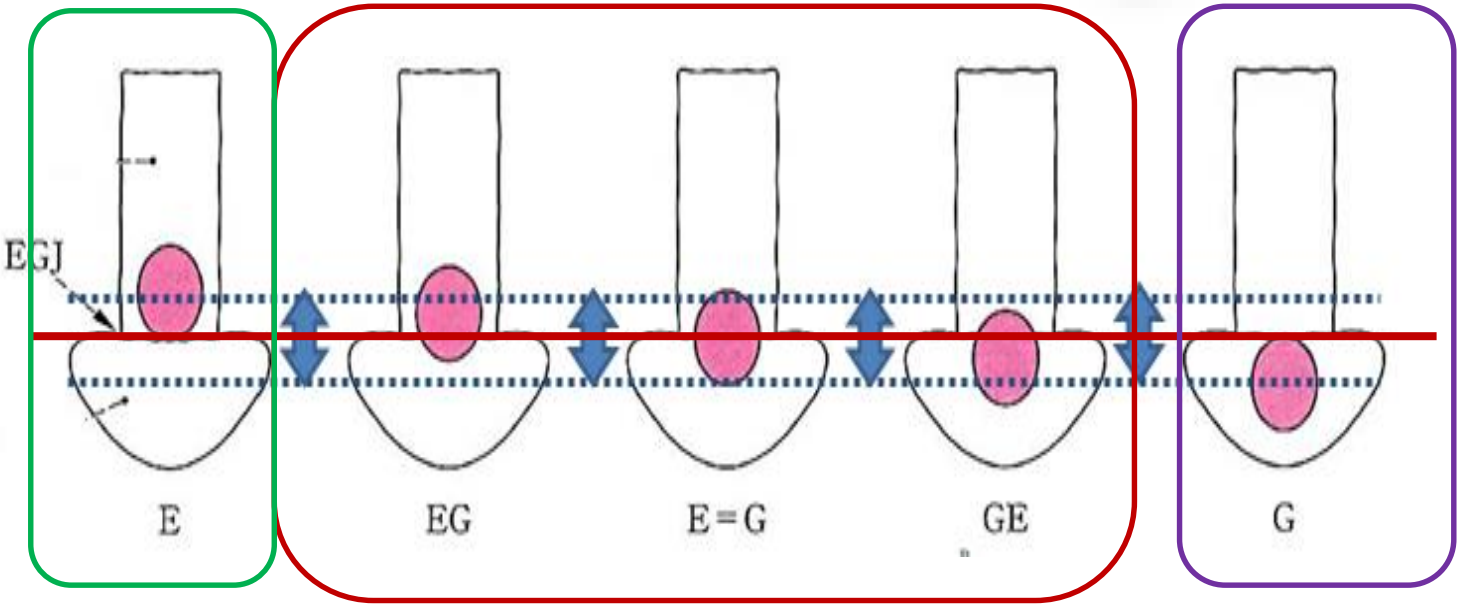
The new TNM classification

8th edition



What's new?

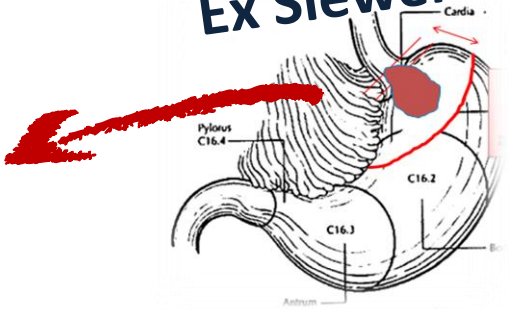
2



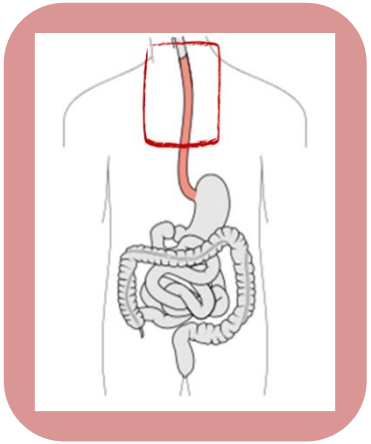
Ex Siewert I

Ex Siewert II

Ex Siewert III



…now classified as a Gastric cancer

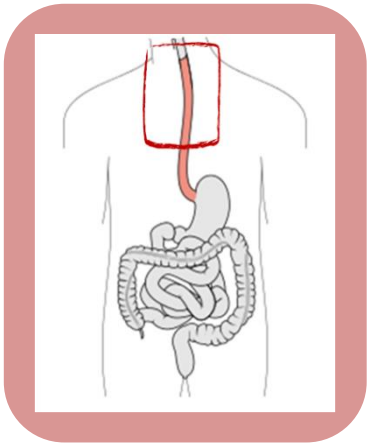


Squamous Cell Carcinoma

Treatment strategy depends on:

Tumor site →
- ✓ Resection margins
- ✓ Nodal diffusion

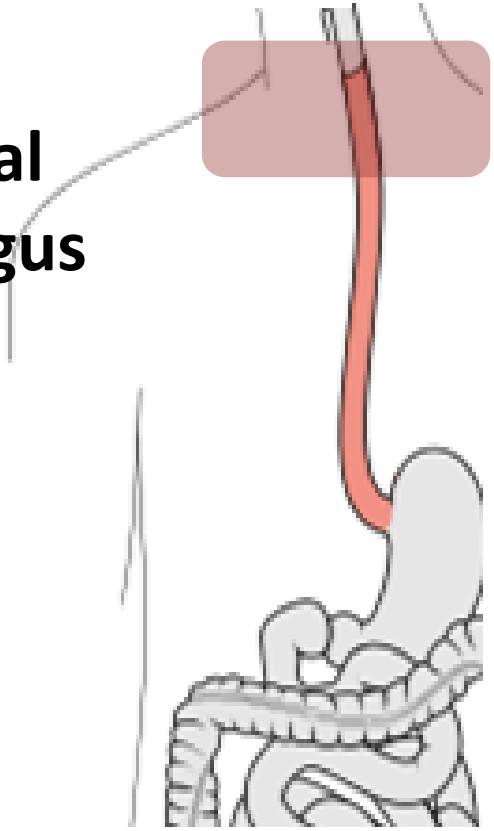
Stage →
- ✓ Risk of nodal involvement



Squamous Cell Carcinoma

Tumor site

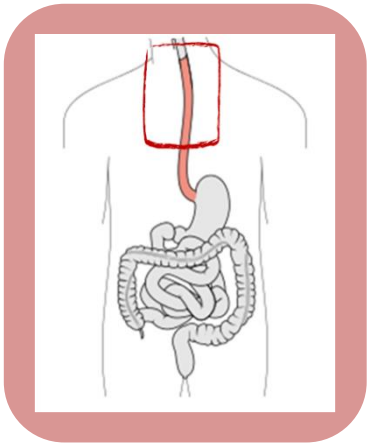
Cervical esophagus



Definitive CRT

+ salvage surgery

Ancona E, et al (2008) Ann Surg Oncol
Altorki N, et al (2002) Ann Surg
Bollschweiler E, et al (2006) Endoscopy
Sepesi B, et al (2010) J Am Coll Surg
Gockel I, et al (2009) J Surg Oncol

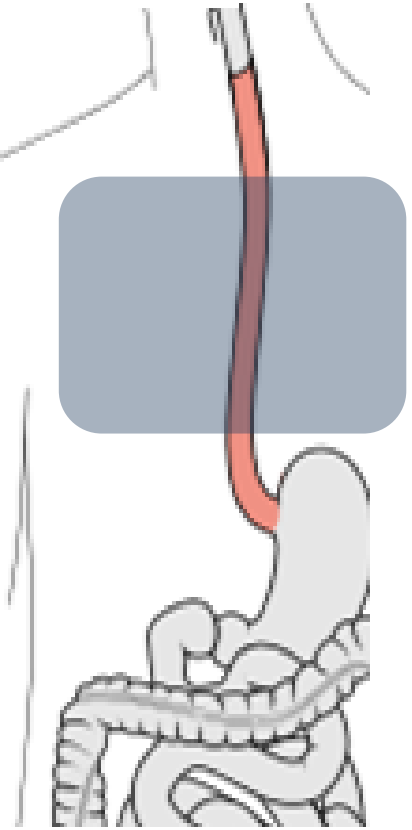


Squamous Cell Carcinoma

Tumor site

Thoracic esophagus

Stage



Early Stage

cT0-2 N0

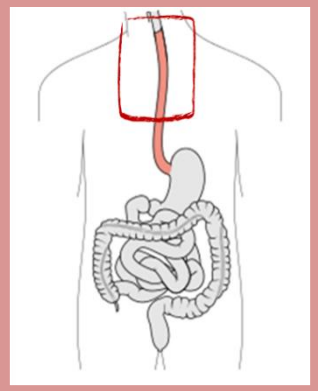
Upfront Surgery

Locally Advanced

cT3N0; any N+

Neoadjuvant CRT + Surgery ?

Ancona E, et al (2008) Ann Surg Oncol Altorki N, et al (2002) Ann Surg Bollschweiler E, et al (2006) Endoscopy Sepesi B, et al (2010) J Am Coll SurgGockel I, et al (2009) J Surg Oncol



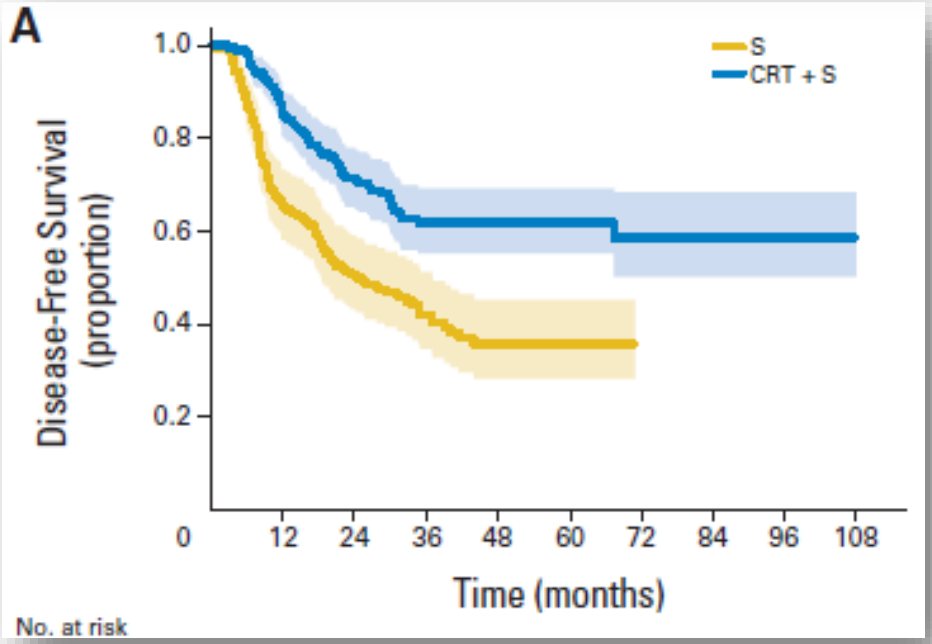
Squamous Cell Carcinoma

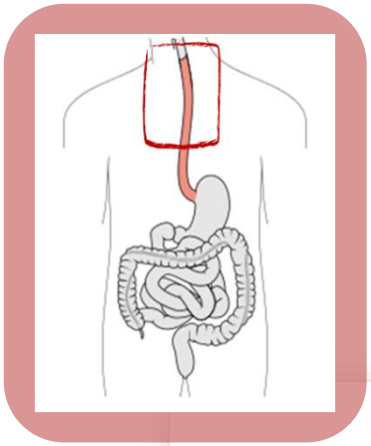
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Patterns of Recurrence After Surgery Alone Versus Preoperative Chemoradiotherapy and Surgery in the CROSS Trials

Vera Oppedijk, Ate van der Gaast, Jan J.B. van Lanschot, Pieter van Hagen, Rob van Os, Caroline M. van Rij, Maurice J. van der Sangen, Jannet C. Beukema, Heidi Rütten, Patty H. Spruit, Janny G. Reinders, Dick J. Richel, Mark I. van Berge Henegouwen, and Maarten C.C.M. Hulshof

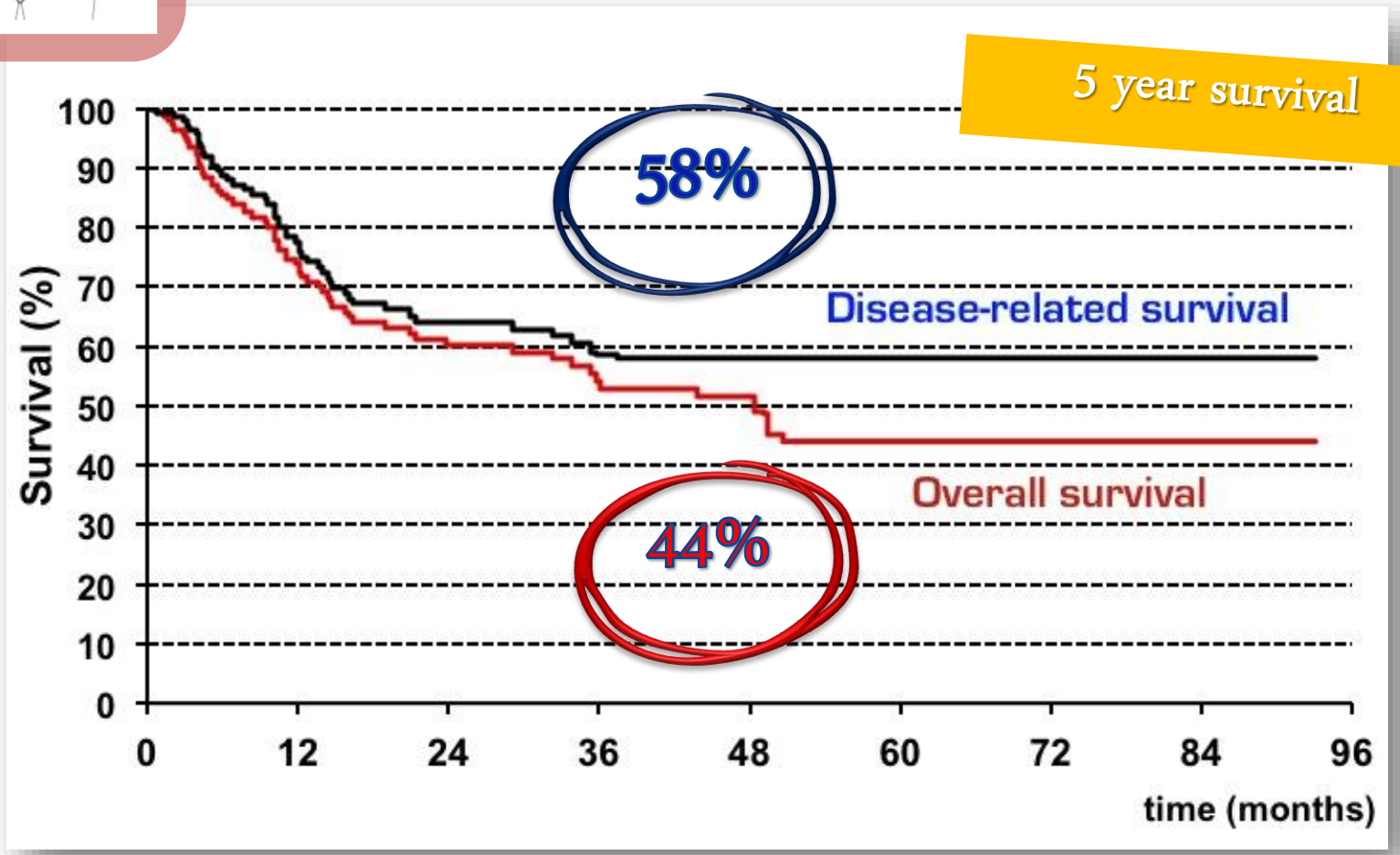
CROSS trial

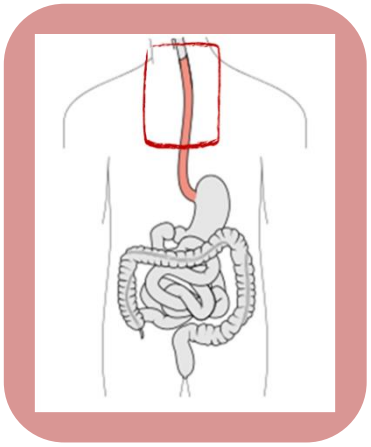




Squamous Cell Carcinoma

Neoadjuvant CRT: our results





Squamous Cell Carcinoma

Thoracic esophagus
Locally advanced

Standard of care:
neoadjuvant CRT + surgery

Pathological complete response!!!

Pathological complete response after CRT?

N ENGL J MED 366;22 NEJM.ORG MAY 31, 2012

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

pCR: 23% of ADK and 49% of SCC

Ann Surg Oncol (2013)

Neoadjuvant Concurrent Chemoradiotherapy for Locally Advanced Esophageal Cancer in a Single High-Volume Center

A. Zanoni, MD[1], G. Verlato, MD[2], S. Giacopuzzi, MD[1], J. Weindelmayer, MD[1], F. Casella, MD[1], F. Pasini, MD[3], E. Zhao, MD[4], and G. de Manzoni, MD[1]

pCR: 45% of ADK and 53% of SCC

"surgery as needed" approach?

...a nonsurgical strategy in patients with a cCR after nCRT, theoretically saves 5% mortality and 60% severe morbidity...

COMING SOON

SANO trial

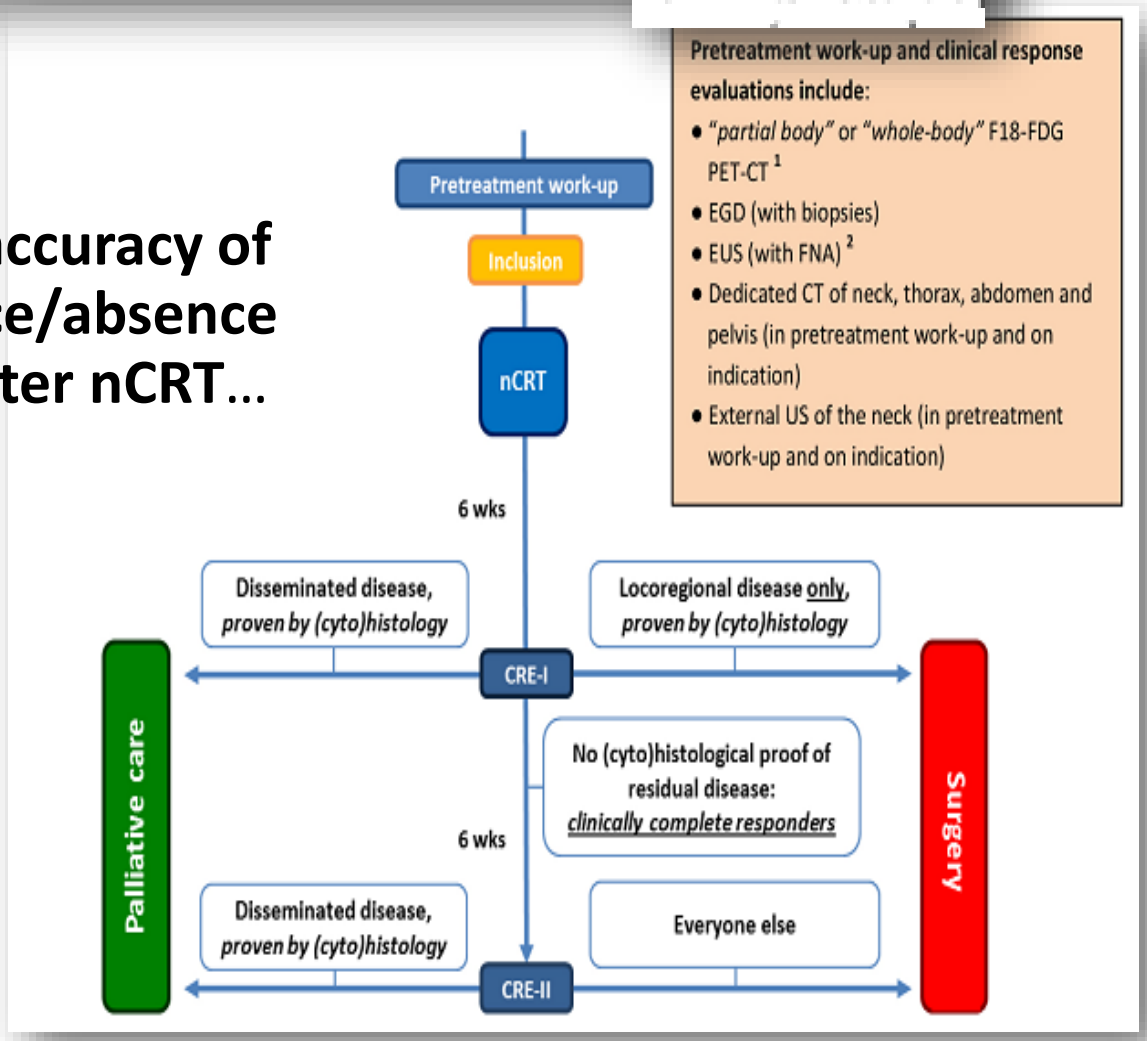
nCRT+surgery vs nCRT + surveillance

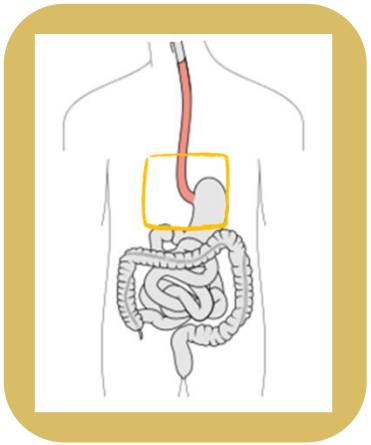
Accuracy of Detecting Residual Disease After Cross Neoadjuvant Chemoradiotherapy for Esophageal Cancer (preSANO Trial): Rationale and Protocol

Noordman et al

JMIR Res Protoc 2015

…to determine the accuracy of detecting the presence/absence of residual disease after nCRT…

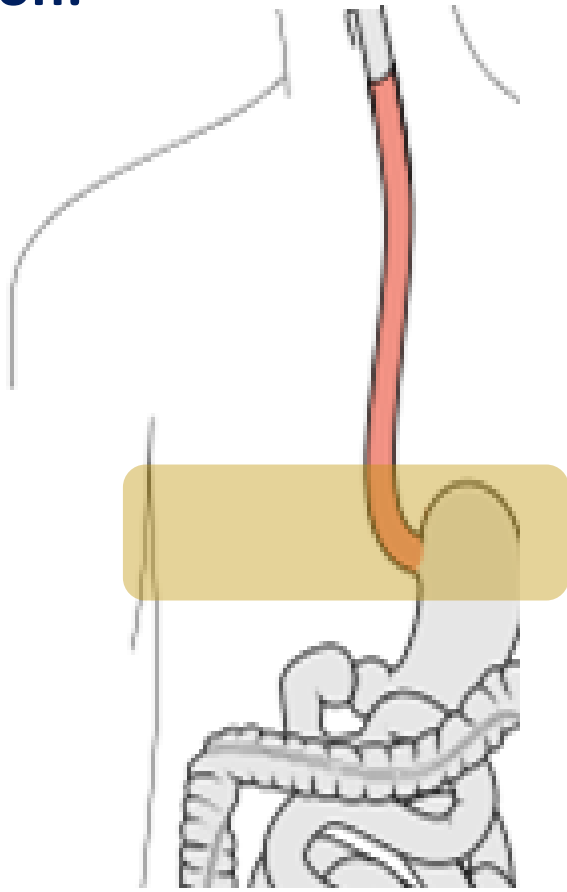




Adenocarcinoma

Treatment strategy depends on:

Stage



Early Stage
cT0-2 N0

Upfront Surgery

Locally Advanced
cT3N0; any N+

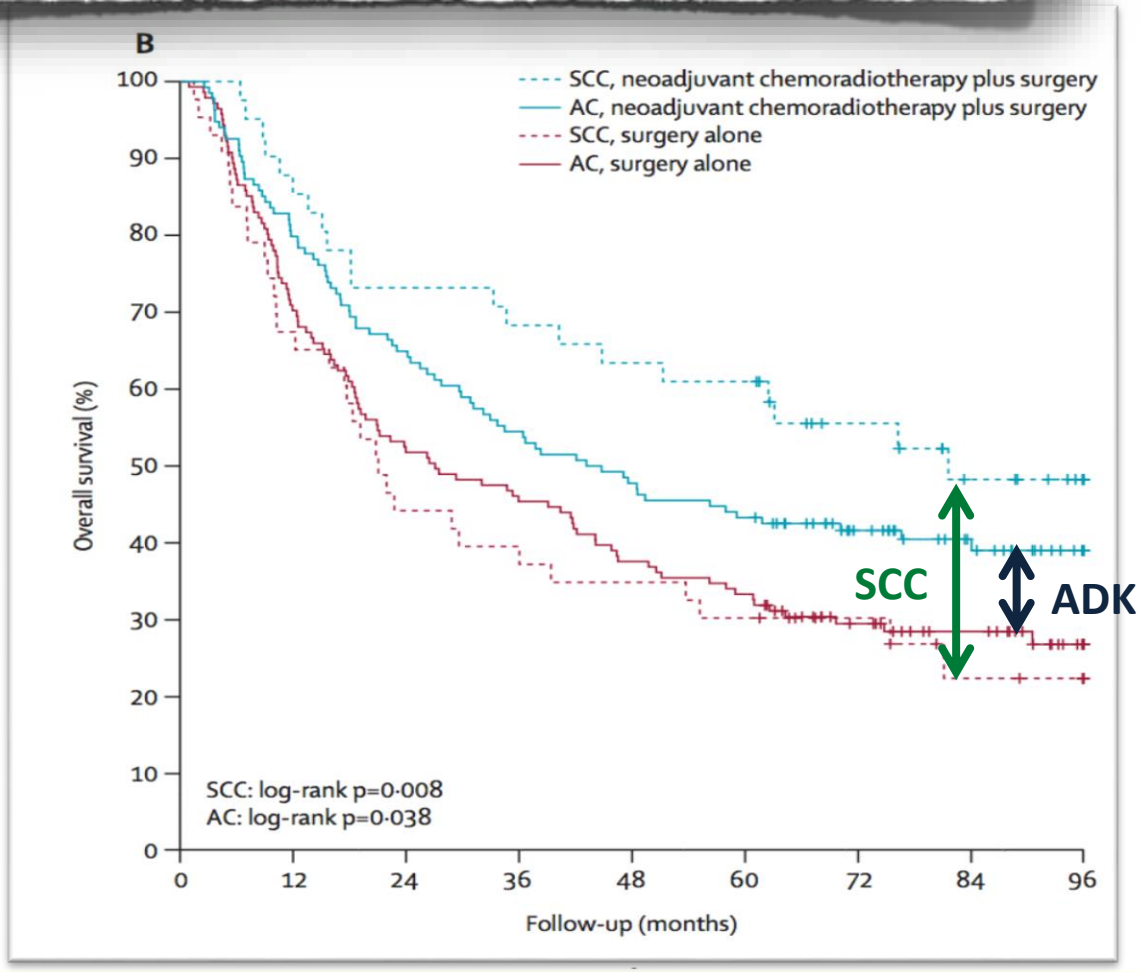
Neoadjuvant treatment + Surgery !

No definitive CRT

CROSS trial long term results

Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): long-term results of a randomised controlled trial

Joel Shapiro, J Jan B van Lanschot, Maarten C C M Hulshof, Pieter van Hagen, Mark I van Berge Henegouwen, Bas P L Wijnhoven, Hanneke W M van Laarhoven, Grard A P Nieuwenhuijzen, Geke A P Hospers, Johannes J Bonenkamp, Miguel A Cuesta, Reinoud J B Blaisse, Olivier R C Busch, Fiebo J W ten Kate, Geert-Jan M Creemers, Cornelis J A Punt, John Th M Plukker, Henk M W Verheul, Ernst J Spillenaar Bilgen, Herman van Dekken, Maurice J C van der Sangen, Tom Rozema, Katharina Biermann, Jannet C Beukema, Anna H M Piet, Caroline M van Rij, Nanny G Reinders, Hugo W Tilanus, Ewout W Steyerberg, Ate van der Gaast, for the CROSS study group



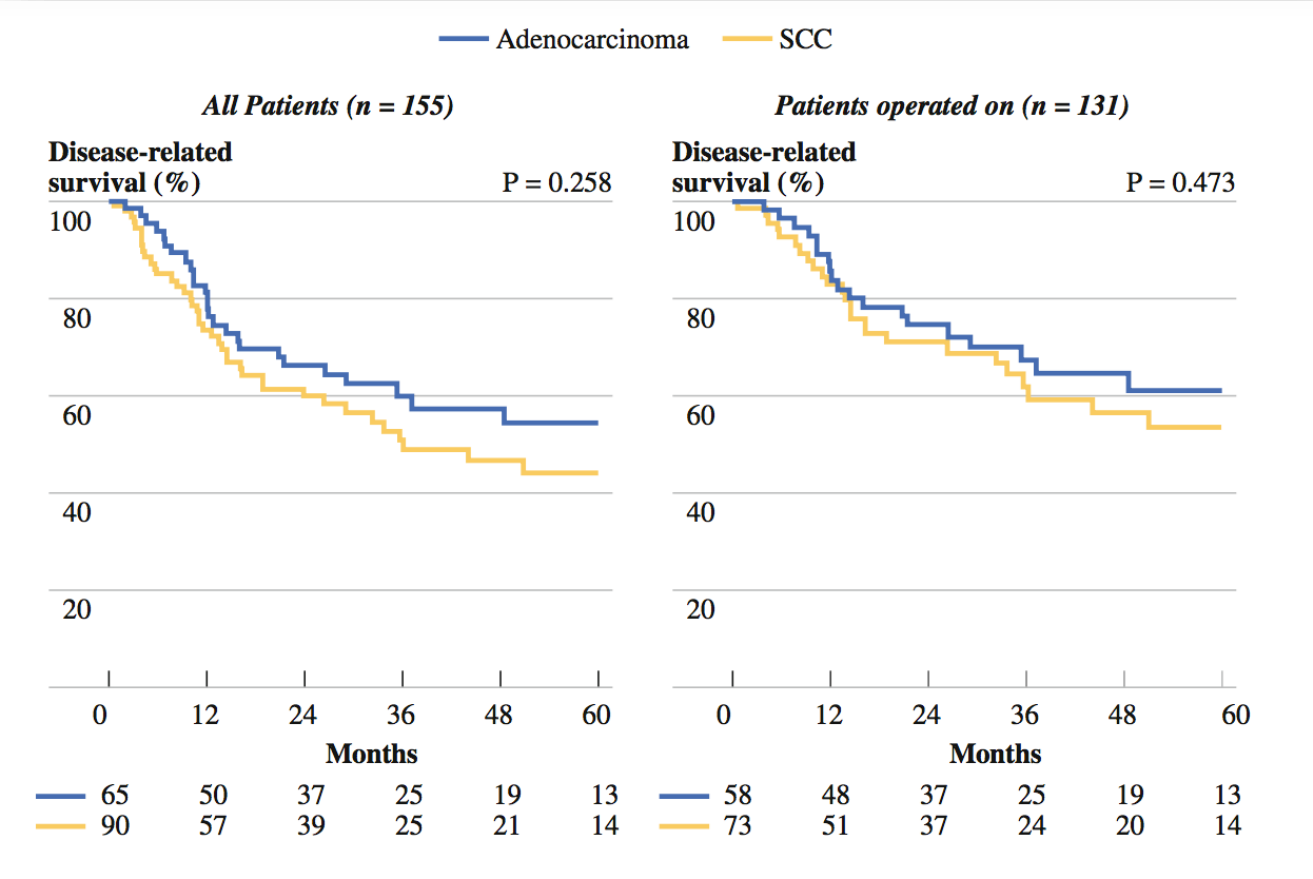
Good but not as good as for SCC

Ann Surg Oncol (2013) 20:1993–1999
DOI 10.1245/s10434-012-2822-4

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Neoadjuvant Concurrent Chemoradiotherapy for Locally Advanced Esophageal Cancer in a Single High-Volume Center

A. Zanoni, MD[1], G. Verlato, MD[2], S. Giacopuzzi, MD[1], J. Weindelmayer, MD[1], F. Casella, MD[1], F. Pasini, MD[3], E. Zhao, MD[4], and G. de Manzoni, MD[1]



Good as for SCC

41.4 Gy

Gy?

50.4 Gy

carboplatin

paclitaxel

Chemo?

5-FU

cisplatin

docetaxel

transthoracic approach with two-field

transhiatal resection

Surgery?

transthoracic approach with two-field

Aims of surgical resection

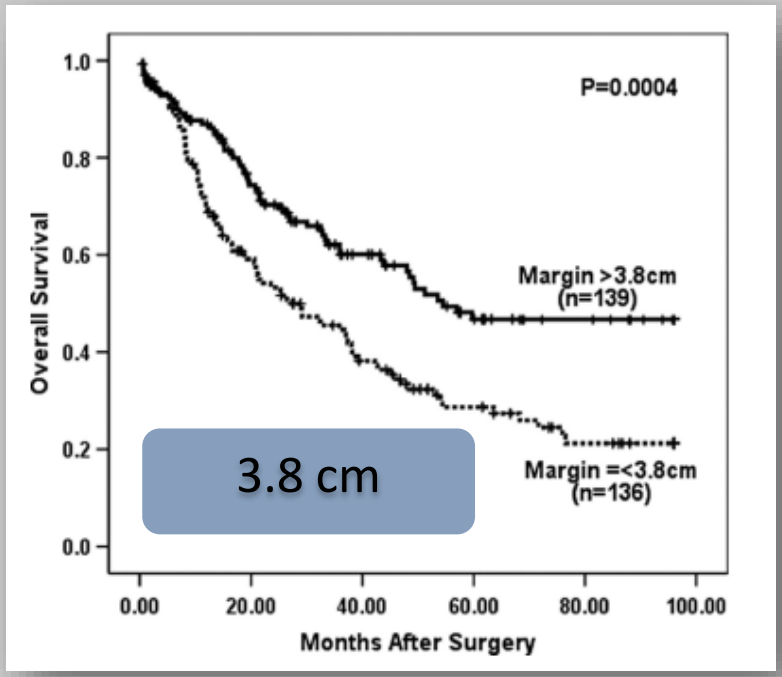
R0

- Resection margins
- Lymphadenectomy

Resection margins

INTRAMURAL spread

Subepithelial spread



Barbour AP et al, *Ann Surg*, 2007.

Intramural metastasis

Metastasis far from the tumour margin

- ✓ Risk of positive margin < 5% if *in vivo margin* > 5 cm
- ✓ Anastomotic recurrence >20% if margin <5 cm

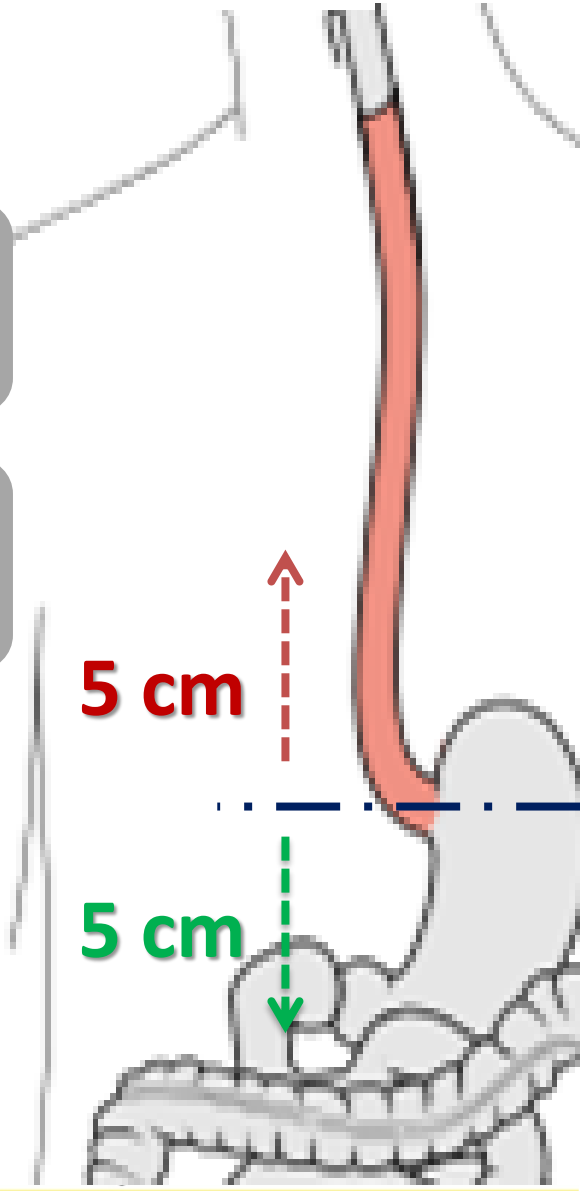
Lam e al, J Clin Pathol (1996)
Tsutsui S, Ann Surg (1995)
Kuwano H, Surgery (2002)
Casson AG et all, Ann Thorac Surg (2000)

Resection margins

Proximal

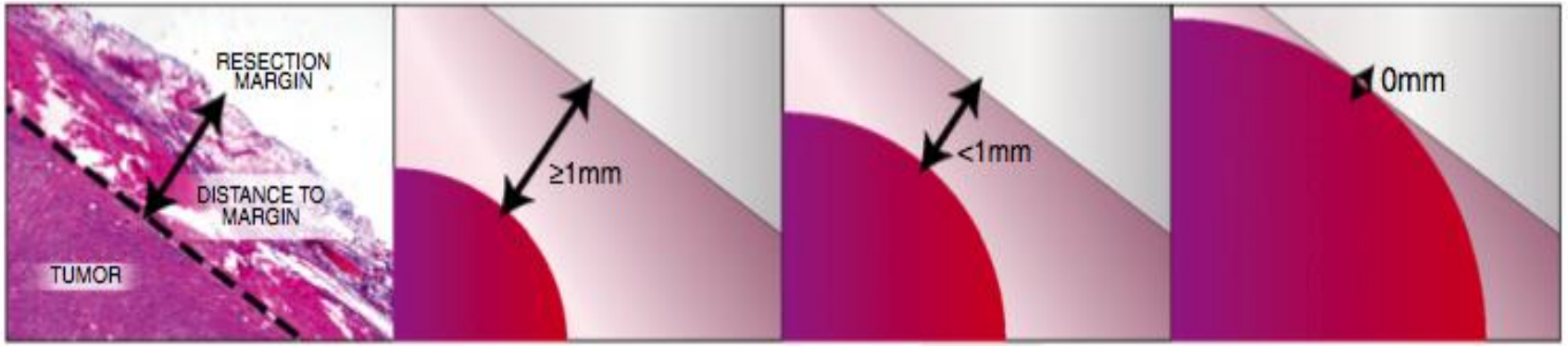
Distal

In vivo



Resection margins

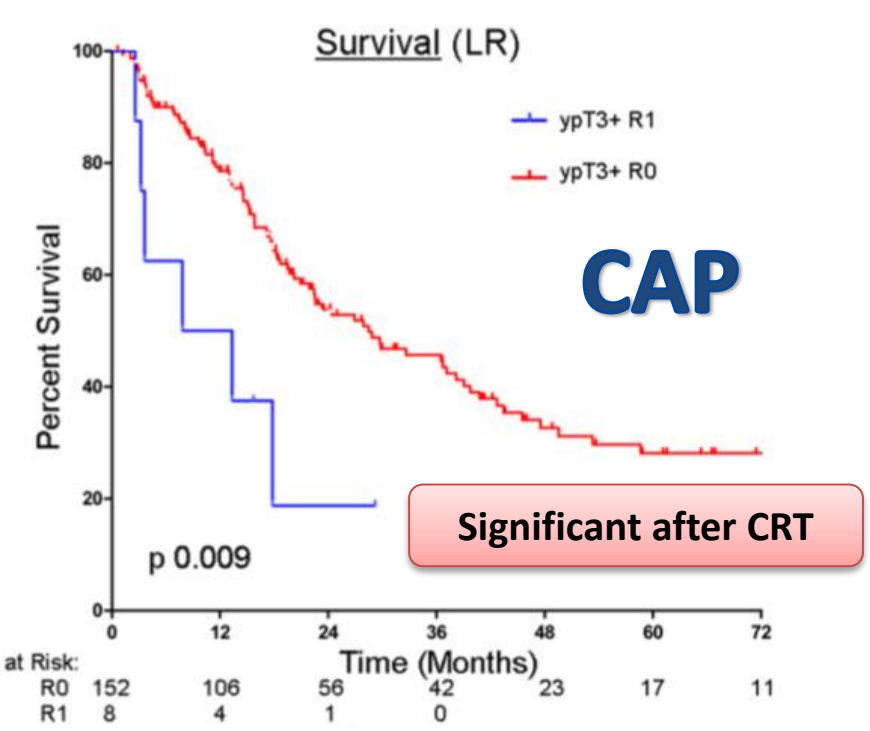
CIRCUMFERENTIAL (CRM)



CAP - College of American Pathologists	**R0**	**R0**	**R1**
RCP - Royal College of Pathologists	**R0**	**R1**	**R1**

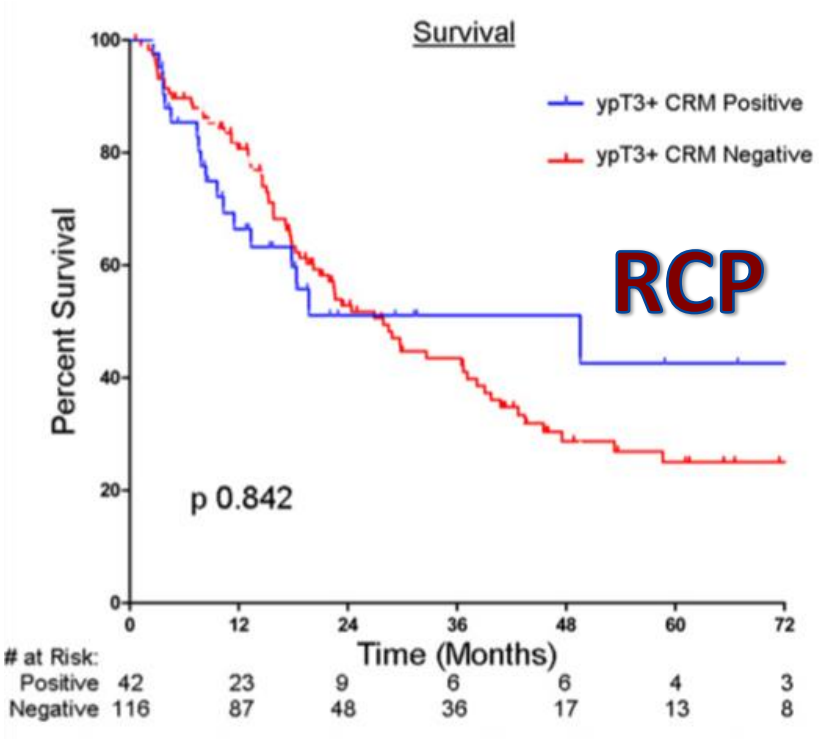
Verhage et al. Am J Surg Pathol 2011

Resection margins



CAP

Significant after CRT



RCP

N.B. **Transhiatal Esophagecomy** results in more POSITIVE circumferential margins

Suttie SA et al, EJSO 2012

Harvin et al, Thorac Cardiovas Surg 2002

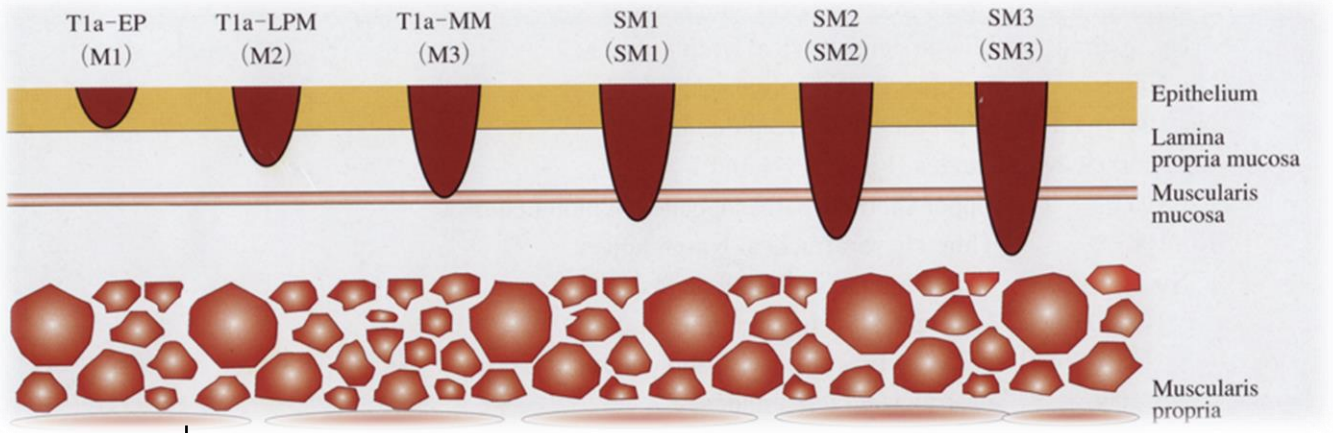
Aims of Surgical resection

R0

- Resection margins
- **Lymphadenectomy**

LYMPHADENECTOMY

Depends on… Tumor Stage



	AdenoK	SCC
m1-m2	0% N+	0% N+
m3	up to 1,5% N+	up to 15% N+
sm1	up to 22% N+	up to 50% N+
sm2-sm3	up to 60% N+	up to 65% N+

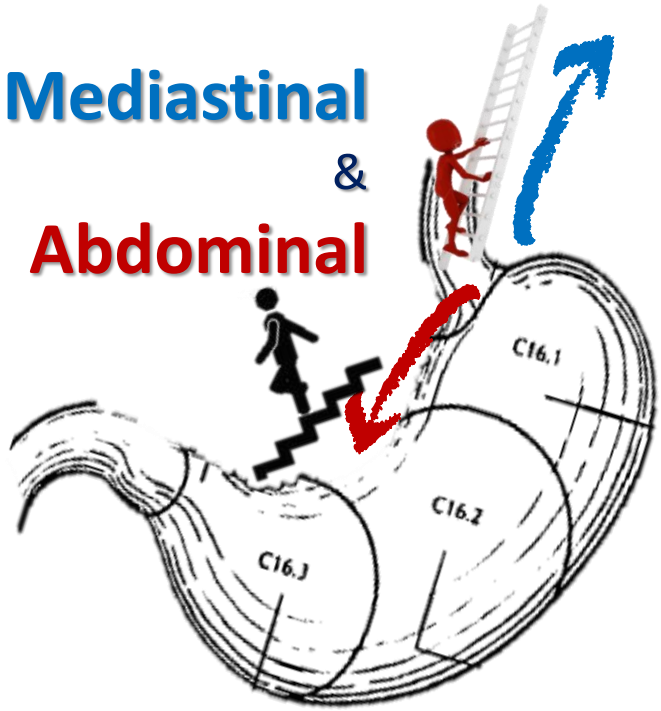
Griffin SM, et al (2011) Ann Surg
Gockel I, et al (2009) J Surg Oncol
Tachibana M, et al (2008) Ann Surg Oncol
Ancona E, et al (2008) Ann Surg Oncol

Sepesi B, et al (2010) J Am Coll Surg
Lerut T, et al (2004) Ann Surg
Mariette C, et al (2004) Eur J Surg Oncol
Altorki N, et al (2002) Ann Surg

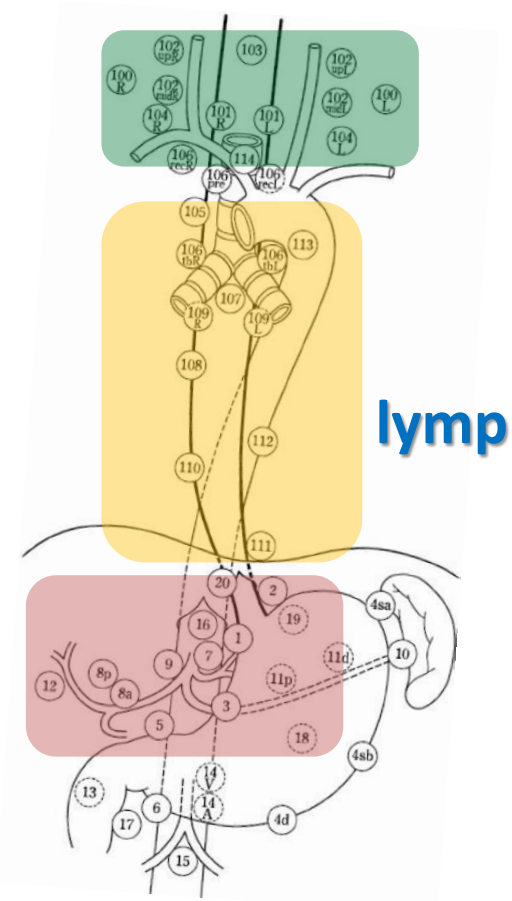
LYMPHADENECTOMY

Depends on… Nodal Spread

Adenocarcinoma



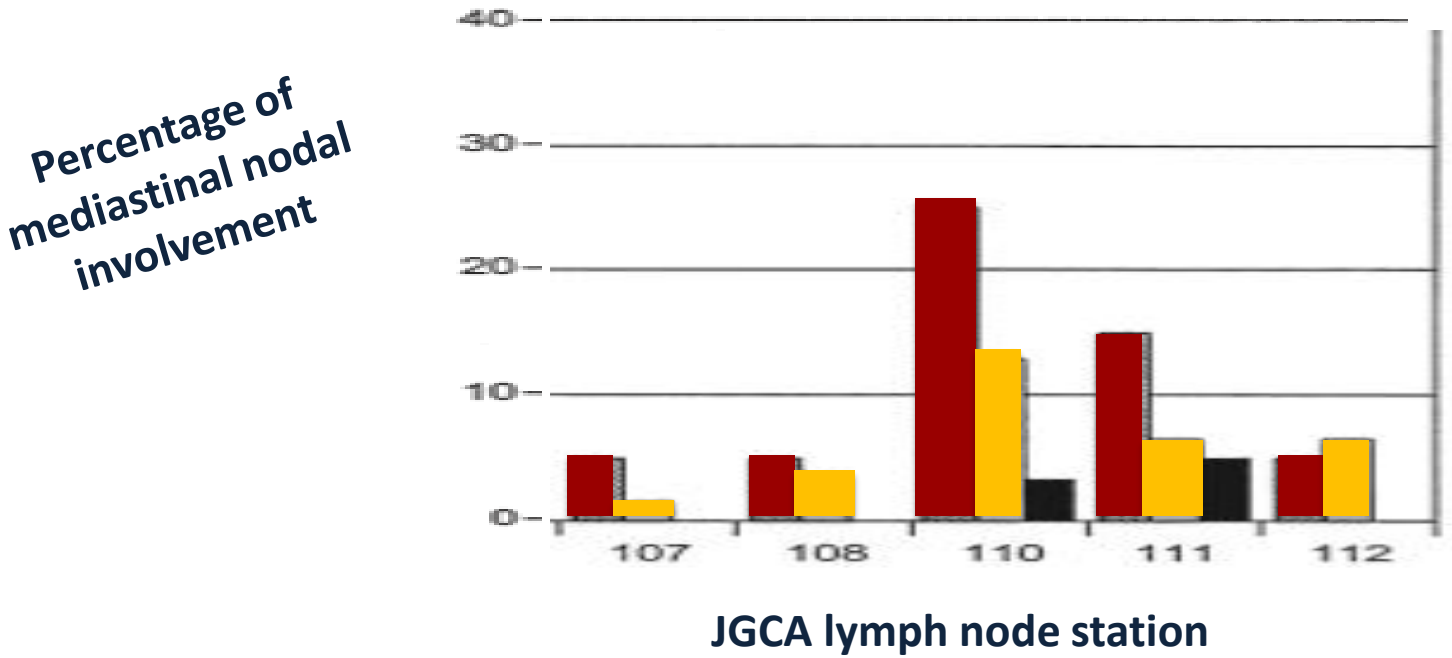
Squamous cell



Fields of lymphadenectomy

Siewert I&II mediastinal lymphatic diffusion

		Siewert 1	Siewert 2	Siewert 3
N+ Site	Abdomen	54%	70%	91%
	Abdomen+Thorax	46%	30%	7%



de Manzoni et al. J Thor Cardiovasc Surgery 2007

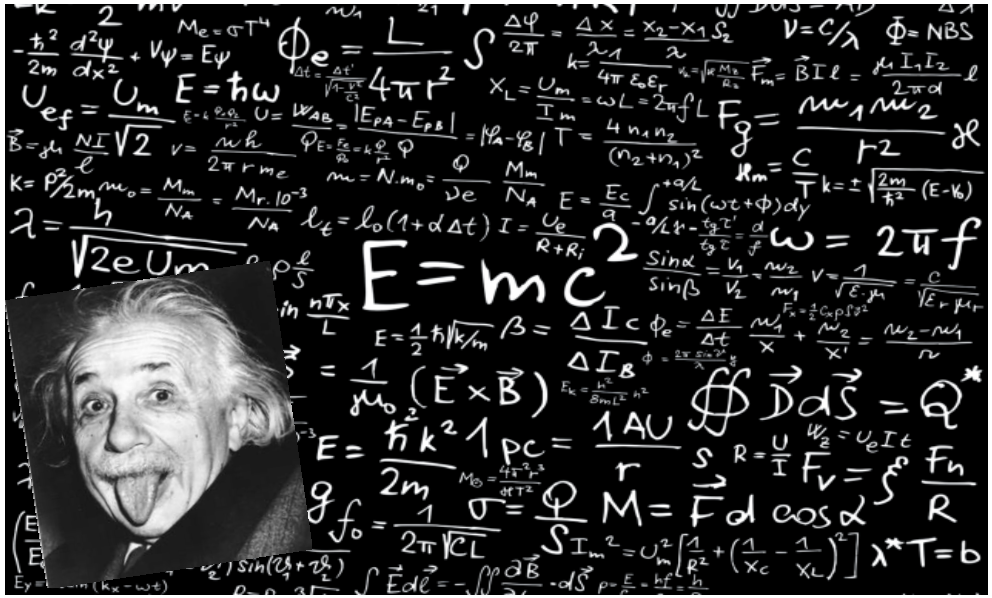
Siewert II lymphatic diffusion

Siewert type II
T2-T4

Mid.Mediast	3-22%
Inf.Mediast.	6-34%
Cardiac	48-74%
Left Gastric	22-56%
Celiac Art.	20-30%
Paraaortic	0-10%

How to explain this variability?

Maybe the reality is more…relative…



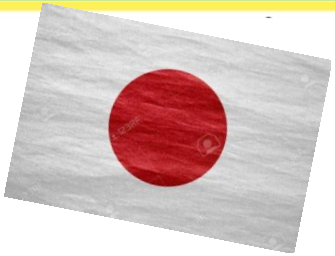
…does esophageal invasion matter?

Peracchia ‘99, Hagen ‘01, Feith ’03 Stein ‘05, Lagarde ‘05, de Manzoni ’07, Parry ‘14

Surgery, March 2015

Mediastinal lymph node metastasis and recurrence in adenocarcinoma of the esophagogastric junction

Yukinori Kurokawa, MD,[a] Naoki Hiki, MD,[b] Takaki Yoshikawa, MD,[c] Kentaro Kishi, MD,[d]



315 EGJ AdenoK SII

60 months FU

Lower mediastinum N+

Lymphonodal metastasis or recurrence rate according to esophageal invasion

	Distance from the EGJ to the proximal edge of primary tumor (cm), % (n/N)			
Location of mediastinal nodes	*0–1.0*	*1.1–2.0*	*2.1–3.0*	*>3.0*
Upper	0.9 (1/115)	1.1 (1/90)	6.8 (5/74)	13.9 (5/36)
Middle	2.6 (3/115)	5.6 (5/90)	9.5 (7/74)	19.4 (7/36)
Lower	1.7 (2/115)	5.6 (5/90)	24.3 (18/74)	30.6 (11/36)

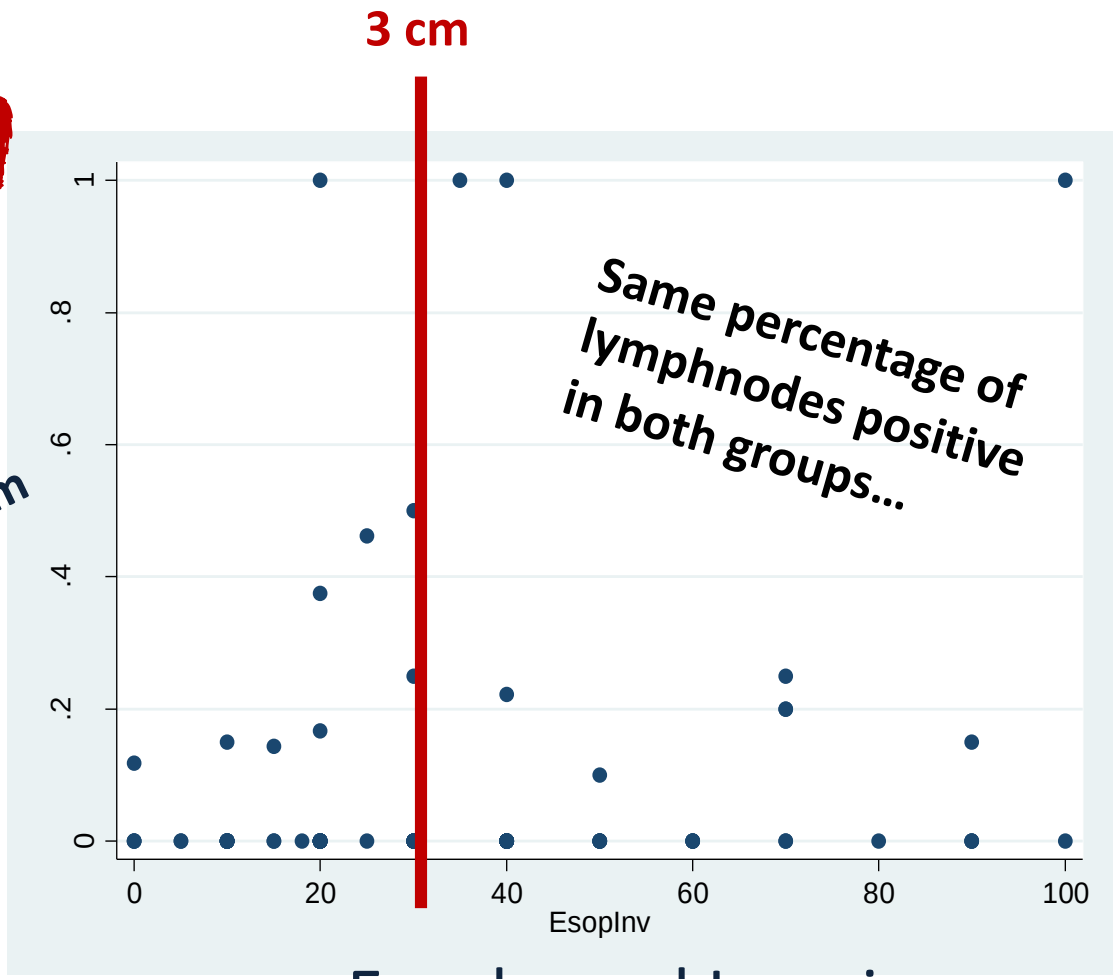
EGJ, Esophagogastric junction.

Up-mid mediastinum N+

WESTERN STRATEGY FOR EGJ CARCINOMA

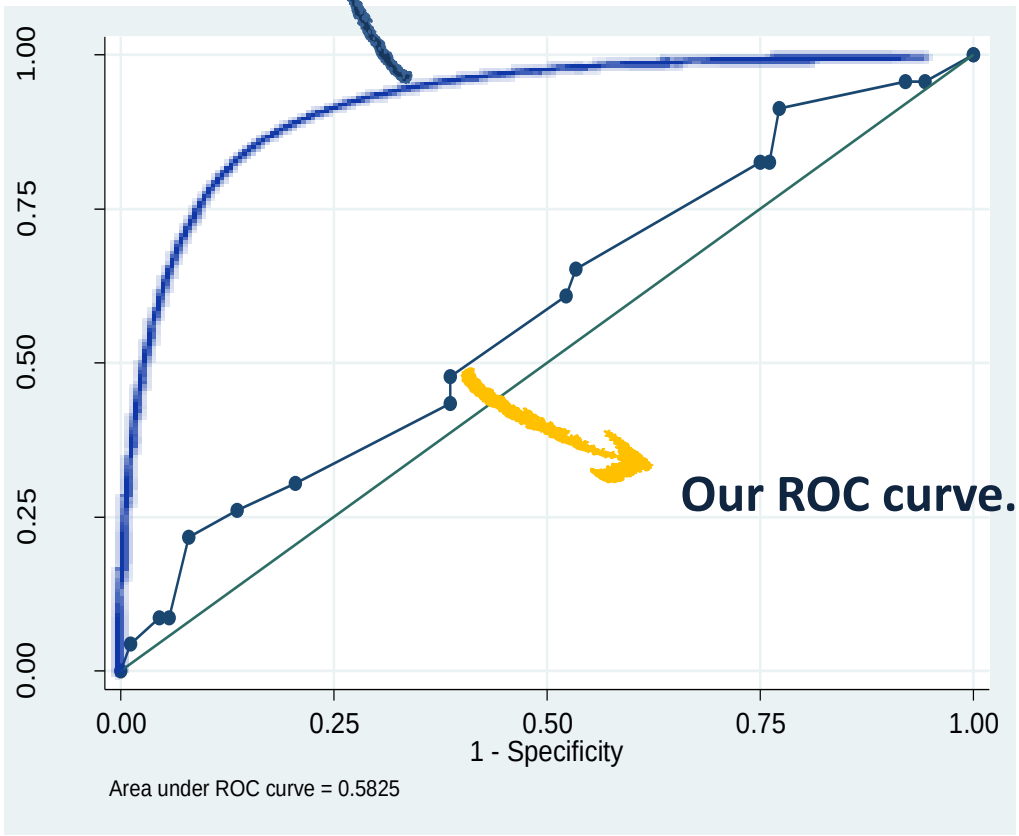
- 135 EGJ Adenok
- 65% neoadjuvant CRT
- 20,7% mediastinal N+

Ratio of positive to retrieved nodes in the **middle-upper mediastinum**



WESTERN STRATEGY FOR EGJ CARCINOMA

Excellent ROC curve

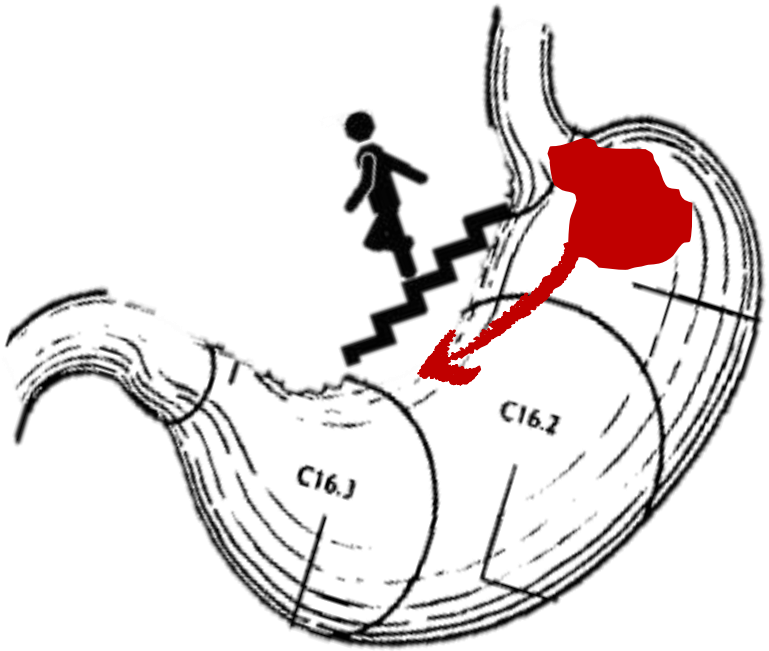


Unusefulness of length of esophageal invasion in predicting mediastinal nodal invasion in EGJ cancer

No relationship

Siewert III lymphatic diffusion

		Siewert 1	Siewert 2	Siewert 3
N+ Site	Abdomen	54%	70%	91%
	Abdomen+Thorax	46%	30%	7%



Mainly **abdominal**

Siewert III lymphatic diffusion

	Siewert III	Fundus	p-value
% N+	66.7%	77.4%	0.419
% N+ Perigastric nodes	69.4%	77.4%	0.583
%N+ II level nodes	16.7%	25.8%	0.385
%N+ Mediastinic nodes	22.2%	12.9%	0.359

The same nodal diffusion of fundus gastric cancer

D2 lymphadenectomy should always be performed !

	Siewert I (N= 13)	**Siewert II** N= 44	**Siewert III** N=54
Level of nodal metastasis			
First tier (n=43)	6 (46,2)	15 (34,1)	22 (40,7)
Non-first tier (n=68)	7 (53,8)	29 (65,9)	32(59,3)

Siewert III
lymphatic diffusion

Lymph node station	Rate of lymph node metastasis (%)			
	Type I	Type II	Type III	Total
7	40.0	22.4	14.5	21.8
8	0.0	6.7	13.6	9.3
9	0.0	13.3	8.6	10.8
10	0.0	3.9	12.3	7.4
11p	0.0	14.0	15.5	14.4
11d	0.0	6.3	7.1	6.5
12	0.0	0.0	3.3	1.5
16	0.0	12.2	20.7	15.1
Mediastinal	40.0	21.3	12.5	22.2

Siewert type III
T2-T3

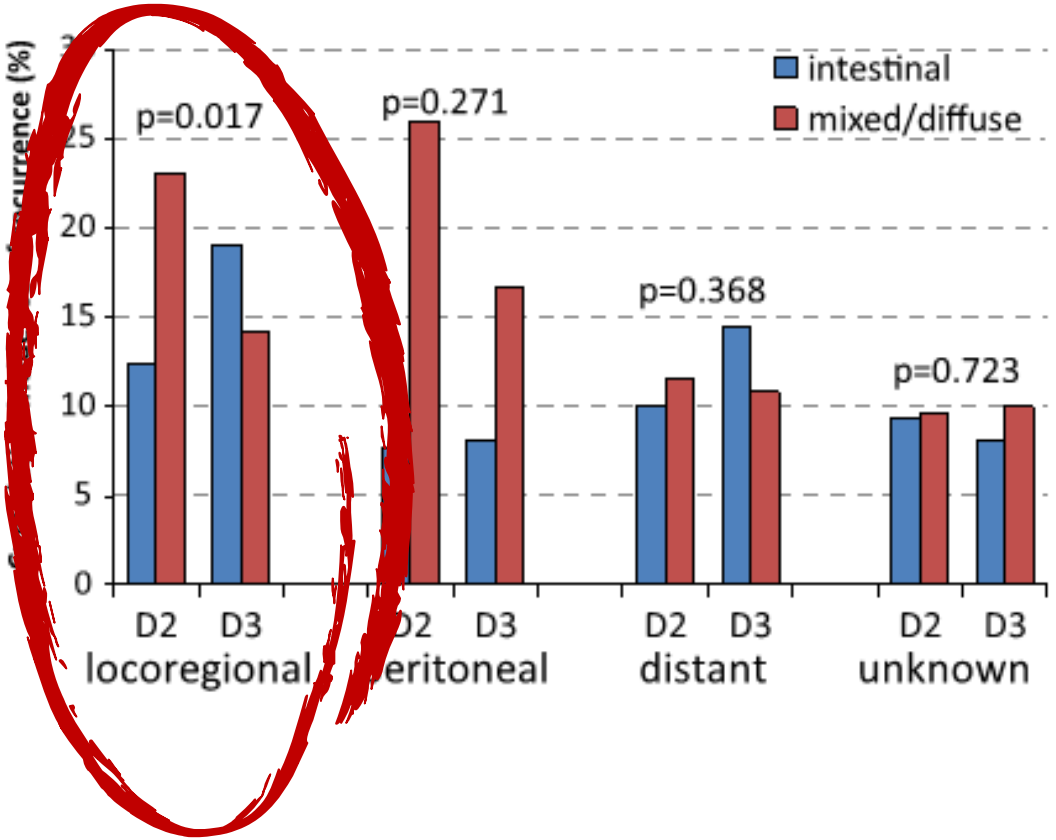
Inf.Mediast	15-17%
Gr.Curvature	13-28%
Subpyloric	6-12%
Left Gastric	21-48%
Celiac Art.	18-39%
Splenic Hilar	0-14%
Para-aortic	26-33%

Available online at www.sciencedirect.com
ScienceDirect
EJSO 41 (2015) 534–540
EJSO the Journal of Cancer Surgery
www.ejso.com

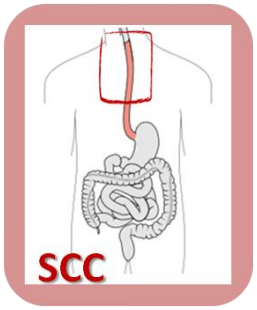
Impact of super-extended lymphadenectomy on relapse in advanced gastric cancer☆

G. de Manzoni [a,*], G. Verlato [b], M. Bencivenga [a], D. Marrelli [c], A. Di Leo [d], S. Giacopuzzi [a], C. Cipollari [a], F. Roviello [c]

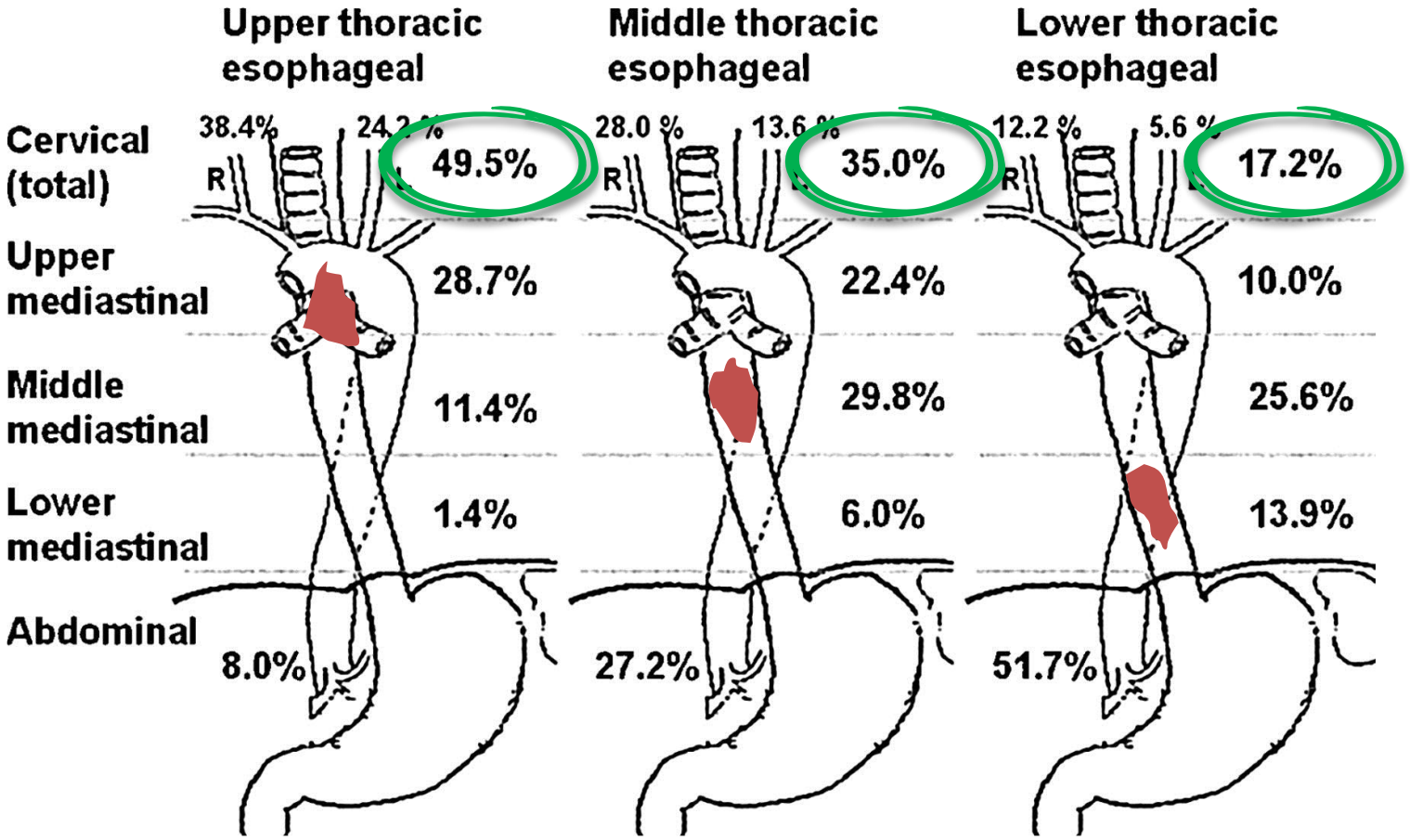
Para-aortic lymph nodes positive in **12,2%** of cases



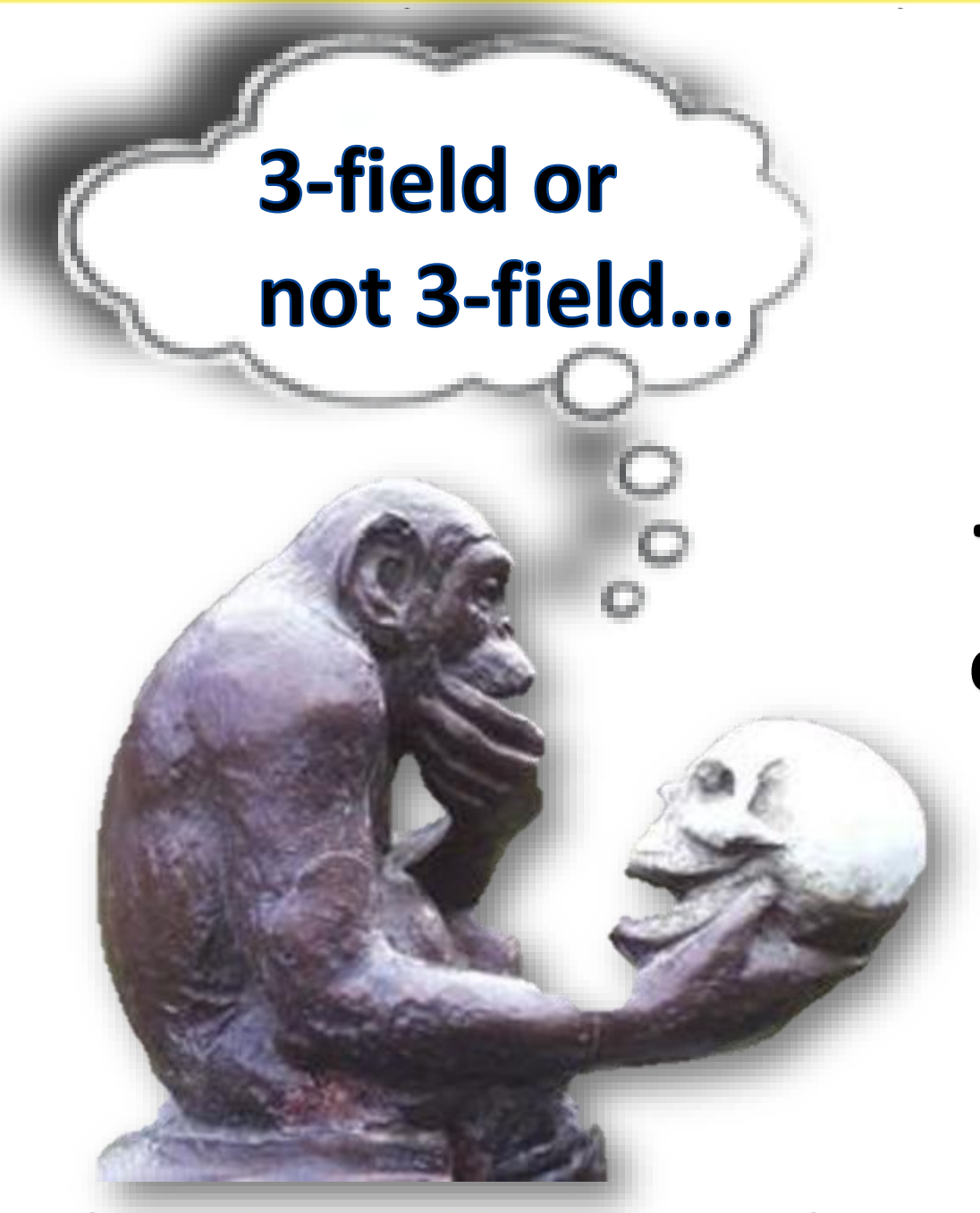
Super-extended lymphadenectomy reduces locoregional relapses in **Lauren mixed-diffuse type** AGC



Squamous Cell Carcinoma



Chen et al, European J of Cardio- thoracic Surg 2009



…higher rate of

complications…

Complications

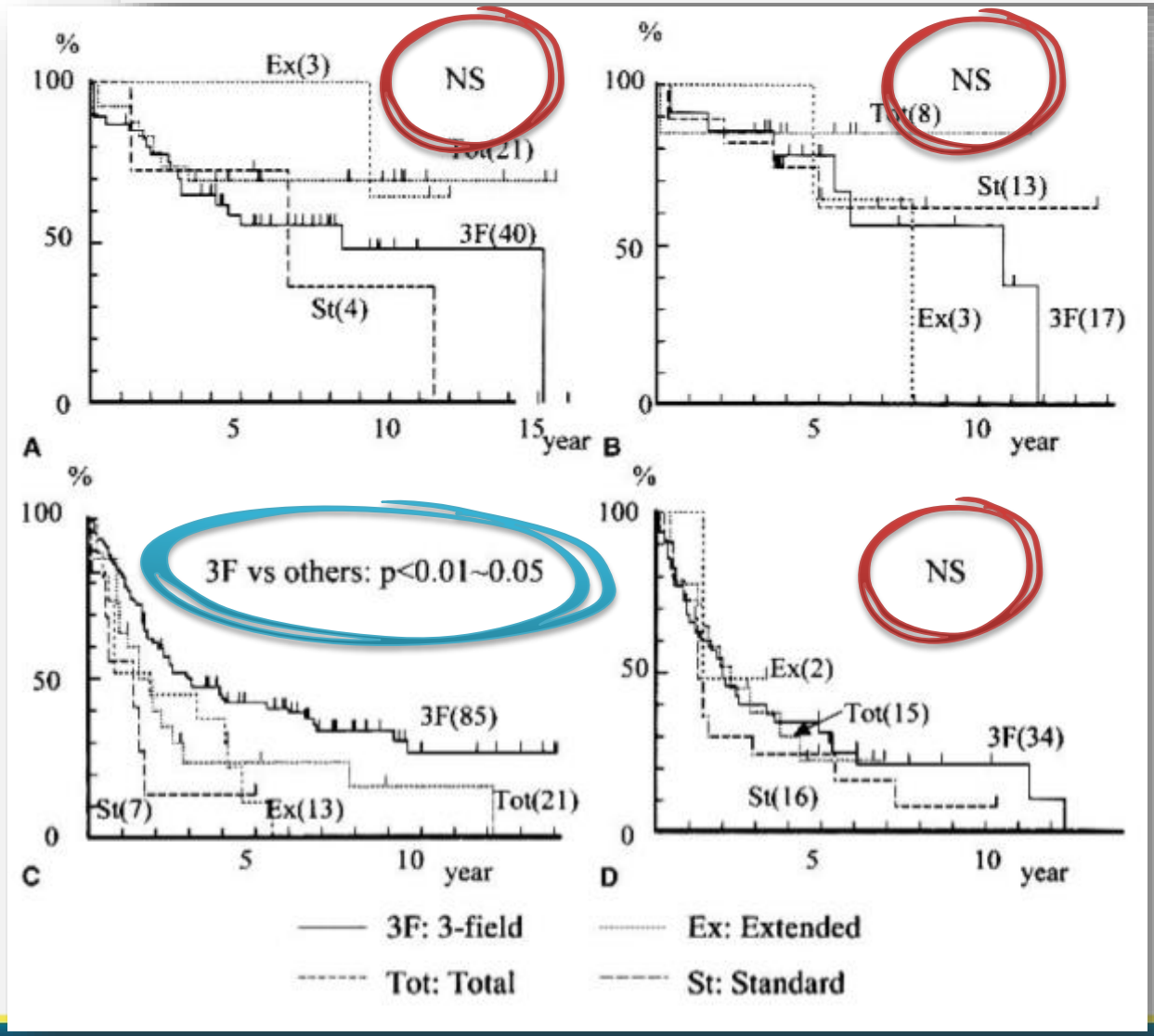
- Monolateral vocal cord paralysis: 12-60%
- Bilateral vocal cord paralysis: 5%
- Permanent vocal cord paralysis: 3-31%
- Pulmonary complications increased by vocal cord paralysis: aspiration pneumonia risk!

Lerut T, et al (2004) Ann Surg
Nakagawa S, et al (2003) Dis Esophagus
Tachibana M, et al (2005) Am J Surg
Fang WT, et al (2007) Dis Esophagus
Nishihira T, et al (1998) Am J Surg

Optimal Lymphadenectomy for Squamous Cell Carcinoma in the Thoracic Esophagus: Comparing the Short- and Long-term Outcome among the Four Types of Lymphadenectomy

Hiromasa Fujita, M.D., Susumu Sueyoshi, M.D., Toshiaki Tanaka, M.D., Teruhiko Fujii, M.D., Uhi Toh, M.D., Takashi Mine, M.D., Hiroko Sasahara, M.D., Tomoya Sudo, M.D., Satoru Matono, M.D., Hideaki Yamana, M.D., Kazuo Shirouzu, M.D.

World J. Surg. 27, 571–579, 2003



A. Upper and Middle N0

B. Lower N0

C. Upper and Middle N+

D. Lower N+

3-field dissection

Upper thoracic

Consensus

Mid-lower thoracic

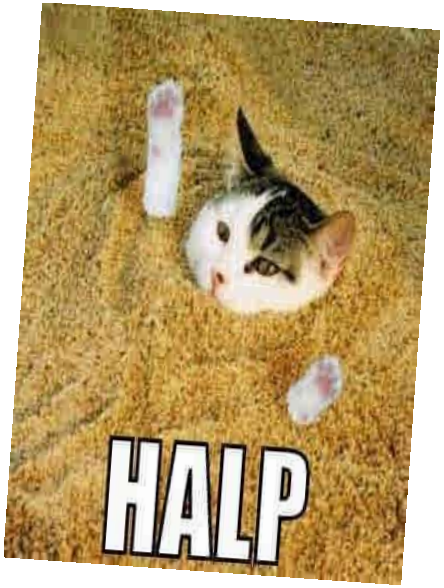
Only if Upper mediastinal
Or cervical cN+

- **Neck US**
- **EUS**

Esophagectomy…"high risk" operation

- Morbidity: 18-57%
- Mortality: 3-10%

Large variability



High volume
vs Low volume

and

Different definitions

Impact of volume

- Morbidity: 18-57% 51%
- Mortality: 3-10% 2%

113 pts

Early diagnosis

Multidisciplinary team

Correct treatment

Our ERAS protocol

	POD 0	POD 1	POD 2	POD 3	POD 4	POD 5	POD6	POD7
Department	ICU	ward	ward	ward	ward	ward	ward	ward
Lung function	Extubation at the end							
Fluid balance	GDT	-	-	+/-	+/-			
Oral intake	CHL	Clear fluids	Clear fluids	Clear fluids	soft	soft	soft	soft
P/E Nutrition		TPN EN 30ml/h	TPN EN 30ml/h	TPN EN 30ml/h	Stop			
Drains								
Central line						Remove		
Urinary cat.			Remove					
Thoracic drain		Remove						
NGT		Remove						
Epidural cat.				Remove				
Analgesia	TEA + EV	TEA + EV	TEA + EV	Remove TEA	EV	EV	OS	OS
Antibiotics	Prophylaxis	Stop						
Radiologic imaging	x-Ray	x-Ray		x-Ray				
Physiotherapy		Start						
Mobilization		In bed/chair	Assisted walk	Assisted walk	200 meters	200 meters	>200 meters	>200 meters

No anastomotic drainage

Intensive respiratory rehabilitation

Early resume of oral intake

Giacopuzzii et al. (in press), Dis Esoph

PERIANASTOMOTIC DRAINAGE IN IVOR LEWIS ESOPHAGECTOMY. DOES HABIT AFFECT UTILITY?

C.A. De Pasqual[1], J. Weindelmayer[1], S. Giacopuzzi[1], S. Laiti[1], R. La Mendola[1], G. de Manzoni[1]

[1]Department of General Surgery and Upper G.I Division, University Hospital of Verona, Italy
E-mail: carlodepasqual@gmail.com

- 160 Ivor Lewis
- 120 drainage – 40 no drainage
- 10 anastomotic leaks

Median drain removal **POD 5**

After oral intake resume

Same complication & mortality rate

Median leak detection **POD 10**

Diagnosis on **CLINICAL SUSPICION**

Treatment
- 1 surgery
- 5 endoscopic
- 4 conservative

Diseases of the Esophagus (2017) **00**, 1–6
DOI: 10.1093/dote/dow024

DISEASES OF THE ESOPHAGUS

ISDE The International Society for Diseases of the Esophagus

Original Article

Enhanced recovery after surgery protocol in patients undergoing esophagectomy for cancer: a single center experience

- Evaluated feasibility and safety compared to standard group
- Standard group VS ERAS group
  17 patients 22 patients

Median LOS
in ERAS groups

9 days

Morbility reduction

44% → 27%

University of Verona
Department of Surgery
Division of Upper G.I. Surgery
Prof. G. de Manzoni

GRAZIE PER L'ATTENZIONE

Negrar, 13 dicembre 2016