



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



# Impatto dell'imaging pre- trattamento sulla chirurgia: scelta terapeutica ed outcome clinico

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Dott. Simone Giacopuzzi

# Esophageal Cancer Management...

...is a teamwork

## ***Diagnosis***

- endoscopist
- pathologist

## ***Re-Staging***

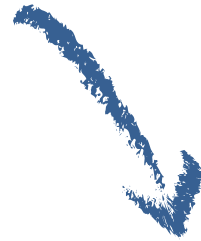
- (eco)endoscopist
- radiologist
- medico nucleare

## ***Treatment***

- surgeon
- oncologist
- radioterapist



Accurate  
staging...



...appropriate treatment



- Endoscopic resection
  - First line surgery
  - Definitive CRT
- Neoadjuvant treatment + surgery

***Surgery is the mainstay of  
curative treatment***

# What does a surgeon need to know?

Step 1

diffuse metastases?

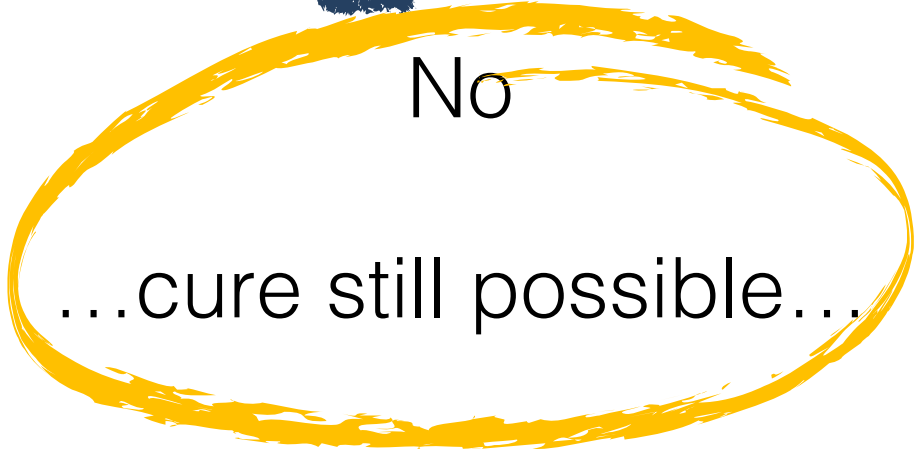


Yes

...palliation...

No

...cure still possible...



cT1N0

## Step 2

Early stage cancer?

Excellent prognosis...

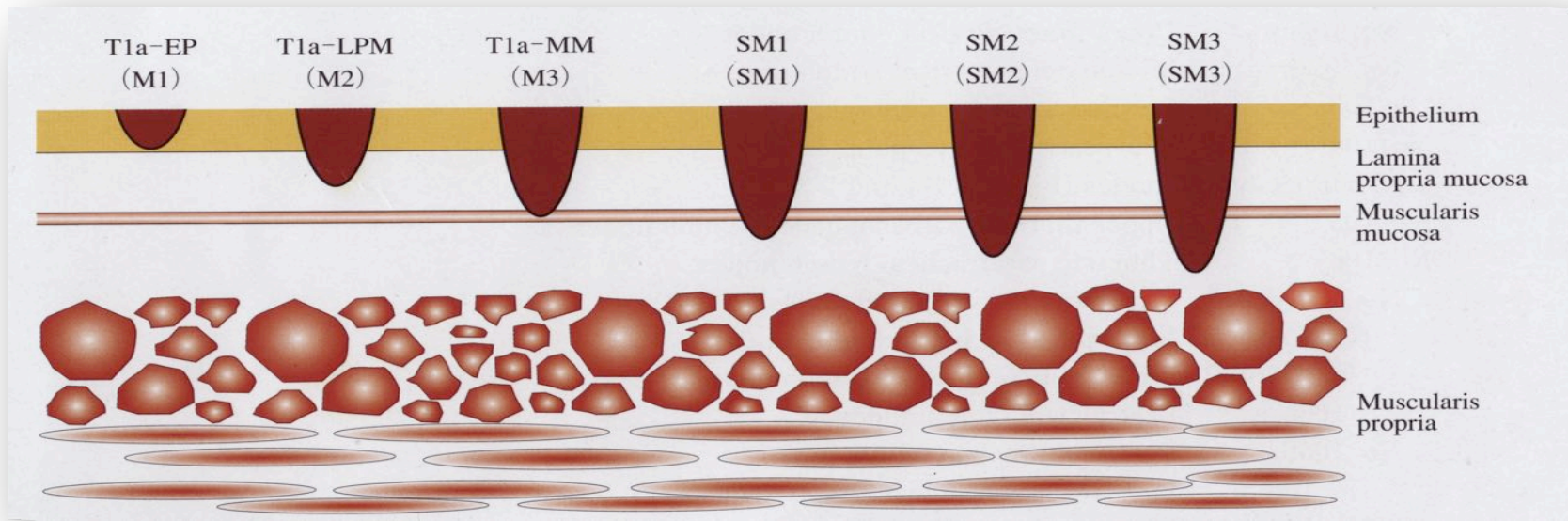
...maybe avoiding esophagectomy...

5-years OS:  
75-90%

Variables	ER (n = 76)	Surgery (n = 38)	P
Major complications	n = 0 (0%)	n = 12 (32%)	<0.001
Mortality			1.0
30 days	0	0	
90 days	0	1 (2.6%)	
Overall	8	4	
Overall survival			0.91
1 years	99%	97%	
3 years	96%	93%	
5 years	89%	93%	
Recurrence	n = 1	n = 0	0.17
Metachronous NPL	n = 4	n = 0	
Disease free follow-up			0.19
1 year	100%	100%	
2 years	94%	100%	
5 years	91%	100%	

*Pech O et al. Ann Surg 2011*

# Risk of nodal invasion



	<i>AdenoCa</i>	<i>SCC</i>
<i>m1-m2</i>	<b>0% N+</b>	<b>0% N+</b>
<i>m3</i>	up to <b>1,5% N+</b>	up to <b>15% N+</b>
<i>sm1</i>	up to <b>22% N+</b>	up to <b>50% N+</b>
<i>sm2-sm3</i>	up to <b>60% N+</b>	up to <b>65% N+</b>

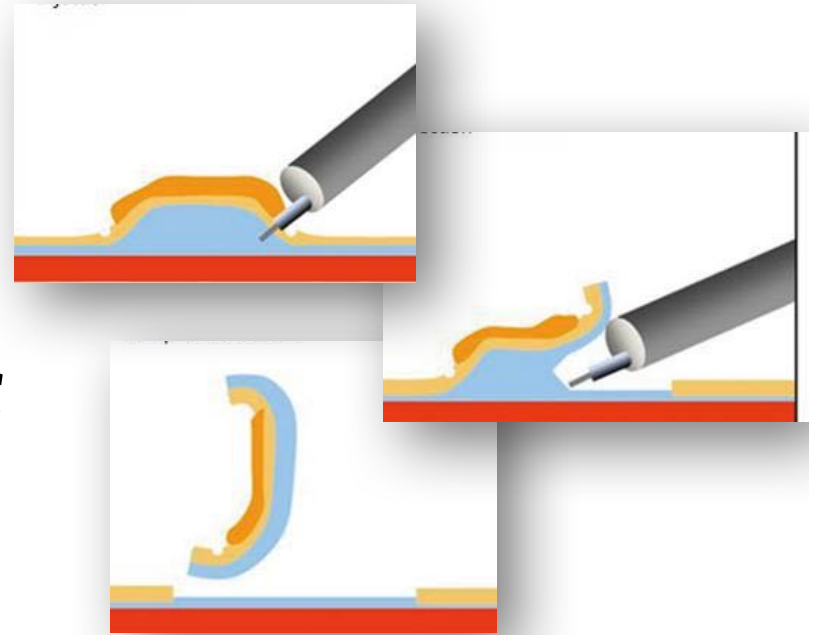
do not reach lymphatic vessels!

Lerut T, et al (2004) Ann Surg  
 Tachibana M, et al (2008) Ann Surg Oncol  
 Mariette C, et al (2004) Eur J Surg Oncol  
 Ancona E, et al (2008) Ann Surg Oncol  
 Altorki N, et al (2002) Ann Surg

ADC cTm1-m2-m3  
SCC cTm1-m2

R0 rate  
75-98%

**Endoscopic  
treatment**



...if **T m1-2-(m3)**  
confirmed by  
pathologist...

...follow-up...

...if **T > m2(m3)**...

...esophagectomy +  
lymphadenectomy...

Barnes JA. *J Clin Gastroenterol* 2015  
Pech O. *Ann Surg* 2011  
Sgourakis G. *J World J Gastroenterol* 2013

Probst A. *Endoscopy* 2015  
Park JS. *Clin Endosc* 2016  
Sun F. *J Cardiothorac Surg* 2014

# How to identify T1 tumors?

**EUS**

	Sensitivity	Specificity
<b>T1</b>	75%	75%
<b>T2</b>	31,8%	58,3%
<b>T3</b>	77,8%	45,2%

de Manzoni G. 2005

## CT scan?



...lacks the ability to clearly differentiate the layers of the esophageal wall...

Sensitivity    Specificity

T1a	85%	87%
T1b	86%	86%

Toshani N. 2012

*...but only with experienced operators...*

**Low volume centers    High volume centers**

	Low volume centers		High volume centers	
	sensitivity	specificity	sensitivity	specificity
T1-2	58%	87%	75-90%	94-97%
T3	85%	57%	88-94%	75-90%

Van Vliet LP. 2006



# How to identify T1 tumors?

...**endoscopic resection** is today the only method to accurately determinate the depth of wall invasion ...

Open Question

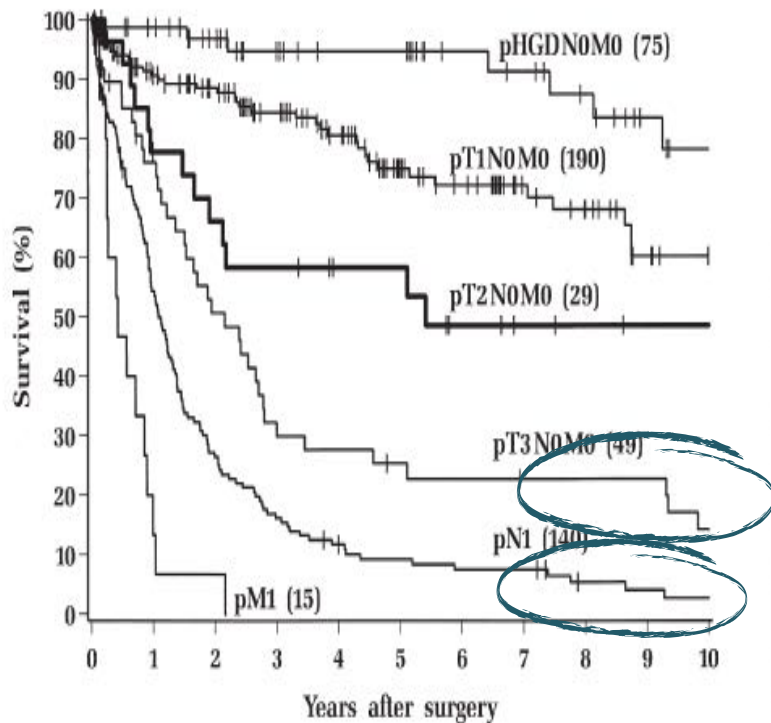
...change in **T staging** in 30-48% of pts

# Step 3

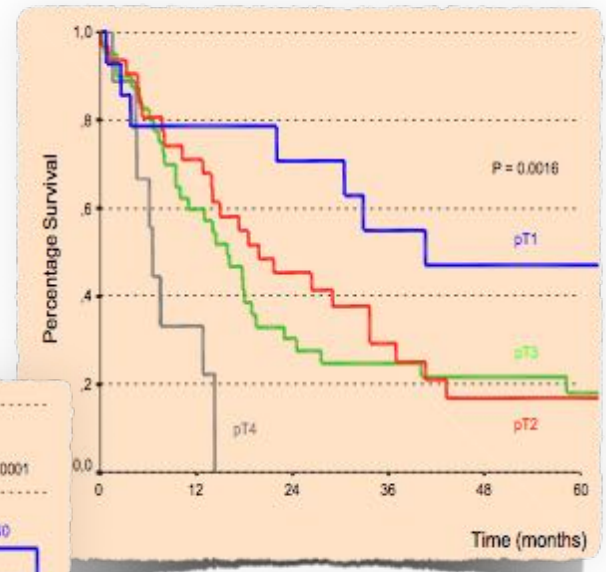
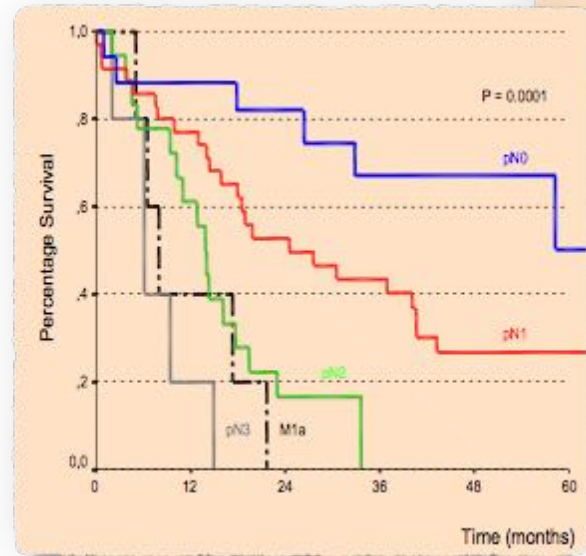
cT3-4 N0  
cTx N+

## Staging of locally advanced cancers

Surgery alone?



Rice et al. J Thorac Cardiovasc Surg. 2007



5y OS R0  
24%

Our experience

2012

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

### Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg

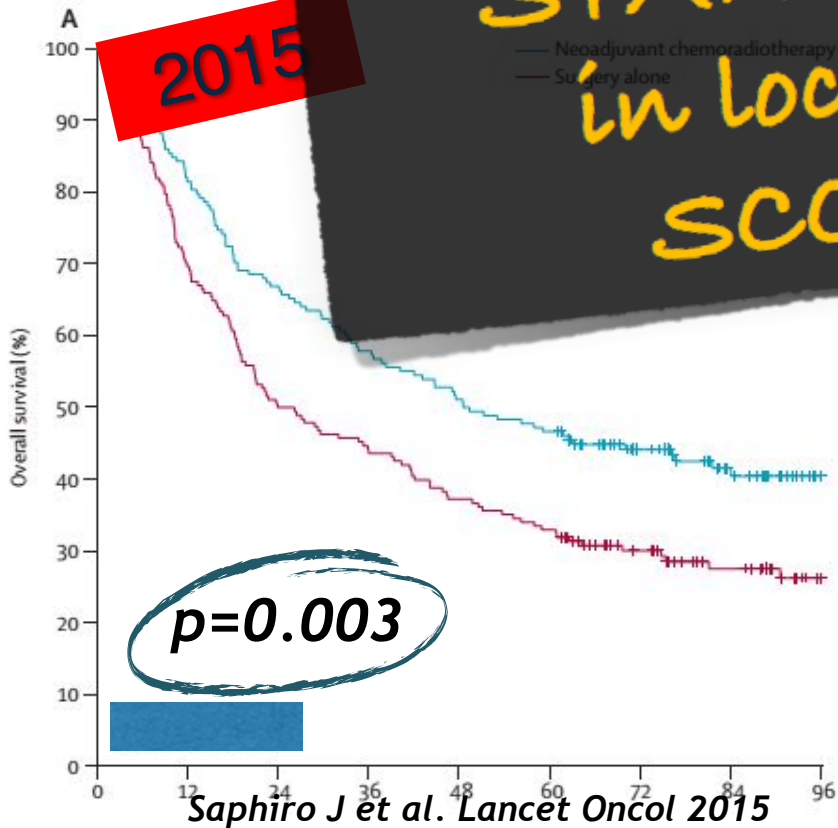
	<b>CRT</b>	<b>Surg alone</b>	<b>p</b>
<b>R0</b>	92%	69%	<0.001
<b>pCR</b>	29%	-	-
<b>Median OS</b>	49.4 mos.	24 mos.	0,003

**STANDARD OF CARE**  
in locally advanced  
SCC and adenok

Our results:

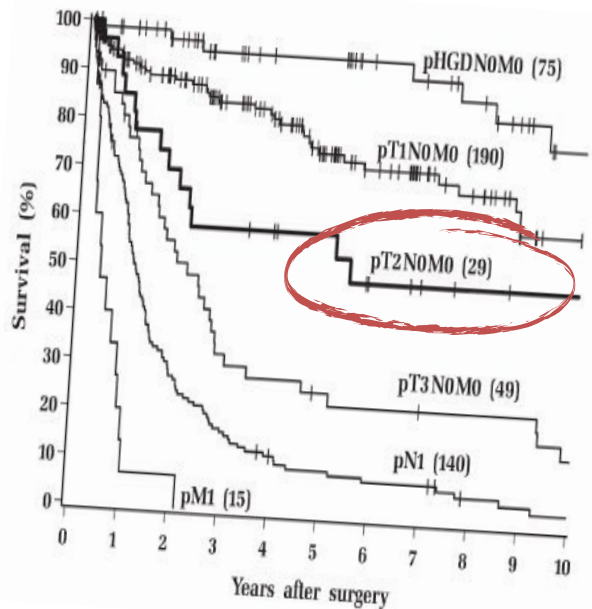


2015



R0 rate: 84%  
 pCR: 47%  
 Median OS: 55 mos

...and in cT2N0?



traditional treatment  
*primary surgery* but...

482 pts cT2N0  
 Upfront surgery

Confirmed as pT2N0	27,4%
Downstaged to pT0-1N0	25,9%
Upstaged to pT3-4 or pTany N+	46,7%

**Exclusive T  
 upstaging**

18,2 %

**Exclusive N  
 upstaging**

44,5 %

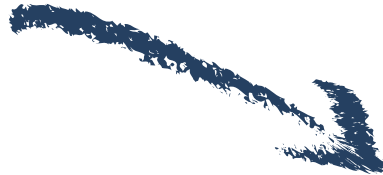
**Combined T-N  
 upstaging**

37,3 %

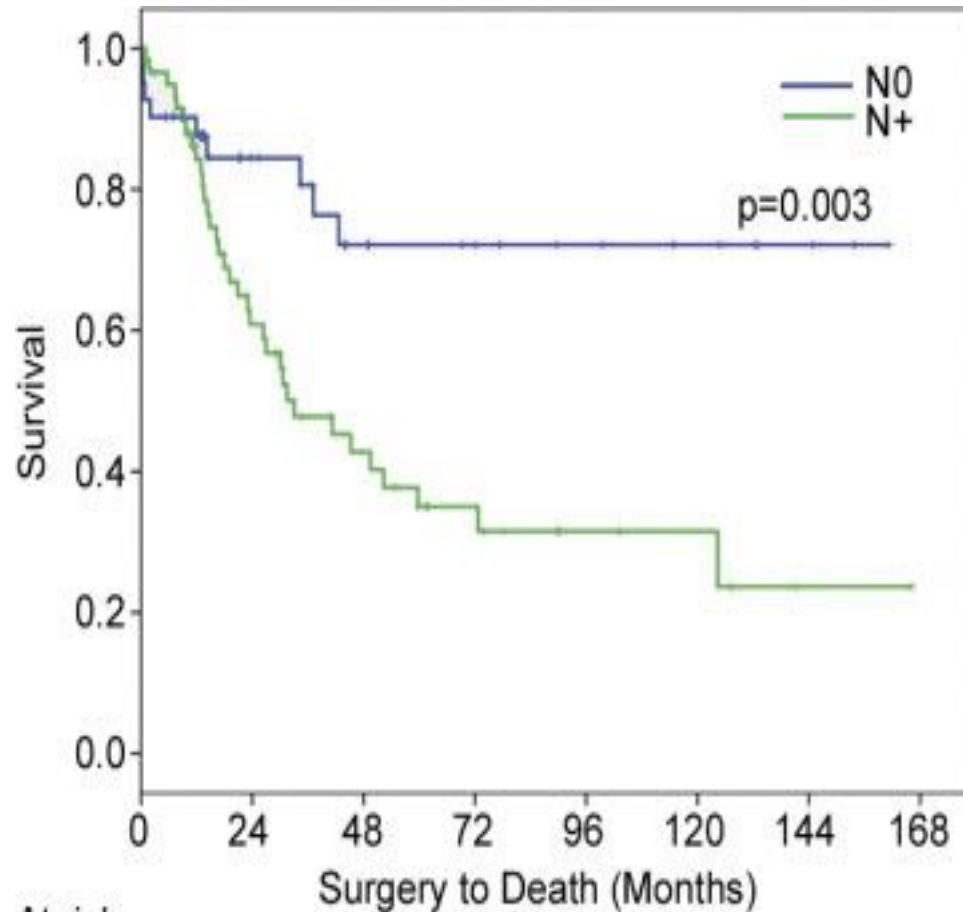
...are they really N0?

# cT2N0

(Staged with CT,  
PET/CT, EUS)



Are actually  
**pT2N+** in 38-69  
% of cases



At risk	0	24	48	72	96	120	144	168
N0	41	33	14	11	8	6	3	0
N+	61	36	17	10	6	4	1	0



*Stiles B et al Ann Thorac Surg. 2011*  
*Samson P. et Ann Thorac Surg 2016*

Is there any advantage by adding neoadjuvant CRT???

J Clin Oncol. 2014 Aug 10;32(23):2416-22. doi: 10.1200/JCO.2013.53.6532. Epub 2014 Jun 30.

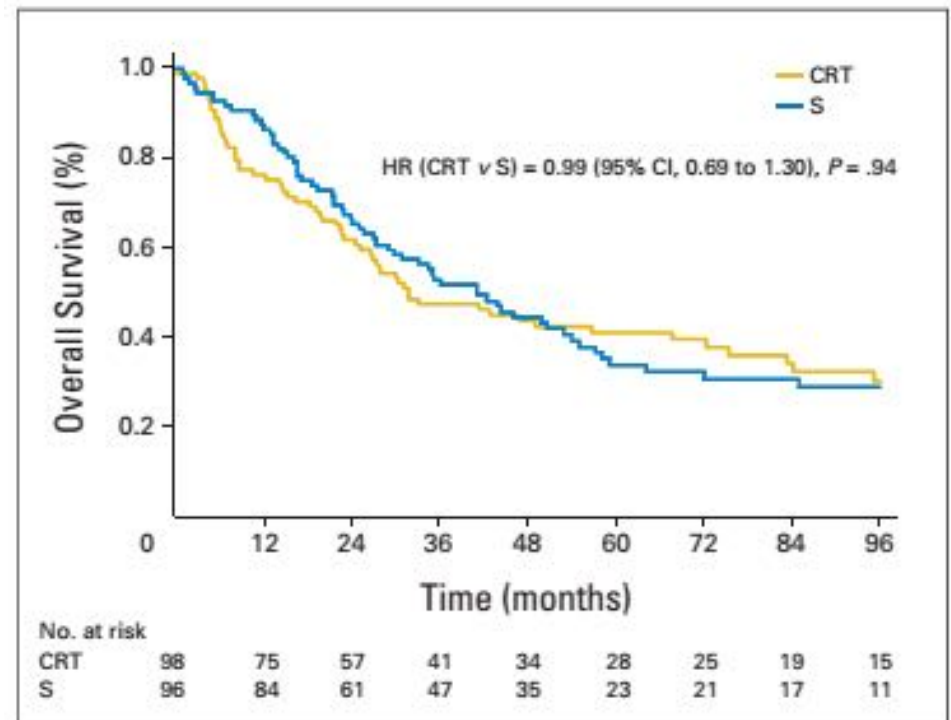
## Surgery alone versus chemoradiotherapy followed by surgery for stage I and II esophageal cancer: final analysis of randomized controlled phase III trial FFCD 9901.

Mariette C<sup>1</sup>, Dahan L<sup>2</sup>, Mornex F<sup>2</sup>, Maillard E<sup>2</sup>, Thomas PA<sup>2</sup>, Meunier B<sup>2</sup>, Boige V<sup>2</sup>, Pezet D<sup>2</sup>, Robb WB<sup>2</sup>, Le Brun-Ly V<sup>2</sup>, Bosset JF<sup>2</sup>, Mabrut JY<sup>2</sup>, Triboulet JP<sup>2</sup>, Bedenne L<sup>2</sup>, Seitz JF<sup>2</sup>.

- Multicenter randomized phase III trial
- nCRT plus surgery (n=98) vs surgery alone (n=97)

No difference in OS and DFS

Higher post-operative morbidity and mortality in CRT group



...so, about cT2N0...

In most cases  
clinically  
*understaged*



survival benefit in locally  
advanced cancer



**CRT** tumor downstaging  
**but Neoadj in PN + ???**

Markar Ann J Cancer 2016  
Jennifer Ann Thorac Surg  
2012

**does not provide**  
survival benefits  
among cT2N0 pts



<i>Author</i>	<i>OS Surg</i>	<i>OS Neoadj+ Surg</i>
<b>Chen 2012</b>	39%	68%
<b>Zhang 2012</b>	49%	53%
<b>Martin 2013</b>	38%	42%
<b>Dolan 2015</b>	37%	37%
<b>Markar 2016</b>	43%	39%

Maybe we don't know how  
to treat **cT2N0** patients...

...because we  
don't know who  
they are!!!



Open Question



May **MRI** be the answer?

on **T** staging

...*in vitro*...

on **N** staging

Sensitivity  
Sensitivity  
Accuracy

Depth of invasion	Sensitivity	Specificity	Accuracy
Mucosa (T1a)	20/20 (100)	0/0 (NA)	20/20 (100)
Submucosa (T1b)	18/18 (100)	2/2 (100)	20/20 (100)
Muscularis propria (T2)	12/12 (100)	8/8 (100)	20/20 (100)
Adventitia (T3/T4)	9/9 (100)	11/11 (100)	20/20 (100)

but in  
*vivo*...

**T detection rate**

**T1a** 0 %

**T1b** 33 %

**T2** 58 %

**T3** 95 %

**T4** 100 %

Wu L. Worl J Gastroenterol 2003

Sakurada M. Eur Radiol 2009

Alper J. Eur Radiol 2011

Van Rossum Eur Radiol 2013

Yamada I. Magn Reson Imaging 2015

**Wu 2003** 62% 68% 64%

**Sakurada 2009** 75% 62% 68%

**Alper 2011** 81% 98% 95%

Our data:



## Up-front surgery

	<i>T</i>	<i>N</i>
Sensibility	98%	67%
Specificity	78%	60%
PPV	92%	67%
NPV	54%	60%
Accuracy	90%	64%



Presented at RSNA 2015  
Courtesy of dr. Montemezzi

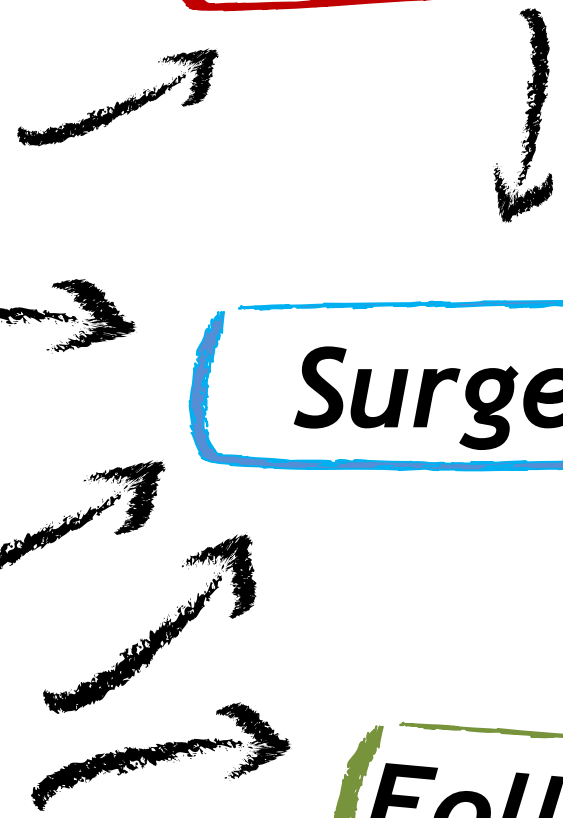
# Step 4 Re-staging after neoadjuvant treatment

- Progression disease
- Stable disease
- Partial response
- Complete response

Still resectable?

**Surgery**

**Follow-up?**



# Hot topics



**1** *Complete response  
after CRT*

**2** *Early recurrence  
after surgery*

# 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<sup>1</sup>, G. Verlato, MD<sup>2</sup>, S. Giacomuzzi, MD<sup>1</sup>, J. Weindelmayer, MD<sup>1</sup>, F. Casella, MD<sup>1</sup>, F. Pasini, MD<sup>3</sup>, E. Zhao, MD<sup>4</sup>, and G. de Manzoni, MD<sup>1</sup>

pCR: 45% of ADK and 53% of SCC



## SANO trial

**“surgery as needed” approach?**

**Ongoing**

Feasibility study: **pre-SANO trial**  
...to determine the accuracy of detecting the presence/absence of **residual disease** after nCRT...

Is cCR = pCR ???

<i>Author</i>	<i>Methods</i>	<i>cCR rate</i>	<i>Residual tumor</i>
<i>Piessen et al. Ann Surg 2013</i>	Endoscopy, CT scan, PET	25%	34,6%
<i>Castoro et al. J Gastrointest Surg 2013</i>	Endoscopy, CT scan, PET	-	30,8%
<i>Liu et al. Ann Surg Oncol 2016</i>	Endoscopy, barium esophagography, CT scan	27,8%	27,3%



# cCR outcomes?

Annals of Surgery • Volume 258, Number 5, November 2013

## Is There a Role for Surgery for Patients with a Complete Clinical Response after Chemoradiation for Esophageal Cancer?

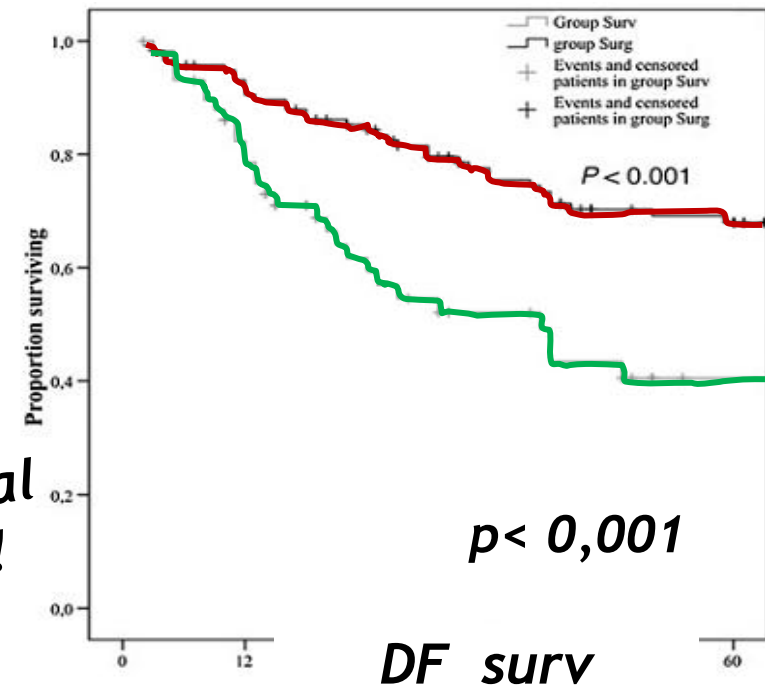
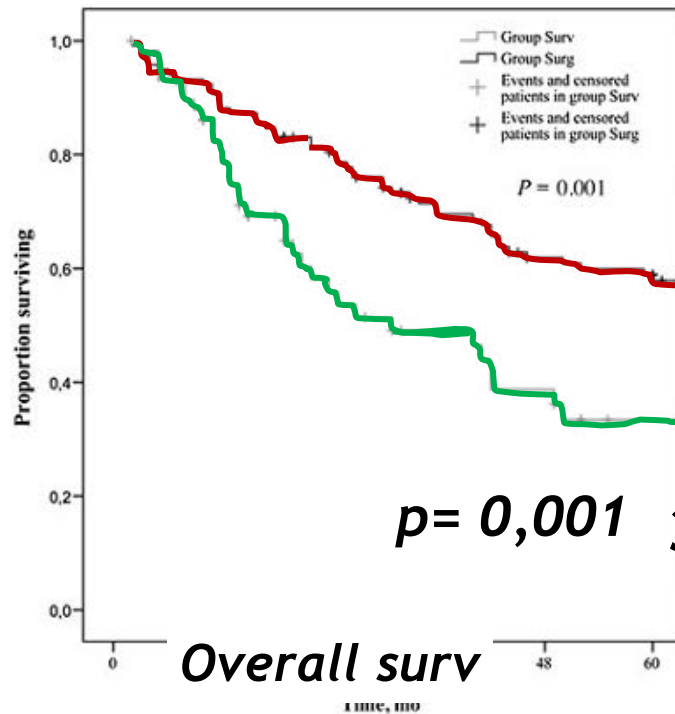
### An Intention-to-Treat Case-Control Study

Guillaume Piessen, MD, PhD,\*†‡ Mathieu Messager, MD,\*†‡ Xavier Mirabel, MD,§¶ Nicolas Briez, MD,\*† William B. Robb, MD,\*† Antoine Adenis, MD,¶ and Christophe Mariette, MD, PhD\*†‡

59 pts, cCR after CRT,  
Follow-up

VS

118 pts cCR after CRT  
Surgical resection



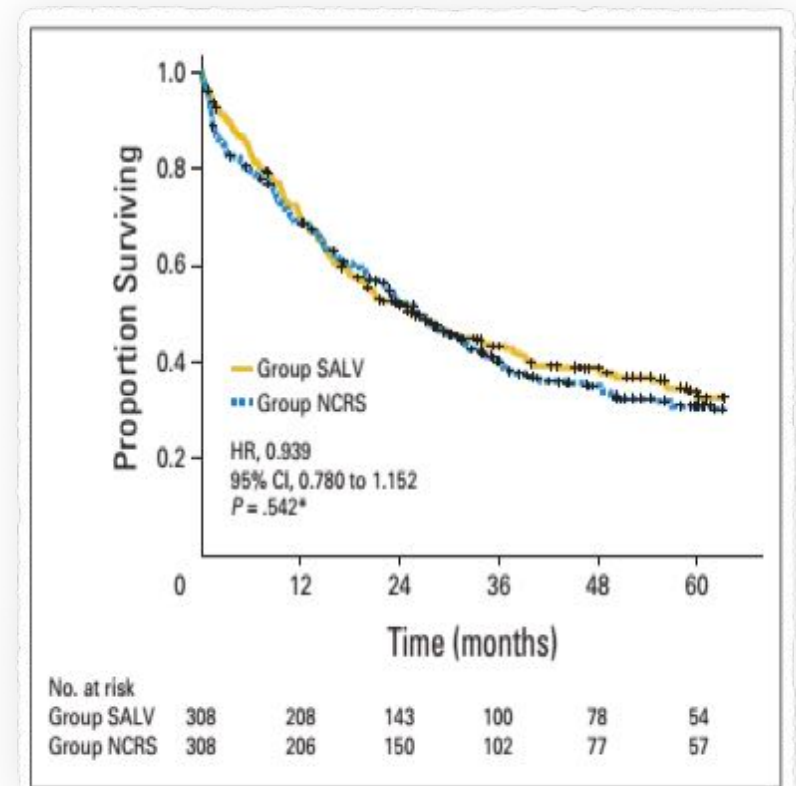
Would surgery be still feasible???

## Salvage Surgery After Chemoradiotherapy in the Management of Esophageal Cancer: Is It a Viable Therapeutic Option?

Sheraz Markar, Caroline Gronnier, Alain Duhamel, Arnaud Pasquer, Jérémie Théreaux, M Jérémie H. Lefevre, Kathleen Turner, Guillaume Luc, and Christophe Mariette

Data from 30 European centers, 2000 -2010,  
**Salvage Surgery (n 308) vs NeoadCRT+ Surgery (n540)**

	<b>SALV</b>	<b>NCRS</b>	<b>p</b>
<b>In-hospital mortality:</b>	8,4%	9,3%	ns
<b>Overall Morbidity</b>	63,6%	61,0%	ns
<b>Anastomotic leak</b>	17,2%	10,7%	0,015





...waiting for **(pre-)SANO** results...

Clinical response assesment is unreliable,  
about 30% of cCR have a residual tumor



Long-term outcome of pCRs without surgery is not clear

**Surgery needed to overcome  
re-staging limitations**

...and **MRI**?



**Our data:**

*After neoadjuvant  
CRT*

	<b>T</b>	<b>N</b>
Sensibility	80%	76%
Specificity	85%	78%
PPV	67%	50%
NPV	92%	91%
Accuracy	89%	91%



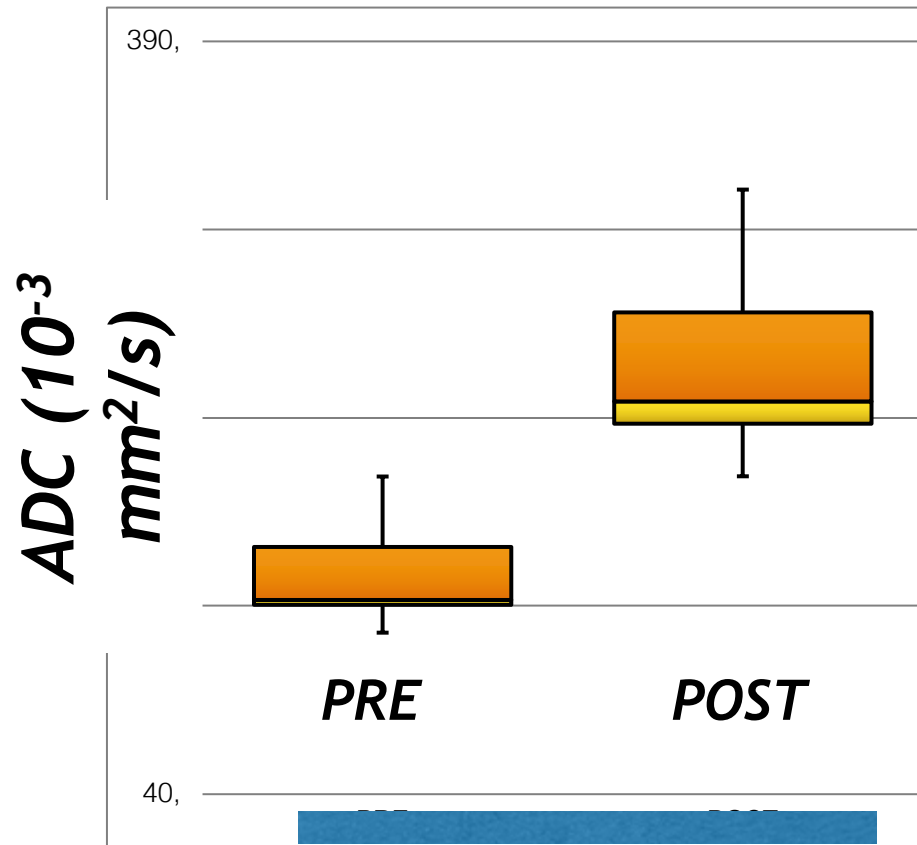
**Any tricks???**

Presented at RSNA 2015  
Courtesy of dr. Montemezzi

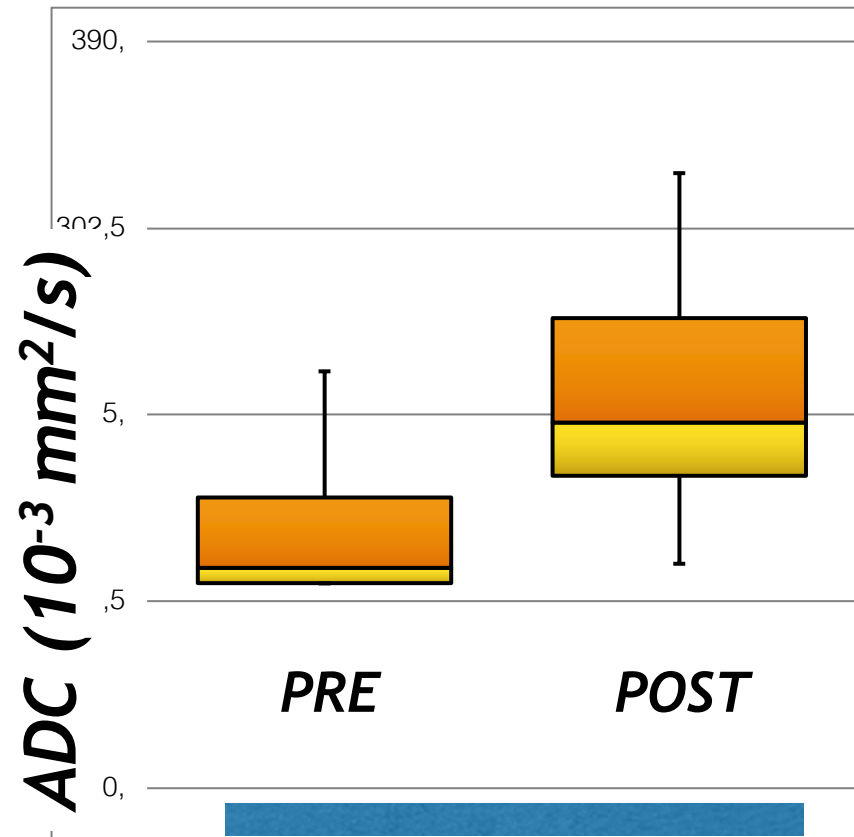
**Is apparent diffusion coefficient (ADC) the answer?**

...inversely correlated with tissue cellularity...tumor response can be detected as an increase of ADC

**Responder**



**Non Responder**



...in Literature...



Eur Radiol (2013) 23:2165–2174

### Apparent diffusion coefficient modifications in assessing gastro-oesophageal cancer response to neoadjuvant treatment: comparison with tumour regression grade at histology

Francesco De Cobelli · Francesco Giganti · Alessandro Del Maschio

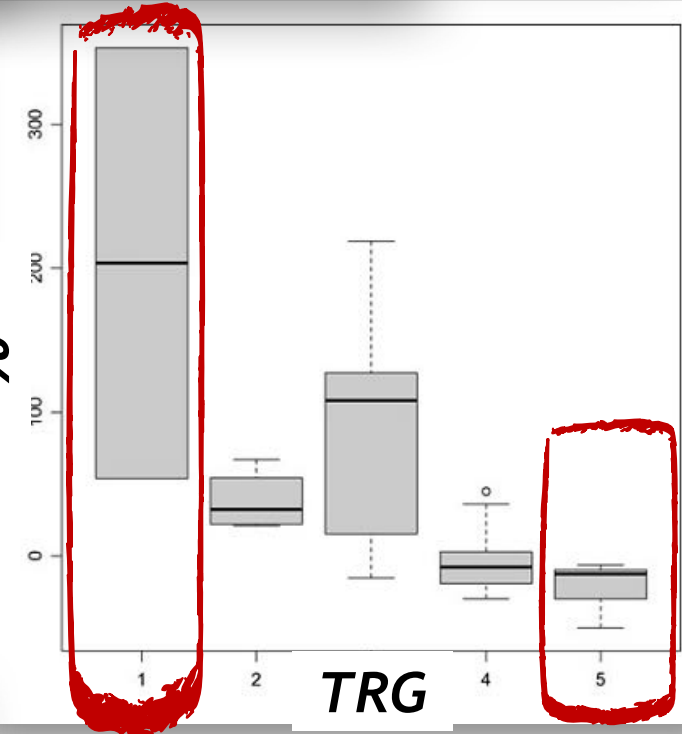
	Responders	Non-responders	P value
$\Delta V$ gastric	-43.52±31.53	-35.11±41.42	0.580
$\Delta V$ oesophageal (%)	-53.63±26.48	-52.52±26.22	0.949
$\Delta ADC$ gastric	48.09±44.43	-10.18±14.28	0.0013
$\Delta ADC$ oesophageal (%)	171.30±102.01	-11.56±49.96	0.0001

Radiotherapy and Oncology 115 (2015) 163–170

Diffusion-weighted magnetic resonance imaging for the prediction of pathologic response to neoadjuvant chemoradiotherapy in esophageal cancer<sup>☆</sup>

Peter S.N. van Rossum<sup>a,b</sup>, Astrid L.H.M.W. van Lier<sup>a</sup>, Marco van Vulpen<sup>a</sup>, Onne Reerink<sup>a</sup>

$\Delta ADC$   
%



**$\Delta ADC < 29\%$  after 8-13 RT fractions**



sensitivity and NPV of **100%** in predicting **non-pCR**

Early recurrence after surgery???

**Hot topic**



**153** locally advanced tumors treated  
with neoadjuvant CRT plus R0 surgery.

**34** early recurrence group  
(within 12 months)

**111** long survivors  
group  
DFS > 24 months

	Early recurrence		Long Survivors	
	n	%	n	%
Local Recurrence	7	20,6	9	42,9
Distant	18	52,9	10	47,6
Mixed	9	26,5	2	9,5
Total	34	100	21	100

Already present  
at surgery?

Remember:  
Esophagectomy  
Morbidity 40-60%  
Mortality 2-10%

**Hot topic**



## Can we identify these patients?

Multivariate analysis

	<i>HR</i>	<i>95% CI</i>	<i>P</i>
<i>Histotype</i>	0,96	0,36-2,55	0,934
<i>ycN</i>	1,21	0,47-3,09	0,698
<i>Tumor Size</i>	2,49	0,93-6,66	0,069
<i>Age</i>	1,7	0,63-4,57	0,293
<i>Completion of CRT</i>	2,89	1,08-7,73	0,035
<i>Grading</i>	0,34	0,09-1,21	0,095

In conclusion:

No answer .... only questions

T2N0

T1m

pCR



M0 post

Any Questions???



if about MRI ask to: [radiologia.bt@aovr.veneto.it](mailto:radiologia.bt@aovr.veneto.it)



# Protocol



Pasini, de Manzoni, ... Cordiano. Ann Oncol. 2005 Jul;16(7):1133-9.