Does response to preoperative therapy modify the extension of surgical resection?

When is salvage surgery indicated?

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UNIVERSITÄT KÖLN
VG CHIRURGIE

Madrid, September 29, 2014

Does response to preoperative therapy modify the extension of surgical resection?

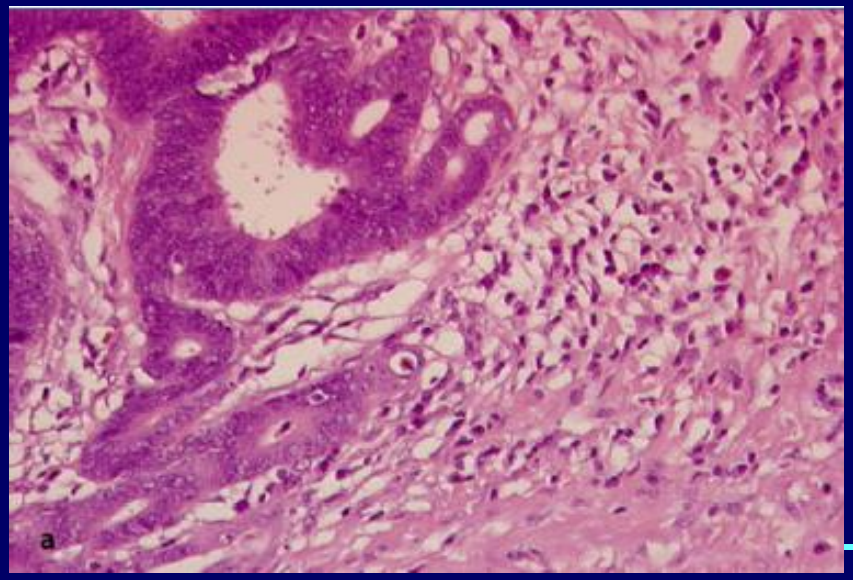
No !

Topics

1. Definition of response
2. Clinical response evaluation
3. The predictive value of biopsy
4. PET
5. Response and Surgery
6. Salvage Surgery

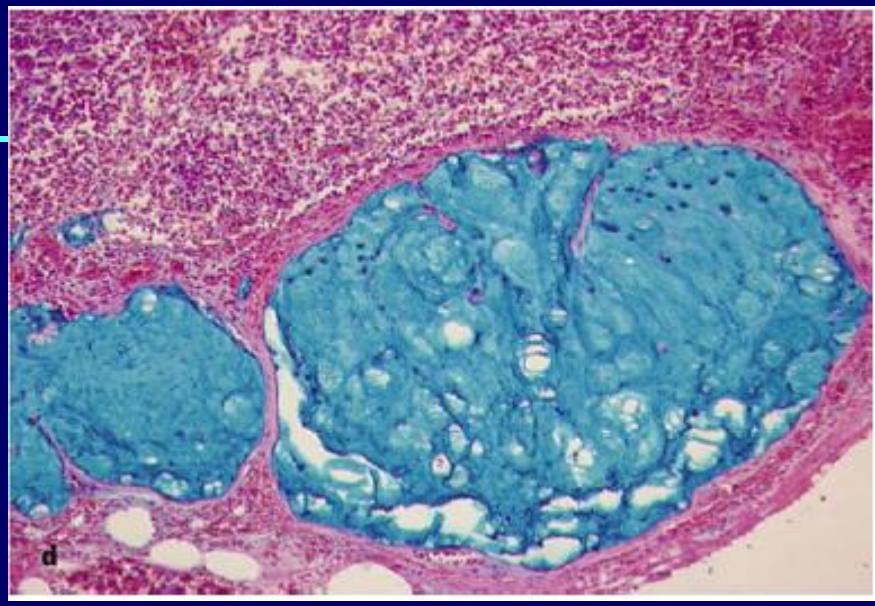
Definition of response

AC of the Esophagus
Histomorphologic regression after neoadjuvant radiochemotherapy



Resorptive and fibrosing reaction

Mucin lakes in lymph nodes



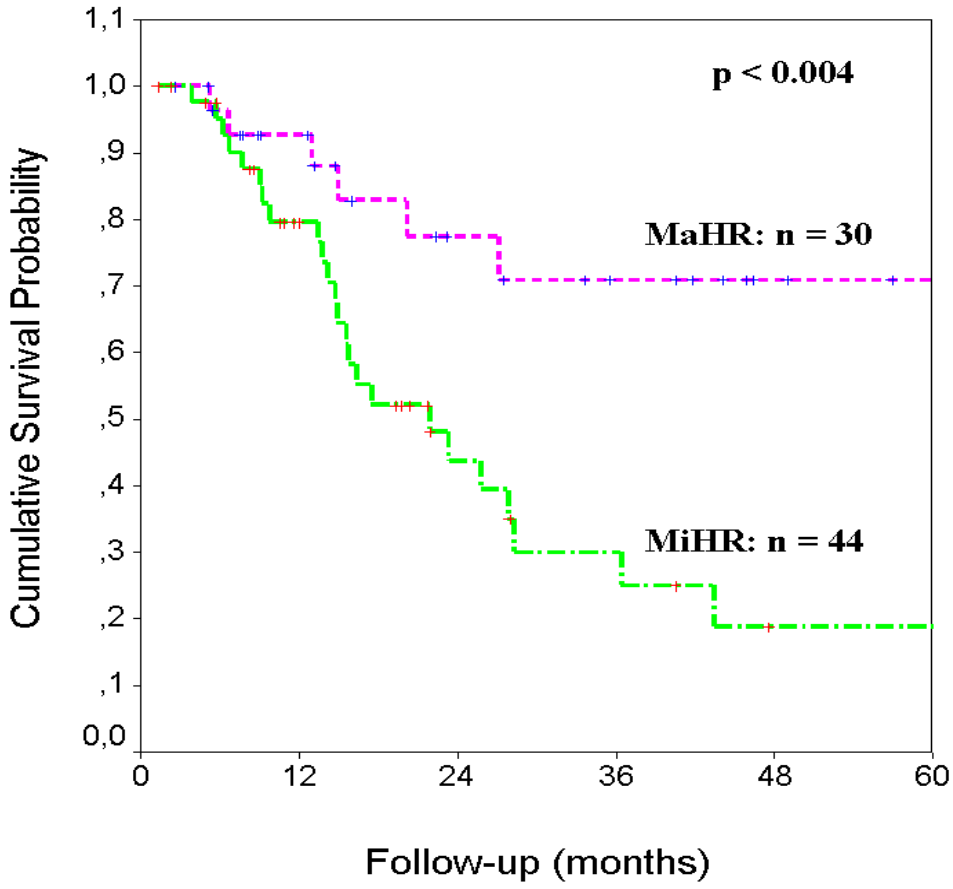
Baldus et al, Pathologe 2004

Histomorphologic Response

- Therapy response after CTx/RTx was evaluated using the
  Cologne Regression Grade
- *minor response:*
  Grade I: > 50% vital residual tumor cells (VRTC)
  Grade II: > 10% VRTC
- *major response:*
  Grade III: < 10% VRTC,
  Grade IV: pathologic complete response

Baldus, Pathologe 2004

HISTOMORPHOLOGIC REGRESSION: PROGNOSIS

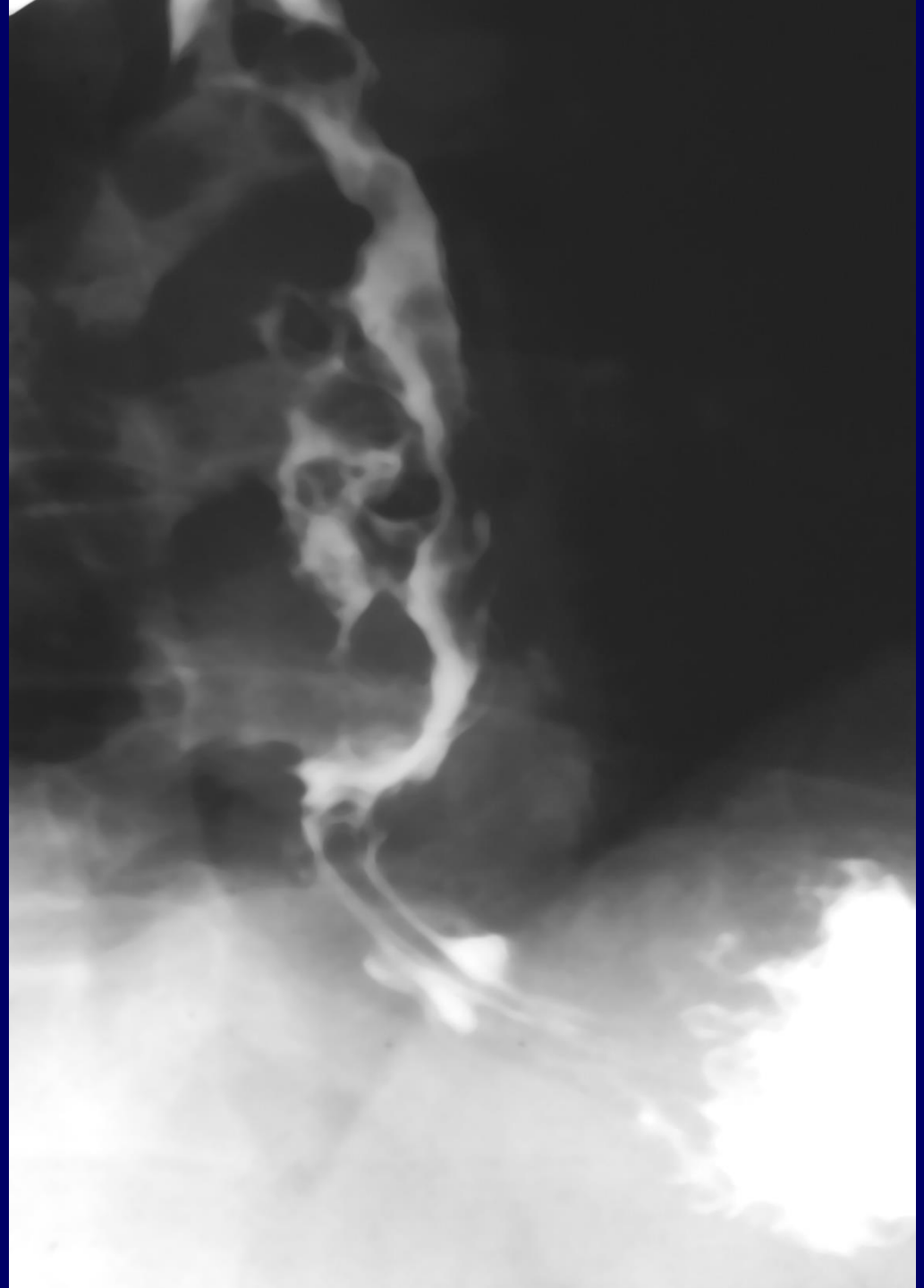


Schneider – Hölscher Ann Surg 2005; 242: 684-692

Clinical response evaluation

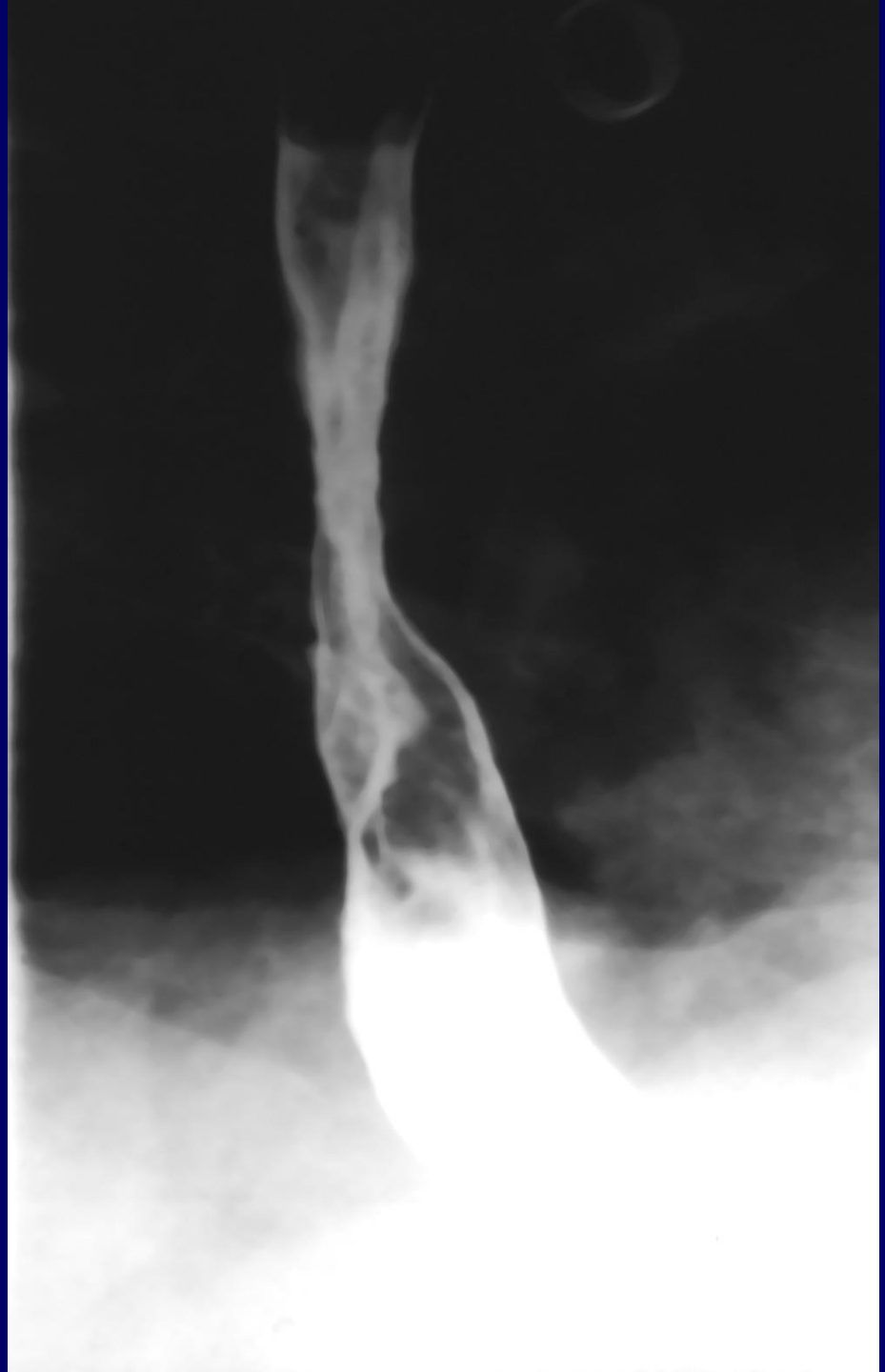
Esophageal Carcinoma

Before RTx/CTx



Esophageal Carcinoma

After RTx/CTx



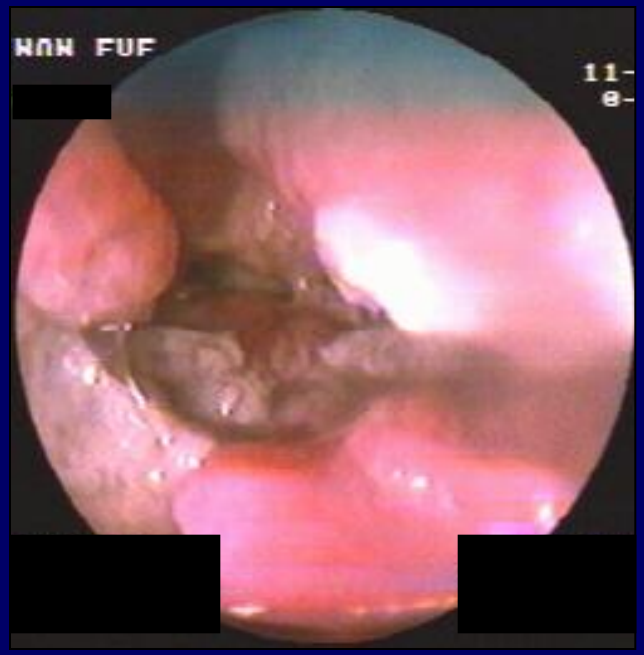
CLINICAL RESPONSE-EVALUATION
n=67

	Sensitivity	Specificity
• Symptoms	67%	50%
• Radiography	39%	85%
• CT-Thorax	11%	91%
• Endoscopy	22%	85%
• Endosonography	17%	93%

Adelstein, Cancer 1997

Preoperative Chemoradiation

Example: endoscopic response of SCC of the esophagus



before neoadjuvant therapy

after neoadjuvant therapy

Endoscopy

- 100 patients neoadj. RTx/CTx
- 30 endoscop. complete response
- 15 histological approved

	Accuracy (%)	Sensitivity (%)	Specificity (%)
Overall	52·0	65·2	50·0
Adenocarcinoma	50·0	57·1	36·3
Squamous cell carcinoma	55·0	68·8	57·9

Brown, Br J Surg 2004

Rebiopsy
after neoadjuvant RTx/CTx

(*Ann Surg* 2008;248: 902–908)

ORIGINAL ARTICLES

Response Evaluation by Endoscopy, Rebiopsy, and Endoscopic Ultrasound Does Not Accurately Predict Histopathologic Regression After Neoadjuvant Chemoradiation for Esophageal Cancer

Paul M. Schneider, MD,† Ralf Metzger, MD,* Hartmut Schaefer, MD,* Frank Baumgarten, MD,**

Study design

- cT3/4 Nx M0
- 1997 to 2004 n = 80
- RTx/CTx (5FU / cisplatin + 36 G)
- Restaging (CT, endoscopy + biopsy, EUS)
- Transthoracic esophagectomy

Rebiopsy after RTx/CTx

- 66 patients with
- 3 or more biopsies (median 4, range 3-15)

• No tumor cells	n=46	70%
• Positive results in at least one biopsy	n=20	30%

Response- Prediction after RTx/CTx Rebiopsy

	response		
	major	minor	total
No tumor cells	27	19	46
Tumor cells	2	18	20
Total	29	37	66

Clinical Response-Evaluation
n=80
Major – minor Response

	Sensitivity	Specificity
• Endoscopy	60%	34%
• Rebiopsy	46%	93%
• Endosonography	7%	76%

Schneider- Hölscher, Ann Surg 2008

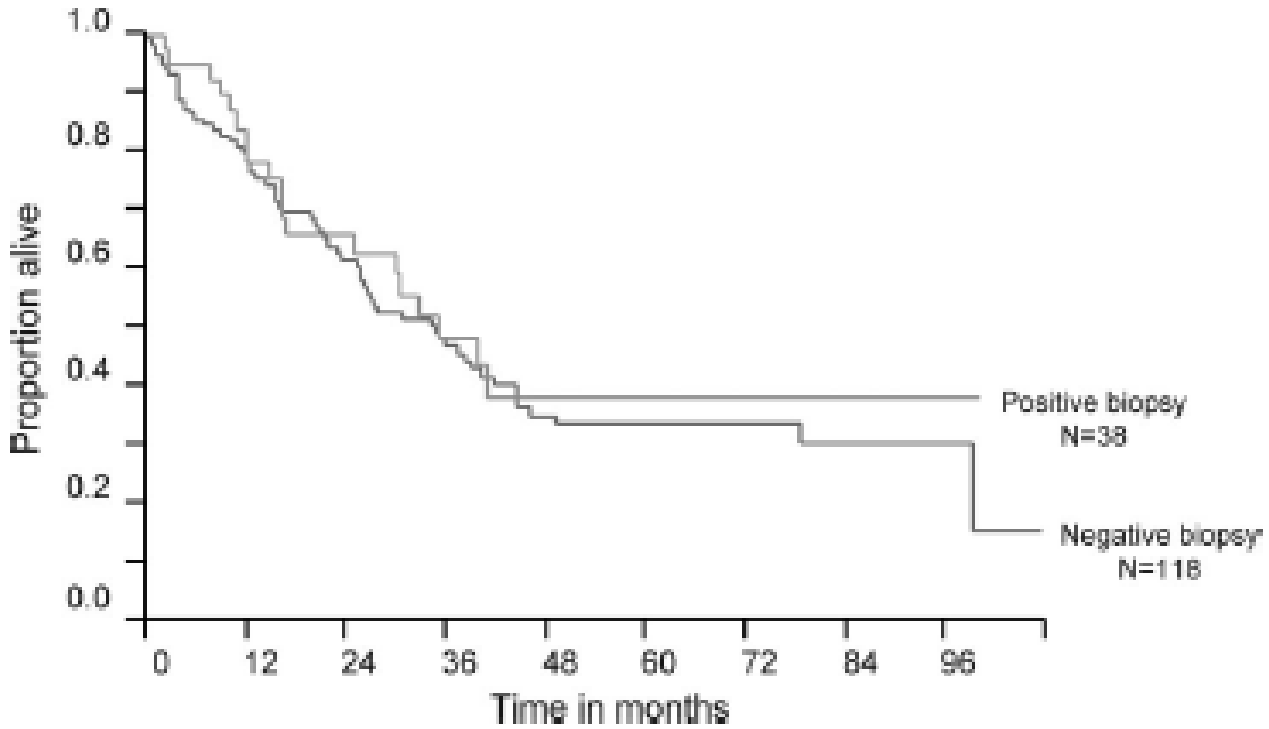
ORIGINAL ARTICLES (*Ann Surg* 2009;249: 764–767)

Post-treatment Endoscopic Biopsy Is a Poor-Predictor of Pathologic Response in Patients Undergoing Chemoradiation Therapy for Esophageal Cancer

Inderpal S. Sarkaria, MD, Nabil P. Rizk, MD,* Manjit S. Bains, MD,* Laura H. Tang, MD, PhD,† David H. Ilson, MD, PhD,‡ Bruce I. Minsky, MD,§ and Valerie W. Rusch, MD**

Biopsy negativ (n=118): Pathologic complete response: 37%

Biopsy positive: n=38



Response evaluation with PET

^{18}F-FDG-PET Evaluation

- 41 patients with neoadj. RTx/CTx
- Complete response
- Best accuracy for the Cut-off point **4** SUV_{max}
  - Sensitivity 61%
  - Specificity 60%
  - Pos. pred. V. 83%
  - Neg. pred. V. 33%

Levine, Ann Surg 2006

SYSTEMATIC REVIEW

18F-Fluorodeoxiglucose Positron Emission Tomography for the Evaluation of Neoadjuvant Therapy Response in Esophageal Cancer

Systematic Review of the Literature

Ángel C. Rebollo Aguirre, PhD, Carlos Ramos-Font, MD,* Román Villegas Portero, MD,† Gary J. R. Cook, PhD,‡ José M. Llamas Elvira, PhD,* and Antonio Romero Tabares, PhD†*

(Ann Surg 2009;250: 247–254)

Summarized Diagnostic Accuracy of FDG-PET in Restaging after Neoadjuvant Therapy

	Sensitivity	Specificity
Wieder 2004	89%	87%
Cerfolio 2004	87%	88%
Song 2005	27%	95%
Levine 2006	61%	60%
Westerterp 2006	75%	75%

[^{18}F]-Fluorodeoxyglucose-Positron Emission Tomography for the Assessment of Histopathologic Response and Prognosis After Completion of Neoadjuvant Chemoradiation in Esophageal Cancer

Daniel Vallböhmer, MD, Arnulf H. Hölscher, MD, FACS, FRCS,* Markus Dietlein, MD,† Elfriede Bollschweiler, MD,* Stephan E. Baldus, MD,‡ Stefan P. Mönig, MD,* Ralf Metzger, MD,* Harald Schicha, MD,† and Matthias Schmidt, MD†*

ypN category*
- ypN0 (n = 66)
- ypN1 (n = 53)

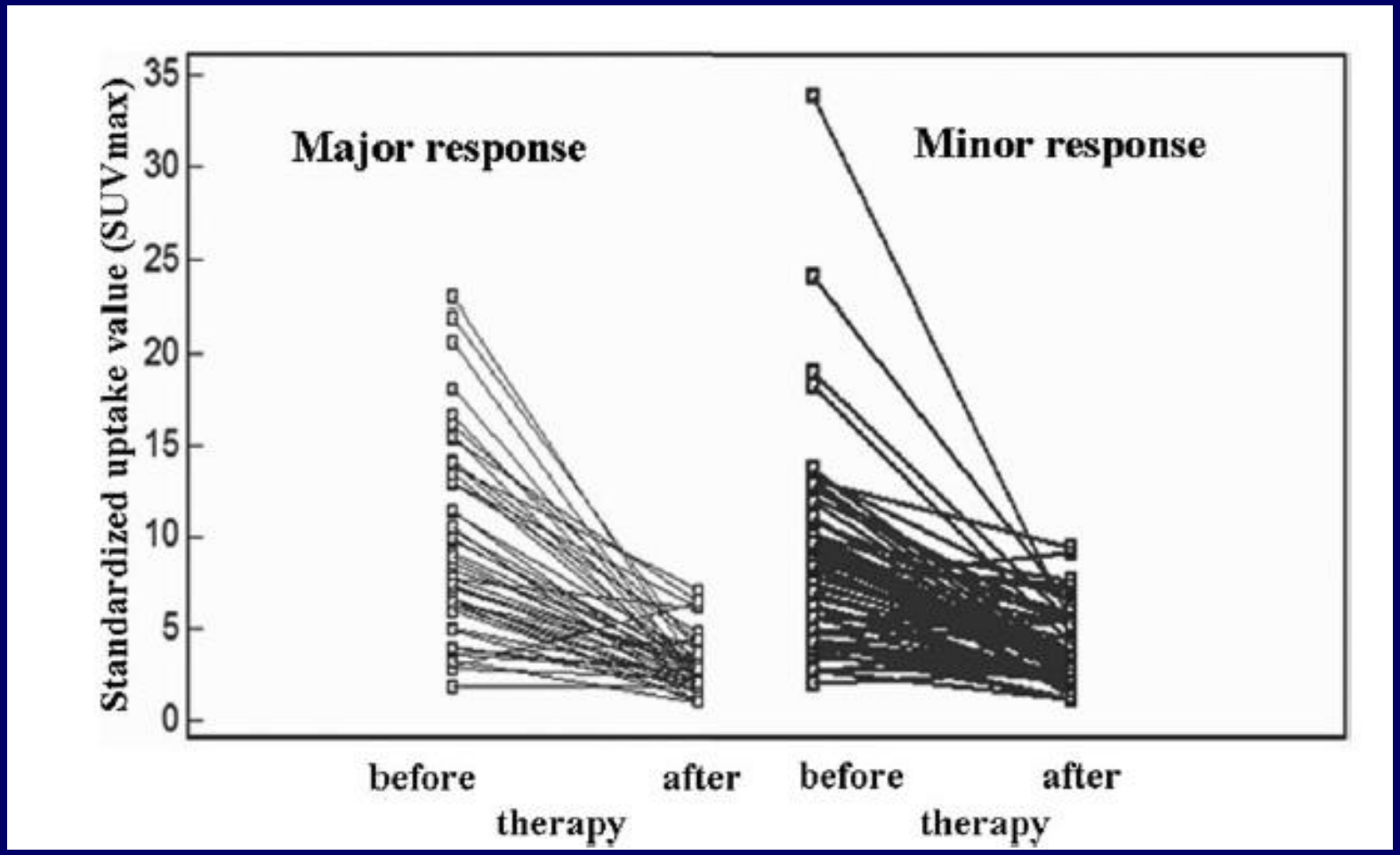
ypT category†
- ypT0 (n = 13)
- ypT1 (n = 8)
- ypT2 (n = 28)
- ypT3 (n = 70)

Histomorphologic regression‡
- major response (n = 47)
- minor response (n = 72)

(*Ann Surg* 2009;250: 888–894)

Response Evaluation with PET

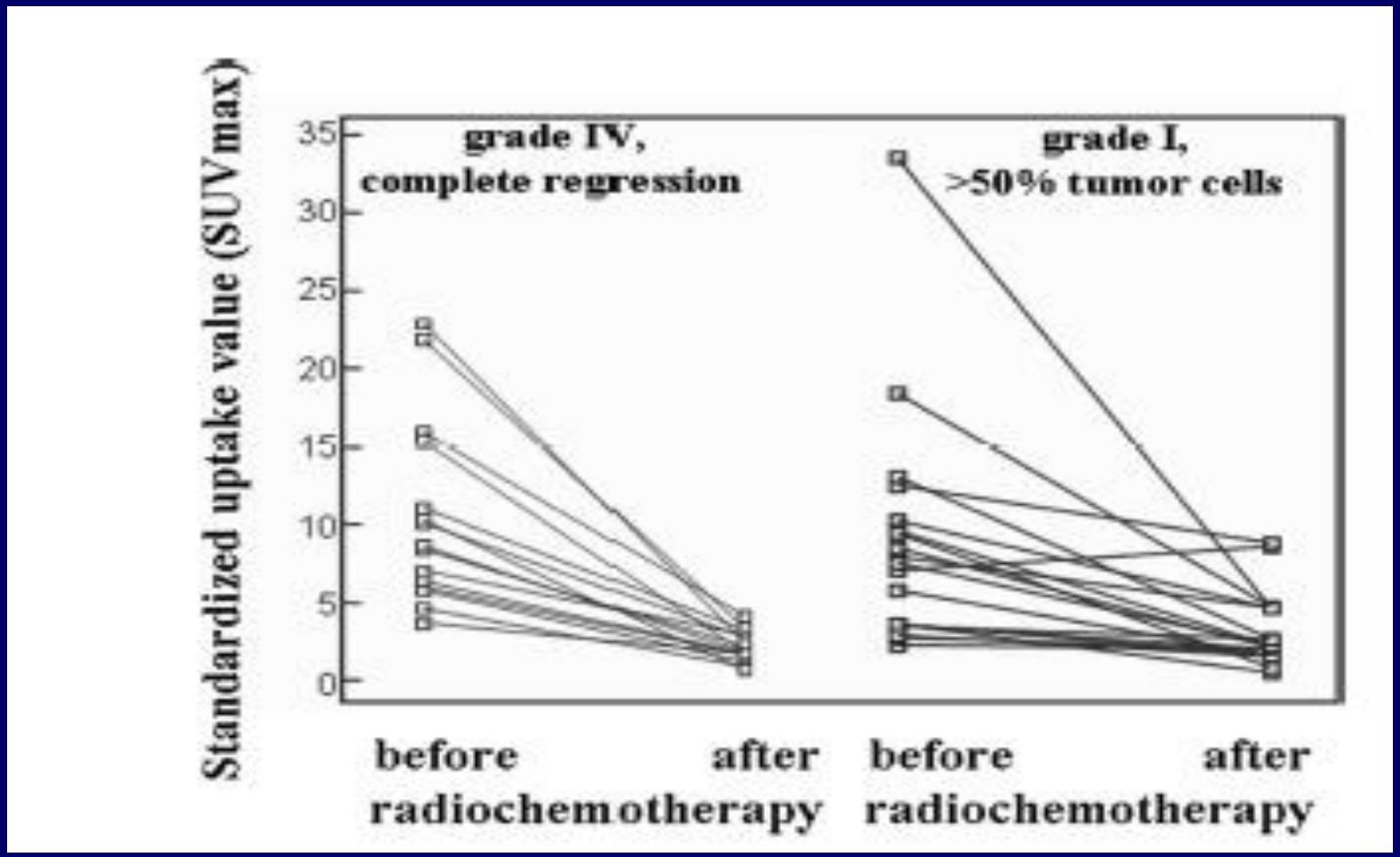
N=119



Vallböhmer - Hölscher, Ann Surg 2009

Response Evaluation with PET

N=119

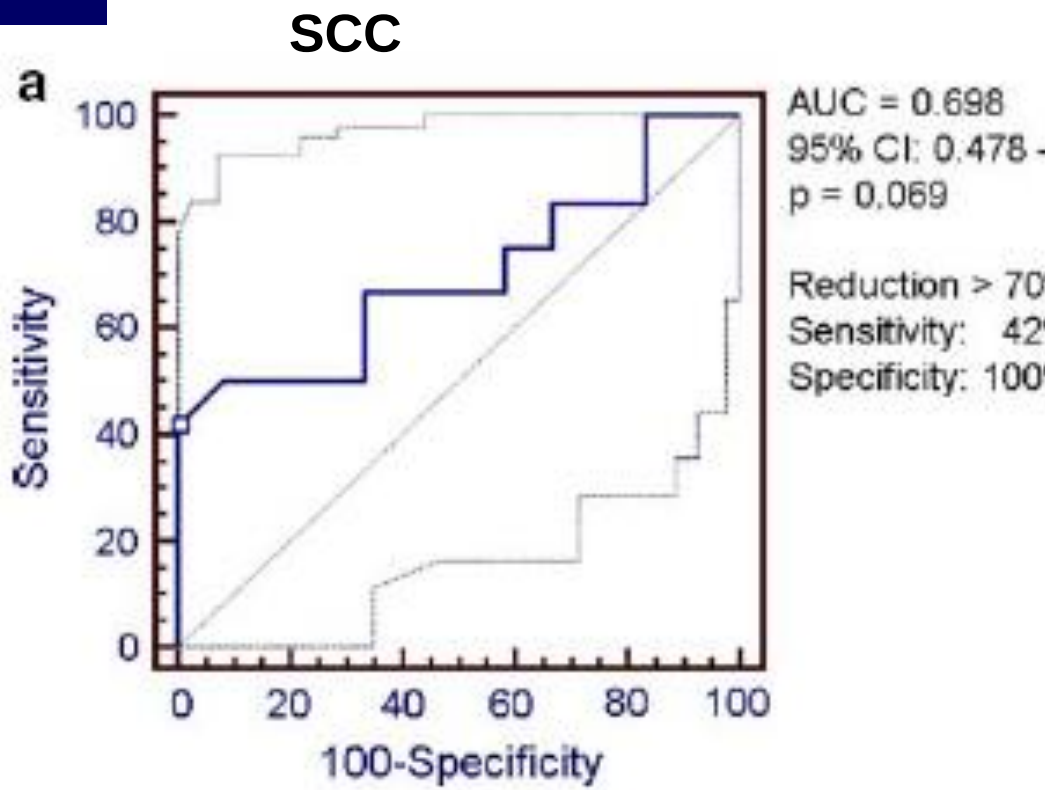


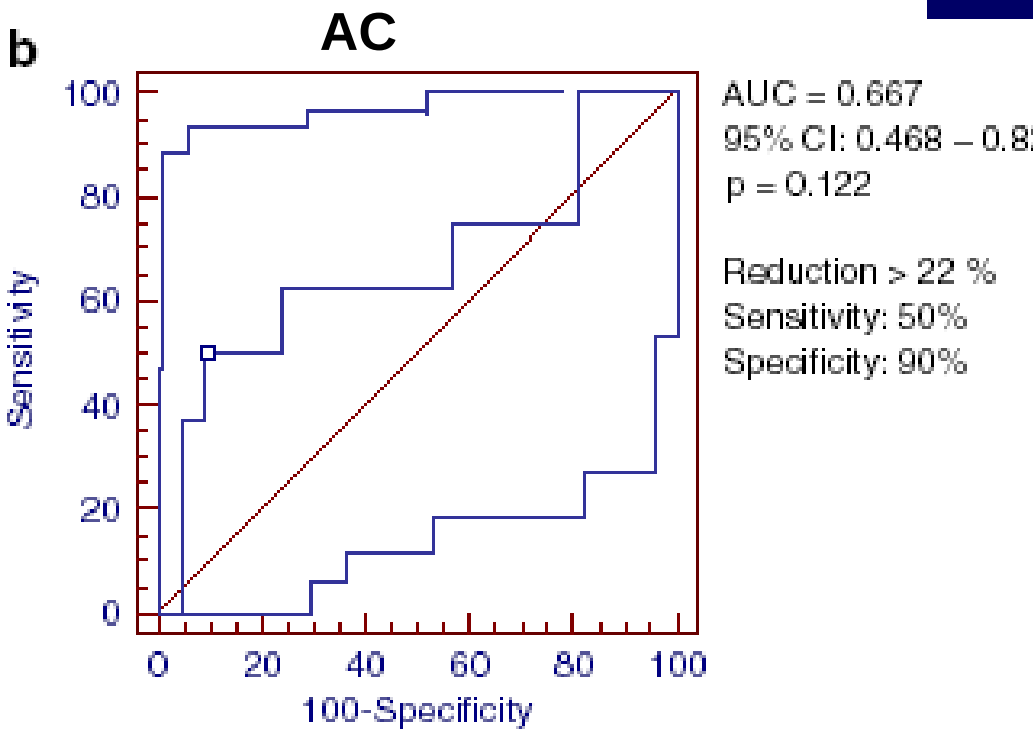
Vallböhmer - Hölscher, Ann Surg 2009

Eur J Nucl Med Mol Imaging (2009) 36:735–744
DOI 10.1007/s00259-008-1011-y

ORIGINAL ARTICLE

Mean and maximum standardized uptake values in [^{18}F] FDG-PET for assessment of histopathological response in oesophageal squamous cell carcinoma or adenocarcinoma after radiochemotherapy





Clinical Response Evaluation

- Symptoms
- Radiography
- CT-Thorax
- Esophagoscopy
- Rebiopsy
- Endosonography
- PET

Not reliable

Histopathologic Response Evaluation

reliable

Surgery after neoadjuvant chemoradiation

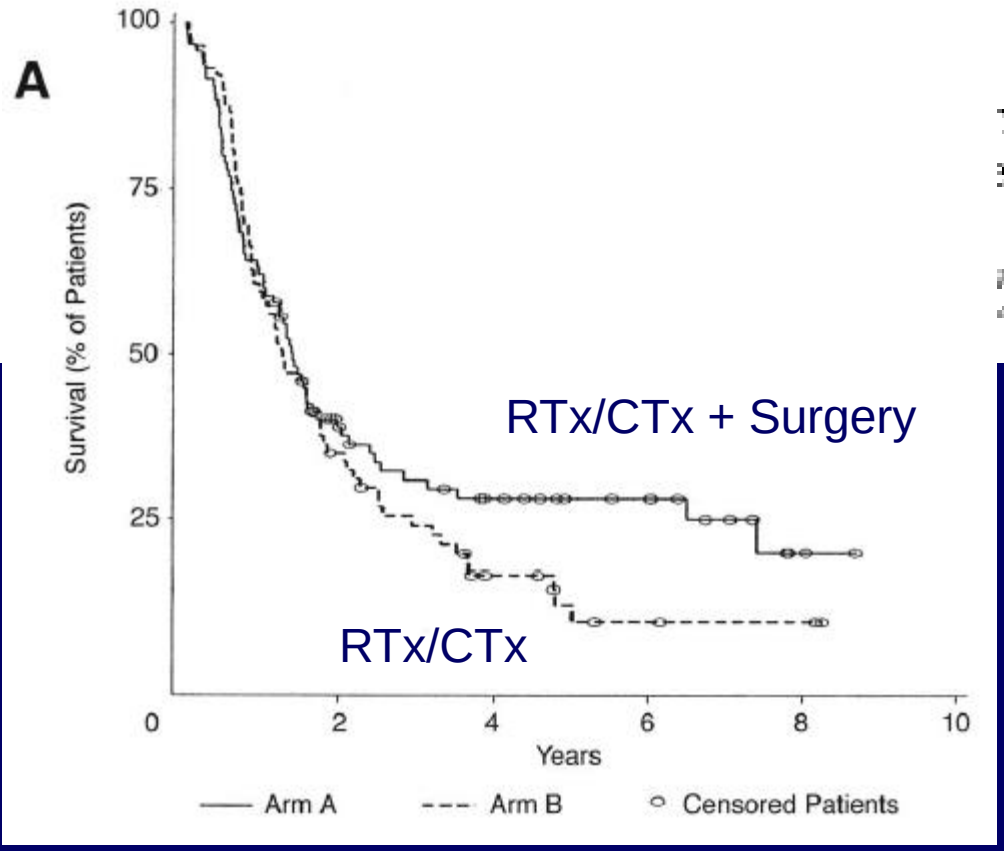
VOLUME 23 · NUMBER 10 · APRIL 1 2005

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

n and Without Surgery in Patients
ed Squamous Cell Carcinoma of

ivanova, Hans-Joachim Meyer, Martin K. Wolz, Siegfried Sauber,
d Teichmann, Marcus Schmitt, Carol Schmitt, Claus Franke,



Stahl, J Clin Oncol 2005

Prognosis – German Trial

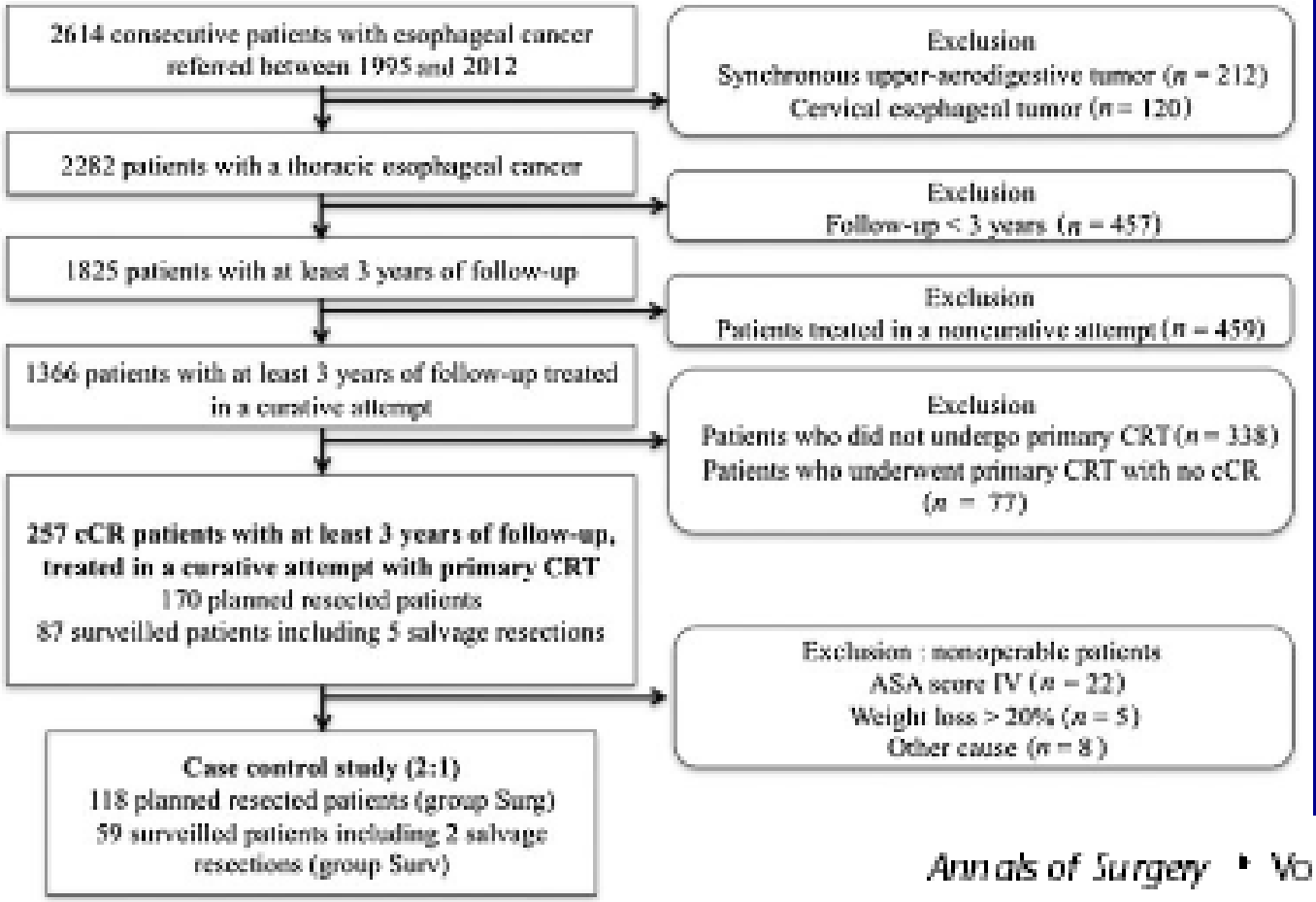
	5 y Survival-Rate	
	all Patients	Responder
RTx/CTx + OP	27.9%	56.5%
RTx/CTx	17.0%	37.0%

Stahl, ASCO 2008

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*†‡*



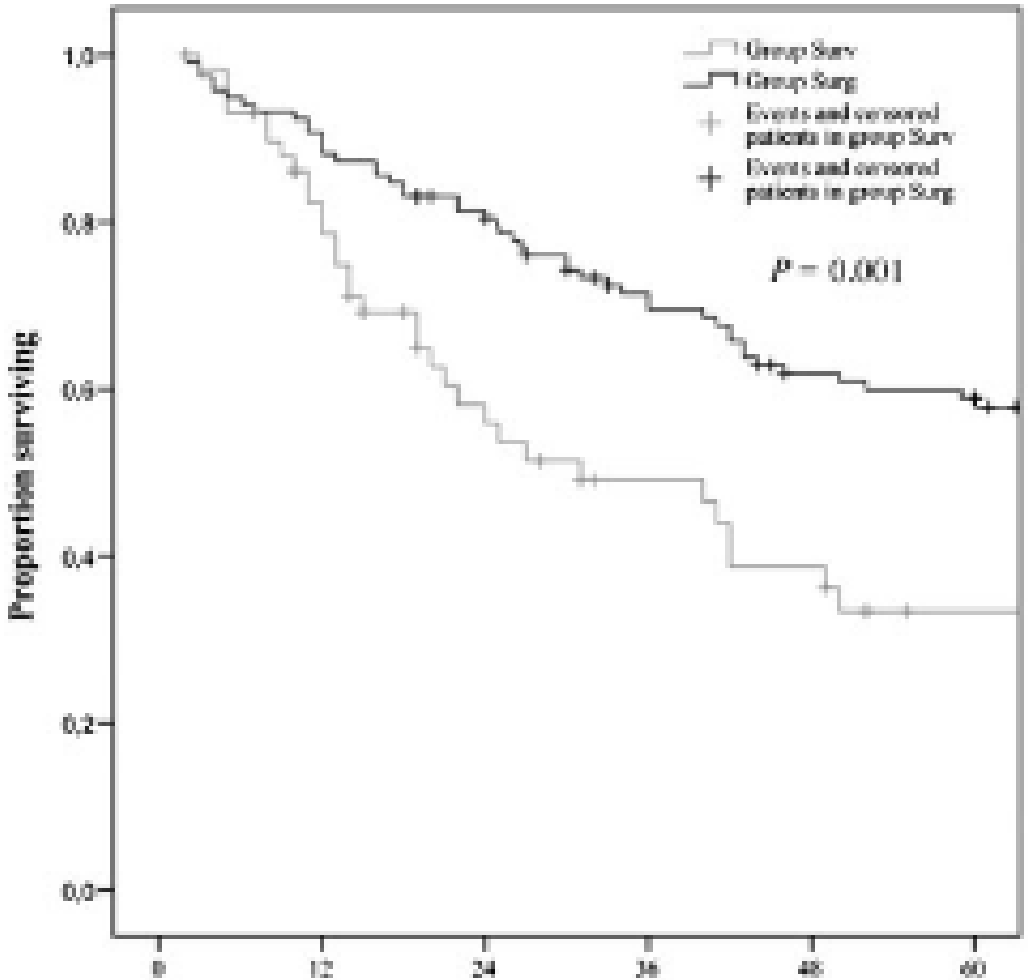
Annals of Surgery • Volume 258, Number 5, November 2013

Neoadjuvant chemoradiation esophagectomy after ‚complete response'?

- 222 patients with morphologic CR after RTx/CTx
- Follow-up: > 3 years
- Matched pairs
  (Age, gender, ASA, tumor location, cTNM, histology-84% SCC, nutritional status)
  n=59 without OP : n=118 OP

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

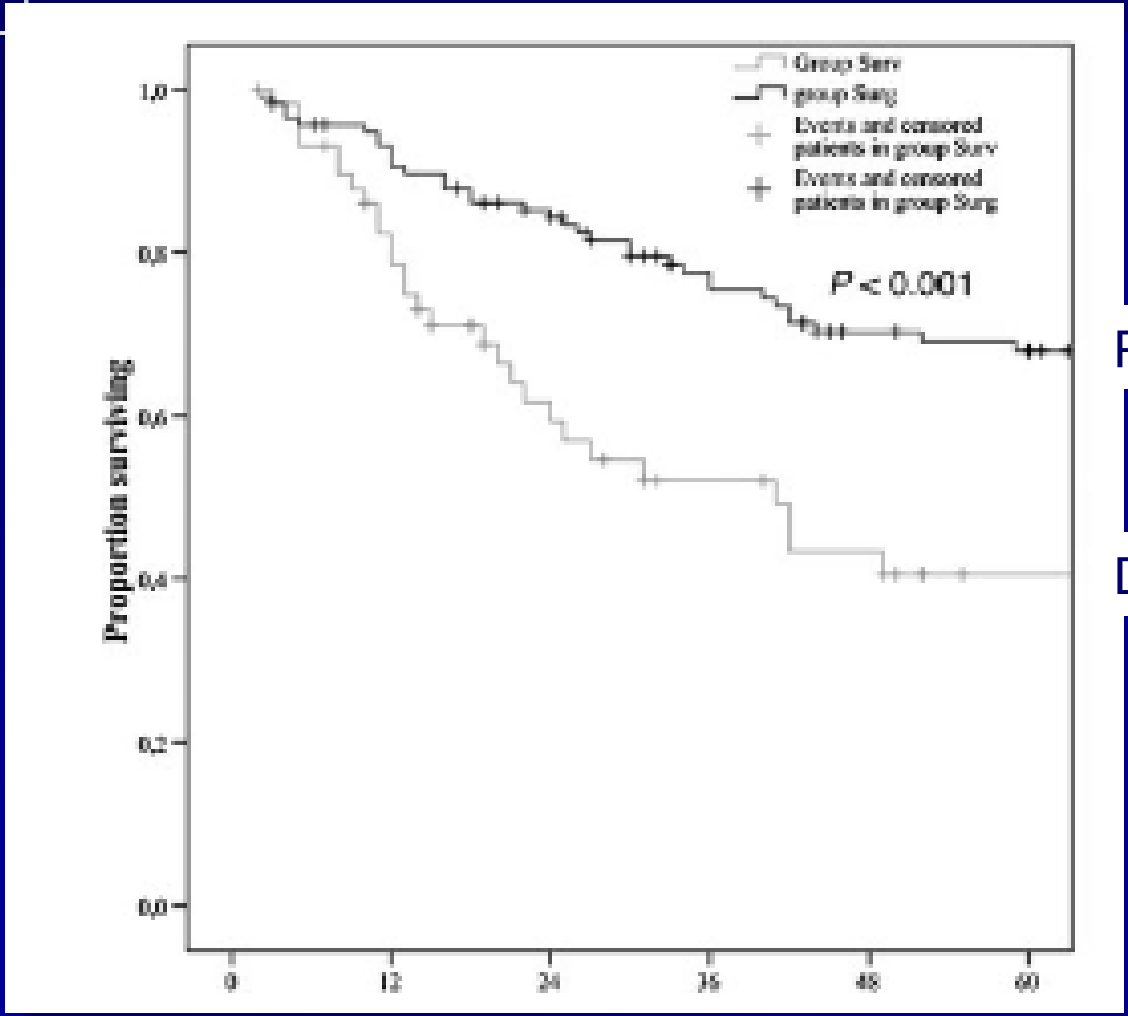
Overall Survival



RTx/CTx+Surgery

Def. RTx/CTx

Cancer specific Survival



RTx/CTx+Surgery

Def. RTx/CTx

Neoadjuvant chemoradiation
Esophagectomy after ‚complete response'?

Results

	RTx/CTx	RTx/CTx+OP	p
Med. Surv :	31 M.	83 M.	0.001
5y OSR:	33%	59%	0.001
Rate of rec:	51%	33%	0.021
Time to rec:	7,8 M.	19 M.	0.002
Lokoreg. rec:	47%	16%	0.008

Piessen, Ann Surg 2013

Salvage Surgery

Ann Surg Oncol
DOI 10.1245/s10434-013-3364-0

2014

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

REVIEW ARTICLE – GASTROINTESTINAL ONCOLOGY

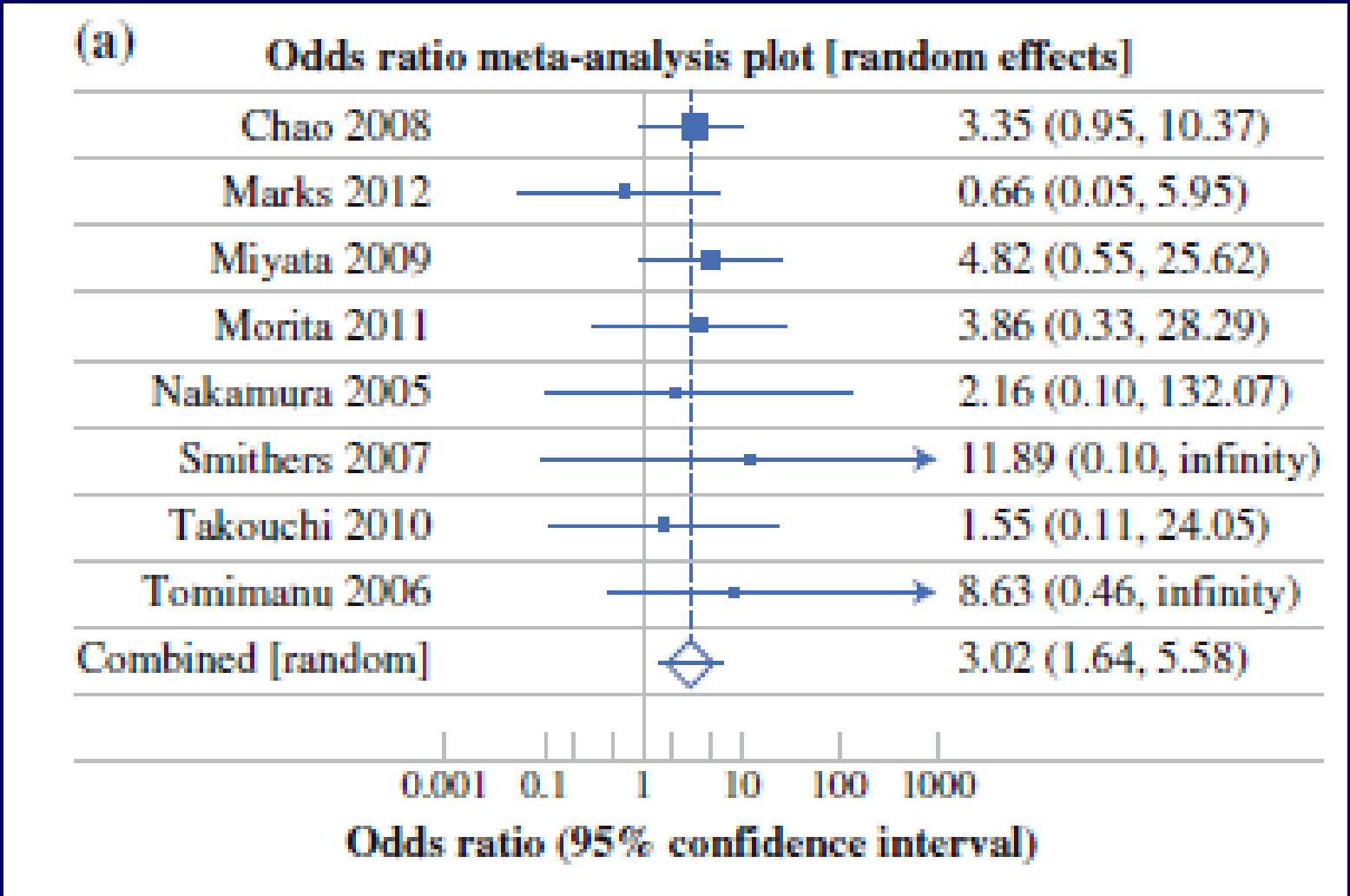
Assessment of Short-Term Clinical Outcomes following Salvage Esophagectomy for the Treatment of Esophageal Malignancy: Systematic Review and Pooled Analysis

Sheraz R. Markar, MRCS, MSc, MA[1], Alan Karthikesalingam, MRCS, MSc, MA[2], Marta Penna, MRCS, BSc[1], and Donald E. Low, FRCS, FACS[1]

The aim of this pooled analysis was to compare short-term clinical outcomes from SALVAGE following definitive chemoradiotherapy with those from planned esophagectomy following neoadjuvant chemoradiotherapy (NCRS).

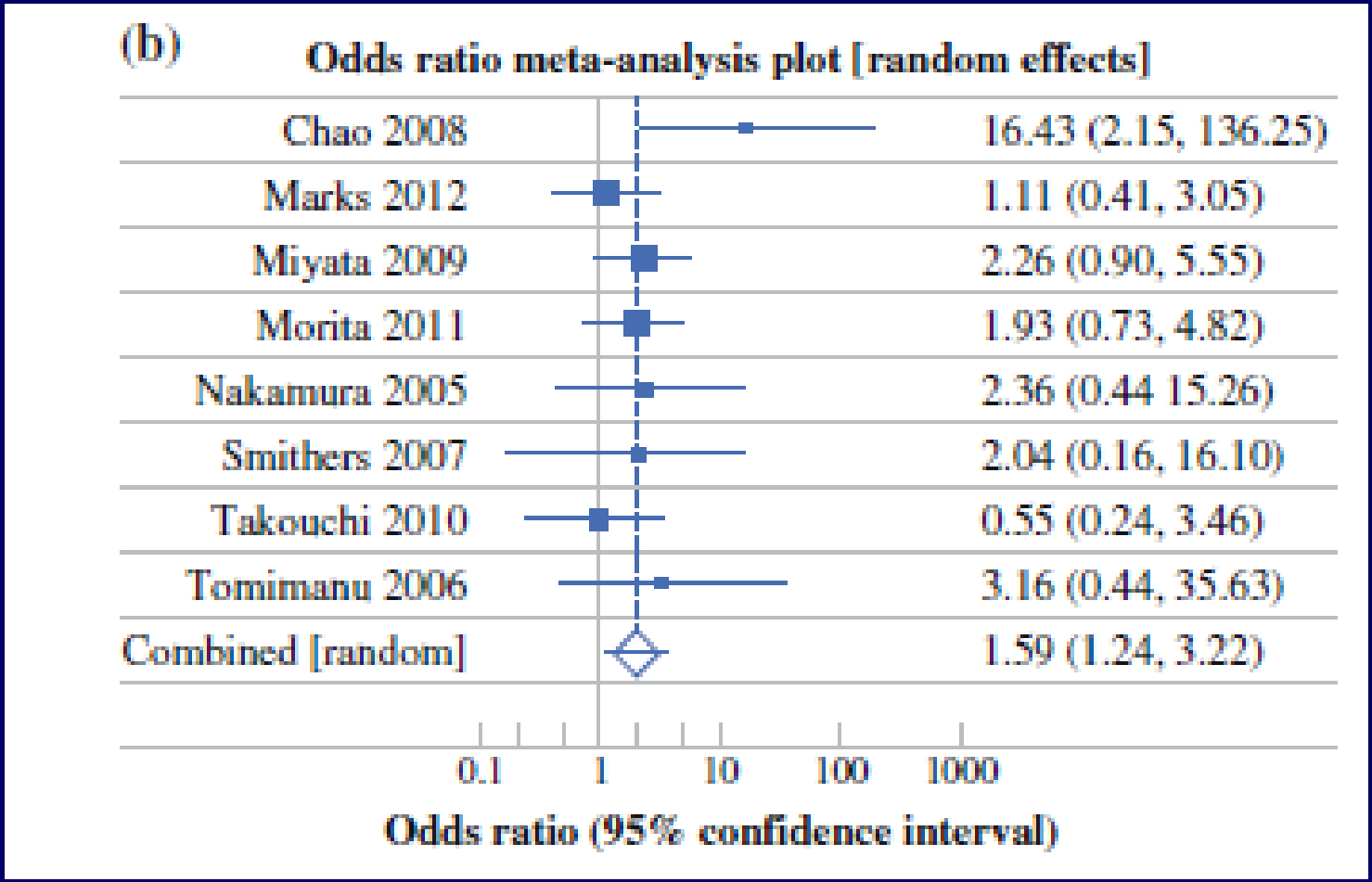
Significant increase of Postoperative mortality

Salvage 9.5% vs. Neoadjuvant 4.1%



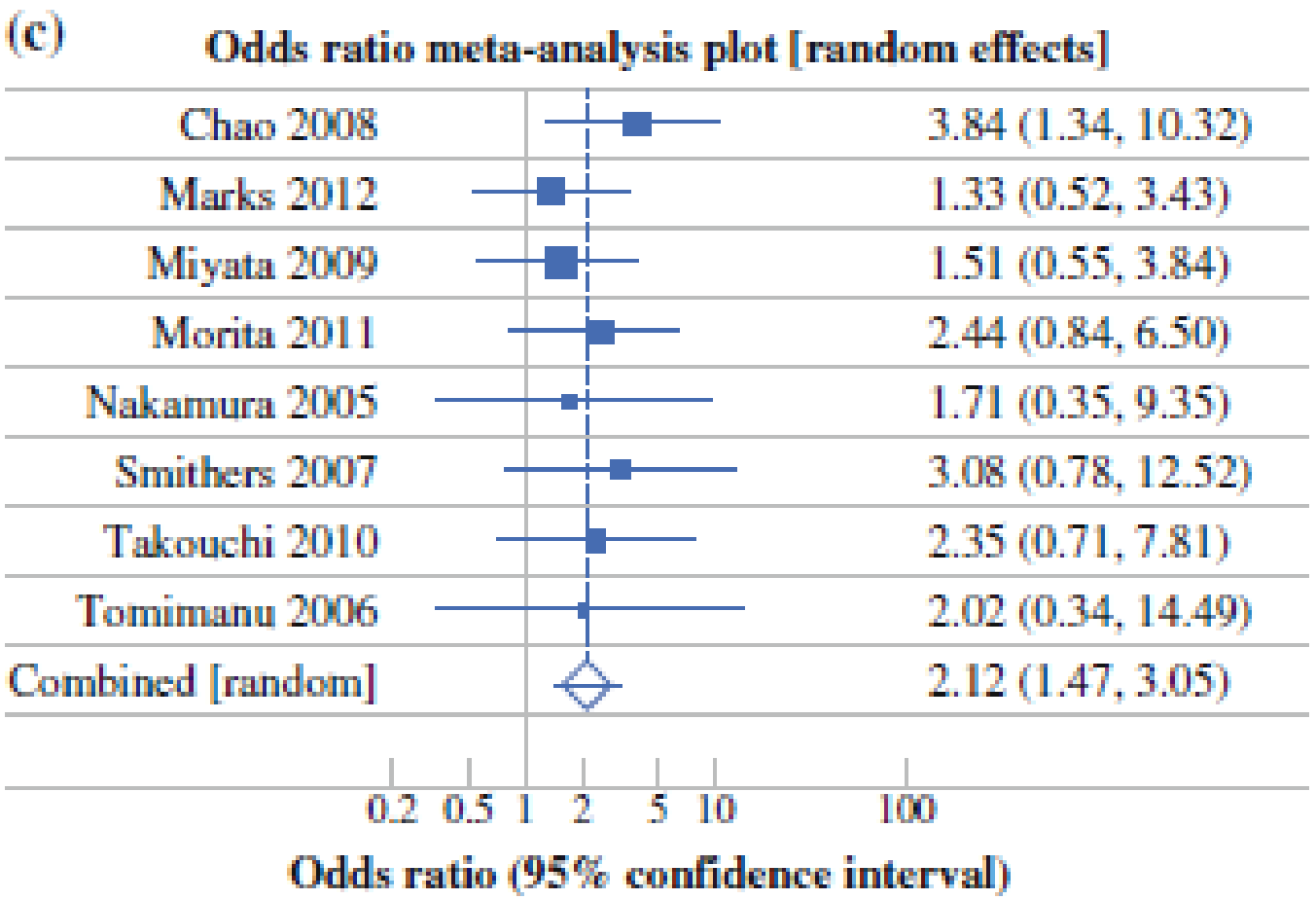
Significant increase of Anastomotic leakages

Salvage 24.0% vs. Neoadjuvant 14.5%



Significant increase of Pulmonary complications

Salvage 29.8% vs. Neoadjuvant 17.0%



Salvage Esophagectomy After Failed Definitive Chemoradiation for Esophageal Adenocarcinoma

Jenifer L. Marks, MD, Wayne Hofstetter, MD, Arlene M. Correa, PhD, Reza J. Mehran, MD, MS, David Rice, MB, BCh, Jack Roth, MD, Garrett Walsh, MD, Ara Vaporciyan, MD, Jeremy Erasmus, MD, Joe Chang, MD, Dipen Maru, MD, Jeffrey H. Lee, MD, Jared Lee, MS, Jaffer A. Ajani, MD, and Stephen G. Swisher, MD

Table 1. Patient Demographics

Factor	Salvage n = 65	Planned n = 521	*p* Value	Matched Pair n = 65	*p* Value
Sex					
Male	59 (90.8%)	472 (90.6%)	0.964	60 (92.3%)	1
Female	6 (9.2%)	49 (9.4%)		5 (7.7%)	
XRT dose, cont					
Mean Gy	50 ± 4	48 ± 3	< 0.000	50 ± 4	0.254
Time to surgery					
Median no. days	216 ± 237	50 ± 27	< 0.000	55 ± 32	< 0.000

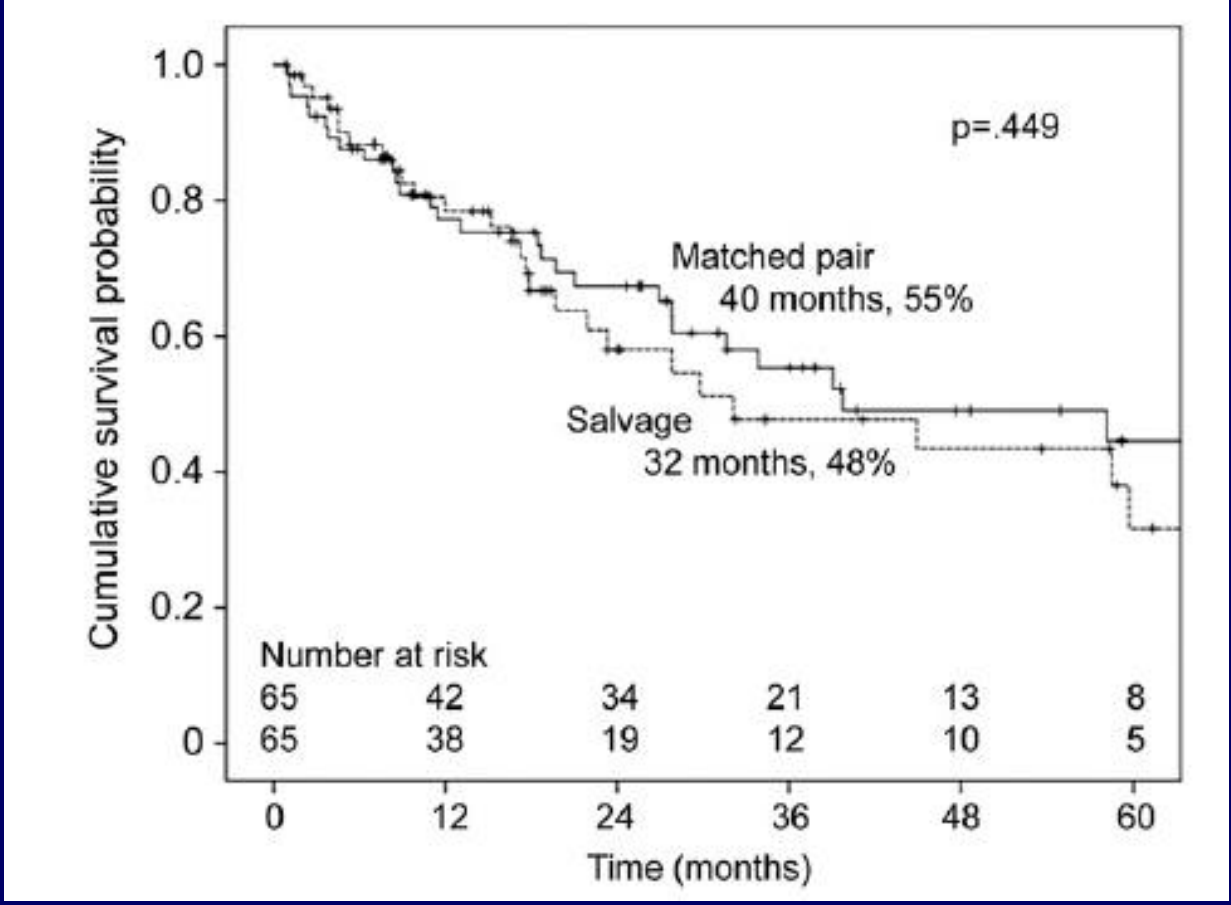
Marks et al. Ann Thorac Surg 2012

Matched pairs - Surgical Results

	Salvage	Matched pairs	p
n	65	65	
R0-resection	90.8%	98.5%	<0.01

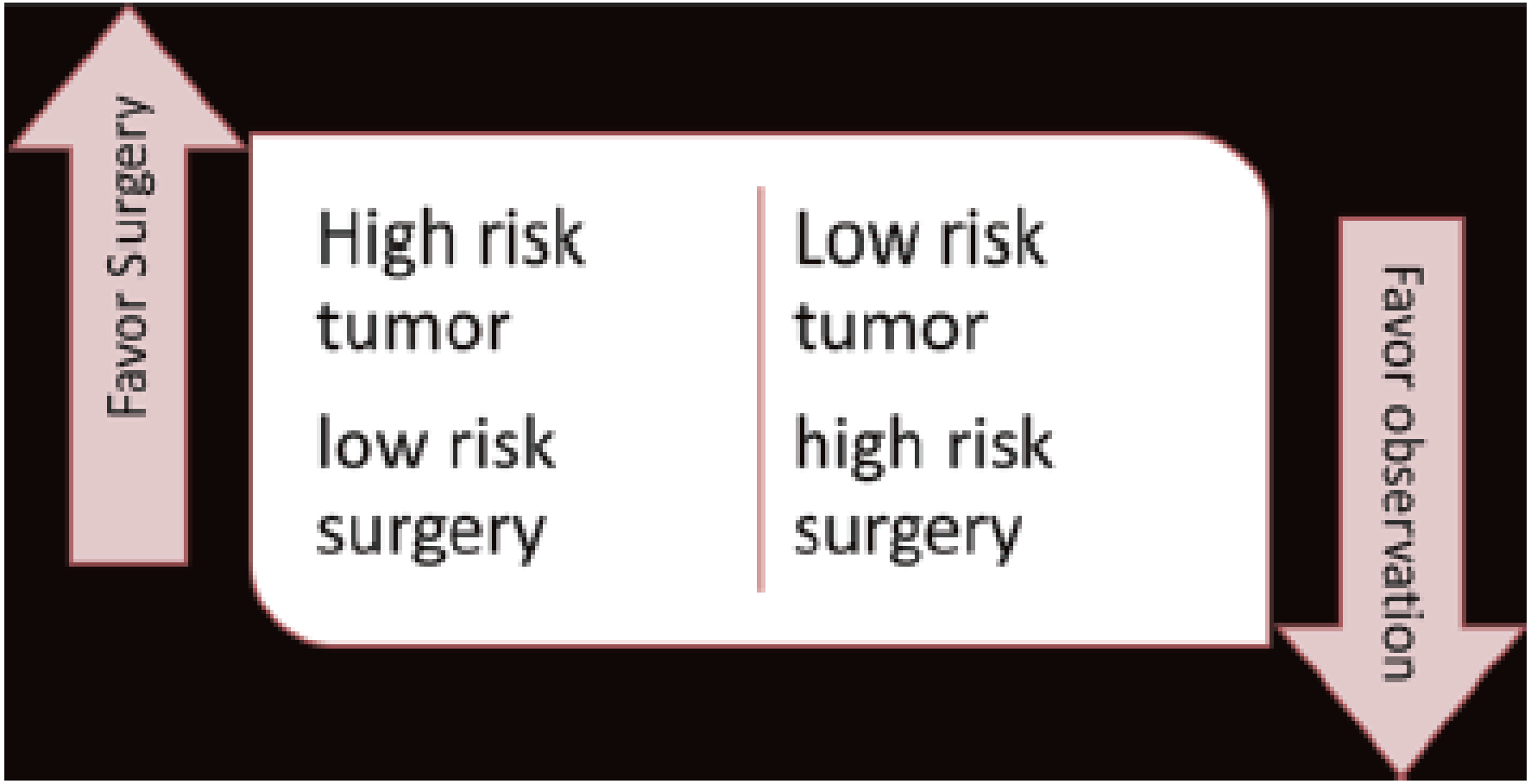
Marks et al. Ann Thorac Surg 2012

Matched pairs - Prognosis



Marks et al. Ann Thorac Surg 2012

Salvage Surgery



Hofstetter. J Thorac Dis 2014

Klinik und Poliklinik für Allgemein, Viszeral und Tumorchirurgie, Uniklinik Köln 2013

esophagectomies

N=161 consecutive patients (5x no carcinoma)

30 day mortality:	n=0	0%
Hospital mortality:	n=1	0.7%
90 day mortality:	n=4	2.5%
Anast.-Insufficency:	n=12	7.5%
Rethoracotomy	n=10	6.2%

68% neoadjuvant therapy

- Does response to preoperative therapy modify the extension of surgical resection?

No

- When is salvage surgery indicated?

  - higher risk than primary surgery
  - very individual indication
  - interdisciplinary tumorboard

University Hospital, Cologne