

Perioperative Chemotherapy Esophageal and Gastric Cancer

Prof. Florian Lordick

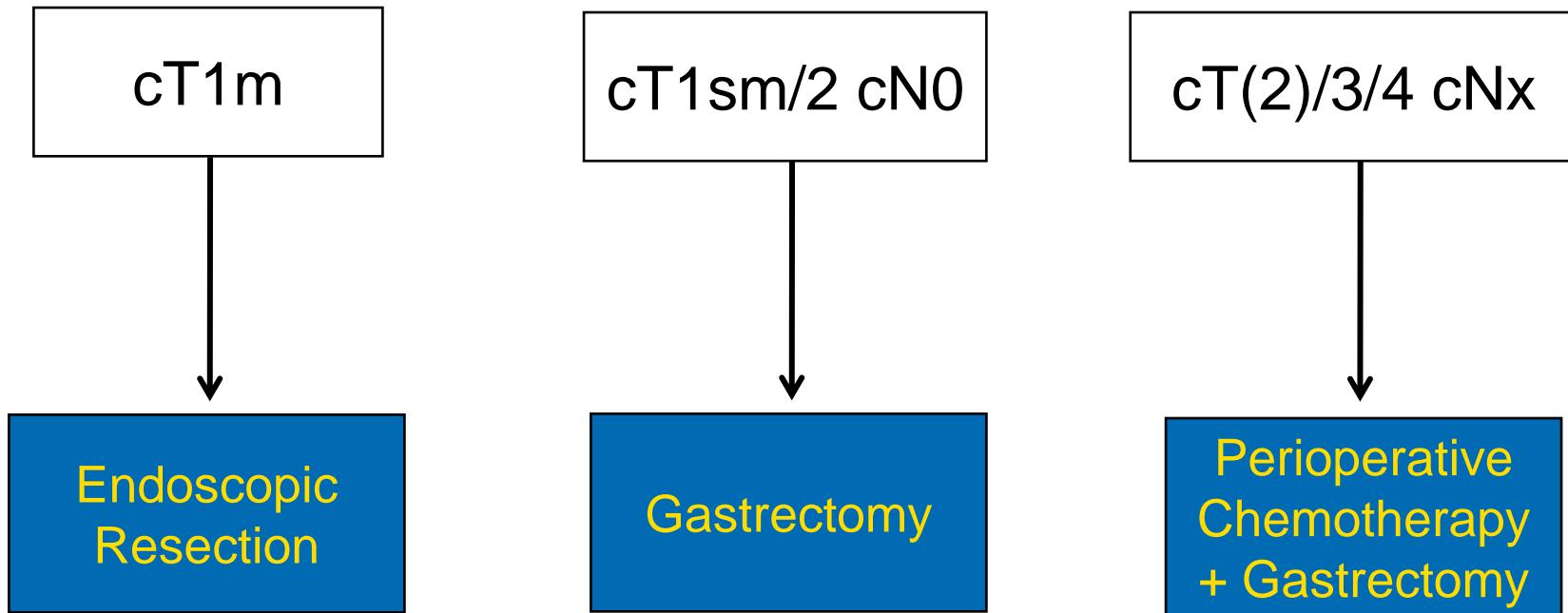
University Cancer Center Leipzig

UCCL

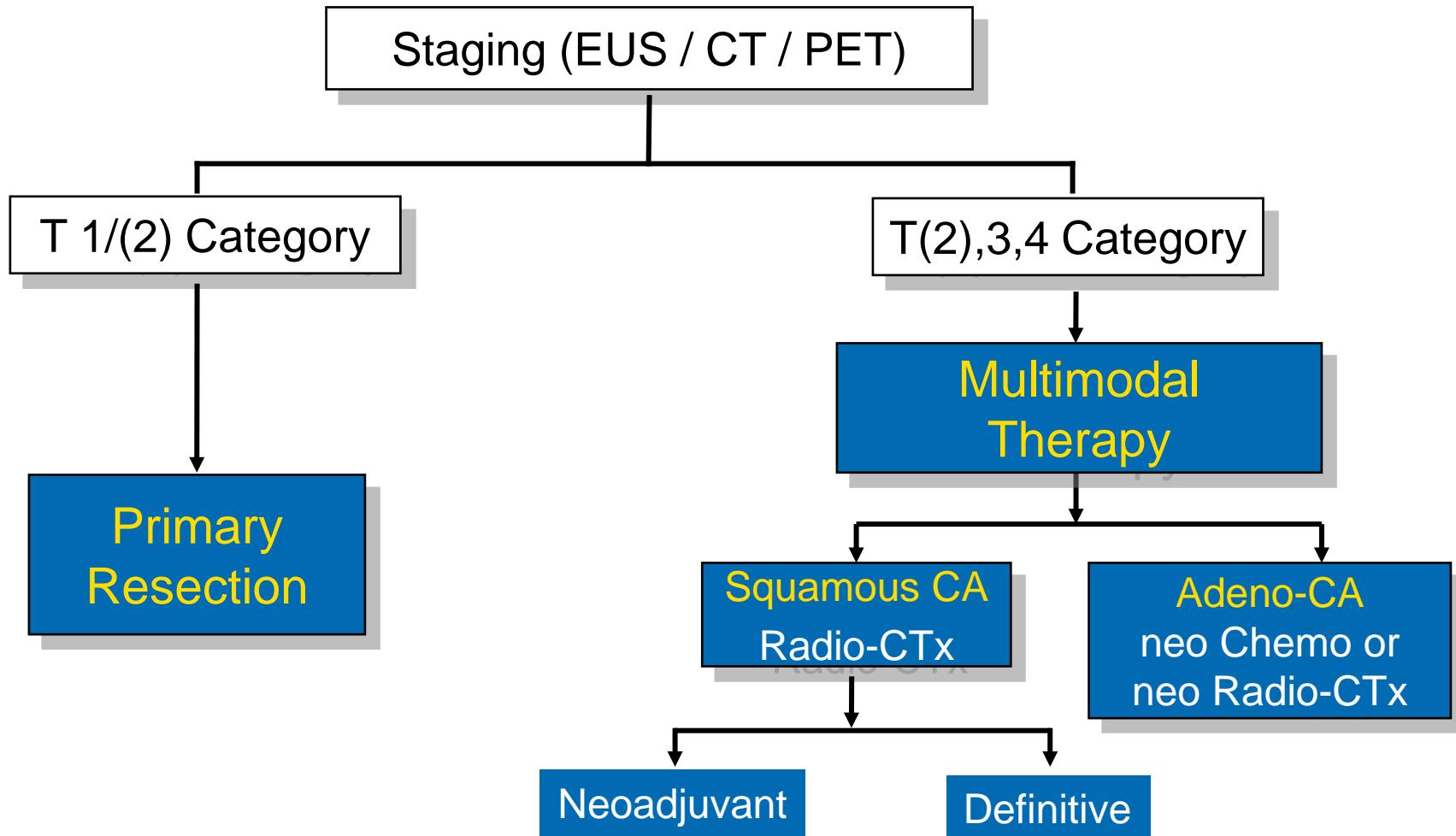


Gastric Cancer 2013

Staging (CT Chest/Abdo, EUS, Laparoscopy)

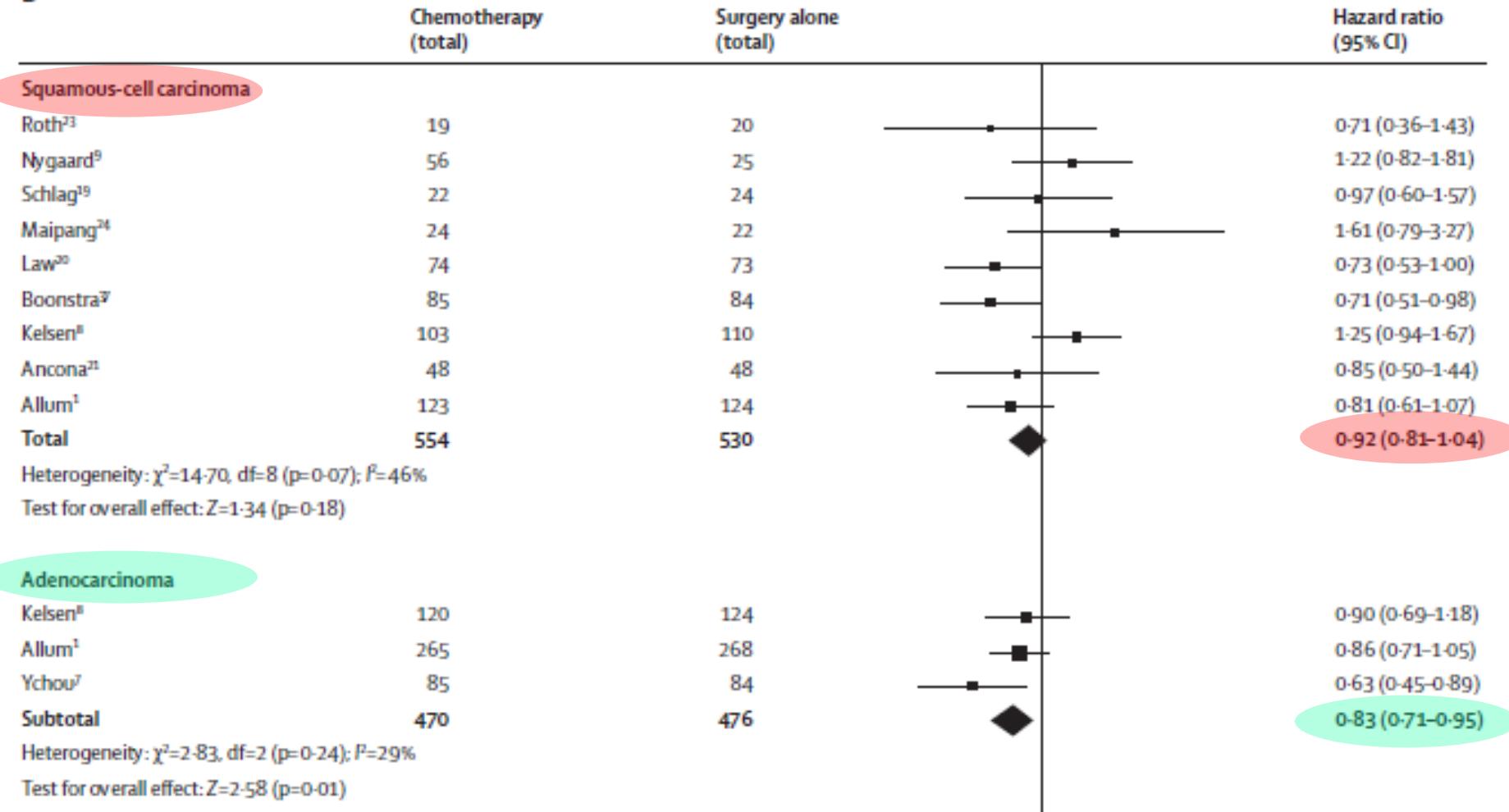


Esophageal Cancer 2013



Chemotherapy - Metaanalysis

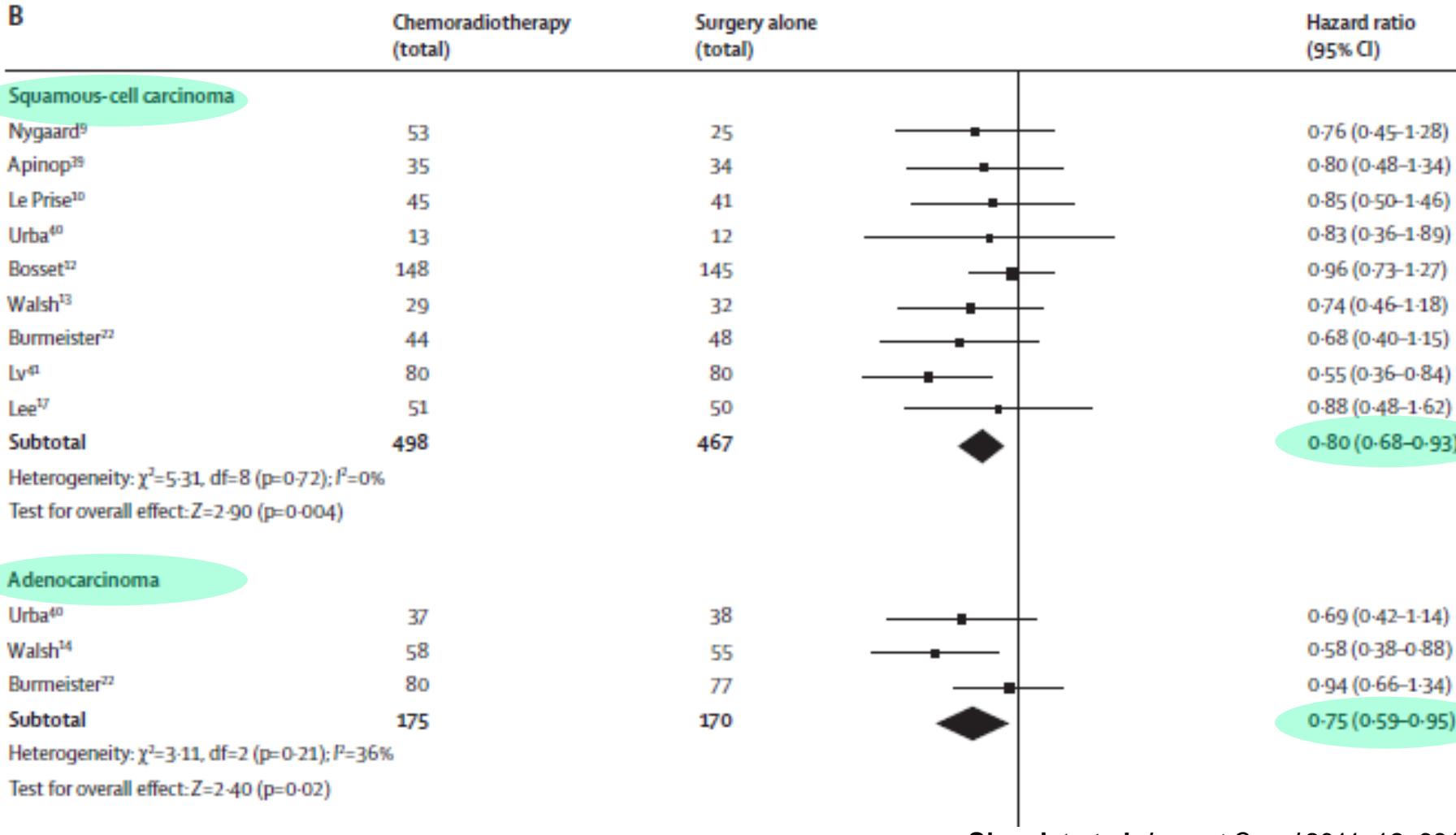
B



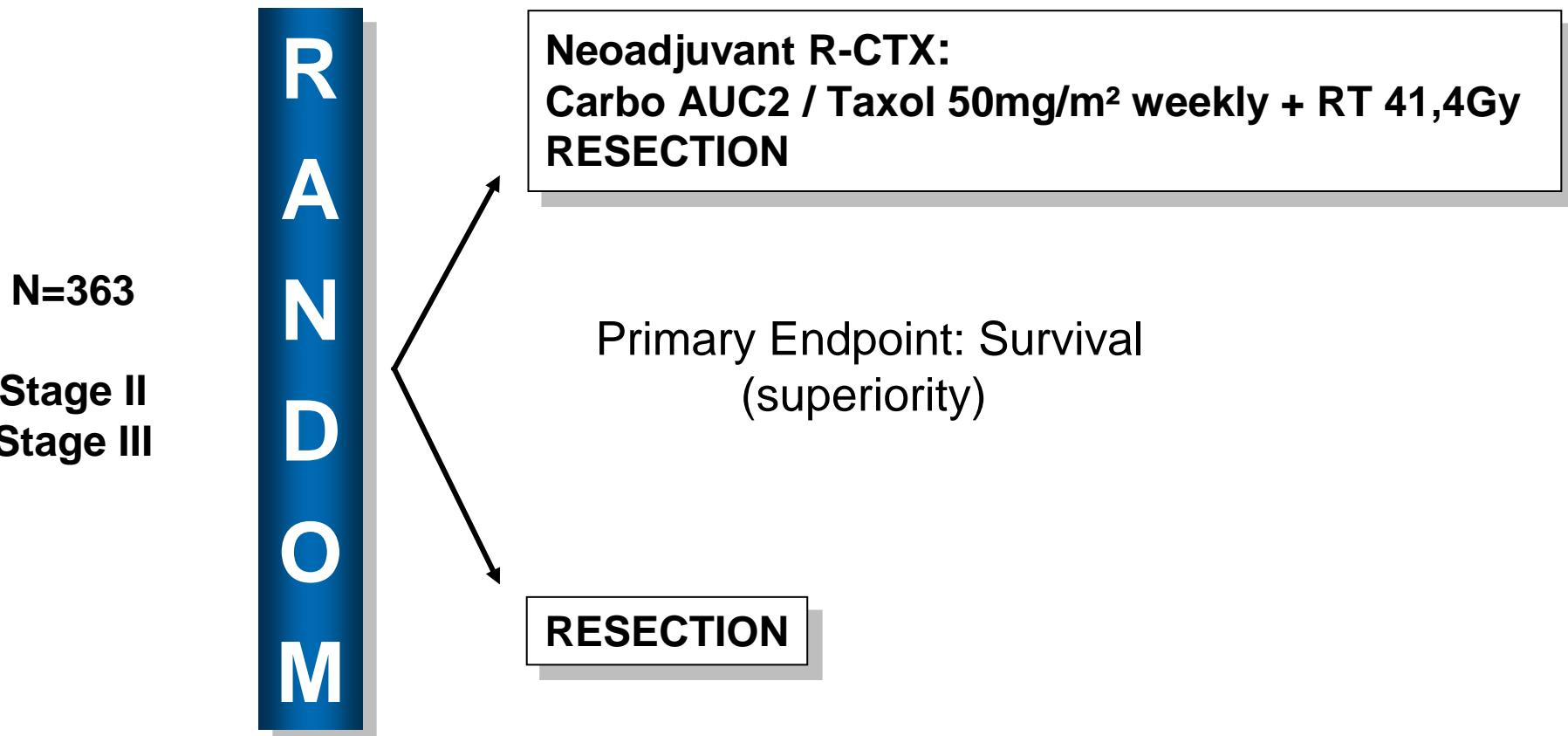
Sjoquist et al. Lancet Oncol 2011; 12: 681-692

Radiochemotherapy - Metaanalysis

B

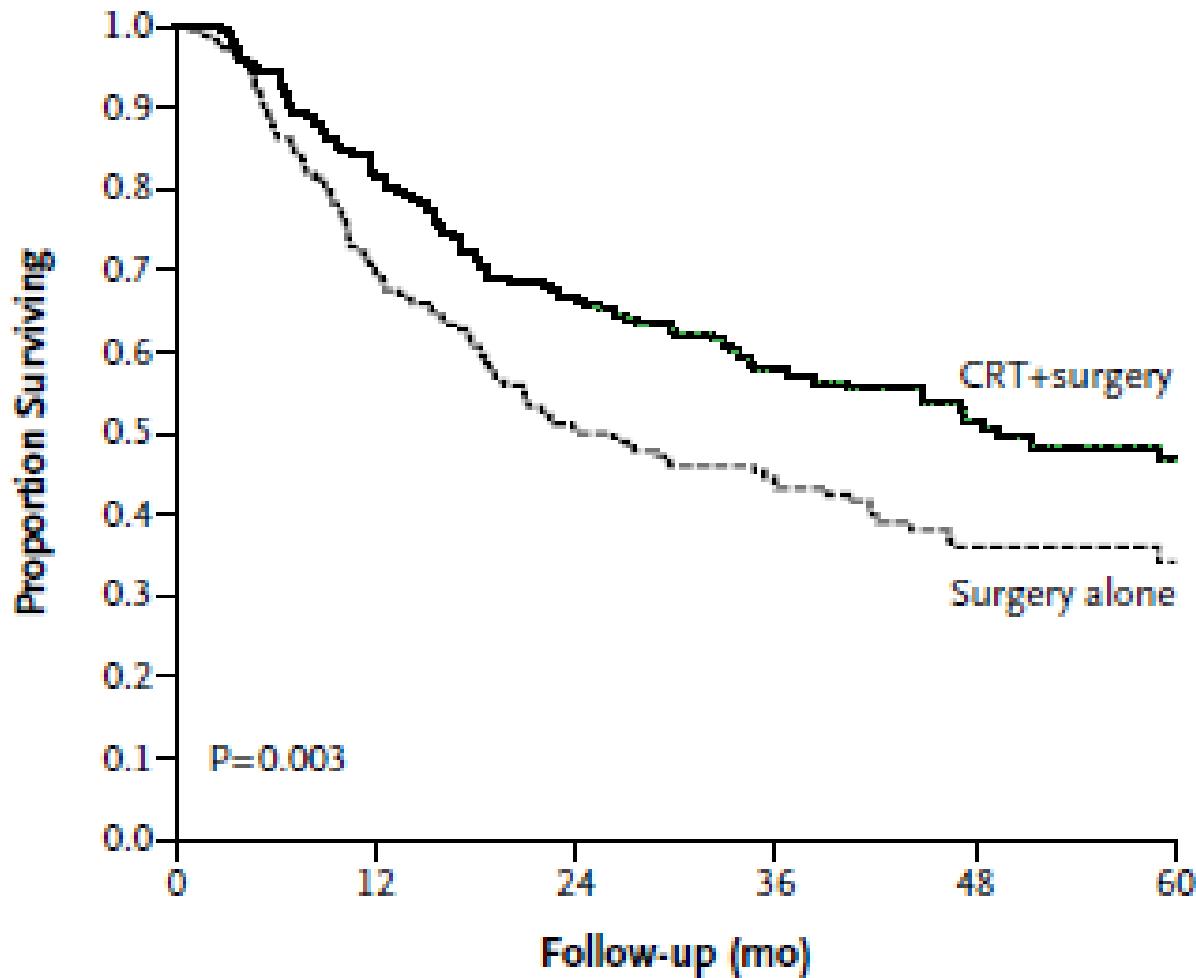


Sjoquist et al. Lancet Oncol 2011; 12: 681-692



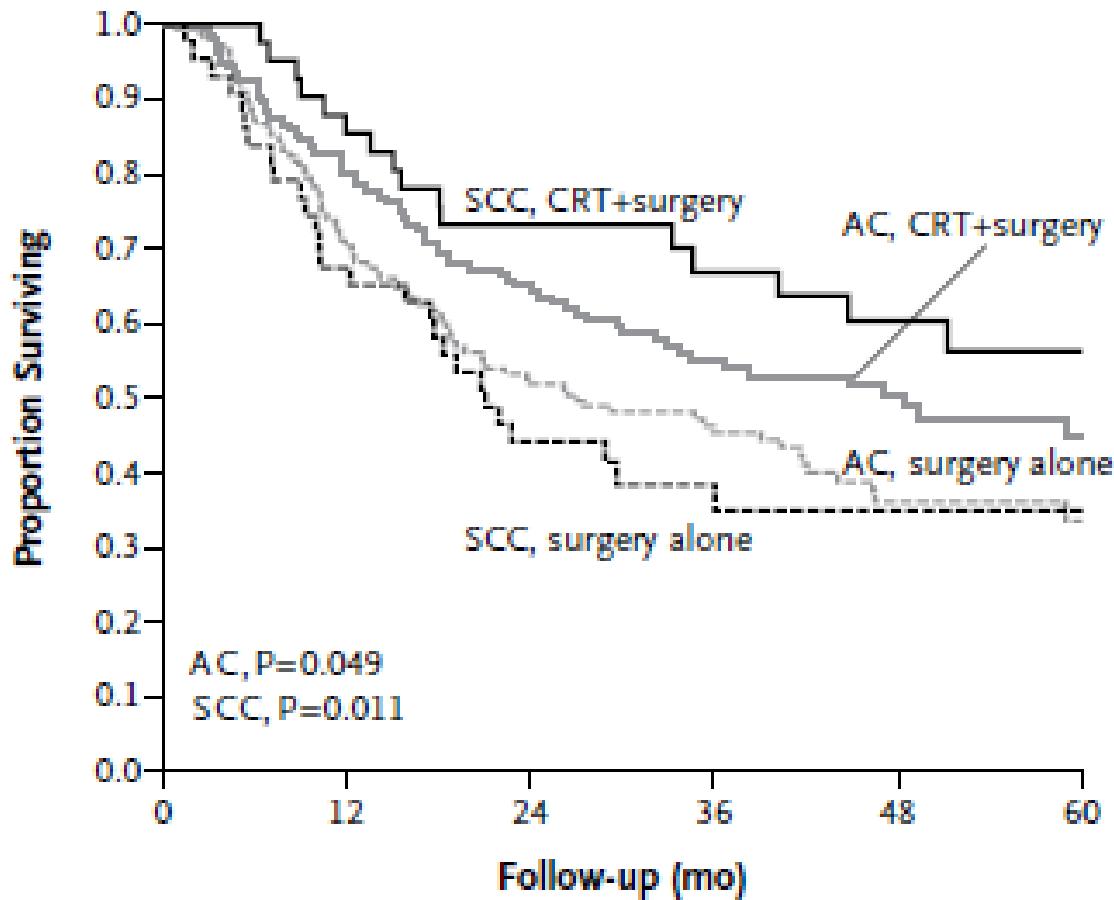
Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084

A Survival According to Treatment Group



Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084

B Survival According to Tumor Type and Treatment Group



SCC: Plattenepithel-CA; AC: Adeno-CA

Van Hagen et al. *N Engl J Med* 2012; 366: 2074-2084

Peri-/Preoperative Therapy Esophago-Gastric Adenocarcinoma

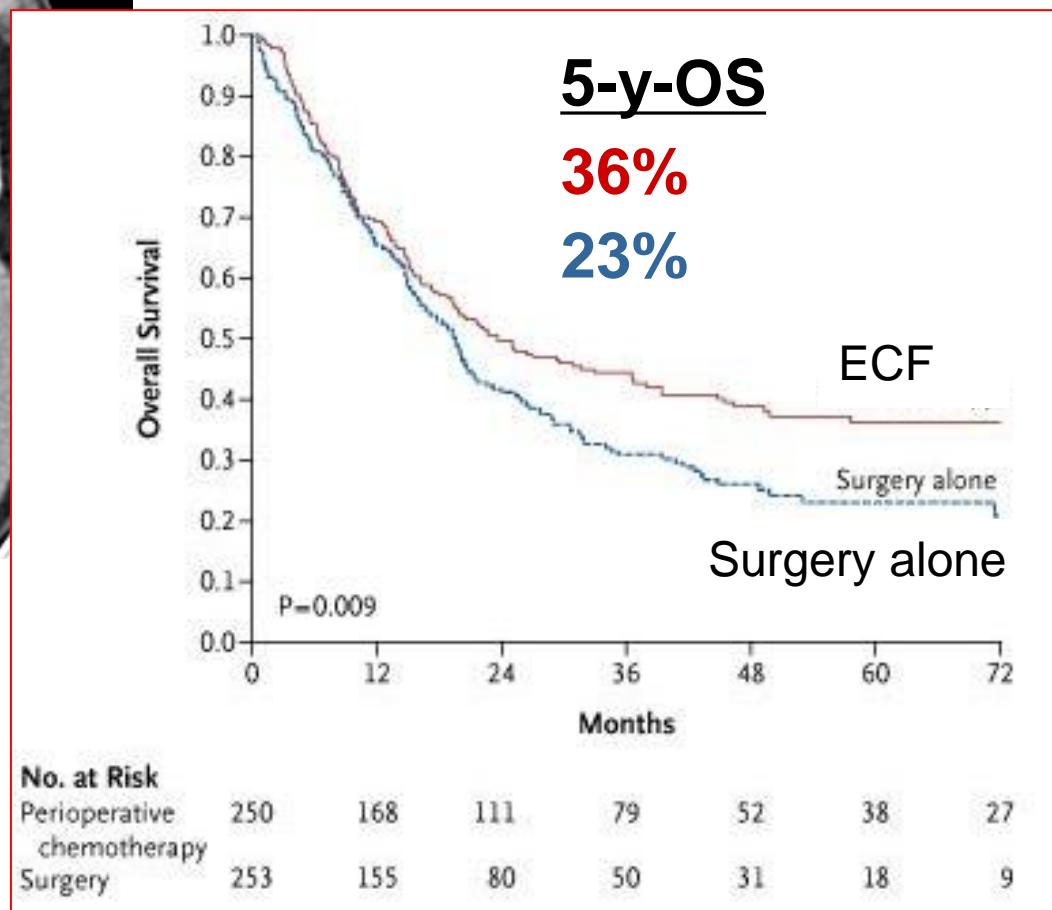
MAGIC 2006 Chemo (ECF) (n=503)	FNCLCC 2011 Chemo (CF) (n=224)	CROSS 2012 Rad-Chemo (n=275)
CTX SURG HR=0.75 (95% KI 0.60; 0.93)	CTX SURG HR=0.69 (95% KI 0.50; 0.96)	R-CTX SURG HR=0.73 (95% KI 0.52; 1.00)

Peri-/Preoperative Therapy Esophago-Gastric Adenocarcinoma



Stomach Cancer 74%
EGJ Cancer 26%

UK MAGIC 2006

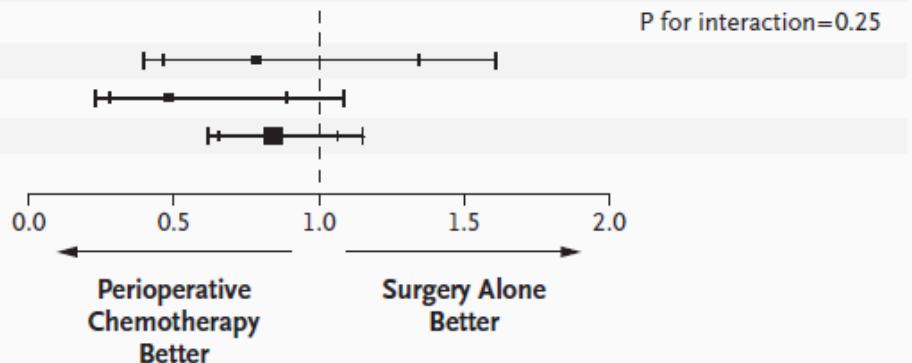


Cunningham D et al. N Engl J Med 2006;355:11-20

Peri-/Preoperative Therapy Esophago-Gastric Adenocarcinoma

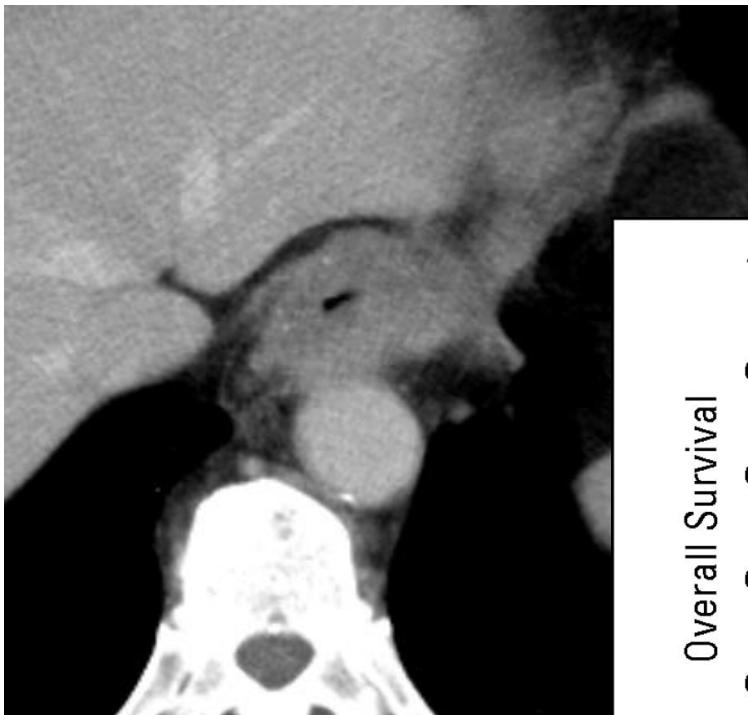
UK MAGIC 2006

Site of primary tumor		
Lower esophagus	23/37	25/36
Esophagogastric junction	13/28	23/30
Stomach	113/185	122/187
Total	149/250	170/253



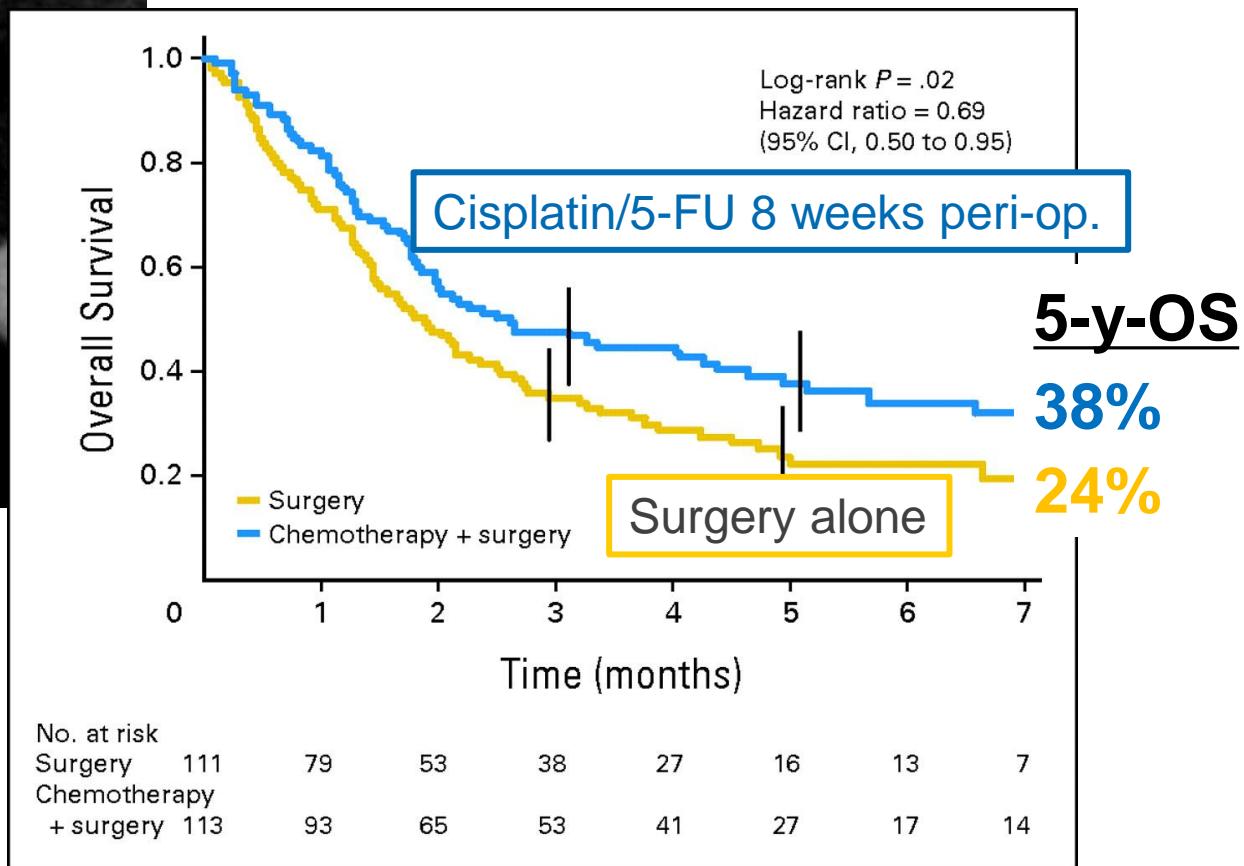
Cunningham D et al. *N Engl J Med* 2006;355:11-20

Peri-/Preoperative Therapy Esophago-Gastric Adenocarcinoma



Stomach Cancer 25%
EGJ Cancer 75%

France FNCLCC 2011



Ychou et al. J Clin Oncol 2011; 29: 1715-21

Peri-/Preoperative Therapy

Cochrane Review, 14 Studies (RCT's)

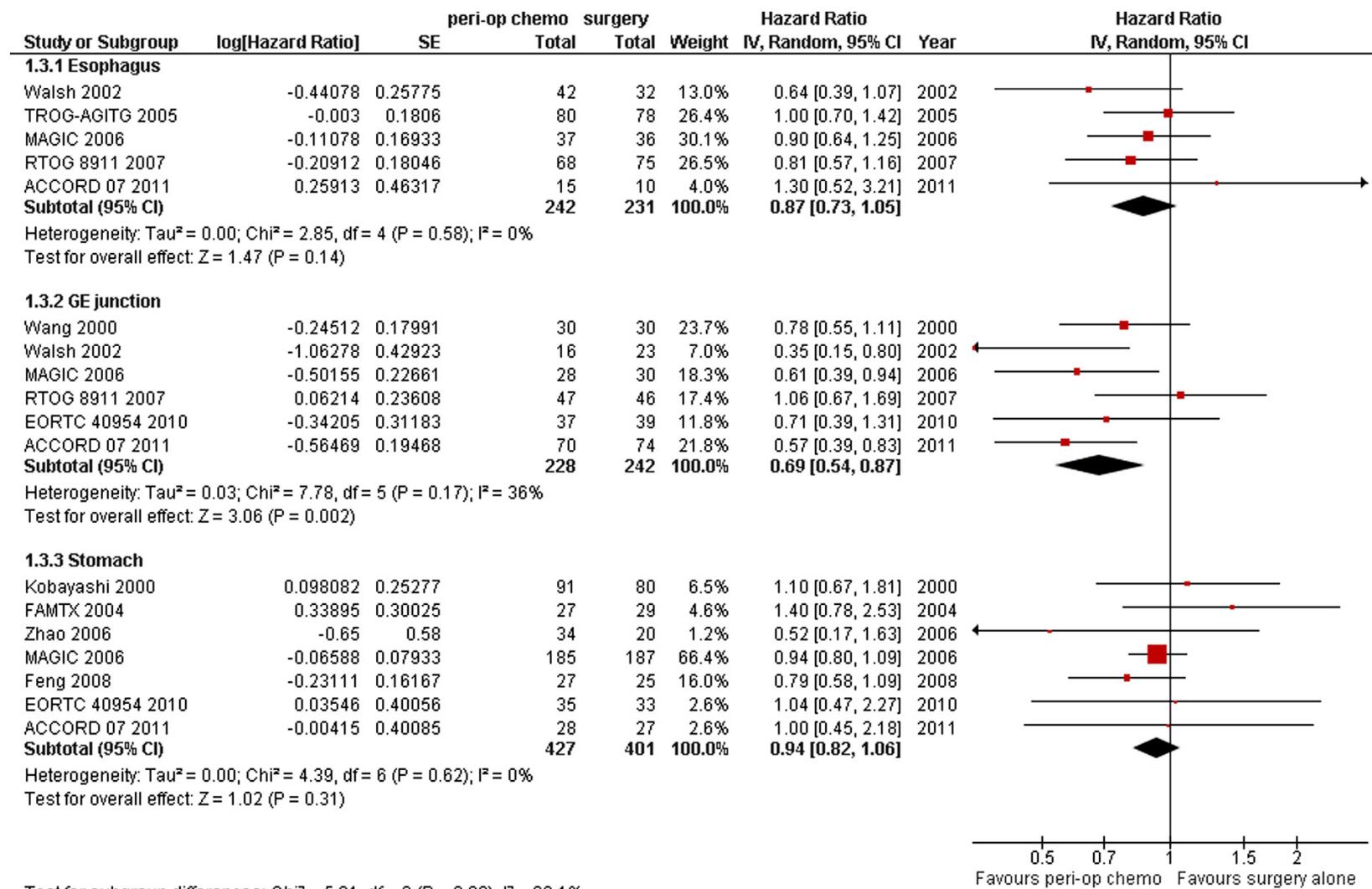
**Perioperative chemo(radio)therapy versus primary surgery
for resectable adenocarcinoma of the stomach,
gastroesophageal junction, and lower esophagus (Review)**

Ronellenfitsch U, Schwarzbach M, Hofheinz R, Kienle P, Kieser M, Slanger TE, Jensen K, GE
Adenocarcinoma Meta-analysis Group



Peri-/Preoperative Therapy

Cochrane Review, 14 Studies (RCT's)



Ronellenfitsch U et al. Cochrane Database of Systematic Reviews 2013

Radiochemotherapy or Chemotherapy?

“A clear advantage of neoadjuvant chemoradiotherapy over neoadjuvant chemotherapy has not been established.”

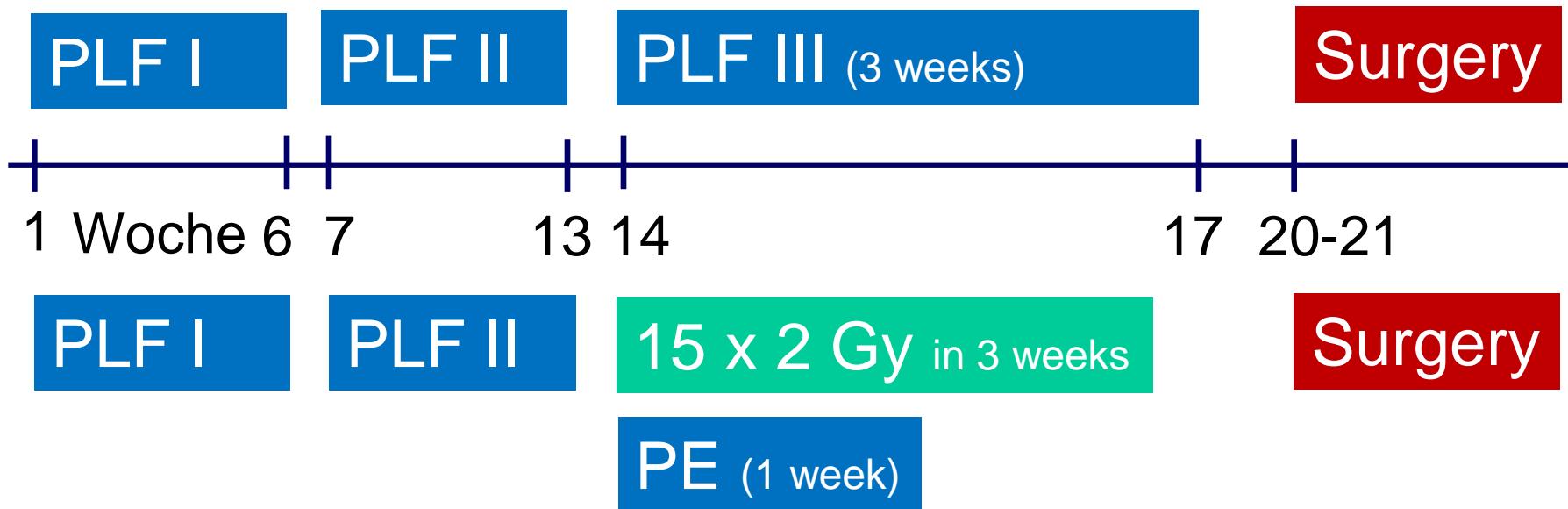
Sjöquist et al. *Lancet Oncol* 2011; 12: 681-692

“Preoperative chemotherapy for locoregional gastroesophageal adenocarcinoma increases survival compared to surgery alone.

.... There appear to be larger survival advantages in tumours of the gastroesophageal junction and for chemoradiotherapy, but these findings require prospective confirmation.

Ronellenfitsch U et al. *Cochrane Database of Systematic Reviews* 2013

Comparing Chemotherapy with Chemoradiation in EGJ Cancer



PLF: Cisplatin 50mg/m², 1h, d 1,15,29. Leukovorin/5-FU 500mg/m² 2h / 2g/m² 24h, d 1,8,15,22,29,36

PE: Cisplatin 50 mg/m², 1h, d 2+8. Etoposid 80 mg/m², 1h, d 3-5

Stahl et al. J Clin Oncol 2009; 27: 851-856

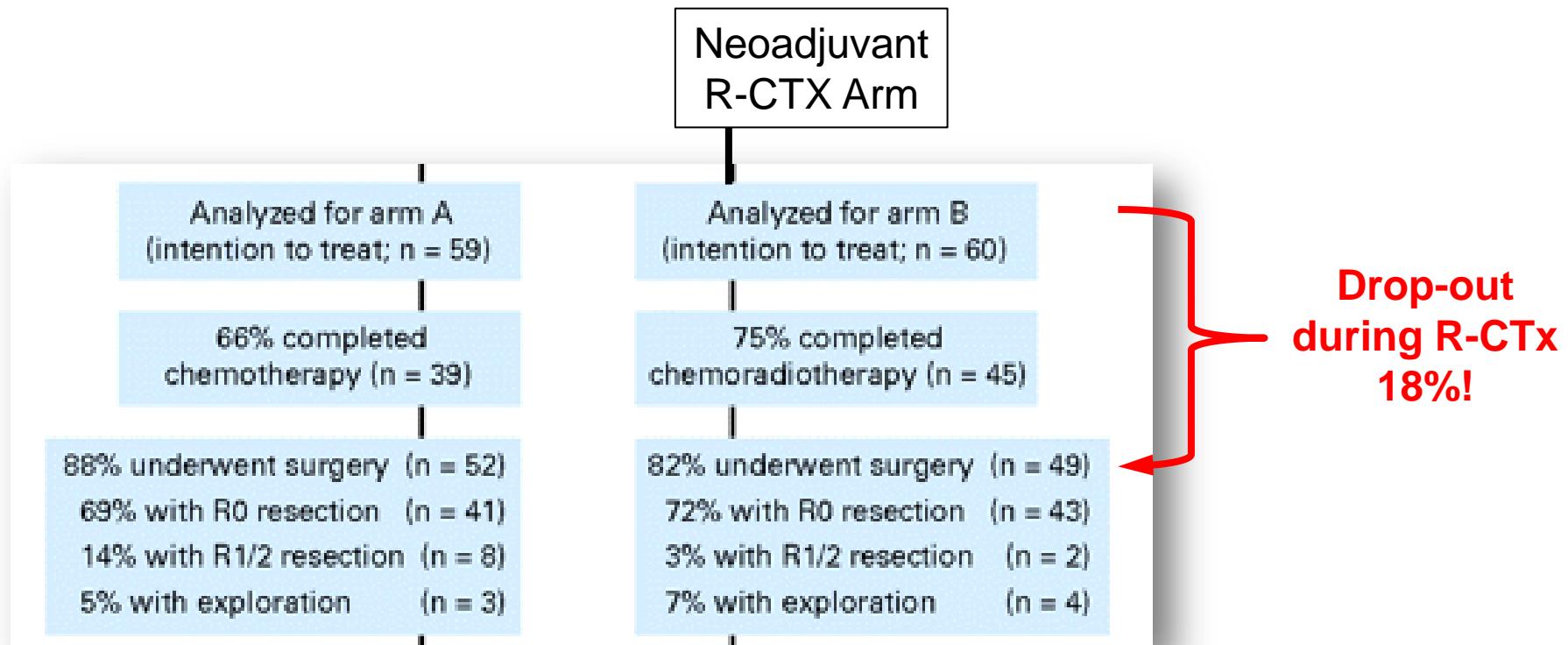
	RCTX + Surgery	Chemo + Surgery
Age (median)	60 y.	60 y.
Gender (male)	90%	92%
Histology		
Adeno	100%	100%
Squamous	0%	0%
T category		
uT3	92%	92%
uT4	8%	8%

Stahl et al. J Clin Oncol 2009; 27: 851-856

Results

	Radio-CTX + Surgery	CTX + Surgery
Clinic mortality	10%	4%
R0 resection	71%	69%
pCR rate	16%	2%
Median survival	33,1 mon	21,1 mon
3-year-survival	47%	28% P=.07

Stahl et al. J Clin Oncol 2009; 27: 851-856

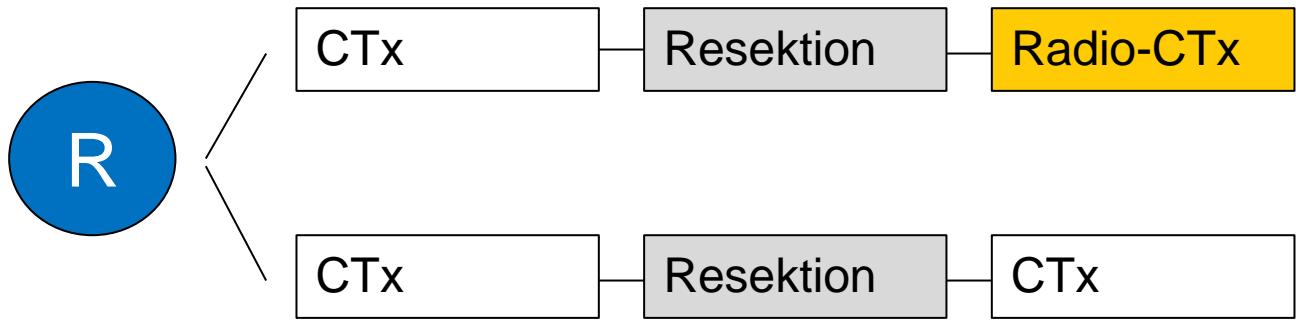


Stahl et al. J Clin Oncol 2009; 27: 851-856

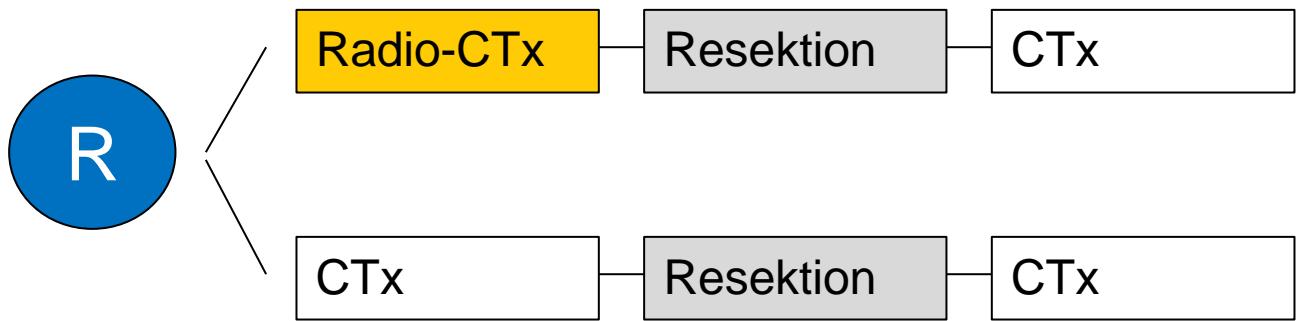
	%
Never arrived at surgery	18%
Never came back from surgery	10%
Overall	28%

Current Studies Eso-gastric Cancer

CRITICS
(NL, Skandinavia)



TOPGEAR
(AUS, CAN, EORTC)

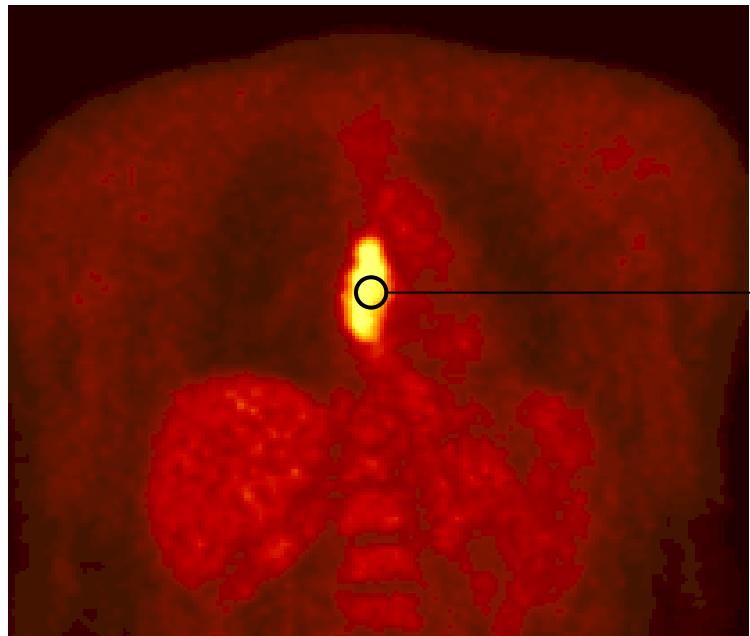


Metabolic response-monitoring

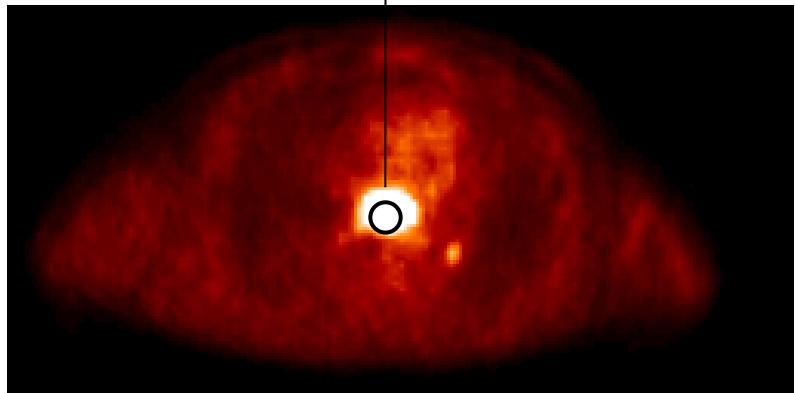
Signatures (genetic – proteomic)

Molecular targets

Metabolic Response



Region of interest (ROI)



Standard uptake value (SUV)

$$SUV_{BW} = \frac{Q_{Tumor} [\text{MBq/l}] \times W [\text{kg}]}{Q_{injected} [\text{MBq/l}]}$$

Young et al. for EORTC PET study group. Eur J Canc 1999;13:1773-82

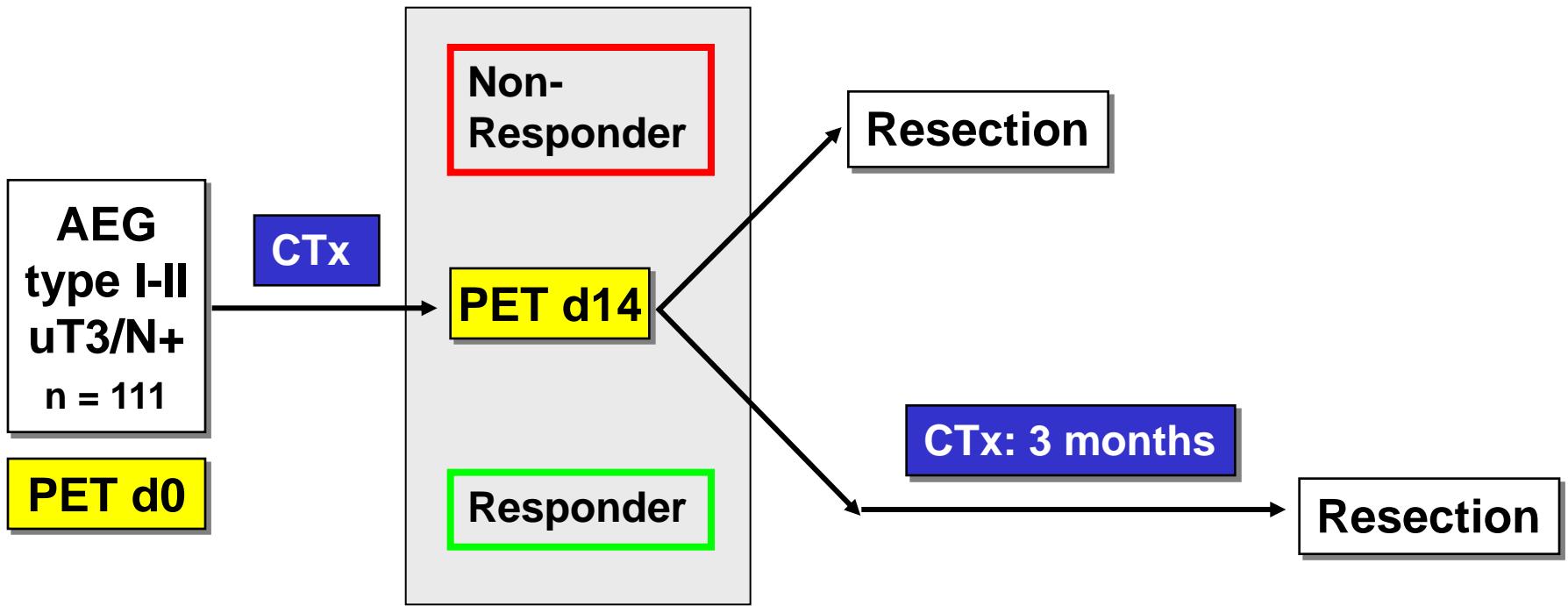
Decrease of SUV of $\geq 35\%$ after 14 days of chemotherapy

Prediction of histopathological response

($< 10\%$ residual tumor)

- negative prediktive value 95%
- positive prediktive value 53%

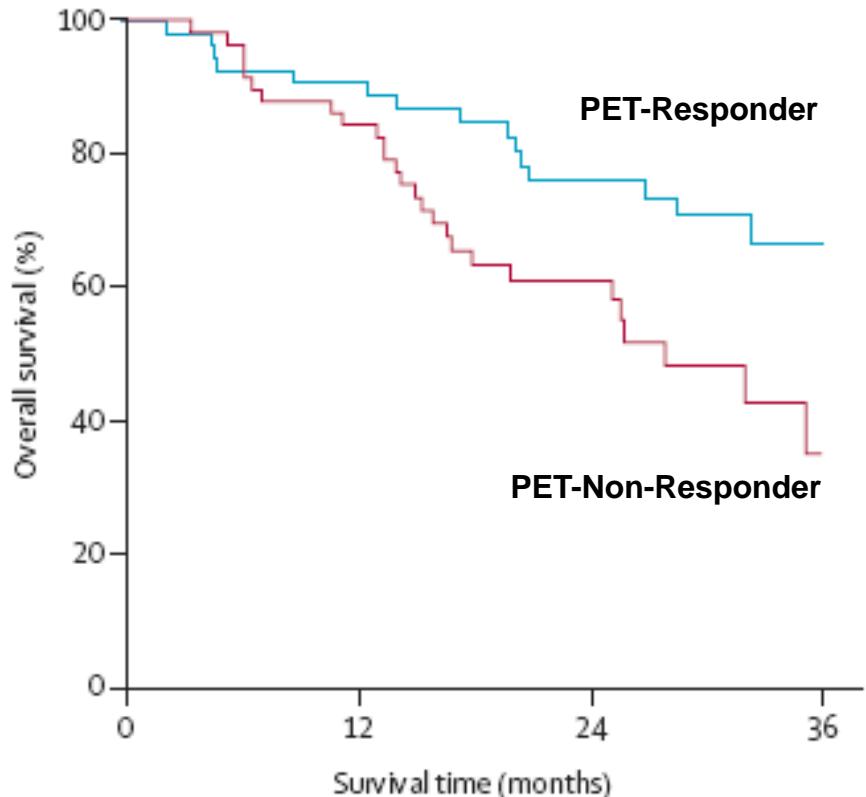
Weber et al. *J Clin Oncol*, 2001; 19:3058-3065



Response definition: Decrease of the SUV_{mean} $PET_{d14} / PET_{baseline} \geq 35\%$

Weber et al. *J Clin Oncol* 2001;19:3058-65 Ott et al. *J Clin Oncol* 2006;24:4692-8

Lordick et al. *Lancet Oncol* 2007 Sep; 8: 797-805



Number at risk

	0	12	24	36
PET responders*	54	46	30	13
PET non-responder†	56	45	21	4

**Median survival
[95% CI] in months:**

**Metabolic Responder:
Not reached**

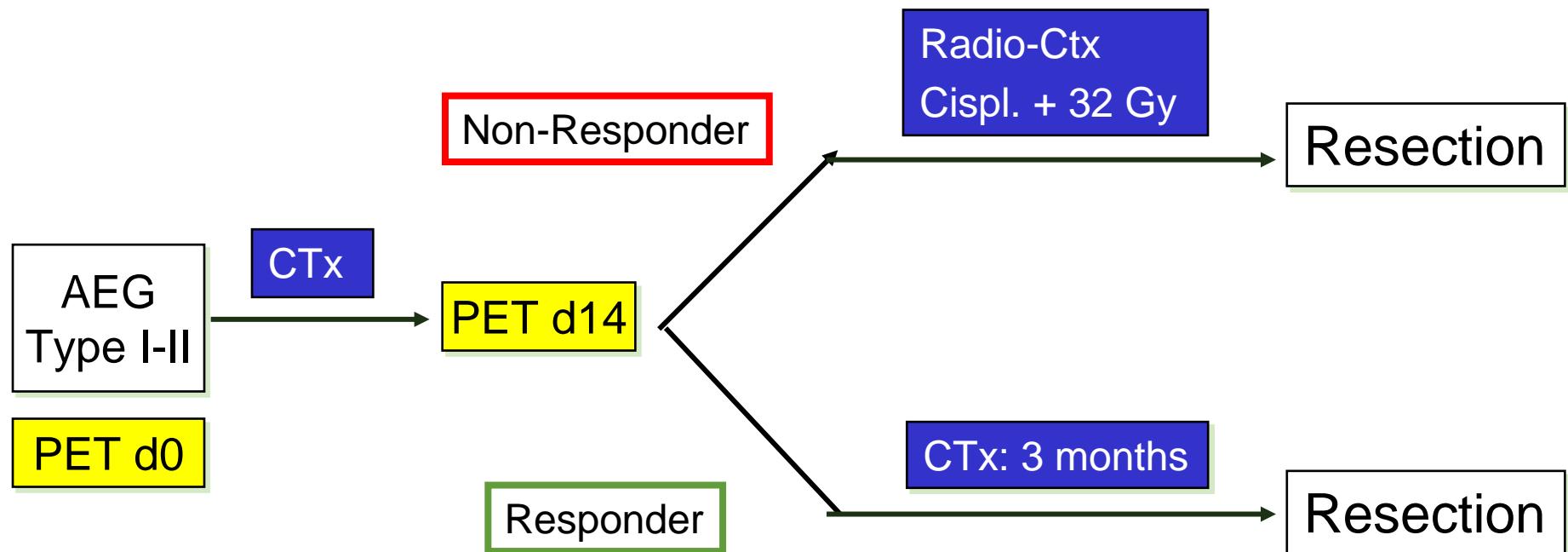
**Metabolic Non-Responder:
25.8 [19.4; 32.3]**

**Hazard ratio 2.13 [1.14-3.99]
Log-rank p-value: p=0.015**

Median follow-up: 28.0 months

Lordick et al. Lancet Oncol 2007 Sep; 8: 797-805

MUNICON II – Design



Response definition: **Decrease of the SUV_{mean} $PET_{d14} / PET_{baseline} \geq 35\%$**

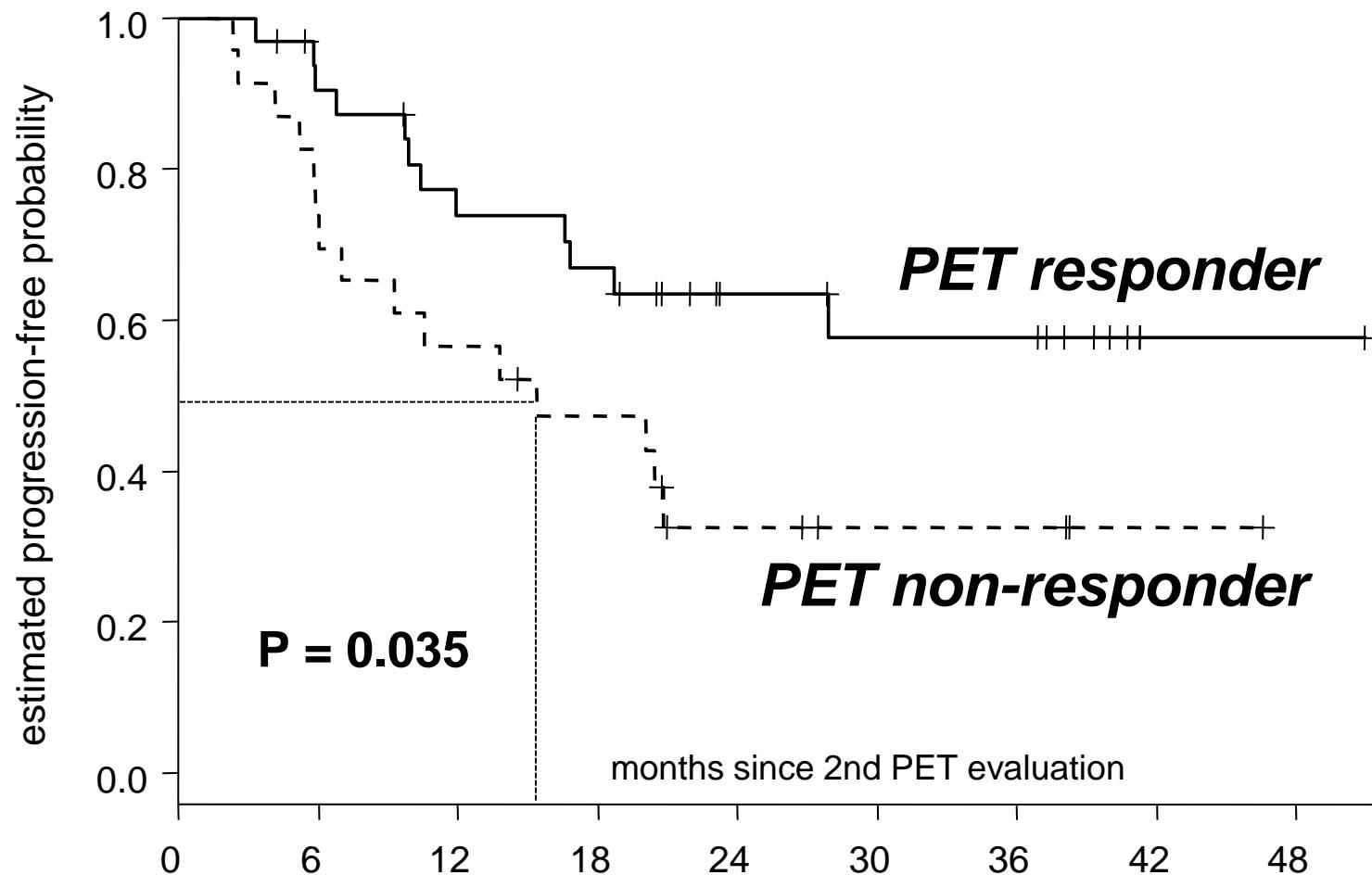
Weber et al. *J Clin Oncol* 2001;19:3058-65

Ott et al. *J Clin Oncol* 2006;24:4692-8

AEG: adenocarcinoma of the esophago-gastric junction; d: day
 CTx: chemotherapy; PET: positron emission tomography; SUV: standard uptake value

Lordick et al. ASCO GI 2011 abstr. 3

MUNICON II – Progression Free Survival



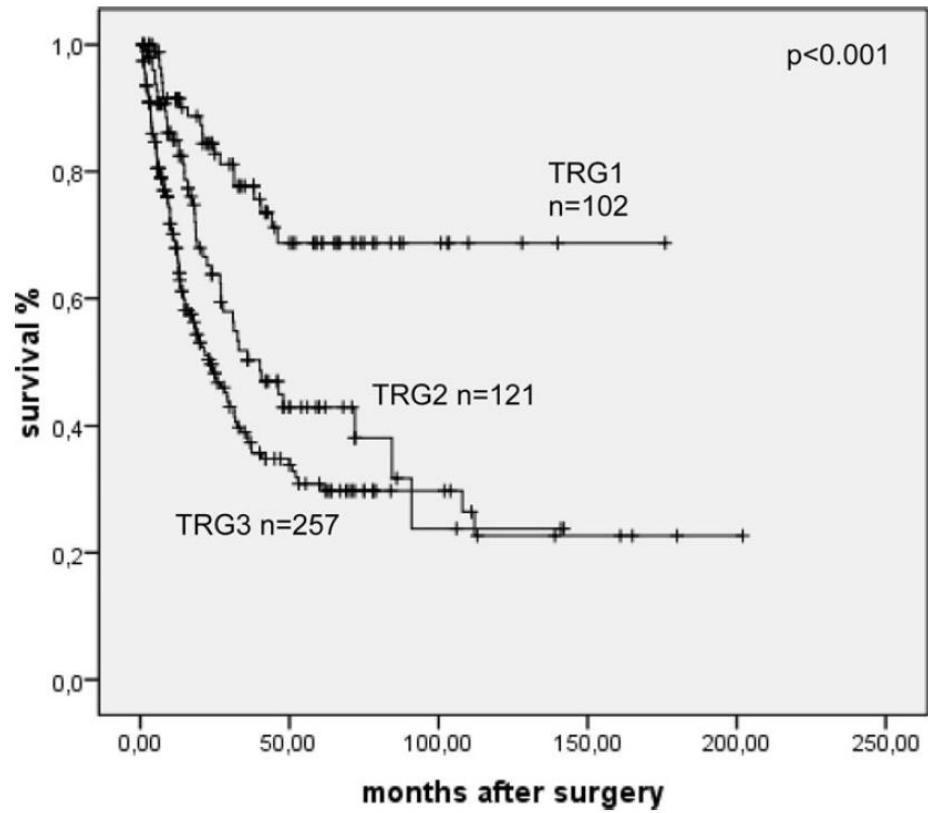
Lordick et al. ASCO GI 2011 abstr. 3

 Metabolic response-monitoring

 Signatures (genetic – proteomic)

 Molecular targets

Personalized Therapy Eso-Gastric Cancer



TRG 1:
< 10% residual tumor

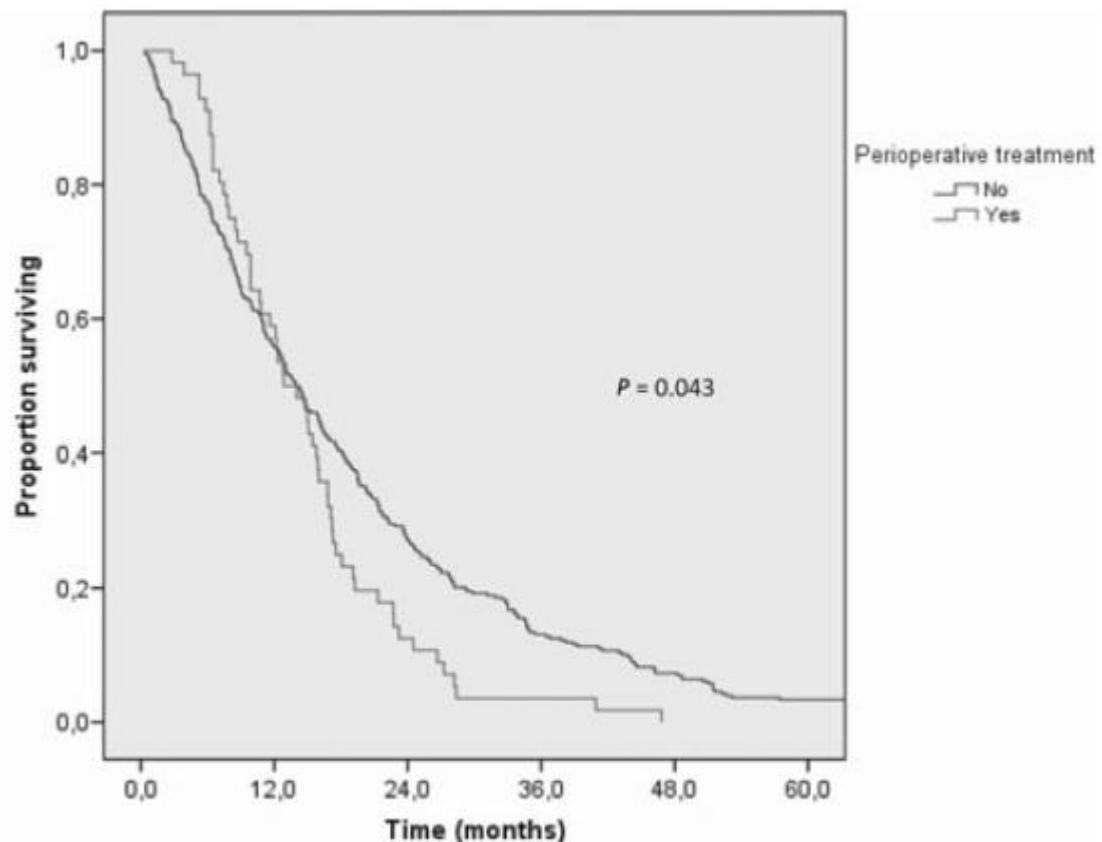
FIGURE 2. Histopathological Tumor Regression Grade (TRG) and survival. $P < 0.001$ for TRG1 vs. TRG2 and TRG3.

Becker et al. Ann Surg 2011;253:934–939

- Responder (TRG1): ca. 20%.
- < 5%: complete histo-pathologic regression (pCR)
- Lower response probability:
 - distal gastric cancers with poor differentiation
 - diffuse subtype according to Laurén

Becker et al. *Ann Surg* 2011;253:934–939

Signet Ring Cell Cancers without benefit from perioperative chemotherapy?



S group	753	420	204	99	55	26
PCT group	171	101	21	6	0	0

Messager et al. Ann Surg 2011; 254:684–6939

Signet Ring Cell Cancers without benefit from perioperative chemotherapy?

Piessen et al. BMC Cancer 2013, **13**:281
<http://www.biomedcentral.com/1471-2407/13/281>



STUDY PROTOCOL

Open Access

Phase II/III multicentre randomised controlled trial evaluating a strategy of primary surgery and adjuvant chemotherapy versus peri-operative chemotherapy for resectable gastric signet ring cell adenocarcinomas – PRODIGE 19 – FFCD1103 – ADCI002

Guillaume Piessen^{1,2,3*}, Mathieu Messager^{1,2,3}, Karine Le Malicot⁴, William B Robb^{1,2}, Frédéric Di Fiore⁵, Marie Guilbert^{1,2}, Marie Moreau⁴, Véronique Christophe⁶, Antoine Adenis⁷ and Christophe Mariette^{1,2,3}

Abstract

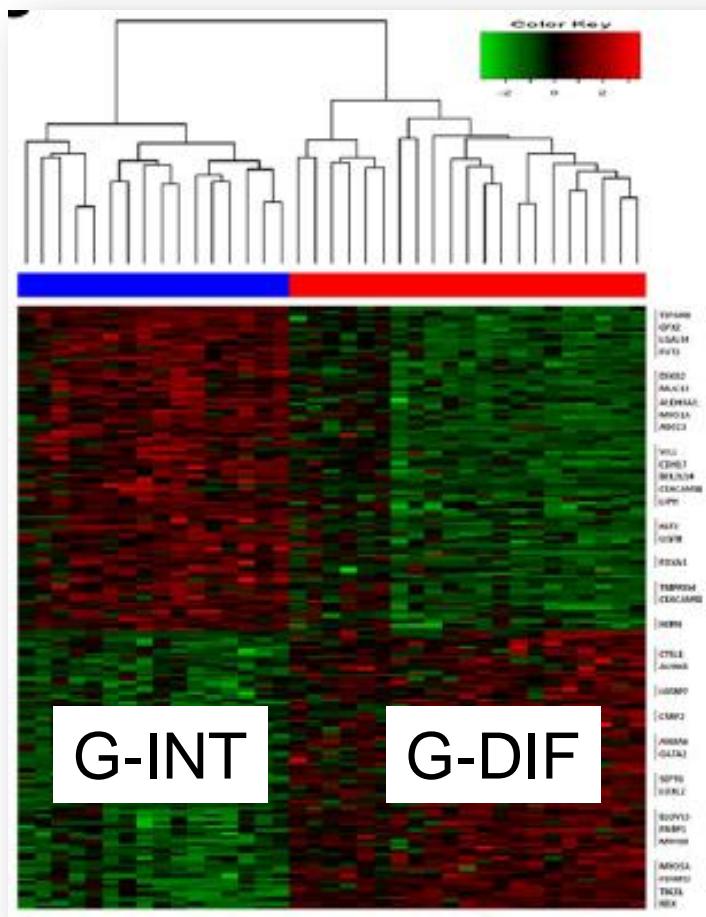
Background: A dramatic increase in the incidence of the diffuse form of gastric adenocarcinomas and particularly signet ring cell carcinomas has been observed in Western countries. Evidence is accruing that signet ring cell carcinomas may have inherent chemo resistance leaving many clinicians unsure of the benefits of delaying surgery to pursue a neoadjuvant approach.

Methods/design: PRODIGE-19-FFCD1103-ADCI002 is a prospective multicentre controlled randomised phase II/III

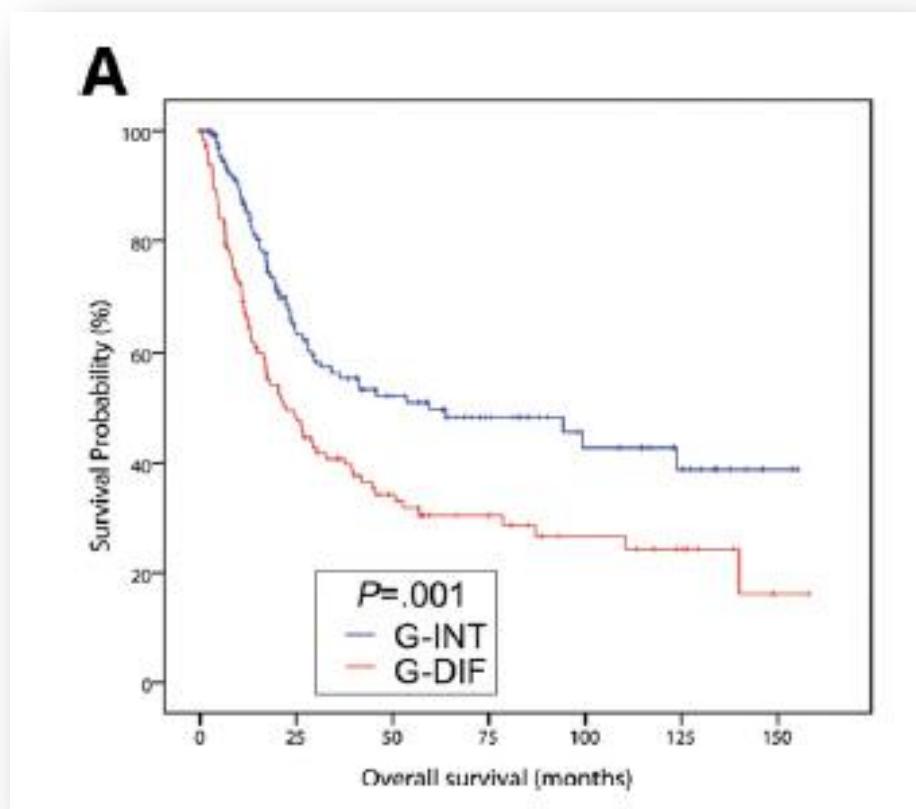
Piessen et al. BMC Cancer 2013; 13: 281

Personalized Therapy Gene signatures

Genetic heatmaps from 37 cell lines



Validation in patients



Tan et al. Gastroenterology 2011;141:476-485

Chemosensitivity in cell lines G-INT vs. G-DIF

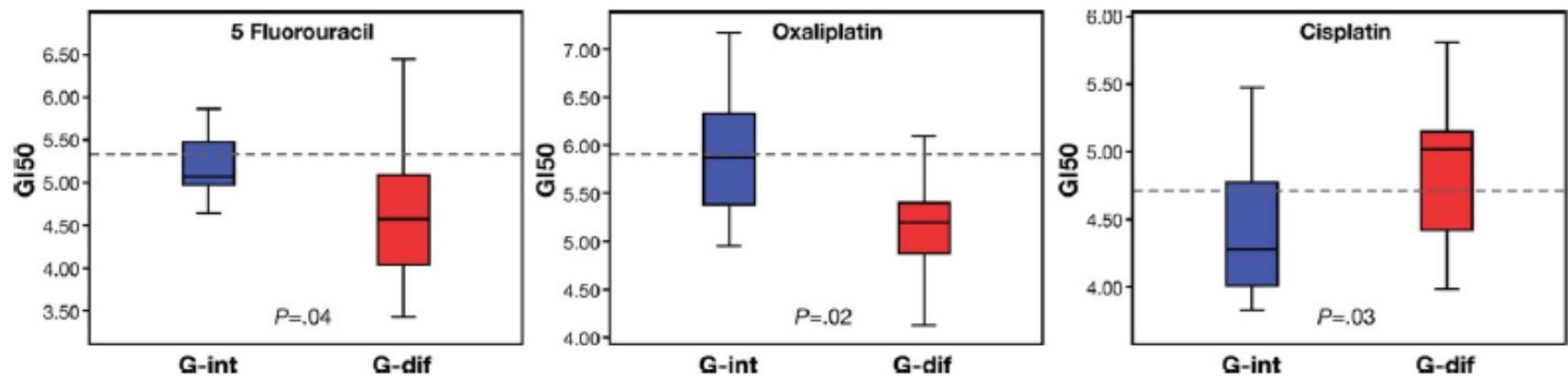


Figure 4. In vitro chemosensitivity of G-INT and G-DIF cell lines. GI-50 values of 11 G-INT and 17 G-DIF cell lines upon treatment with 5-FU, oxaliplatin, and cisplatin. GI-50 refers to the drug concentration at which 50% growth inhibition is achieved (y-axis: GI-50 enumerated in negative log₁₀). The horizontal gray lines represent the therapeutic concentration patients are exposed to based on pharmacokinetic data.²⁵⁻²⁷ Mean GI-50 concentrations for G-INT and G-DIF cell lines were as follows, respectively: 5-FU, 5.20 $\mu\text{mol/L}$ and 23.22 $\mu\text{mol/L}$; cisplatin, 38.61 $\mu\text{mol/L}$ and 13.35 $\mu\text{mol/L}$; oxaliplatin, 1.33 $\mu\text{mol/L}$ and 5.49 $\mu\text{mol/L}$.

Tan et al. Gastroenterology 2011;141:476-485

Personalized Therapy Proteomics

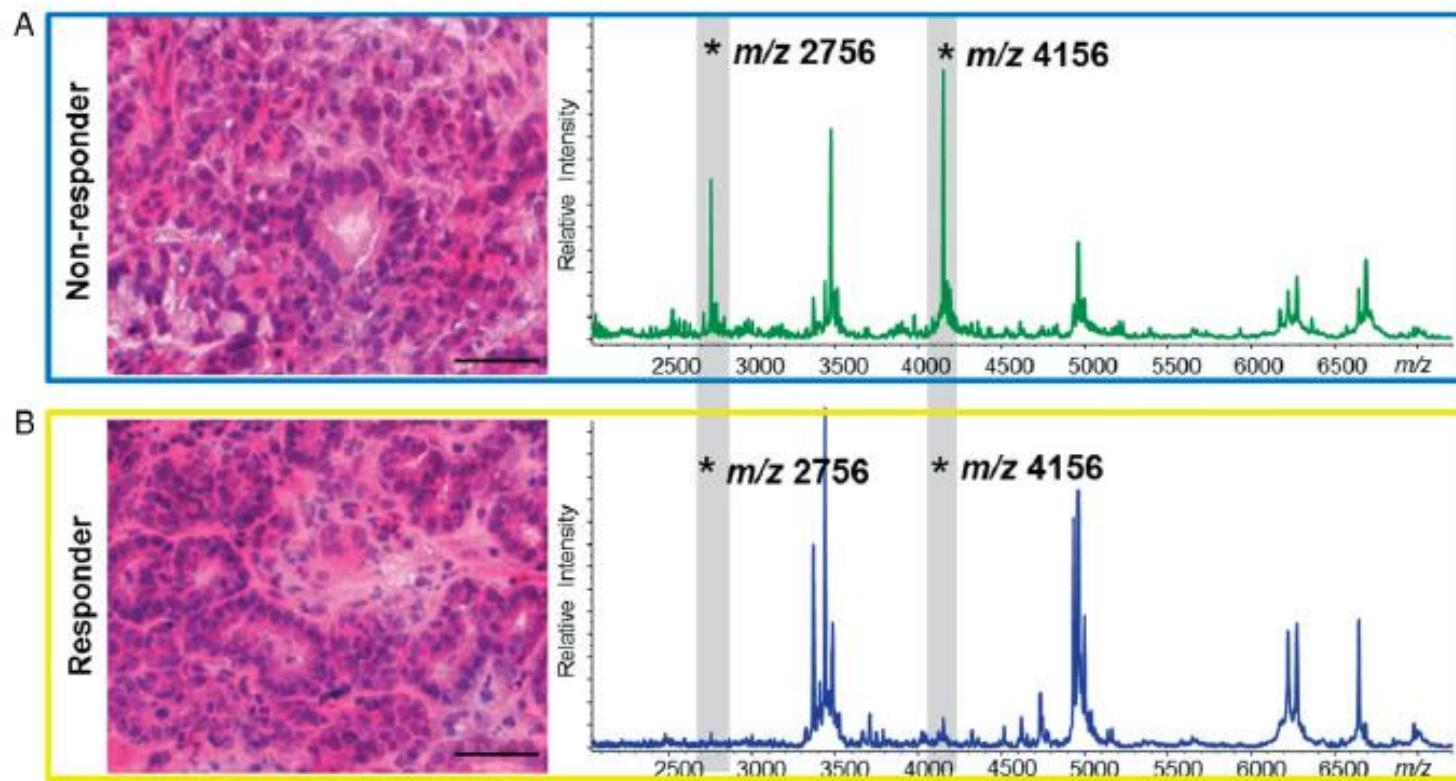
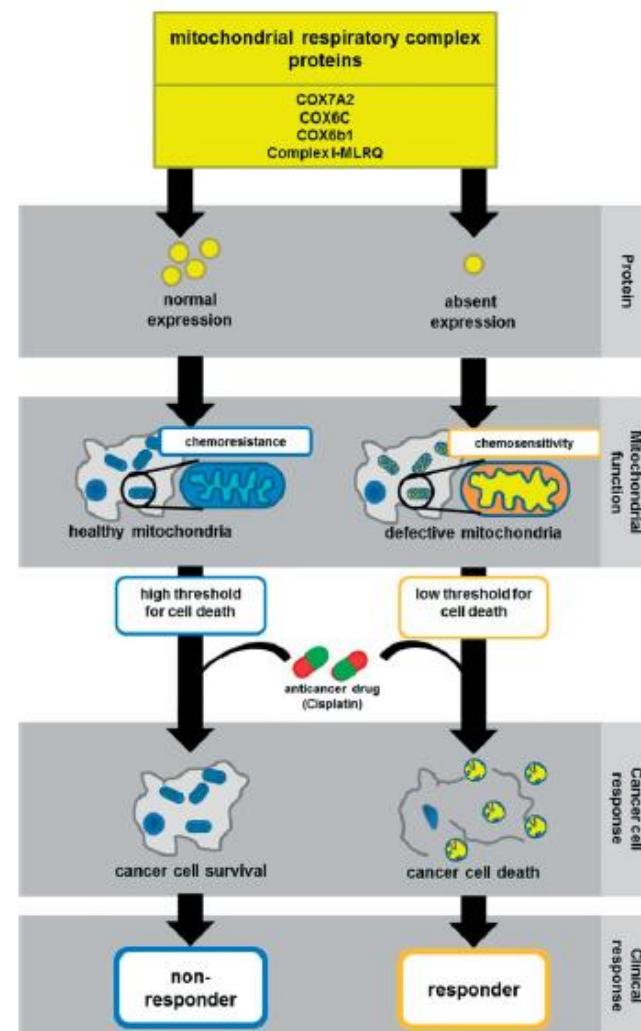
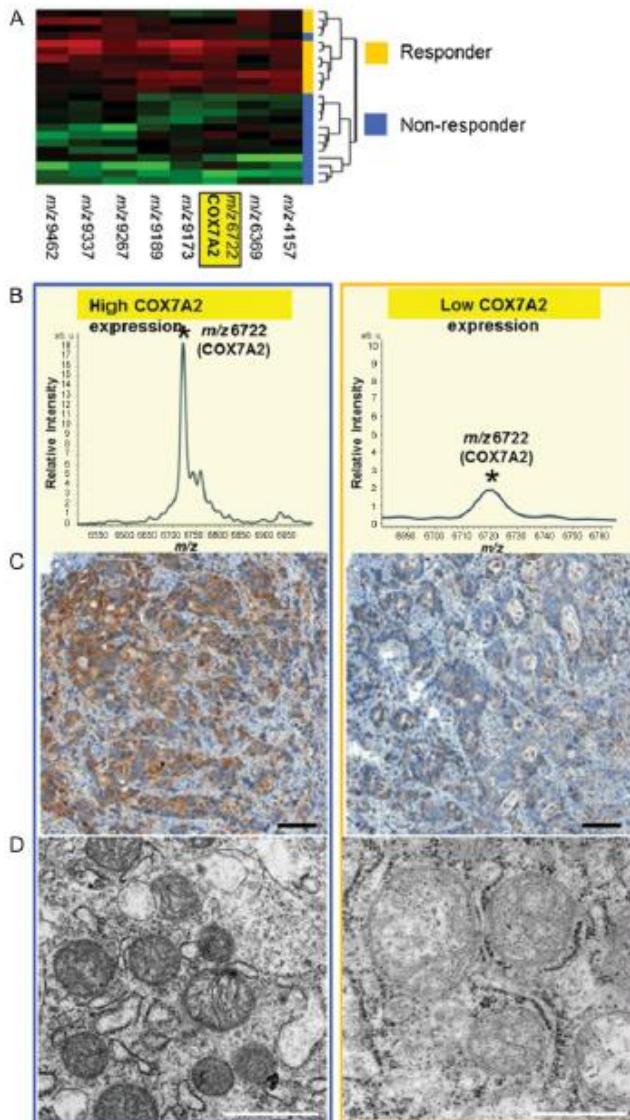


Figure 1. Discriminative protein spectra from two individual patients who responded or did not respond to neoadjuvant chemotherapy, detected by MALDI imaging mass spectrometry of pretherapeutic oesophageal adenocarcinoma biopsies. (A) Average spectrum and haematoxylin and eosin (H&E) staining of a sample of non-responding patient tissue; scale bar = 25 μ m. (B) Average spectrum and H&E staining of a sample of responding patient tissue; *significantly differentially expressed proteins. In this example, two proteins (m/z = 2756 and 4156) are more strongly expressed in non-responding patients.

Aichler et al. J Pathol 2013;230:410-19

Personalized Therapy Proteomics



Aichler et al. J Pathol 2013;230:410-19

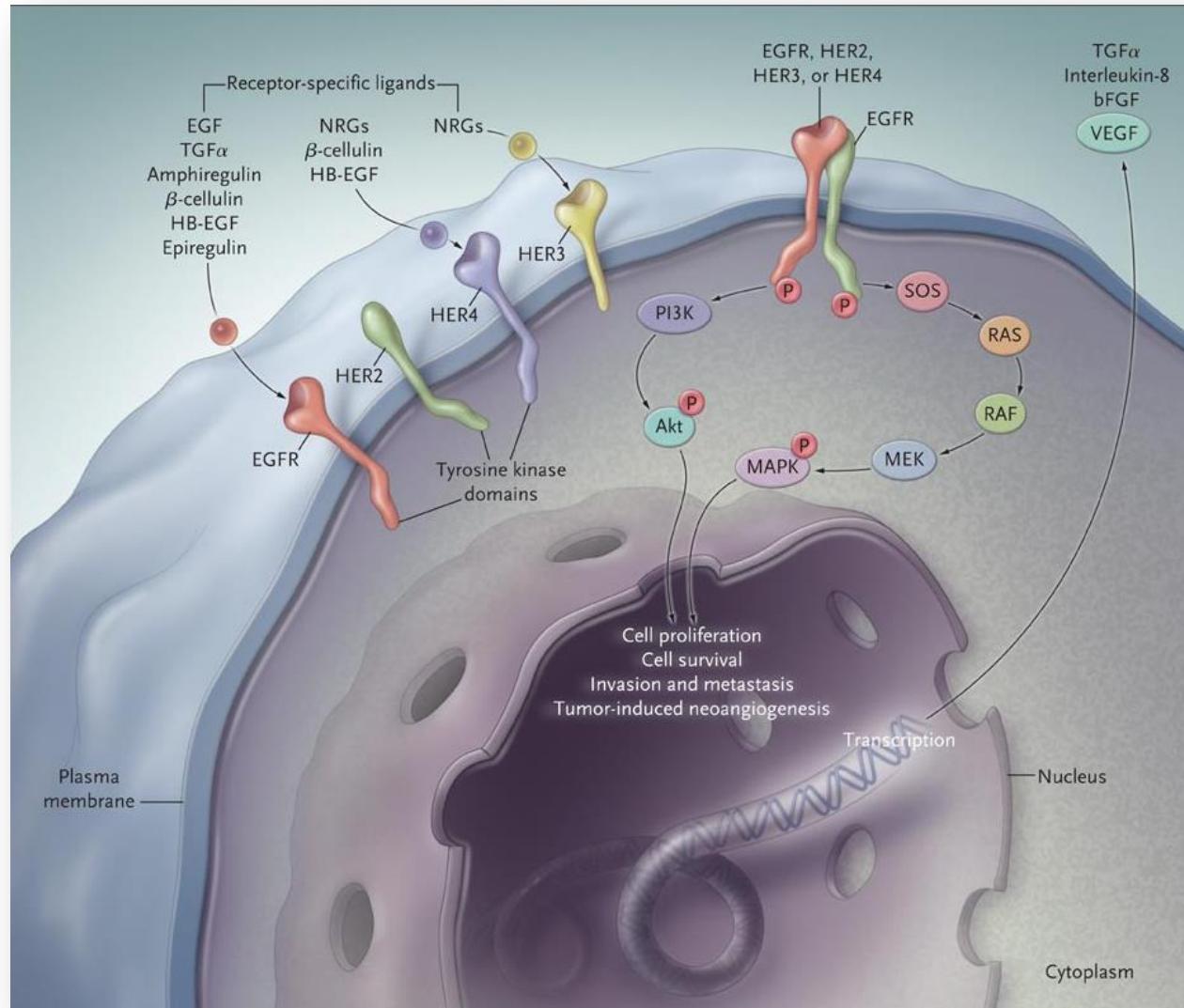
 Metabolic response-monitoring

 Signatures (genetic – proteomic)

 Molecular targets

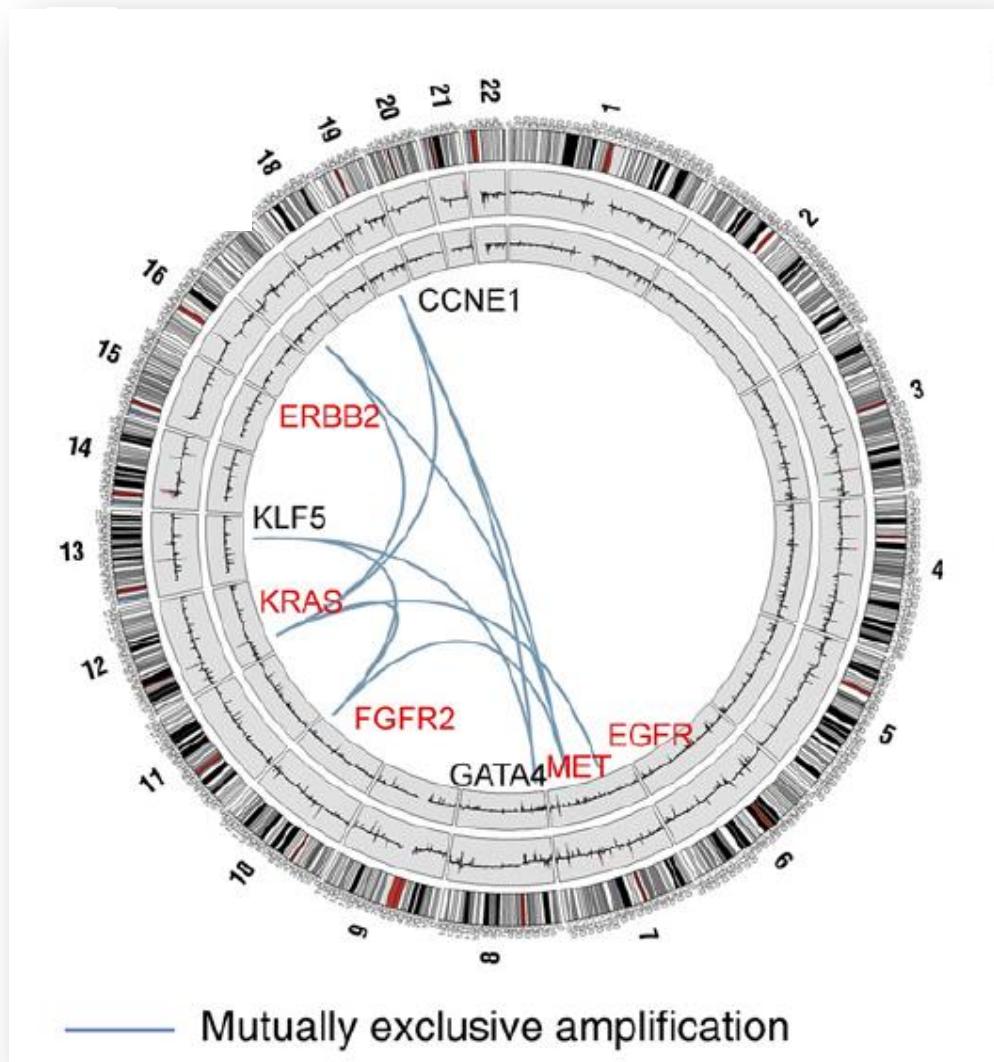
Molecular Targets

Epidermal Growth Factor Receptor Family



from: Ciardello F, Tortora G. *N Engl J Med.* 2008; 358: 1160-1174

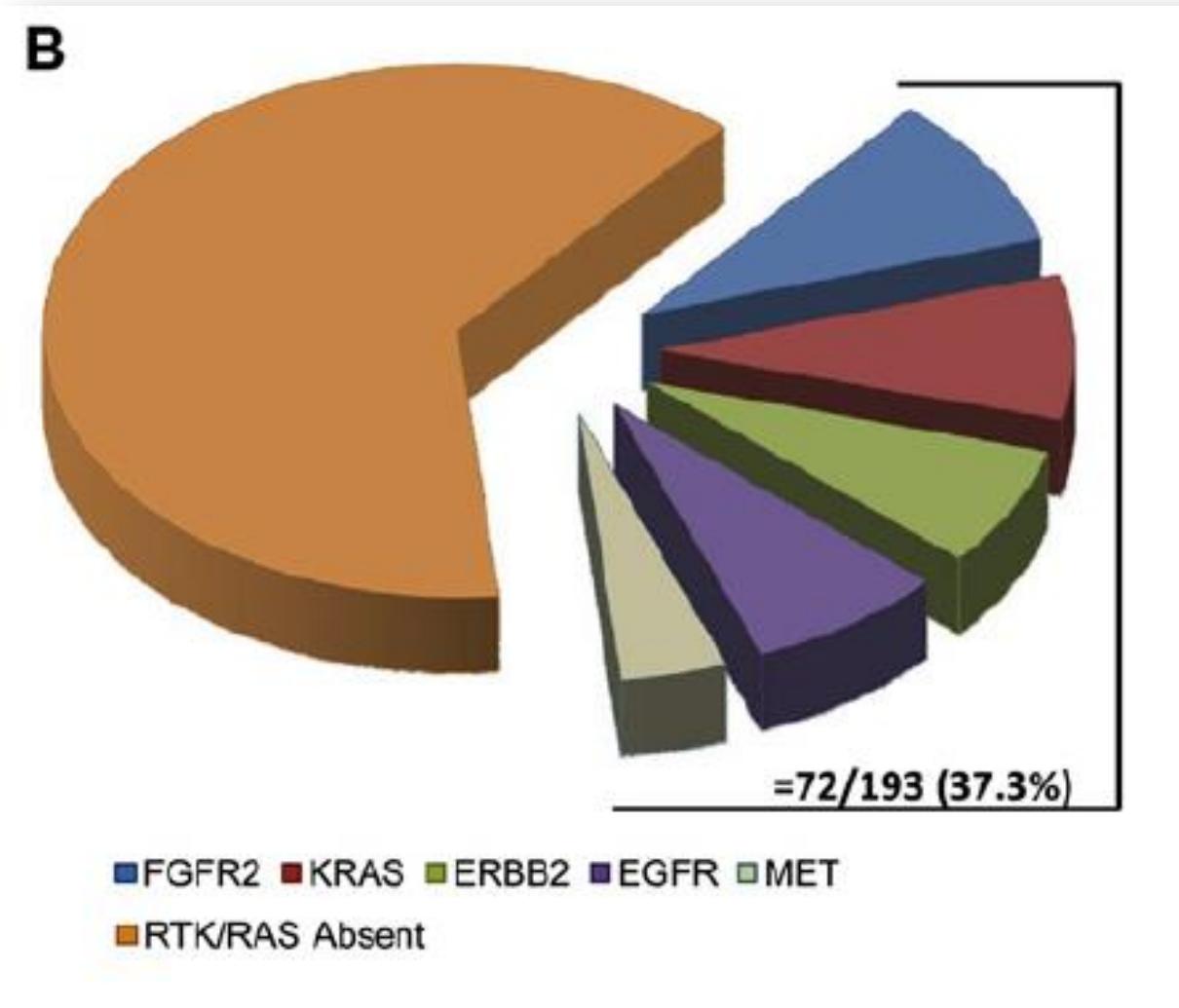
Gastric Cancer - Genomics



Patrick Tan,
Duke Univ Singapore

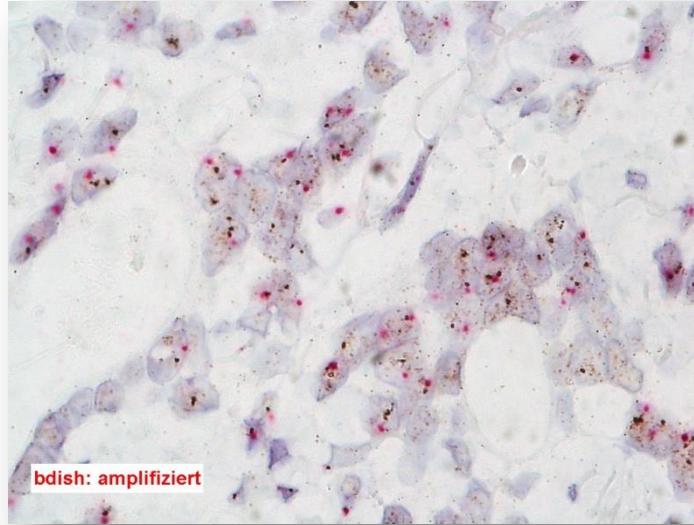
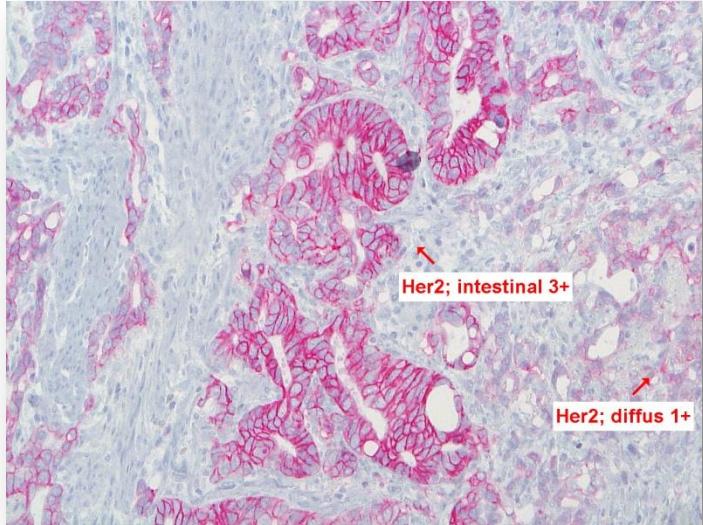
Genomic DNA were extracted from flash-frozen tissues or cell pellets using a Qiagen genomic DNA extraction kit (Qiagen, Hilden, Germany), and profiled on Affymetrix SNP 6.0 arrays (Affymetrix, Santa Clara, California, USA)

Deng et al. Gut 2012; 61: 673-684



Deng et al. Gut 2012; 61: 673-684

HER2 Positive Gastric Cancer



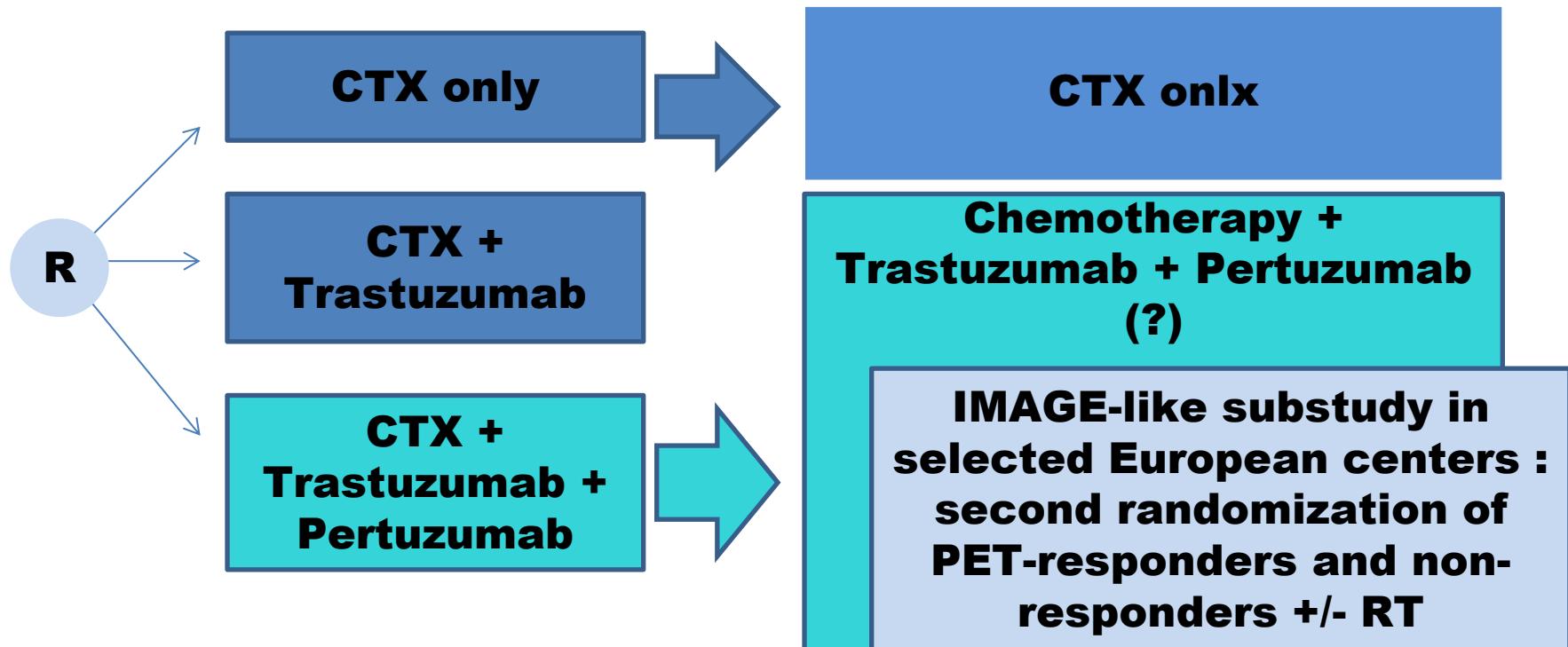
With courtesy of Prof. Donhuijsen, Pathologie ,Braunschweig

- Therapeutic relevant overexpression HER2: ca. 16%
- Trastuzumab (Herceptin) in HER2-overexpression:
Survival 16.0 vs. 11.8 months (HR=0.65; 95%CI 0.51-0.83)

Bang Y et al. *Lancet* 2010; 376: 687-697

STAGE 1:
Randomized phase II
« pick-the winner »
of two experimental arms
1:2:2 randomization

STAGE 2:
Randomized phase III
with best experimental arm of
STAGE 1
1:3 randomization



Primary endpoint: near path. CR

Primary endpoint: 5-year overall survival

Thank you for your attention!

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Leipzig**
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