Selection of patients for multimodality treatment decision

Wilfried Ernst Erich Eberhardt, MD

Department of Medical Oncology, West German Cancer Centre, Essen, University Duisburg-Essen, E-mail: wilfried.eberhardt@uni-duisburg-essen.de

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Organisers IASLC International Association for the Study of Lung Cancer; ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE European Society for Medical Oncology

Partners ESTRO European Society for RADIOTHERAPY & ONCOLOGY; European Society of Thoracic Surgeons 1993; etop

Disclosures

- Honoraria for advisory boards
  - BMS, Celgene, Teva, Boehringer, Novartis, Roche, Eli Lilly, Astra Zeneca, Bayer, GSK, Merck, Daiichi, Pfizer, Medimmune, Amgen
- Honoraria for educational lectures
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- Research funding
  - Eli Lilly

Introduction

- multimodality treatment of stage III NSCLC has a clear curative intent
- five-year survival rates between 10 and 40% can be achieved by radical treatment strategies including local treatments such as S and RTx
- based on the broad heterogeneity of patients within stage III treatment descisions have to be individualized

Eberhardt W, et al, ELCC 2015

Patient population of stage III

- important prognostic factors I – accepted factors
  - stage (IIIA vs IIIB) (UICC)
  - T-factor (IASLC/UICC) (including tumor diameter/volume)
  - N-factor (IASLC/UICC) (N3 vs N2 vs N1 vs N0)
  - specific TN-groups T4N0/1 versus others
  - performance status 0/1 versus 2
  - weight loss

Eberhardt W, et al, ELCC 2015

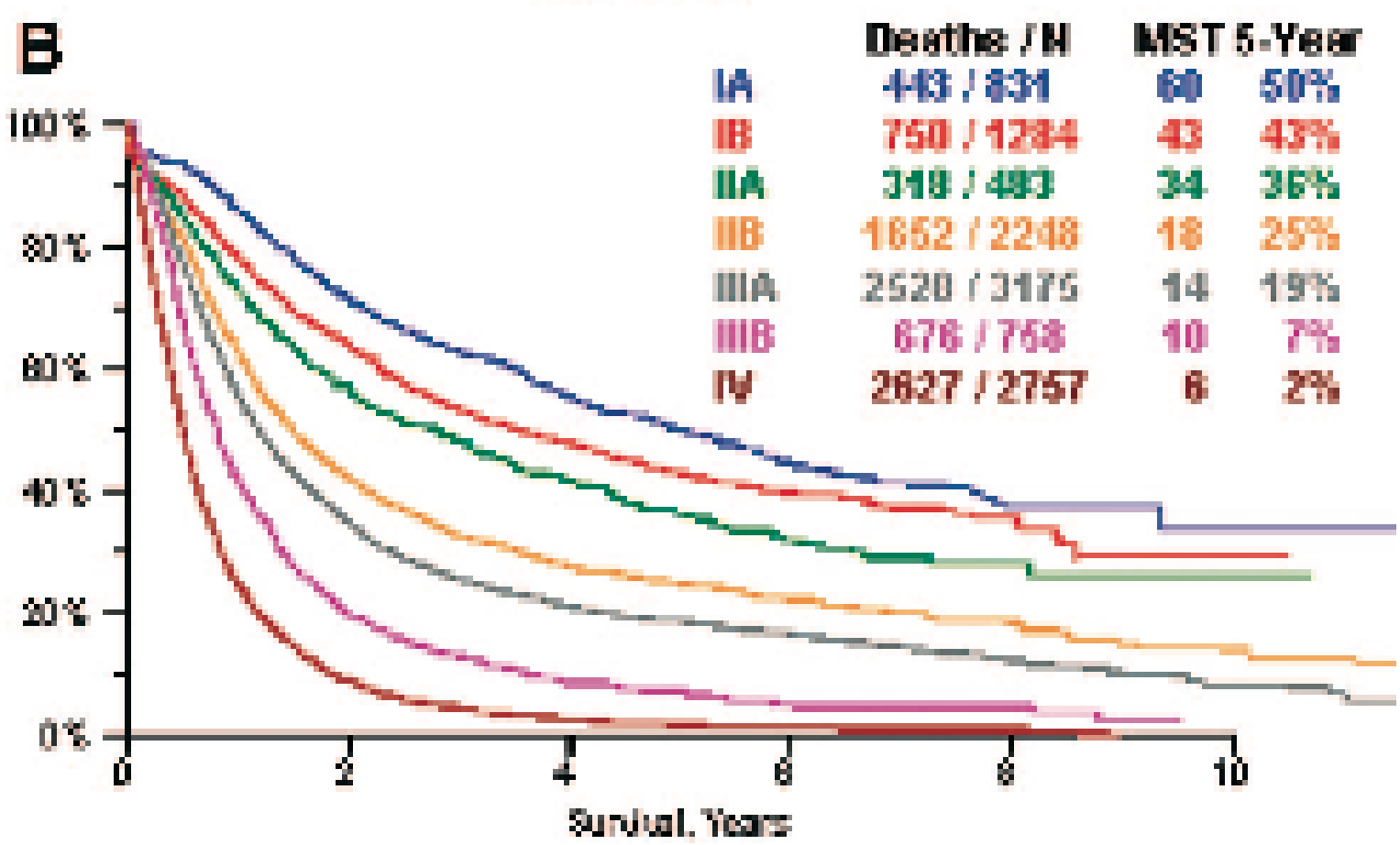
- IASLC Staging classification -

0	Tis	N0	M0
IA	T1a/b	N0	M0
IB	T2a	N0	M0
IIA	T1a/b T2a	N1	M0
	T2b	N0	M0
IIB	T2b	N1	M0
	T3	N0	M0
IIIA	T1a/b/2a/b	N2	M0
	T3	N1/2	M0
	T4	N0/1	M0
IIIB	jedes T	N3	M0
	T4	N2	M0
IV	jedes T	jedes N	M1a/b

Goldstraw et al, J Thorac Oncol 2007

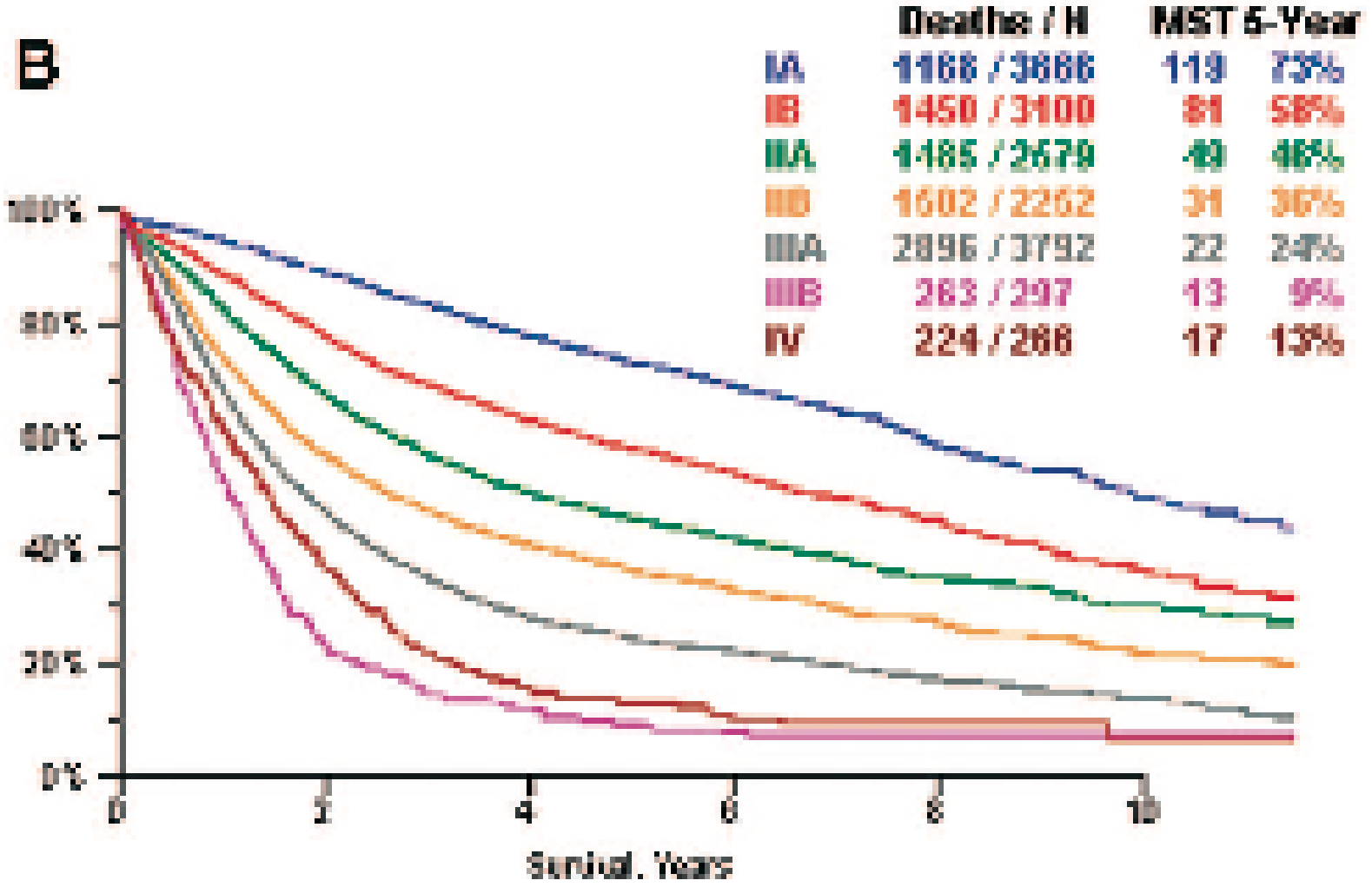
UICC 2002 und 2009

Overall survival based on clinical staging



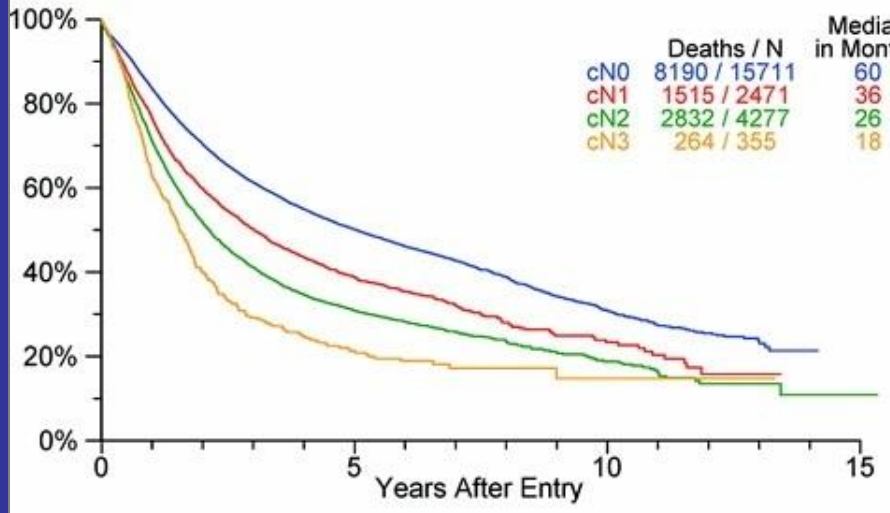
Goldstraw et al, J Thorac Oncol 2007

Overall survival based on pathological staging



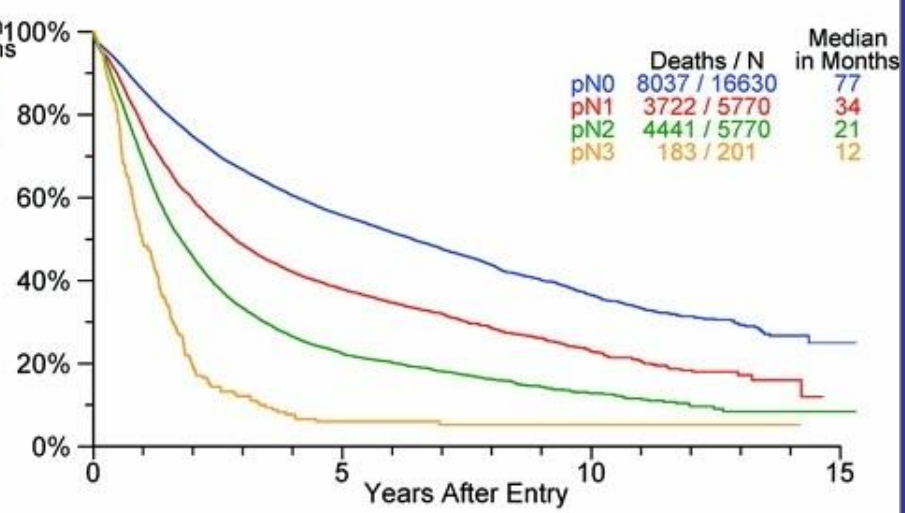
Goldstraw et al, J Thorac Oncol 2007

Clinical Staged, By cN



	1 Yr	5 Yrs		HR	P
cN0	84%	50%			
cN1	77%	39%	vs cN0:	1.37	<.0001
cN2	71%	31%	vs cN1:	1.24	<.0001
cN3	63%	21%	vs cN2:	1.31	<.0001

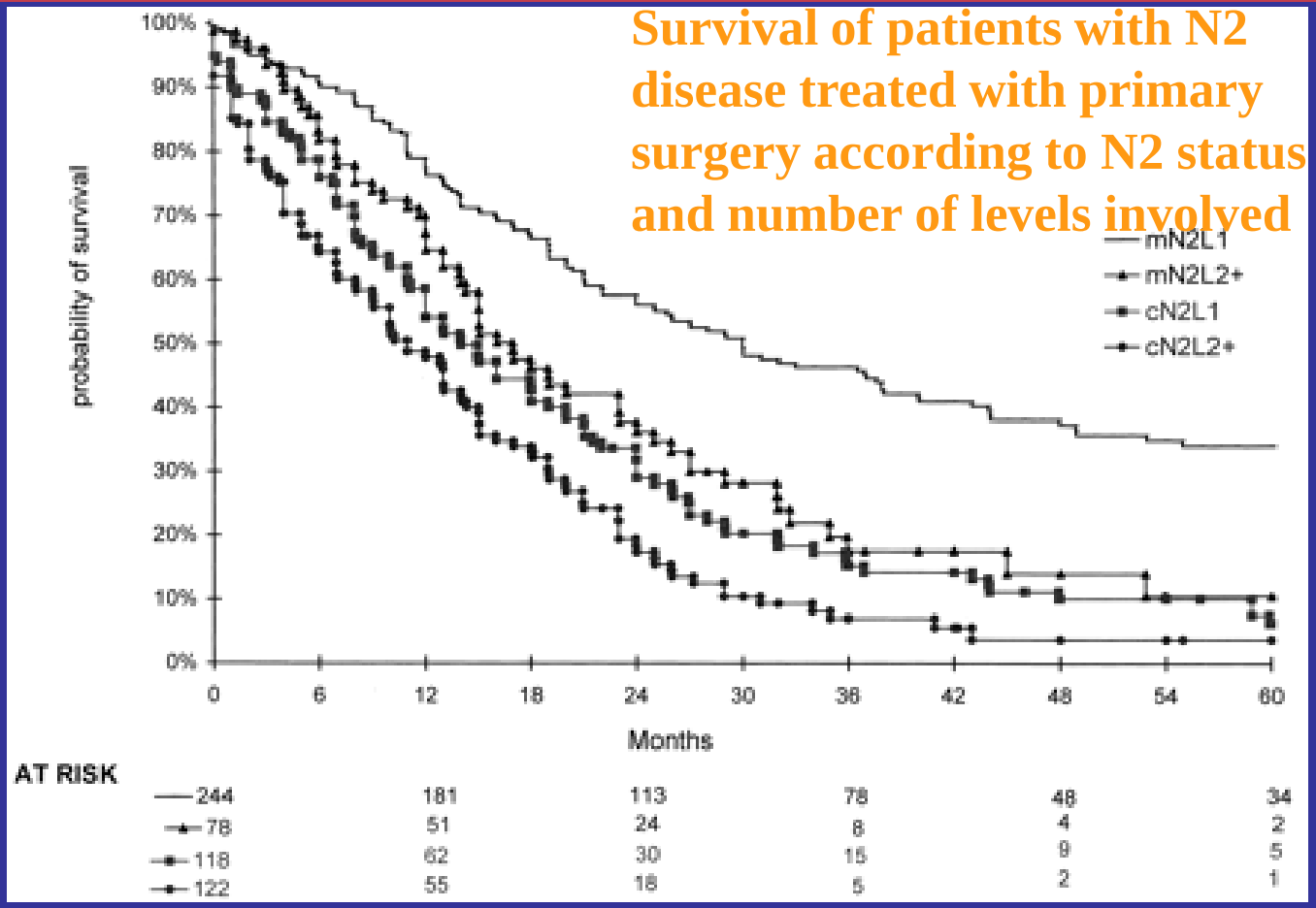
Pathologically Staged, By pN



	1 Yr	5 Yrs		HR	P
pN0	86%	56%			
pN1	77%	38%	vs pN0:	1.63	<.0001
pN2	69%	22%	vs pN1:	1.51	<.0001
pN3	49%	6%	vs pN2:	1.81	<.0001

Rush et al, J Thoracic Oncol 2007 ; 2: 603-612

Survival of patients with N2 disease treated with primary surgery according to N2 status and number of levels involved



Andre, Grunenwald et al, JCO 2000 ; 18: 2981-2989 2000

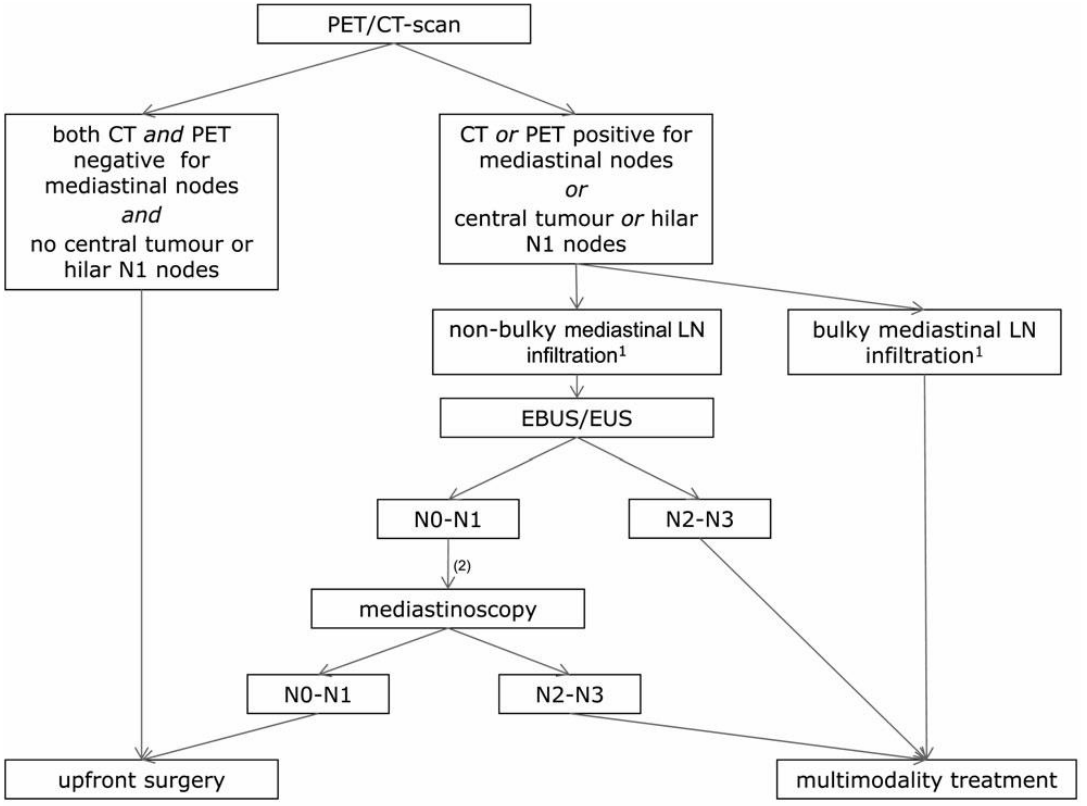
Subsets of Stage IIIA(N_2)*

Subset	Description
$IIIA_1$	Incidental nodal metastases found on final pathology examination of the resection specimen
$IIIA_2$	Nodal (single station) metastases recognized intraoperatively
$IIIA_3$	Nodal metastases (single or multiple station) recognized by prethoracotomy staging (mediastinoscopy, other nodal biopsy, or PET scan)
$IIIA_4$	Bulky or fixed multistation N2 disease

*** adapted from Ruckdeschel**

Robinson, Ruckdeschel, Chest 2007

Suggested algorithm for lymph node staging



[1] Category description according to CT (and PET) imaging as in ACCP staging document [Chest 143 Suppl 5:211S-250S, 2013], see text for more details.
[2] A negative result of EBUS/EUS is usually confirmed by mediastinoscopy, as the latter has the highest negative predictive value.

Vansteenkiste, et al, ESMO clinical practice guidelines, Ann Oncol 2013 and ACCP guidelines Chest 2013

Patients subsets and substages included into stage III NSCLC

Table 2. Patient subsets and substages included into stage III non-small-cell lung cancer

IASLC/UICC 7	Definition	TNM subsets	Description	Robinson Classification
IIIA	incidental N2 (unforeseen N2)	T1-3 N2	N2 found at surgery macroscopic N2 microscopic N2	 IIIA1 IIIA2
IIIA	potentially resectable N2	T1-3 N2	minimal N2/single station at staging	IIIA3
IIIA	potentially resectable N2 But: risk of incomplete resection	T1-3 N2	Pancoast tumour subsets, T3-4 N1, T3 N2 selective centrally located IIIA(N2)	------ IIIA3
IIIA	unresectable N2	T1-3 N2	bulky and/or multilevel N2 at staging	IIIA4
IIIA	potentially resectable T4 But: risk of incomplete resection	T4 N0-1	pulmonary artery, carina, spine, trachea, vena cava, right atrium	------
IIIB	unresectable T4	T4 N0-1 T4 N2	oesophagus, heart, aorta, pulmonary veins	------
IIIB	unresectable N3	T1-4 N3	N3 nodes at staging	

Eberhardt, et al, ESMO Consensus, accepted for publication Ann Oncol 2015

Patient population of stage III

- Important prognostic factors II – accepted factors
  - pulmonary function (COPD grade, FEV1, CO-diffusion capacity, spiroergometric evaluation)
  - cardiac function (FS, calculated EF)
  - smoking cessation
  - potential resectability (?) – specific T4 groups
  - Pancoast tumors (superior sulcus) versus others

Eberhardt W, et al, ELCC 2015

Cardiac assessement

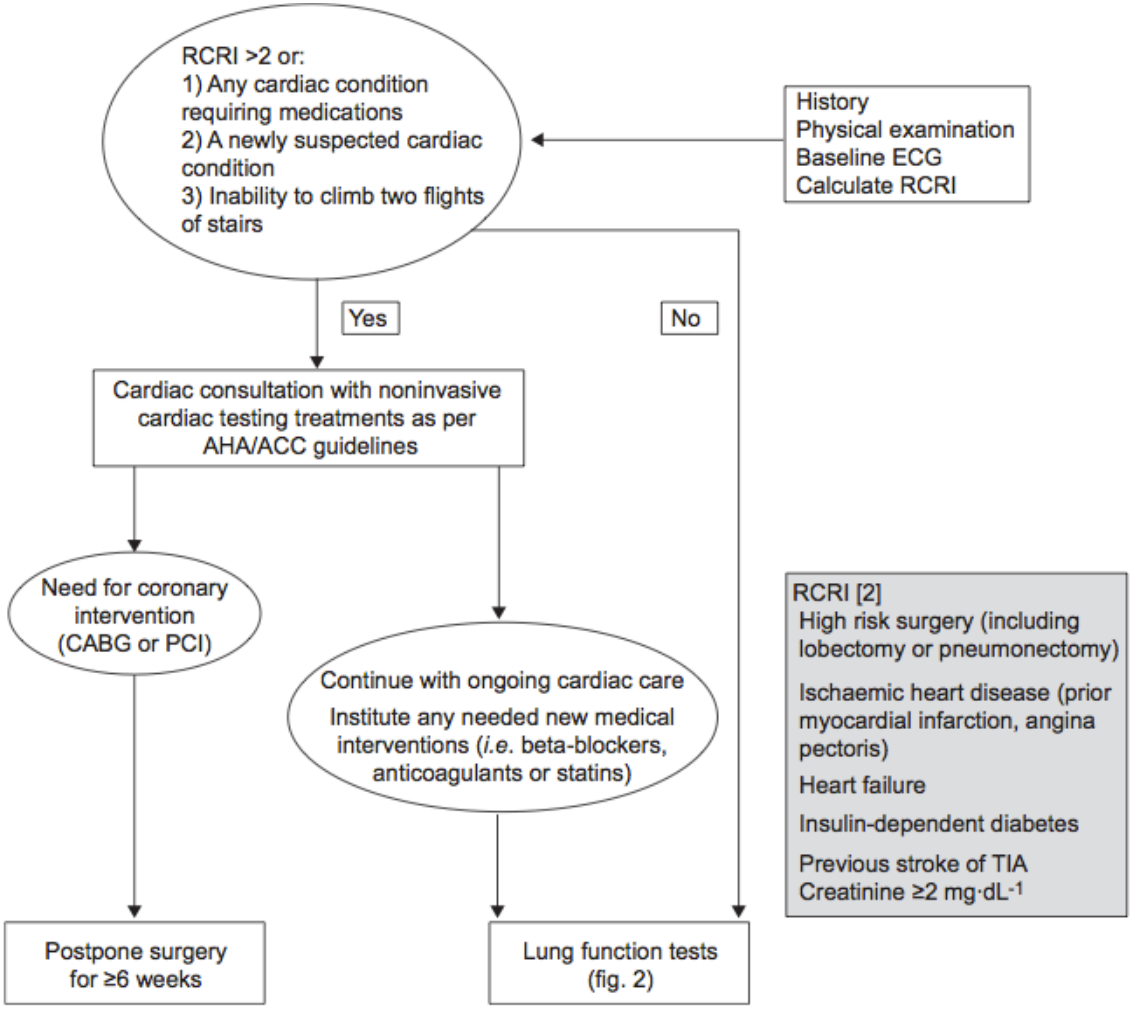
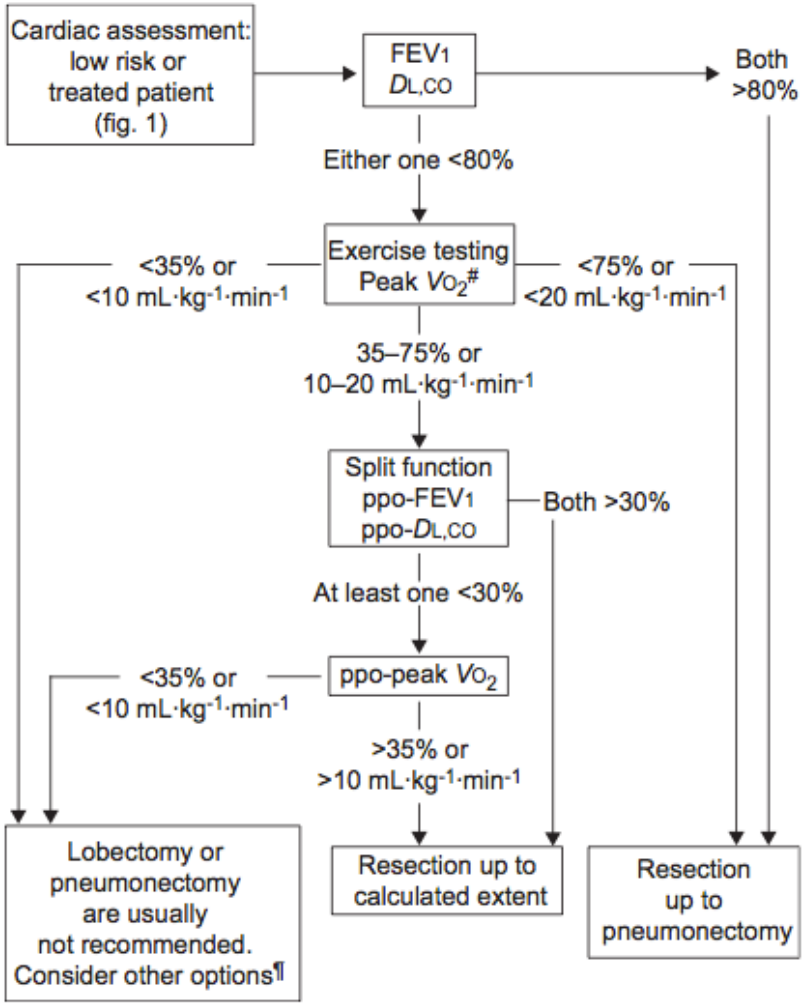


FIGURE 1. Algorithm for cardiac assessment before lung resection in lung cancer patients. For American College of Cardiology Foundation/American Heart Association (AHA/ACC) guidelines see [2–6]. CABG: coronary artery bypass graft; PCI: primary coronary intervention; TIA: transient ischaemic attack.

Brunelli A et al, ERS/ESTS guidelines on fitnes for radical therapy ERJ 2009

Cardiopulmonary function testing



Brunelli A et al, ERS/ESTS guidelines on fitnes for radical therapy ERJ 2009

Risk factors for radical treatment

TABLE 3 Admission criteria in the high dependency unit: moderate- to high-risk patients

Pre-operative comorbidities and functional status

- Coronary artery disease (angina pectoris, prior myocardial infarction, myocardial revascularisation)
- Cardiac insufficiency (left ventricular ejection fraction <40%, history of heart failure)
- Cardiac arythmias or heart conduction block
- Renal dysfunction (plasma creatinine >220 $mg \cdot dL^{-1}$)
- Symptomatic peripheral arterial or cerebrovascular disease
- Severe COPD (FEV_1 <50% pred)
- Anticipated need for noninvasive ventilation (*e.g.* central or obstructive sleep apnoea)
- Liver dysfunction (Child–Turcotte–Pugh score class A and or MELD score >8)#
- Maximal V_{O_2} max <15 $mL \cdot kg^{-1} \cdot min^{-1}$
- Pneumonectomy, bilobectomy; bilateral lung resection
- Extended lung resection involving the diaphragm, pericardium or parietal wall
- Intra-operative major bleeding

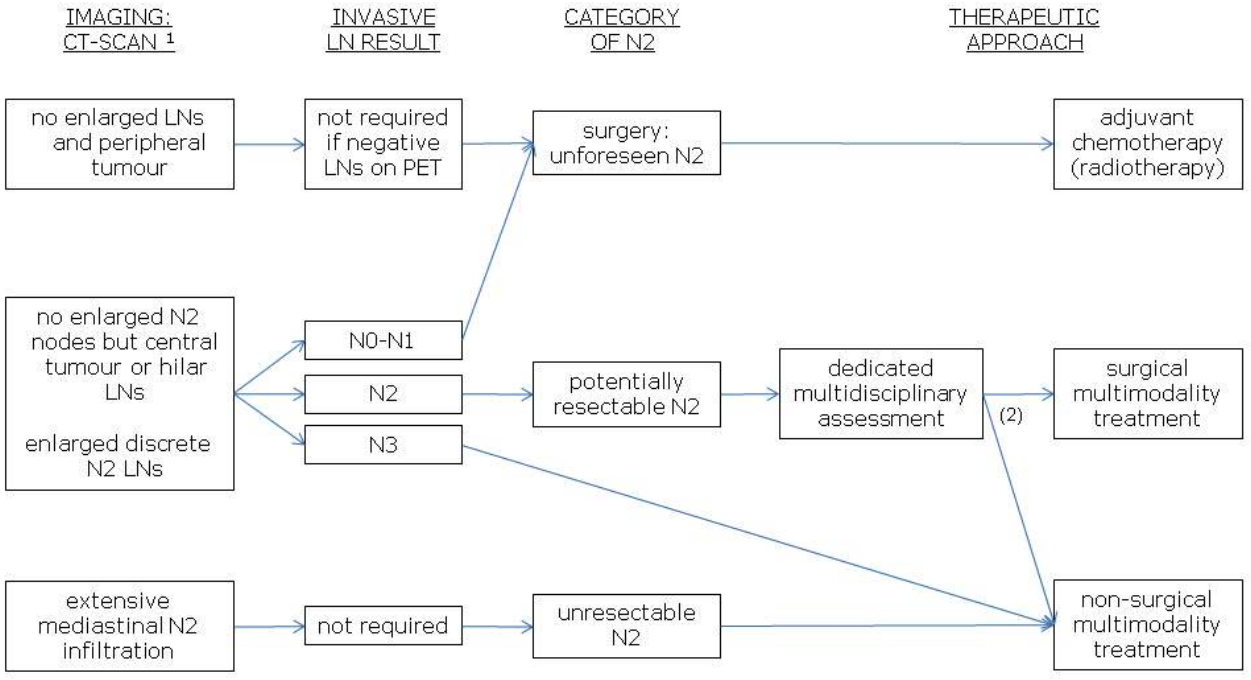
Early post-operative time course in the post-anesthaesia care unit

- Unstable haemodynamics
  - ECG signs of myocardial ischaemia
  - Need for vasopressor support (other than related to epidural anaesthesia)
  - Fluid/blood replacement
- Need for noninvasive ventilation support

#: according to [185]. COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 s; MELD: model for end-stage liver disease; V_{O_2}: oxygen consumption.

Brunelli A et al, ERS/ESTS guidelines on fitnes for radical therapy ERJ 2009

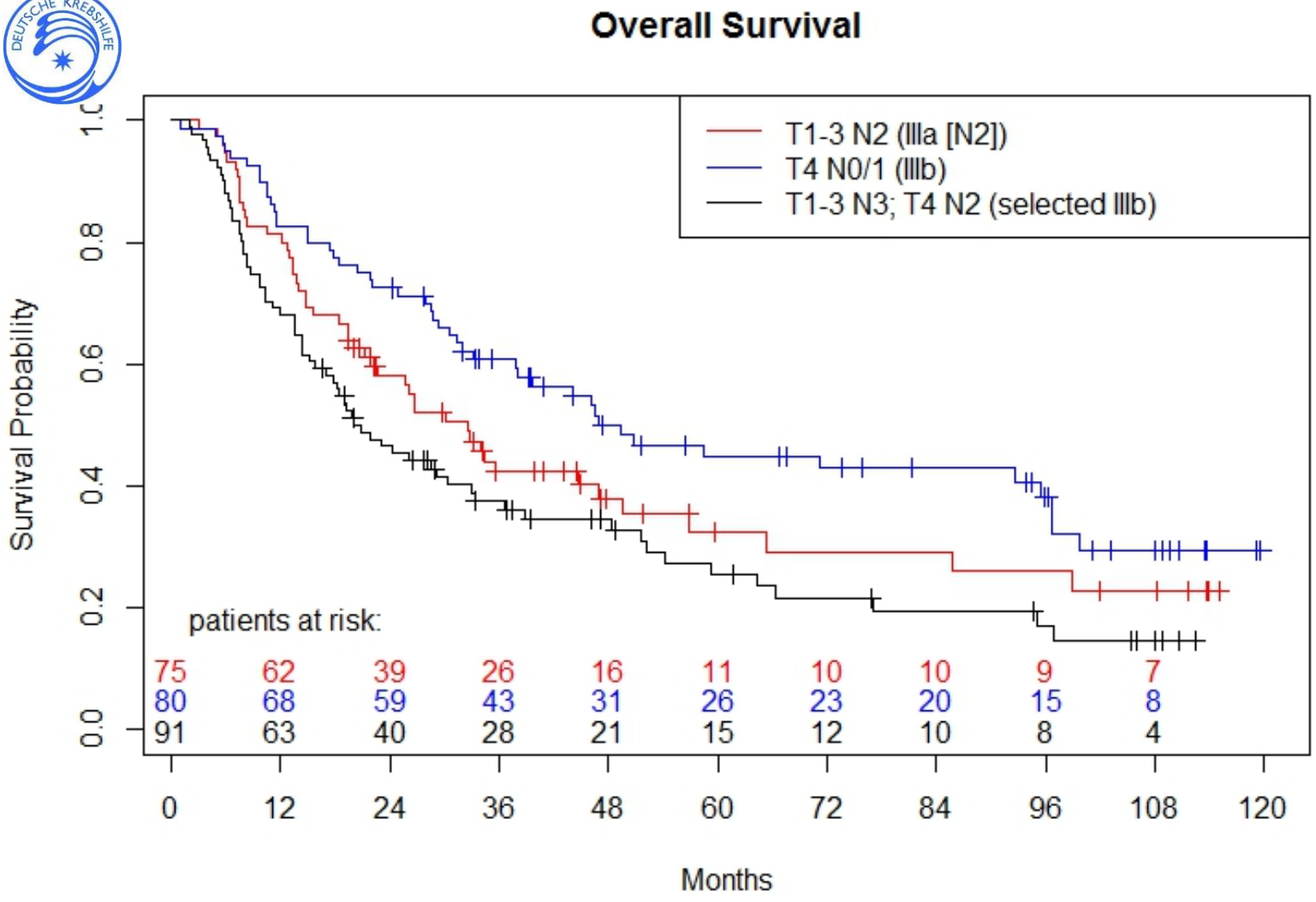
Heterogeneity of stage IIIA



[1] Category description according to CT imaging as in ACCP staging document [Chest 143 Suppl 5:211S-250S, 2013], see text for more details.
[2] See text for factors involved in the choice between non-surgical and surgical multimodality treatment.

Vansteenkiste, et al, ESMO clinical practice guidelines, Ann Oncol 2013

Results – TN-groups

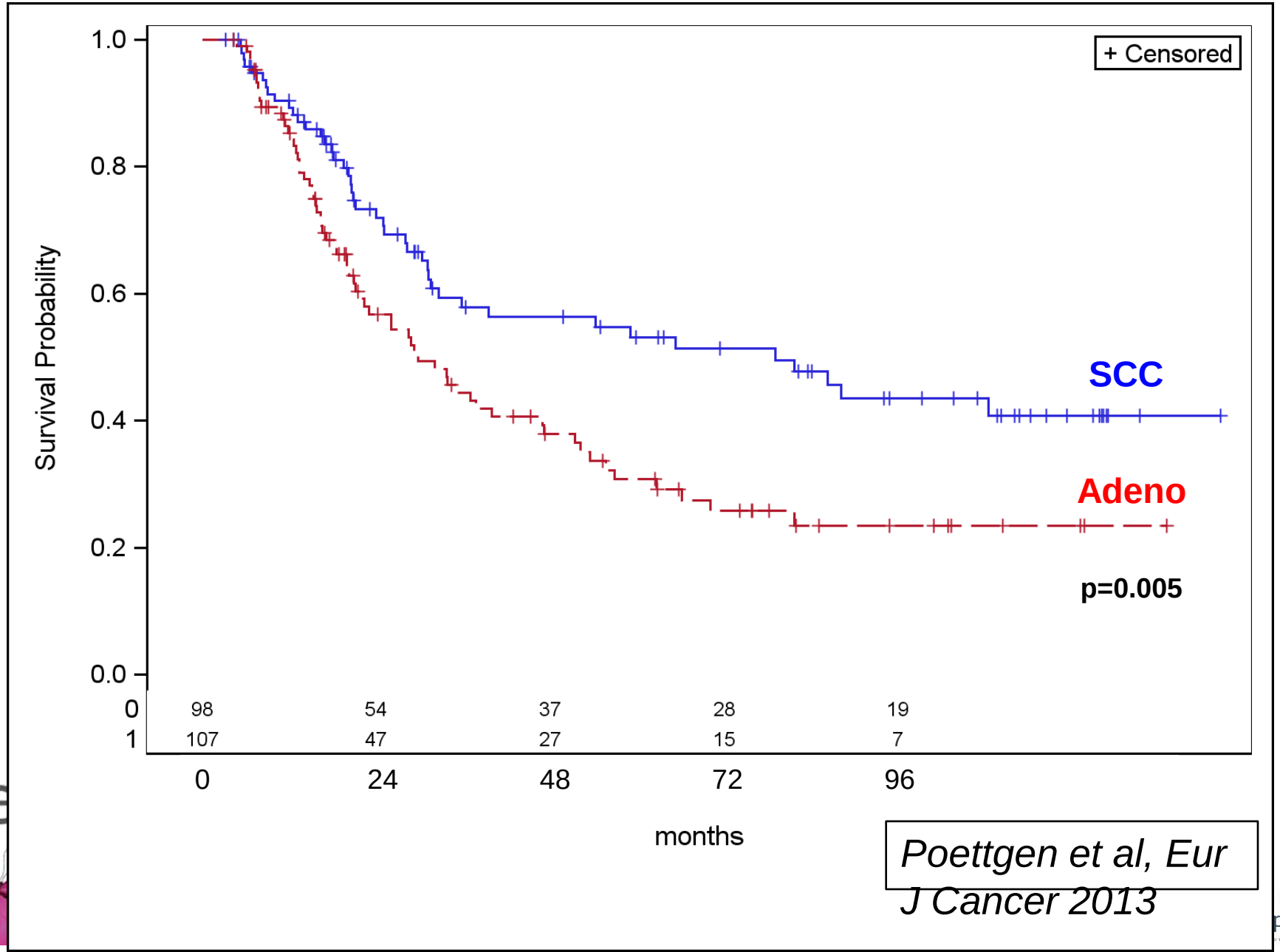


Patient population of stage III

- Important prognostic factors III – not fully accepted but existing data
  - pretreatment LDH
  - FDG-PET-SUV value of primary tumor
  - histopathology: squamous cell carcinoma vs large cell carcinoma versus adenocarcinoma
  - high chance for complete resection (R0) vs high chance of incomplete resection (R1,R2)

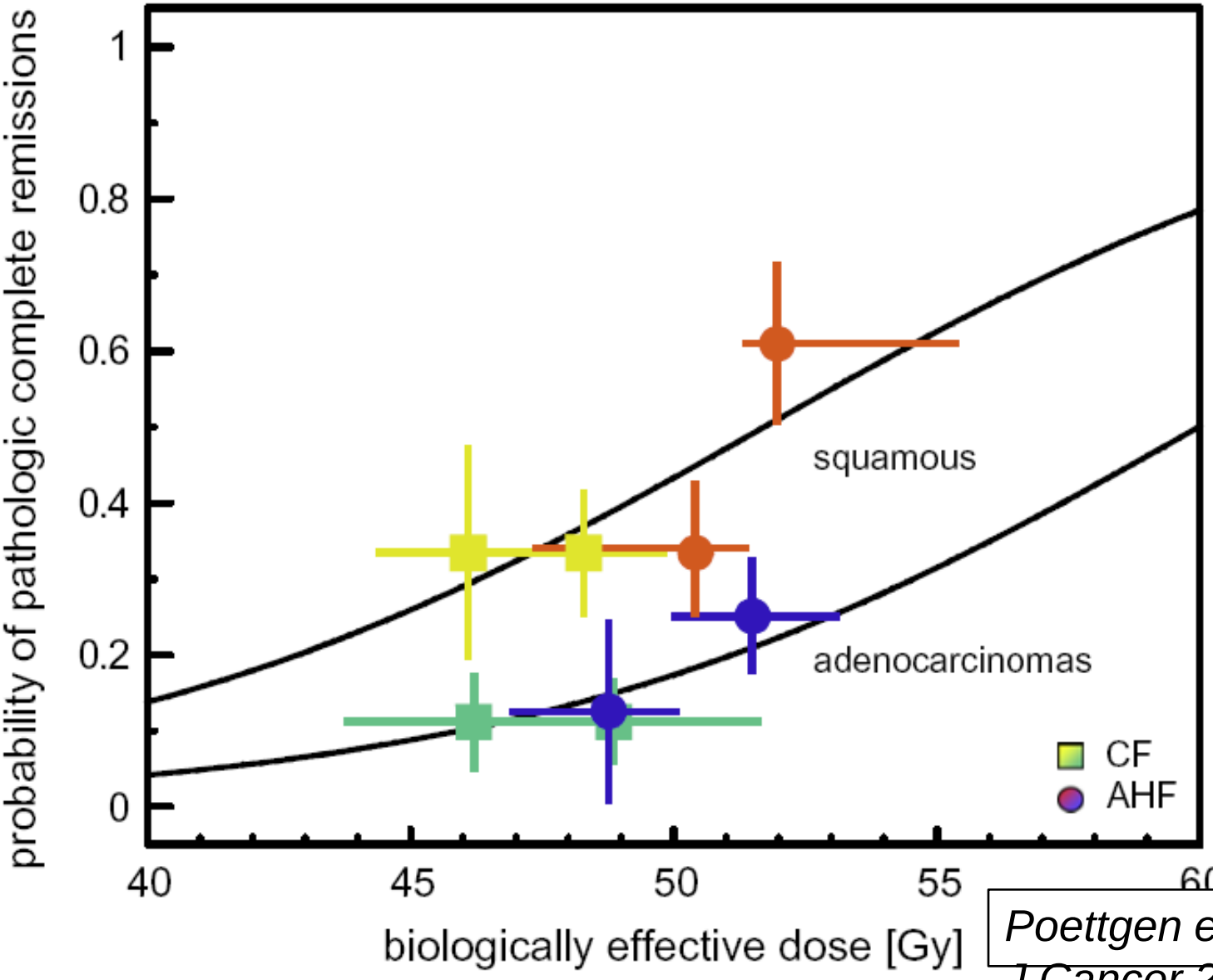
Eberhardt W, et al, ELCC 2015

Overall Survival by Histology



Poettgen et al, Eur J Cancer 2013

neoadjuvant RT/CTx in NSCLC, histopathologic complete response in 239 patients



Poettgen et al, Eur J Cancer 2013

Patient population of stage III

- Important prognostic factors IV – no clear evidence available
  - adenocarcinoma: driver mutations
  - comorbidity score (Charlson ?)
  - age (conflicting results ! no clear boundary)
  - ability to deliver cisplatinum versus carboplatin (?)

Eberhardt W, et al, ELCC 2015

Patient population of stage III

- treatment dependant prognostic factors V
  - clinical RECIST response (CR/PR vs NC/PD)
  - pathological CR to induction therapy in mediastinal nodes (pCR)
  - pathological CR in the primary to induction therapy (pCR)
  - PET response to induction therapy
  - PET response to definitive chemoradiotherapy

Eberhardt W, et al, ELCC 2015

Mediastinal downstaging to induction

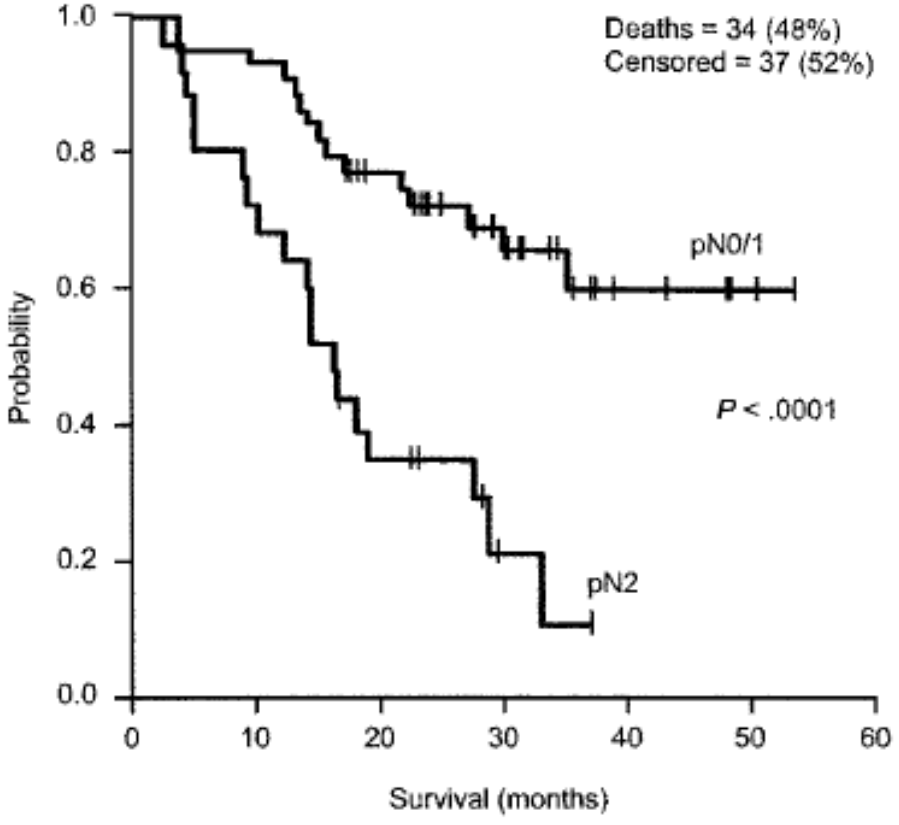


Fig 2. Overall survival dependent on pN2 clearance in the univariate analysis (patients with tumor resection, n = 71; *P* = log-rank test *P* value). Data were unavailable for four patients.

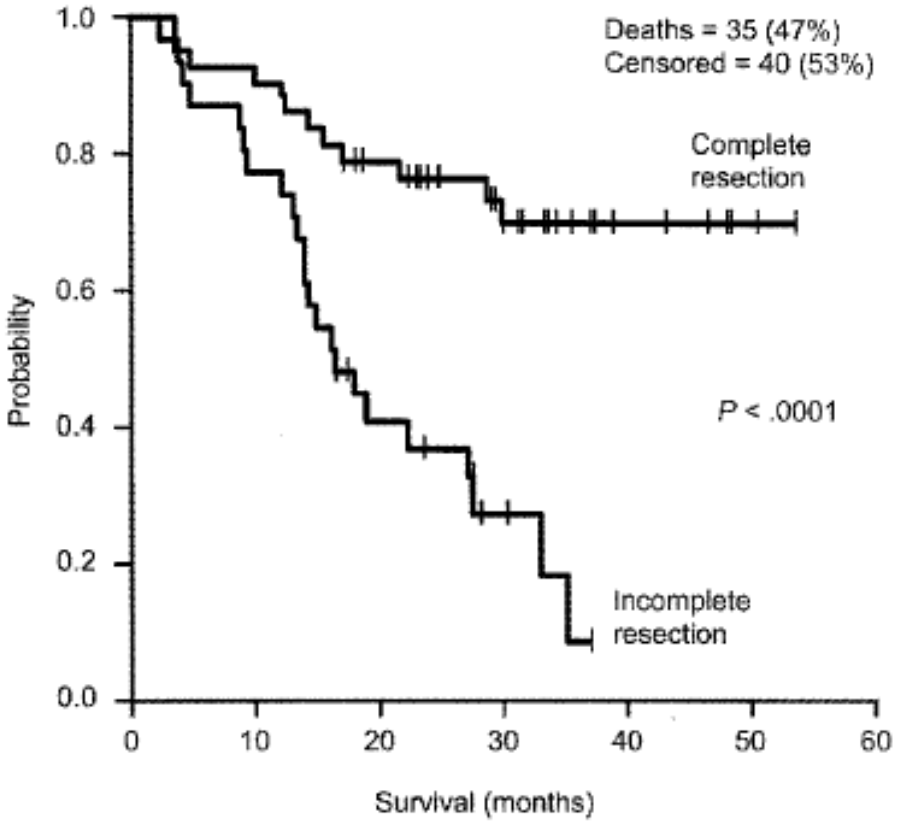
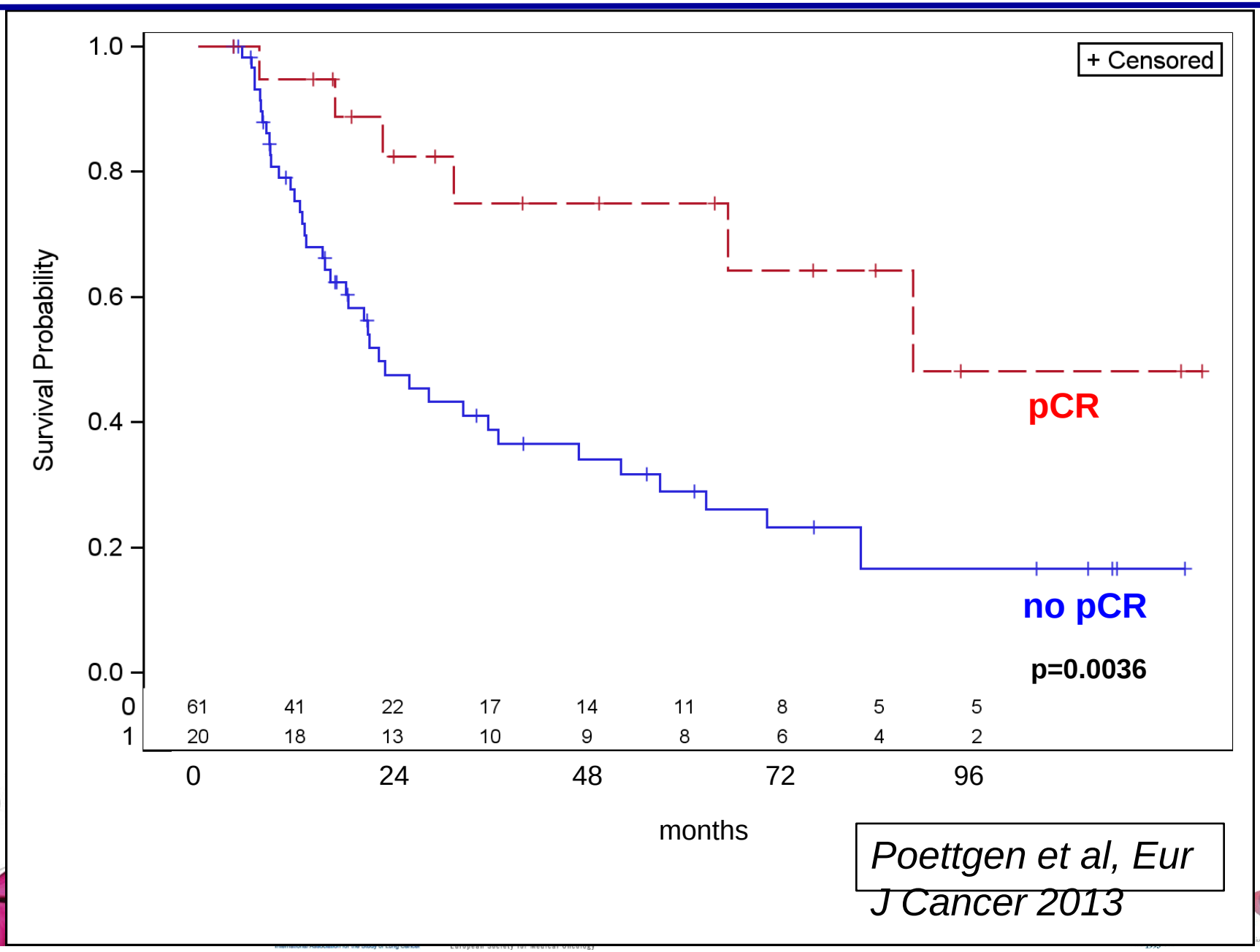


Fig 3. Overall survival dependent on complete resection in the univariate analysis (patients with tumor resection, n = 75, *P* = log-rank test *P* value).

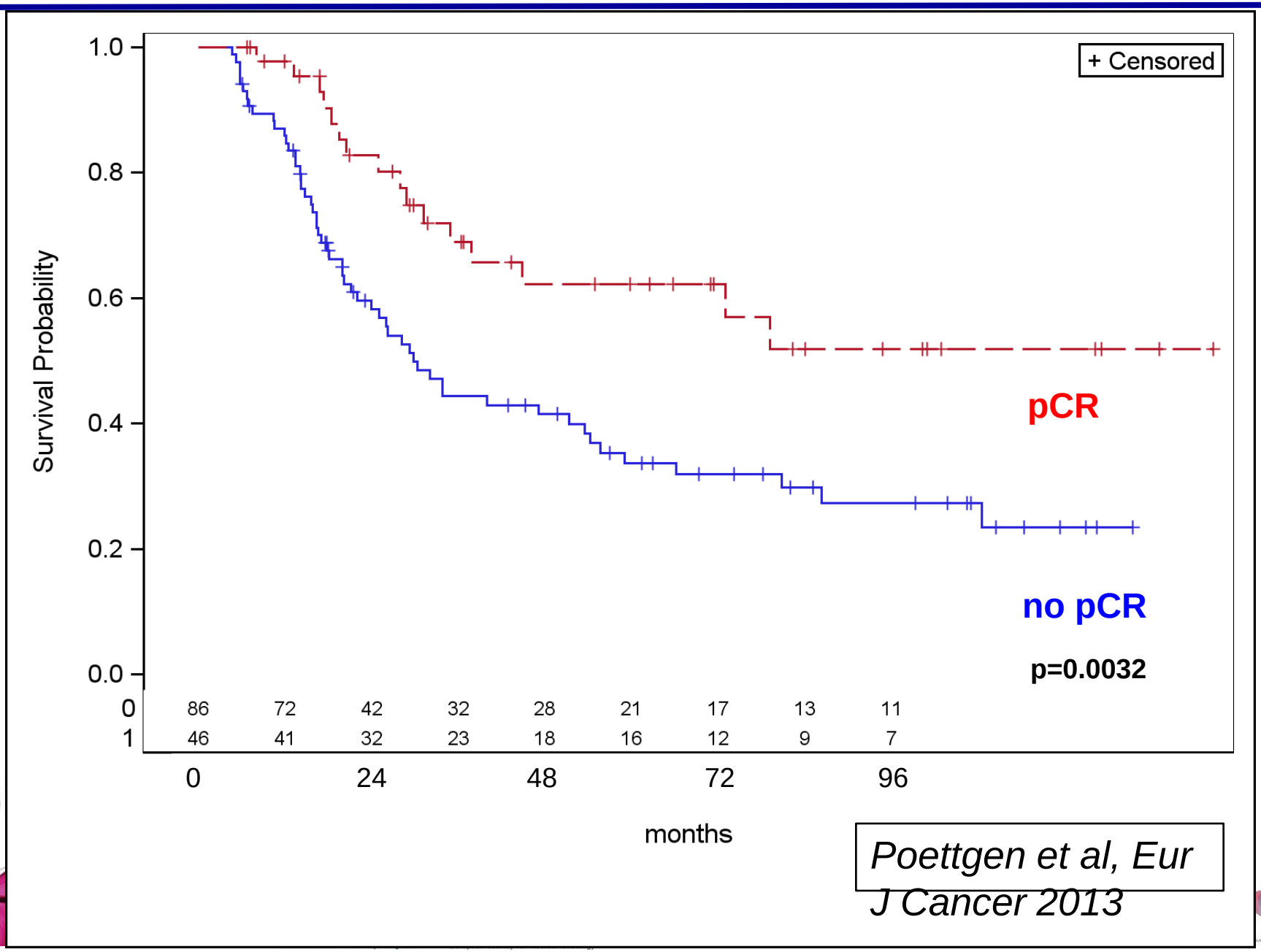
Betticher, et al, JCO 2007

Overall Survival – pCR yes/no in stage IIIA



Poettgen et al, Eur J Cancer 2013

Overall Survival – pCR yes/no in stage IIIB



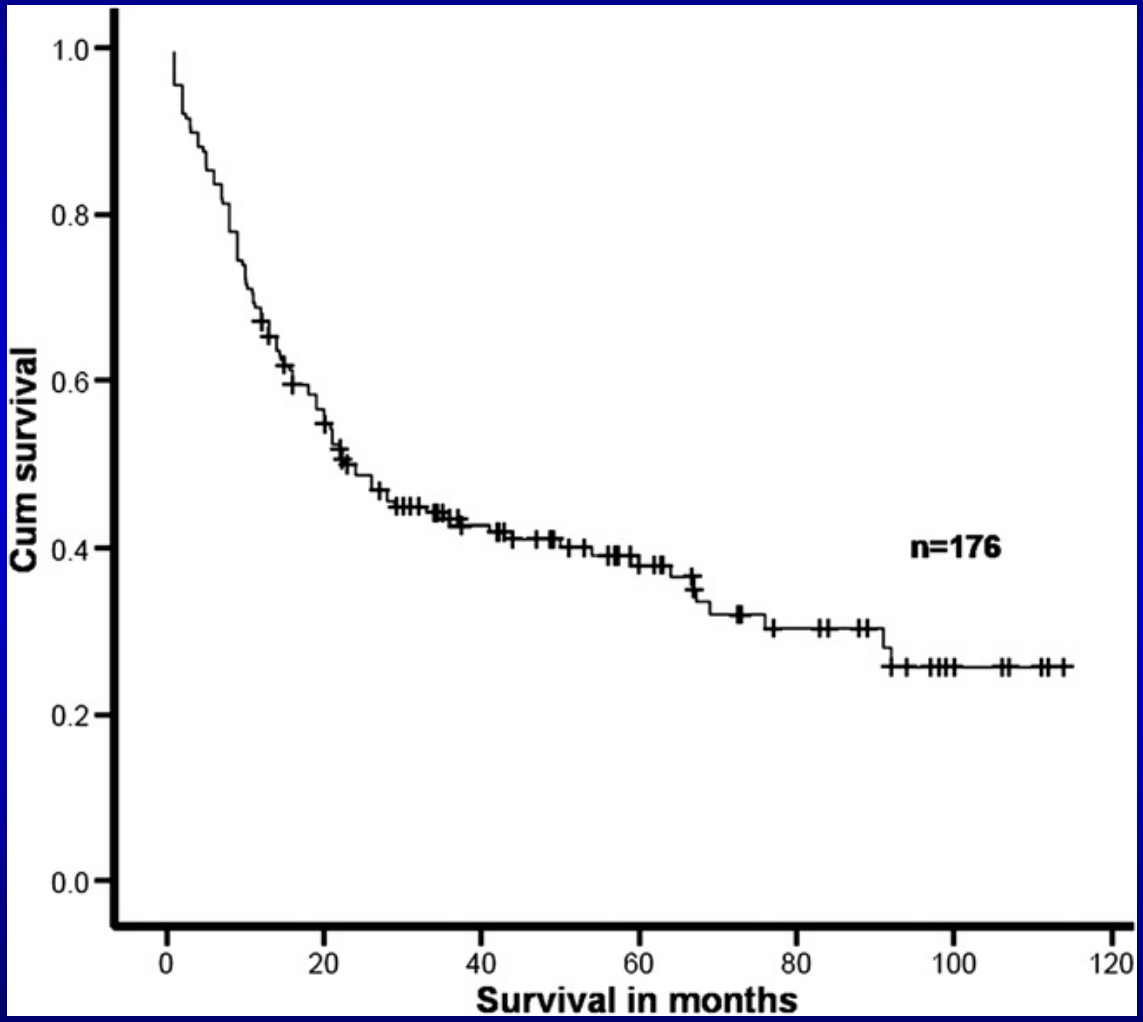
Poettgen et al, Eur J Cancer 2013

Patient population of stage III

- treatment dependant prognostic factors VI
  - Pneumonectomy versus lobectomy/other techniques

Eberhardt W, et al, ELCC 2015

Essen-Zürich Pneumonectomy post induction



Weder W, Collaud S, Eberhardt W et al, J Thoracic Cardiovasc Surg 2010

Conclusions I

- stage III NSCLC is considerably heterogeneous
- several accepted pretreatment prognostic factors exist
- as treatment is best performed as a multimodality treatment (CTx/RTx, induction CTx followed by S, induction CTx/RTx followed by S) risk factors according to local treatments (surgery, radiotherapy) have to be considered

Eberhardt W, et al, ELCC 2015

Conclusions - II

- The best guided descision making is probably performed within dedicated (certified) thoracic oncology centres within a platform of a dedicated chest tumor boards including pulmonologists, medical oncologists, radiation oncologists and thoracic surgeons !

Eberhardt W, et al, ELCC 2015

Outlook

There are way too few large randomized trials that have been performed in stage III NSCLC !

Eberhardt W, et al, ELCC 2015