Locally advanced non-small cell lung cancer therapy

- complex therapy-

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Interdisciplinary Therapy - Today !

stage	IA1-3	
	IB	Operation
	IIA	
stage	IIB	Operation+ Chemotherapy
	IIIA-C	Operation/RT/CT/Immune

Multimodal Therapy Concept

stage	IV A-B	**Systemic Therapy**
		Immune, CT
		Best supportive care

Locally advanced NSCLC

Characteristics std III

Surgery for N2 (?) **Studies**

Specifical Options

Locally advanced NSCLC

heterogeneous stage

30% stage III

5 y survival rate
IIIA 24%
IIIB 9%

Locally advanced NSCLC

clinical heterogenity

T – status-heterogenity

Stage IIIA	**T1a-c**	**N2**	**M0**
	T2a-b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	**T1a-c**	**N3**	**M0**
	T2a-b	N3	M0
	T3	**N2**	**M0**
	T4	N2	M0
Stage IIIC	**T3**	**N3**	**M0**
	T4	**N3**	**M0**

Locally advanced NSCLC

clinical heterogenity

T – status-heterogenity

T3	**Tumor >5 cm but ≤7 cm in greatest dimension** or associated with separate tumor nodule(s) in the same lobe as the primary tumor or directly invades any of the following structures: chest wall (including the parietal pleura and superior sulcus tumors), phrenic nerve, parietal pericardium
T4	**Tumor >7 cm in greatest dimension** or associated with separate tumor nodule(s) in a different ipsilateral lobe than that of the primary tumor or invades any of the following structures: **diaphragm,** mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, and carina

Locally advanced NSCLC

clinical heterogenity

N – status-heterogenity

10-15% IIIA-N2

micro N2 ⟷ bulky N2

N2 heterogeneous disease

favorable N2-Disease (10-20%)

mono-station
microscopical
PET-negativ
incidental finding at surgery

non-favorable N2-Disease

multi-station
fixed
bulky
extra-nodal

N2 incidental

N2 potentially resectable

N2 potentially resectable risk of incomplete resection

N2 non-resectable

N2 heterogeneous disease

III A: T1-3, N2

Robinson et al. Chest 123, 202S, 2003

IIIA1
Detection N2 postoperativly
„incidental“

IIIA2
Detection N2 intraoperativly
1 Level

IIIA3
Detection N2 preoperativly
1 or more by MSC, TBNA, PET

IIIA4
Detection N2 preoperativly
1 or more „Bulky“ or „Fixed“

Patient heterogenity

ORIGINAL CONTRIBUTION

Surgery for Non-Small Cell Carcinoma in Geriatric Patients: 15-Year Experience

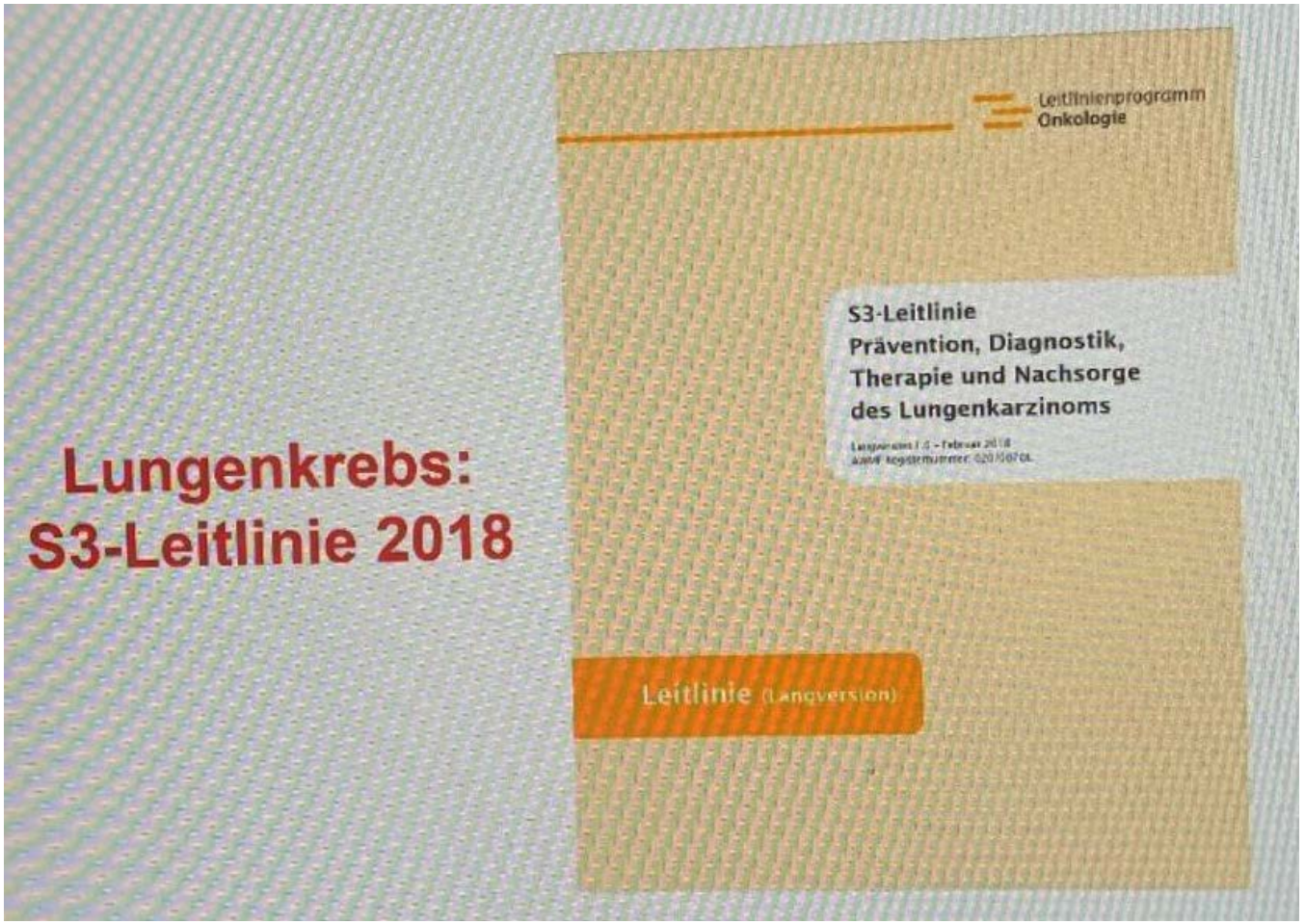
Horia Sirbu, MD, Waldemar Schreiner, MD, Harald Dalichau, PhD, Thomas Busch, PhD

Department of Thoracic and Cardiovascular Surgery

Institutional heterogenity

Data heterogenity

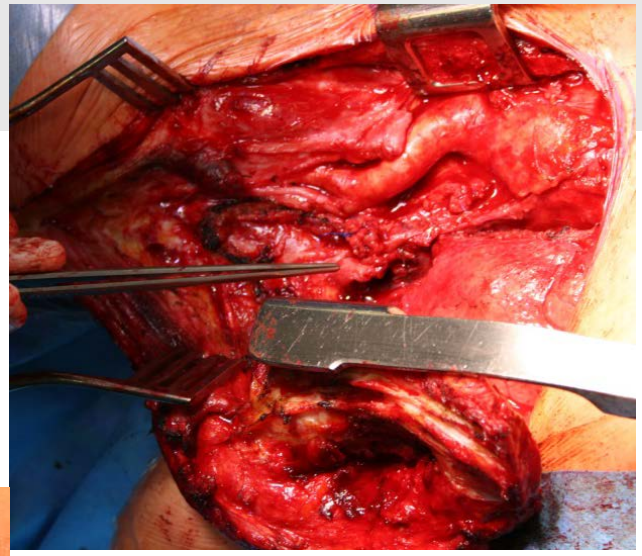
Locally advanced NSCLC

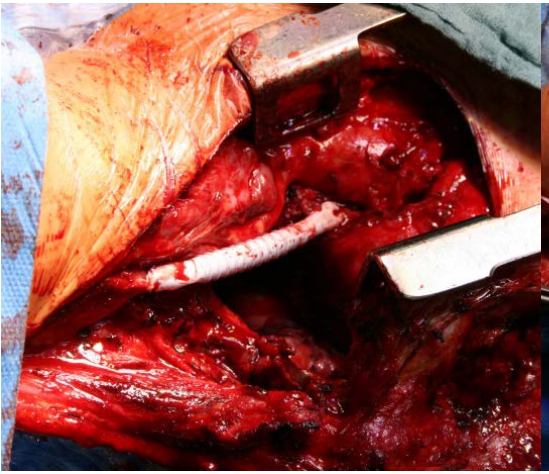


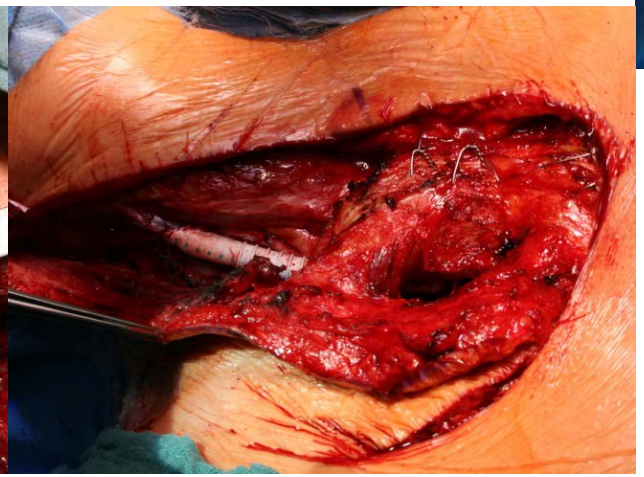
Locally advanced NSCLC

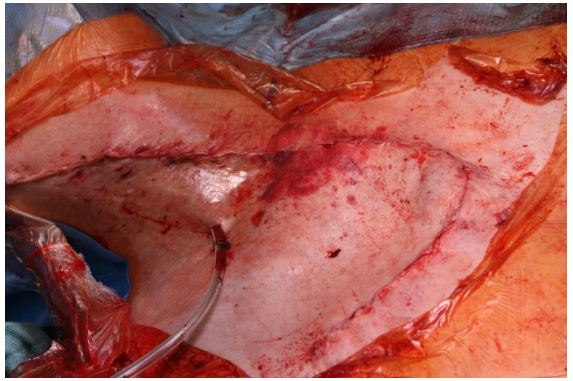
is there a radical therapy possible ?

high T — ***surgeon*** — **local resection ?**





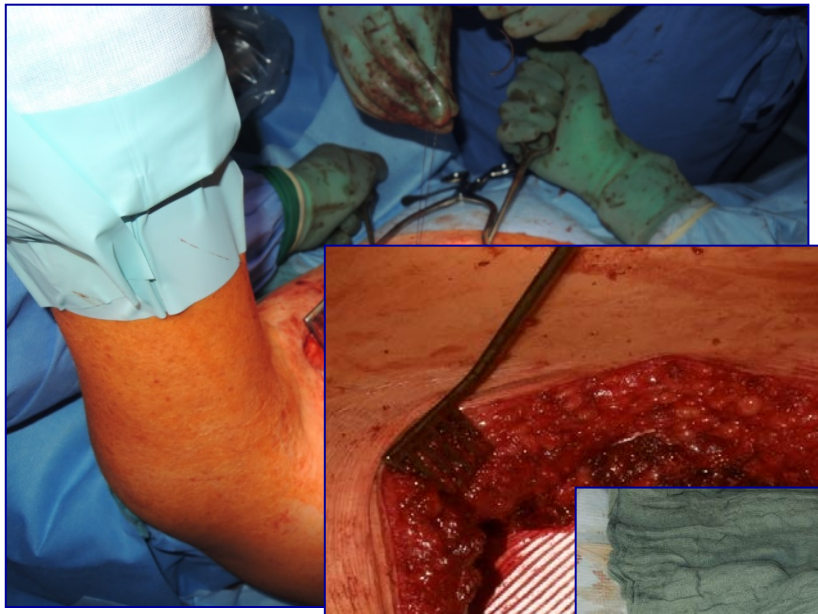


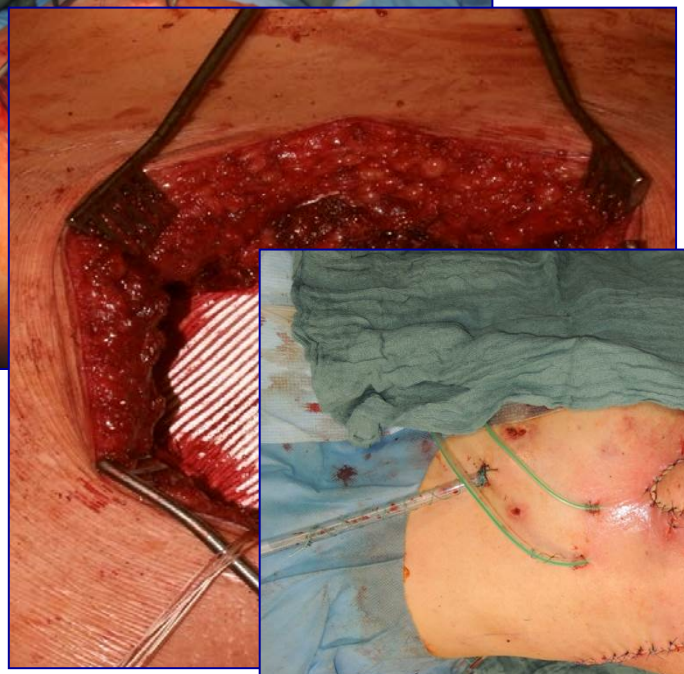


19.08.2016 Extended cervico-sternal resection with segmental resection ML, C1 rib, V. jug. int

high T

combined lung and chest wall resection in T3





interdisciplinary operations

Locally advanced NSCLC

is there a radical therapy possible ?

high N ***interdisciplinary*** **neoadjuvant therapy ?**

high N

interdisciplinary treatment concept

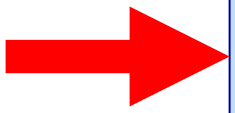
no standard

goals

chemotherapy

radiotherapy

surgery



local tumor control	**<10%** recurrence
down staging	**pTNM**
survival	**>15-30%** 5J

Neoadjuvant treatment

potential benefits of RCT :

improved local therapy :

directly — **local T-reduction**
bulky N2

early control of micrometastatic disease?

Neoadjuvant treatment

Studies

Studie (Erstautor)	Rekrutierung	Eingeschlossene Patienten
INT 0139 (Albain)	1994-2001	Primär resektabel (IIIA3)
SAKK (Pless)	2001-2012	Primär resektabel (IIIA3)
ESPATUE (Eberhardt)	2004- 2012	Primär fraglich resektabel (IIIA4/IIIB)
EORTC 08941 (Meerbeck)	1994-2002	Primär nicht resektabel (IIIA4)

Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyau Chen, Robert B Livingston, Richard H Feins, David R Gandara, Willard A Fry, Gail Darling, David H Johnson, Mark R Green, Robert C Miller, Joanne Ley, Willliam T Sause, James D Cox

Lancet 2009; 374: 379–86

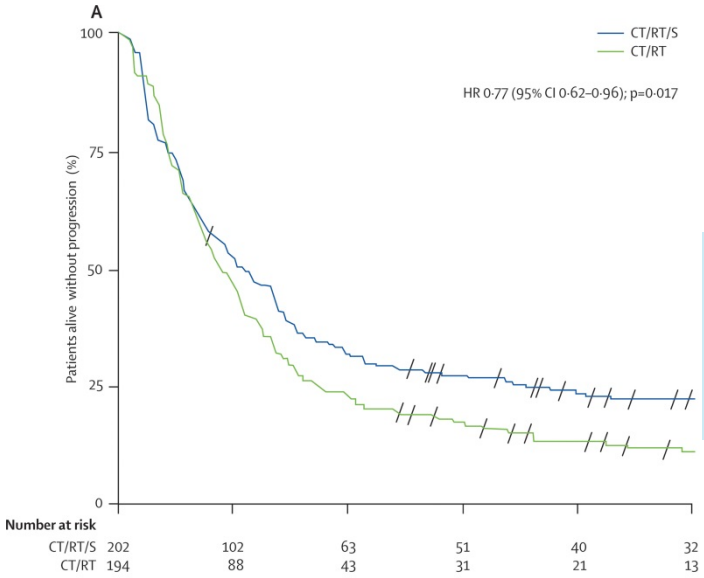
Lung Intergroup Trial 0139

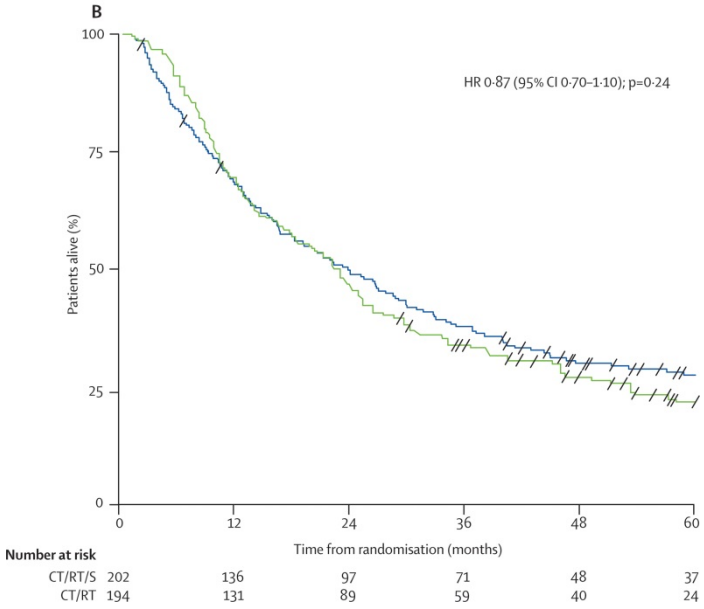
n=429 **IIIa (pN2)**

Arm 1 **216** **sRCT 2(Cis, Eto)+45Gy+Res.+2(Cis, Eto)**

Arm 2 **213** **sRCT 2(Cis, Eto)+61Gy+2(Cis, Eto)**

primary end point **OS** **(p=0,24)**
secondary end point **PFS** **(p=0,017)**





Arm1 CT/RT/S

Progression-free survival (PFS) **(*P*=0,017)**

29% vs 19% 3y

22% vs 11% 5y

Overall survival (OS) not significant

Arm 1 (38%) vs Arm 2 (33%)

Albain KS et al. Lancet 2009;374:379-86

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Mortality

6%

no mortality during induction of RCT

Arm 1 (CT/RT/S) **16 (8%) mortality**

14 of 16 after pneumonectomy

ARDS	9
Pneumonia	4
Cardiac	2
Bleeding	1

Arm 2 (CT/RT) **4 (2%)**

Albain KS et al. Lancet 2009;374:379-86

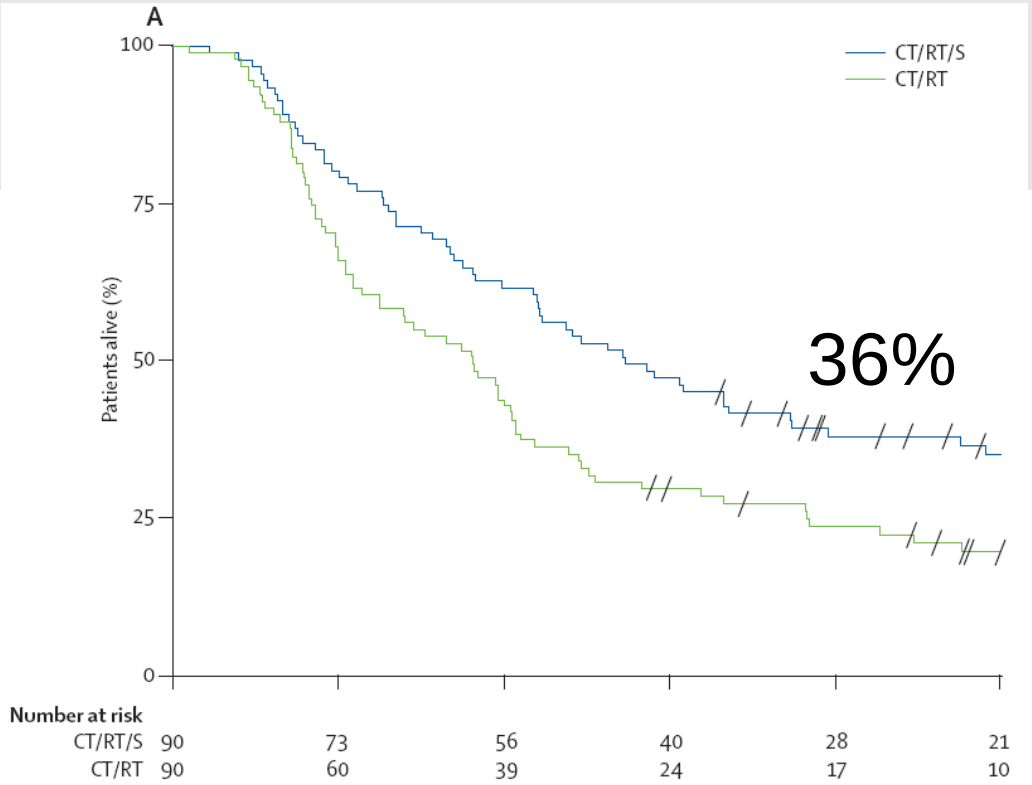


Figure 4: Overall survival of a subset of patients from the intention-to-treat population given lobectomy (A) or pneumonectomy (B) in group 1 versus matched cohorts in group 2

sub-group-analysis

lobectomy patients

Albain KS et al. Lancet 2009;374:379-86

Overall survival (OS) of lobectomy patients in arm 1 (CT/RT/S)

33,6 mo vs 21,2 mo (*P*=0,002)
36% vs 18% 5y

Neoadjuvant RCT

advantges of RCT + surgery

improved local therapy:

directly 12%

selective surgery (e.g. lobectomy, sleeve resections)

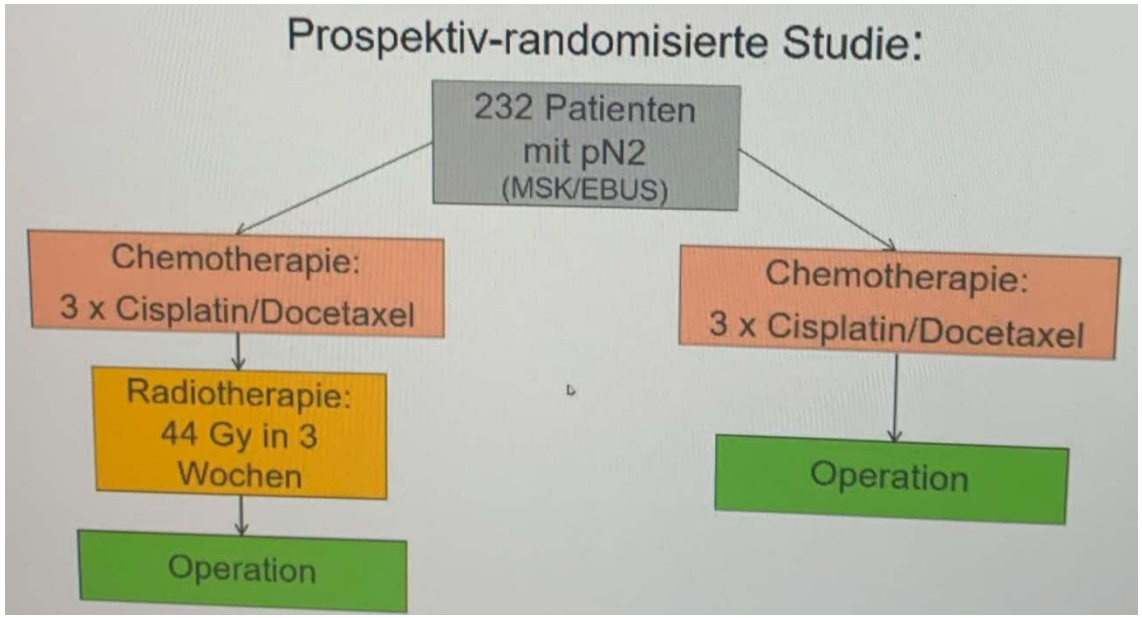
Albain KS et al. Lancet 2009;374:379-86

SAAK

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

Miklos Pless, Roger Stupp, Hans-Beat Ris, Rolf A Stahel, Walter Weder, Sandra Thierstein, Marie-Aline Gerard, Alexandros Xyrafas, Martin Früh, Richard Cathomas, Alfred Zippelius, Arnaud Roth, Milorad Bijelovic, Adrian Ochsenbein, Urs R Meier, Christoph Mamot, Daniel Rauch, Oliver Gautschi, Daniel C Betticher, René-Olivier Mirimanoff, Solange Peters, on behalf of the SAKK Lung Cancer Project Group

Lancet 2015; 386: 1049–56

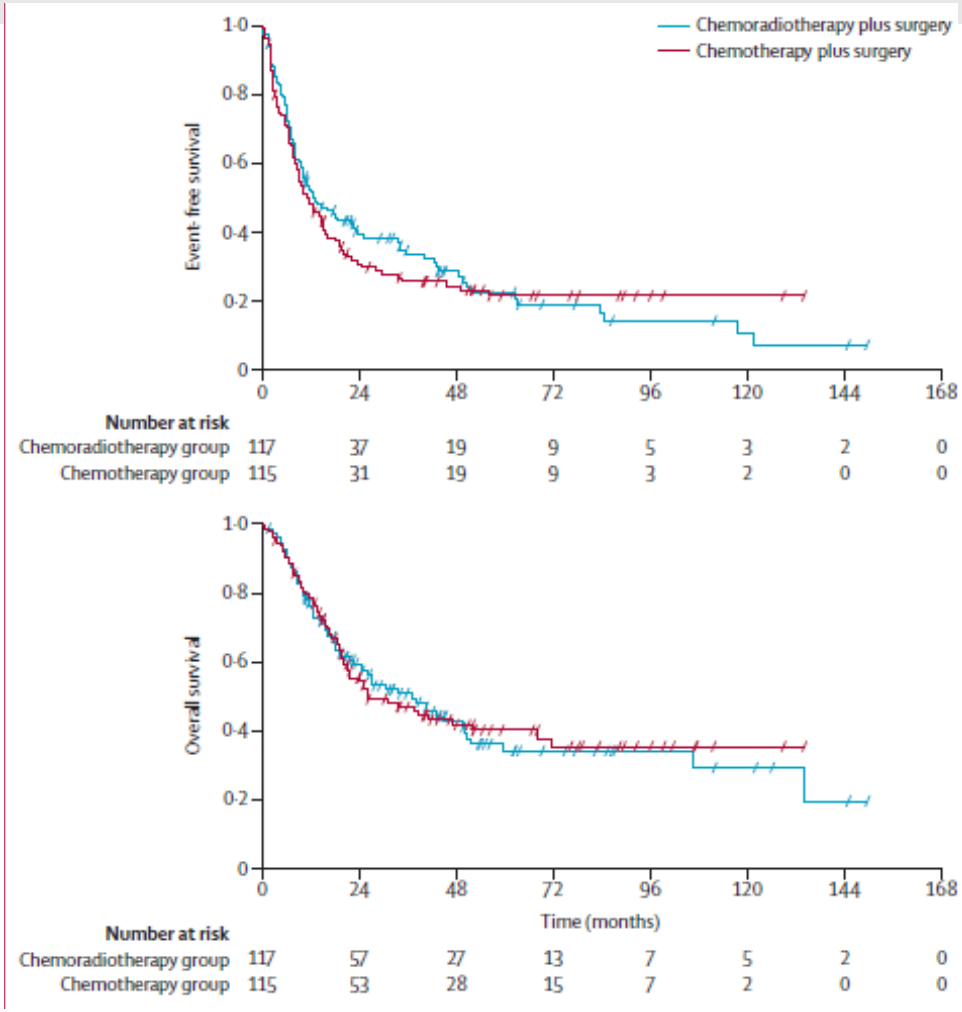


SAAK

	CT-RT-OP	CT-OP
3 Zyklen Chemotherapie	93%	89%
Bestrahlung abgeschlossen	85%	Nd
Operiert	82%	81%
Komplete Resektion	90%	80%
Lokalrezidiv	22%	24%
Event free Survival (median, months)	12.8	11.8
Survival (median, months)	27.1	26.2

Lancet 2015; 386: 1049–56

SAAK



Event-free survival

Overall survival

Lancet 2015; 386: 1049–56

SAAK

- preop RT no improvement in overall survival
- CT + Operation good long term survival

Criticism: - no simultaneous RCT
- 16% postoperative RT

Lancet 2015; 386: 1049–56

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1. ***Simultaneous RCT***

   RT 45 Gy
   2 CT (Cis + Eto)

   control (PET + cerebral MRI) after RT

2. ***Surgery***

   6 weeks after RT

3. ***Follow up***

   first 2 y at 3 Mo. CT-chest

Locally advanced NSCLC

Neoadjuvante Radiochemotherapie gefolgt von kurativer Resektion im fortgeschrittenen Stadium IIIA/IIIB eines nicht kleinzelligen Lungenkarzinoms: prognostische Faktoren und Ergebnisse

Neoadjuvant Radiochemotherapy Followed by Curative Resection in Patients with Advanced Non-Small Cell Lung Cancer in Stage IIIA/IIIB: Prognostic Factors and Results

Autoren W. Schreiner[1], W. Dudek[1], S. Lettmaier[2], S. Gavrychenkova[1], R. Rieker[3], R. Fietkau[2], H. Sirbu[1]

Institute
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[3] Pathologisches Institut, Universitätsklinikum der Friedrich-Alexander-Universität, Erlangen-Nürnberg, Deutschland

Zentralbl Chir 2016; 141: 323–329

Locally advanced NSCLC

Erlangen Group

n=46 (2,8%) IIIA

age 52,9 ± 15,3 y

N2 76%

65% responder 96% R0

16% down staging

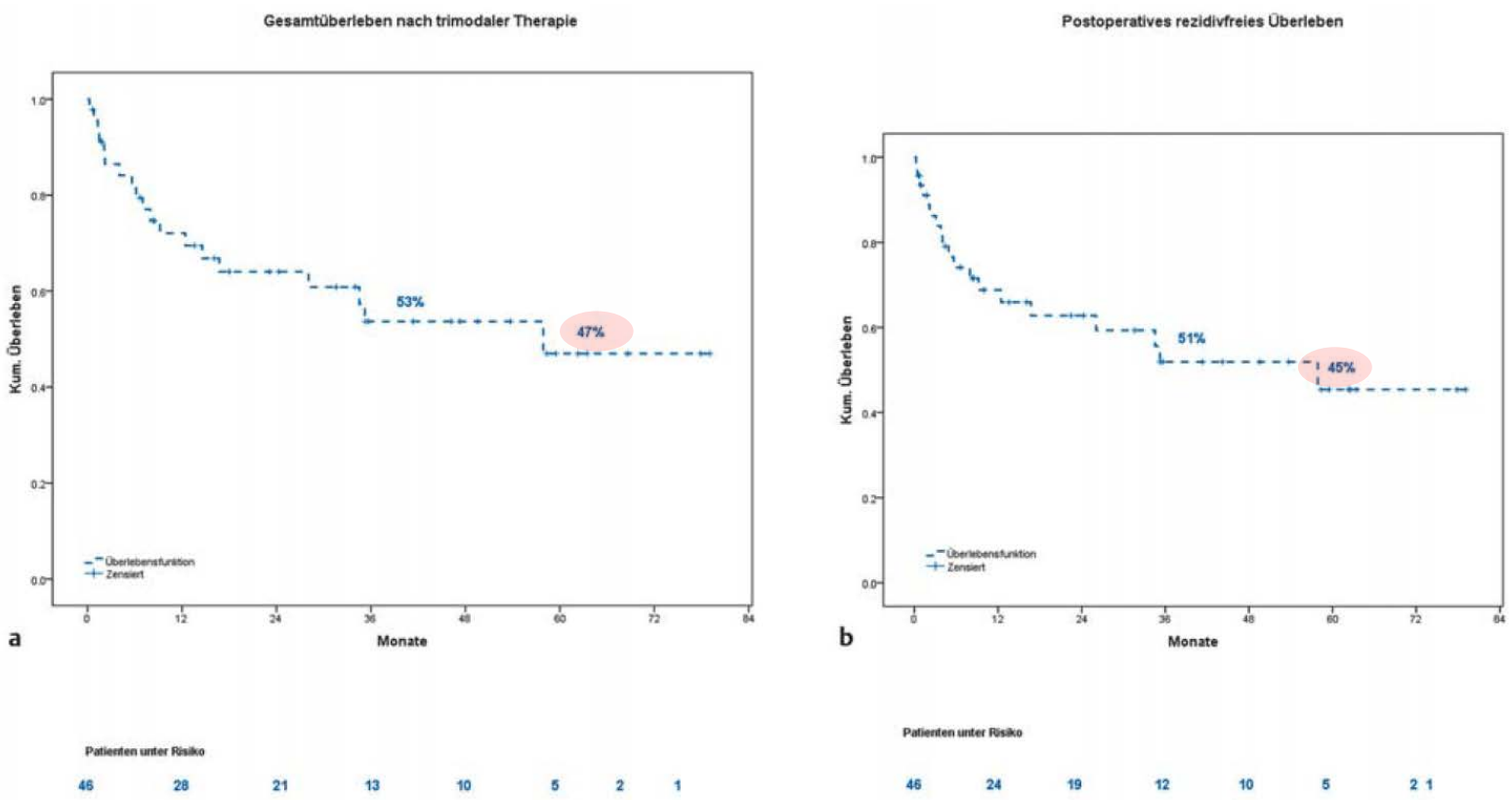
4 segment-, 22 lobectomy-, 10 sleeve-,

11 pneumonectomy+adv. res.

17% morbidity

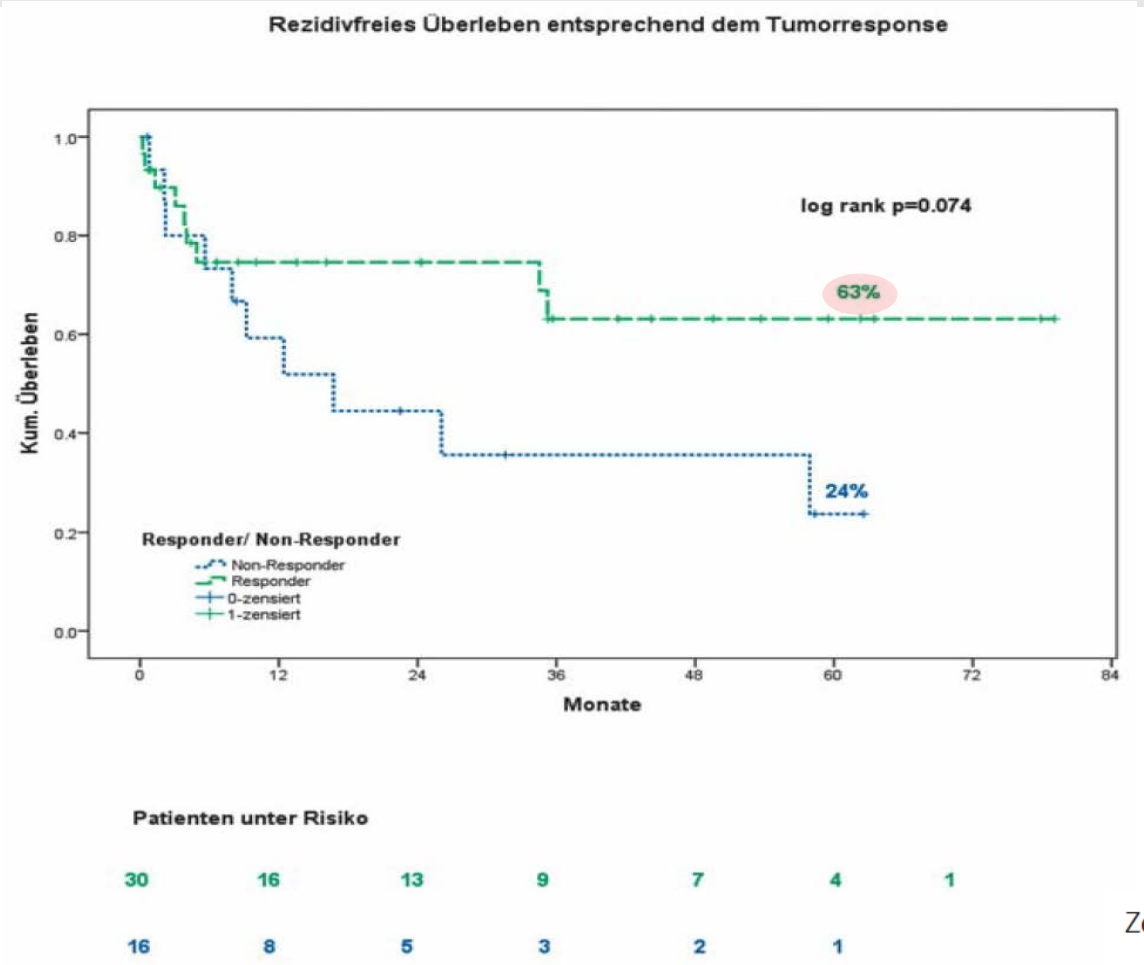
Zentralbl Chir 2016; 141: 323–329

Locally advanced NSCLC



Zentralbl Chir 2016; 141: 323–329

Locally advanced NSCLC



responder

non-responder

Zentralbl Chir 2016; 141: 323–329

Literature

Autor	Jahr	N	Histologie	RT	Gy	Operation	median disease-free (m)	median survival (m)	Überleben	Letalität
Neri	2010	7	2 NSCLC/ 5 Meta`s	SRT	75-105	6 lobectomy/ 1 segment	9	21		0%
Chen	2010	5	NSCLC	SRT	105	5 lobectomy	17	25		0%
Bauman	2008	24	NSCLC	def. RCT	63.9	23 > lobectomy 1 wedge	5	12	3J 47%	4% (1)
Kuzmik	2013	14	NSCLC	def. RCT	57	11 > lobectomy 2 segmectomy 1 wedge	33	9	2J 49%	0%

Locally advanced NSCLC

„Be balanced“

- **therapy in std III requires always a "nuanced" decision**
- **always an interdisciplinary decision with risk / benefit ratio**
- **R0-resection after neoadj. RCT is important**
- **a pneumonectomy should be avoided, but not defamed**
- **multimodal therapy should be performed only in experienced departments with extended specialized facilities**

NSCLC – frühe und lokal fortgeschrittene Stadien

ASCO 2021

Zielgerichtete Therapie

Setting	Studie Intervention	Seite
***EGFR*+ IIIA, Adjuvanz**	**EVAN, Phase 2** OS-Update, explorative Analysen, Erlotinib vs. Chemotherapie	6
***EGFR*+ IIA-IIIA, Adjuvanz**	**ICOMPARE, Phase 2** Verschiedene Behandlungszeiten, Icotinib	11
***EGFR*+ Stadium IIIA N2, Neoadjuvanz, Adjuvanz**	**CTONG1103, finales OS** Erlotinib vs Gemcitabin + Cisplatin	16
***EGFR*+ Stadium III-III, Adjuvanz**	**IMPACT, Phase 3, Japan** Gefitinib vs. Cisplatin/Vinorelbin	22

Immuntherapie

Setting	Studie Intervention	Seite
Stadium III, nicht operabel	**AFT-16, Phase 2** Neoadjuvant CRT + Atezolizumab gefolgt von adjuvant Atezolizumab	29
Stadium III, nicht operabel	**PACIFIC 5-Jahres-OS** CRT gefolgt von Durvalumab	33
Stadium IB-IIIA Adjuvanz	**IMpower010** Atezolizumab nach adjuvanter Chemotherapie	38
Stadium IB(≥ 4cm)-IIIA Neoadjuvanz	**CM-816, chirurgische Ergebnisse** neoadjuvant Nivolumab + Chemotherapie vs Chemotherapie	47

Thank you !

www.thoraxchirurgie.uk-erlangen.de