

Case #2—Non-Small Cell Lung Cancer Stage IIIb

Paul Van Houtte, MD, PhD
Department Radiation Oncology
Institut Bordet
Brussels, Belgium

Do We Need Any Additional Tests ?

- **Positive PET-CT: False positive uptake due to inflammatory disease**
- **Mediastinoscopy or EBUS**
 - Depending on location of nodes
 - On the treatment strategy (neoadjuvant approach with a restaging)
 - On the local expertise
- **Brain imaging: MRI > CT**

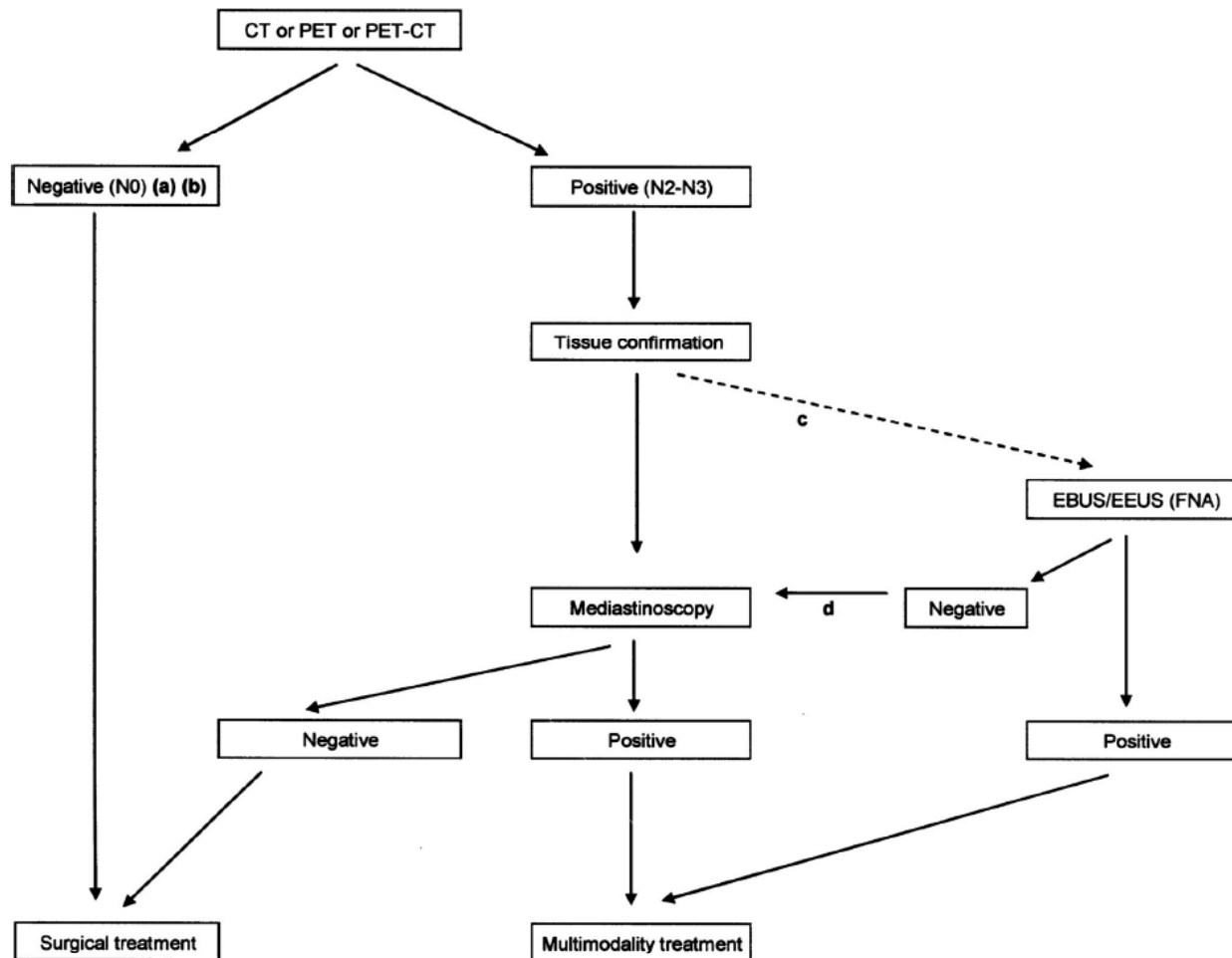
CT, computed tomography; EBUS, external beam ultrasound; MRI, magnetic resonance imaging; PET, positron emission tomography

Indication: Mediastinal Staging

- In patients with abnormal results of FDG-PET scanning, further evaluation of the mediastinum with sampling of the abnormal lymph node should be performed prior to surgical resection of the primary tumor. Level of evidence, fair; benefit, substantial; grade of evidence, B.

ACCP guidelines, 2003

ESTS Guidelines



- a : In central tumors, tumors with large LNs (= 1,6 cm) and/or PET N1 disease invasive staging remains indicated
- b : if no PET is available, mediastinoscopy is indicated except for T1N0 squamous cell carcinoma
- c : Endoscopic techniques are minimally invasive and can be the first choice
- d : Due to its higher NPV mediastinoscopy remains indicated

EUS : endoscopic esophageal ultrasound
EBUS : endobronchial ultrasound
NPV : negative predictive value

FIGURE 2. Proposed algorithm for mediastinal staging.

Access to Lymph Node Station

Station	Mediast Scopy	T.thorac FNA	T.bronch. FNA	Tesoph. FNA
1. Highest med.	Yes	Yes	No	No
2. Paratracheal	Yes	Yes	Yes	No
3. Prevascular retrotracheal	Yes No	Yes Yes	Yes No	No Yes
4. Lower paratracheal	Yes	Yes	Yes	No
5. AoP window	Difficult	Difficult	No	Difficult
6. Paraaortic	No	Yes	No	No
7. Subcarinal	Yes	Yes	Yes	Yes
8. Paraoesophageal	No	Yes	No	Yes
9. Pulmonary lig.	No	Yes	No	Yes

Detecting Brain Metastases in Locally Advanced, Resectable NSCLC (Stage IIIA)

Incidence: 3% to 8% of patients carry brain metastases, thus investigations are recommended:

- Specificity >99%, false positive < 1%**
- Sensitivity 95% for CT, 98% for MRI**
 - 5% false negative for CT,**
 - ~2% for MRI**

The TNM Staging

- Do you agree with the proposed staging?
- Right upper lobe T 2 cm
- Right lower lobe T 5 cm
- Mediastinoscopy 2R, 4R, 7 are positive
- T3N2M0 stage IIIb?
- Depending on the TNM classification

Recommendations: Additional Nodules

Reclassify T4 tumors by
**additional nodules in the
primary lobe as T3**

Reclassify M1 by additional
**nodules in a different
ipsilateral lobe as T4**

Australasian and
European data and
most databases, and
SEER

Revised TNM Subgroups

T and M		N0	N1	N2	N3
UICC descriptor	New T/M	stg	stg	stg	stg
T1 ≤2cm	T1a	Ia	Ia	IIa	IIIb
T1 > 2-3 cm	T1b	Ia	Ia	IIa	IIIb
T2 ≤ 5 cm	T2a	Ib	Ia	IIa	IIIb
T2 >5-7 cm	T2b	Ia	Ib	IIa	IIIb
T2 > 7 cm	T3	Ib	IIa	IIa	IIIb
T3 invasion		Ib	IIa	IIa	IIIb
T4 same lobe nodule		Ib	IIa	IIa	IIIb
T4 extension	T4	IIa	IIa	IIIb	IIIb
M1 ipsilat nodul	M1a	IIa	IIa	IIIb	IIIb
T4 pleural effusion		IV	IV	IV	IV
M1 contralateral lung		IV	IV	IV	IV
M1 distant	M1b	IV	IV	IV	IV

Old TNM stage IV or T2N2M1 New TNM stage IIIb T4N2M0

Stage III Disease

- **The major challenge due to the great range of disease presentations**
- **The wide range of treatment possibilities:**
 - **From curative treatment to best supportive care**
 - **From single modality to trimodalities**
 - **Require a multidisciplinary approach in most cases**

IASLC Vancouver-Frisco Interactive Session

You Recommend for a T2N2

	2003	2009
Proceed to surgical resection	7%	14%
Preoperative chemotherapy	35%	25%
Preoperative chemoradiotherapy	22%	21%
Sequential chemotherapy followed by radiotherapy (without surgery)	8%	3%
Concurrent chemoradiotherapy (without surgery)	28%	37%

III (pN2) Disease Is Heterogeneous

One Proposed Subset Classification

- **N2(1)**: Incidental nodal metastases found on final pathologic examination of the resection specimen
- **N2(2)**: Nodal metastases recognized only intraoperatively
- **N2(3)**: Nodal metastases, single or multistation, recognized on prethoractomy staging (potentially resectable)
- **N2(4)**: Bulky or fixed multistation disease

Consensus Predictors of Long-term Survival Induction Followed by Surgery Trials

Important Predictors

- Nodal downstaging to N0
- Pathologic CR
- Complete resection
- T4N0-1
- LDH, female (not all trials)

Not Significant

- IIIA(N2) versus IIIB
- Response to induction on CT scan
- Histology

BUT... there are no consensus predictors at diagnosis of who might benefit from surgical resection after chemoRT

Induction→S for Stage III Disease: Phase II Trial Summary

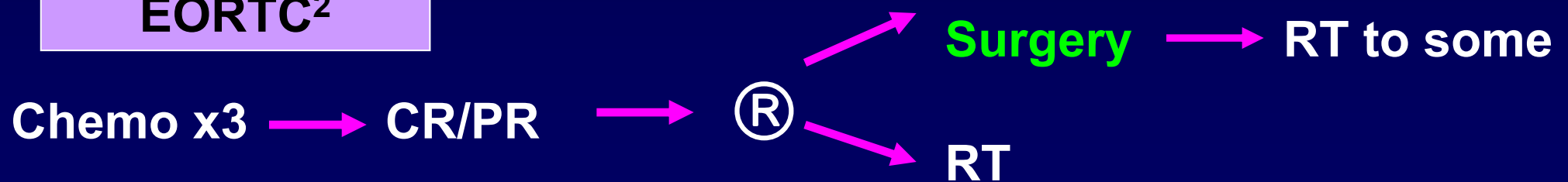
Variable	Chemotherapy	Chemoradiotherapy
Toxicity	Pneumonitis (drug dependent)	Higher rates of esophagitis and postop ARDS
Radiographic response rate	30% to 60+%	40% to 75%
pCR	≤10%	20% to 30%
Nodal downstaging	Downstaging to N0 less frequent	Higher rate pN0 (correlates with ↑ survival)

Intergroup and EORTC Phase III Trials IIIA(pN2) NSCLC

Intergroup¹



EORTC²



Difference in MS can't be explained by later (R) in EORTC, since denominator not included in the randomization; instead most likely due to lack of concurrent chemoRT, more advanced disease

RANDOMIZED TRIALS PATHOL. STAGE IIIa “Radiotherapy vs Surgery”

Trial	Treatment	Patients	Median Survival, Months	5-Yr Survival %
Intergroup ¹	R+C → S → C	202	23.6	27.2
	R+C → C	194	22.2	20.3
EORTC ²	C → Resp → R	165	17.5	14
	→ S	167	16.4	15.7
RTOG	C → R S	45		



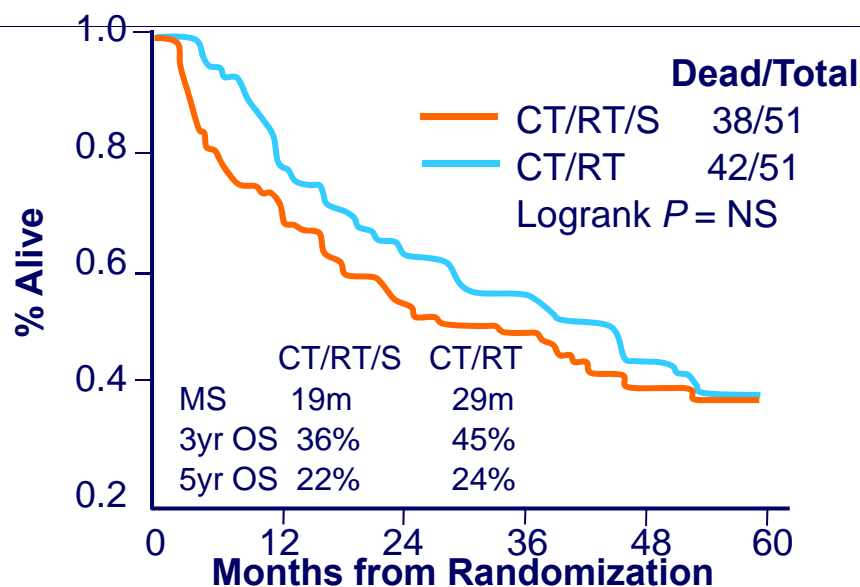
No statistical difference in survival

1. Albain KS, et al. *J Clin Oncol.* 2005;23(16S): Abstract 7014. 2. van Meerbeeck JP, et al. *J Natl Cancer Inst.* 2007;99 (6):442-450. 3.

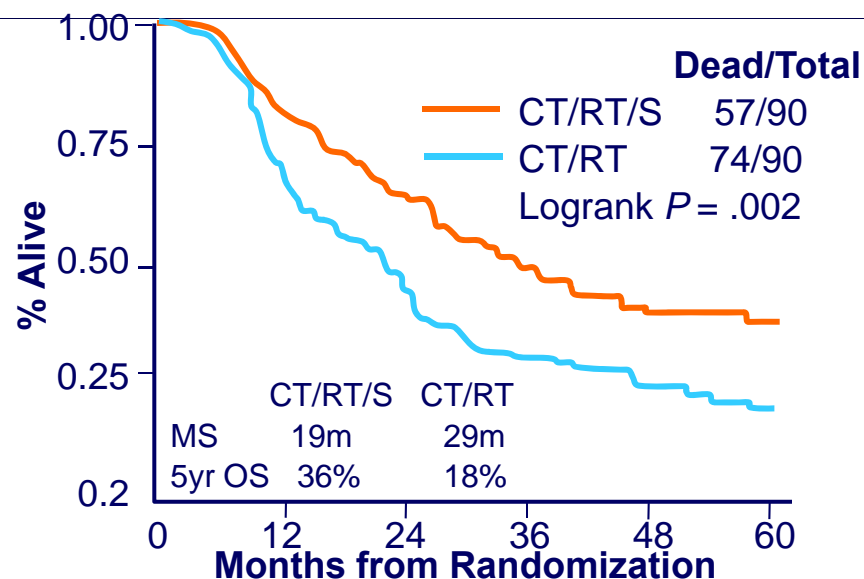
EXPLORATORY ANALYSIS

Intergroup Trial Surgery vs Radiochemotherapy

OVERALL SURVIVAL OF
PNEUMONECTOMY SUBSET VS
MATCHED CT/RT SUBSET



OVERALL SURVIVAL OF
LOBECTOMY SUBSET VS
MATCHED CT/RT SUBSET



Induction Treatment for NSCLC IIIa/b GLCCG Randomized Trial

	DDP-VP16 x3 Surgery Postop RT	DDP-VP16 x3 RT + Carbo-VDS Surgery
N patients	260	264
Surgery	154	142
Complete resection RO	84	98
Downstaging mediastinal N0	24 17	45 59
RC pathologic		
Survival without disease	10 m	9.5 m
Median	16 %	14 %
5 years		

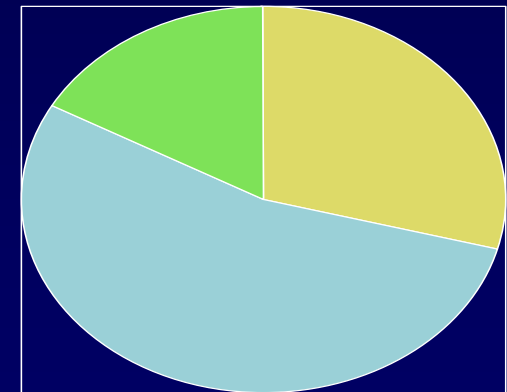
Induction Chemotherapy for Stage IIIApN2 with 59 Months Follow-Up

- 3 cycles of docetaxel and cisplatin
- Surgery
- Postop RT if R1-2 resection
- 90 patients
- 75 tumor resection
- R0 resection in 57 %
- Local relapse: 60 %

Factors :

- RO resection
- Chemotherapy efficacy

First documented site relapse



■ local ■ distant ■ both

→ *Radiotherapy?*

Decision Making in Radiotherapy for NSCLC

Factors to Take into Consideration

- Tumor (T,N,M) but also

Extent

Volume

Localization

- *Patient*

Performance status

Comorbidity

Weight loss

- *Radiation parameters*

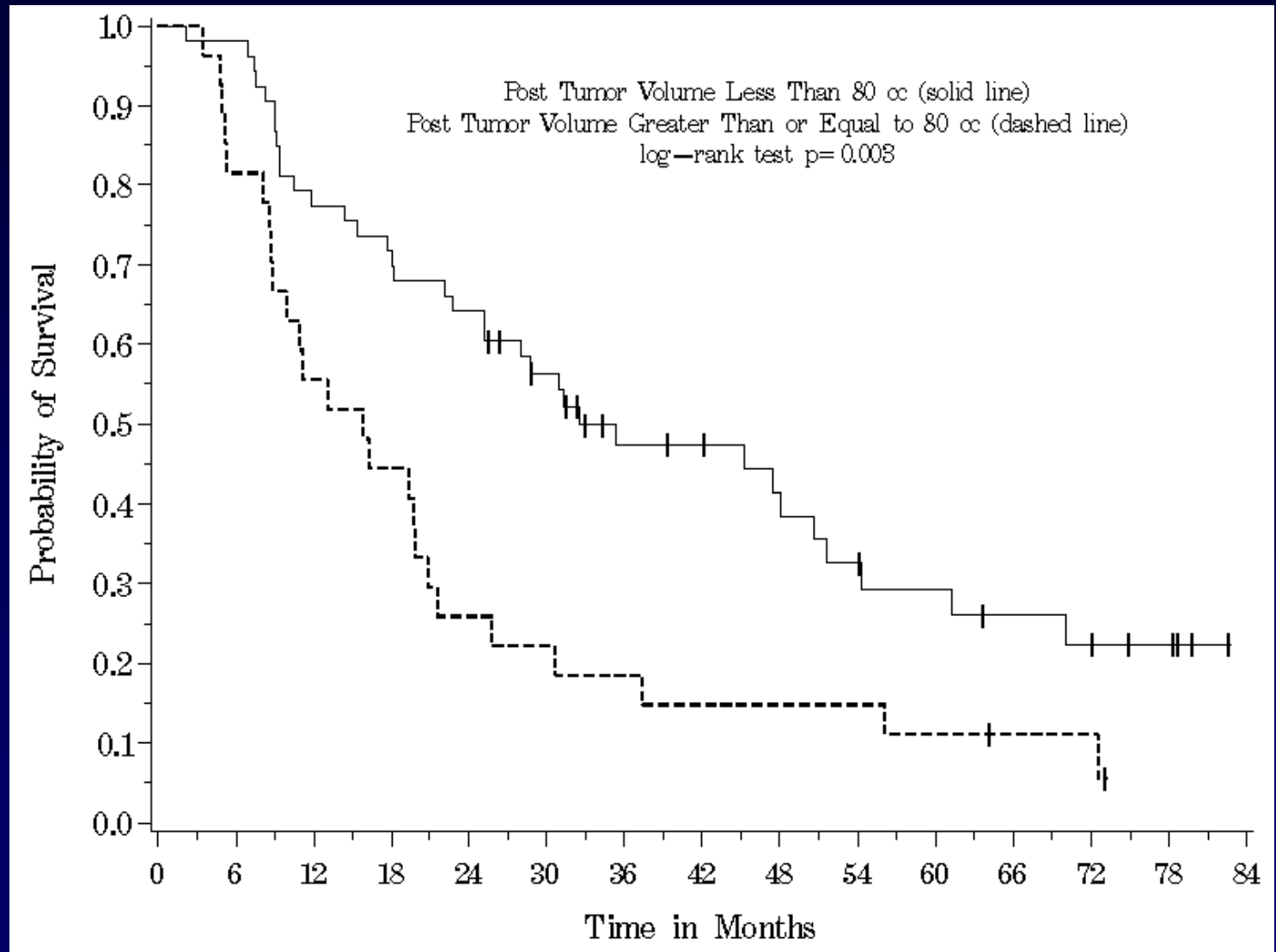
Dose constraints due normal tissue tolerance...

Post-Induction Gross Tumor Volume—UNC Experience. Rationale for the Induction Approach

102 stage III patients receiving induction chemo followed by TCRT >70 Gy

Volumes defined by 3-D plan both pre-induction and post-induction chemo

Post-induction GTV predictive of survival



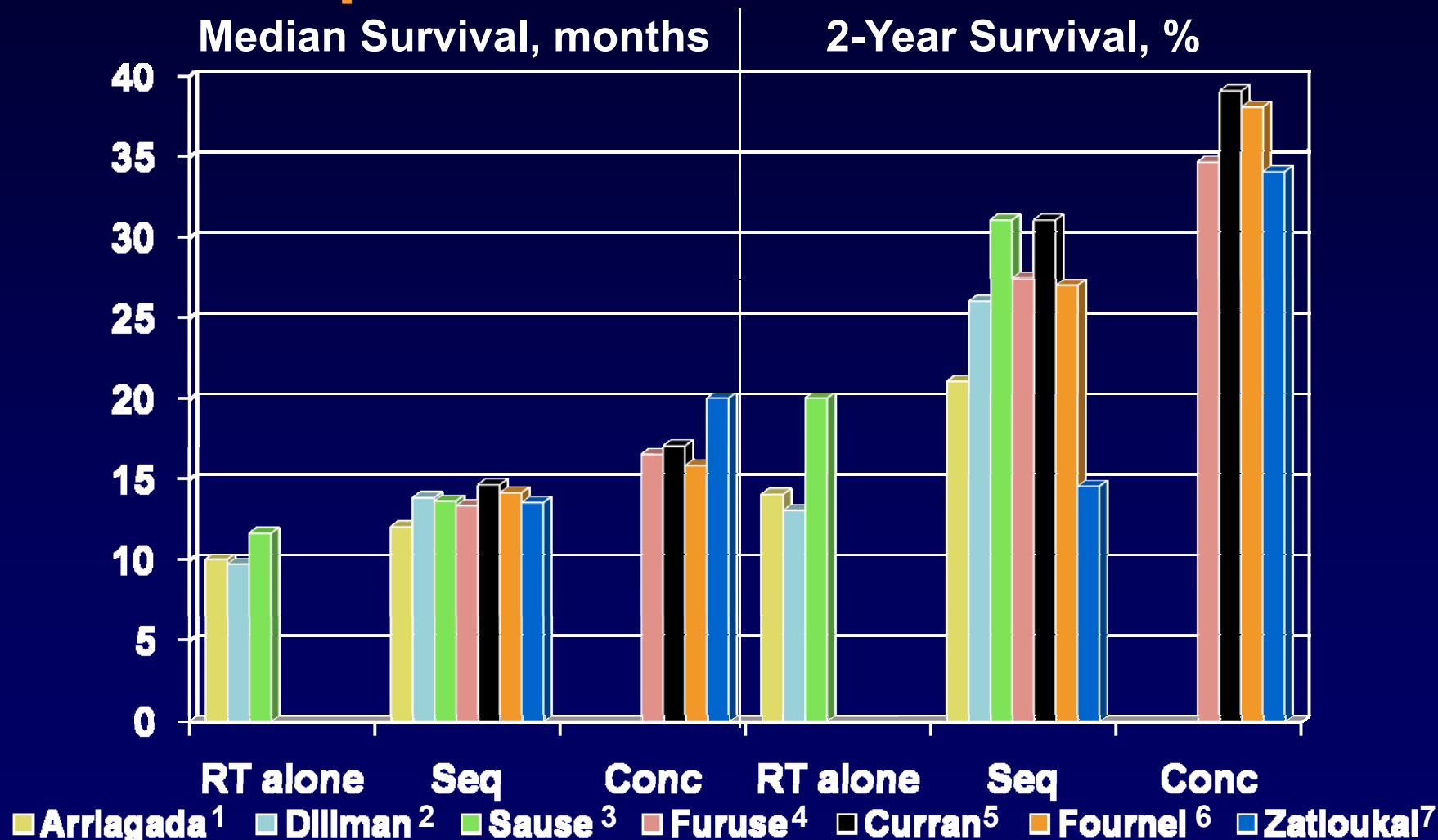
Concurrent Chemoradiotherapy

versus

**Sequential Chemotherapy →
Radiotherapy**

RADIOCHEMOTHERAPY LUNG CANCER

RT vs Sequential vs Concurrent CT-RT Trials

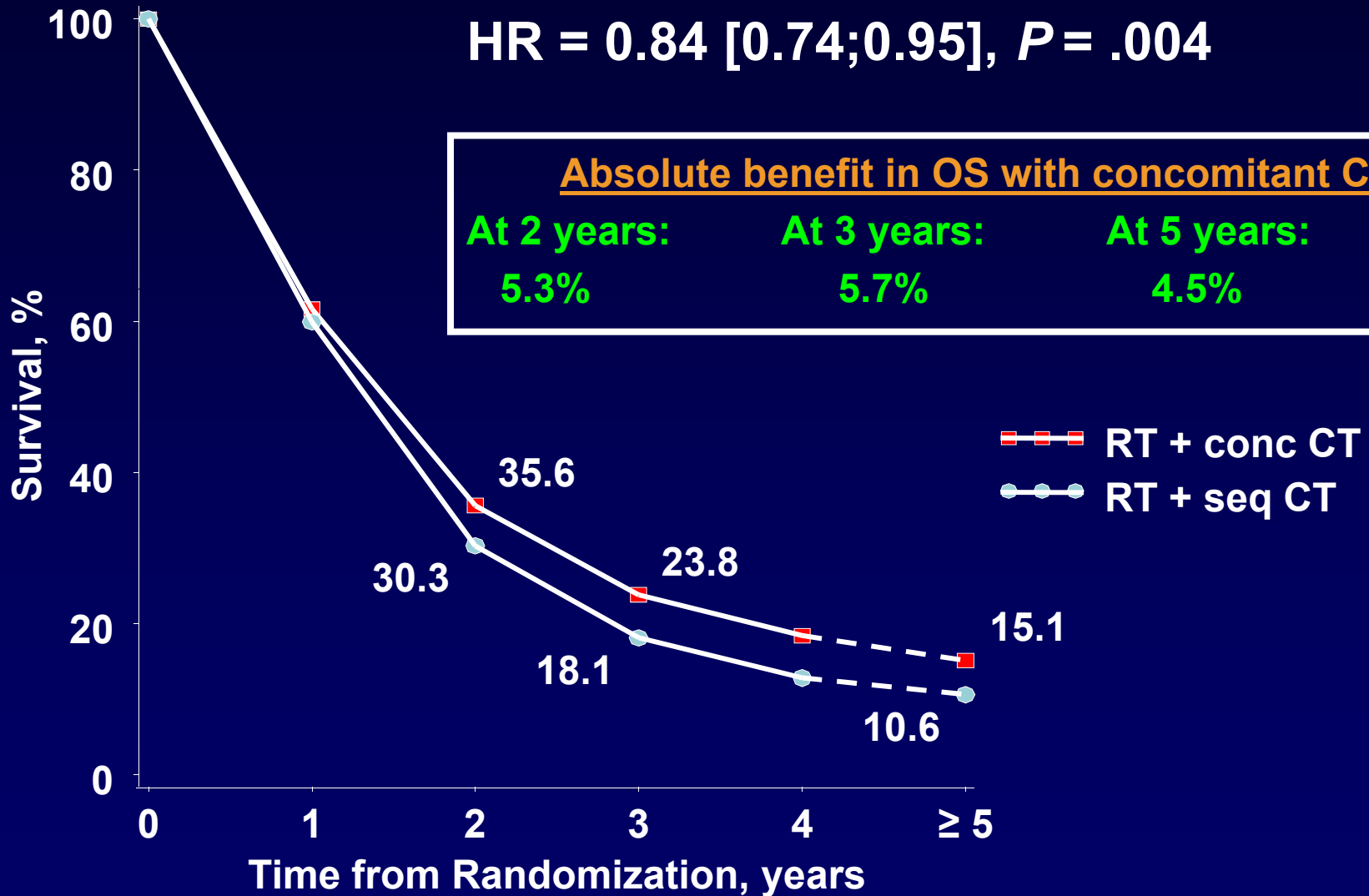


1. Le Chevalier T, et al. *J Natl Cancer Inst.* 1991;83(6):417-423. 2. Dillman RO, et al. *N Engl J Med.* 1990;323(14):940-945. 3. Sause W, et al. *Chest.* 2000;117(2):358-364. 4. Furuse K, et al. *J Clin Oncol.* 1999;17(9):2692-2699. 5. Curran W Jr, et al. *Proc Am Soc Clin Oncol.* 2000;19: Abstract 1891. 6. Fournel P, et al. *J Clin Oncol.* 2005;23(25):5910-5917. 7. Zatloukal P, et al. *Lung Cancer.* 2004;46(1):87-98.

**Concomitant Radio-Chemotherapy (RT-CT) Versus
Sequential RT-CT in Locally Advanced Non-Small Cell
Lung Cancer (NSCLC):
A Meta-Analysis Using Individual Patient Data From
Randomised Clinical Trials**

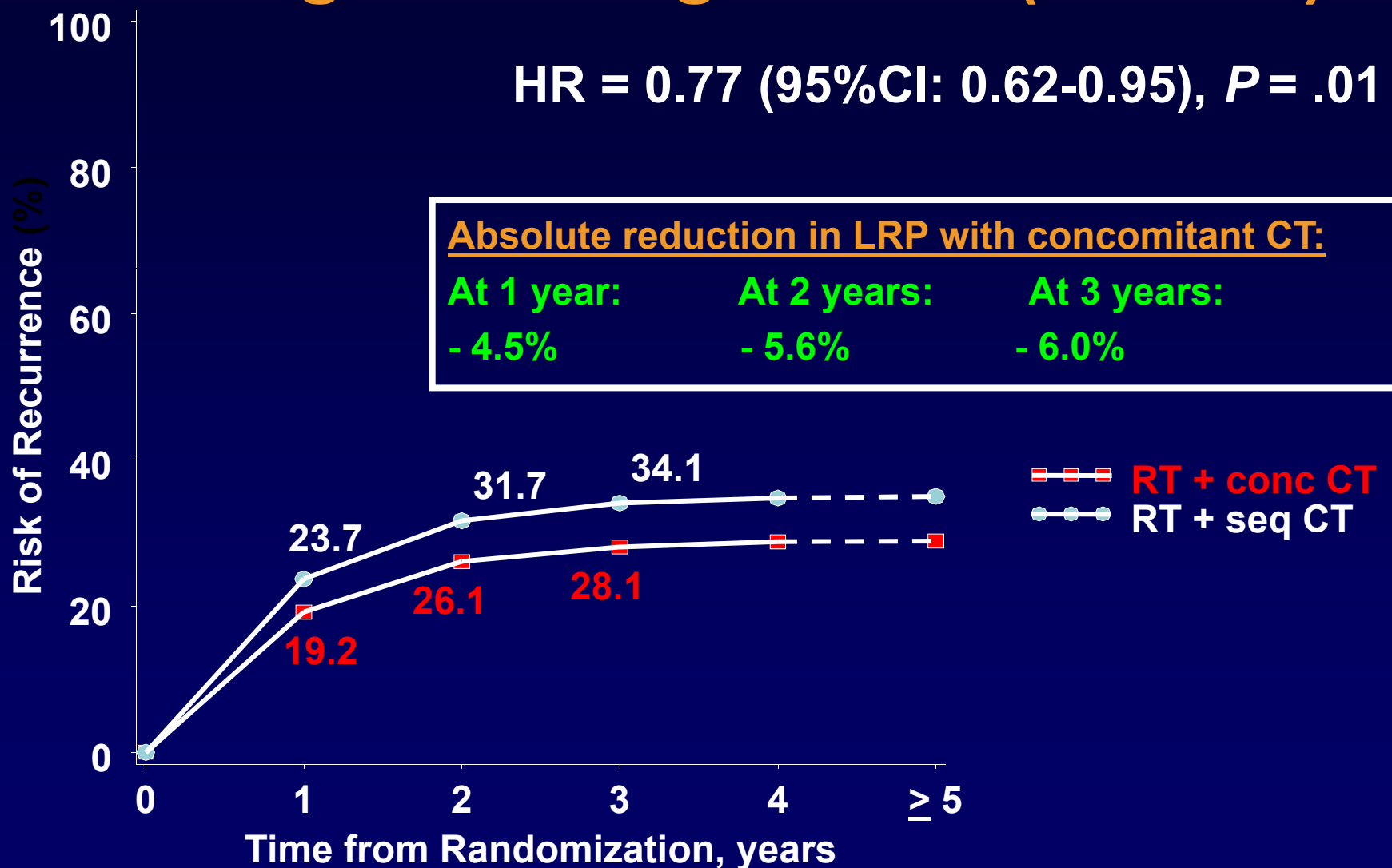
**Auperin A, Rolland E, Curran WJ, Furuse K, Fournel P,
Belderbos J, Clamon G, Ulutin HC, Stewart L, Le Pechoux
C, on behalf of the NSCLC Collaborative Group**

Meta-Analysis Overall Survival



Cumulative Incidence of Locoregional Progression (5 Trials)

HR = 0.77 (95%CI: 0.62-0.95), P = .01

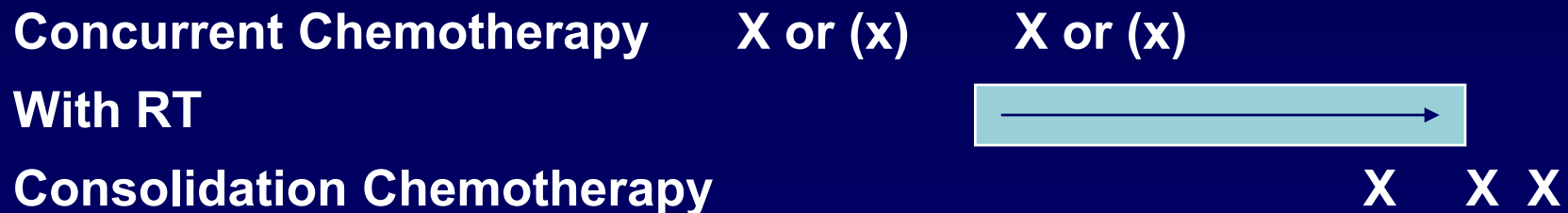


Designs for Optimal Chemoradiotherapy?

Induction Chemotherapy → Concurrent ChemoRT



Concurrent ChemoRT → Consolidation Chemotherapy



X: full dose; (x): reduced dose

ECLWP PROTOCOL for NSCLC Induction vs Adjuvant Chemotherapy

	Adjuvant CT		Induction CT	
	CT-RT	CT	CT	CT-RT
N	21		28	
Whole treatment	67%		86%	
CT dose intensity	63%		79%	
Response rate	57%		79%	
Median survival	17 months		24 months	
2-year survival	38%		50%	

The Role of Docetaxel as Maintenance After CT-RT The HOG LUN 01-24/USO-23 Trial

DDP 50 mg/m² IV days 1, 8, 29, 36
Etoposide 50 mg/m² IV days 1-5, 29-33
RT 59.4 Gy 203 patients

No Prog.

Observation 74 p

R

Docetaxel 73 p
75 mg/m² x 3 q3weeks

	Observation	Docetaxel
Toxicity >G2		
Hosp.	8%	29%
Toxic death		5%
Febrile neutr.		11%
Pneum.		9.6%
Results		
PFS	12.9	12.3
MST	23.2	21.2

Chemoradiotherapy for NSCLC Questions

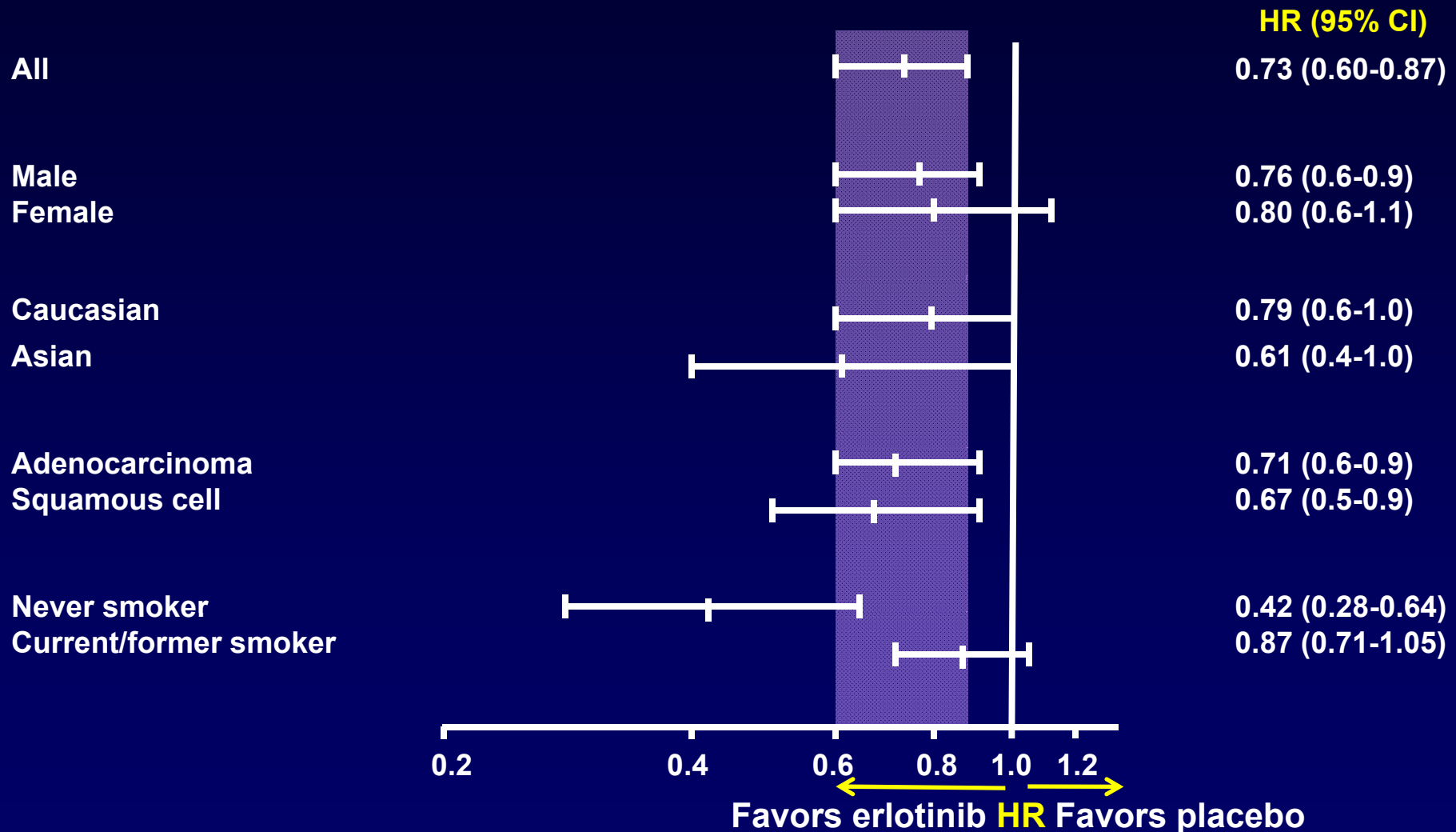
- **Should the chemotherapy be adapted to pathology**
- **Is there a place of for targeted agents**
- **What is the place of maintenance (chemo or ...)**
- **Should PCI be considered**

- **Current trials are ongoing to answer those questions**

Second-Line Treatment

- Be sure there is a tumor progression and not a RT induced lung damage
- Should patient with a performance status 2 (PS2) be treated?
- Better than Best Supportive Care
- 4 drugs demonstrated their efficacy:
 - Docetaxel
 - Pemetrexed
 - Erlotinib
 - Gefitinib
- How to select a drug based on efficacy or toxicity profile?

Patient Subgroups and OS Benefit BR.21 Study



Second-Line Study of Pemetrexed vs Docetaxel: Efficacy by Histology

	Nonsquamous Group		Squamous	
	Pemetrexed (n = 205)	Docetaxel (n = 194)	Pemetrexed (n = 78)	Docetaxel (n = 94)
% ECOG PS 2	12.5	10.1	8.3	17.4
% TSPC <3 months	51.0	51.0	48.7	41.9
% Stage IV	81.5	78.9	57.7	66.0
% Male	60.5	69.1	89.7	88.3
Median OS, months	9.3	8.0	6.2	7.4
Adjusted OS HR (95% CI)	0.778 (0.607, 0.997)		1.563 (1.079, 2.264)	
Median PFS, months	3.1	3.0	2.3	2.7
Adjusted PFS HR (95% CI)	0.823 (0.664, 1.020)		1.403 (1.006, 1.957)	

Treatment by histology interaction: Survival adjusted for cofactors ($P = .001$)