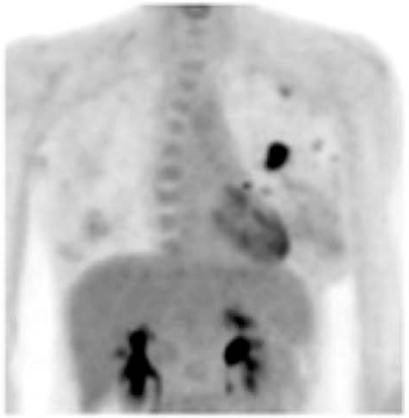
Case #1—Stage IIIA NSCLC: A Multidisciplinary Treatment Approach

Part III

Umberto Ricardi, MD, PhD
University of Turin
Turin, Italy

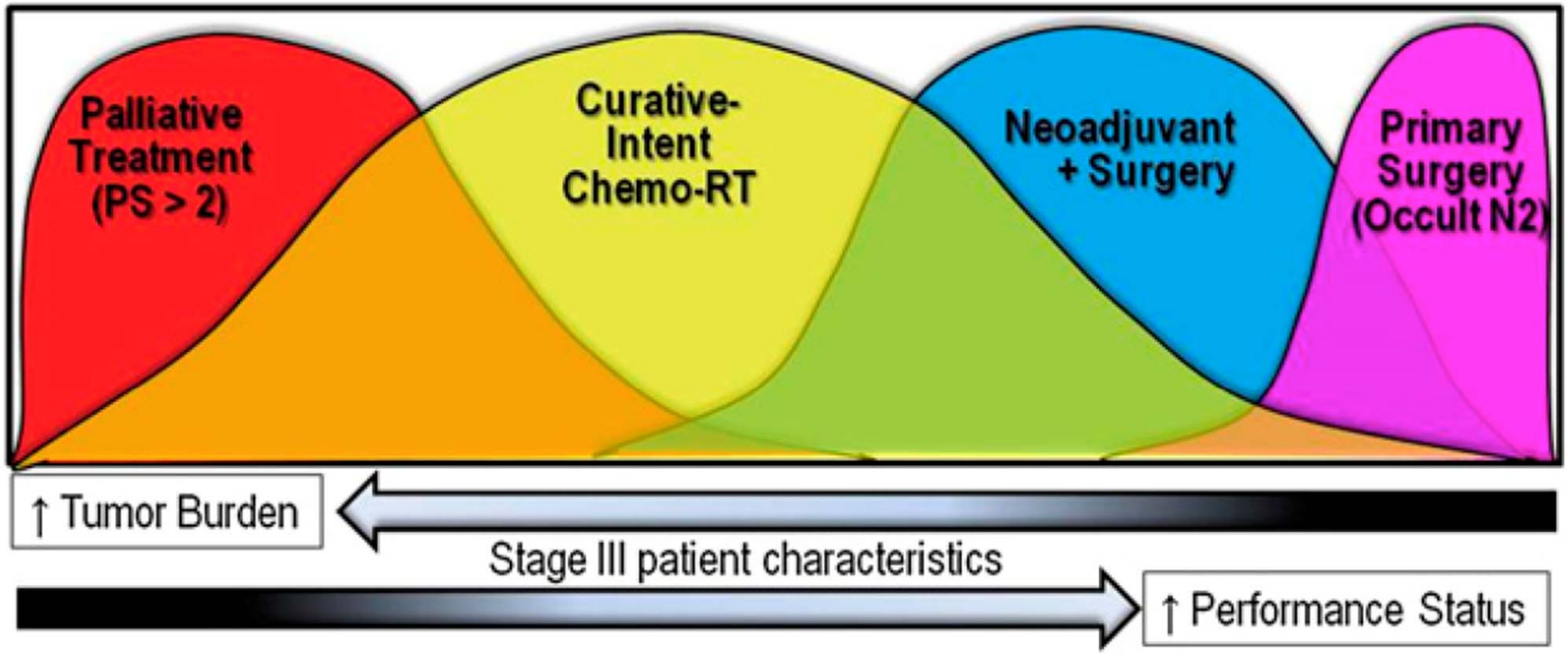
Mediastinal Infiltration

Discrete node enlargement



Clinically occult N2

Schematic of types of patients included in studies using different treatment approaches



Good PS Stage III NSCLC
What Positive Level 1 Evidence Do We Have?

- Chemo-RT:
  - Better survival than RT alone
- Concurrent chemo-RT:
  - Better survival than sequential chemo-RT

RT, radiation therapy

VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

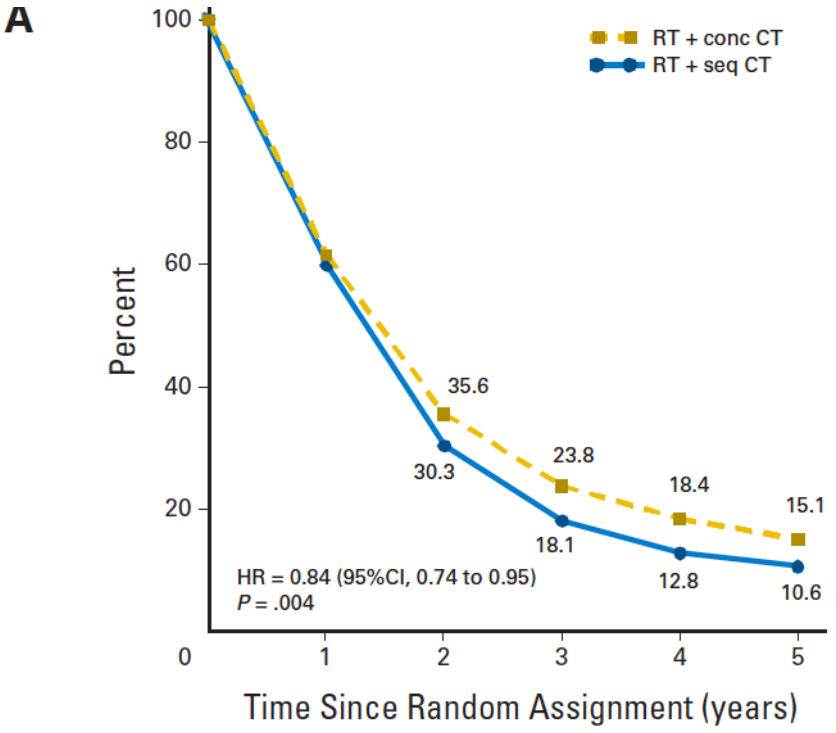
ORIGINAL REPORT

Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

Absolute survival benefit with concomitant chemoradiotherapy:

- **5.7% at 3 years**
- **4.5% at 5 years**



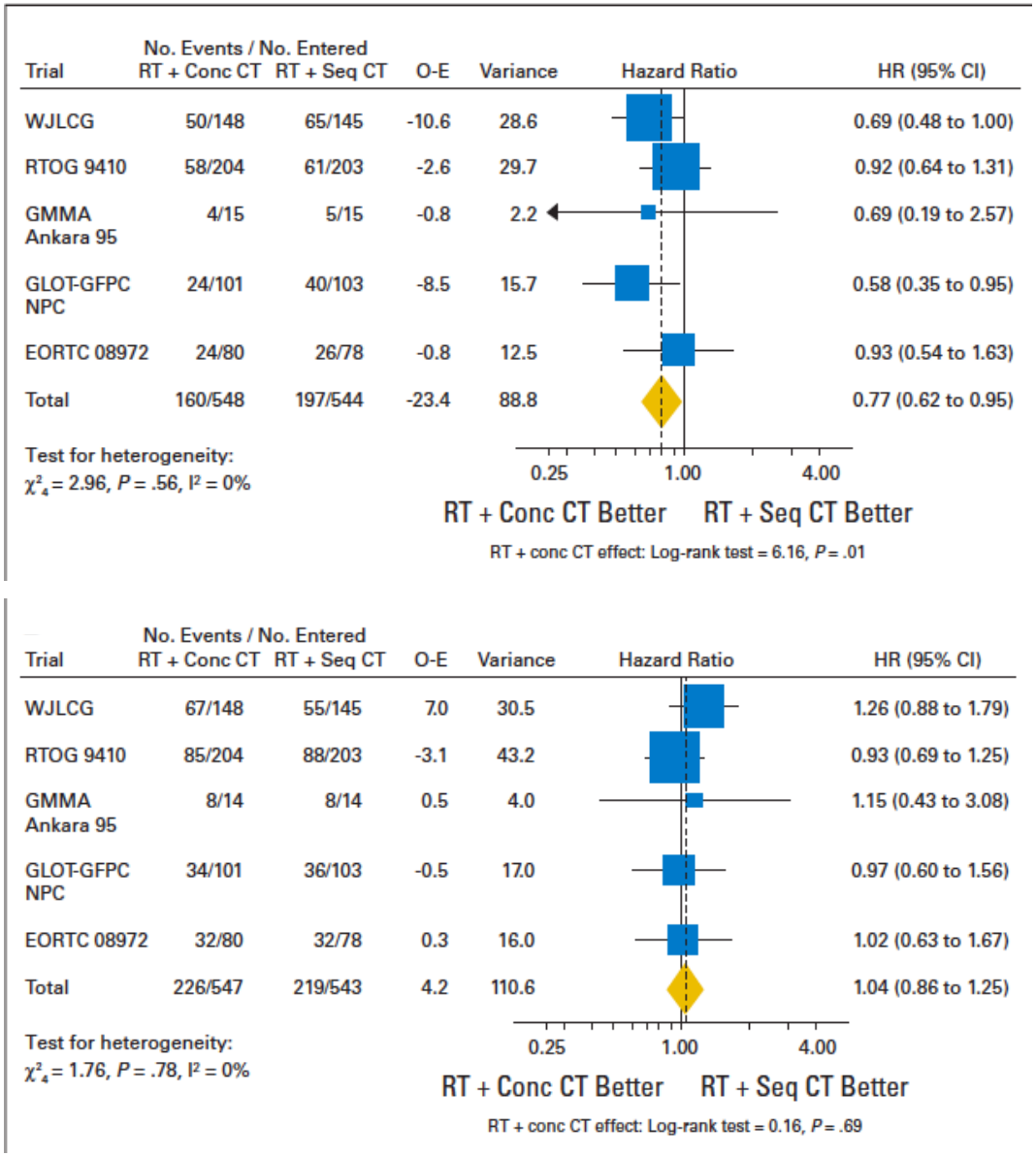
Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

CI, confidence interval; CT, chemotherapy; HR, hazard ratio

Aupérin A, et al. *J Clin Oncol.* 2010;28(13):2181-2190.

Hazard Ratio Plots for Local Progression and Distant Progression



Aupérin A, et al. *J Clin Oncol.* 2010;28(13):2181-2190

VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Results

Of seven eligible trials, data from six trials were received (1,205 patients, 92% of all randomly assigned patients). Median follow-up was 6 years. There was a significant benefit of concomitant radiochemotherapy on overall survival (HR, 0.84; 95% CI, 0.74 to 0.95; $P = .004$), with an absolute benefit of 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years. For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; $P = .07$). Concomitant treatment decreased locoregional progression (HR, 0.77; 95% CI, 0.62 to 0.95; $P = .01$); its effect was not different from that of sequential treatment on distant progression (HR, 1.04; 95% CI, 0.86 to 1.25; $P = .69$). Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; $P < .001$). There was no significant difference regarding acute pulmonary toxicity.

Aupérin A, et al. *J Clin Oncol.* 2010;28(13):2181-2190.

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi89–vi98, 2013
doi:10.1093/annonc/mdt241
Published online 16 July 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

- The preferred treatment of unresectable LA-NSCLC is definitive concurrent chemotherapy and radiotherapy [I, A]
- Definitive thoracic radiotherapy should be no less than the biological equivalent of 60 Gy in 2.0 Gy fractions [I, A]
- In patients who are unfit to receive concurrent chemotherapy and radiotherapy, the sequential approach should be offered as an alternative treatment with curative intent [I, A]

LA, long acting

Vansteenkiste J, et al. *Ann Oncol.* 2013;24 Suppl 6:vi89-vi98.

Concurrent CT-RT Is Not the Standard Treatment in Locally Advanced NSCLC, Unless Treating Only:

Highly “FIT” patients

- Age
- Performance status
- Weight loss
- Pulmonary function tests
- Stage/tumor burden
- Dose to critical organs

EDITORIAL

Dutch Statistics on Lung Cancer

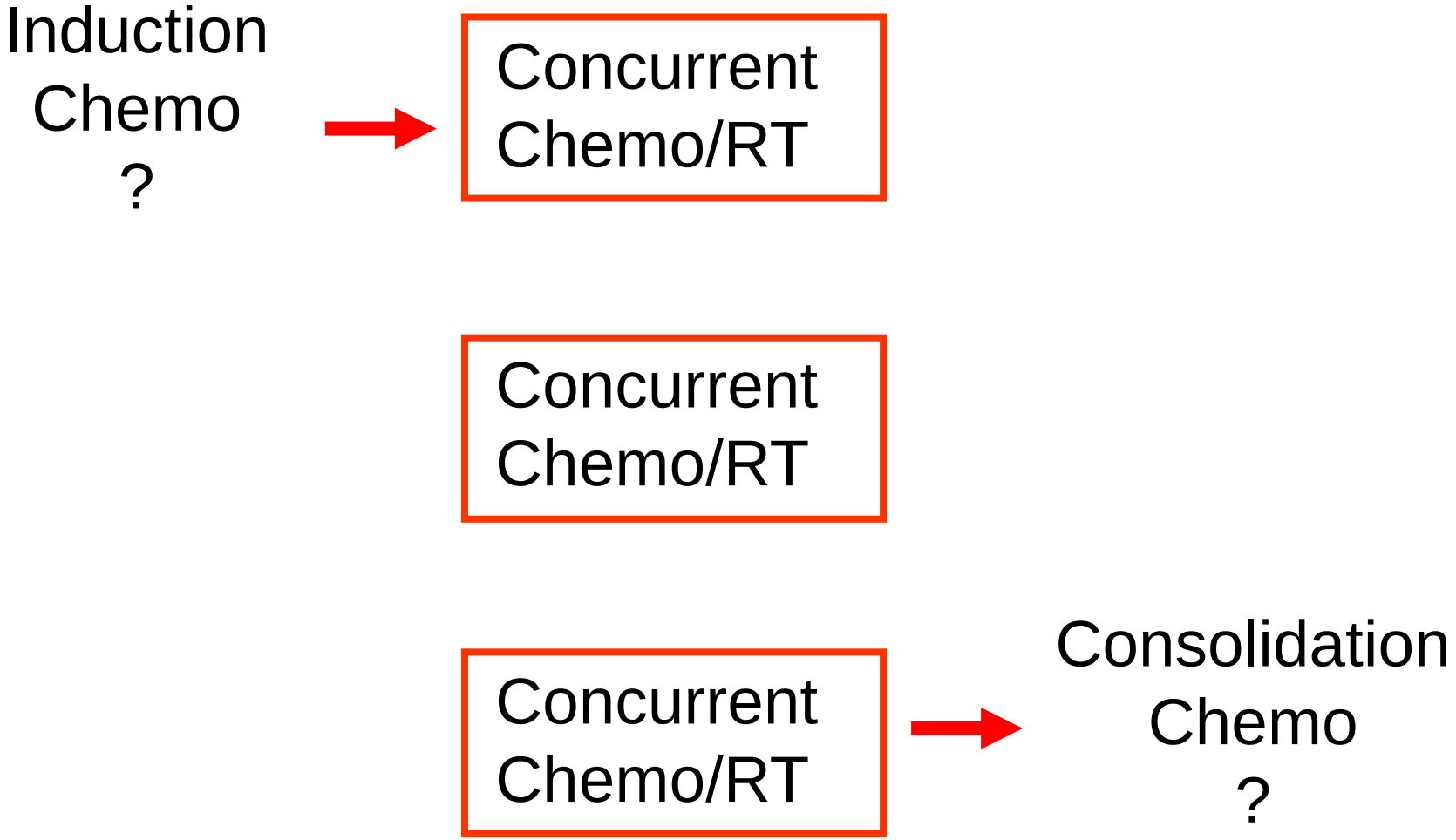
Sobering Experience for a New Approach

Matjaz Zwitter, MD, PhD

- Half of patients with NSCLC did not receive treatment according to the well accepted guidelines
- EBM is based on selected series of patients and is not applicable to an average patient in clinical practice
- Stage III NSCLC: The gap between an ideal patient from the guidelines and the average patient from clinical practice is especially wide
- Vast majority of patients present bulky tumors and/or suffer from significant comorbidity

Zwitter M. *J Thorac Oncol.* 2012;7(2):269-271.

Current Standard
Concurrent Chemoradiotherapy



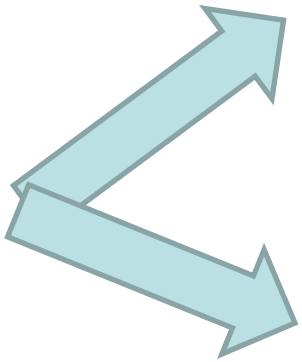
Good PS Stage III NSCLC: What Negative/Null Evidence Do We Have?

- Induction chemotherapy
  - No advantage when added to concurrent chemo-RT
- Consolidation chemotherapy
  - No advantage when added to concurrent chemo-RT

TKI, tyrosine kinase inhibitor

CALGB 39801: Trial Design

R E G I S T E R



A (Concurrent Chemo/RT)

Paclitaxel 50 mg/m^2 IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total)

B (Induction→ Concurrent Chemo/RT)

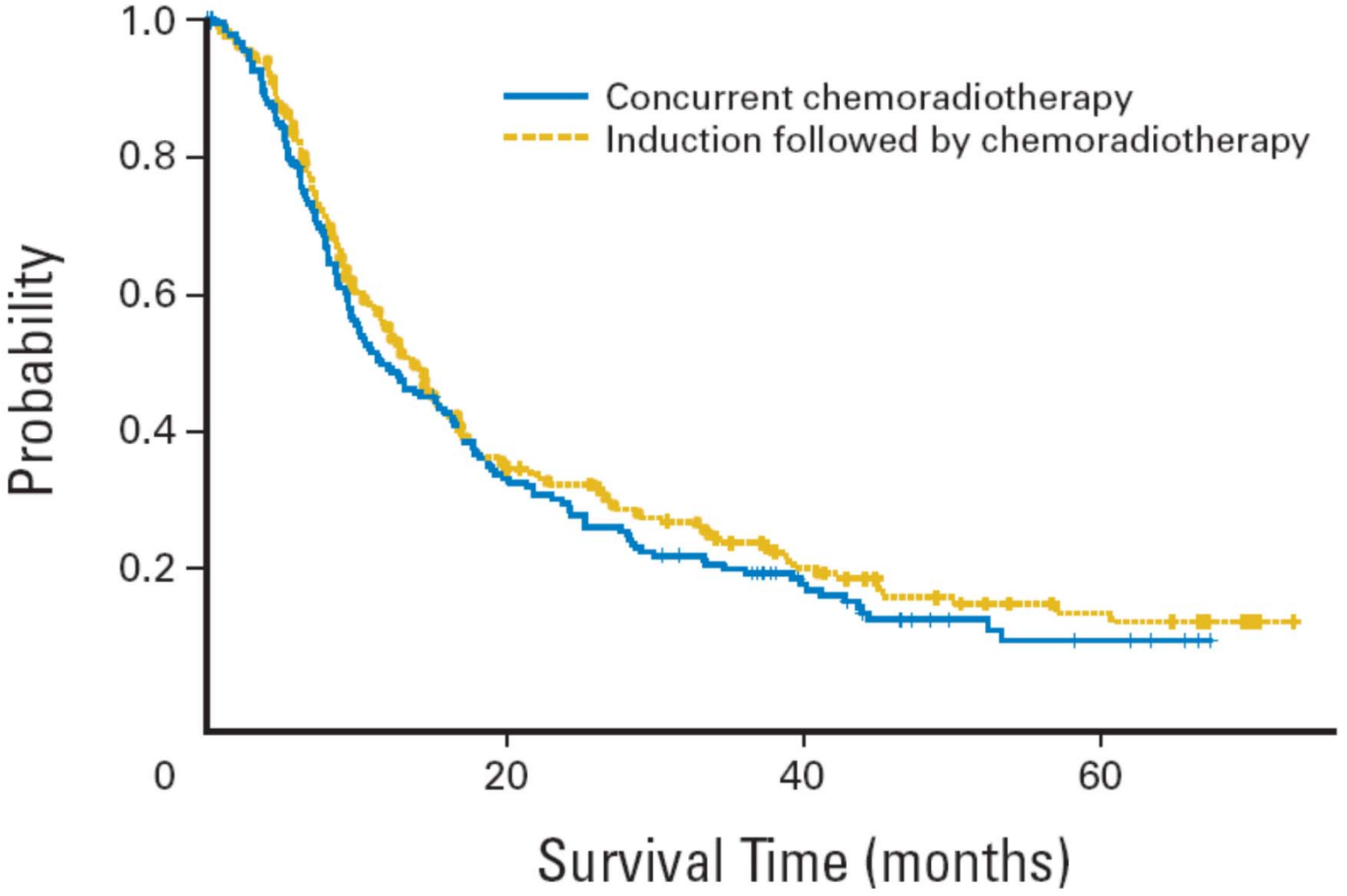
Paclitaxel 200 mg/m^2 IV/3h
Carboplatin AUC 6 IV/30 min
q 21 days for a total of 2 cycles

Paclitaxel 50 mg/m^2 IV/1h/week
Carboplatin AUC 2 IV/30 min/wk
XRT 6600 cGy (total) (d 43)

AUC, area under the curve

Vokes EE, et al. *J Clin Oncol.* 2007;25(13):1698-1704.

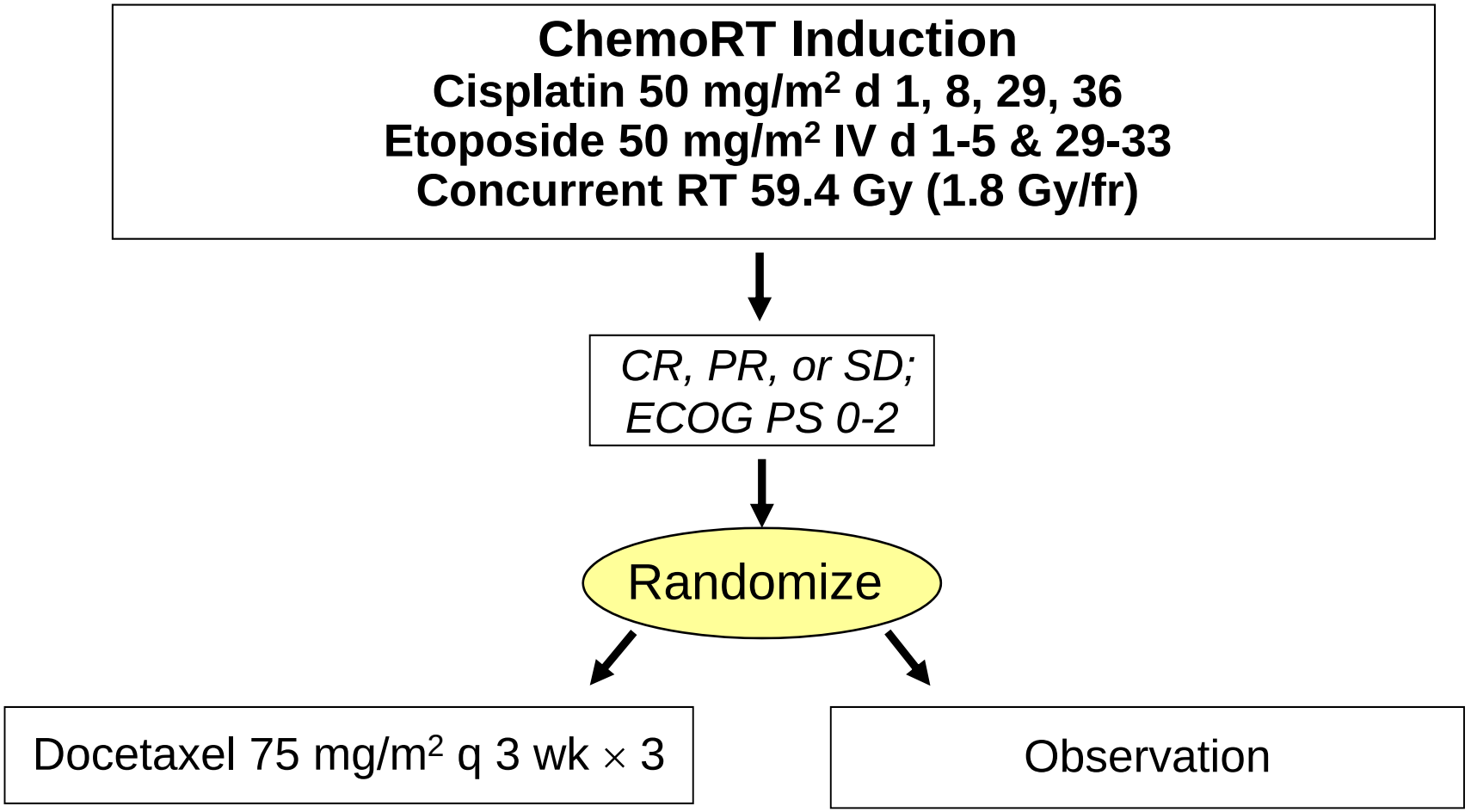
CALGB 39801: Overall Survival (OS)
Intent-to-Treat (ITT)



ITT, intent-to-treat

Vokes EE, et al. *J Clin Oncol.* 2007;25(13):1698-1704.

Optimizing Chemotherapy: Confirmation Study for Consolidation Hoosier Oncology Group (LUN 01-24)

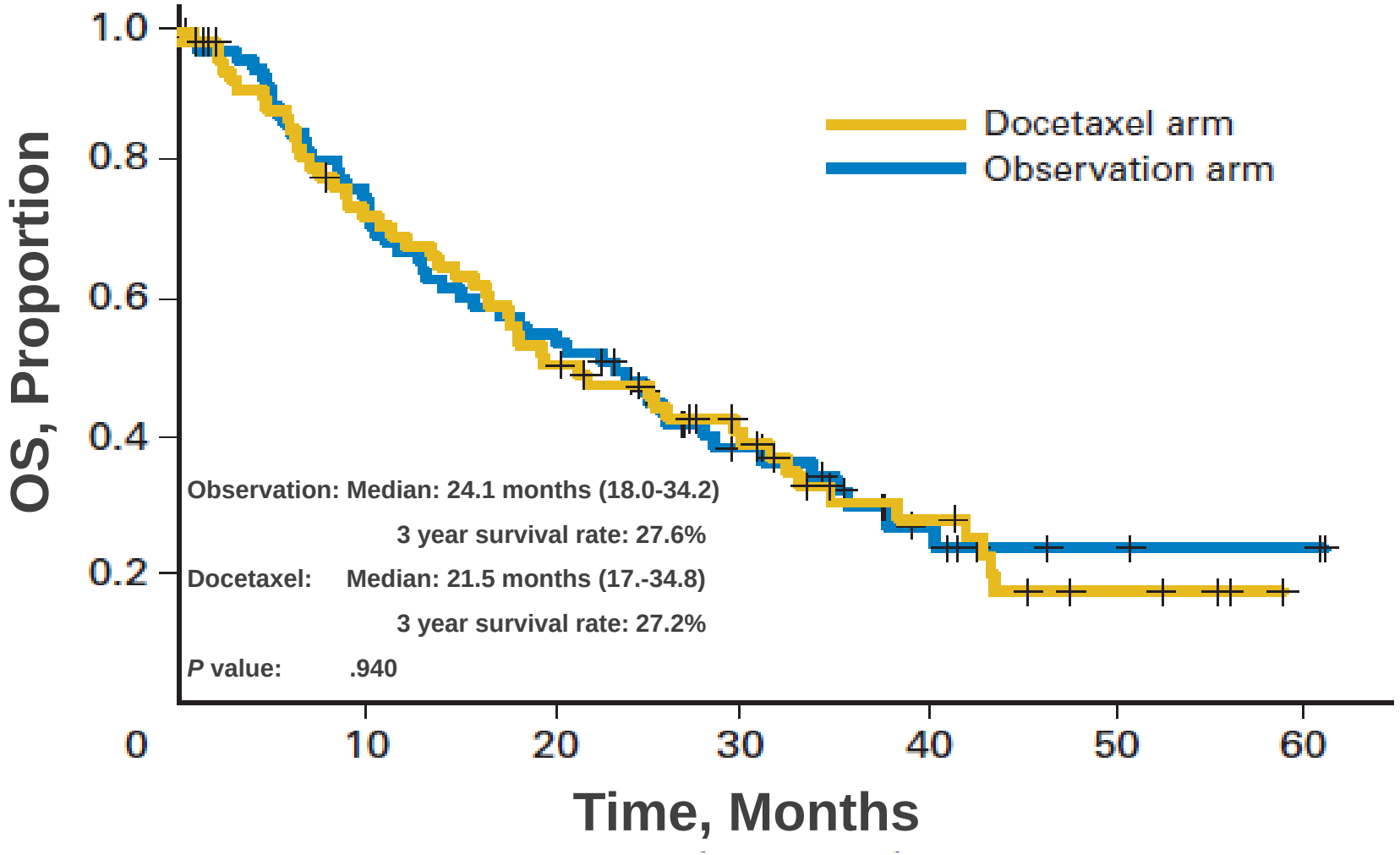


CR, complete response; PR, partial response; SD, stable disease

Hanna N, et al. *J Clin Oncol.* 2008;26(35):5755-5760.

LUN 01-24: OS (ITT)

Randomized Patients (n = 147)



Hanna N, et al. *J Clin Oncol.* 2008;26(35):5755-5760.

Treatment Algorithm For Locally Advanced NSCLC: 2014

Locally Advanced Stage NSCLC & PS 0-1

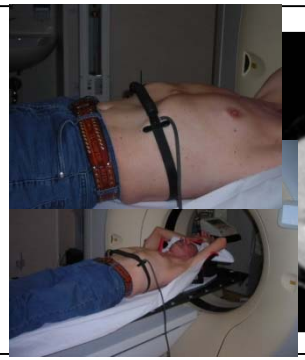
Unresectable Stage III NSCLC
Optimal Radiation Dose

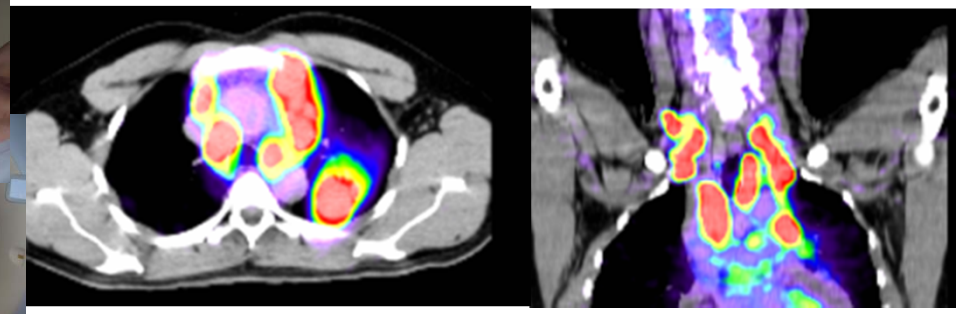
- **Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemoradiation**

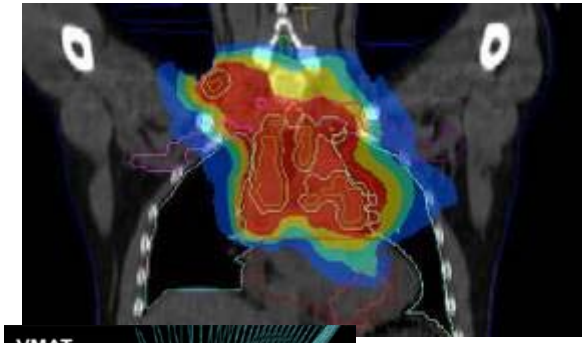
Image Guided, PET-Assisted Radiotherapy of Lung Cancer

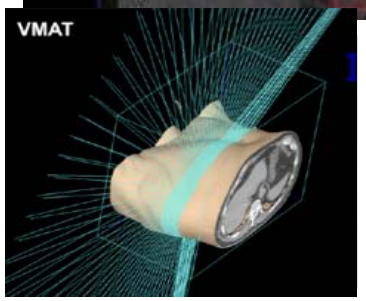
Target Volume Reduction and RT-Optimization for Critical Tumor-to-Lung Ratio

1. **Use of 4D-CT**: Accounting for tumor motion during breathing
2. **CTV-Definition**: Minimization based on functional Imaging (PET-CT) and shift to smaller volumes

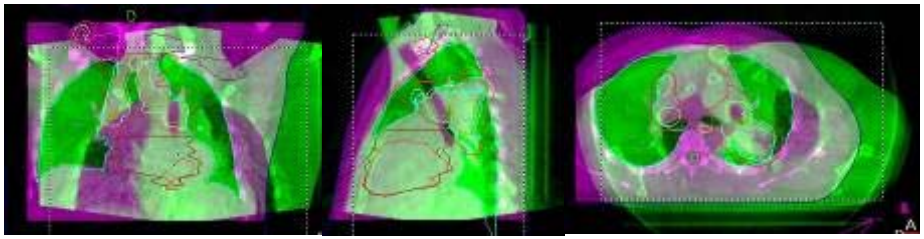




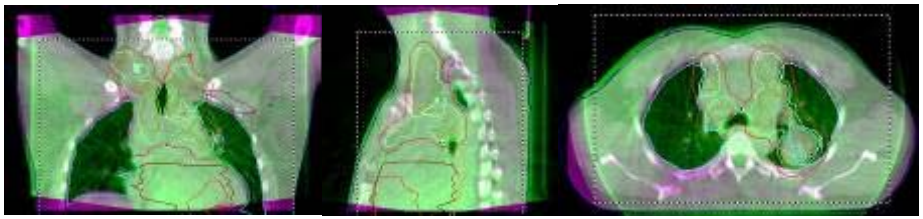




2. Treatment Planning as IMRT based on Monte-Carlo dose calculation (dose-painting)



Suboptimal Positioning

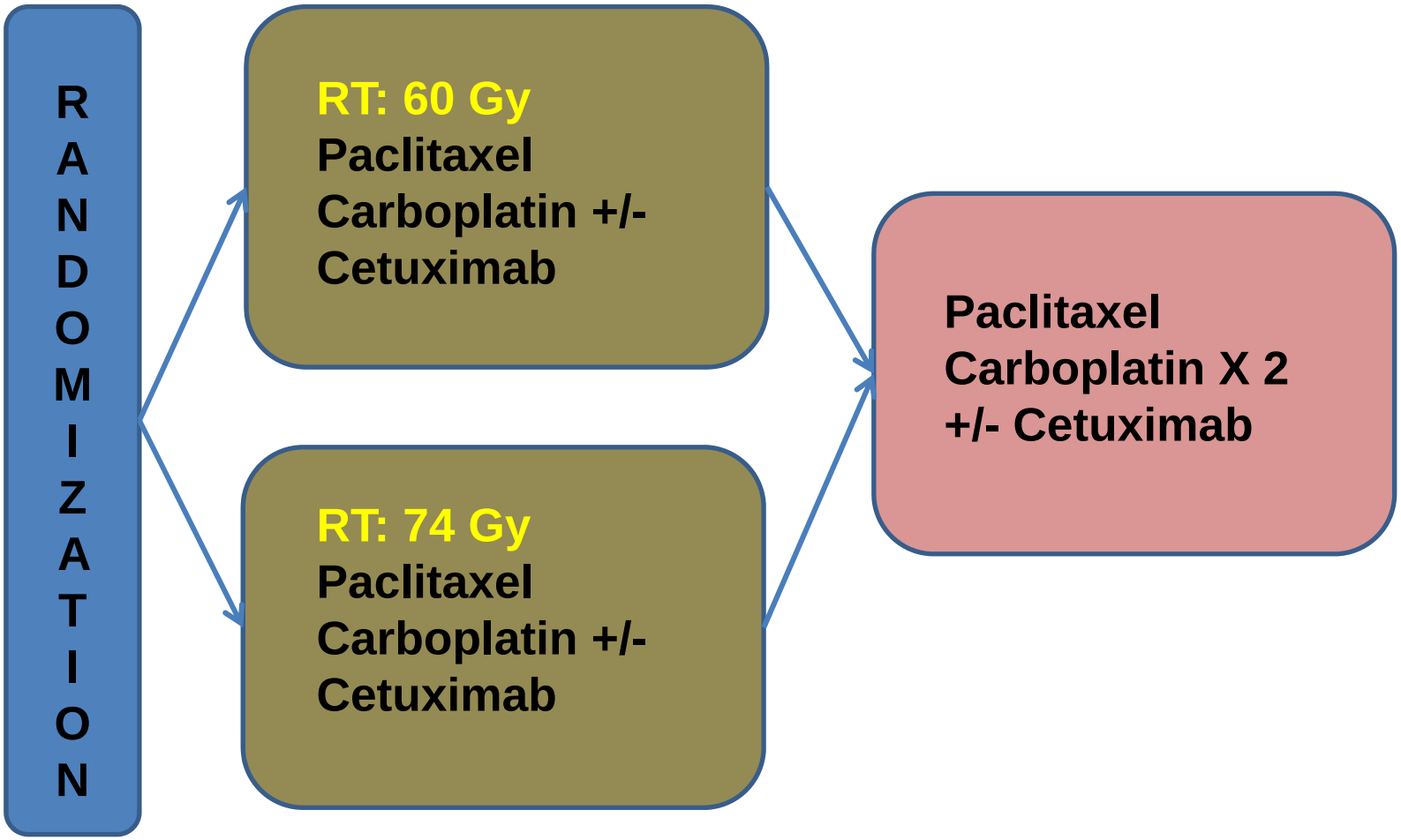


Optimal Positioning

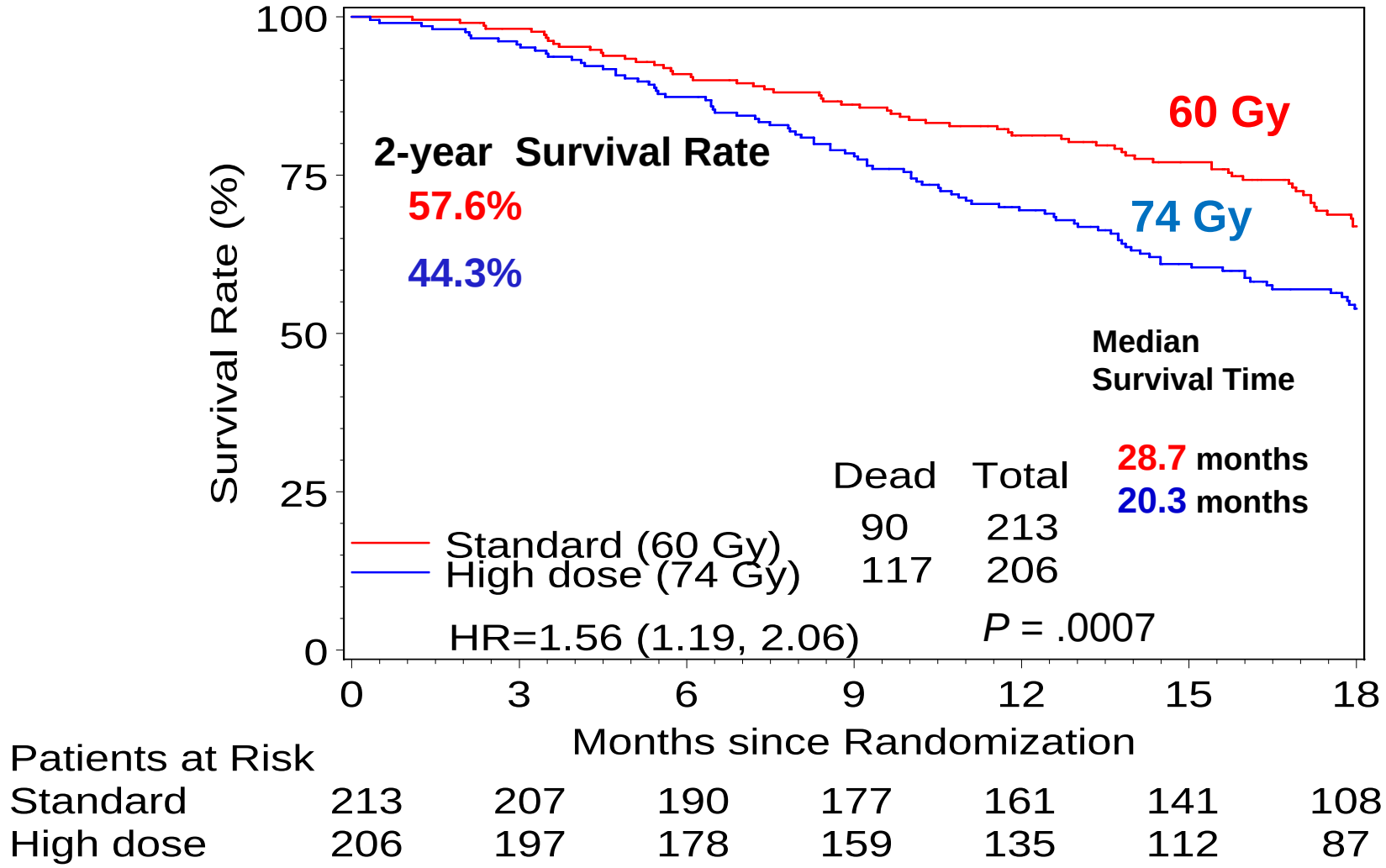
3. Image Guided Radiotherapy Treatment with Cone-Beam-CT at Linac for margins reduction

CT, computed tomography

RTOG 0617, NCCTG N0628, CALGB 30609: Conventional vs High=Dose RT



RTOG 0617: OS

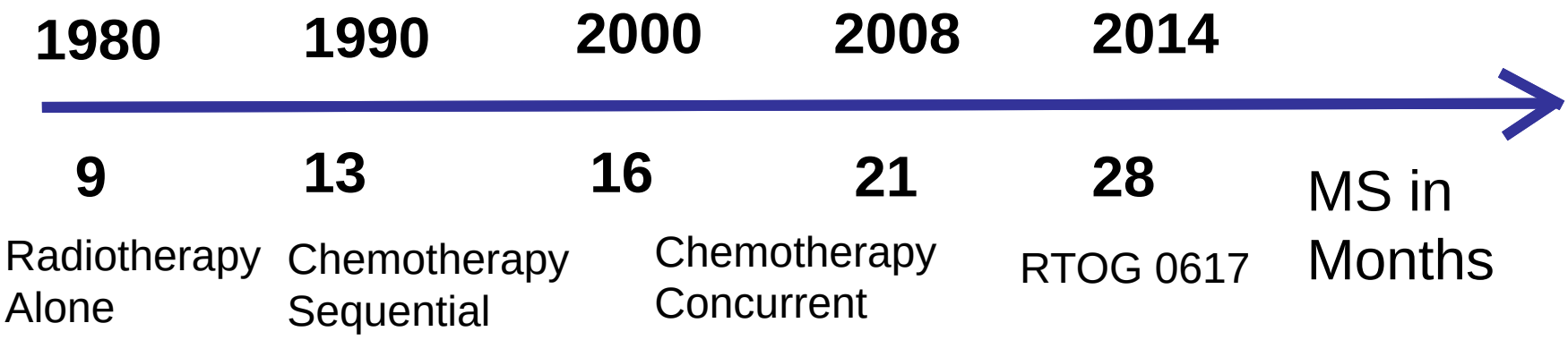


Bradley J, et al. Presented at the American Society for Therapeutic Radiology and Oncology Annual Meeting. Atlanta, Georgia, United States; September 21-25, 2013.

Unresectable Stage III NSCLC

- **At present, concurrent chemotherapy with radiotherapy to a dose of 60 Gy in 30 daily fractions is considered to be the standard treatment**

Survival of Stage III NSCLC:



1. **Stage Migration**
2. **Concurrent Chemoradiation Therapy**
3. **Improved Radiation Technology**

Good PS Stage III NSCLC: Lack of Evidence

- Use of any advanced technology RT tools
- **Selection of best chemo to give concurrently with RT**
- Role of induction or consolidation therapy in the context of chemobeam
- Use of targeted agents concurrent with chemo-RT

CHEST 2013; 143(5)(Suppl):e314S–e340S

CHEST Supplement

DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Treatment of Stage III Non-small Cell Lung Cancer

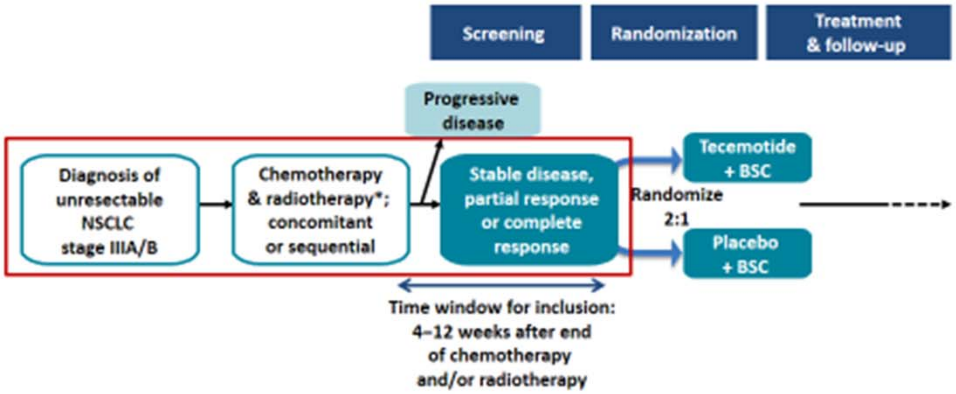
Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

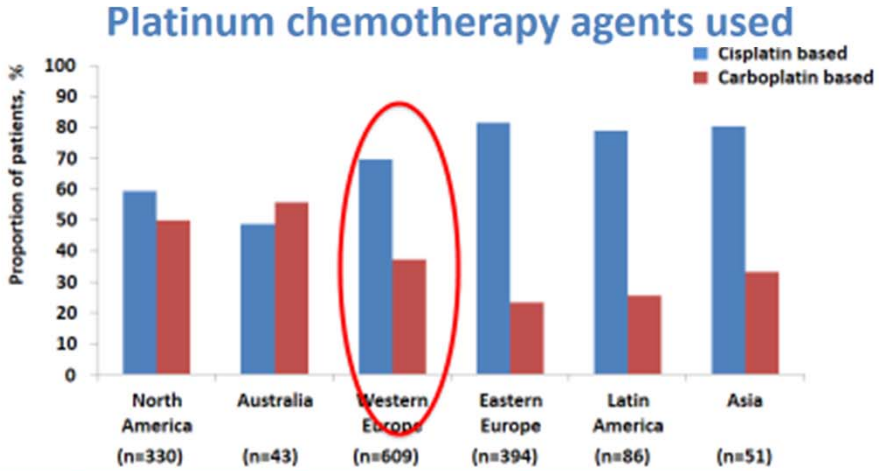
2.3.7. In patients with infiltrative stage III (N2,3) NSCLC, performance status 0-1, and minimal weight loss being considered for curative-intent treatment, a platinum-based doublet chemotherapy is suggested (Grade 2C).

Remark: An optimal agent to be combined with platinum cannot be defined; one should choose a regimen with an acceptable toxicity profile for the individual patient among several combinations that have demonstrated activity when used concurrently with radiation in stage III NSCLC.

Ramnath N, et al.
***Chest.* 2013;143(5 Suppl):e314S-e340S.**

Geographic Differences in the Combined-Modality Treatment of Stage III Unresectable NSCLC: Results From a Global Phase III Trial of Tecemotide (L-BLP25)





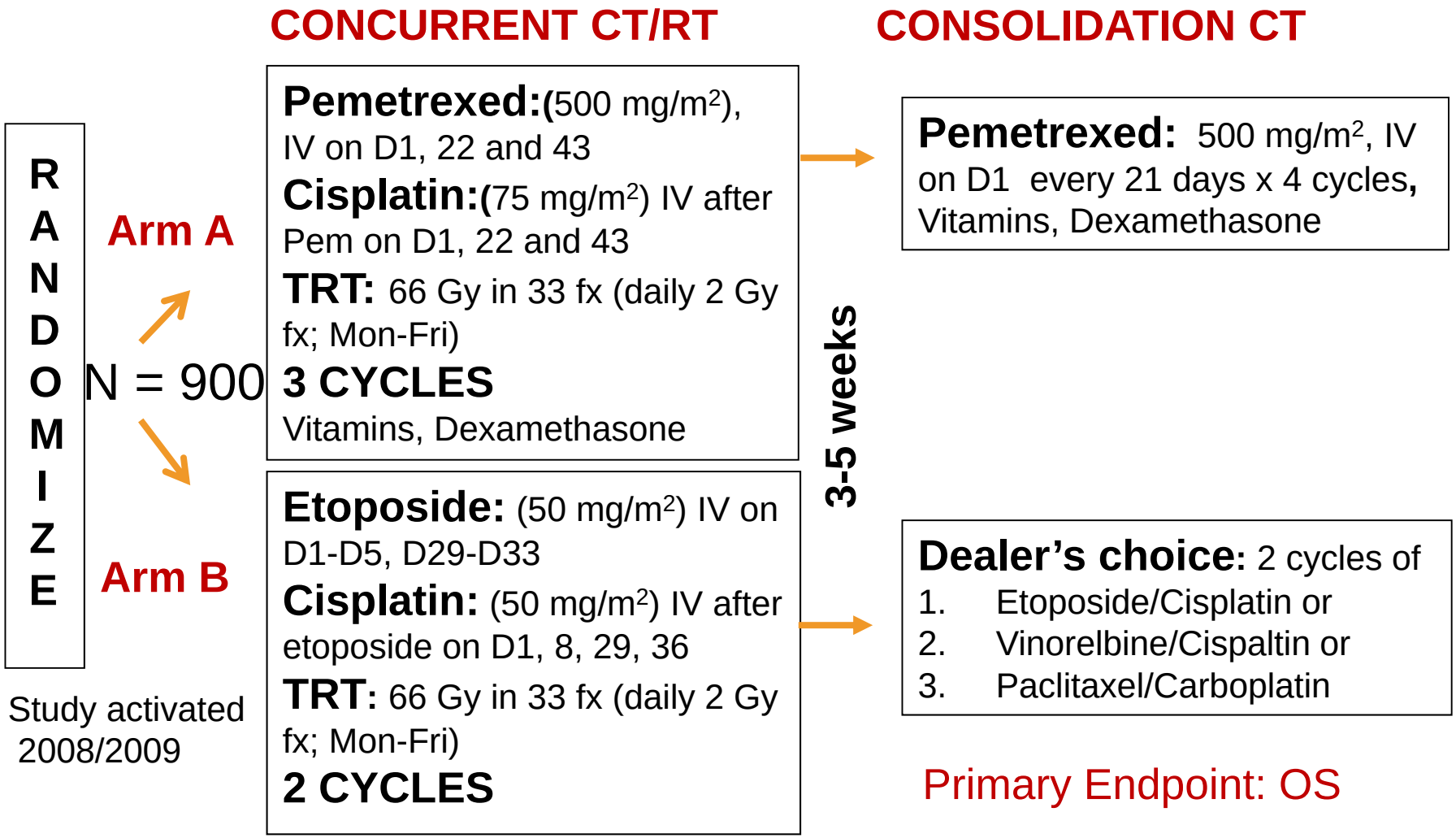
	North America (N=330) n (%)	Australia (N=43) n (%)	Western Europe (N=609) n (%)	Eastern Europe (N=394) n (%)	Latin America (N=86) n (%)	Asia (N=51) n (%)
Carboplatin-based doublet therapy						
Gemcitabine	11 (3.3)	0	**43 (7.1)**	12 (3.0)	3 (3.5)	2 (3.9)
Paclitaxel	106 (32.1)	21 (48.8)	**97 (15.9)**	16 (4.1)	13 (15.1)	8 (15.7)
Vinorelbine	8 (2.4)	1 (2.3)	**61 (10.0)**	55 (14.0)	3 (3.5)	2 (3.9)
Cisplatin-based doublet therapy						
Docetaxel	5 (1.5)	3 (7.0)	**63 (10.3)**	4 (1.0)	1 (1.2)	14 (27.5)
Etoposide	164 (49.7)	19 (44.2)	**57 (9.4)**	46 (11.7)	28 (32.6)	3 (5.9)
Gemcitabine	3 (0.9)	0	**83 (13.6)**	42 (10.7)	11 (12.8)	3 (5.9)
Vinorelbine	22 (6.7)	0	**187 (30.7)**	211 (53.6)	11 (12.8)	7 (13.7)

Thatcher N, et al. *J Thorac Oncol.* 2013;8(Suppl 2): Abstract O02.01.

Locally Advanced NSCLC
Future Directions

- Better staging and stratification
- **Improved systemic therapy**
  - **New chemotherapy platform**
  - **Patient selection**
- Continued improvement of radiation therapy
- Careful integration of molecularly targeted therapy
- Good supportive care and pulmonary rehabilitation
- Post therapy risk stratification

PROCLAIM: Phase III International Trial
Stage III NSCLC (Closed)



Chemo to commence with the first day of RT

National Institutes of Health. Available at: https://clinicaltrials.gov/ct2/show/NCT00686959. Accessed 12 December 2014.

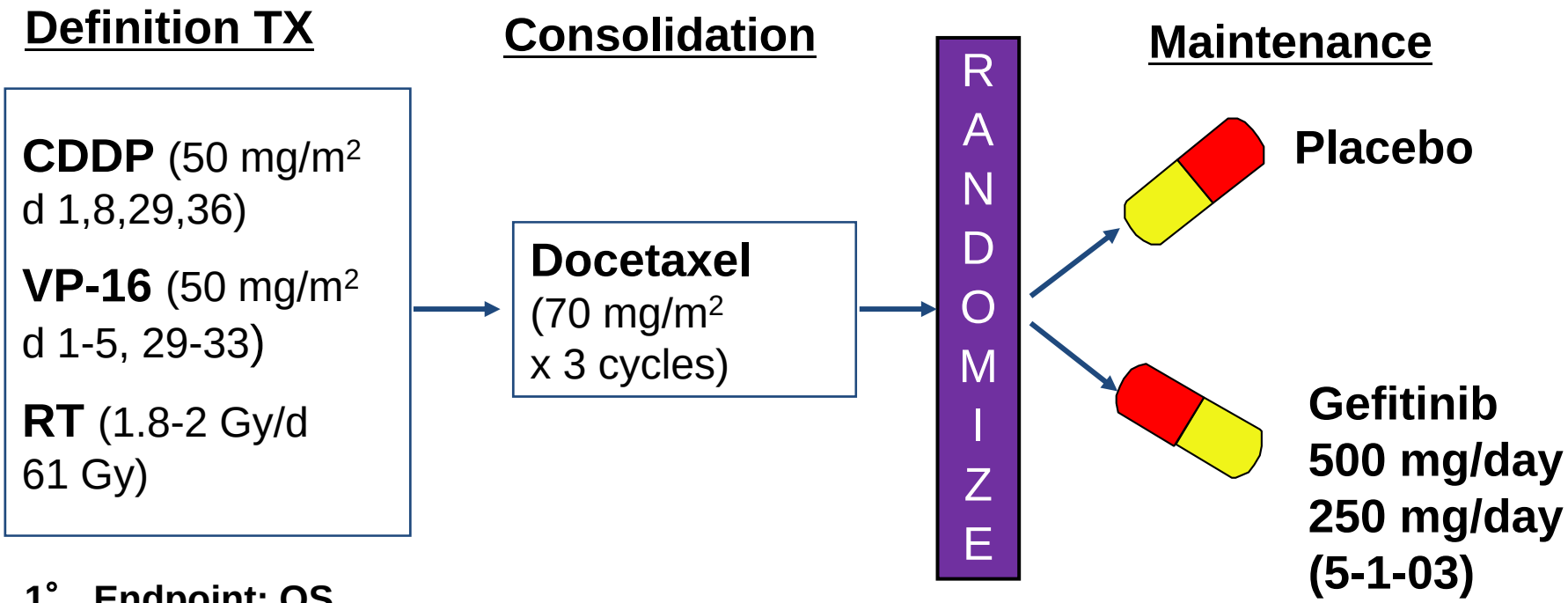
Locally Advanced NSCLC
Future Directions

- Better staging and stratification
- Improved systemic therapy
  - New chemotherapy platform
  - Patient selection
- Continued improvement of radiation therapy
- **Careful integration of molecularly targeted therapy**
- Good supportive care and pulmonary rehabilitation
- Post therapy risk stratification

Role of targeted therapy remains unclear and is yet unproven

SWOG 0023: Gefitinib vs Placebo After Chemoradiation Followed by Docetaxel in Stage IIIA (N2) or IIIB

Study Schema



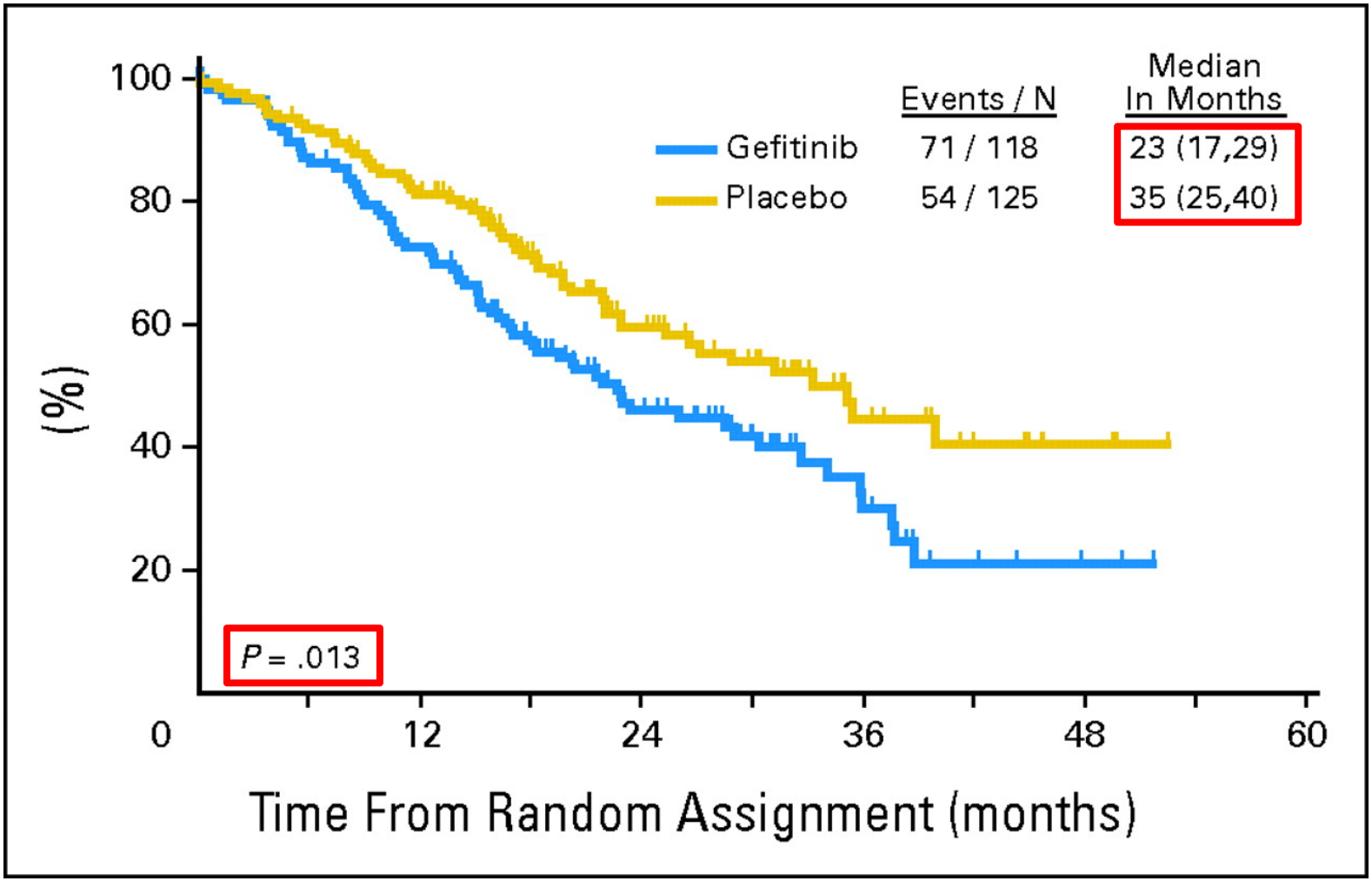
1° Endpoint: OS
2° Endpoint: PFS, toxicity, and correlative science

Maintenance therapy could continue for a maximum of 5 years

Stratification factors: IIIA vs IIIB; measurable vs nonmeasurable disease; squamous vs nonsquamous

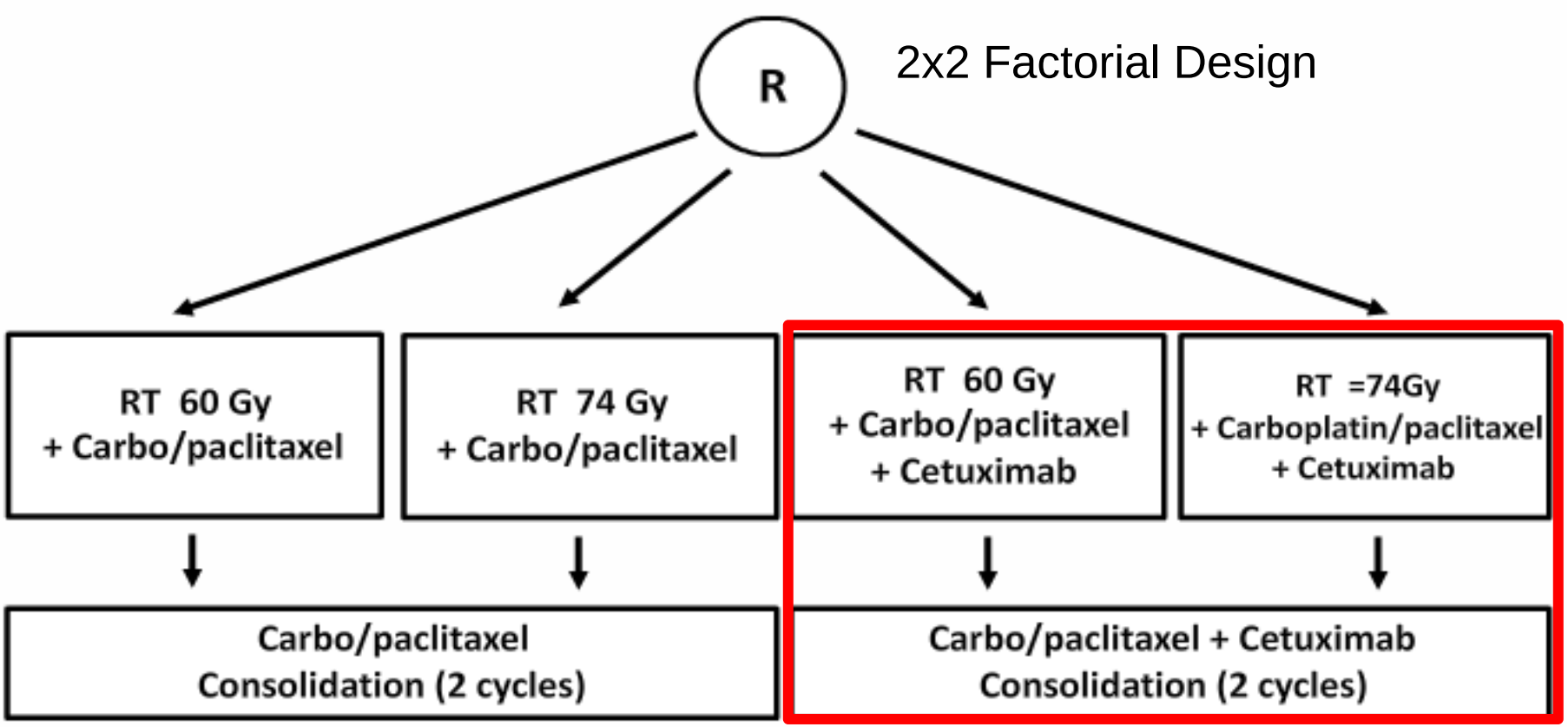
Kelly K, et al. *J Clin Oncol.* 2007;25(18S): Abstract 7513. Kelly K, et al. *J Clin Oncol.* 2008;26(15):2450-2456.

SWOG 0023: OS for Patients Receiving Maintenance Gefitinib or Placebo



Kelly K, et al. *J Clin Oncol.* 2008;26(15):2450-2456.

Phase III RTOG 0617/US Intergroup Trial: Chemoradiation + Cetuximab



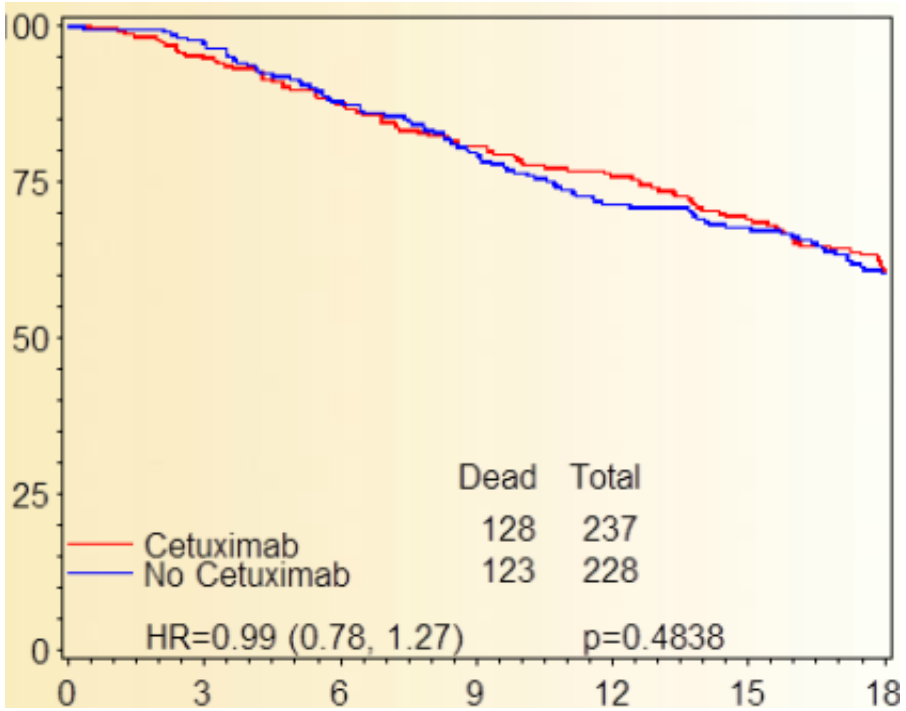
Co-primary Objective:

- Compare the OS of patients treated with concurrent CT-RT plus cetuximab versus CT-RT alone

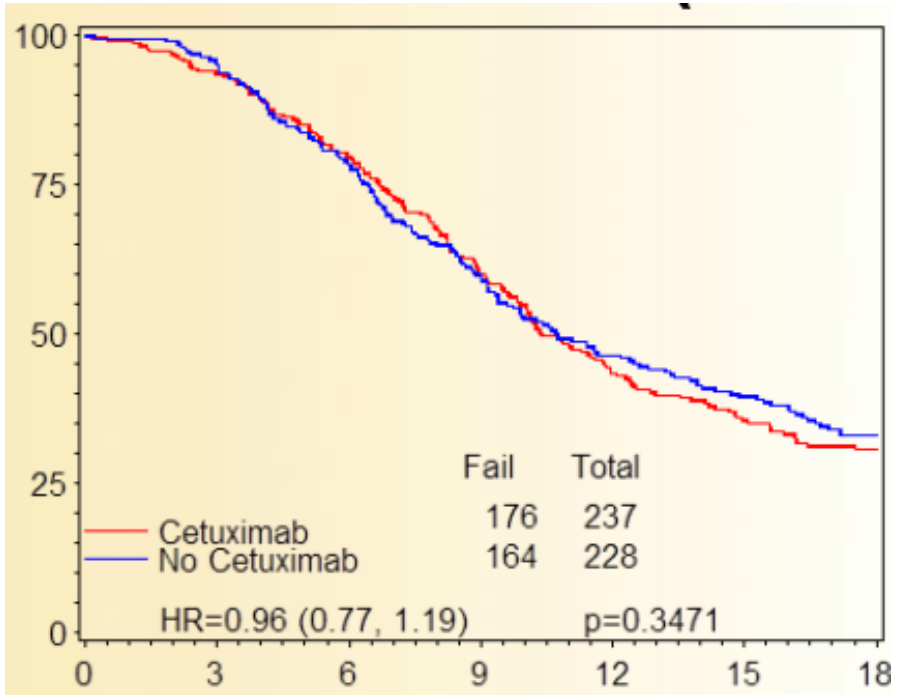
Bradley J, et al *J Thorac Oncol.* 2013;8(Suppl 2): Abstract PL03.05

Chemoradiation + Cetuximab: OS and PFS

OS



PFS

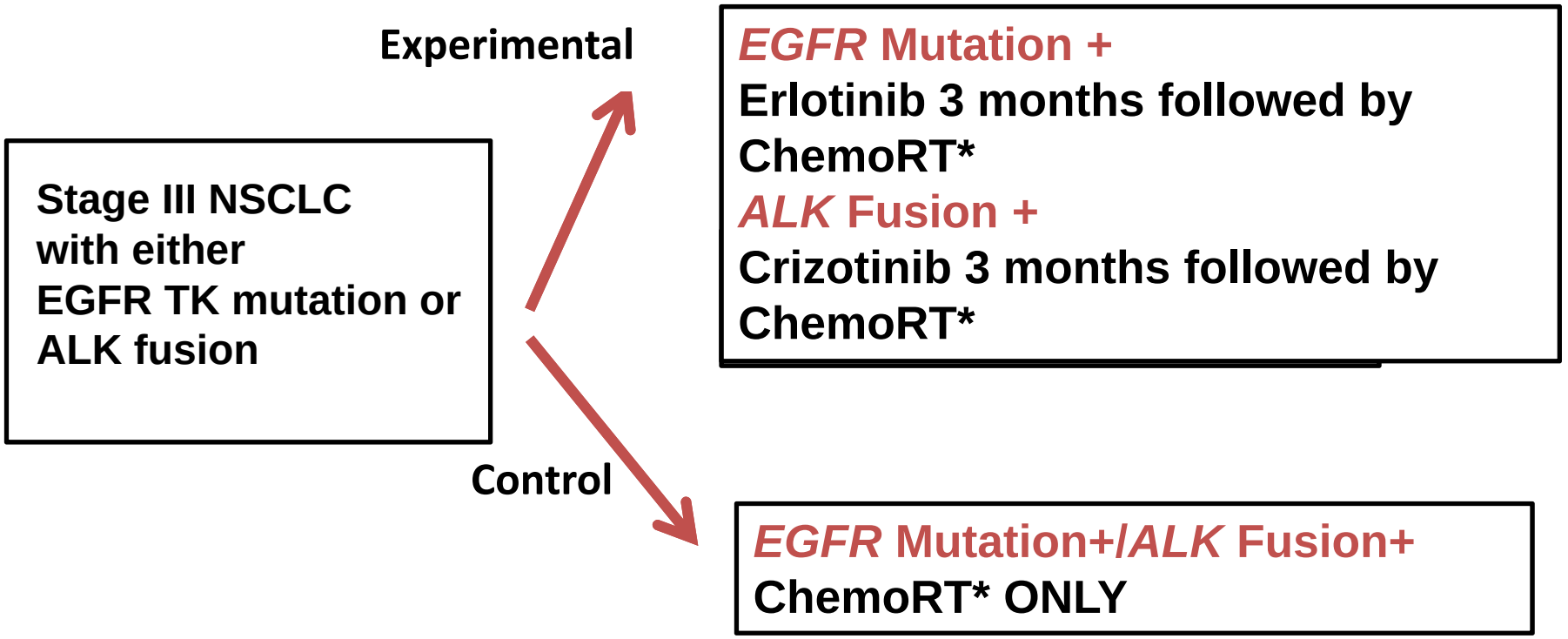


- **Cetuximab did not improve overall survival of PFS in the overall population, when added to standard chemoradiotherapy for unresectable stage III NSCLC**
- **Cetuximab increases overall grade 3-5 toxicities (85% vs 69%, *P*<.0001), and grade 3-5 nonhematologic toxicities (70.5% vs 50.7%, *P*<.0001) when added to standard chemoradiotherapy**

Bradley J, et al *J Thorac Oncol.* 2013;8(Suppl 2): Abstract PL03.05

RTOG 1210/ Alliance 31101
Submitted to NCI

A Randomized Phase II Trial



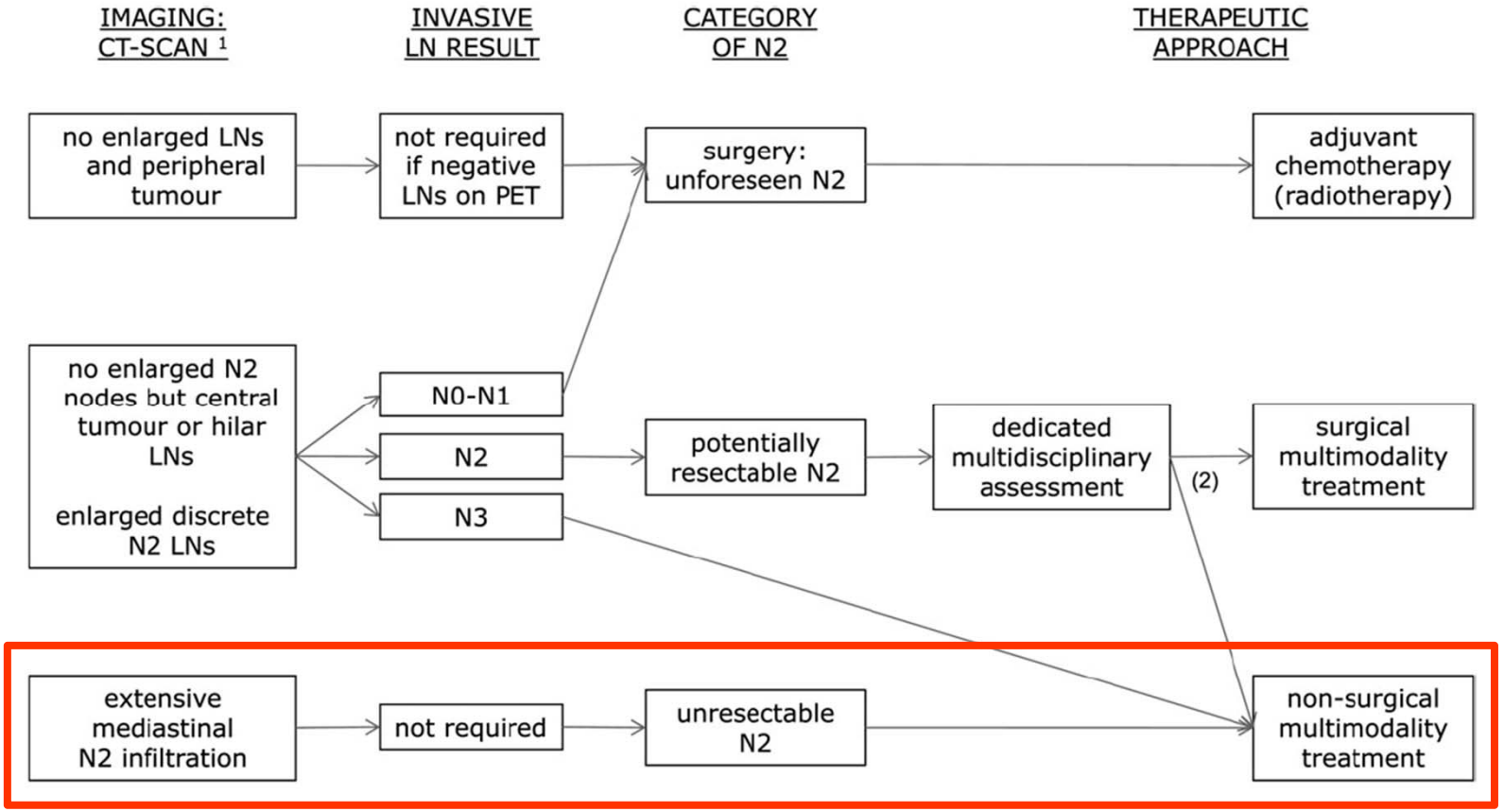
*Pemetrexed 500 mg/m^2 q 3 weekly x 4 carboplatin AUC 5 (4 cycles) with thoracic radiation 64 Gy

NCI, National Cancer Institute

clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi89–vi98, 2013
doi:10.1093/annonc/mdt241
Published online 16 July 2013

Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†



ESMO, European Society for Clinical Oncology; LN, lymph node

Vansteenkiste J, et al. *Ann Oncol.* 2013;24 Suppl 6:vi89-vi98.

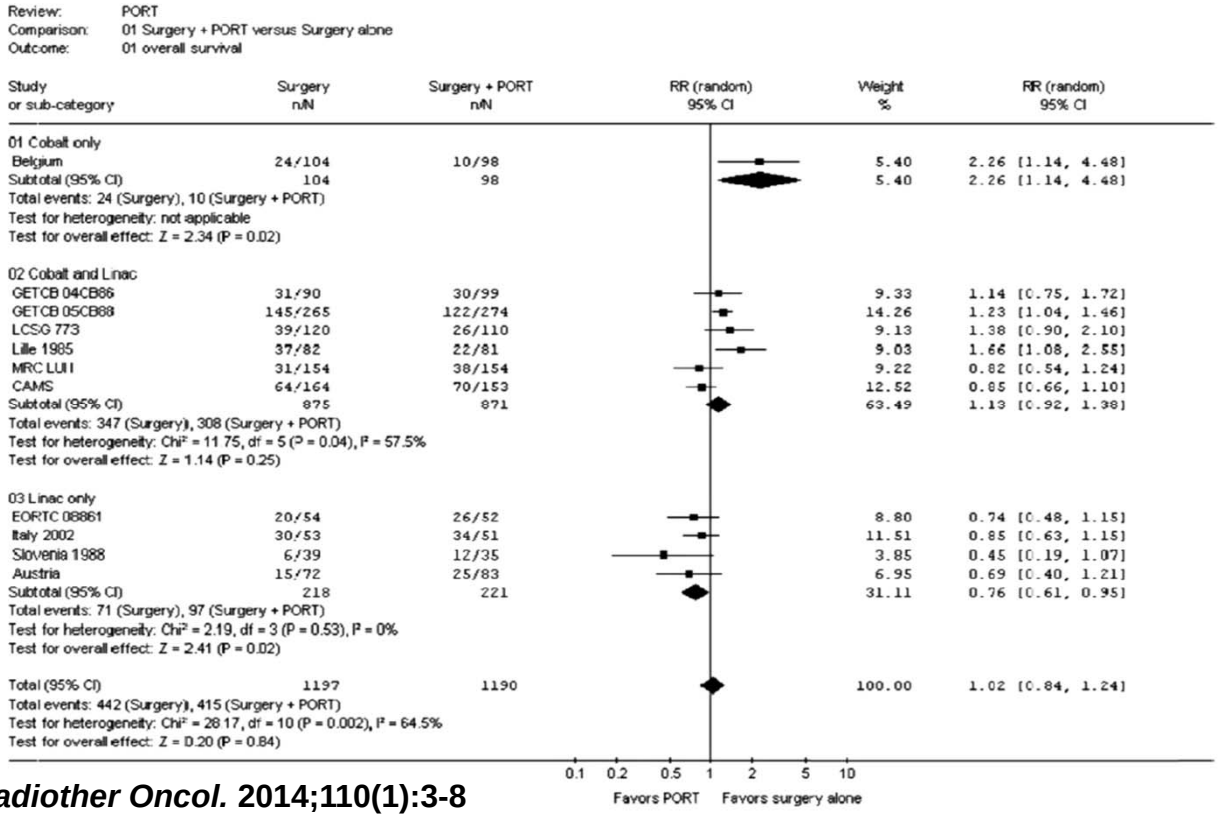
55-year-old man, T2aN2M0 (IIIAN2); 5 cm tumor in RUL and 1.7-cm LN, 4R region; adenocarcinoma, *EGFR* mutation (deletion 19), PS 0

- **Induction chemotherapy (carboplatin-pemetrexed)**
- **Surgery, if responding**
- **PORT, if pN2**

PORT, postoperative radiotherapy

Modern post-operative radiotherapy for stage III non-small cell lung cancer may improve local control and survival: A meta-analysis

Abbreviation	# Patients	Stage	Beam quality	Dose/fraction (Gy)	EQD_2 (tumor) (Gy)	$EQD_{2,T}$ (Gy)
Belgium [23]	224	I–III	Cobalt only	60/30	60	50.76
CAMS [24]	317	II, III	Cobalt and Linac	60/30	60	50.76
GETCB 04CB86 [25]	189	I–III	Cobalt and Linac	60/24–30	60	50.76
GETCB 05CB88 [26]	539	I–III	Cobalt and Linac	60/24–30	62.50	57.88
LCSG 773 [27]	230	II, III	Cobalt and Linac	50/25–28	50	45.38
Lille 1985 [28]	163	I	Cobalt and Linac	45–60/22–30	45	43.68
MRC LUI I [29]	308	II, III	Cobalt and Linac	40/15	42.23	42.23
Slovenia 1988 [30]	74	III	Linac only	30/10–12	32.50	32.50
Austria [31]	155	III	Linac only	50–56/28	50	45.38
EORTC [32]	106	II, III	Linac only	56/28	55.07	48.47
Italy [33]	104	I	Linac only	50.40/28	49.56	42.96



Billiet C, et al. *Radiother Oncol.* 2014;110(1):3-8

Same patient, but with multiple sites N2 disease (size of the lymph nodes 1.5-3.5 cm)?

- **Definitive concurrent chemoradiotherapy**
- **CDDP-ETO or CARBO-PACLI as chemo regimen**
- **60-66 Gy in 2 Gy daily fractions**