



*Integrated approaches  
in Locally Advanced Non-Small Cell Lung Cancer*

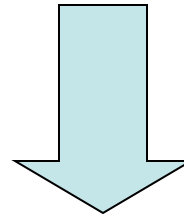
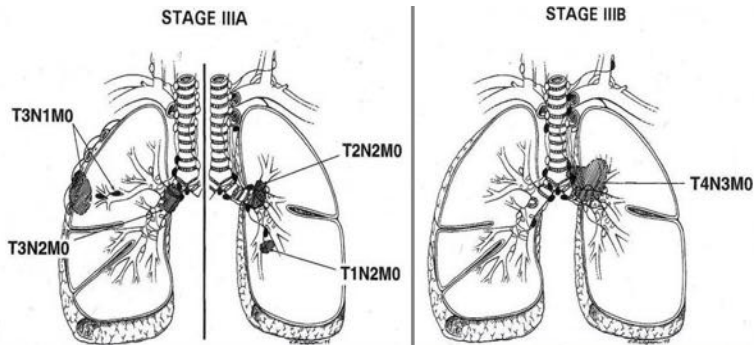
*Michele Fiore*



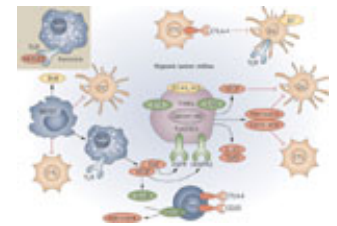
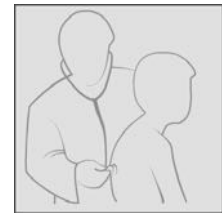
# *Locally Advanced NSCLC*

*is*

*a widely heterogeneous disease*



*Staging*  
*Clinical factors*  
*Tumor biology*

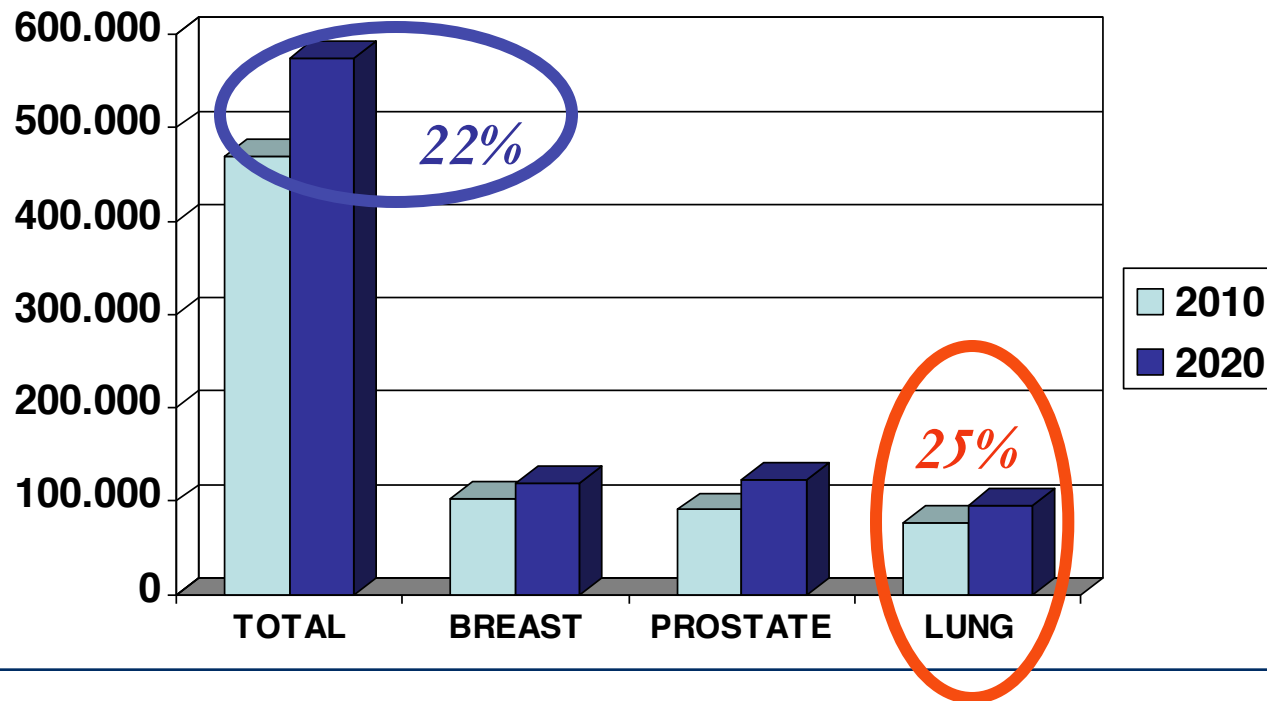


*Non-Small Cell Lung Cancer:  
The End of the Era of Therapeutic  
Nihilism?*



## The Future of Radiation Oncology in the United States From 2010 to 2020: Will Supply Keep Pace With Demand?

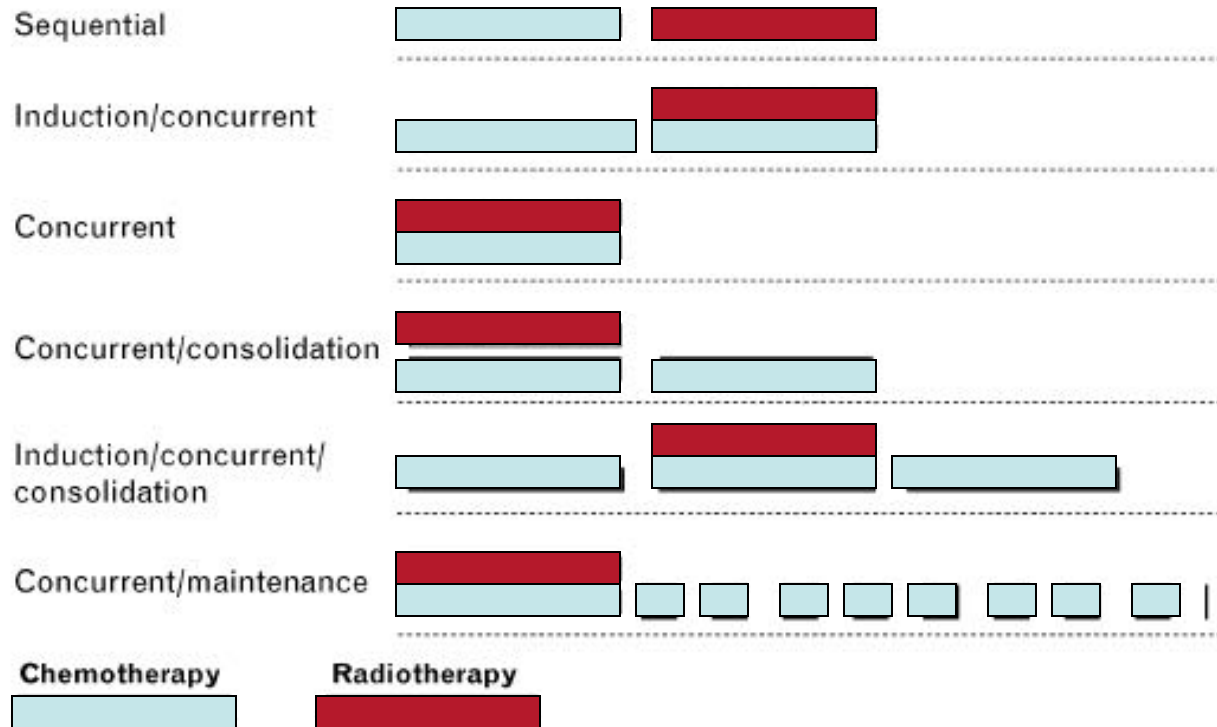
*Benjamin D. Smith, Bruce G. Haffty, Lynn D. Wilson, Grace L. Smith, Akshar N. Patel,  
and Thomas A. Buchholz*



In the last decade, we have witnessed a wealth of **clinical trials** showing that radiotherapy is an important component in the treatment with curative intent.



# *What is the Optimal Sequence of Chemoradiation?*



# CONCURRENT vs SEQUENTIAL RT-CT



THE COCHRANE  
COLLABORATION®

711 patients  
3 randomized trials

*O'Rourke N. Clin Oncol 22:347–355, 2010*



1205 patients  
6 randomized trials

*Auperin A., J Clin Oncol 28:2181-2190, 2010*

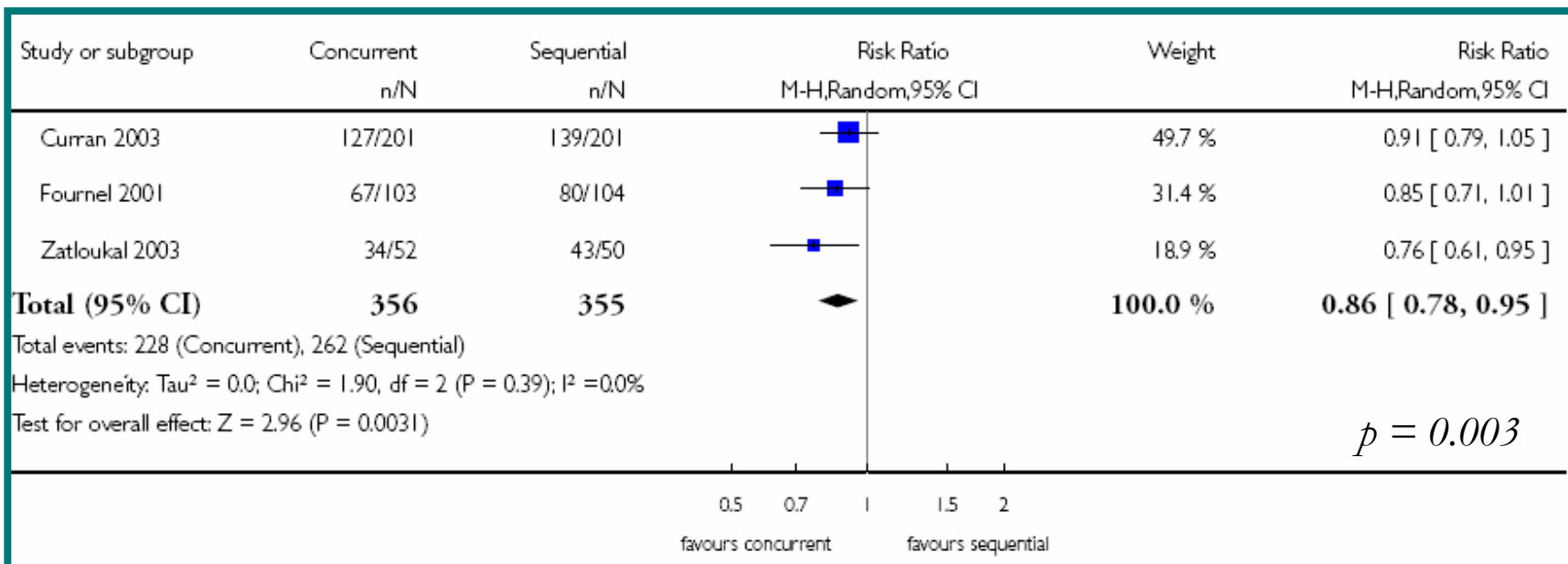


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THE COCHRANE  
COLLABORATION®

14% reduction in risk of death at 2y



O'Rourke N. Clin Oncol 2010







Contents lists available at ScienceDirect

## Clinical Oncology

journal homepage: [www.elsevier.com/locate/clon](http://www.elsevier.com/locate/clon)



### Overview

## Is Concurrent Chemoradiation the Standard of Care for Locally Advanced Non-small Cell Lung Cancer? A Review of Guidelines and Evidence

N. O'Rourke\*, F. Macbeth†

\* *Cochrane Lung Cancer Group, Beatson Oncology Centre, Gartnavel General Hospital, Glasgow, UK*

† *National Institute for Health and Clinical Excellence, London, UK*

	Median Survival (months)	Treatment- related mortality	G3 oesophagitis
Concurrent	16-17	3 %	19 %
Sequential	13-15	1,7 %	3 %

*O'Rourke N. Clin Oncol 2010*



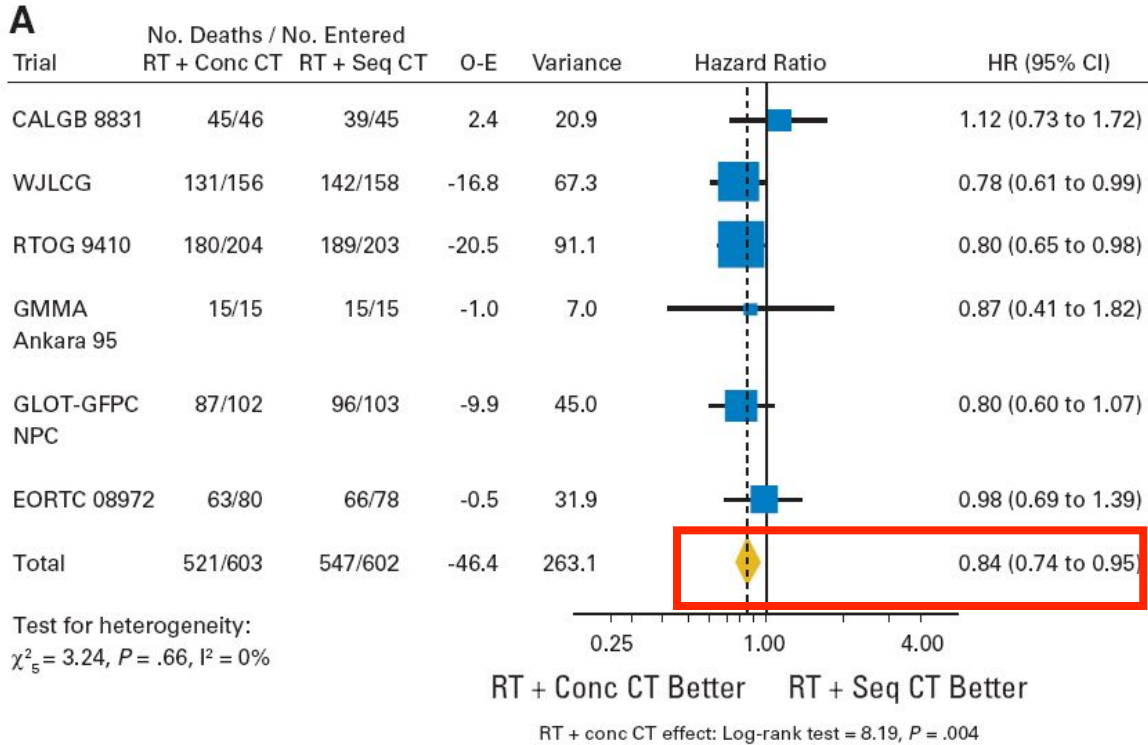
# Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non-Small-Cell Lung Cancer

6 Trials  
1205 pts  
Median Follow-up 6 years



*Auperin A., J Clin Oncol 28: 2181-2190, 2010*





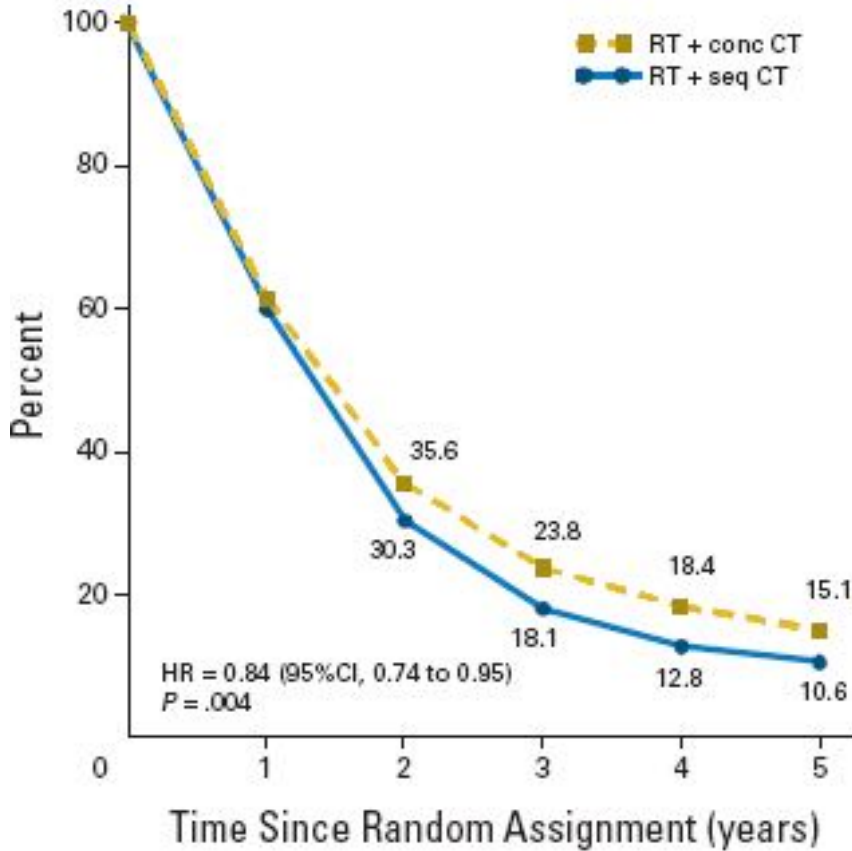
Benefit concomitant  
RT-CT:

HR 0.84 95% CI,  
0.74 to 0.95; p.004

*Overall Survival*

*Auperin A., J Clin Oncol 28: 2181-2190, 2010*

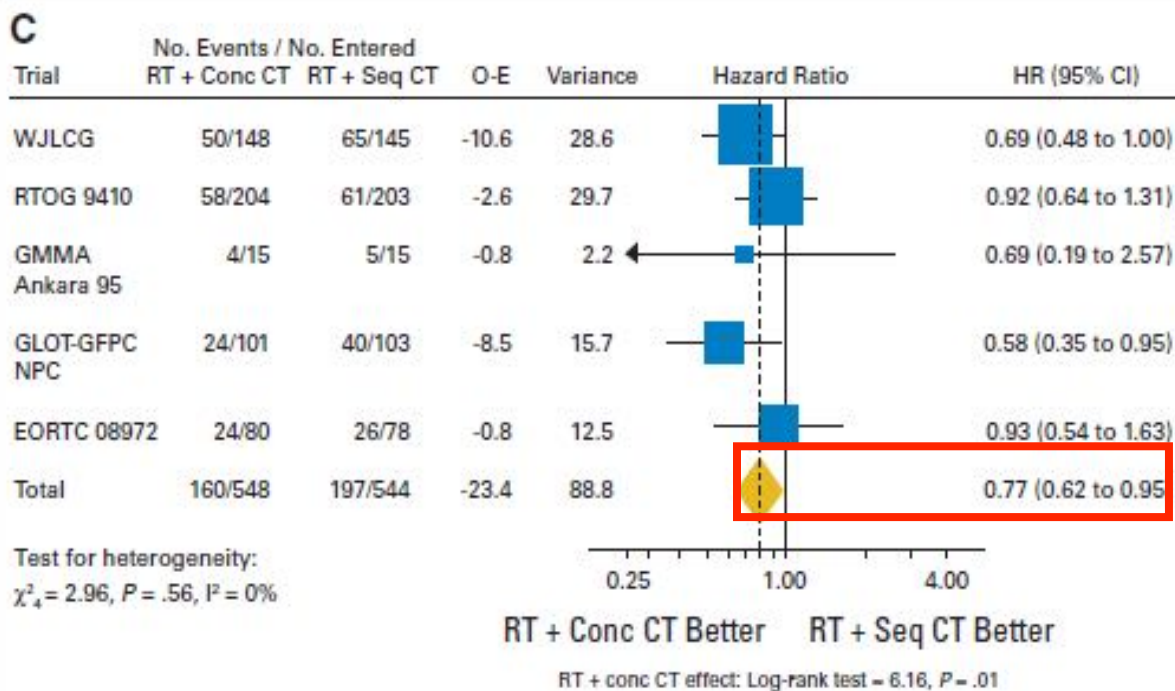




Absolute survival benefit of **5.7% at 3 years** and an absolute benefit of **4.5% at 5 years**

*Auperin A., J Clin Oncol 28: 2181-2190, 2010*





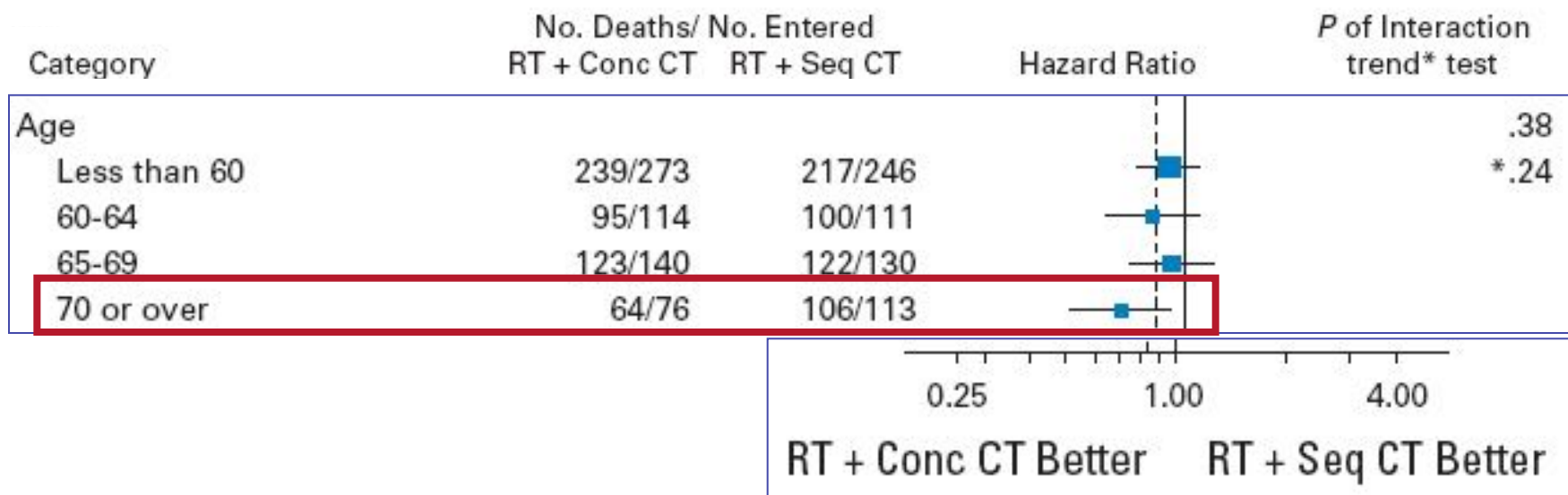
Benefit  
concomitant  
RTCT:  
HR 0.77; p.001

*Loco-regional Control*

*Auperin A., J Clin Oncol 28: 2181-2190, 2010*



## ELDERLY PATIENTS



*Auperin A., J Clin Oncol 28: 2181-2190, 2010*



# Sequential vs Concurrent Chemoradiation for Stage III NSCLC:

## Randomized Phase III Trial RTOG 9410

601 patients

R  
A  
N  
D  
O  
M  
I  
Z  
E

### Arm 1:

vinblastine 5 mg/m<sup>2</sup> IV  
bolus weekly first 5 weeks  
cisplatin 100 mg/m<sup>2</sup> IV over  
30-60 minutes, days 1 & 29



(starting day 50)  
63 Gy/7 wks/34 daily  
fractions (1.8 Gy x 25 fx, then  
2.0 Gy x 9 fx)

*Sequential*

### Arm 2:

vinblastine 5 mg/m<sup>2</sup> IV bolus weekly first 5 weeks  
cisplatin 100 mg/m<sup>2</sup> IV over 30-60 minutes, days 1 & 29  
63 Gy/7 wks/34 daily fractions (1.8 Gy x 25 fx, then 2.0 Gy x 9 fx)

*Concurrent*

### Arm 3:

oral etoposide 50 mg twice daily x 10 only on RT treatment days 1-5, 8-12, 29-33 and 36-40 (75 mg/day if body surface area < 1.7 m<sup>2</sup>)  
cisplatin 50 mg/m<sup>2</sup> IV over 30-60 minutes on days 1 and 8 and 29 and 36  
69.6 Gy/6 wks/58 x 1.2 Gy twice-daily fractions (at least 6 hours apart)

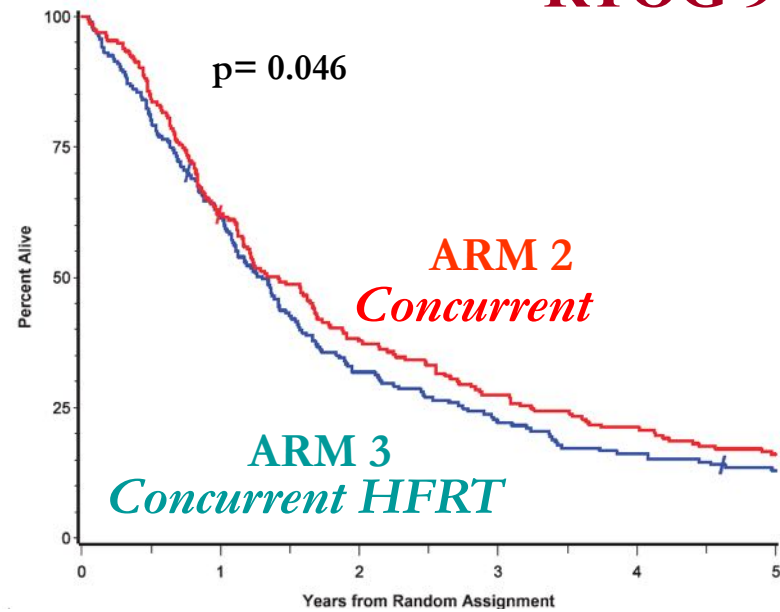
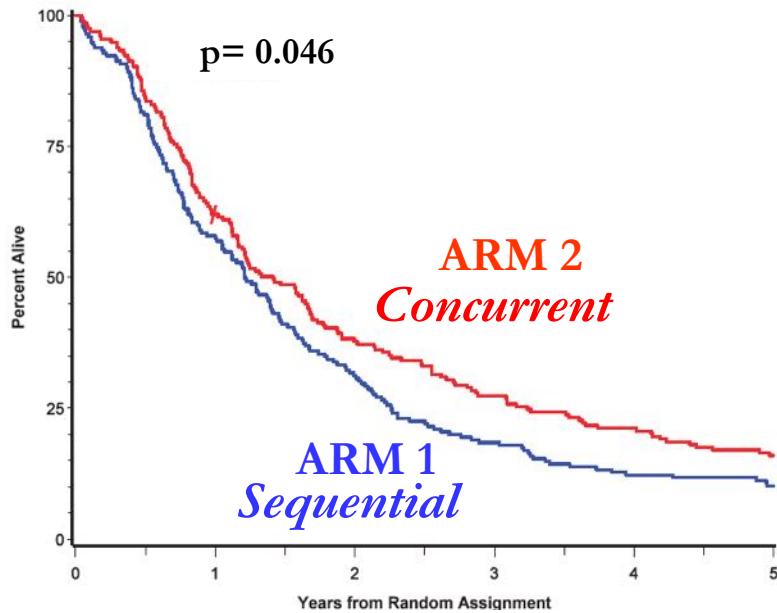
*Concurrent  
HFRT*

*Curran et al, JNCI 2011*



# RTOG 9410

FUP 11 years



	<i>Median SVV (months)</i>	<i>SVV @ 5y (%)</i>
<i>Arm 1</i>	14.6	10
<i>Arm 2</i>	17	16
<i>Arm 3</i>	15.6	13

*Similar late toxic effects*

*Curran et al, JNCI 2011*





# *What is the Optimal Sequence of Chemoradiation?*

*These data suggest that chemotherapy, concurrently given with radiotherapy, improves the efficacy of the radiotherapy by its radiosensitizing effect.*



*Currently, **concurrent chemoradiation** is the standard treatment in patients with locally advanced NSCLC.*

# *Chemoradiation in Neoadjuvant Setting*

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

*Lancet* 2009; 374: 379–86

*Kathy S Albain, R Suzanne Swann, Valerie W Rusch, Andrew T Turrisi III, Frances A Shepherd, Colum Smith, Yuhchyan 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, William T Sause, James D Cox*

**RANDOM**



201 pts

## **Radical RT-CT**

**RT: 61 Gy – Standard fx**

**CT: CDDP 50 mg/m<sup>2</sup> d1,8,29,36**

**VP16 50 mg/m<sup>2</sup> d1-5,29-33**

191 pts

## **Neoadj RT-CT → Surgery**

**RT: 45 Gy – Standard fx**

**CT: CDDP 50 mg/m<sup>2</sup> d1,8,29,36**

**VP16 50 mg/m<sup>2</sup> d1-5,29-33**

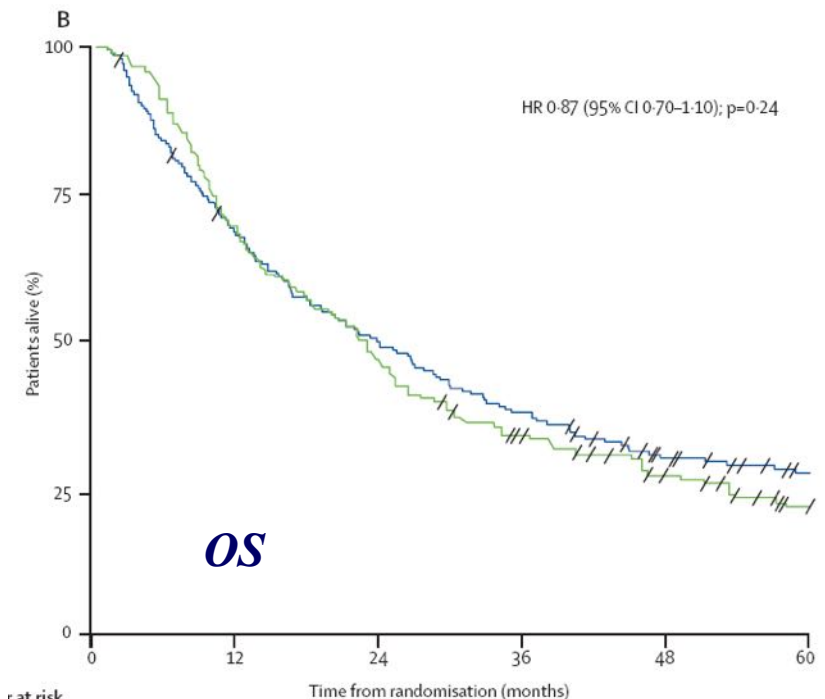
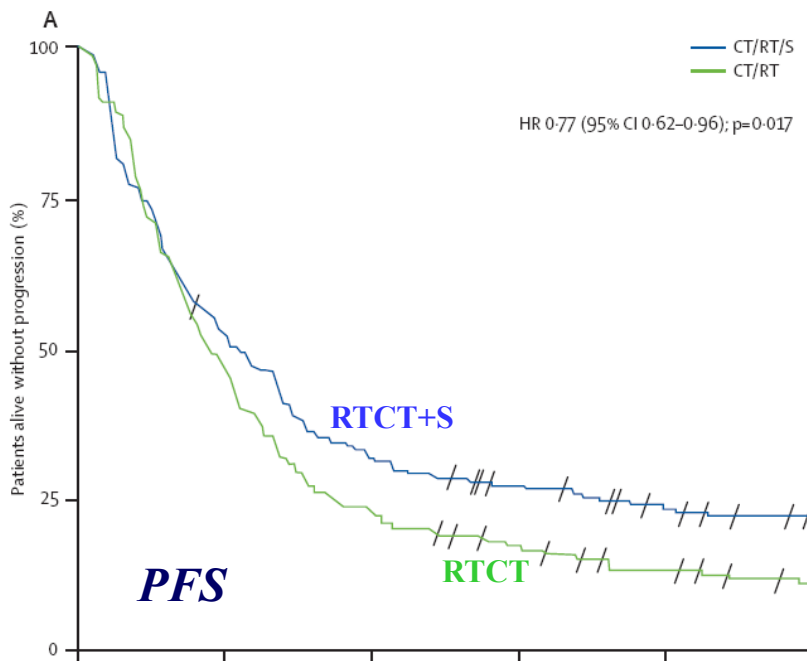


# Chemoradiation in Neoadjuvant Setting

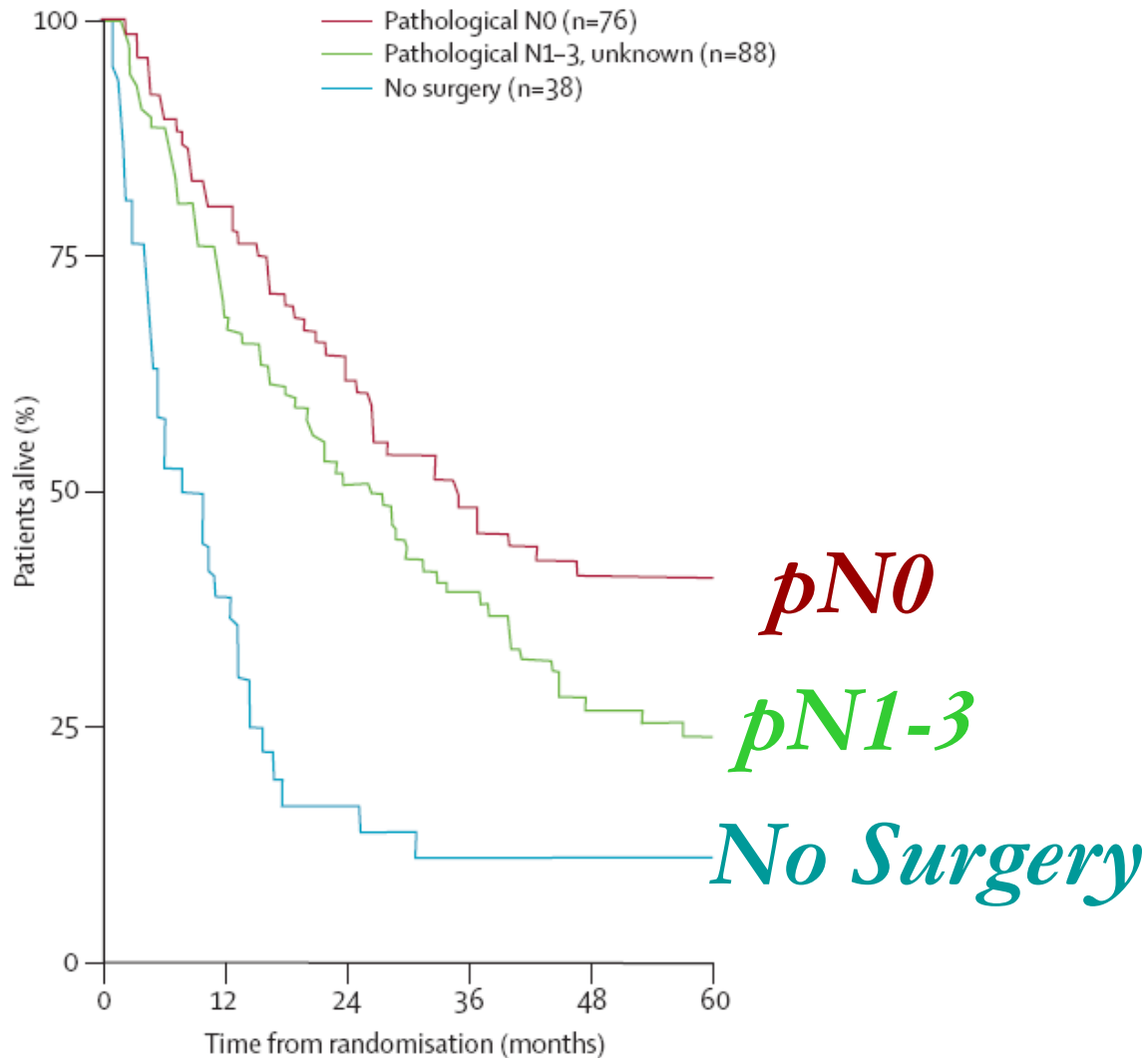
Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial

Lancet 2009; 374: 379–86

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# INT 0139



Lancet 2009; 374: 379-86

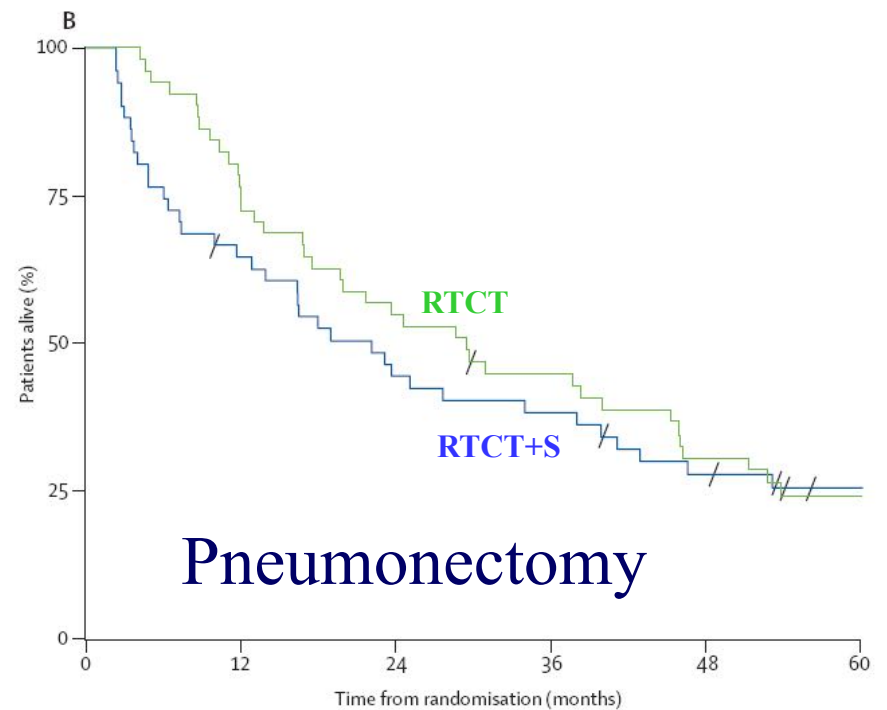
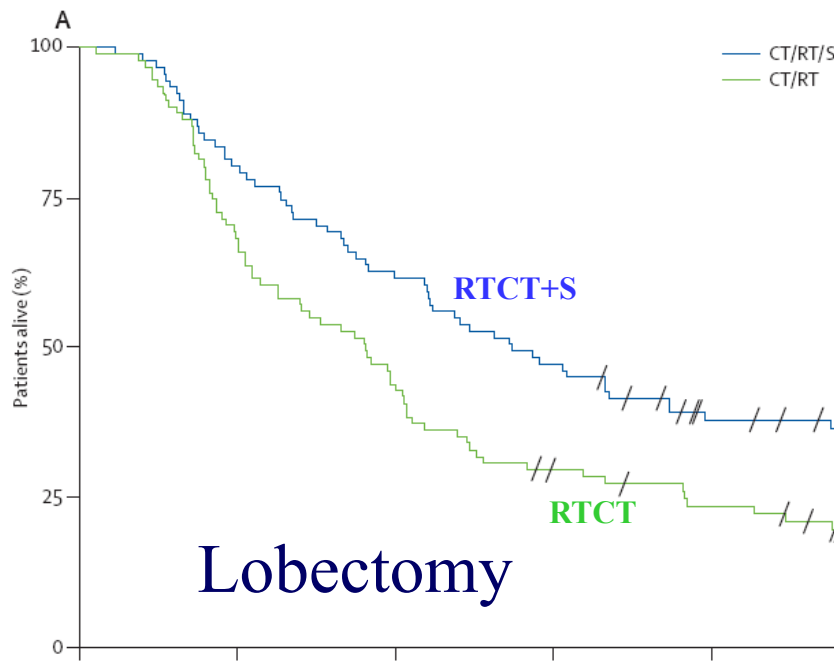


**INT 0139**

# Overall Survival

THE LANCET

"Obama's health-care reform package is intended to fulfil two aims: universal health coverage and the creation of a government-run public health insurance...Yes, it can be done."



Lancet 2009; 374: 379-86



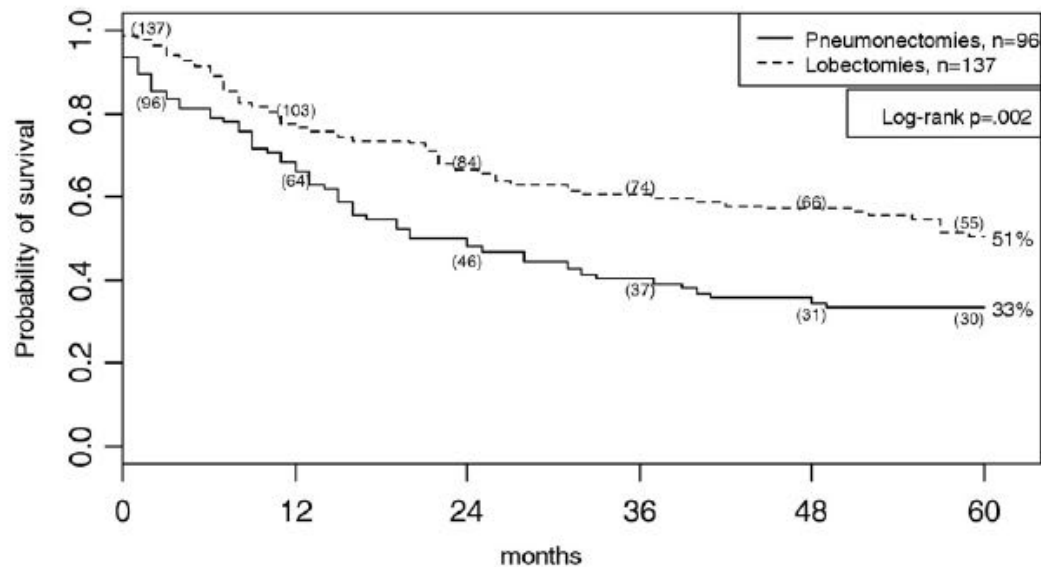
# Neoadjuvant Chemoradiation for Clinically Advanced Non-Small Cell Lung Cancer: An Analysis of 233 Patients

## Neoadjuvant chemoradiation

Survival: median 40 months, 5-y 43%

Mortality 30 days: 3%, 90 days 8%

T0 or N0 or T0N0 is associated with the best survival rate



*Lobectomy is better than pneumonectomy*

Kim et al., Ann Thorac Surg 2011;92: 233-43



# *Chemoradiation in Neoadjuvant Setting*

*Trimodality therapy offers a promising  
chance of long-term survival*



*Choice of concomitant drugs:  
What is the Optimal Combination?*

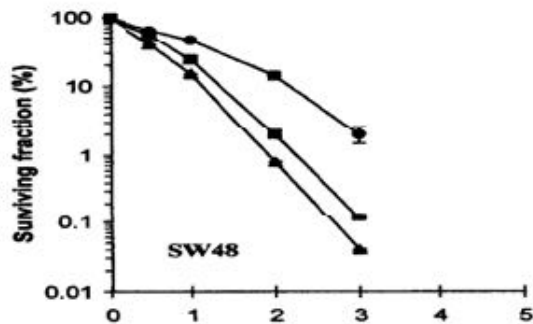




- The **most efficacious** chemotherapy drugs to be combined with thoracic radiotherapy is NOT established

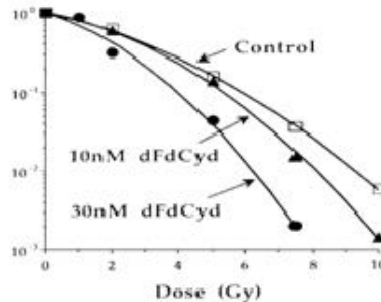
***Docetaxel***

*Amanda L. Dunne,  
 Oncology Research 2004*



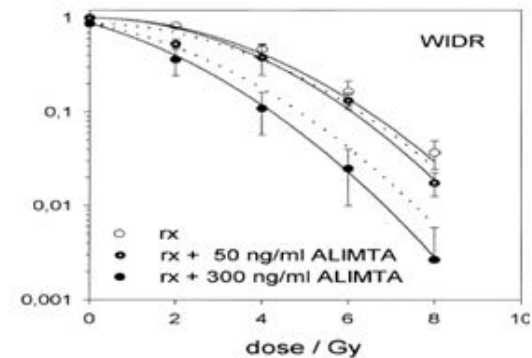
***Gemcitabine***

*Shewach et al  
 Cancer Research 1994*

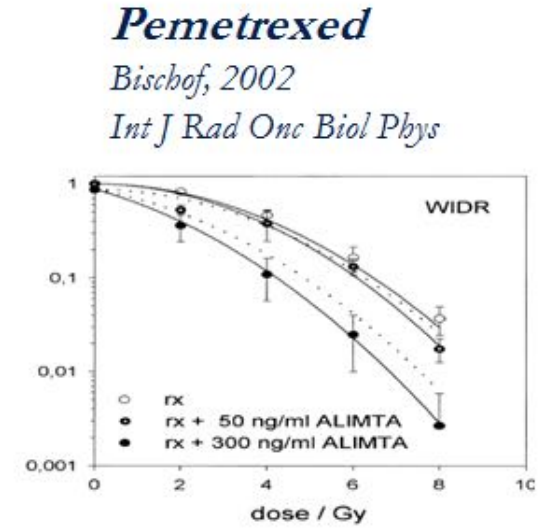
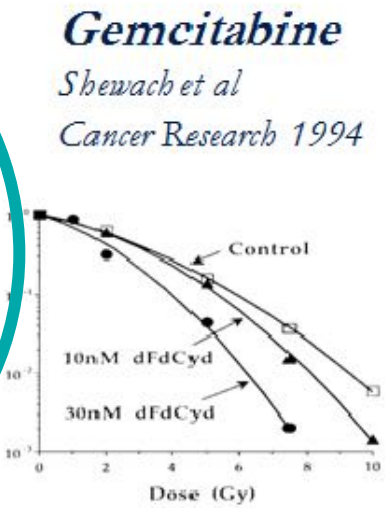
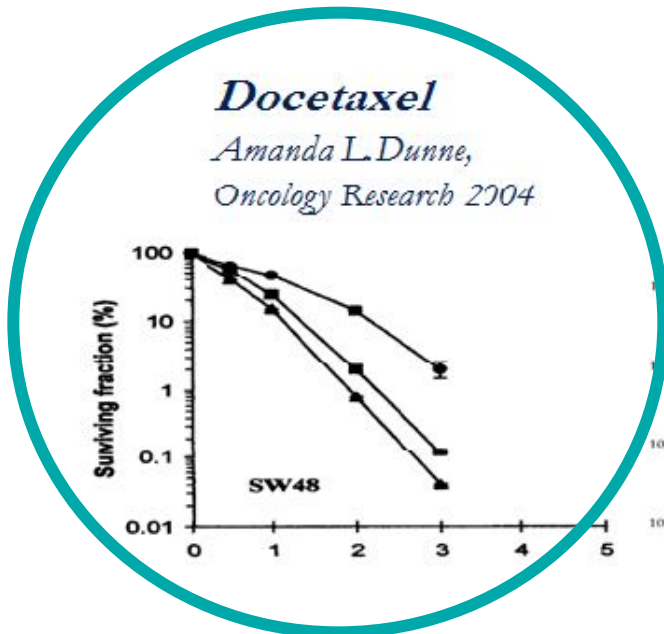


***Pemetrexed***

*Bischof, 2002  
 Int J Rad Onc Biol Phys*



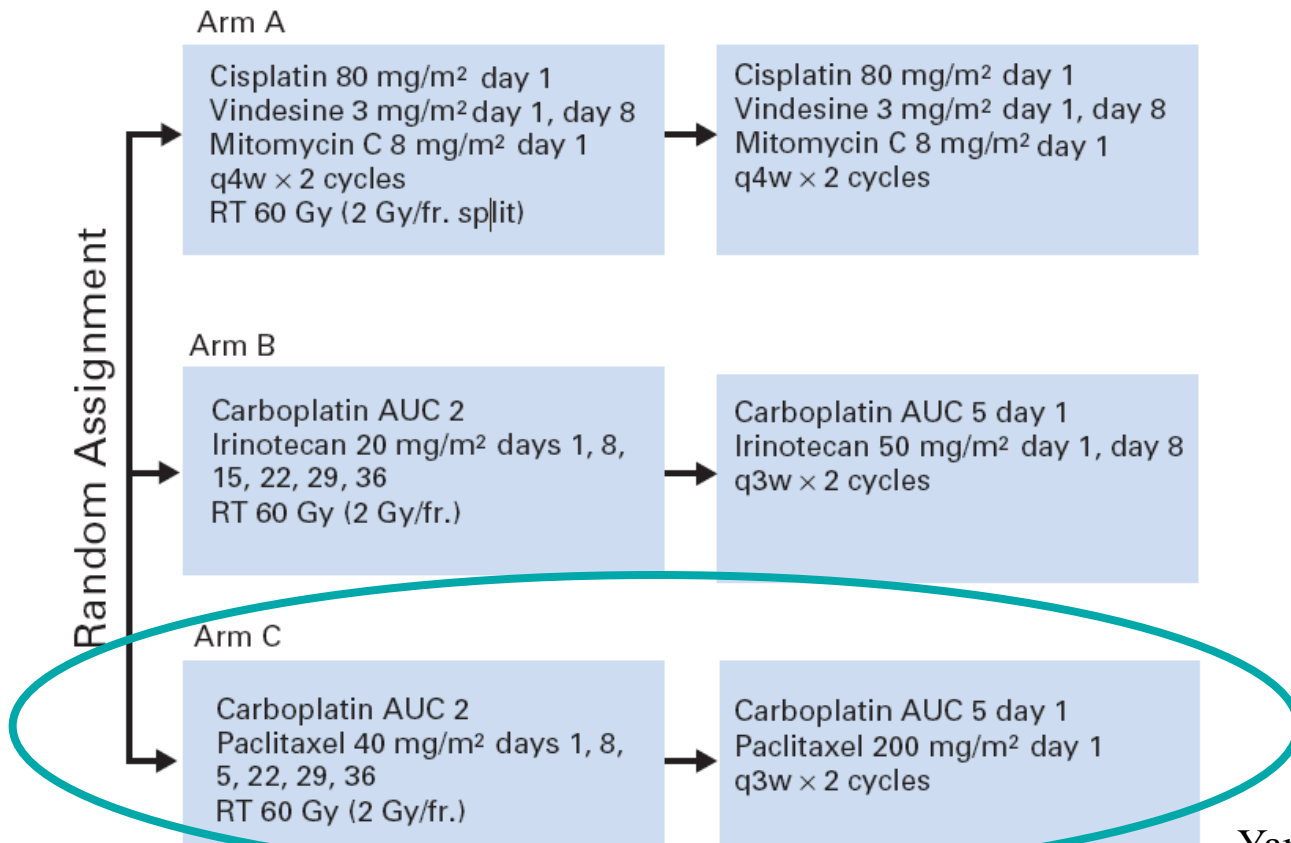
- The **most efficacious** chemotherapy drugs to be combined with thoracic radiotherapy is NOT established



# Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105



456 pts



Yamamoto, J Clin Oncol 2010



# Phase III Study Comparing Second- and Third-Generation Regimens With Concurrent Thoracic Radiotherapy in Patients With Unresectable Stage III Non–Small-Cell Lung Cancer: West Japan Thoracic Oncology Group WJTOG0105



456 pts

	<i>Median SVV (months)</i>	<i>SVV @5y (%)</i>	<i>Neutropenia ≥G3 (%)</i>	<i>Treatment interruptions (%)</i>
<i>Arm A</i>	20.5	17.5	<b>95.9</b>	18.5
<i>Arm B</i>	19.8	17.8	60.5	<b>32.7</b>
<i>Arm C</i>	22	19.8	61.9	12.2

*Arm C was equally efficacious and exhibited a more favorable toxicity profile*

Yamamoto, J Clin Oncol 2010, 28:3739-45



# Phase III Trial Comparing Docetaxel and Cisplatin Combination Chemotherapy With Mitomycin, Vindesine, and Cisplatin Combination Chemotherapy With Concurrent Thoracic Radiotherapy in Locally Advanced Non-Small-Cell Lung Cancer: OLCSG 0007

200 pts

Patient Population

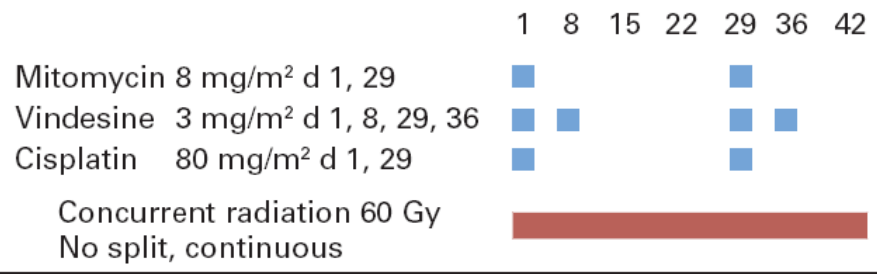
- Unresectable locally advanced NSCLC (Stage IIIA/IIIB)
- No prior treatment

Stratification

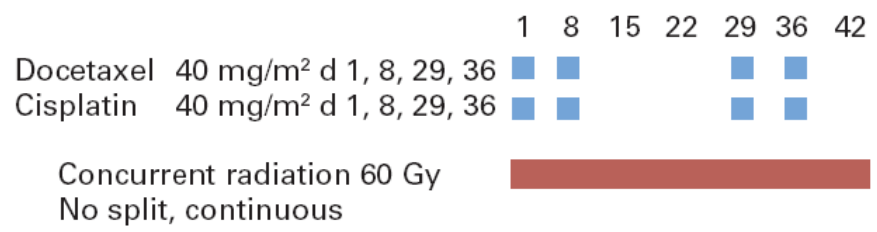
- Stage (IIIA/IIIB)
- PS (0 v 1)
- Institution

R  
a  
n  
d  
o  
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e

MVP arm (modified WJLCG regimen)



DP arm (experimental regimen)



Segawa J Clin Oncol 2010, 28: 3299-3306

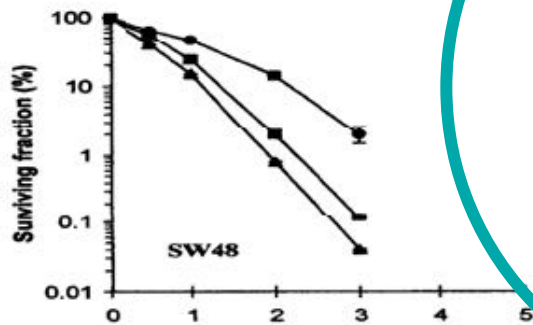




- The **most efficacious** chemotherapy drugs to be combined with thoracic radiotherapy is NOT established

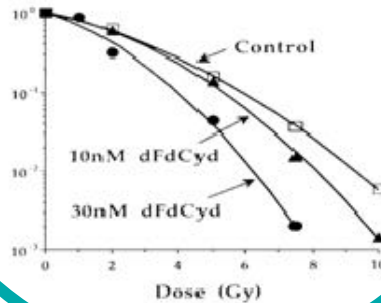
**Docetaxel**

*Amanda L. Dunne,  
 Oncology Research 2004*



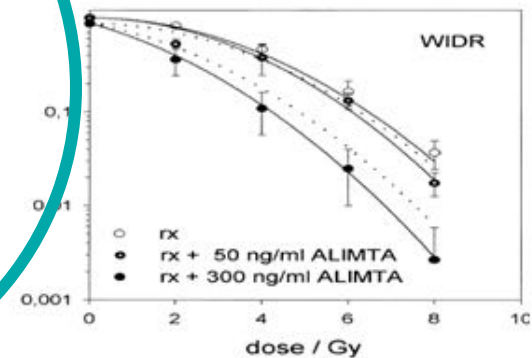
**Gemcitabine**

*Shewach et al  
 Cancer Research 1994*



**Pemetrexed**

*Bischof, 2002  
 Int J Rad Onc Biol Phys*



# *Gemcitabine*

<b>Study</b>	<b>CT</b>	<b>N of pts</b>	<b>ORR</b>	
Van Putten	Gemcitabine	24	63%	68%
Trodella	Gemcitabine	62	74%	
CALGB 9431	CDDP+Gemcitabine	62	74%	80%
Trodella	CDDP+Gemcitabine	50	93%	

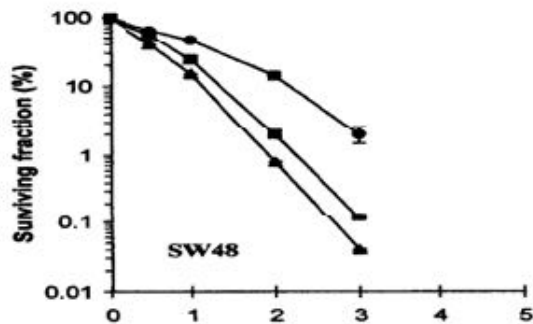




- The **most efficacious** chemotherapy drugs to be combined with thoracic radiotherapy is NOT established

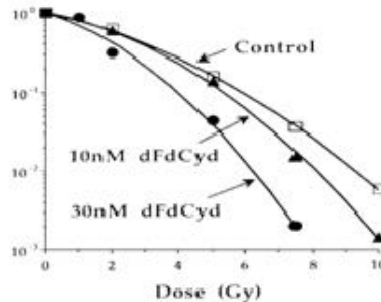
**Docetaxel**

*Amanda L. Dunne,  
 Oncology Research 2004*



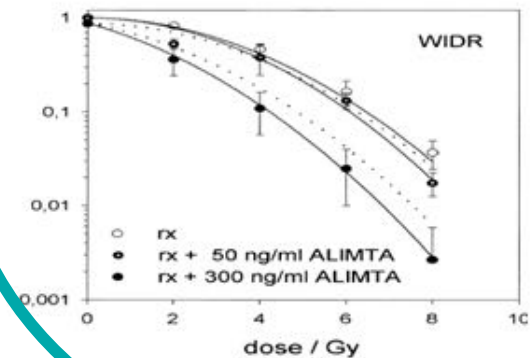
**Gemcitabine**

*Shewach et al  
 Cancer Research 1994*



**Pemetrexed**

*Bischof, 2002  
 Int J Rad Onc Biol Phys*



<b>Pemetrexed</b>	<b>Trial</b>	<b>CHT</b>	<b>RT Gy</b>	<b>Limiting Toxicity</b>	<b>Efficacy</b>
Gadgel <i>J Clin Oncol 2008</i>	Phase I	CBCDA AUC 6 and biweekly Pemetrexed 300 mg/mq	63 Gy	esophagitis infection	78%
Brade <i>Int J Radiat Oncol Biol Phys 2010</i>	Phase I	Pemetrexed 500 mg/mq CDDP 75-80 mg/ mq	64 Gy	pulmonary	88%
Surmont <i>Lung Cancer 2010</i>	Phase I	Pemetrexed 500 mg/mq and CDDP (60-80 mg/mq)	66 Gy	none	NA
Brade <i>J Clin Oncol 2010</i>	Phase II	Pemetrexed 500 mg/mq+CDDP 20mg/mq 1-5 q 21	61-65 Gy	none	OS 19.7 months PFS 11.8months
Vokes <i>J Clin Oncol 2011</i>	Phase II	Pemetrexed 500+ CBCDA AUC 5	70 Gy	none	RR=77% OS 23 months





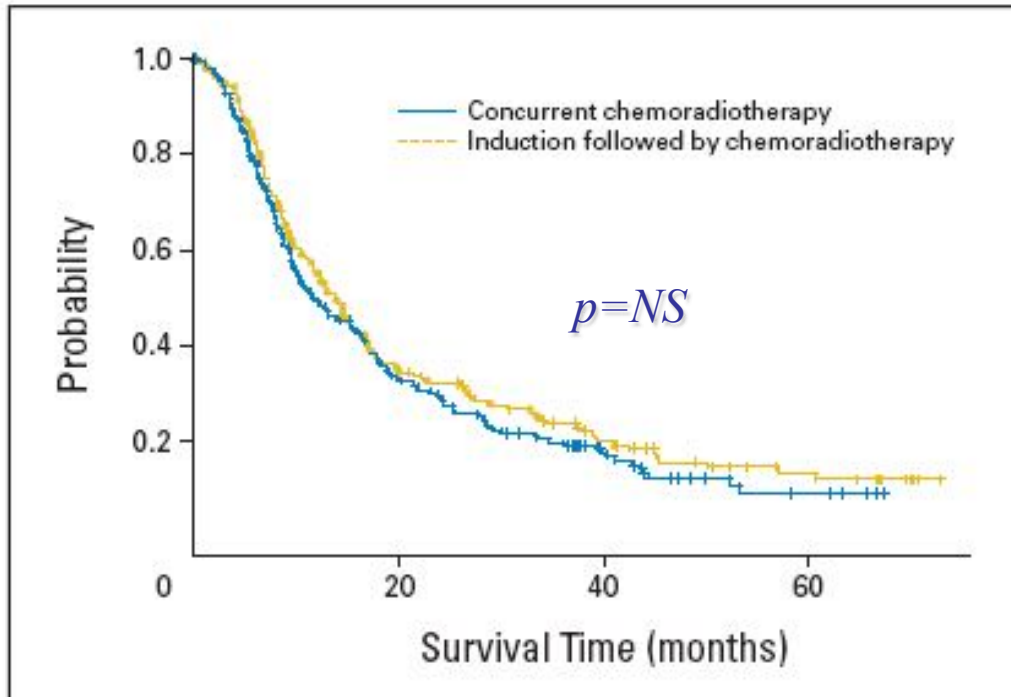
PROCLAIM: A Phase III Study of Pemetrexed, Cisplatin, and Radiation Therapy Followed by Consolidation Pemetrexed Versus Etoposide, Cisplatin, and Radiation Therapy Followed by Consolidation Cytotoxic Chemotherapy of Choice in Locally Advanced Stage III Non-Small-Cell Lung Cancer of Other than Predominantly Squamous Cell Histology

Vokes et al Clin Lung Cancer 2009 May;10(3): 193-8



# Induction Chemotherapy

## CALGB 39801



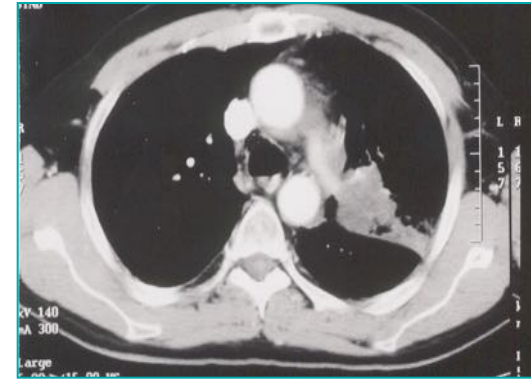
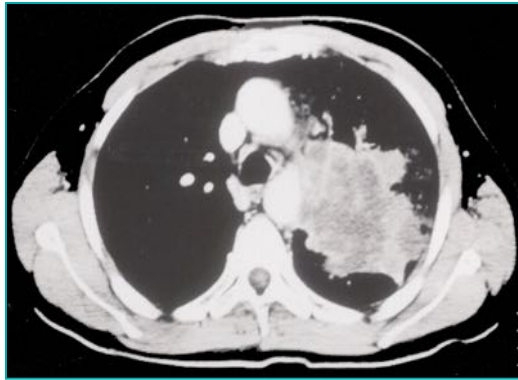
RESULTS	RTCT	CT → RTCT
Median survival	12 mo	14 mo
Failure free survival	7 mo	8 mo
Distant failure	86 pts	84 pts

*“The addition of induction chemotherapy does not provide a survival benefit over concurrent therapy alone...”*

Vokes, JCO 2007



*Induction chemotherapy does not improve OS and PFS...but could*

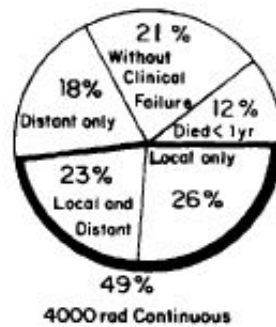
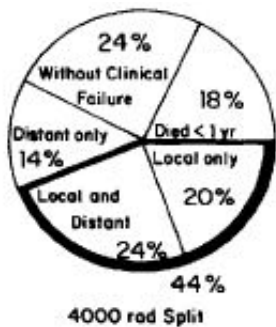


- ✓ Decrease tumor volume
- ✓ Decrease irradiated volume
- ✓ Decrease tumor spread (metastasis)
- ✓ Select a good prognostic group of patients before RT-CT

# A Prospective Randomized Study of Various Irradiation Doses and Fractionation Schedules in the Treatment of Inoperable Non-Oat-Cell Carcinoma of the Lung

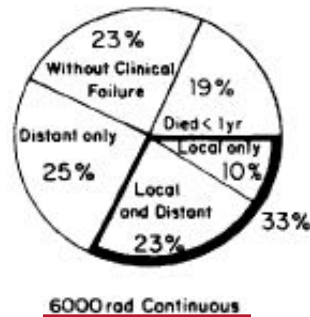
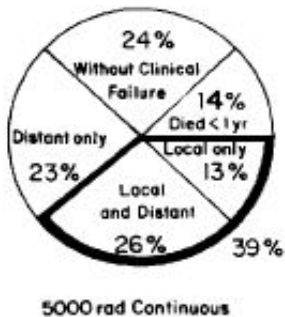
Preliminary Report by the Radiation Therapy Oncology Group

C. A. PEREZ, MD,\* K. STANLEY, PhD,† P. RUBIN, MD,‡ S. KRAMER, MD§, L. BRADY, MD,¶ R. PEREZ-TAMAYO, MD,# G. S. BROWN, MD,† J. CONCANNON, MD,\*\* M. ROTMAN, MD,†† AND H. G. SEYDEL, MD‡‡



## RTOG 73-01

“The current study strongly suggests that dosages in the range of 5000-6000 cGy yield higher tumor response, better survival and less intrathoracic recurrences”



Perez CA, Cancer 1980; 45(2): 2744-2754



**TOXICITY AND OUTCOME RESULTS OF RTOG 9311: A PHASE I-II DOSE-ESCALATION STUDY USING THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY IN PATIENTS WITH INOPERABLE NON-SMALL-CELL LUNG CARCINOMA**

JEFFREY BRADLEY, M.D.,\* MARY V. GRAHAM, M.D.,† KATHRYN WINTER, M.S.,‡  
JAMES A. PURDY, Ph.D.,§ RITSUKO KOMAKI, M.D.,|| WILSON H. ROA, M.D.,¶ JANICE K. RYU, M.D.,#  
WALTER BOSCH, D.Sc.,§ AND BAHMAN EMAMI, M.D.\*\*

Group 1 (V20<25%)			
<b>70.9 Gy</b>	<b>77.4 Gy</b>	<b>83.8 Gy</b>	<b>90.3 Gy</b>
<i>n 28</i>	<i>n 26</i>	<i>n 33</i>	<i>n 40</i>

Group 2 (V20 25-36%)	
<b>70.9 Gy</b>	<b>77.4 Gy</b>
<i>n 21</i>	<i>n 27</i>

*Bradley J, IJROBP 2005; 61(2):318-328*



## RTOG 93-11

Treatment (Gy)	Estimate Rate Grade 3 Lung Toxicity at 18 mo (%)
<b>Group 1 (&lt;25%)</b>	
70.9	7
77.4	16
83.8	0
90.3	13
<b>Group 2 (25-36%)</b>	
70.9	15
77.4	15

Treatment (Gy)	Estimate Rate Grade 3 Esophageal Toxicity at 18 mo (%)
<b>Group 1 (&lt;25%)</b>	
70.9	8
77.4	0
83.8	4
90.3	6
<b>Group 2 (25-36%)</b>	
70.9	0
77.4	5

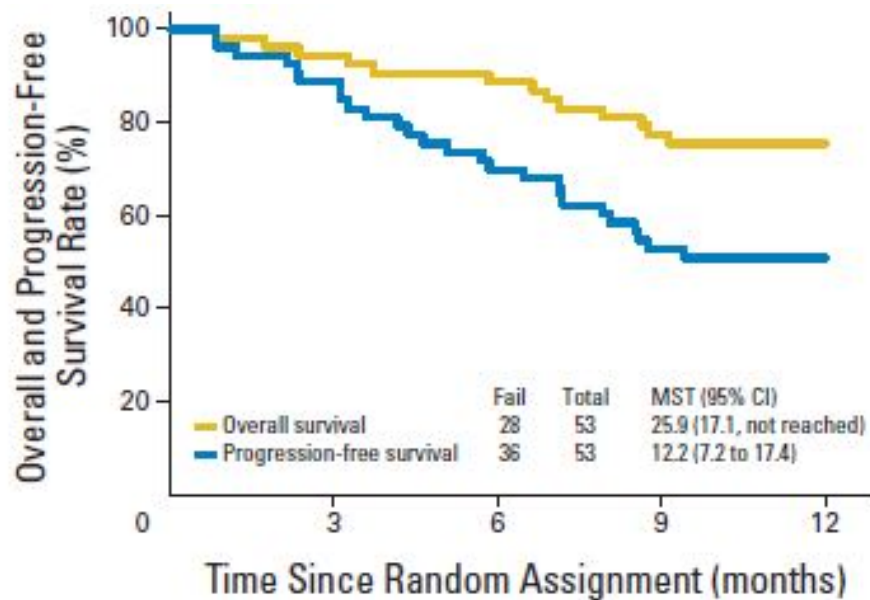
The radiation dose was safely escalated using 3D-CRT techniques to **83.8 Gy** for patients with V20 values of <25% (Group 1) and to **77.4 Gy** for patients with V20 values between 25% and 36% (Group 2), using fraction sizes of 2.15 Gy.

*Bradley J, IJROBP 2005; 61(2):318-328*





## A Phase I/II Radiation Dose Escalation Study with Concurrent Chemotherapy for Patients with Inoperable Stages I-III Non-Small Cell Lung Cancer: The Phase I Results of RTOG 0117



The MTD was determined to be 74 Gy/37 fractions (2.0 Gy per fraction) using 3DCRT with concurrent paclitaxel and carboplatin

OS and PFS rates at 12 months were 72.7% and 50.0%, respectively.

*Bradley J, IJROBP 2010; 77(2):367-372*



## RESULTS OF A PHASE I TRIAL OF CONCURRENT CHEMOTHERAPY AND ESCALATING DOSES OF RADIATION FOR UNRESECTABLE NON-SMALL-CELL LUNG CANCER

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PAUL L. SCHAEFER, M.D.,# ALEX ADJEI, M.D.,\* AND JAMES JETT, M.D.\*

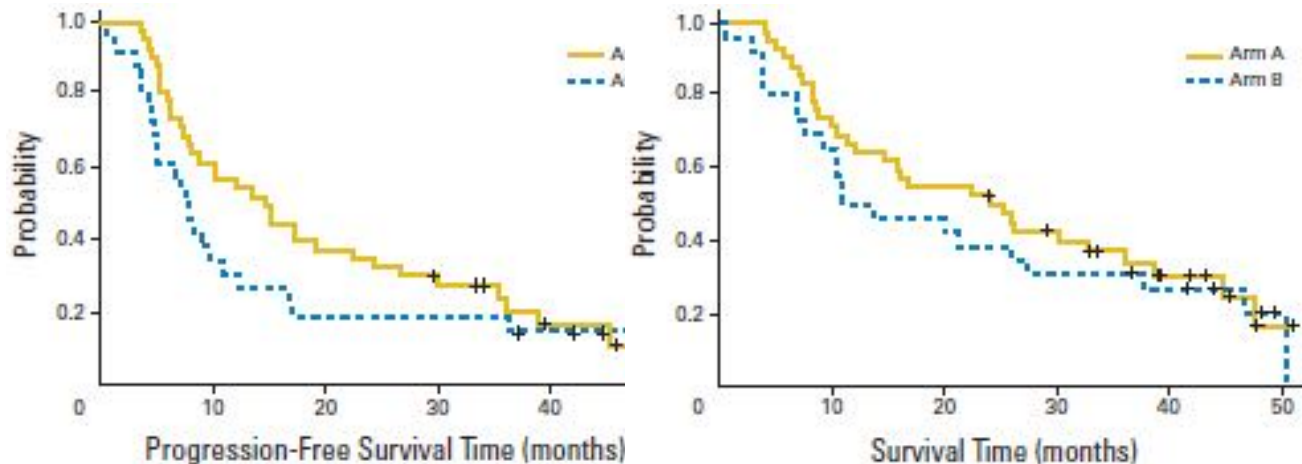
<i>Dose level</i>	<i>Dose RT (Gy)/fxs</i>	<i>N pts</i>	<i>N DLT</i>
<b>1</b>	<b>70/35</b>	<b>3</b>	<b>0</b>
<b>2</b>	<b>74/37</b>	<b>6</b>	<b>1</b>
<b>3</b>	<b>78/39</b>	<b>4</b>	<b>2</b>

*The MTD of the RT was 74 Gy with weekly carboplatin and paclitaxel*

*Schild SE, IJROBP 2006; 65: 1106-1111*



# Randomized Phase II Trial of Induction Chemotherapy Followed by Concurrent Chemotherapy and Dose Escalated Thoracic Conformal Radiotherapy (74 Gy) in Stage III Non-Small Cell Lung Cancer: CALGB 30105



MST was 24 months and 26% of patients survived 5 years.

The grade of 3 to 4 esophagitis was less than 10% and no grade 3 to 4 pulmonary toxicity was observed.

*Socinski MA, J Clin Oncol 2008; 26(2): 2457-63*



# DOSE ESCALATION and CONCURRENT CHEMOTHERAPY

- **NCCTG 0028**

Schild S. *IJROBP* 2006

- **CALGB 30105**

Socinski MA. *JCO* 2008

- **RTOG 0117**

Bradley J, *IJROBP* 2010

Feasibility of escalated total dose with concurrent chemotherapy (Carboplatin AUC2 and Paclitaxel 50 mg/mq/weekly)

74 Gy-2Gy/fx



# **RTOG 0617**

A Randomized Phase III Comparison of Standard-Dose (60 Gy) versus High-Dose (74 Gy) Conformal Radiotherapy with Concurrent and Consolidation Carboplatin/Paclitaxel +/- Cetuximab in Patients with Stage IIIA/IIIB Non-Small Cell Lung Cancer

Intergroup Participation:  
RTOG, NCCTG, CALGB



# RTOG 0617

<i>Concurrent Treatment</i>	<i>Consolidation Treatment</i>
<u><i>Arm A</i></u> Concurrent chemotherapy RT to 60 Gy, 5 fx per wk for 6 wks	<u><i>Arm A</i></u> Consolidation chemotherapy
<u><i>Arm B</i></u> Concurrent chemotherapy RT to 74 Gy, 5 fx per wk for 7.5 wks	<u><i>Arm B</i></u> Consolidation chemotherapy
<u><i>Arm C</i></u> Concurrent chemotherapy and Cetuximab RT to 60 Gy, 5 fx per wk for 6 wks	<u><i>Arm C</i></u> Consolidation chemotherapy and Cetuximab
<u><i>Arm D</i></u> Concurrent chemotherapy and Cetuximab RT to 74 Gy, 5 fx per wk for 7.5 wks	<u><i>Arm D</i></u> Consolidation chemotherapy and Cetuximab





ASTRO's Annual Meeting

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## RTOG 0617

Between November 2007 and April 2011, 423 study participants were enrolled in the RTOG trial

423 patients	Median OS
High dose RT (74 Gy)	20.7 months
Standard dose (60 Gy)	21.7 months
	P=0.02

There was no significant difference in treatment-related toxicity between treatment arms

*“High dose conformal radiotherapy (74 Gy) did not improve survival, compared standard dose (60 Gy) in patients with unresectable NSCLC”*





doi:10.1016/j.ijrobp.2011.12.032

## EDITORIAL

### ARE THE RESULTS OF RTOG 0617 MYSTERIOUS?

JAMES D. COX, M.D.



*“It is incumbent on the entire radiation oncology community to **improve the planning and delivery of RT** to avoid irradiating the normal lung and heart better than the standard techniques do today, so that dose-intensified schedules of RT can be safely administered”*

*Cox J, IJROBP 2012; 82(3): 1042-1044*





# *Integrated approaches in Locally Advanced Non-Small Cell Lung Cancer*

In patients with locally advanced NSCLC *concomitant chemo-radiotherapy* is the standard of care.

In patients with good performance status with bulky disease, *induction chemotherapy* should be considered primarily for cytoreductive intent.

*Higher biological tumor doses* could result in better survival.

*Improvement in local control represents a principal goal in designing new strategies to treat NSCLC*





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### Editorial

## Radiotherapy with curative intent for lung cancer: A continuing success story

Dirk De Ruysscher\*, Wouter van Elmpt, Philippe Lambin

Department of Radiation Oncology, Maastricht University Medical Centre, The Netherlands

*“The dynamism of lung cancer research deals with important aspects where significant gains can be expected in the coming years”*

