NSCLC STADIO III
TRATTAMENTI INTEGRATI RADICALI

S. Arcangeli

U.O.C. Radioterapia

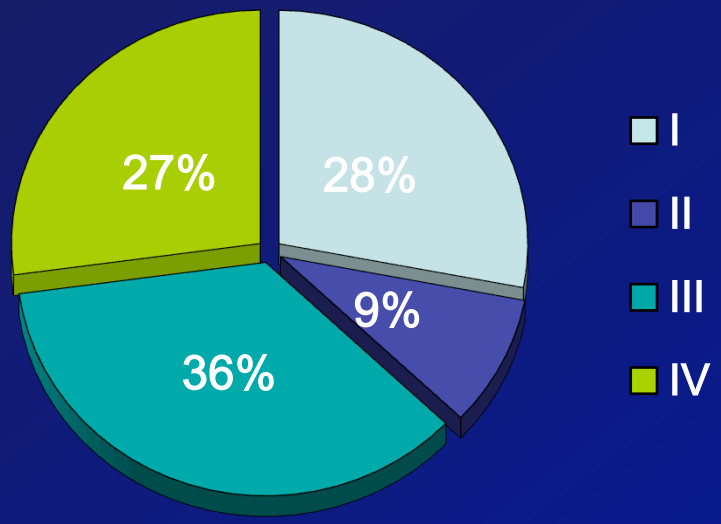
Azienda Ospedaliera San Camillo – Forlanini

Roma

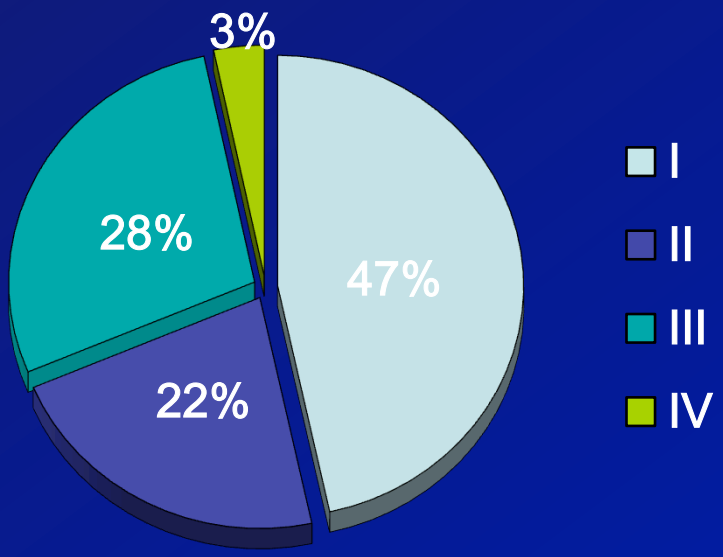
NSCLC Incidence

The IASLC Lung Cancer Database

Clinically Staged Cases, N = 53,646

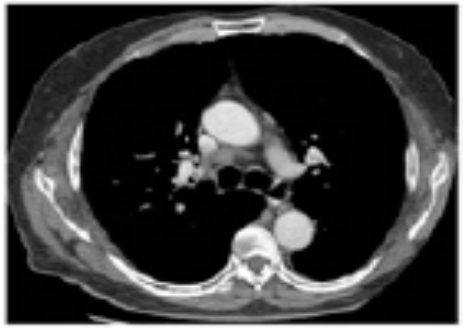


Pathologically Staged Cases, N = 33,933

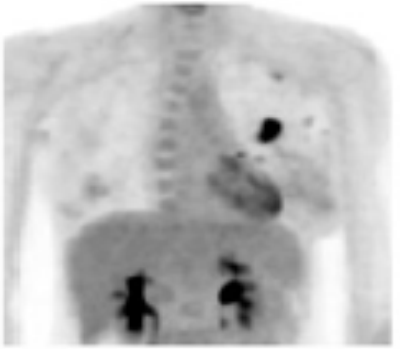


Stage III NSCLC Heterogeneity

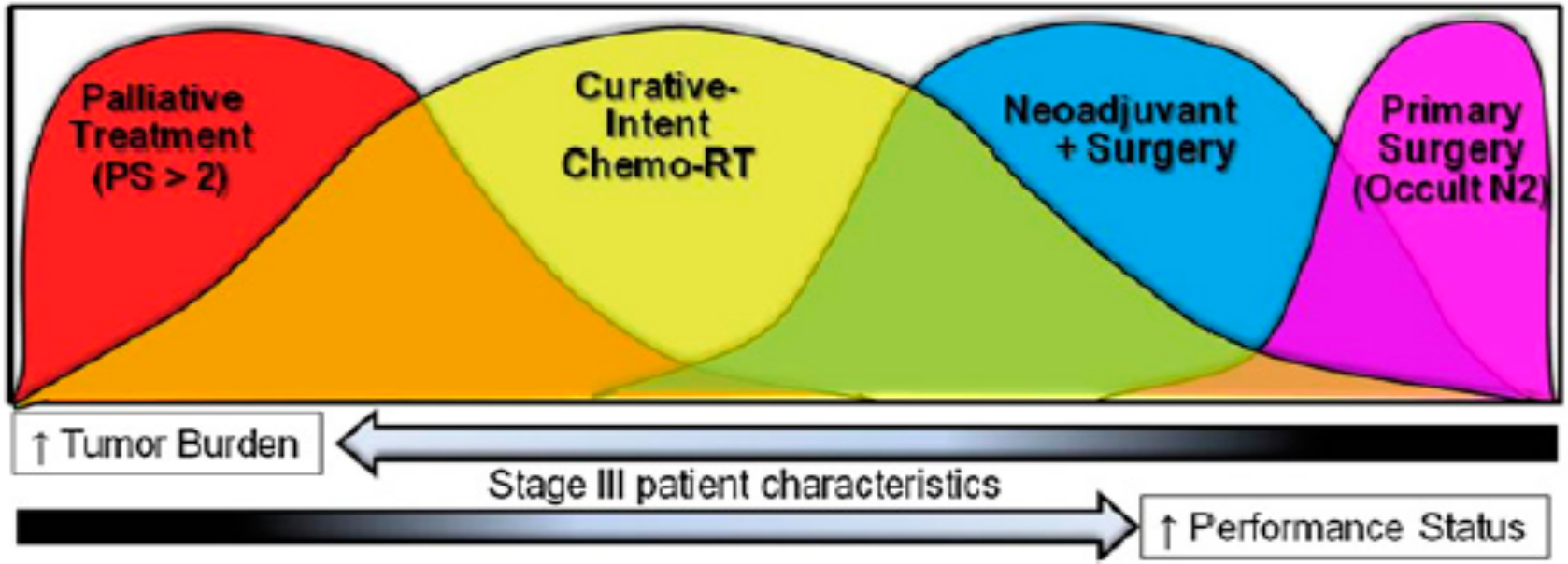
Mediastinal Infiltration



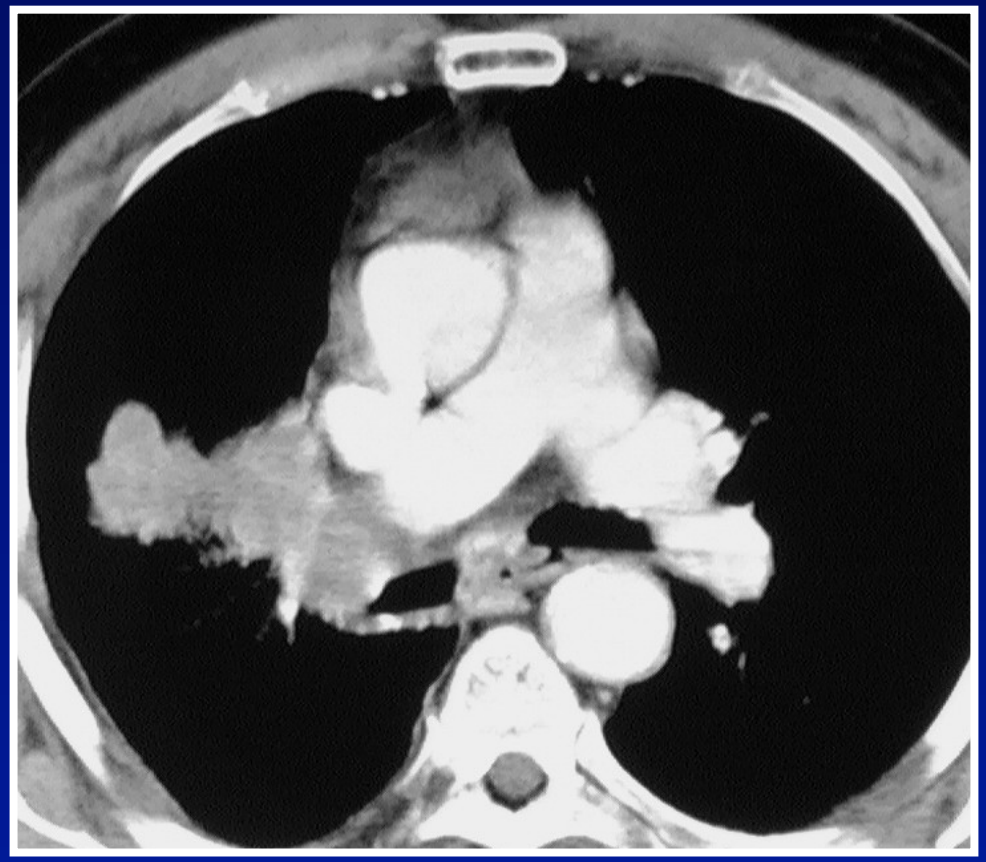
Discrete node enlargement



Clinically occult N2



Stage III “N2/N3 Disease“



Paramount goals :

- **to eradicate both visible, intrathoracic disease**
- **to reduce the incidence of extrathoracic metastases**

Stage III "N2/N3 Disease" AND Sequential/Concurrent RT

THE COCHRANE COLLABORATION®

711 patients
3 randomized trials

O'Rourke N. Clin Oncol 2010

1205 patients
6 randomized trials

Auperin A. J Clin Oncol 2010

Stage III "N2/N3 Disease" AND Sequential/Concurrent RT

Clinical Oncology 22 (2010) 347–355

Contents lists available at ScienceDirect

Clinical Oncology

journal homepage: 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

14% risk of death reduction @ 2y

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

Stage III "N2/N3 Disease"
AND Sequential/Concurrent RT

VOLUME 28 · NUMBER 13 · MAY 1 2010

JOURNAL OF CLINICAL ONCOLOGY

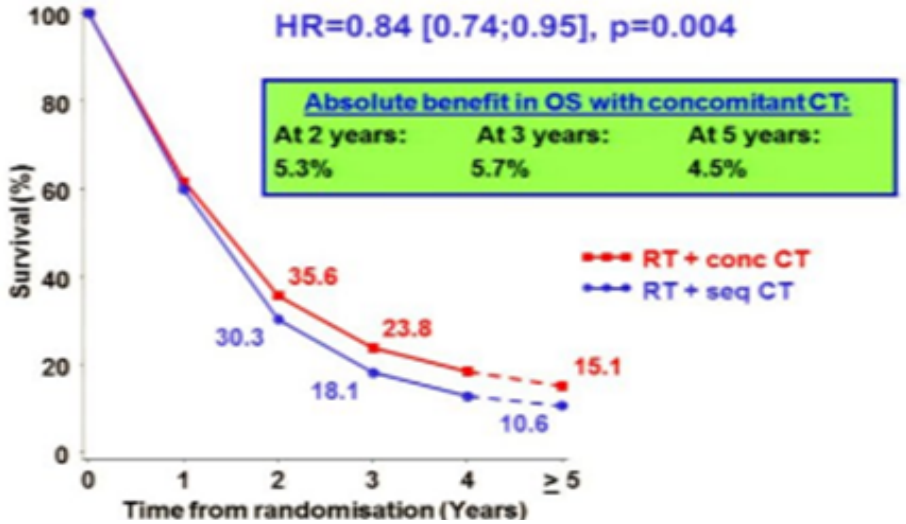
ORIGINAL REPORT

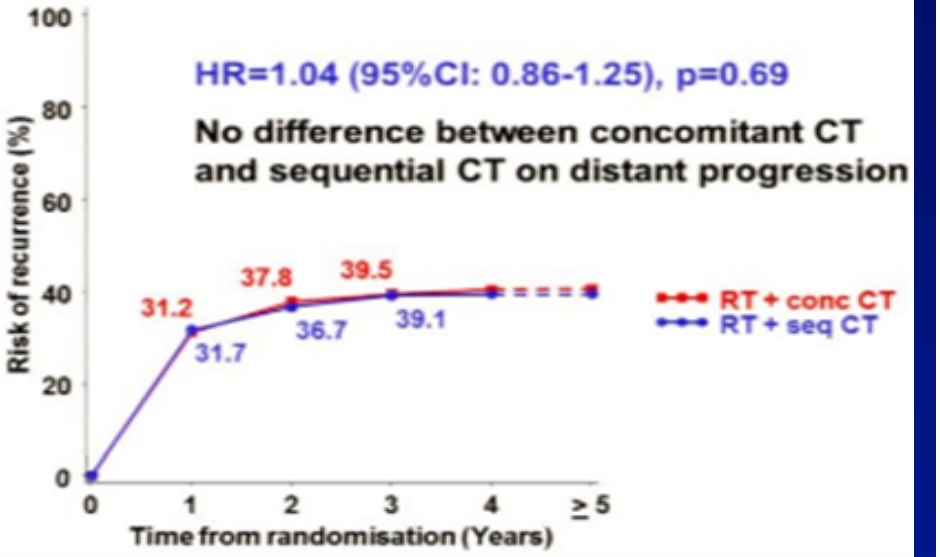
Meta-Analysis of Concomitant Versus Sequential Radiochemotherapy in Locally Advanced Non–Small-Cell Lung Cancer

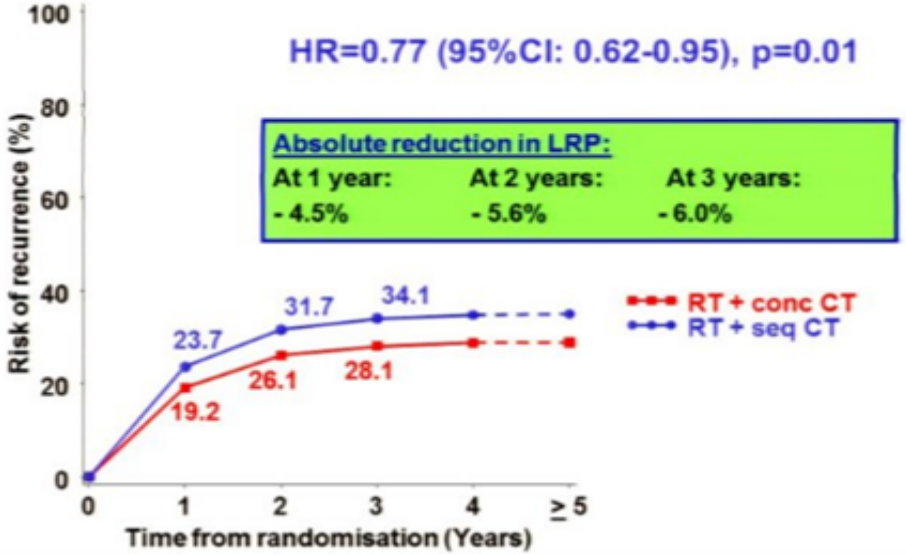
Anne Auperin, Cécile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Sarwar, Rodrigo Arriagada, Sarah Bunn, and Jean-Pierre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

MRC Clinical Trials Unit

Stage III "N2/N3 Disease" AND Sequential/Concurrent RT







- Oesophageal: Concomitant CT increased oesophageal toxicity as compared to sequential CT RR=4.9 (95%CI: 3.1-7.8), p<0.0001
  from 4% to 18%
- Pulmonary: No significant difference between concomitant and sequential CT
  RR=0.69 (95%CI: 0.42-1.12), p=0.13

Stage III "N2/N3 Disease" AND Sequential/Concurrent RT

In patients with stage III (N2,3) NSCLC and performance status 0-1 combination platinum-based chemotherapy and radiotherapy (60-66 Gy) are recommended (Grade 1A)

AMERICAN COLLEGE OF CHEST PHYSICIANS®

ESMO CLINICAL PRACTICE GUIDELINES NEW AND UPDATED 2013

NCCN National Comprehensive Cancer Network®

National Comprehensive Cancer Network

Your Best Resource in the Fight Against Cancer®

NSCLC
A GRIM TALE

NSCLC

- 1980s: Definitive XRT
- 1990s: Sequential chemoradiotherapy
- 2000s: Concurrent chemoradiation

5-y Survival

Site	1976	1982	1994	2008
Breast	75	76	85	90
Colon	50	55	63	65
Prostate	67	73	93	100
Rectum	48	52	61	68
Lung	12	13	14	17

CA CANCER J CLIN 2013

NSCLC

PAST

- Simple histologic classification
- 2-D techniques, ENI
- Pneumonectomy, lobectomy

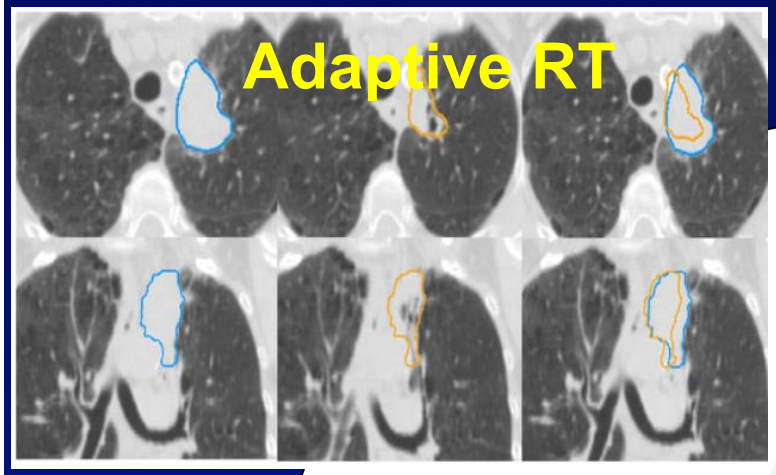
PRESENT

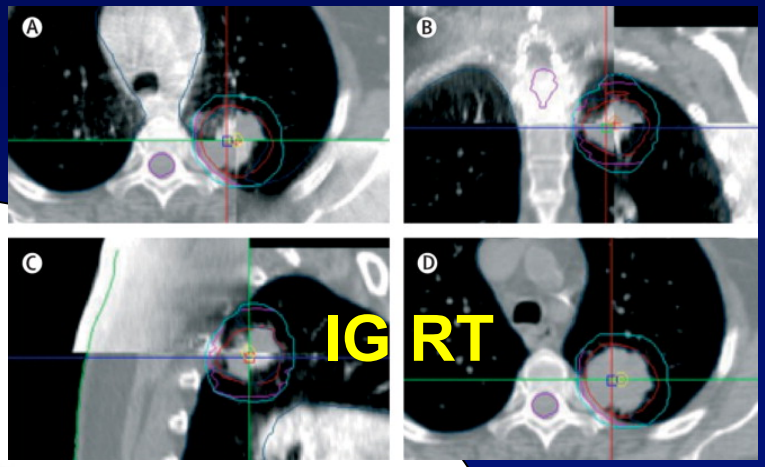
- Characterization of aberrant growth factor signaling pathways

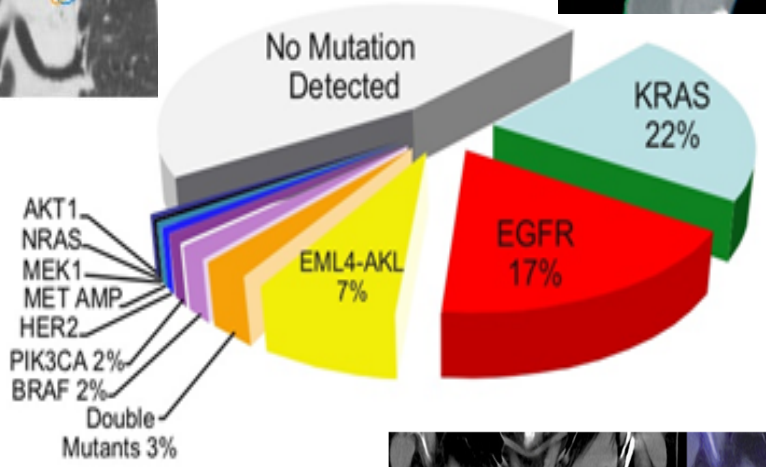
↓

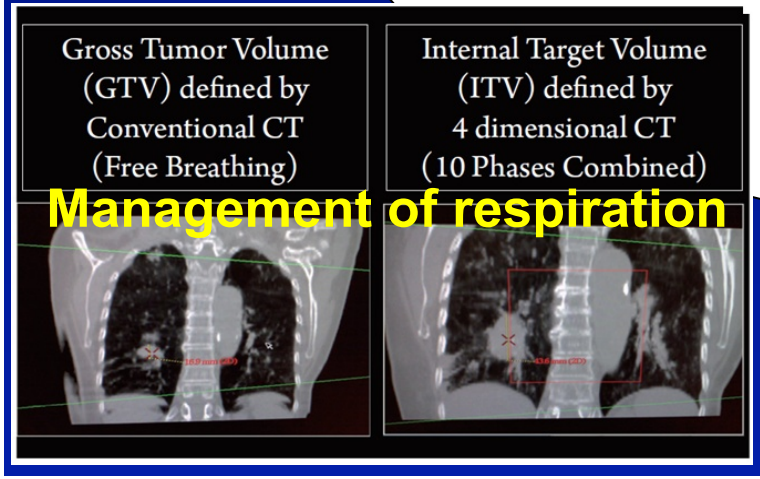
Development of targeted therapies

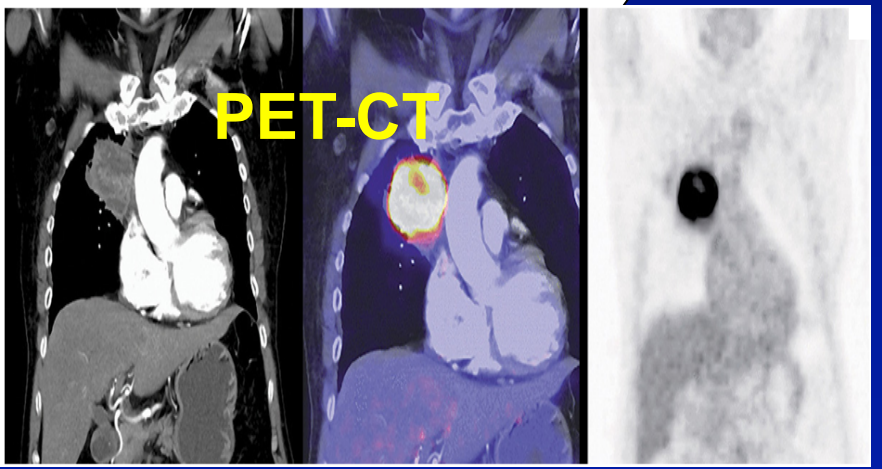
- IMRT/IGRT, IFI
  Management of respiration
  Adaptive treatment delivery
- VLS/Robotic sublobar resection


Adaptive RT


A
B
C
D
IG RT


No Mutation Detected
KRAS 22%
EGFR 17%
EML4-AKL 7%
AKT1
NRAS
MEK1
MET AMP
HER2
PIK3CA 2%
BRAF 2%
Double Mutants 3%


Gross Tumor Volume (GTV) defined by Conventional CT (Free Breathing)
Internal Target Volume (ITV) defined by 4 dimensional CT (10 Phases Combined)
Management of respiration

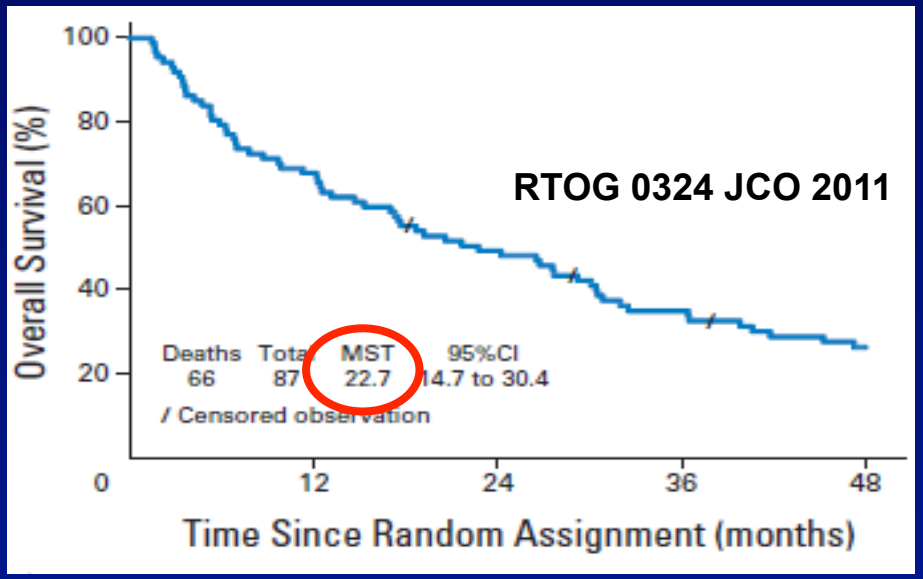

PET-CT

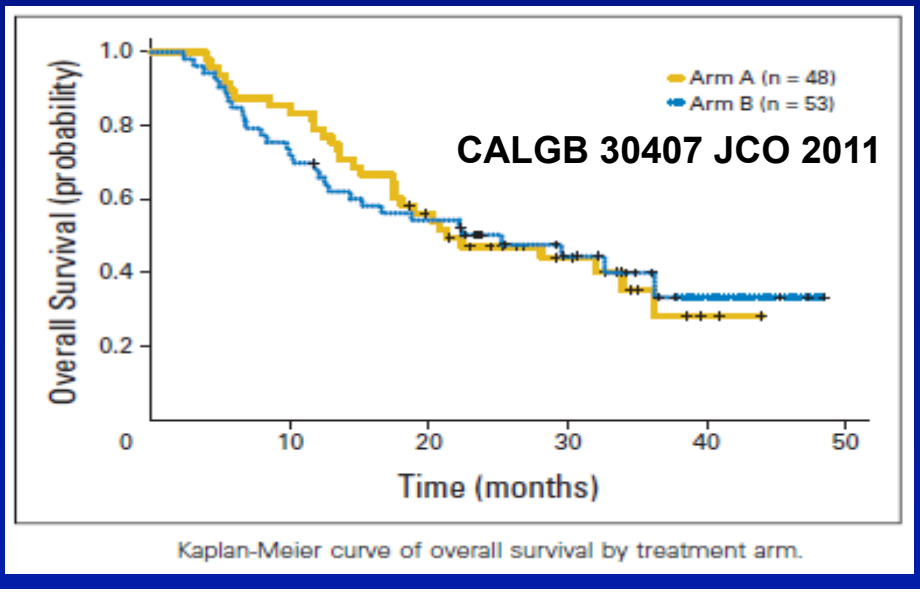
Stage III NSCLC
AND Third-Generation Chemotherapy

Phase II trials of platinum and pemetrexed and thoracic radiation for stage III disease

Authors	Treatment	Number of patients	Thoracic radiation therapy (Gy)	Median overall survival, months (95% CI)
Govindan et al.[13]	Arm A: Carboplatin (AUC = 5) Pemetrexed (500 mg/m^2) every 21 days[a] × 4, followed by pemetrexed (500 mg/m^2) × 4	48	70	21.2 (17.1-NA)
	Arm B: Carboplatin (AUC = 5) Pemetrexed (500 mg/m^2) Cetuximab[a] × 4 followed by pemetrexed (500 mg/m^2) × 4	53	70	25.2 (14.4-NA)
Gadgeel et al.[14]	Cisplatin (75 mg/m^2) Pemetrexed (500 mg/m^2) every 21 days × 3 followed by docetaxel (75 mg/m^2) every 21 days × 3[b]	28	66	34
Xu et al.[16]	Carboplatin (AUC = 5) Pemetrexed (500 mg/m^2) every 21 days × 5 cycles	21	60–66	NA
Brade et al.[15]	Cisplatin 20 mg/m^2 on days 1–5 Pemetrexed (500 mg/m^2) every 21 days × 4 cycles	39	61–66	19.7
Choy et al.[17]	Arm A: Carboplatin (AUC = 5) Pemetrexed (500 mg/m^2) every 21 days × 3 followed by pemetrexed 500 mg/m^2 × 3	34[c]	64–68	NA
	Arm B: Cisplatin (75 mg/m^2) Pemetrexed (500 mg/m^2) × 3 followed by pemetrexed (500 mg/m^2) × 3	38[c]	64–68	NA

Stage III NSCLC
RT & Monoclonal Antibodies





Kaplan-Meier curve of overall survival by treatment arm.

Stage III NSCLC
RT & Monoclonal Antibodies

Tracheoesophageal Fistula Formation in Patients With Lung Cancer Treated With Chemoradiation and Bevacizumab

Induction **Break** **Consolidation for CR, PR, Stable Disease**

Week 1 2 3 4 5 6 7 8 – 12 – 15 16 17 18 19 20 21 22 23 24 25

↑ BPC ↑ BPC — Restage ↑ BPC ↑ BPC ↑ BPC — Restage

| —— RT —— | → Progression Off study → Progression Off study

Induction (weeks 1-7)
Bevacizumab (B) 15 mg/kg IV, weeks 1 and 4 (2 courses)
Pemetrexed (P) 500 mg/m² IV, weeks 1 and 4 (2 courses)
Carboplatin (C) AUC 5 IV, weeks 1 and 4 (2 courses)
Radiation (RT) 1.8 Gy single daily dose, Monday–Friday, to total dose 61.2 Gy

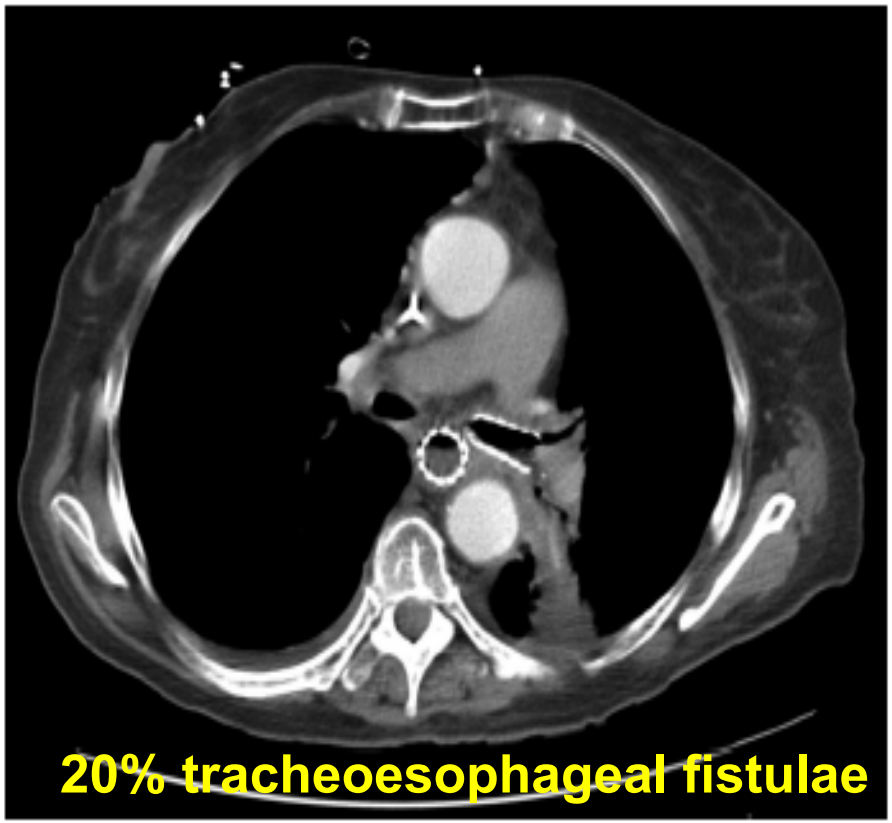
Break (weeks 8-15)

Consolidation (weeks 16-24)
Bevacizumab (B) 15 mg/kg IV weeks 16, 19, and 22 (3 courses)
Pemetrexed (P) 500 mg/m² IV, weeks 16, 19, and 22 (3 courses)
Carboplatin (C) AUC 6 IV, weeks 16, 19, and 22 (3 courses)

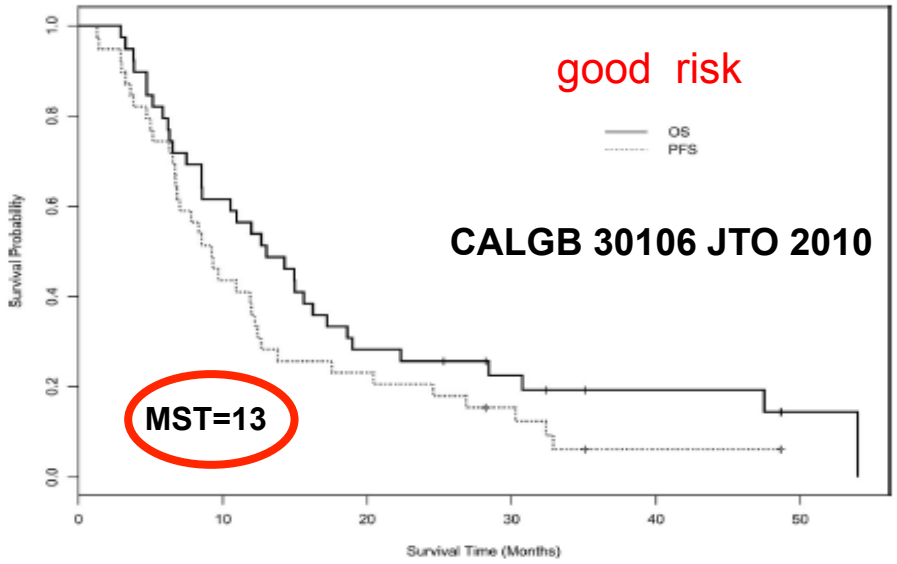
Maintenance (weeks 25-51) for CR, PR, Stable Disease

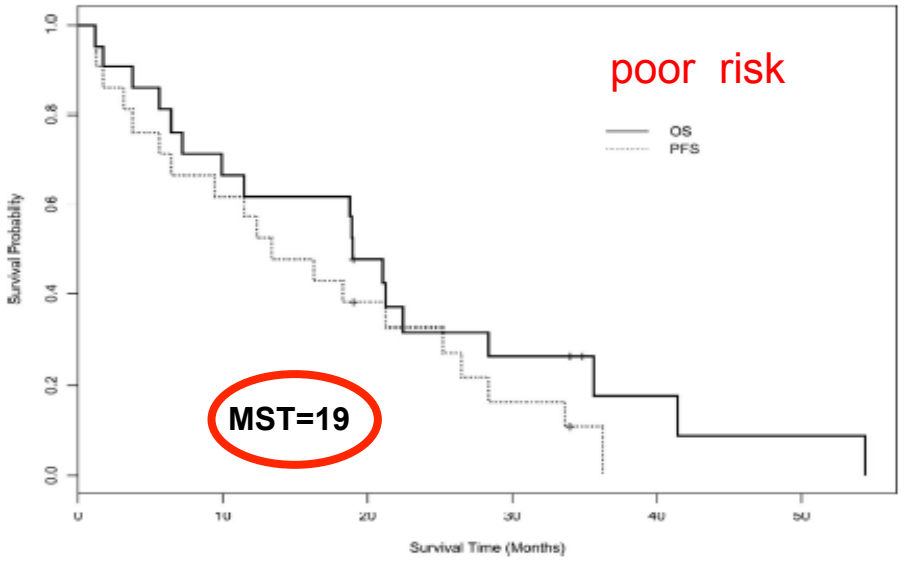
Week 25 | —— | 51 Restaging was every 9 weeks. Off study for disease progression.
↑
B

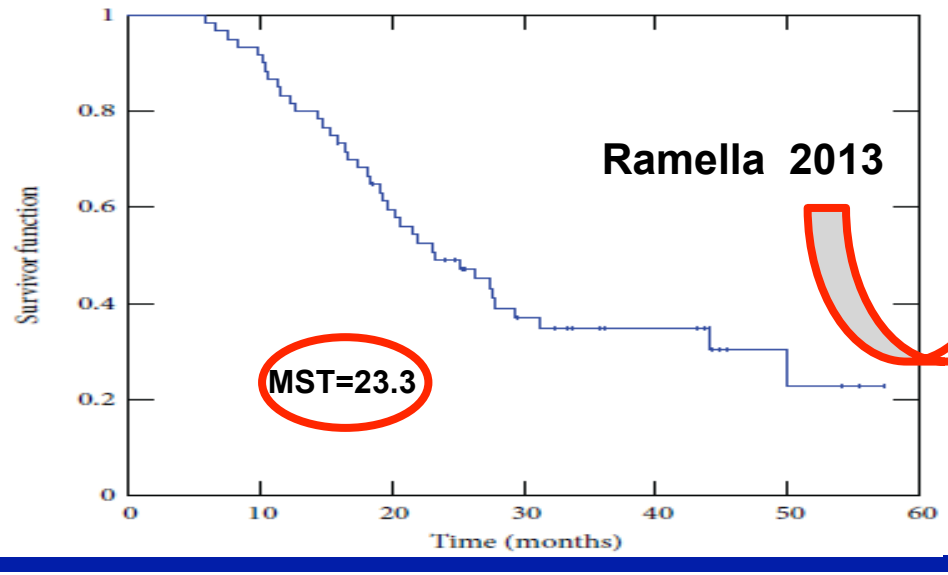
Bevacizumab (B) 15 mg/kg IV every 3 weeks (weeks 25, 28, 31, 34, 37, 40, 43, 46, and 49; 9 courses)



Stage III NSCLC
RT & TKI's inhibitors







Komaki 2011

1-year OS 84%, MST 25.8 m

Stage III NSCLC
AND Novel Biologic Agents

Novel biologic agents in combination with chemoradiation are not recommended outside a clinical trial

A confirmatory intergroup trial, RTOG 0617, is currently evaluating the addition of cetuximab to CRT in a phase III setting

Stage III NSCLC AND Focus on RT

Underuse of Radiotherapy in Lung Cancer Has Negative Consequences for Patients

Indication for Initial Radiotherapy Treatment in Lung Cancer, Number of Cases, Potential Survival Benefit and Benefit not Received

NSCLC/Stage	RT Type	Indication[a]	Percentage of Cases in Stage	Benefit (mo)	Source	Difference R/T[b]	Months of Benefit not Received
I/II inoperable	RTr	1b	20±1.8	14/18	23, 24, 25	−80	1120/1440
I/II /IIIa postsurgery	RTr	2c	8	4.8	26, 27	−41	196.8
IIIa potentially resectable	RTr+CT	1b	75±10	5–8	28, 29, 30	−66.5	332/532
IIIb PS 0–1	RTr+CT	1a		5–8	30, 31, 32	−98.25	491/786
IIIb PS>2, weight loss	RTp	1a		1.8	33, 34 , 35	−98.25	176.8
IV	RTp	1a	35±7	1.8	21	−230	419.4
SCLC limited	RTc.	1a	34±3	2.4	36	−126	302.4
						Total	Total
						−740	3038.4/3553.4

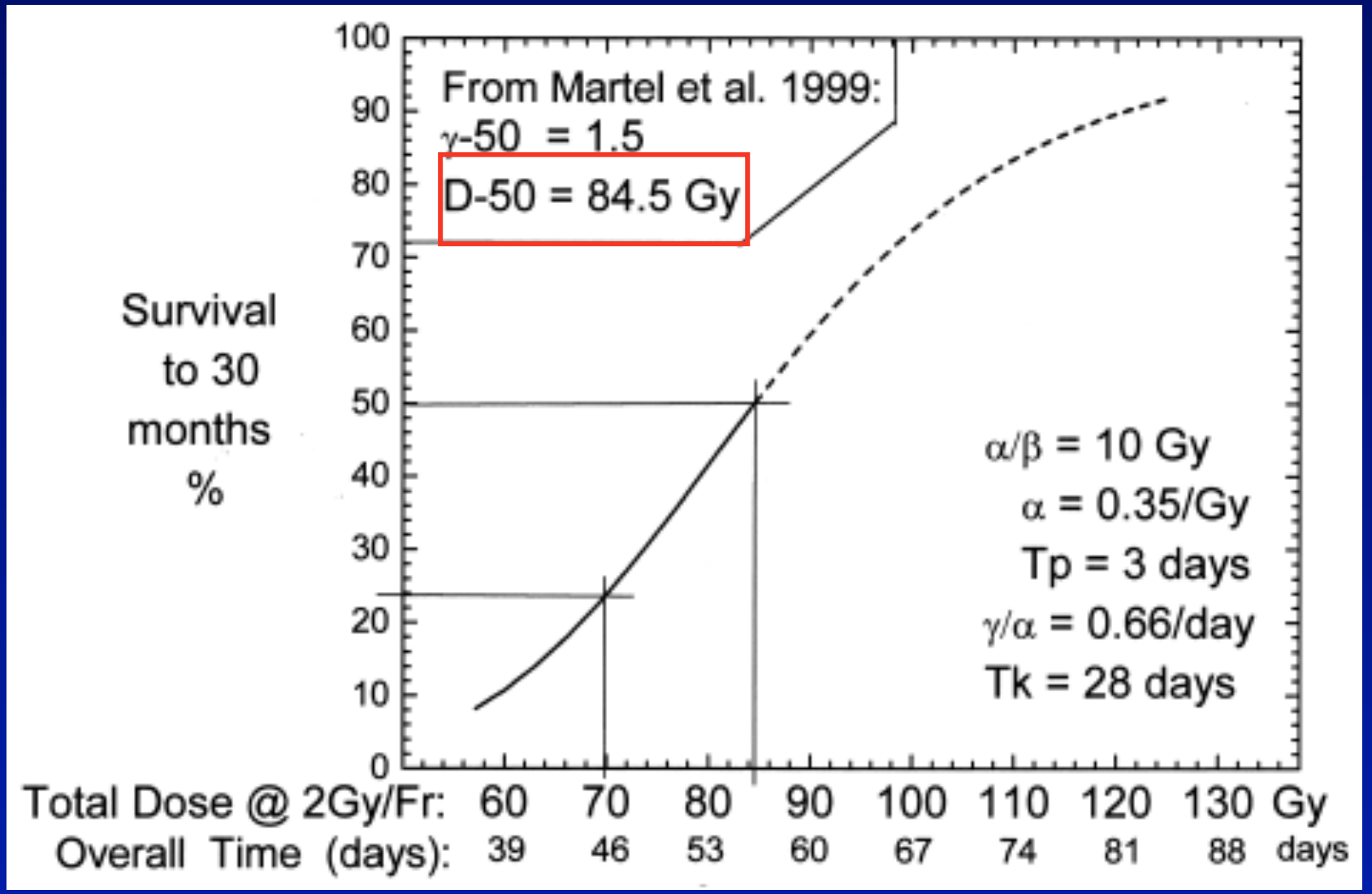
Stage III NSCLC
AND Focus on RT

So far, concurrent chemotherapy with radiotherapy to a dose of 60 Gy in 30 daily fractions is considered the standard treatment

Locoregional control rate @ 3 yrs = 38%

Journal of Thoracic Oncology 2012

Stage III NSCLC
AND Focus on RT



Stage III NSCLC
AND Focus on RT

HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

IJROBP 2012

RT dose intensity ensure a 4% relative improvement in survival for every 1 Gy BED increase

Stage III NSCLC AND Focus on RT

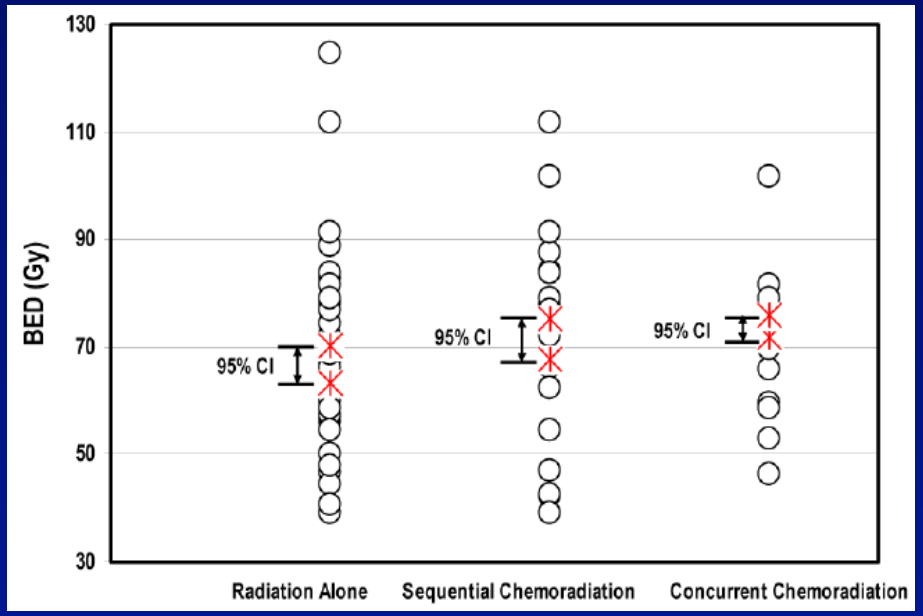
HIGHER BIOLOGICALLY EFFECTIVE DOSE OF RADIOTHERAPY IS ASSOCIATED WITH IMPROVED OUTCOMES FOR LOCALLY ADVANCED NON–SMALL CELL LUNG CARCINOMA TREATED WITH CHEMORADIATION: AN ANALYSIS OF THE RADIATION THERAPY ONCOLOGY GROUP

IJROBP 2012

Chemoradiotherapy dose intensity and outcome: review of selected literature

Study	No. of Patients	Nominal RT dose/fraction size: Conventiona	Approximate RT dose intensity (BED): RT dose intensity	Type of chemotherapy	Survival
West Japan	148	56 Gy/2	67	MVdP	16.5 mo.
RTOG 9410 Arm #2	201	60 Gy/2	72	Cis/Vlb	17.0 mo.
LAMP	92	63 Gy/1.8	74	Cbo/Tax	16.1 mo.
SWOG 9504	83	61.2 Gy/1.8	72	Cis/Etop/Doc	26.0 mo.
Intermediate dose intensity RT					
Japanese Jeremic trial	65	69.6 Gy/1.2 bid	78	Cbo/Etop	22.0 mo.
RTOG 9410 Arm #3	193	69.6 Gy/1.2 bid	78	Cis/Etop	15.2 mo.
CALGB 39801	366	66 Gy/2	79	Cbo/Tax	14.0 mo.
Dose intense RT					
RTOG 0117	63	74 Gy/2	89	Cbo/Tax	26 mo.
CALGB 30105	43	74 Gy/2	89	Cbo/Tax	25 mo.
NCCTG N0028	20	70-78Gy/2	89	Cbo/Tax	42 mo.
University of North Carolina Consortium	62	74 Gy/2	89	Cbo/Tax	25 mo.

Stage III NSCLC AND Focus on RT



Factors	Estimated HR of death (95% CI)	*p* value*
KPS	0.964 (0.934 – 0.994)	0.020
Weight loss < 5%	0.702 (0.524 – 0.939)	0.017
Pre-RT oxygen use (yes vs. no)	1.393 (0.824 – 2.354)	0.215
Stage (IIIA vs. IIIB)	1.062 (0.799 –1.413)	0.677
Concurrent CT-RT vs. RT alone	0.461 (0.322 – 0.662)	< 0.001
Sequential CT-RT vs. RT alone	0.692 (0.502 – 0.955)	0.025
BED (Gy)	0.976 (0.966 – 0.985)	< 0.001

The effect of radiation dose on survival is independent of whether chemotherapy is given

Wang L. IJROBP 2009

Stage III NSCLC
AND Dose escalated RT & Concurrent Chemo

Phase I-II trials

Study	Radiation dose (Gy)	Chemotherapy	Median survival time (months)
RTOG 0117 PET FDG	74	Carboplatin/paclitaxel	21.6
NCCTG 0028 PET FDG	74	Carboplatin/paclitaxel	37
North Carolina	74	Carboplatin/paclitaxel	24
Wake Forest	74	Gemcitabine	18
CALGB 30105 PET FDG	74	Carboplatin/paclitaxel	24

Stage III NSCLC AND RTOG 0617

Arm A

Concurrent chemotherapy:
Carboplatin & Paclitaxel

RT to 60 Gy, 5 x per week
for 6 weeks

Arm B: Closed 6/17/11

Concurrent chemotherapy:
Carboplatin & Paclitaxel

RT to 74 Gy, 5 x per week
for 7.5 weeks

1-year OS: 81% in the 60 Gy arm vs 70.4% in the 74 Gy arm (p=0.02)

Arm C

Cetuximab Loading Dose:
Week 1, Day 1
then
Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab

RT to 60 Gy, 5 x per week
for 6 weeks

Arm D: Closed 6/17/11

Cetuximab Loading Dose:
Week 1, Day 1
then
Concurrent chemotherapy, Carboplatin Paclitaxel, and Cetuximab

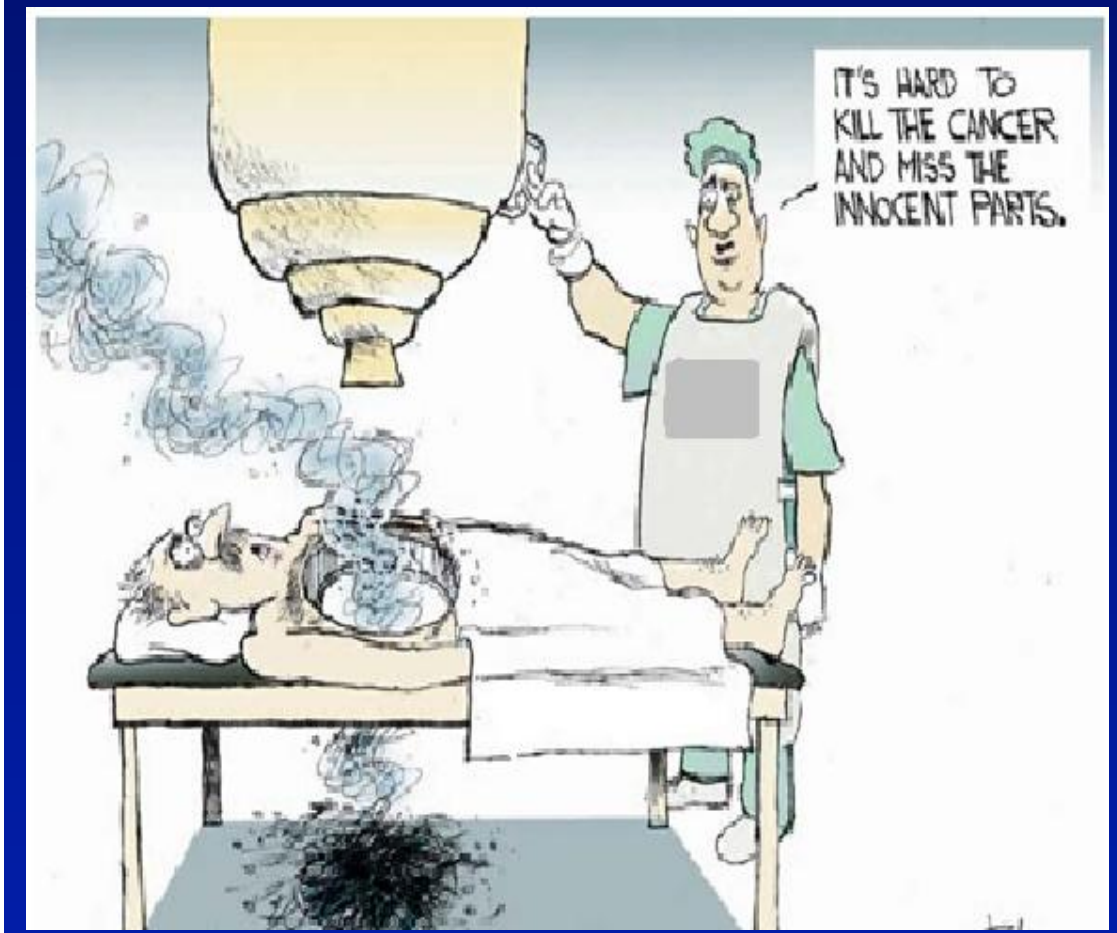
RT to 74 Gy, 5 x per week
for 7.5 weeks

EDITORIAL

ARE THE RESULTS OF RTOG 0617 MYSTERIOUS?

JAMES D. COX, M.D.

Division of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX



Deaths related to the effects on the normal lungs and perhaps the heart from high-dose 3D-CRT and IMRT?

Letter

Dose-escalated Radiotherapy for Stage III Unresectable Non-small Cell Lung Cancer: Have We Come to a Standstill?

S. Arcangeli, V. Donato
Radiotherapy Department, S. Camillo-Forlanini Hospital, Rome, Italy

Arm B: Closed 6/17/11

Concurrent chemotherapy:
Carboplatin & Paclitaxel

RT to 74 Gy, 5 x per week
for 7.5 weeks

Arm D: Closed 6/17/11

Cetuximab Loading Dose:
Week 1, Day 1
then
Concurrent chemotherapy, Carboplatin
Paclitaxel, and Cetuximab

RT to 74 Gy, 5 x per week
for 7.5 weeks

Dose escalation by extending the course of treatment over more days incurs extra tumor cell repopulation during the course of treatment, lessening the benefit of the extra dose

Letter

Dose-escalated Radiotherapy for Stage III Unresectable Non-small Cell Lung Cancer: Have We Come to a Standstill?

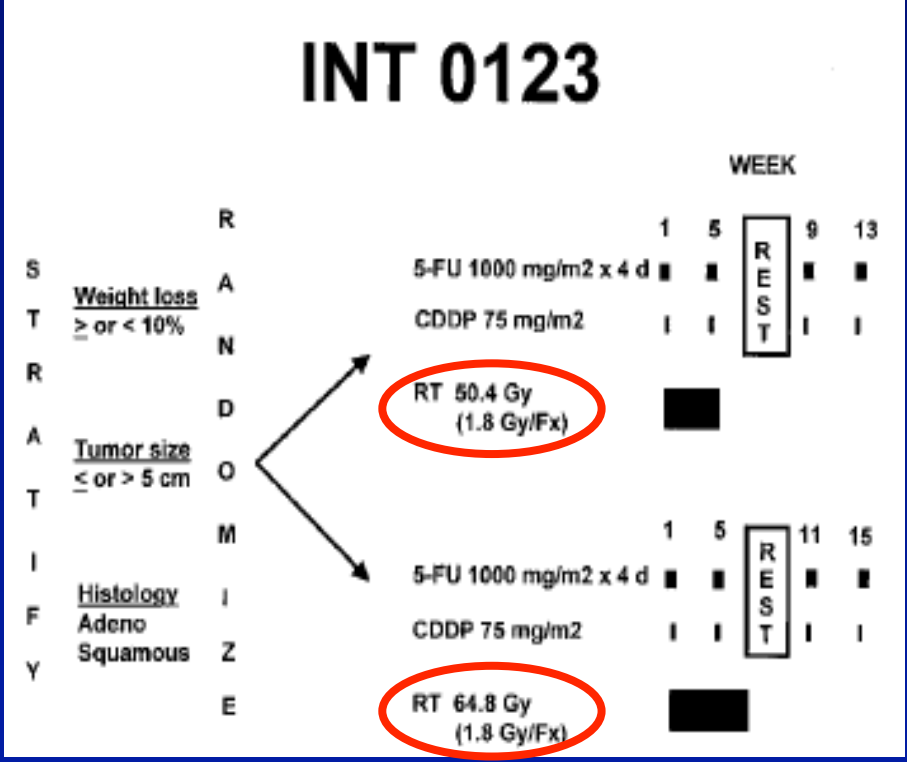
S. Arcangeli, V. Donato
Radiotherapy Department, S. Camillo-Forlanini Hospital, Rome, Italy

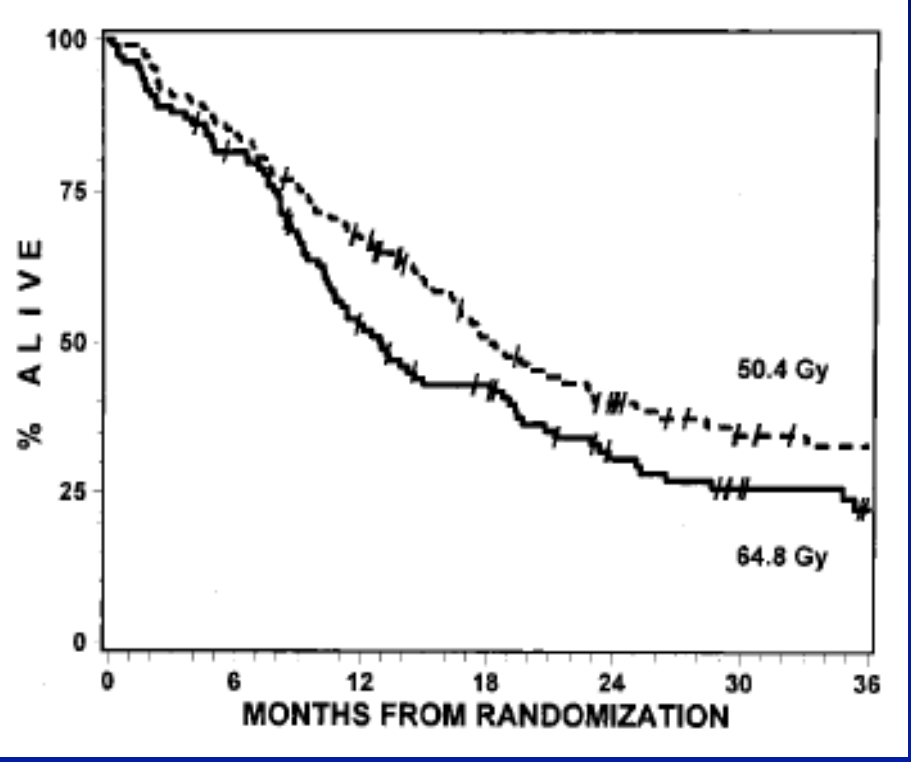
3 RTOG trials

- loss of survival of 1.6% per day of prolongation >6 weeks [Fowler '02]
- risk of death >2% for each day of prolongation in concurrent CT-RT [Machtay '05]

Stage III NSCLC
A lesson NOT learned!

INT 0123 (Radiation Therapy Oncology Group 94-05) Phase III Trial of Combined-Modality Therapy for Esophageal Cancer: High-Dose Versus Standard-Dose Radiation Therapy





Minsky JCO 2002

Stage III NSCLC
How to go beyond 60 Gy ?

Stage III NSCLC
AND Hyperfractionatated RT

Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial

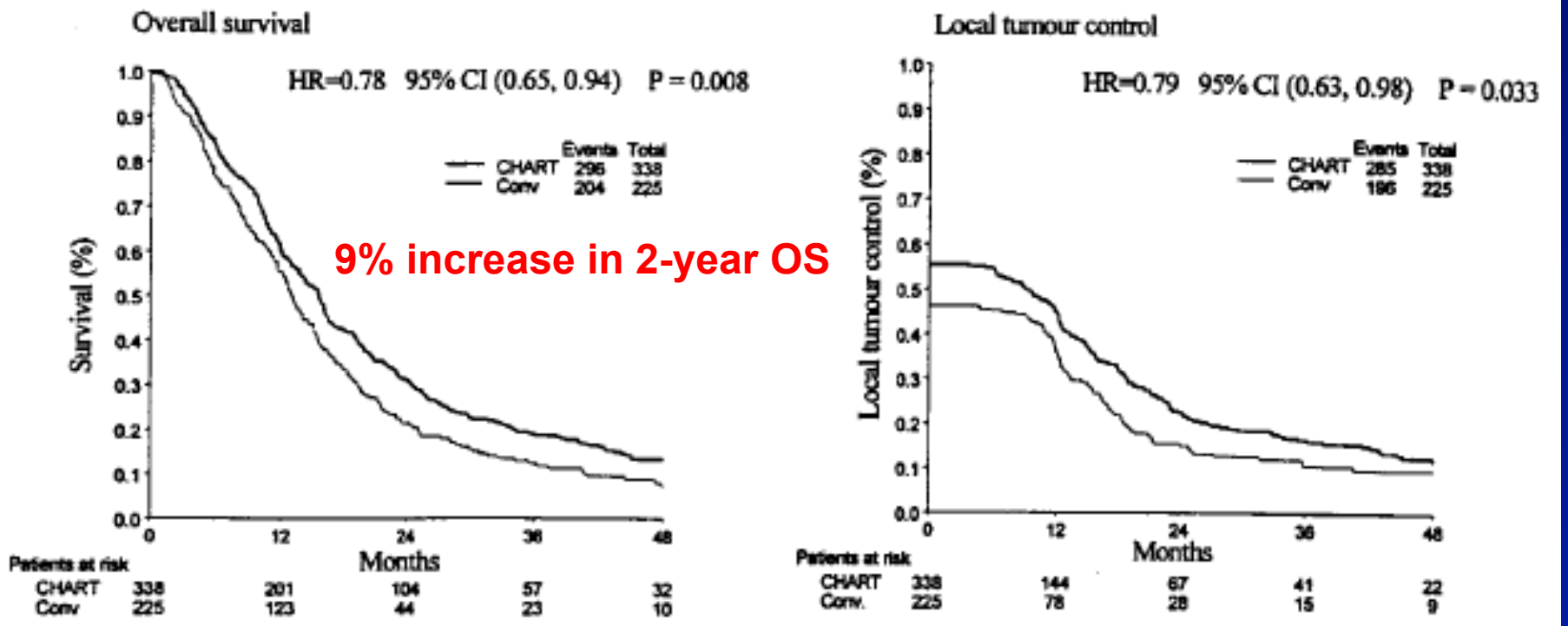


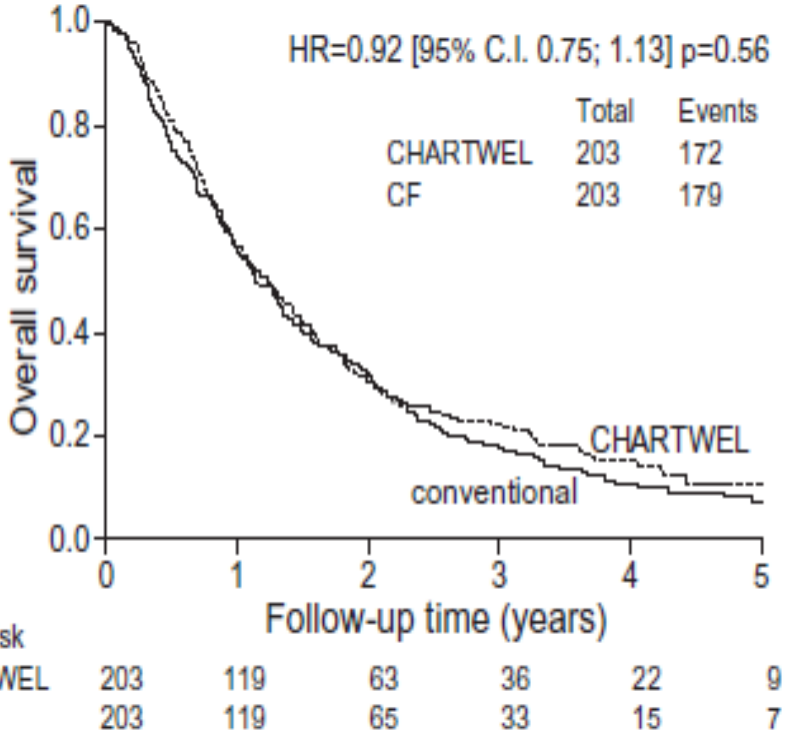
CHART: 54 Gy/12 days (1.5 Gy/fr TID)

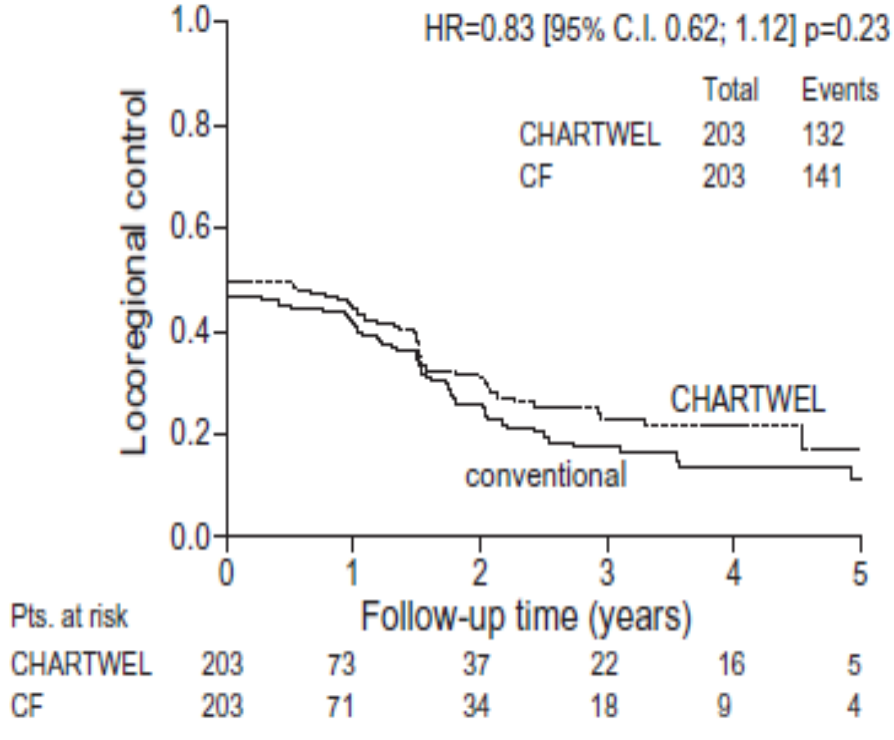
Radiother Oncol 1999

Stage III NSCLC
AND Hyperfractionatated RT

Phase III randomised trial

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)





CHARTWEL: 60 Gy/40 fr/2.5 wks

Radiother Oncol 2011

Stage III NSCLC
AND Hyperfractionatated RT

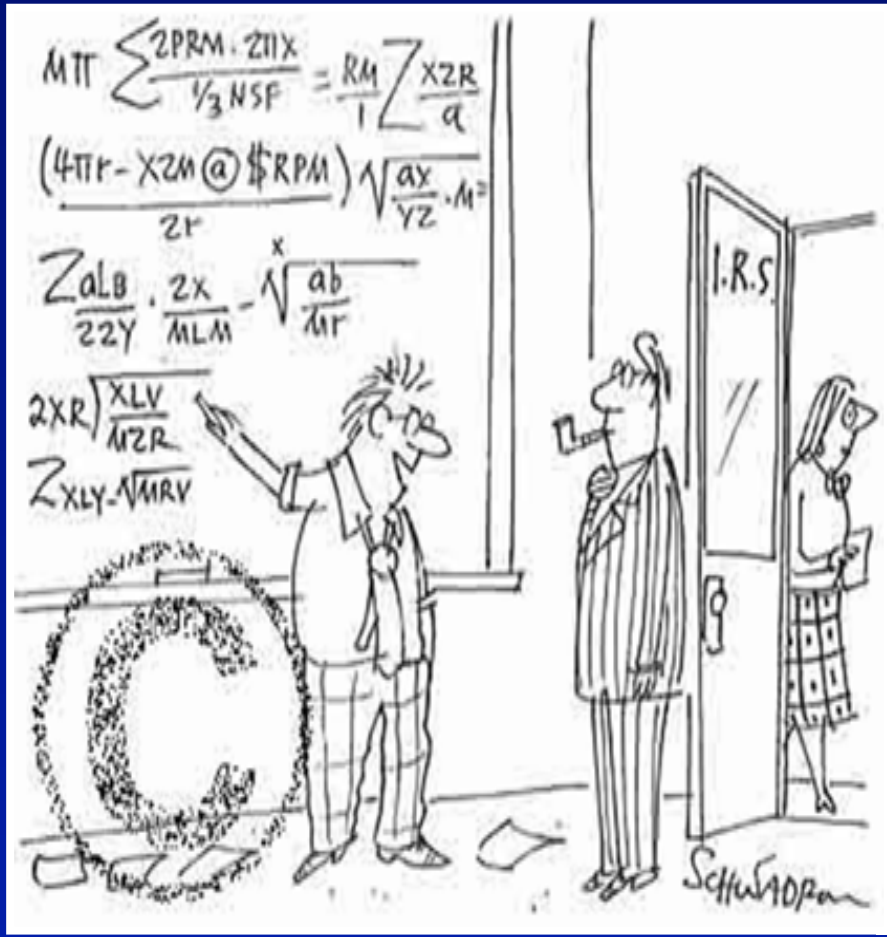
Meta-Analysis of Radiotherapy in Lung Cancer
MAR-LC

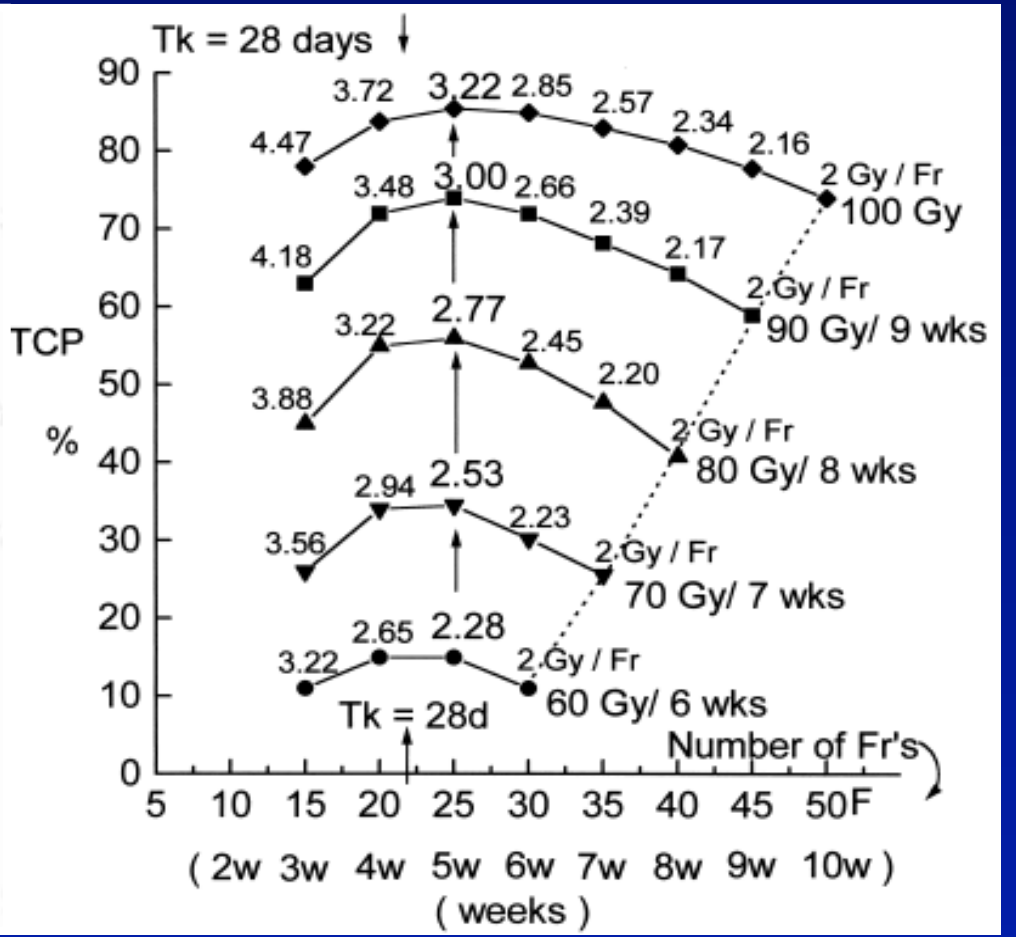
- **2000 patients with NSCLC/10 trials**
- **Modified fractionation (accelerated or hyperfractionated RT) improved OS as compared to conventional RT**
- **HR=0.88 (95% CI 0.80-0.97, p=0.009), resulting in an absolute benefit of 2.5% at 5 years (from 8.3% to 10.8%)**

Mauguen A. JCO 2012

Stage III NSCLC
AND Hypofractionated RT

A NEW APPROACH TO DOSE ESCALATION IN NON–SMALL-CELL LUNG CANCER





Stage III NSCLC AND Hypofractionated RT

Image guided hypofractionated 3-dimensional radiation therapy in patients with inoperable advanced stage non-small cell lung cancer.

- **30** patients with advanced NSCLC
- **57%** stage IIIA-B
- **60 Gy/20 fr** to primary tumor and positive nodes
- **grade 3** late adverse effects: 2 pneumonitis, 1 esophagitis
- **OS @ 2 years: 38%**

Osti MF et al. IJROBP 2013

Stage III NSCLC
AND Hypofractionated RT&CT

EJC 2007

Randomised trial of sequential *versus* concurrent chemo-radiotherapy in patients with inoperable non-small cell lung cancer (EORTC 08972-22973)

Inoperable NSLC
T1-4 N0-3
WHO 0-1
Weight loss < 10%
FEV_1 > 1 l
Diffusion capacity > 60%

Randomly assigned N=158

Arm 1: Concurrent CRT
N=80

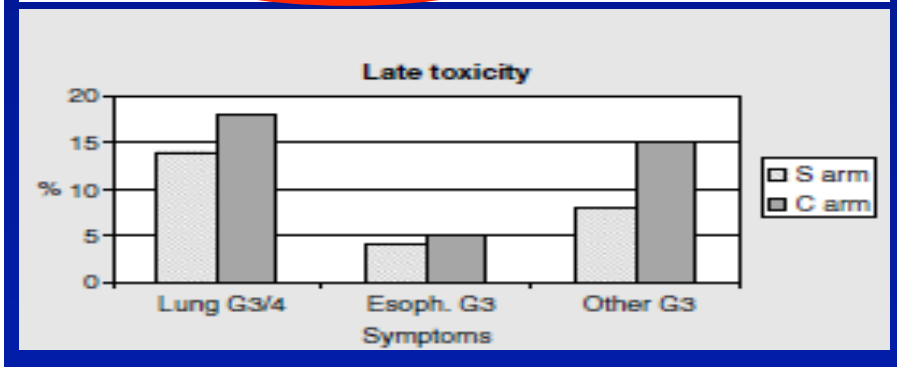
Daily low-dose Cisplatin
(6 mg/m^2) Concurrent with RT*

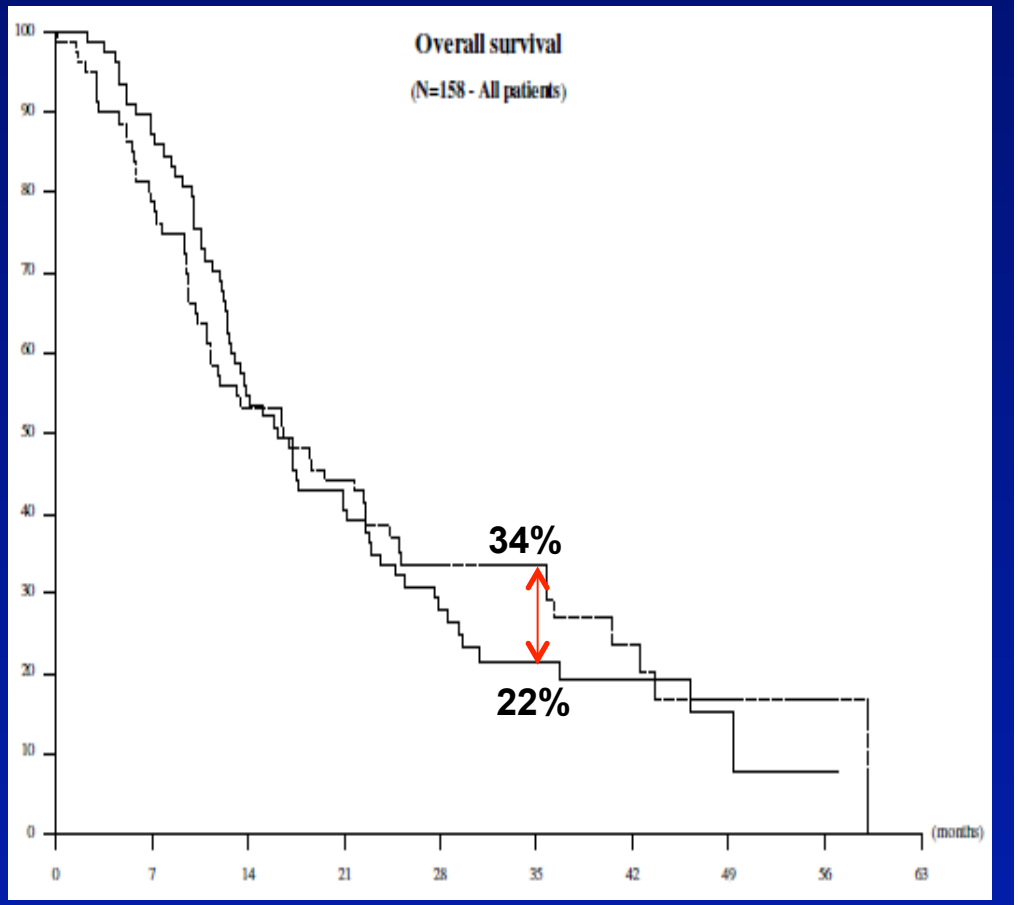
Arm 2: Sequential CRT
N=78

2 cycles: Gemcitabine (1250 mg/m^2 d 1, 8) + Cisplatin (75 mg/m^2 day 2) followed by RT*

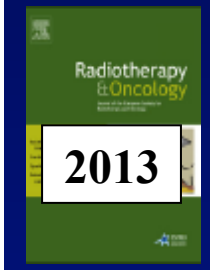
NSCLC = non-small cell lung cancer
CRT = chemo-radiotherapy
RT* = radiotherapy (66 Gy in 24 fractions in 32 days)

ENI





Stage III NSCLC
AND Hypofractionated RT&CT



Original article

Accelerated hypo-fractionated radiotherapy for non small cell lung cancer: Results from 4 UK centres

- **609 NSCLC patients from 4 UK centers**
- **36% stage IIIA-B**
- **55 Gy/20 fr/4 weeks (without ENI)**
- **1/3 received sequential chemo-radiotherapy**
- **no grade III – V toxicities**
- **OS @ 2 years: 50%**
  @ 5 years: 20%

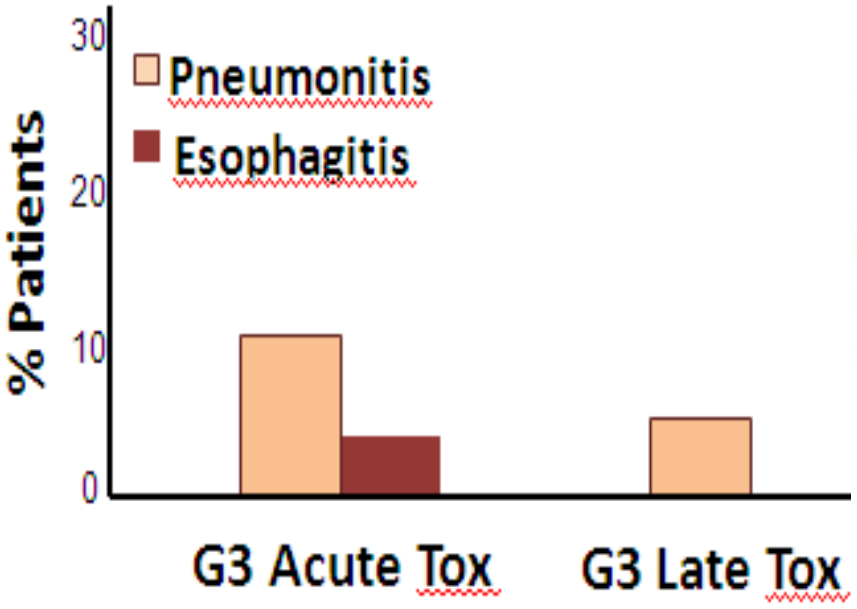
Stage III NSCLC
AND Hypofractionated RT&CT

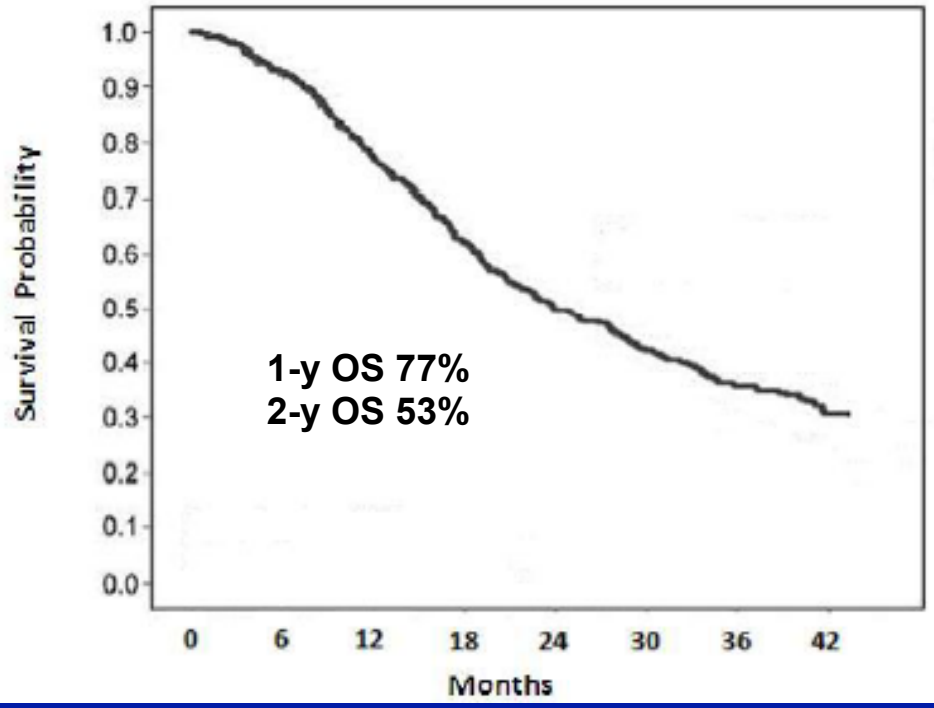
frontiers in
IN RADIATION ONCOLOGY

Moderately Escalated Hypofractionated (Chemo)Radiotherapy Delivered with Helical Intensity-Modulated Technique in Stage III Unresectable Non-Small Cell Lung Cancer

in press

Vittorio Donato, Stefano Arcangeli, Alessia Monaco, Cristina Caruso, Michele Cianciulli, Genoveva Boboc, Cinzia Chiostrini, Roberta Rauco and Maria Cristina Pressello





Stage III NSCLC AND Ongoing Trials

RTOG®
RADIATION THERAPY ONCOLOGY GROUP

RTOG 1106/ACRIN 6697

RANDOMIZED PHASE II TRIAL OF INDIVIDUALIZED ADAPTIVE RADIOTHERAPY USING DURING-TREATMENT FDG-PET/CT AND MODERN TECHNOLOGY IN LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

STRATIFY		RANDOMIZE	
	Stage 1. IIIA 2. IIIB **Primary Tumor Size** 1. > 5 cm 2. ≤ 5 cm **Histology** 1. Squamous 2. Non-Squamous	[3]	**Arm 1: Concurrent Chemoradiotherapy** RT to 50 Gy in 25 fractions (nominally 5 fx/week) [4]Carboplatin and paclitaxel weekly **Arm 2: Concurrent Chemoradiotherapy** RT to 46.2 Gy in 21 fractions (nominally 5 fx/week) [4]Carboplatin and paclitaxel weekly

FDG PET

Arm 1: Continuation of radiotherapy, per the initial plan, not based on during-RT FDG-PET/CT scan with carboplatin and paclitaxel for a total of 6 weekly cycles. No adaptation is allowed.

A total of 60 Gy in 30 daily fractions (nominally 5 fx/week)

Arm 2: Adaptive radiotherapy, based on during-RT FDG-PET/CT scan and resimulation with CT scan with carboplatin and paclitaxel for a total of 6 weekly cycles

19.8-34.2 Gy in 9 fractions; overall total of up to 80.4 Gy in 30 daily fractions in 6 weeks Individualized to MLD 20 Gy

ClinicalTrials.gov

Dose Escalation by Boosting Radiation Dose Within the Primary Tumor Using FDG-PET-CT Scan in Stage IB, II and III NSCLC (PET Boost)

Whole tumor boost

Patients in this arm will receive radiotherapy (66Gy) in 24 fractions of 2.75 Gy with an integrated boost to the primary tumor as a whole

Boost 50% SUV area

Patients in this arm receive radiotherapy (66Gy) in 24 fractions of 2.75Gy with an integrated boost to the 50% SUVmax area of the primary tumor (of the pre-treatment FDG-PET-CT scan)

NSCLC

The End of the Era of Therapeutic Nihilism?

Seminars in Radiation Oncology 2010