

RADIOCHEMIOTERAPIA MODERATAMENTE IPOFRAZIONATA SOMMINISTRATA MEDIANTE HT NEL TRATTAMENTO DEL NSCLC LOCALMENTE AVANZATO NON RESECABILE



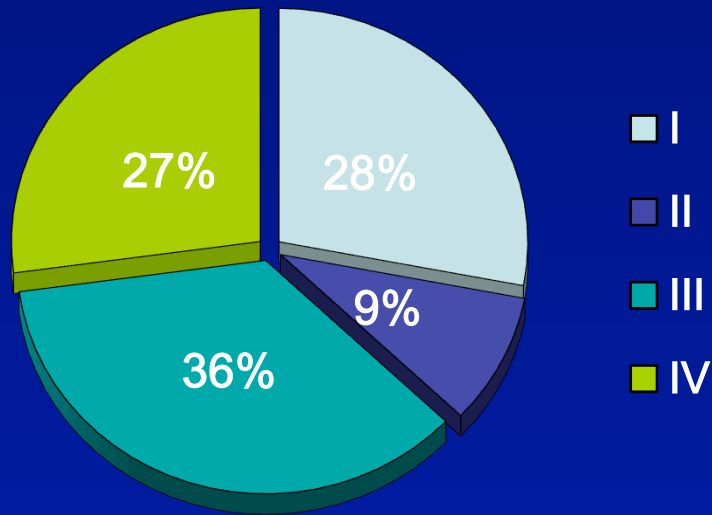
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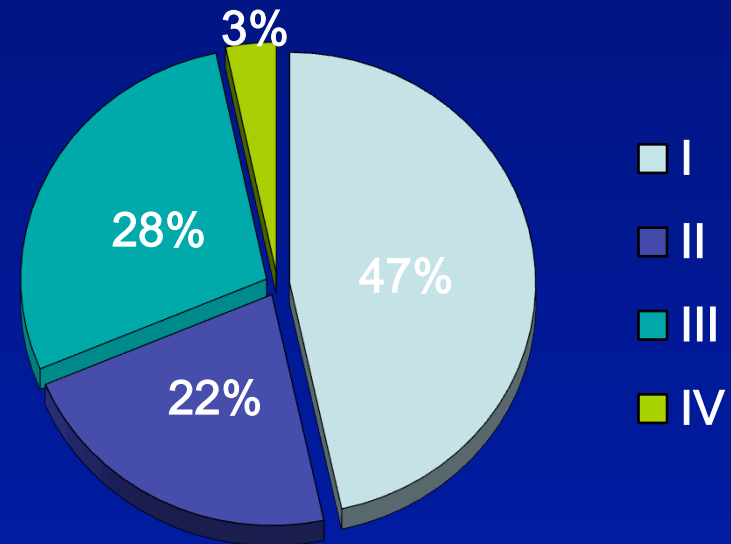
NSCLC Incidence

The IASLC Lung Cancer Database

Clinically Staged Cases,
N = 53,646



Pathologically Staged
Cases, N = 33,933



Stage III “N2/N3 Disease” AND Sequential/Concurrent RT



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

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)**



National Comprehensive Cancer Network
Your Best Resource in the Fight Against Cancer®

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

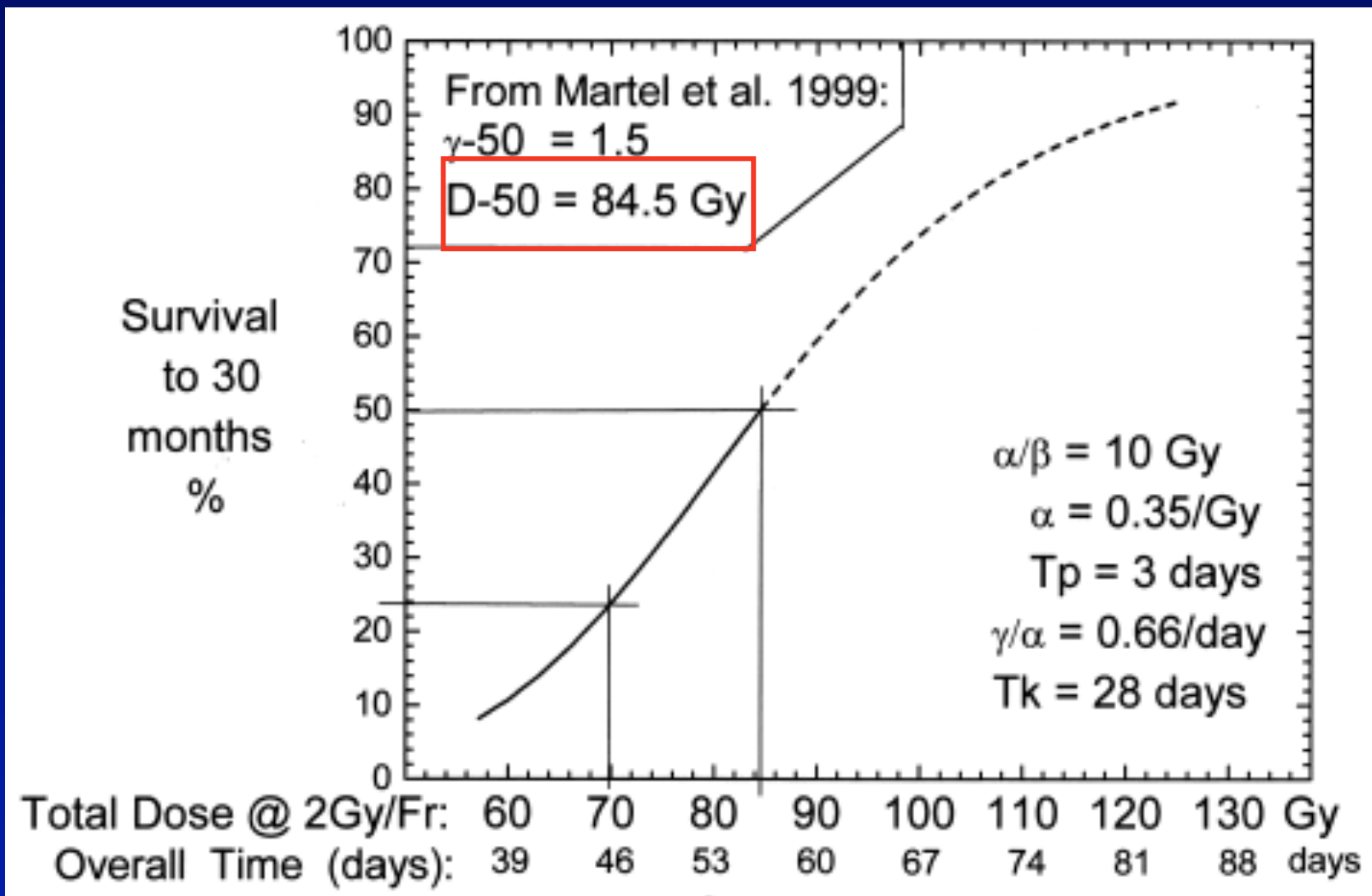
Stage III NSCLC AND Focus on RT

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 RT CONSIDERATIONS

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

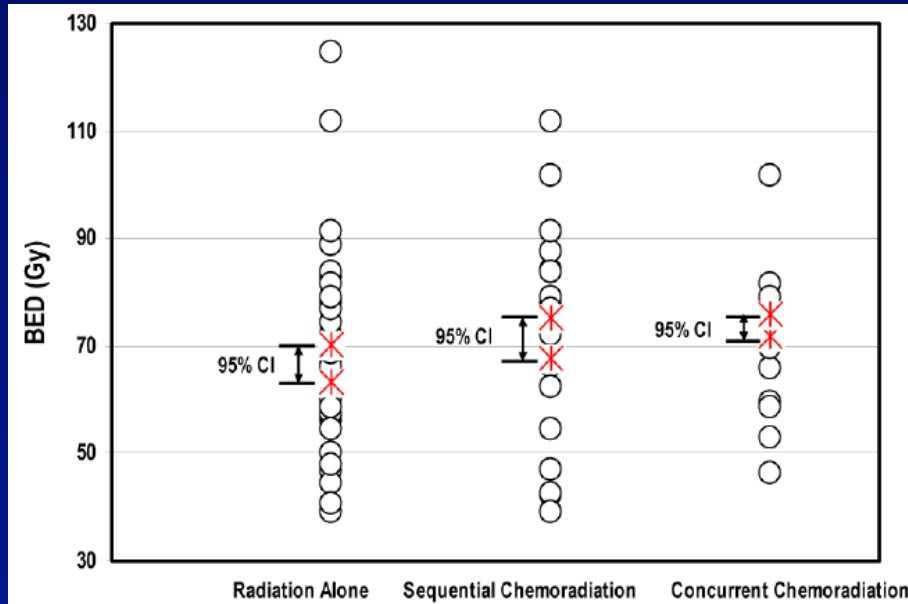
IJROBP 2012

RADIATION THERAPY ONCOLOGY GROUP

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

BED increase

Stage III NSCLC AND RT CONSIDERATIONS



Factors	Estimated HR of death (95% CI)	<i>P</i> 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

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

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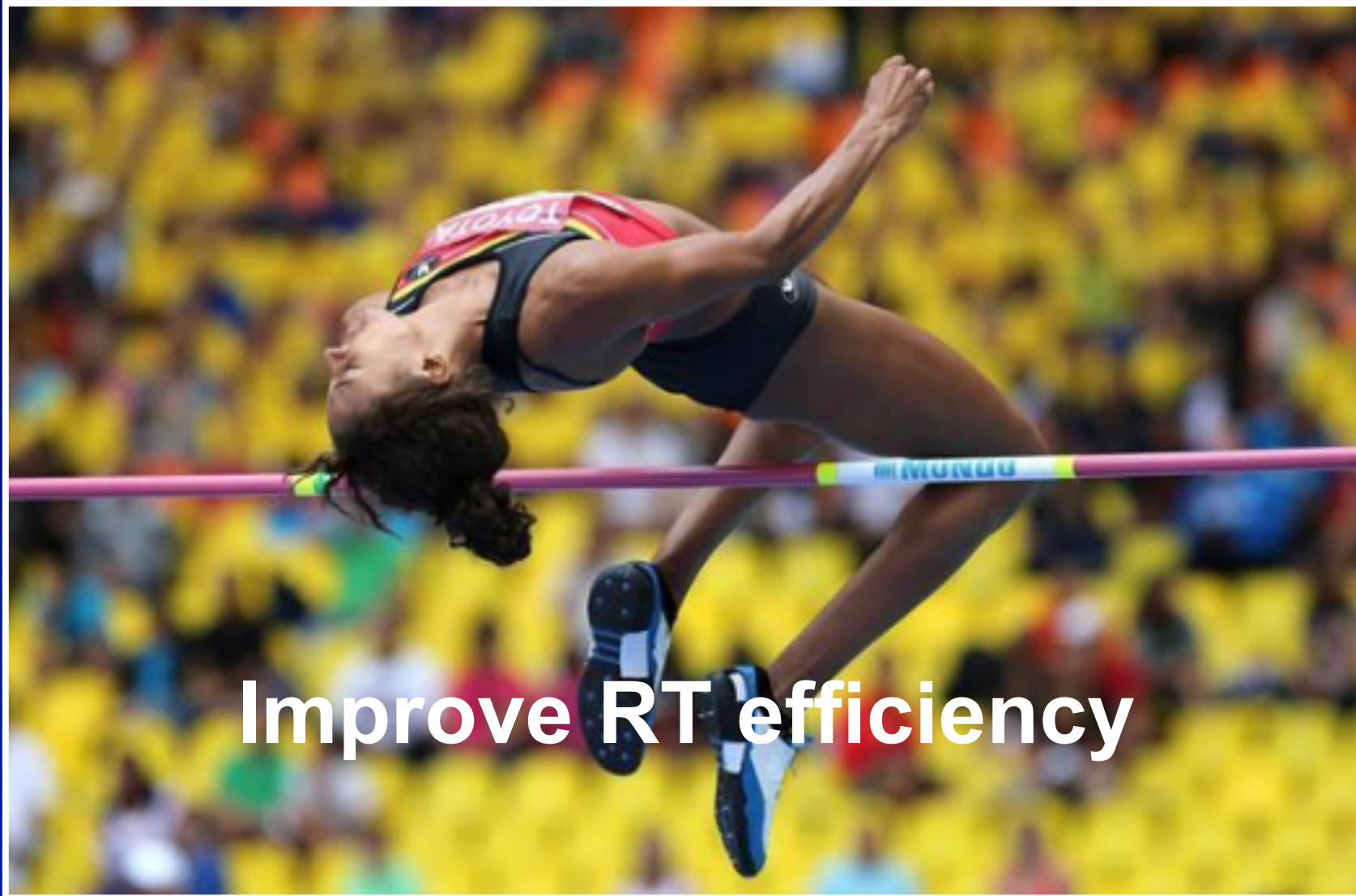


3 RTOG trials

- 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

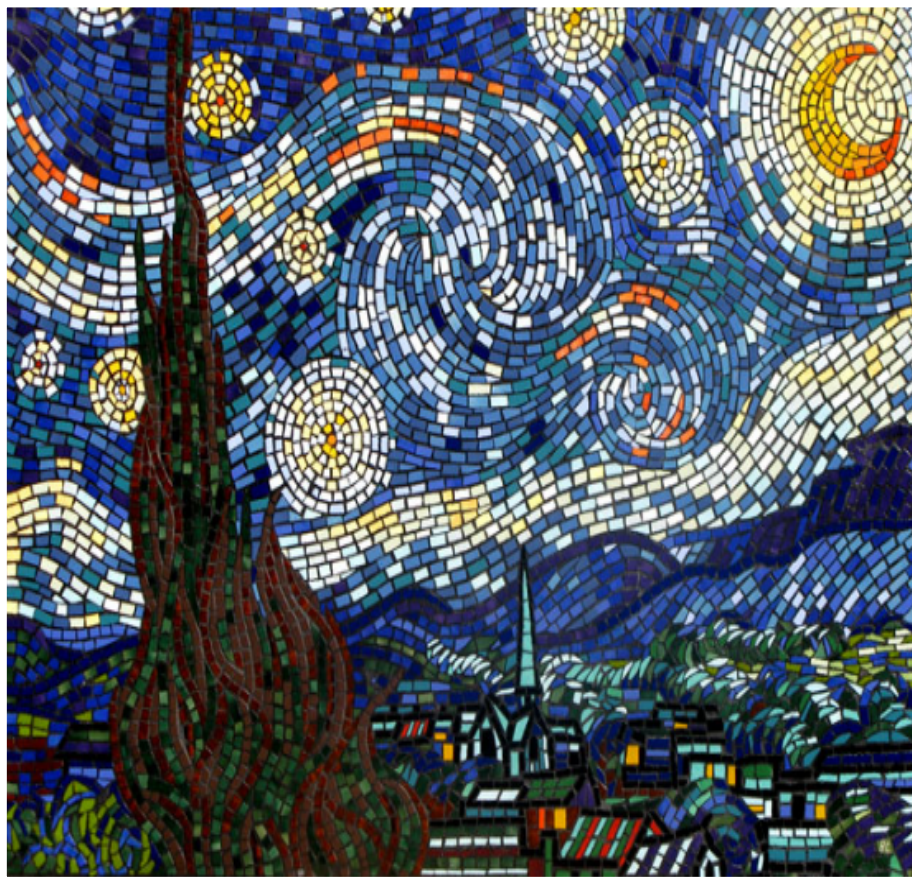
How to go beyond 60 Gy ?



Improve RT efficiency

Stage III NSCLC

Improving RT efficiency I



Vincent Van Gogh- The Starry Night

A dose that conforms more tightly to the target volume means less normal tissue irradiated.

Highly conformal doses can be achieved using **intensity-modulated RT**

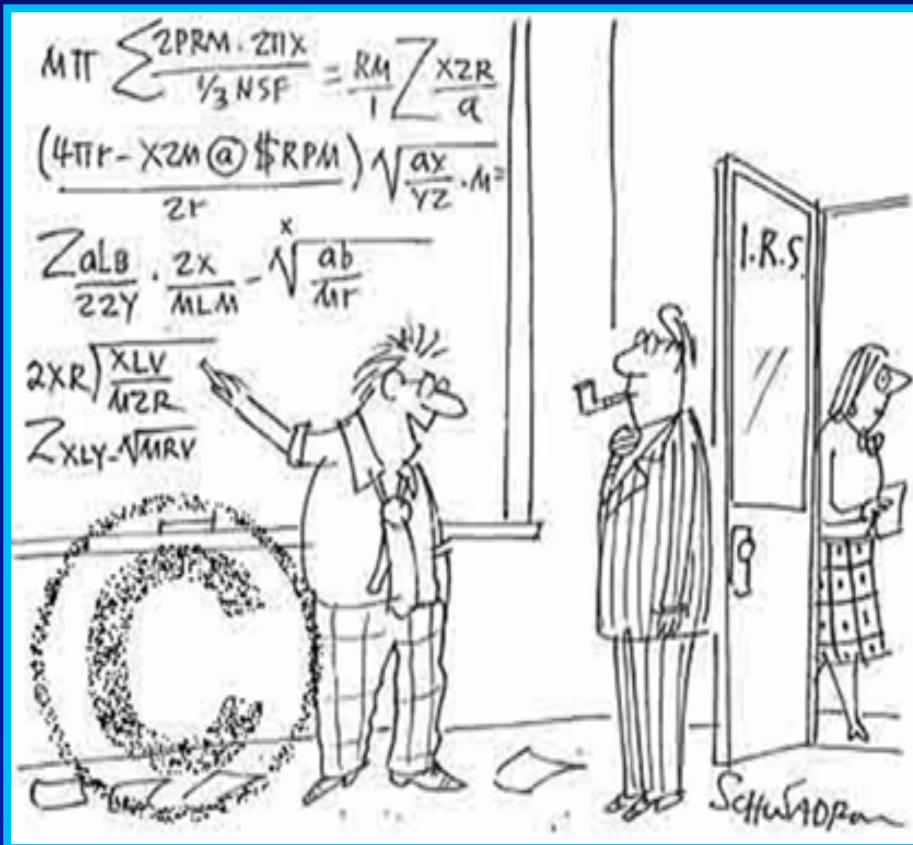
Yom IJROBP 2007

Stage III NSCLC

Improving RT efficiency II

Hypofractionation

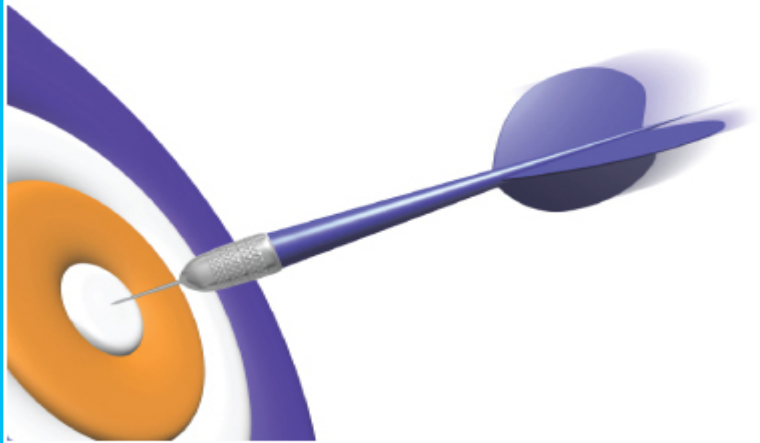
increases dose per day
 reducing the number of
 treatment fractions thus
 counteracting the effect of
 tumour repopulation due to a
 prolonged treatment time



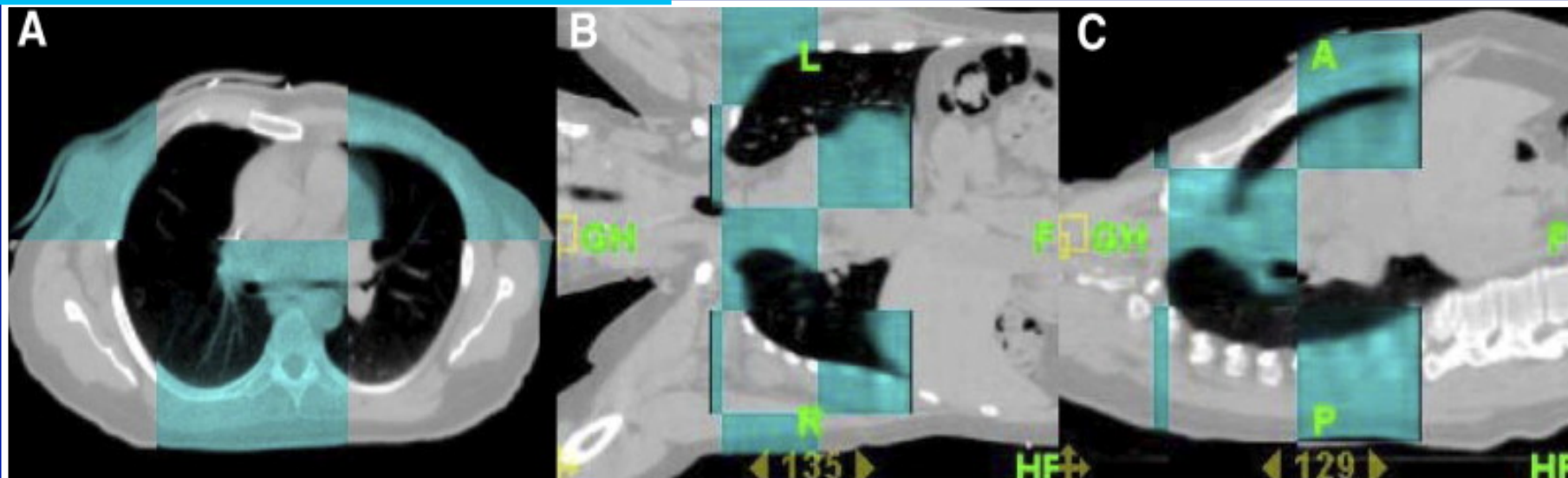
Stage III NSCLC

Improving RT efficiency III

Hit Your Target



Uncertainty in patient setup is reduced using image-guided radiotherapy (**IGRT**)



- ✓ IMRT
- ✓ HYPOFRACTIONATION
- ✓ IGRT





Trial outline

2.25-2.28 Gy/fx x 30 fxs

- Fewer and larger fractions are delivered within 6 wks
- 2.25-2.28 Gy x 30 fxs = 67.5-68.4Gy has the same biologic effective dose (BED) for tumouricidal effects equal to **70Gy** in 2Gy fractions



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

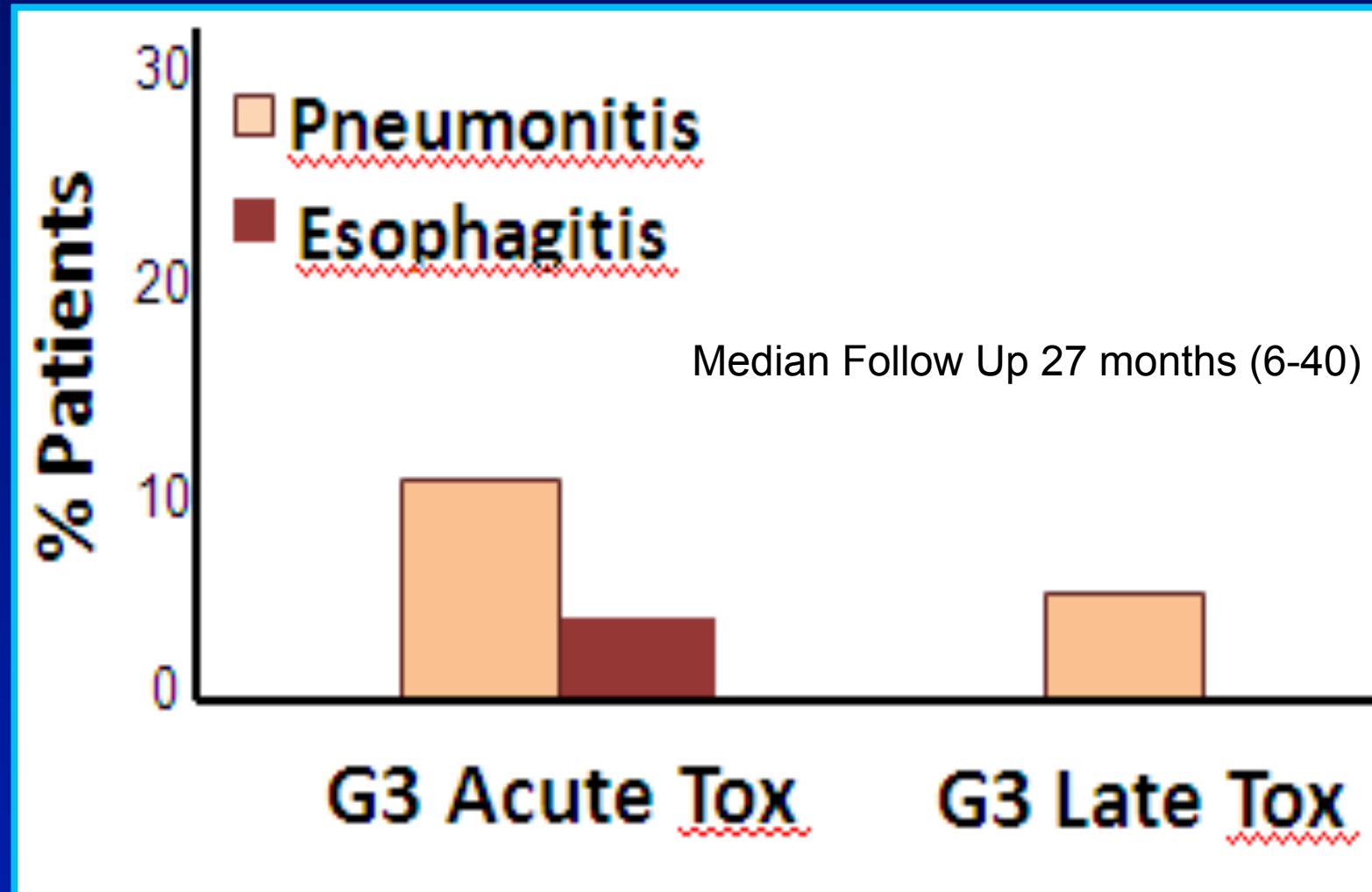
Donato V. et al 2013

Patients characteristics	Value
No. of patients	61
Age (y)	67 (range 40 – 78)
Type of carcinoma	31 Adenocarcinoma 23 Squamous cell 7 Unspecified NSCLC
Stage	IIIA 35 IIIB 26
Chemotherapy	32 Sequential 29 Concomitant
Median OTT days	42 (42—45)



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

Donato et al 2013

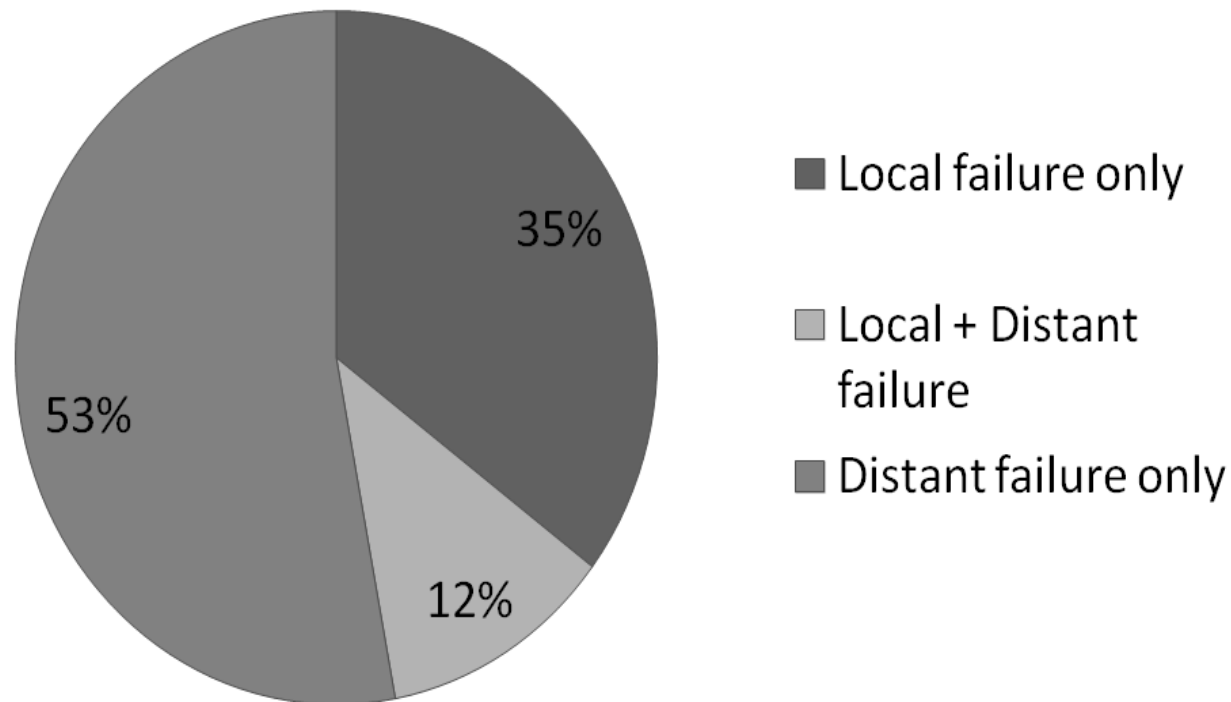




Moderately Escalated Hypofractionated (Chemo)Radiotherapy Delivered with Helical Intensity-Modulated Technique in Stage III Unresectable Non-Small Cell Lung Cancer

Donato et al 2013

Pattern of failure

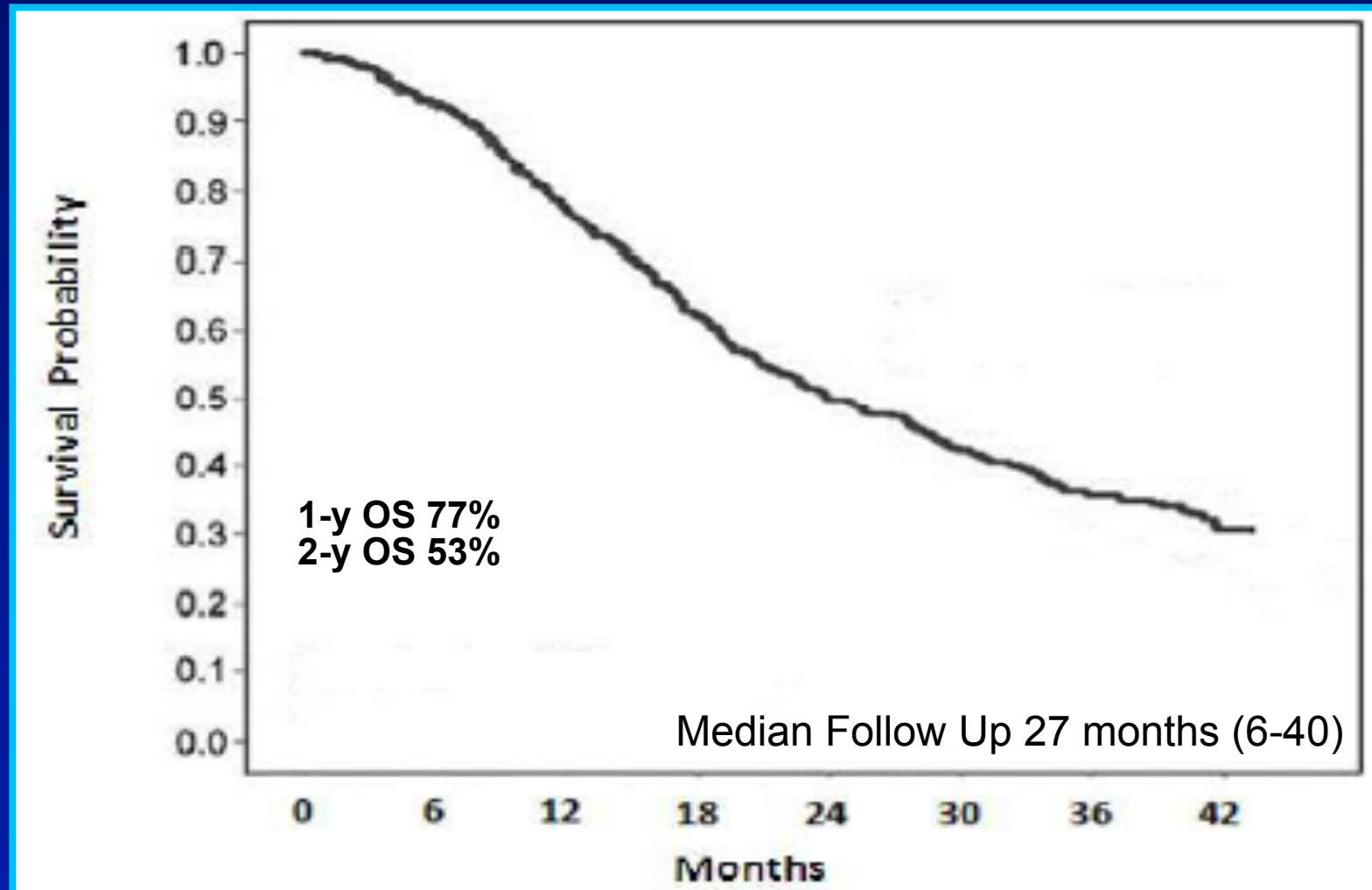


Median Follow Up 27 months (6-40)



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

Donato et al 2013





- Hypofractionated RT increase radiation effect on the tumor cells allowing higher total dose and keeping the treatment course **within 6 weeks**
- Dose escalation utilizing the dose-per-fraction is safe **even when associated with chemotherapy** (either sequential or concurrent)



Stage III NSCLC AND Ongoing Trials

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)

S T R A T I F Y	Stage 1. IIIA 2. IIIB	³ R A N D O M I Z E	
	Primary Tumor Size 1. > 5 cm 2. ≤ 5 cm		
	Histology 1. Squamous 2. Non-Squamous		

Arm 1: Concurrent Chemoradiotherapy
RT to 50 Gy in 25 fractions (nominally 5 fx/week)
⁴Carboplatin and paclitaxel weekly

Arm 2: Concurrent Chemoradiotherapy
RT to 46.2 Gy in 21 fractions (nominally 5 fx/week)
⁴Carboplatin and paclitaxel weekly

F
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G

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T

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)