DICHIARAZIONE

Relatore: Gianpiero Catalano

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

Standard terapeutico del NSCLC localmente avanzato: Radio-chemioterapia concomitante

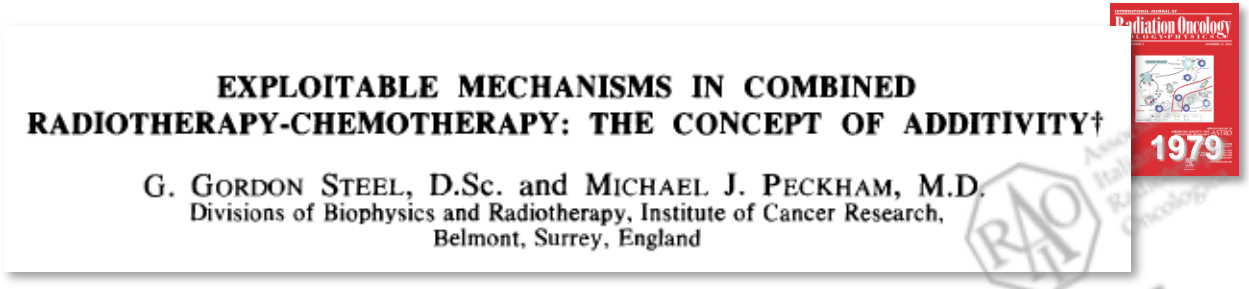
Gianpiero Catalano

SC Radioterapia Oncologica

IRCCS MultiMedica, Sesto S. Giovanni (Mi)

Istituto Ospedaliero MultiMedica, Castellanza (Va)

Why concomitant RT should be better than sequential?



EXPLOITABLE MECHANISMS IN COMBINED RADIOTHERAPY-CHEMOTHERAPY: THE CONCEPT OF ADDITIVITY†

G. GORDON STEEL, D.Sc. and MICHAEL J. PECKHAM, M.D.
Divisions of Biophysics and Radiotherapy, Institute of Cancer Research, Belmont, Surrey, England

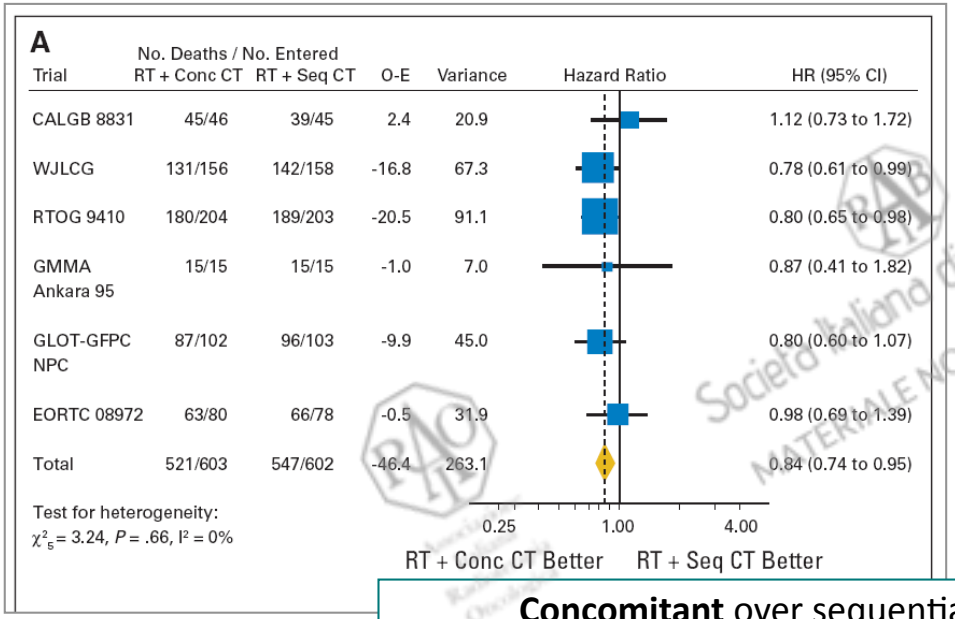
- *Disease **progression** during induction CT →*
  - → *less pts. completing CT schedule (58% vs. 83%)*
  - *less pts. receiving RT (64% vs. 94%)* *(Zatloukal 2003)*
- *Accelerated tumor cell **repopulation** after induction CT*
- *Sequential treatments increase overall **treatment time***
- *CT-induced **selection** of radioresistant clones*
- *CT- induced anaemia → more **hypoxia** in irradiated tissue*

Superior outcome compared to sequential CT-RT. Standard of care in selected patients

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

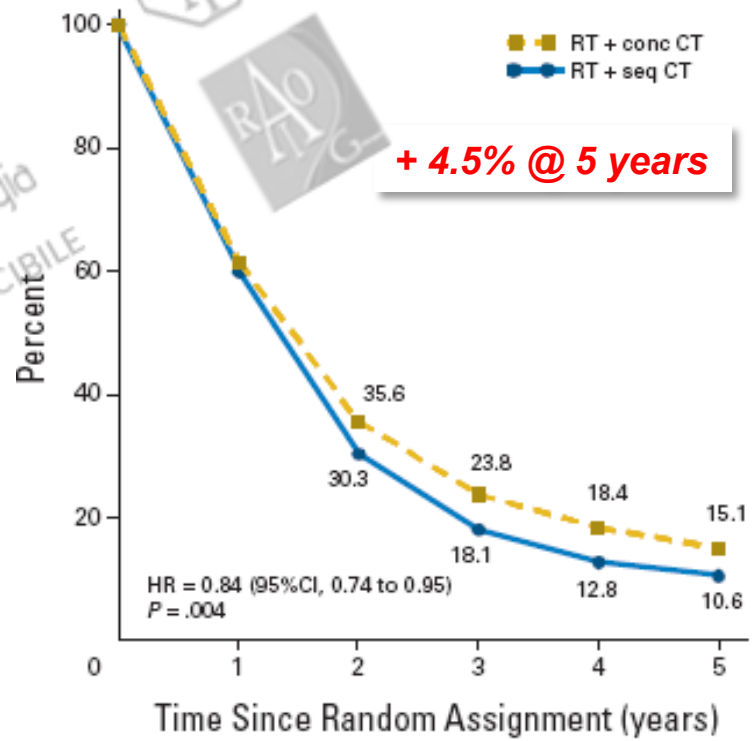
Auperin A. JCO 2010



1.205 patients, 6 RCTs

Concomitant over sequential

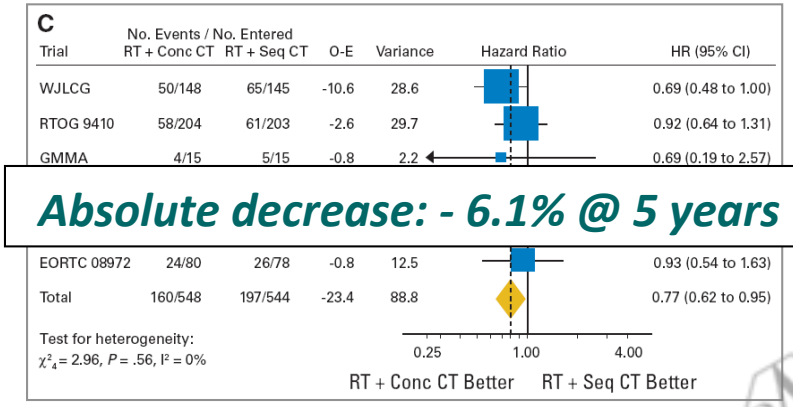
HR 0.84 *(95% CI, 0.74 -0.95)* ***p .004***



The "cost of benefit" is an increased severe acute oesophagitis incidence

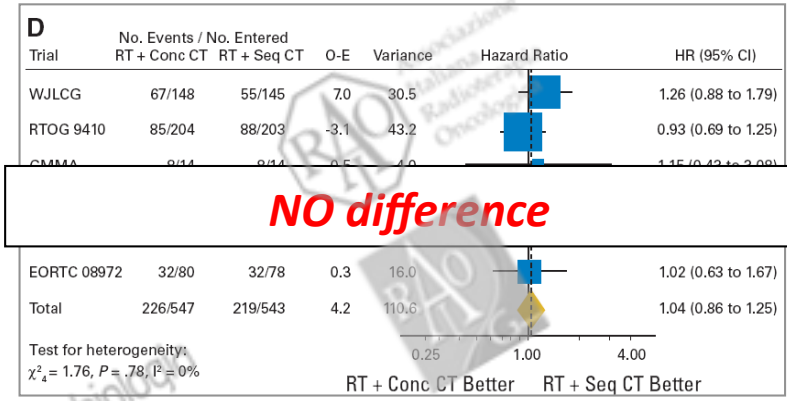
How to improve results?

Loco-regional Progression



Absolute decrease: - 6.1% @ 5 years

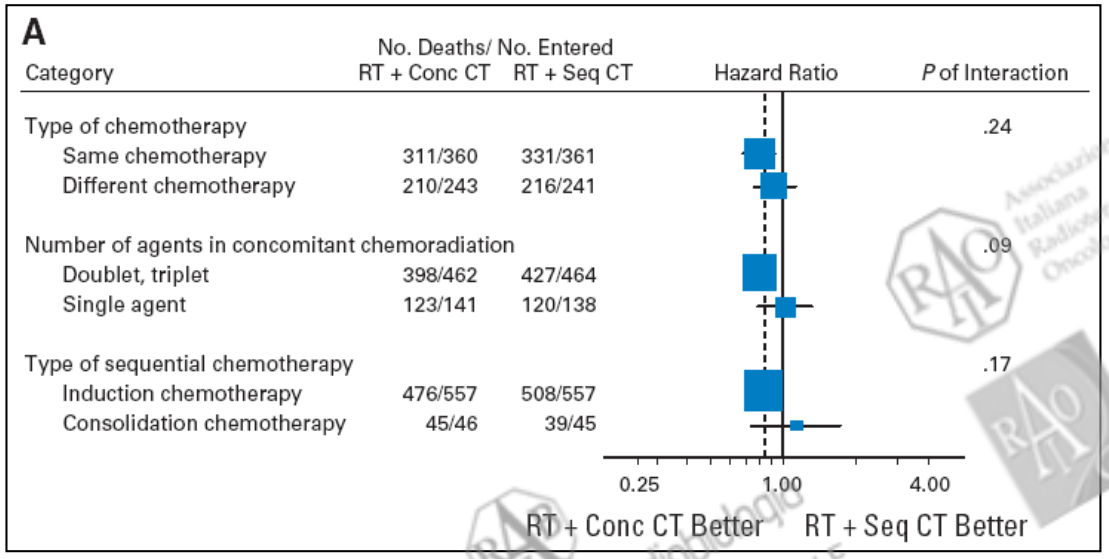
Distant Progression



NO difference

- ***Should Systemic treatments be optimized to reduce metastatic spread?***
- ***Should Radiotherapy be enhanced to improve / preserve local control?***

The most efficacious chemotherapy combined with thoracic RT is not established



Auperin A. JCO 2010

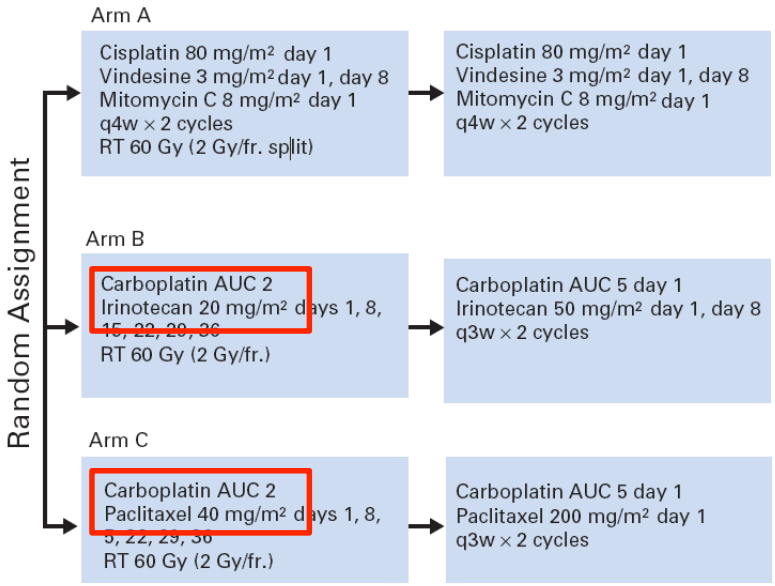
No RTCs proved significant superiority of a specific schedule, in concomitant setting

- ***Full-dose, "old"-generation regimens***
  cisplatin-etoposide, cisplatin-vindesine-mitomycin, cisplatin-vinorelbine

- ***Daily/Weekly low-dose single-agent chemotherapy***
  cisplatin, carboplatin

- ***"New-generation" combinations***
  paclitaxel-carboplatin

Slight evidence for a third-generation regimens significant benefit

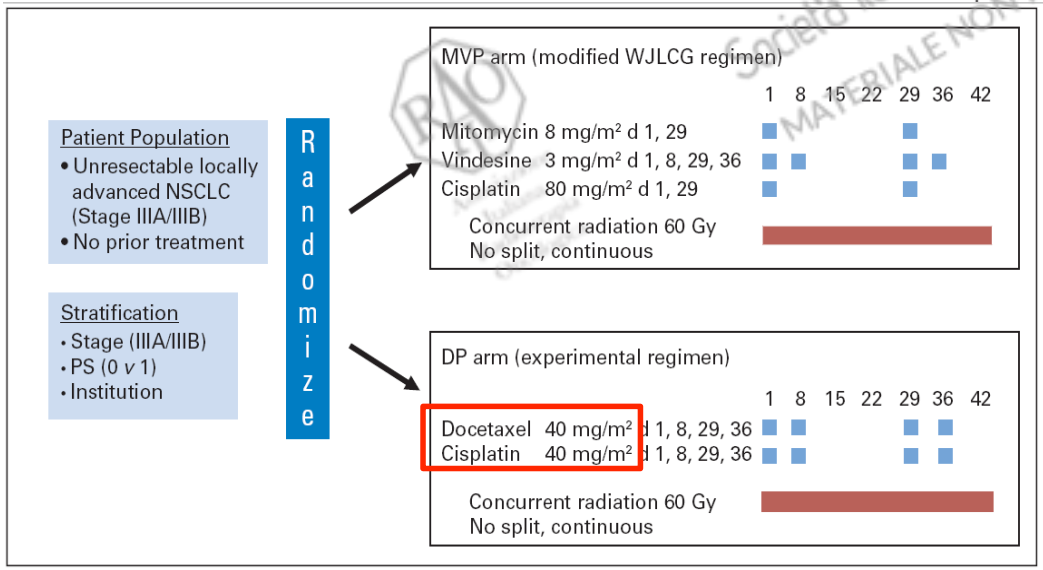


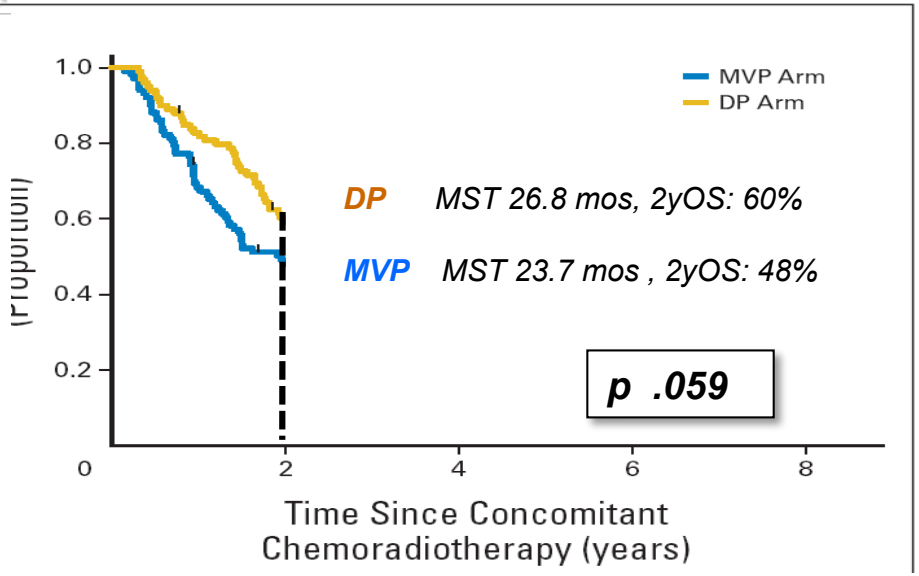
MST 20.5 months, 5yOS 17.5%

MST 19.8 months, 5yOS 17.8%

MST 22 months, 5yOS 19.8%

Yamamoto, JCO 2010





Segawa, JCO 2010

Slight evidence for a third-generation regimens significant benefit

Phase III Study Comparing Second- and Third-Generation Regim… Concurrent Thoracic Radiotherapy in Patients With L… Non–Small-Cell Lung Cancer. **West Japan T… …Group 0105**

MST 22 vs. 20.5 months

Yamamoto, JCO 2010

Phase III Trial Comparing Docetaxel and Cisplatin Combination Chemotherapy With Mitomycin, Vindesi… and Cisplatin Combination Chemotherapy… Concurrent Thoracic Radioth… …anced Non–Small-Cell Lung Cancer… …0007

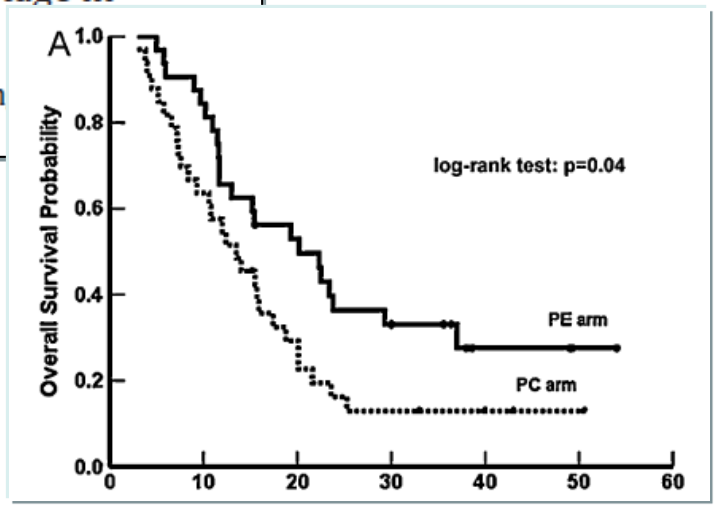
MST 26.8 vs. 23.7 months (p .059)

Segawa, JCO 2010

Randomized phase II study of concurrent cisplatin/etoposide or paclitaxel/carboplatin and thoracic radiotherapy in patients with stage III non-small cell lung cancer☆

Luhua Wang[a,*], Shixiu Wu[b], Guangfei Ou[a], Nan Bi[a], Wenfeng Li[b], Hua Ren[a], Jianzhon… Junling Li[c], Zongmei Zhou[a], Jima Lv[a], Xiangru Zhang[c]

MST 13.5 vs. 20.2 months

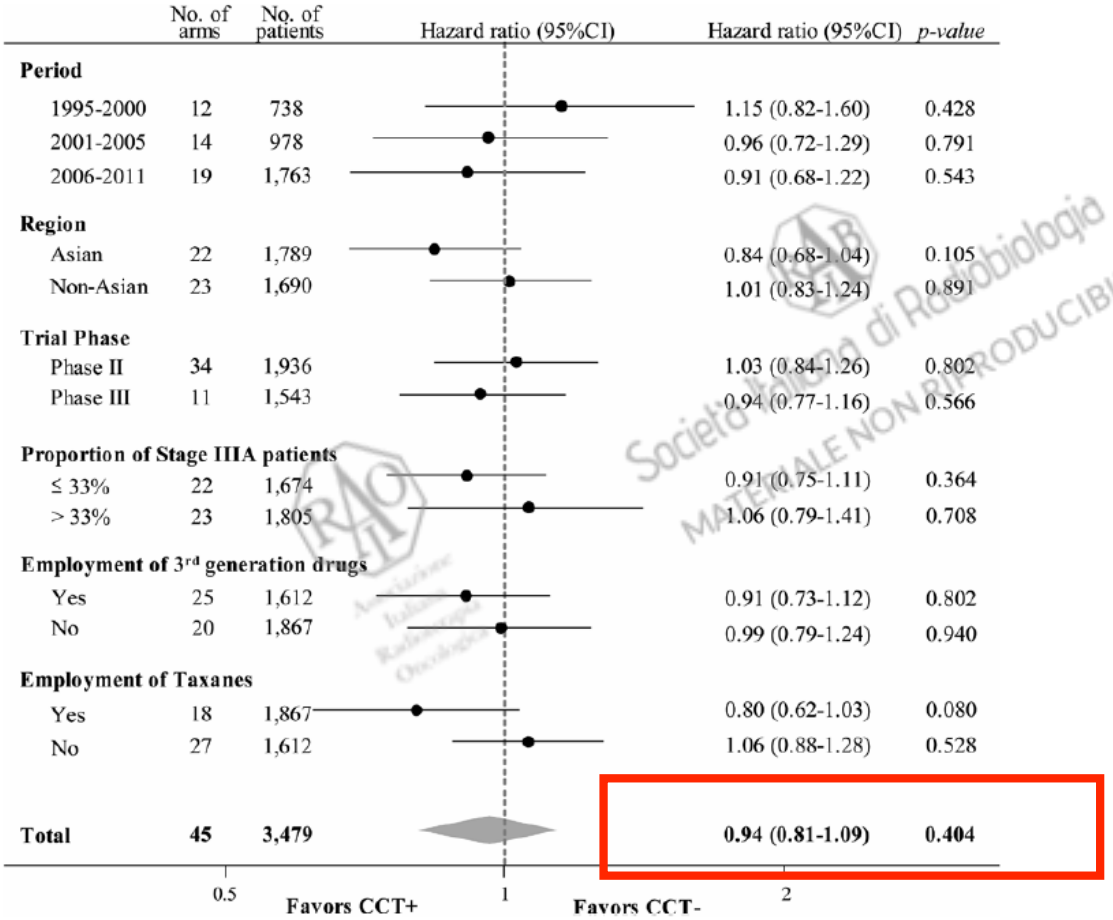


Choice should take in account the different toxicity profiles

No evidence to suggest that consolidation CT after cRTCT improves survival

Is Consolidation Chemotherapy after Concurrent Chemo-Radiotherapy Beneficial for Patients with Locally Advanced Non–Small-Cell Lung Cancer?

A Pooled Analysis of the Literature



Tsujino, J Thor Oncol 2013

3.479 patients

7 Phase III Trials

34 Phase II Trials

MST 19 vs. 17.9 mos

HR 0.94 *(95% CI, 0.81 -1.09)*

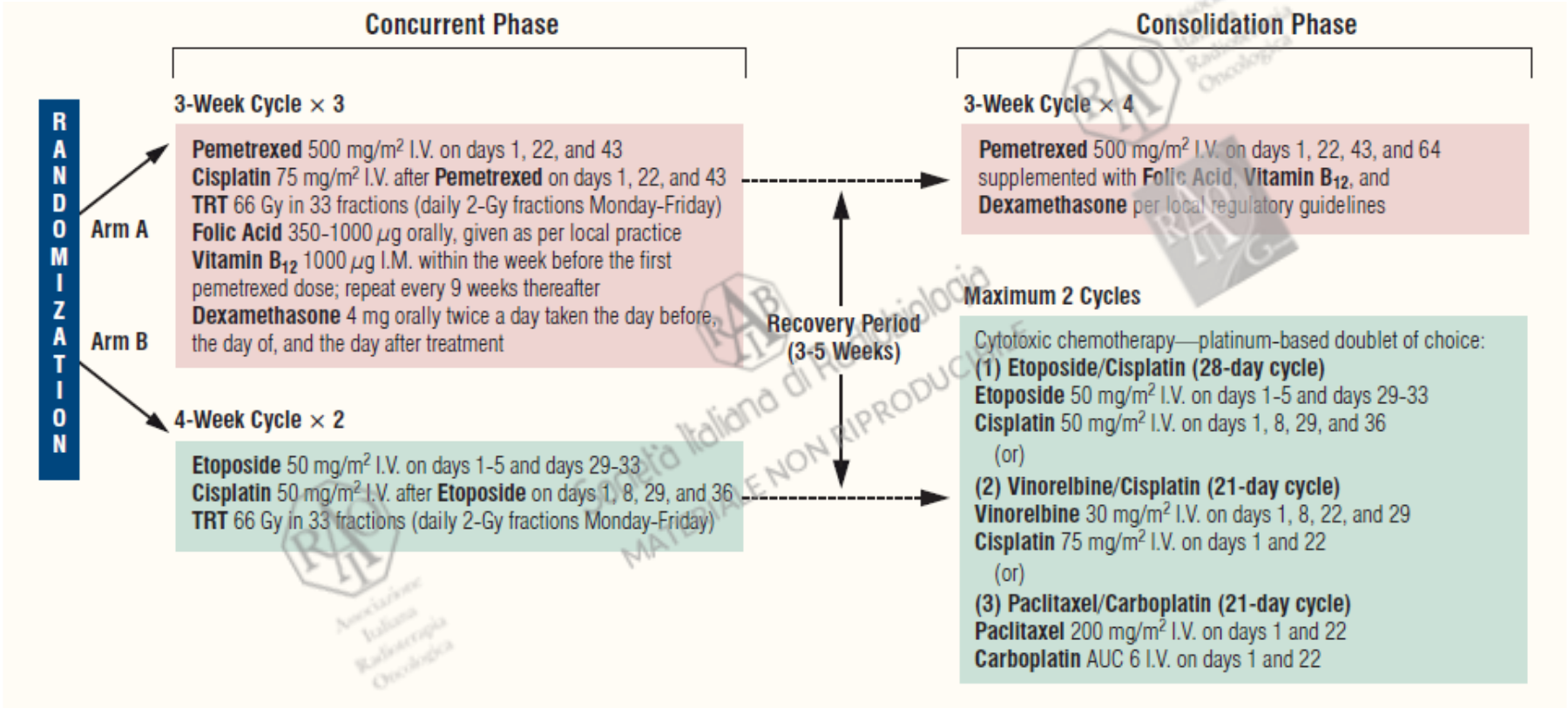
p 0.4

Histology-based strategy: PEMETREXED

Phase II

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

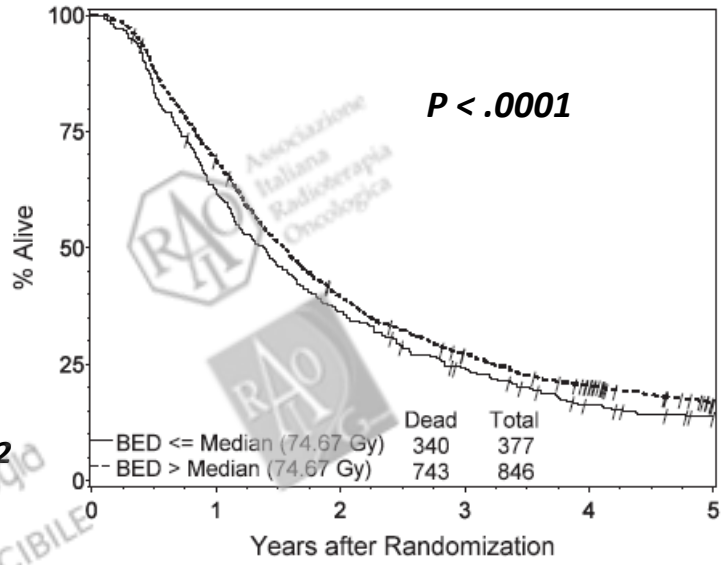
Waiting for PROCLAIM Trial…



Enhancing Radiotherapy?...Fractionation

RTOG

1 Gy BED increase → + 4% relative improvement in survival



Machtay, IJROBP 2010; 2012

RTOG 9410 – Ph III

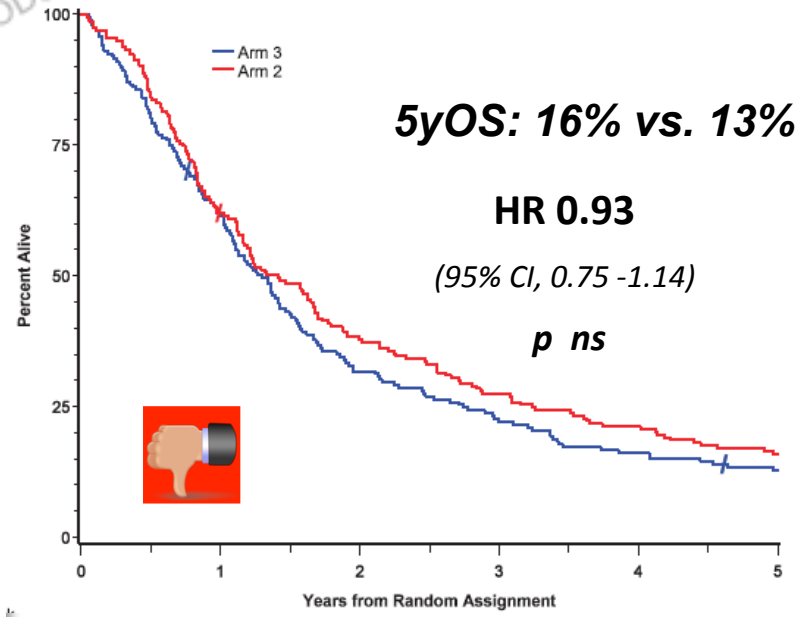
RANDOMIZE

Arm 1:
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
cisplatin 100 mg/m² 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)

Arm 2:
vinblastine 5 mg/m² IV bolus weekly first 5 weeks
cisplatin 100 mg/m² 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)

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 m²)
cisplatin 50 mg/m² 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)



5yOS: 16% vs. 13%

HR 0.93

(95% CI, 0.75 -1.14)

p ns

Curran WJ. JNCI 2011

Enhancing Radiotherapy?...Dose Escalation

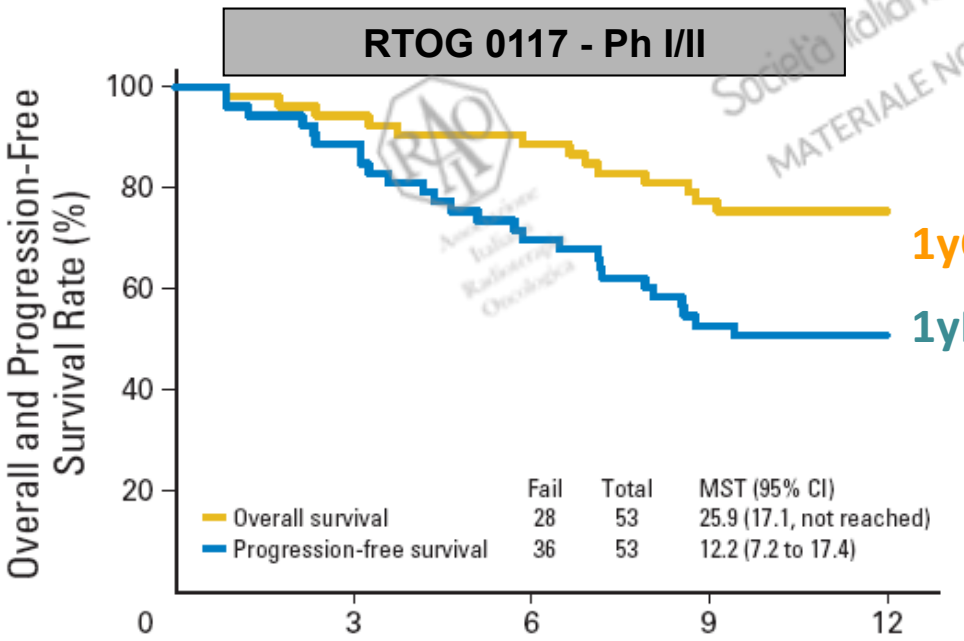
Feasibility of escalated total dose with concurrent chemotherapy

High Dose RT Approaches with ChemoRT

Group	RT Dose	Med Surv
RTOG 0117*	74 Gy	21.6 mo
NCCTG N0028*	74 Gy	37 mo
CALGB 30105*	74 Gy	24.6 mo
UNC*	74 Gy	24 mo
Historic Context		
RTOG 9410	63 Gy	17.1 mo

* Weekly Pac/Carbo for 7 weeks followed by P/C X2

Washington University in St. Louis School of Medicine

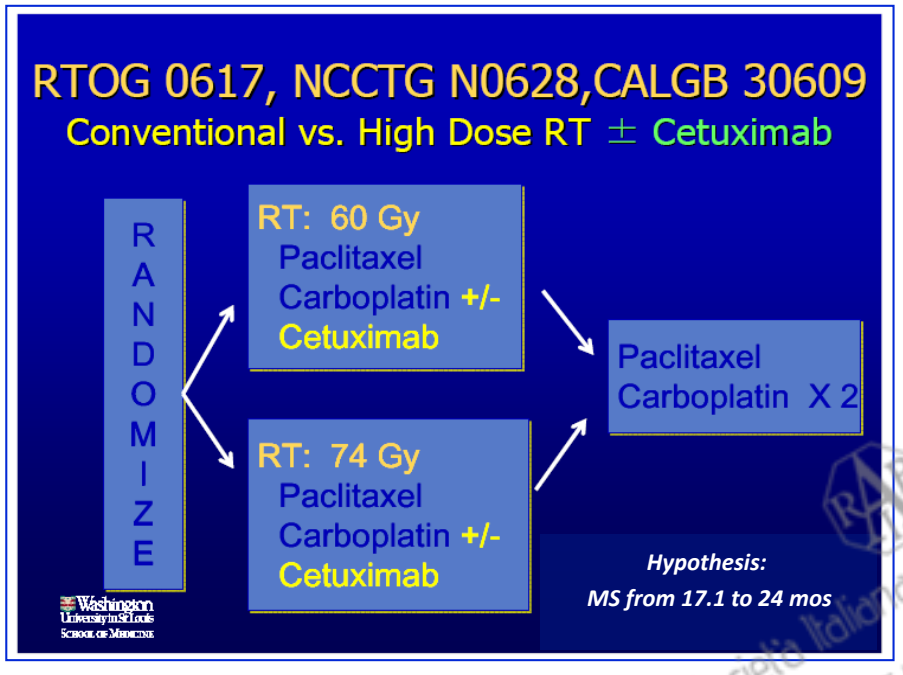


1yOS 72.7% (MST 21.6 mos)

1yPFS 50% (MST 10.8 mos)

Bradley, JCO 2010

Enhancing Radiotherapy?...the RTOG 0617 "Affair"



Overall time → Repopulation

Cardiac-related deaths

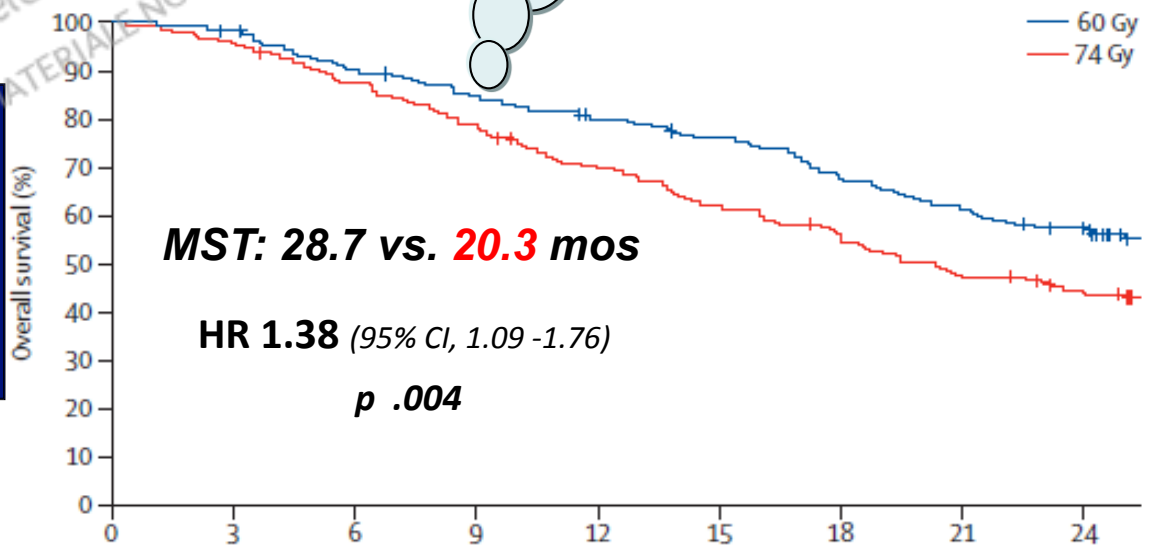
…….

Nov. 2007- Nov. 2011

185 Institutions

544 patients, Stage IIIA-B, PS 0-1

Age 37-83 (median 64)



MST: 28.7 vs. 20.3 mos

HR 1.38 *(95% CI, 1.09 -1.76)*

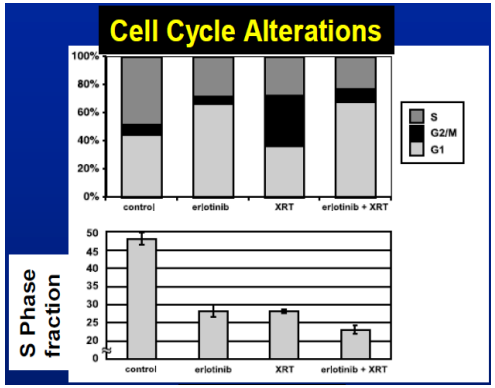
p .004

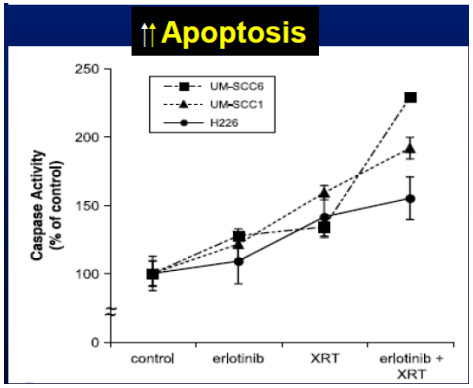
Bradley, Lancet 2015

Extending the limits of combined modality treatment: Targeted therapy

- *EGFR –Targeting agents*
  - ✓ *Antibodies (Cetuximab)*
  - ✓ *TKIs (Gefitinib, Erlotinib)*
- *Anti-angiogenic agents (Bevacizumab)*

- *"Endorsement" from preclinical data*
- *Improved outcome in advanced disease*





EGFR inhibitors + RT alone

A phase II study of cetuximab and radiation in elderly and/or poor performance status patients with locally advanced non-small-cell lung cancer (N0422)

57 pts
- age > 65, PS 0-1
- Any age, PS 2

CETUXIMAB d1	CETUXIMAB w RT 60 Gy

ENI 2D-RT NO PET/CT

Compliance	MST	G3-4 tox
86%	15 mos	54% (mainly fatigue)

Jatoi, Ann Oncol 2010

Combined Treatment of Nonsmall Cell Lung Cancer NSCLC Stage III With Intensity-Modulated RT Radiotherapy and Cetuximab

NEAR Trial

30 pts; IKPS ≥ 70

CETUXIMAB RT 66 Gy	CETUXIMAB w x 13 weeks

ENI IMRT-IGRT PET/CT

Compliance	MST	G3-4 tox
90%	19.6 mos	40% (10% lung)

Jensen, Cancer 2011

TKIs + RT after Induction CT

CALGB 30106
Phase II

Arm 1

Poor risk[c] (PS > 2, WL >5%) 21 pts

Induction:
Carboplatin (AUC = 6), paclitaxel (200 mg/m^2) every 3 weeks for 2 cycles and gefitinib 250 mg daily

Concurrent:
Gefitinib 250 mg daily

Consolidation:
Gefitinib 250 mg daily

RT dose: 66 Gy

ENI, 2D-RT, NO PET

G3/4: 10% (G5: 5%)

19 mos

Arm 2

Good risk' (PS 0-1, WL <5%) 39 pts

Induction:
Carboplatin (AUC = 6), paclitaxel (200 mg/m^2) every 3 weeks for 2 cycles and gefitinib 250 mg daily

Concurrent:
Carboplatin (AUC = 2) and paclitaxel (50 mg/m^2) weekly, gefitinib 250 mg daily

Consolidation:
Gefitinib 250 mg daily

RT dose: 66 Gy

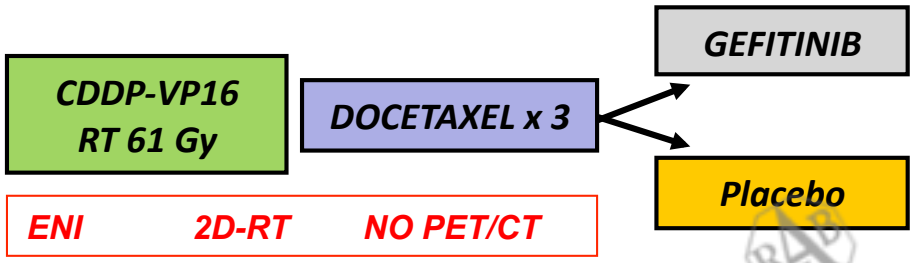
ENI, 2D-RT, NO PET

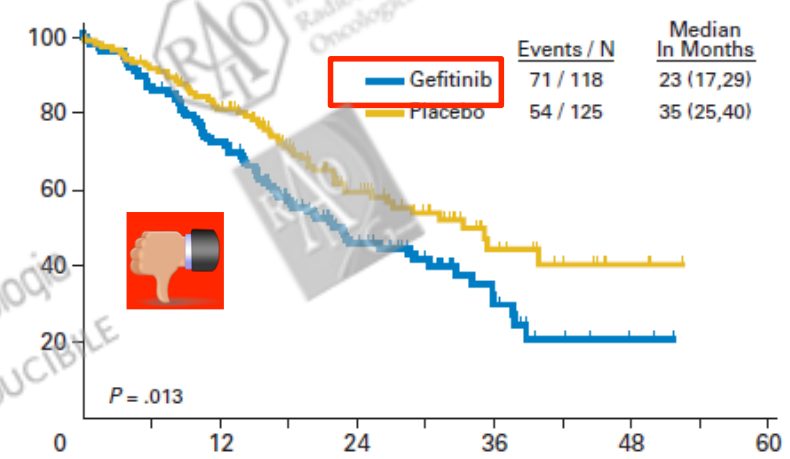
MST 13 mos

Ready, *J Thor Oncol 2010*

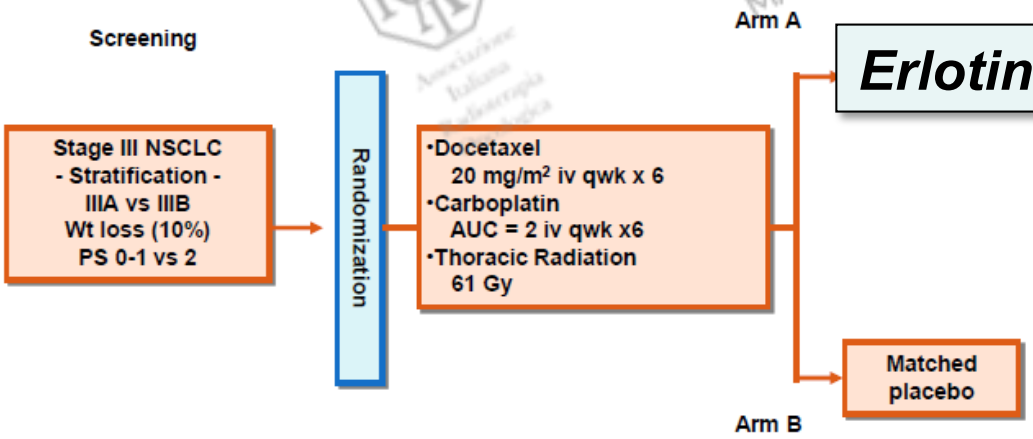
TKIs as maintenance

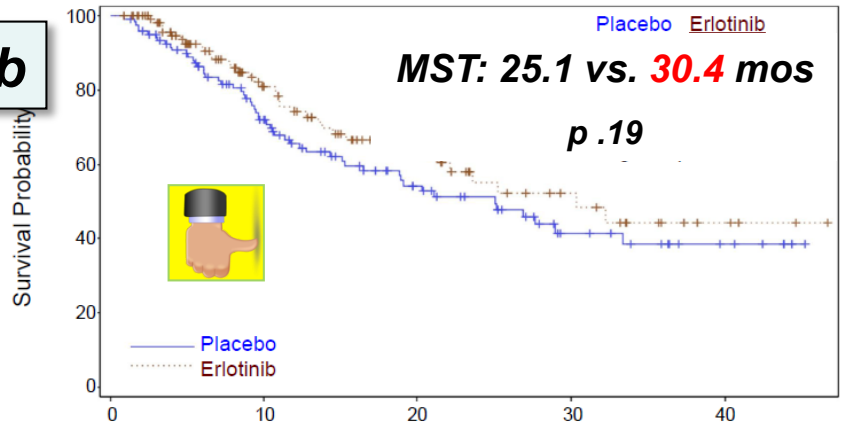
Phase III Trial of Maintenance Gefitinib or Placebo After Concurrent Chemoradiotherapy and Docetaxel Consolidation in Inoperable Stage III Non–Small-Cell Lung Cancer: SWOG S0023





Kelly, J Clin Oncol 2008





Rigas, *J Thor Oncol 2009*

Cetuximab + RT after Chemo

Concurrent cetuximab and radiotherapy after docetaxel–cisplatin induction chemotherapy in stage III NSCLC: Satellite—A phase II study from the Swedish Lung Cancer Study Group

71 pts

PS 0-1 (37% WL>5%)

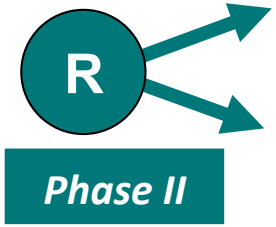
CDDP-DOCETAXEL x 2	CETUXIMAB w RT 68 Gy

NO ENI 3D-RT+IGRT PET/CT

Compliance	MST	G3-4 tox
82%	17 mos 24 mos (WL<5%)	Lung 5.1% 1 G5!

Hallqvist, Lung Cancer 2011

Cetuximab concomitant to RTCT



CBDCA-PEMETREXED x 4 RT 70 Gy	PEMETREXED x 4
CBDCA-PEMETREXED x 4 RT 70 Gy CETUXIMAB w	PEMETREXED x 4

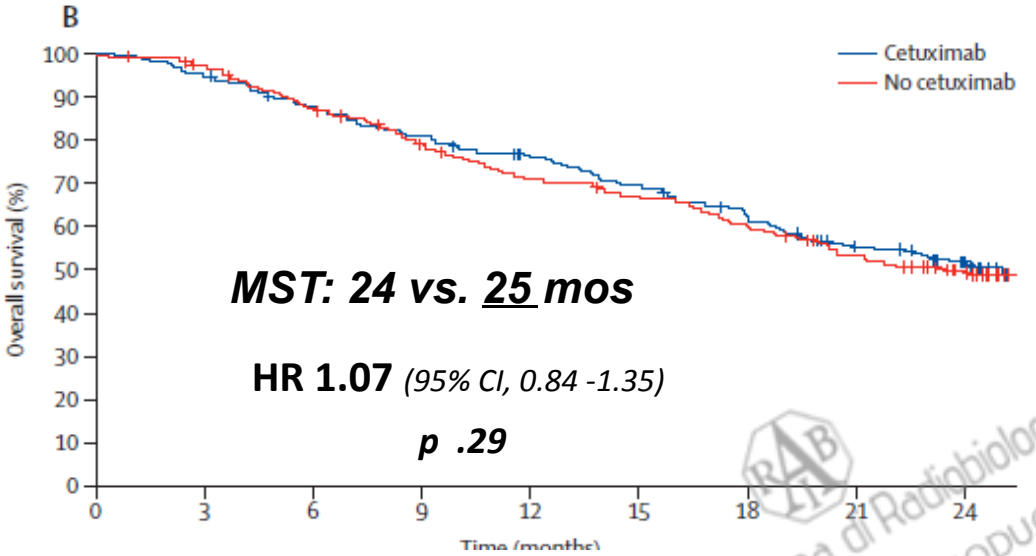
NO ENI 3D-RT PET/CT

Compliance	MST	G3-4 tox
54%	21.2 mos	46%* (2 deaths related)
52%	25.2 mos	46%* (3 deaths related)
		* hematological

101 pts **Good PS** **Adeno + Squamo !!**

Govindan, J Clin Oncol 2011

Need for predictive biomarkers to identify subsets responsive to Targeted agents



MST: 24 vs. 25 mos

HR 1.07 *(95% CI, 0.84 -1.35)*

p .29

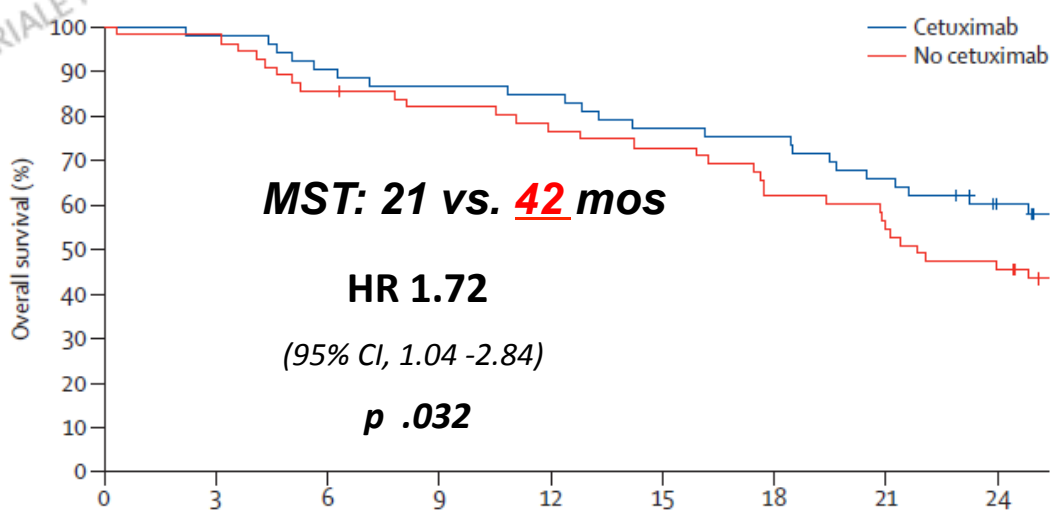
ALL PATIENTS

Bradley, Lancet 2015

203 Patients with

HIGH EGFR expression

H-score > 200



MST: 21 vs. 42 mos

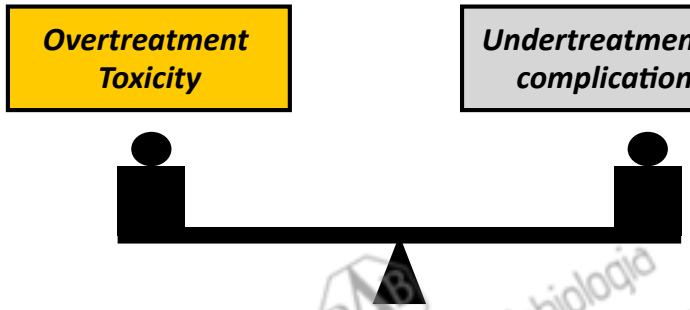
HR 1.72

(95% CI, 1.04 -2.84)

p .032

Should cRTCT be considered Standard of Care in the elderly?

- *Lung cancer is a typical disease of the Elderly (median age of diagnosis 71 yrs)*
- *Age-related comorbidities start after 70 years*



Elderly are often undertreated and less likely selected for cRTCT

SELECTION

Category	No. Deaths/ No. Entered RT + Conc CT	RT + Seq CT	Hazard Ratio	*P* of Interaction trend* test
Age				.38
Less than 60	239/273	217/246		*.24
60-64	95/114	100/111		
65-69	123/140	122/130		
70 or over	64/76	106/113		

Auperin A. JCO 2010

Should cRTCT be considered Standard of Care in the elderly?

SELECTION

Sequential vs Concurrent Chemoradiation for Stage … Cell Lung Cancer: Randomized Phase III Trial RTOG 9410

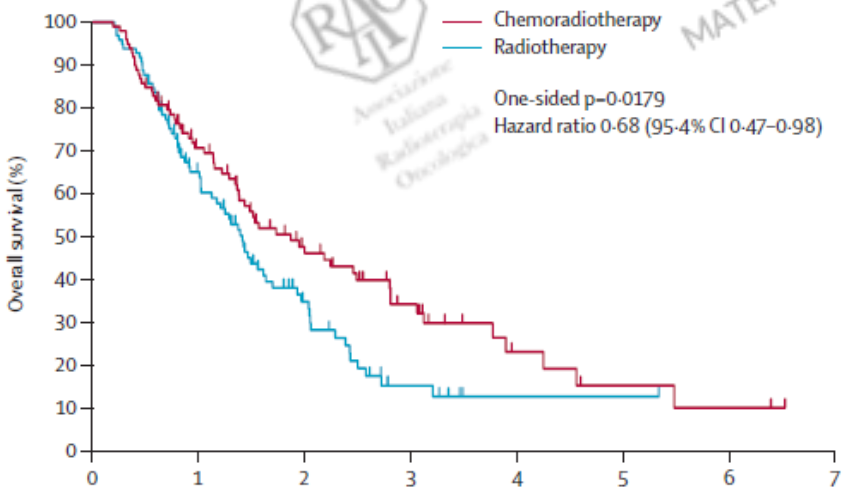
Walter J. Curran Jr, Rebecca Paulus, Corey J. Langer, Ritsuko Komaki, Jin S. Lee, Stephen Hauser, Benjamin Movsas, Todd Wasserman, Seth A. Rosenthal, Elizabeth Gore, Mitchell Machtay, William Sause, James D. Cox

Subgroup analysis of 104 pts > 70 yrs (17%): MST 10.5 vs. 22.4 mos

(p .069, analysis not pre-planned) *Langer, ASCO 2002*

SELECTION

…radiotherapy with or without daily low-dose carboplatin in elderly patients with non-small-cell lung cancer: a randomised, controlled, phase 3 trial by the Japan Clinical Oncology Group (JCOG0301)



194 patients > 70 years

96.5% PS 0-1

< 10% severe comorbidity

MS 22.4 vs. 16.9 mos

Atagi, Lancet Oncol 2012

Comorbidity and PS impact at least equal than age itself on final outcome

Age dependent prognosis in concurrent chemo-radiation of locally advanced NSCLC

478 patients (137 cRTCT) ***Stage IIA/IIIB, 1995 - 2012***

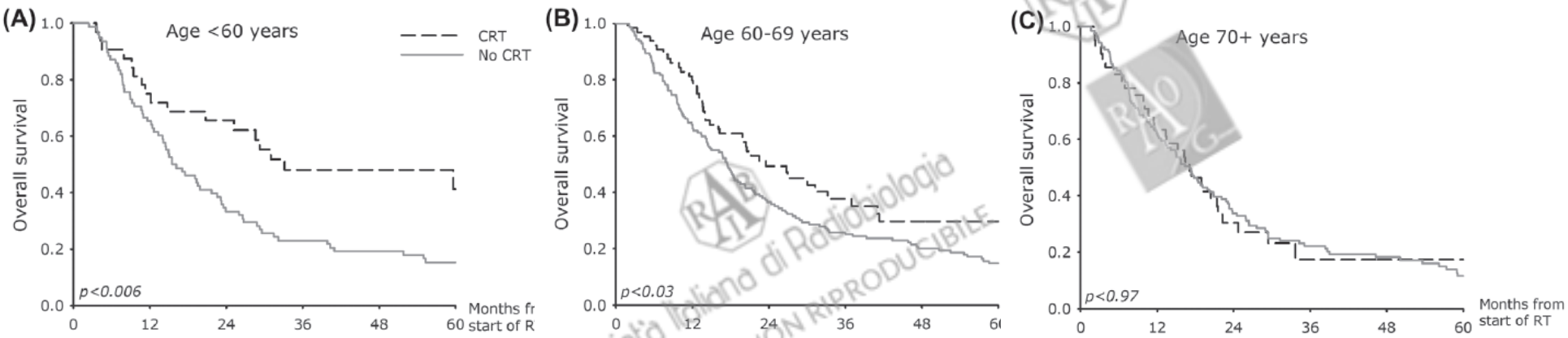


Table III. Multivariate Cox proportional hazard regression in overall survival and lung cancer specific survival.

Overall survival	Hazard ratio (95% CI)	p-Value
Concomitant chemo-radiation (CRT+)	0.44 (0.20; 0.94)	0.034
Age*	1.02 (0.88; 1.19)	0.79
Interaction CRT × Age*	1.39 (1.01; 1.93)	0.050
Performance status (2–3)	1.53 (1.15; 2.03)	0.003
FEV_1 (<75% of normal)	1.27 (1.04; 1.55)	0.020
Treatment year (≥2006)	0.78 (0.61; 1.00)	0.046

Hansen, Acta Oncologica 2014

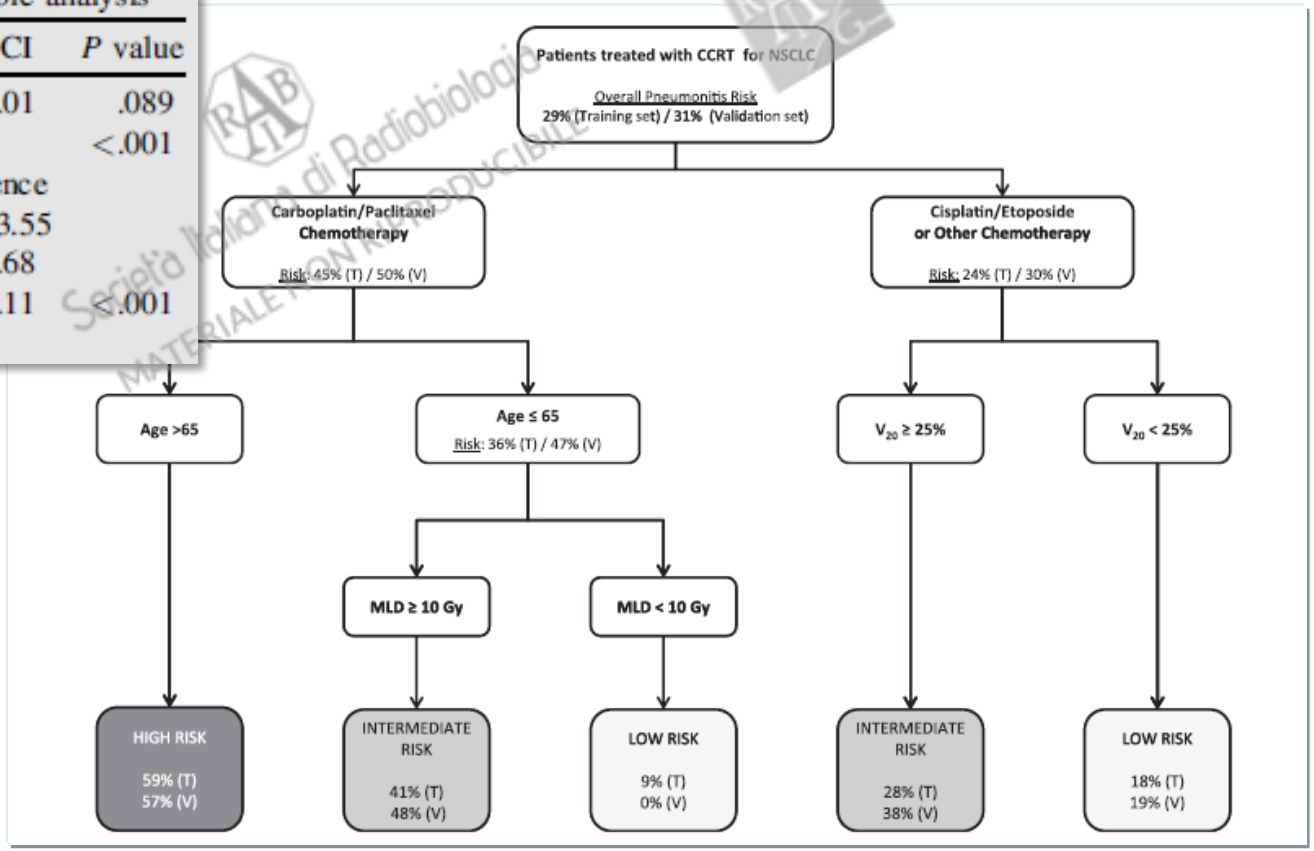
Older patients seem to have higher risk for toxicity

Predicting Radiation Pneumonitis After Chemoradiation Therapy for Lung Cancer: An International Individual Patient Data Meta-analysis

836 patients from 12 Institutions

cRTCT +/- Induction / Manteinance

Factor	Multivariable analysis OR	95% CI	*P* value
Age (per 10-y increase)	1.38	0.95-2.01	.089
Chemotherapy regimen			<.001
Cisplatin-etoposide	1	Reference	
Carboplatin-paclitaxel	5.52	2.25-13.55	
Other	3.39	1.50-7.68	
Volume of lung receiving ≥20 Gy (V_{20})	1.07	1.03-1.11	<.001



Palma, IJROBP 2013

Key points

1. **Concurrent** RTCT remains the standard care for **fit** patients
2. **Conventionally-fractionated** 60-66 Gy is the standard regimen
3. **No** evidence exists for **superiority** of a specific CT **schedule**
4. **Newer** drugs still need further evidence
5. **Target** therapy **might** have the potential to improve the outcome, **but…**
6. …**selection**, based on **molecular characteristics** is crucial
7. **Elderly** patients can benefit if **well** selected**.** Higher **toxicity** is expected

…changing the paradigm: from "pushing the dose" to "Individualize"!