CALGB 30610

Thoracic Radiotherapy for Limited Stage Small Cell Lung Cancer

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Small Cell Lung Cancer

- Estimated 33,000 cases in 2013
  - ~ One-third limited stage
    - Impact of FDG-PET
  - Majority stage III (2-5% stage 1)
  - Evenly split M = F
- IASLC (AJCC v 7) Stage Prognostic

Survival by Stage

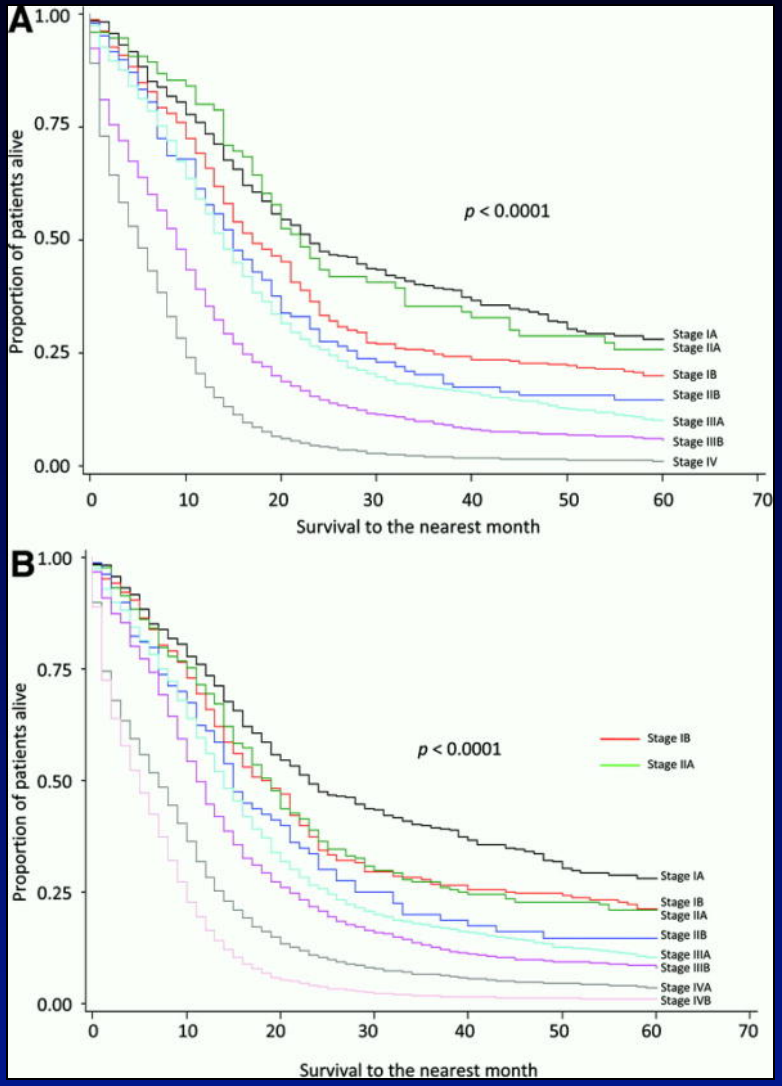


TABLE S2. Cox Multivariate Analysis of the IASLC Staging System for SCLC

UICC6	Hazards Ratio	95% Confidence Interval	*p*
Stage			
Stage IA	1.000	(0.996–1.492)	
Stage IB	1.219	(1.205–1.842)	0.0548
Stage IIA	1.490	(1.166–2.033)	0.0002
Stage IIB	1.540	(1.584–2.178)	0.0023
Stage IIIA	1.858	(2.010–2.792)	<0.0001
Stage IIIB	2.369	(2.649–3.615)	<0.0001
Stage IVA	3.095	(3.653–4.947)	<0.0001
Stage IVB	4.251		<0.0001
Age	1.014	(1.012–1.016)	<0.0001
Gender			
Male	1.000		<0.0001
Female	0.877	(0.842–0.913)	
Ethnicity			
Caucasian	1.000		
African American	0.939	(0.863–1.021)	0.1425
Hispanic	1.002	(0.932–1.077)	0.9583
Chinese	0.823	(0.685–0.988)	0.0364
Non-Chinese Asian	0.843	(0.757–0.938)	0.0017
Other	0.912	(0.593–1.402)	0.6752
Marital status			
Married	1.00		
Unmarried	1.101	(1.056–1.148)	<0.0001
Unknown	1.185	(1.011–1.389)	0.0359
Socioeconomic status	0.967	(0.952–0.982)	<0.0001
Surgery			
No	1.000		<0.0001
Yes	0.445	(0.386–0.513)	
Radiation			
No	1.000		<0.0001
Yes	0.722	(0.692–0.753)	
Chemotherapy			
No	1.000		<0.0001
Yes	0.379	(0.361–0.397)	

SCLC, small cell lung cancer; IASLC, Internal Association for the Study of Lung Cancer.

Ou, Journal of Thoracic Oncology. 4(3):300-310,

Select US Cooperative Group Studies

Study	Phase	Median OS (Months)	5-yr OS	Notes
INT 0096 1989 - 92	III	19 - 23	16 - 26%	BID v QD (45 Gy)
NCCTG 1990 -96	III	21	20 %	BID vs QD (50.4 Gy)
CALGB 9235 1993-99	III	21		Tamoxifen (50 Gy QD)
RTOG 9609 1996 - 98	II	24	---	PET 45 BID
ECOG 2596 1997 - 98	II	16		PET 63 Gy QD
SWOG 9713 1998 - 99	II	17		Adj paclitaxel (61 Gy QD)
SWOG 0222 2003 - 06	II	21	---	Tirapazemine (61 Gy QD)

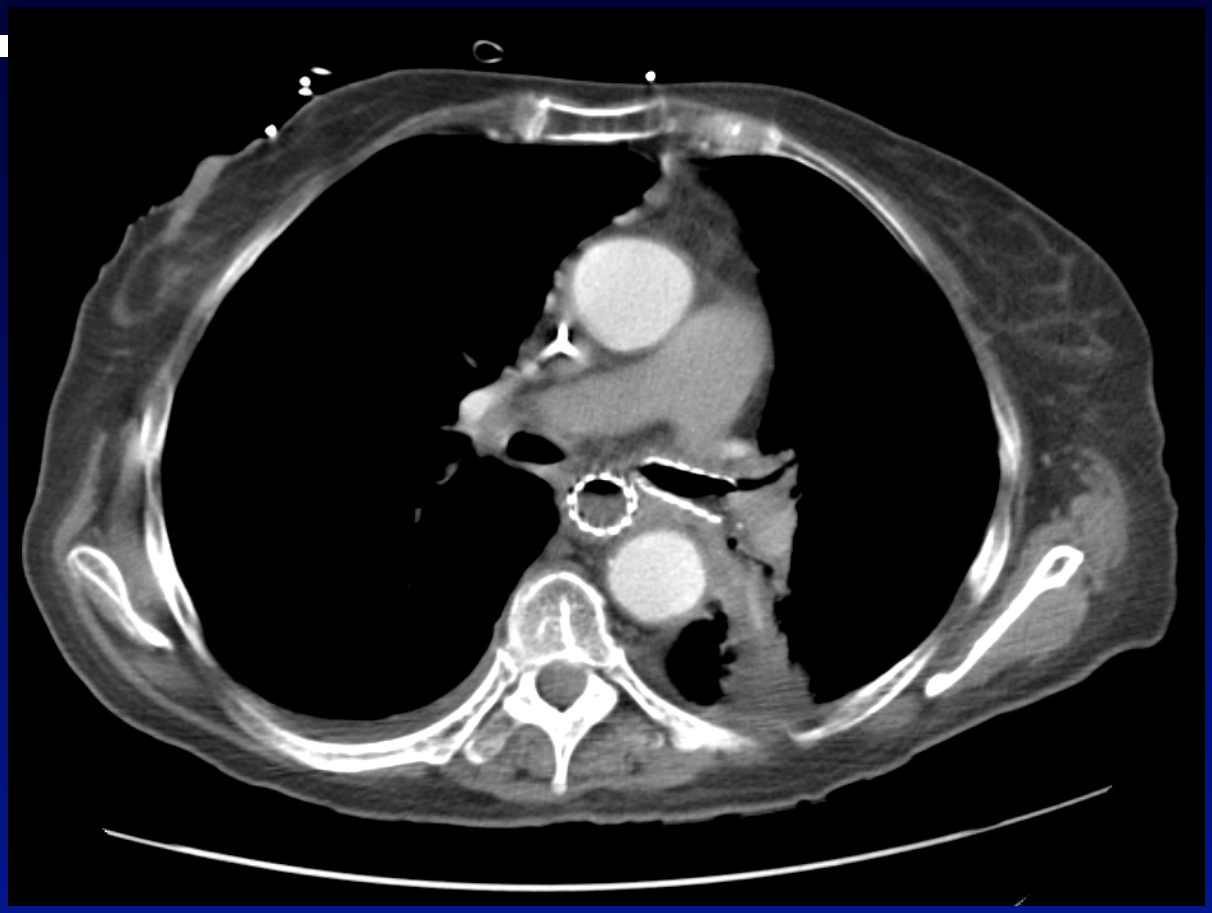
Small Cell Lung Cancer

- Progress has been slow!!!

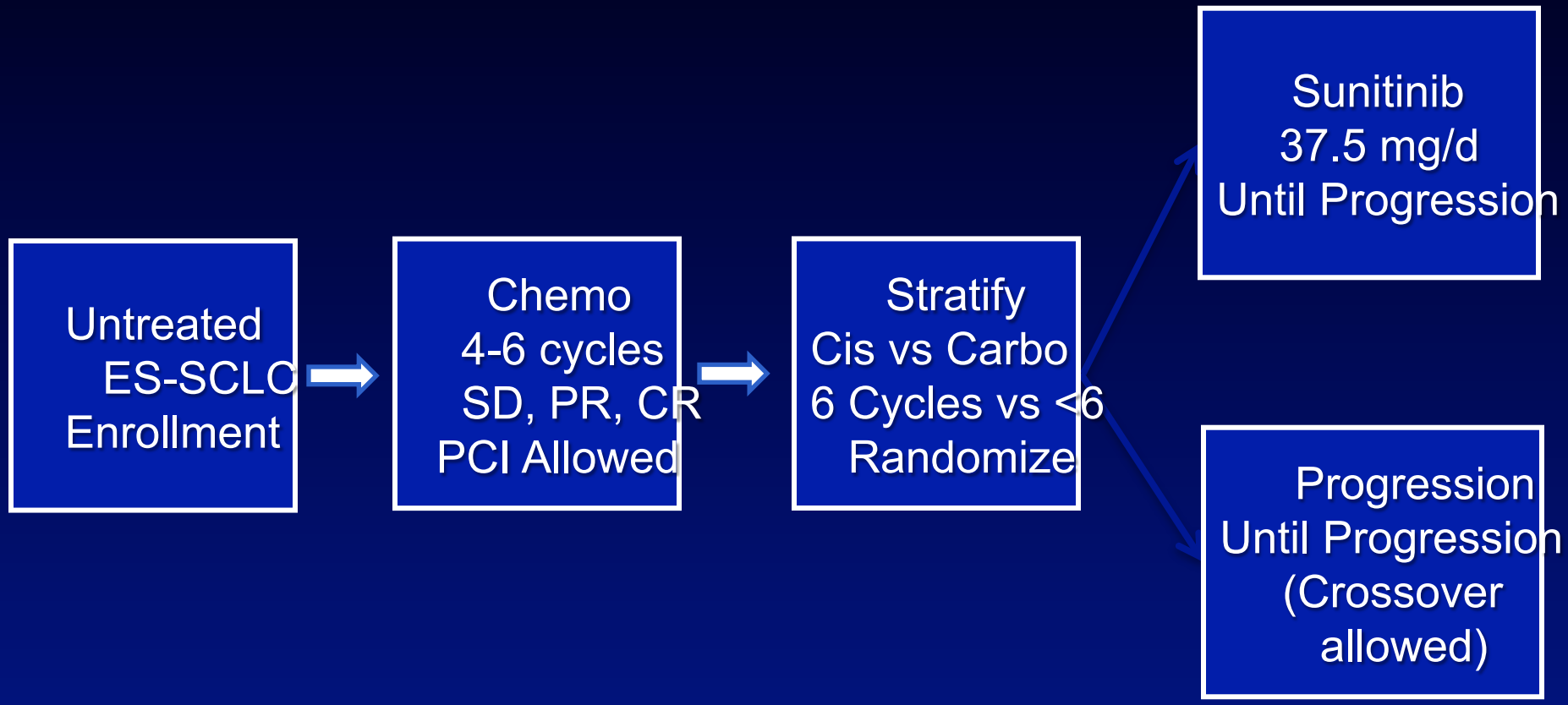
- Third generation chemotherapy
  - **Substituting Irinotecan** :extensive disease in Japan is an exception
  - **Adding Paclitaxel**: PET more toxic than ET

- Targeted agents
  - Bevacizumab toxic in limited stage (SWOG)

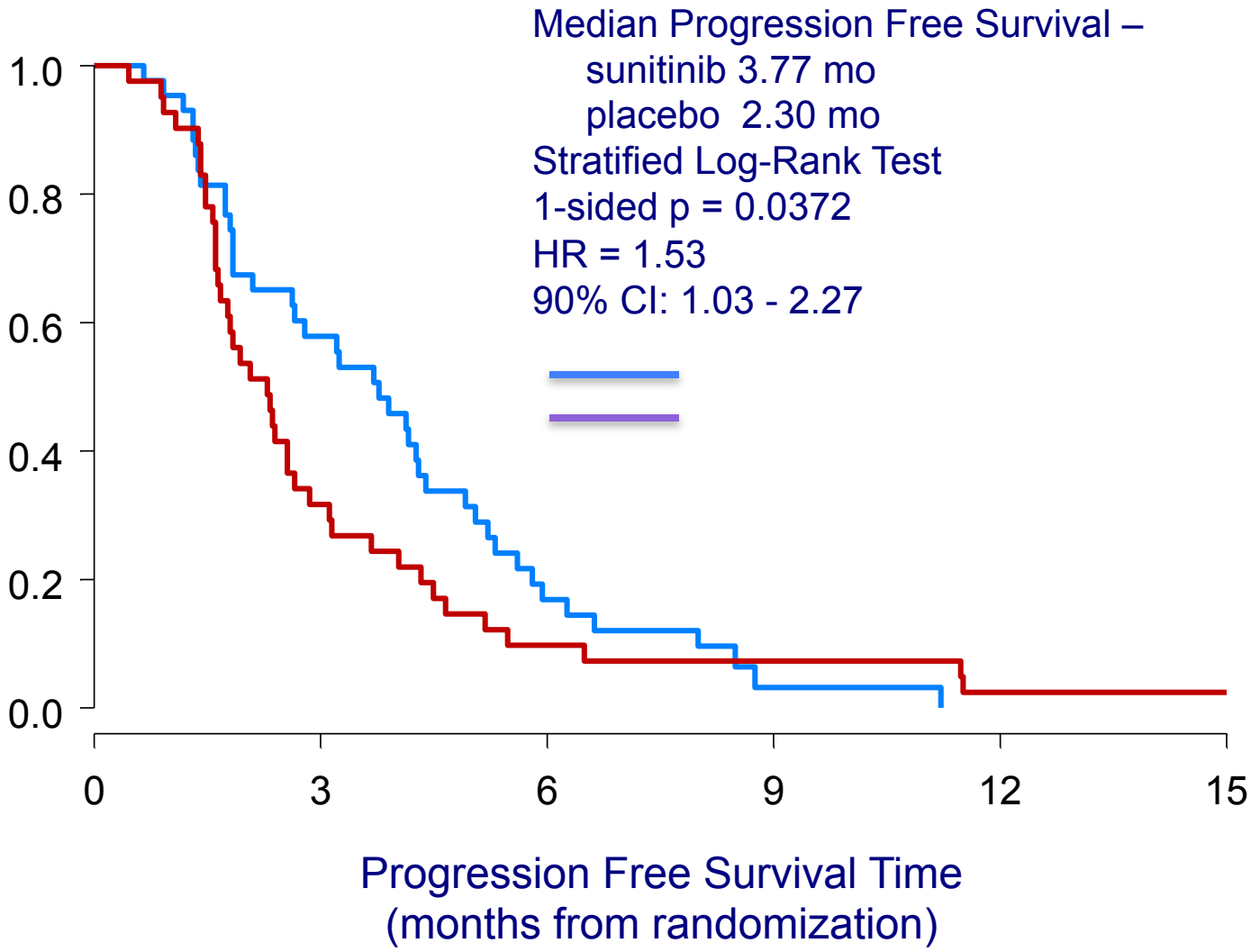
Targeted therapy

- Bevacizumab +RT
  - 

CALGB 30504
Study Design



Progression Free Survival



Limited Stage Small Cell

- The Integration of Radiotherapy for LSCLC is a Unique Success Story in the Field
- Several positive phase III trials
  - Adding RT to chemotherapy
  - Timing of RT
  - Altered Fractionation
- Few other examples where changing the radiotherapy regimen, in combination with chemotherapy, impacts Overall Survival

Limited Stage Small Cell

Impact of Thoracic Radiotherapy

Pignon et al NEJM 92

- 13 Trials , >2000 patients
- 3 yr OS: 14.3 vs 8.9 %

Warde et al JCO 92

- 2 yr OS: 16 vs 22% (2 yr LC: 40 v 65 %)
- Toxic Death Rate ↑ 1.2%

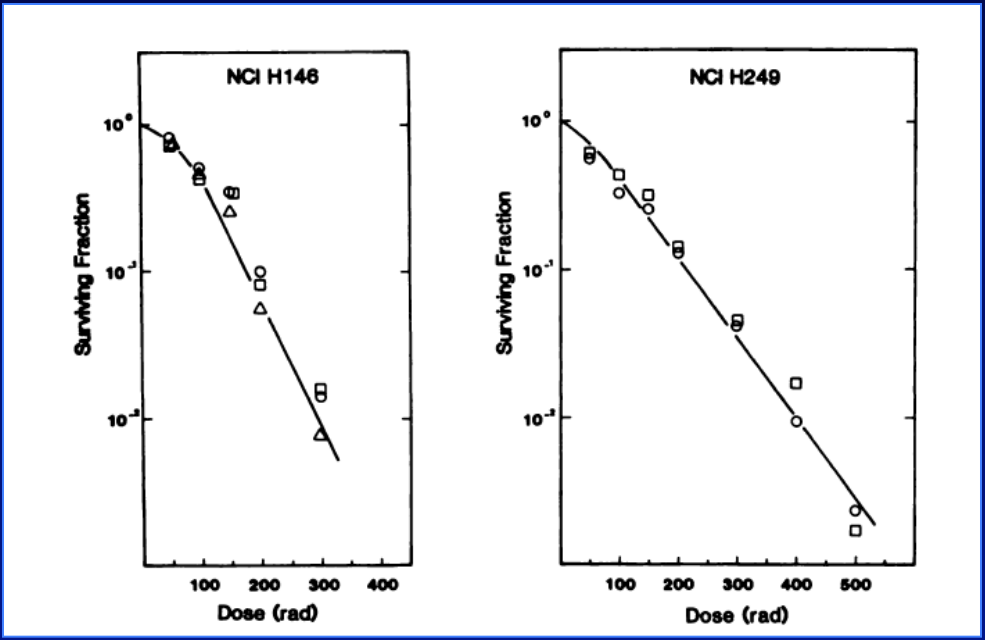
Limited Stage Small Cell

Meta-analysis underestimates TRT impact?

- Antiquated Staging
- Cisplatin seldom utilized
- Modest TRT Dose: 35 - 50 Gy
- Sequential therapy in majority of trials
- 2D (CXR) Radiotherapy Planning

Radiobiology: Pre-clinical

- Radiation survival curves for SC lines characterized
- Large Cell variant less sensitive



Carney 1983

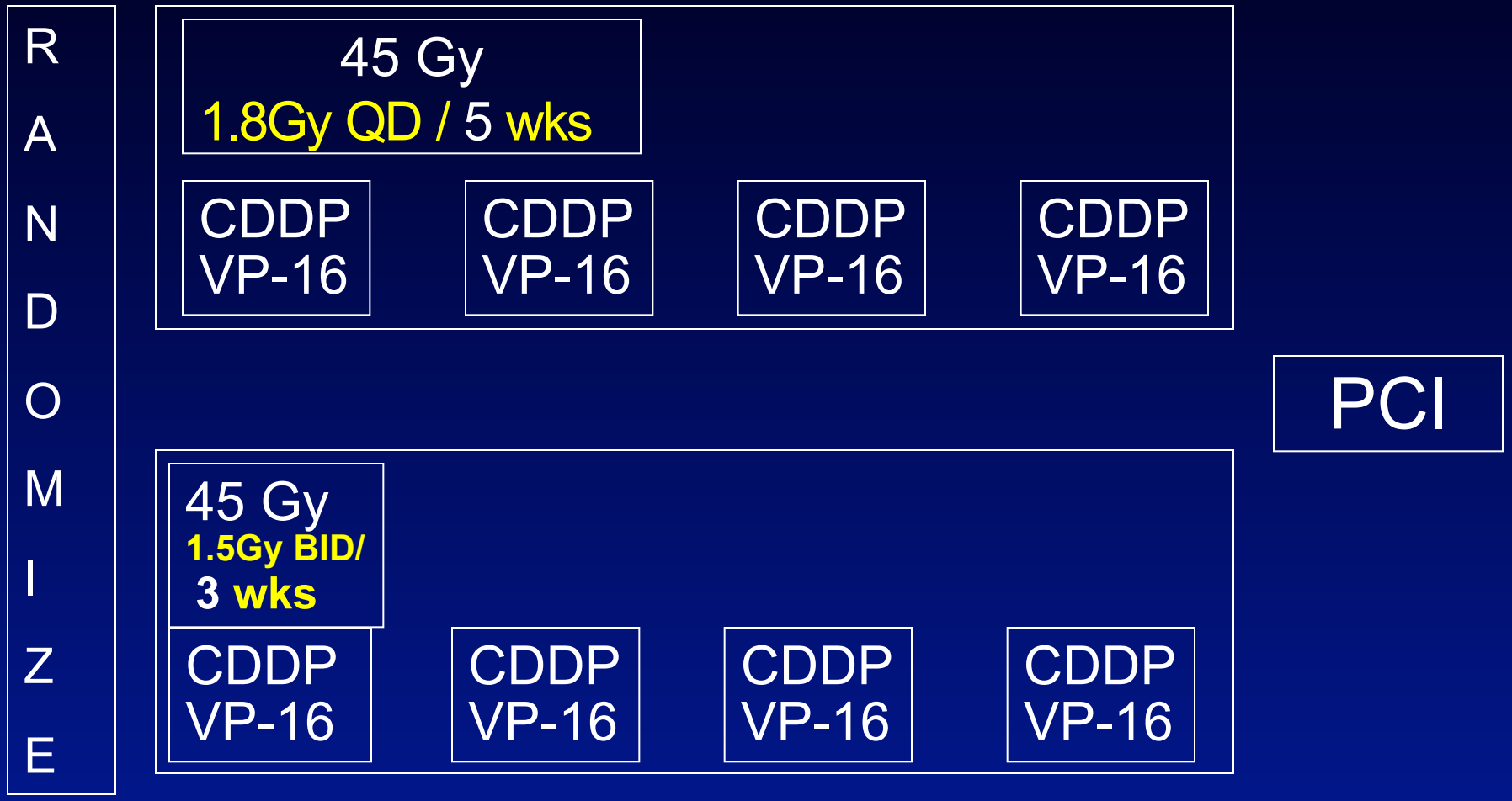
Dose / Fractionation

Twice-Daily Radiotherapy

- HospitalUnivPennsylvania
  - 45 Gy (1.5 BID) / 3 weeks (Cycle 1 PE)
  - **Limited ENI / CT planning**
  - 56% 2 year OS
  - 13% severe esophagitis (73% any)

Turrisi 1988

Intergroup Trial 0096 (ECOG)



INTERGROUP 0096

- Initially reported as a null trial (twice)
  - ASCO 1994 - initial report
  - ASCO 1996 - “final report”
- OS benefit emerged with 5 yr follow-up
  - 5-yr OS: 16 % (daily) vs 26% (twice-daily)
  - Gr 3/4 Esophagitis : 16% (daily) vs 32 % (twice-daily)

Turrisi NEJM 1999

INTERGROUP 0096

Relapse	BID	QD	P value
Local alone	36%	52%	.058
Local + distant	6%	23%	.006

"Local treatment significantly influences survival and failure patterns"

Turrisi ASCO 1998

INT 0096: Clinical Impact

Patterns of Care

- 1998-99 (JCO 2003) : 6% Patients Received BID RT , Median Daily RT = **50.4 Gy**
- ASTRO Survey 2006 : 28 % *would* use 45 Gy BID

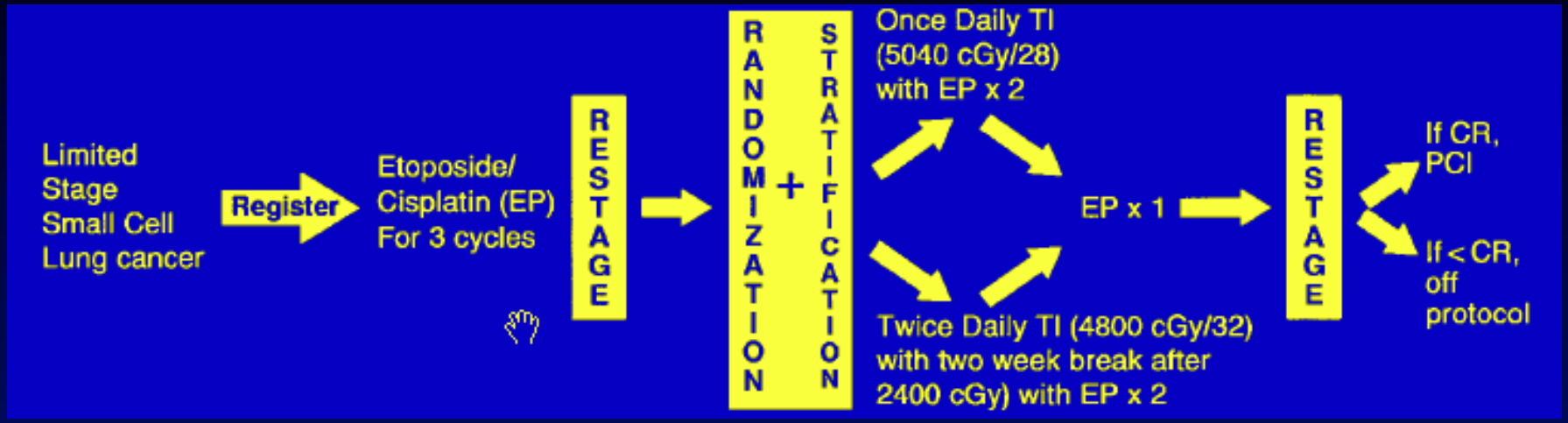
Not widely adopted in clinical trials (in U.S.)

- Acute Toxicity concerns?
- 45 Gy daily arm biologically appropriate comparison?

NCCN guidelines allow daily RT (60–70 Gy)

Movsas 2003 Kong 2007

NCCTG



- Randomized after cycle 3 PE
  - 50.4 Daily vs 48 Gy Twice -Daily
- 2 week RT treatment Interruption in BID arm
- No difference in survival b/w arms

Bonner 1999

Beyond 45 Gy BID?

Are there further therapeutic gains to be achieved by altering the delivery of thoracic RT?

- Traditional Dose Escalation
- Altered Fractionation Dose Escalation

Daily RT Dose Response?

- Data from early prospective trials did not suggest a dose response
  - NCI Canada: OS 25 Gy = 37.5 Gy (Seq)
  - **FNCLCC**: no dose response 45 - 65 Gy (Alt)

- Select retrospective studies suggest Dose response for daily RT
  - MGH: 5-yr OS 47% if > 50 Gy daily RT
  - Yale: 60 Gy RT – only 4% local failure

Coy 1988,Choi 1988, Roof 03, Papac 1987, Arriagada 1994

High Dose TRT: CALGB 8837

- Randomized phase I RT dose:
  - Cytoxan/PE X 3 → PE / RT
  - RT : BID or QD (56-70 Gy)

Regimen	n	Median OS	6 Year OS
Daily	22	29.8 months	36 %
Twice Daily	25	24	20

Median QD dose= 66 GY BID MTD = 45 Gy

Choi JCO 98

Phase II : High Dose Daily RT

Study	n	Induction	RT	Concurrent
CALGB 39808	63	Paclitaxel Topotecan **x2**	**70 Gy** **7 weeks**	Carboplatin Etoposide x3

- 70 Gy tolerable (21% esophagitis, 6% pulmonary)
- Median survival 23 months (31 months if wt loss<5%)
- Encouraging outcomes considering delayed RT and absence of cisplatin, inclusion of PS 2 and weight loss

Bogart 2004

39808/ 0096 Comparison (*2-yr FU)

	INT 0096 (45 Gy BID)	C 39808 (70 GY QD)
Male	58 %	54 %
Wt loss > 5%	**18 %**	**33 %**
Age (med)	61	60
Med. OS	20.3* mo	22.4 mo
2-yr OS	44 %	48 %
2-yr DFS	29 %	33 %
Esophagitis (3+)	**32 %**	**19 %**

39808: Novel induction, Cycle 3 TRT, *No* Cisplatin

* ~ 2 yr follow-up (ASCO 1994)

High Dose Concomitant Boost

- Improved control in H&N SCC (RTOG)
- Phase I (RTOG 9712) defined 61.2 Gy/PE as MTD in LSCLC
- Phase II completed (RTOG 0239) with acceptable toxicity (18% Esophagitis)
  - Preliminary report 2yr-OS 37%, 80 % LC

IIIIIIIIIIIIII IIIII**XXXXX**
XXXXXXXXX

(1.8 Gy /fx
5 weeks)

I = large field, X = boost field

Avoids BID "large field" TRT

Komaki 2005, 2009

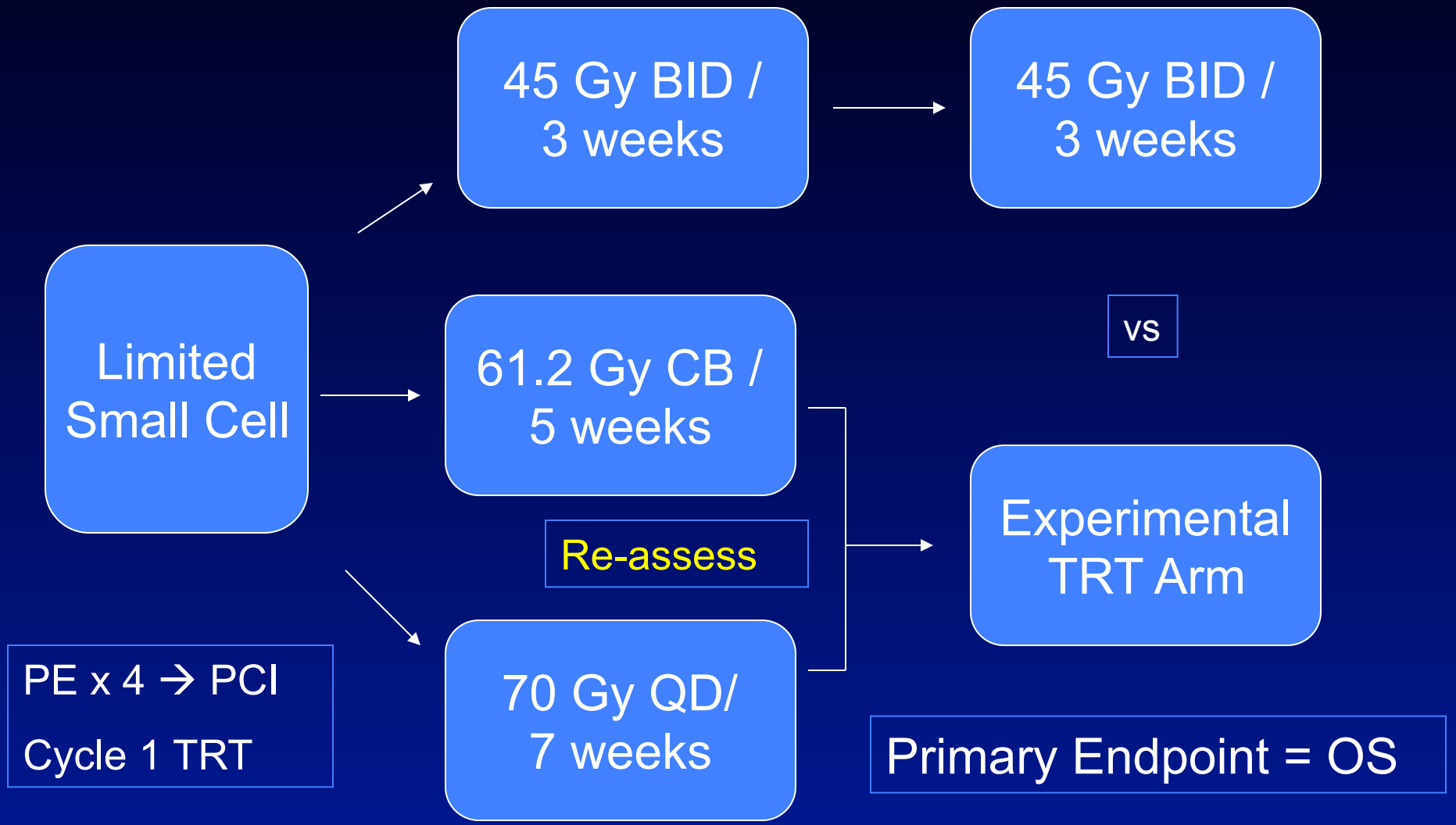
High Dose TRT Regimens

RT Regimen	Nominal Dose	BED	BED-time	Relative BED
INT 0096	45 Gy twice-daily	52	43	---
CALGB	70 Gy daily	82	63	~ 1.5
RTOG	61.2 Gy conc boost	72	57	~ 1.4

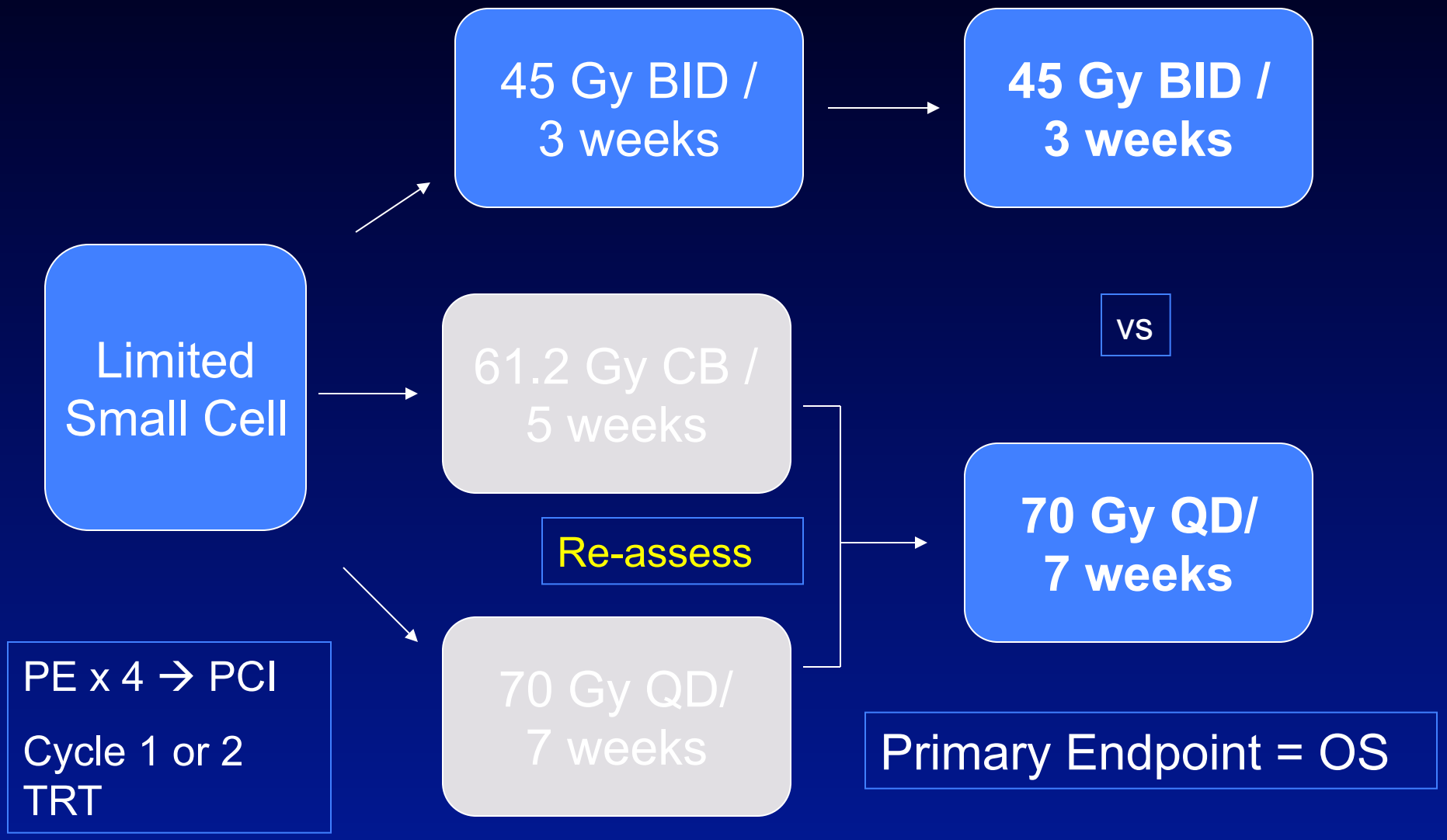
- Higher *predicted* efficacy with CALGB & RTOG regimens
- 70 Gy represents > 50% nominal dose escalation

(BED = biologic equivalent dose)

Phase III: CALGB 30610/ RTOG 0538



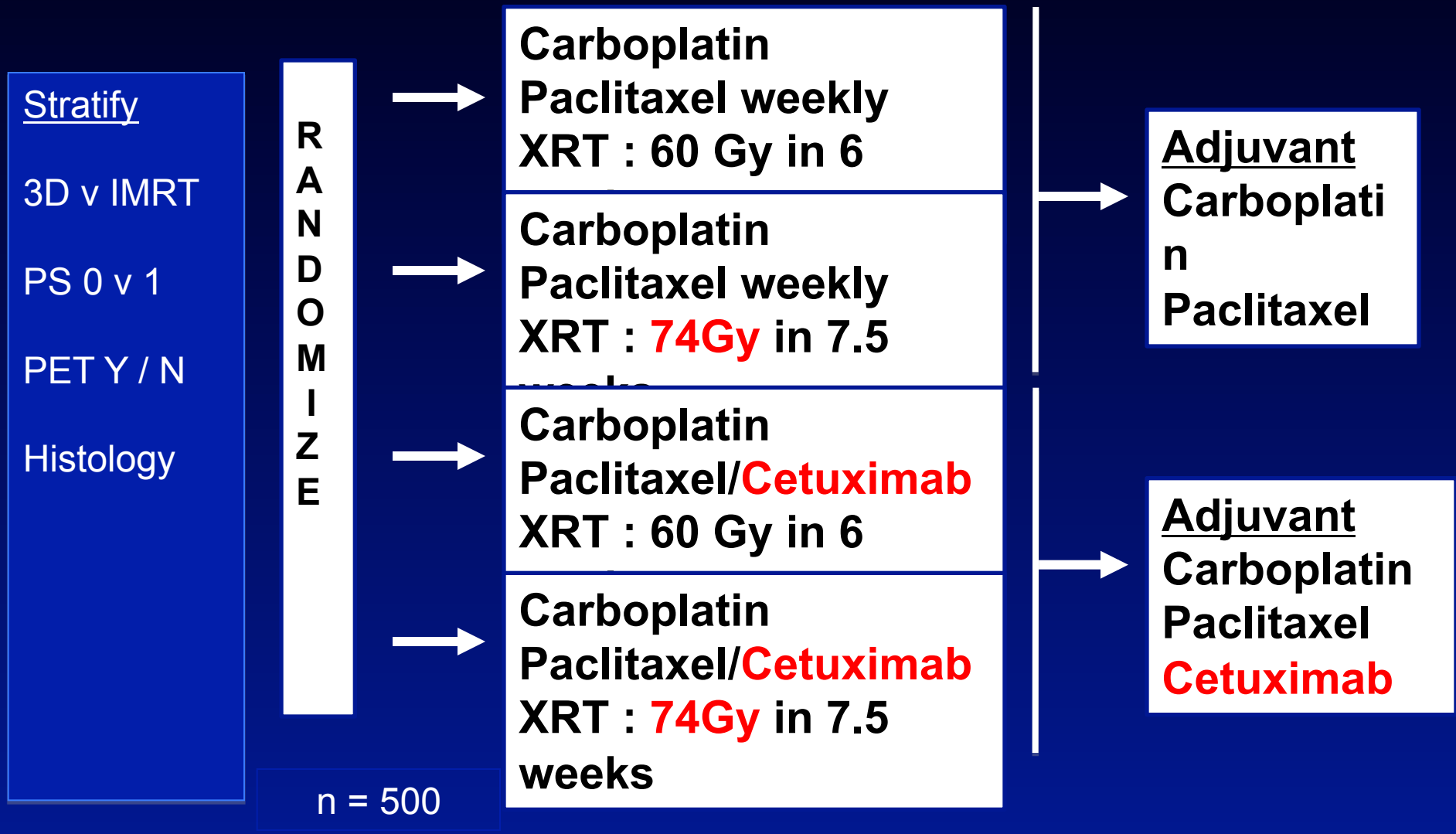
Phase III: CALGB 30610/ RTOG 0538



Status of Phase III trials

- CALGB 30610
  - Accrued 360 + patients / 700+
  - No significant difference in toxicity
    - CB arm dropped 3/2013

RTOG 0617 (Stage III NSCLC)



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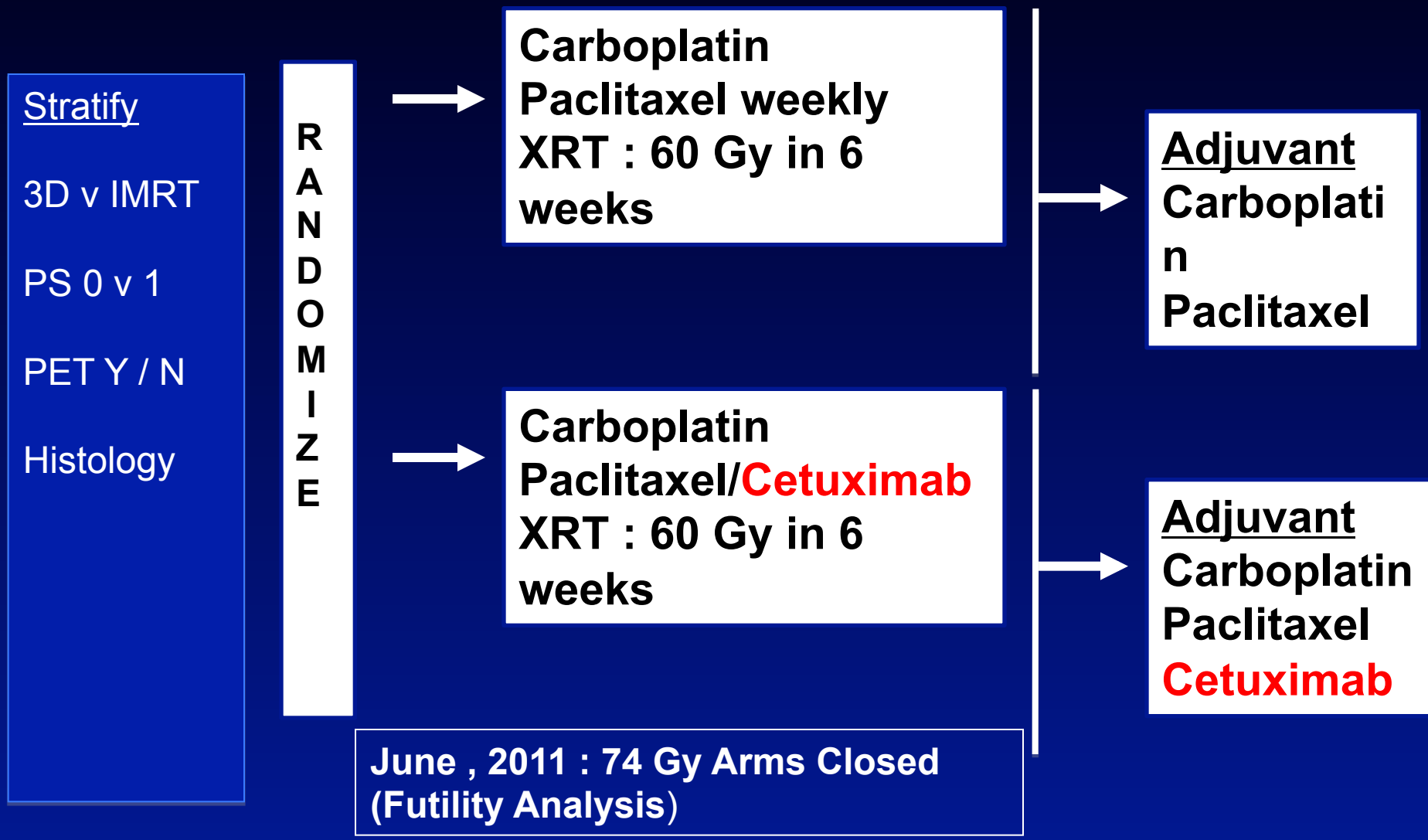

Major Amendments

- Allow RT to be given with either 1st or 2nd cycle of chemotherapy
- Reduced to 2 arm trial
- Allow Registration after 1st cycle of chemotherapy
- Planning to allow substitution of carboplatin for cisplatin

Summary

- Optimizing thoracic RT critical in LSCLC

- 45 Gy BID not widely accepted and **Protracted** High dose QD RT now routinely used in practice *without* sufficient evidence
  - Are the results of RTOG 0617 for NSCLC a lesson learned? 74 Gy + chemo not better than 60 Gy +chemo
  - CALGB and CONVERT critical test for dose escalation paradigm