Associazione Italiana Radioterapia Oncologica

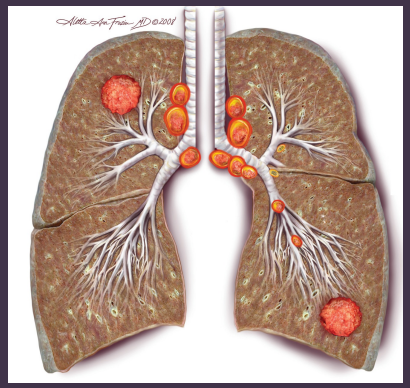
XXIII CONGRESSO
AIRO 2013
Giardini Naxos - Taormina, 26 - 29 ottobre

TRATTAMENTI INTEGRATI NELLO STADIO III NSCLC

Le terapie neoadiuvanti ed adiuvanti

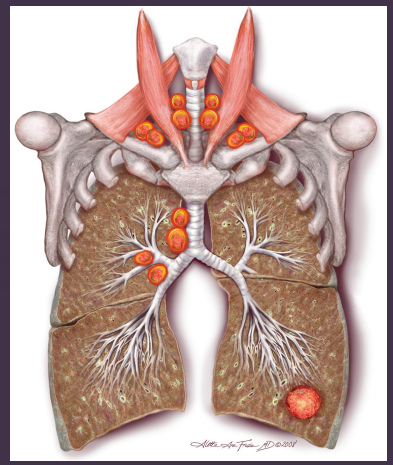
Sara Ramella
Radioterapia Oncologica
Università Campus Bio-Medico, Roma

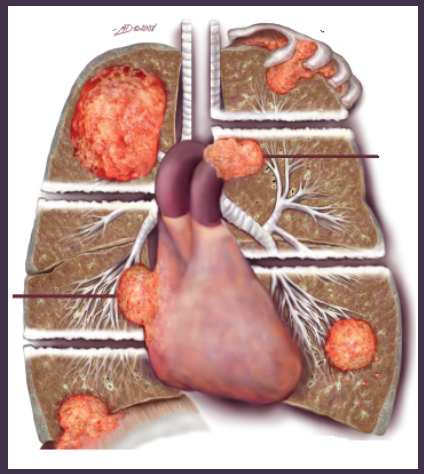
1993 2013 | VENTESIMO ANNIVERSARIO

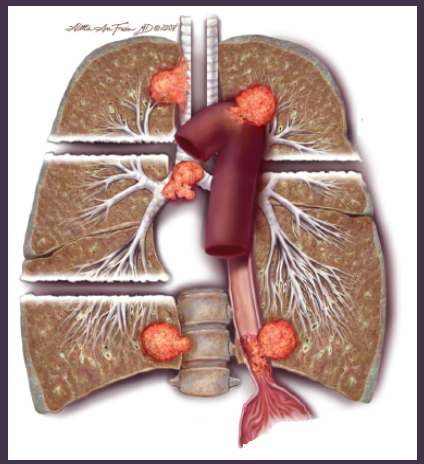


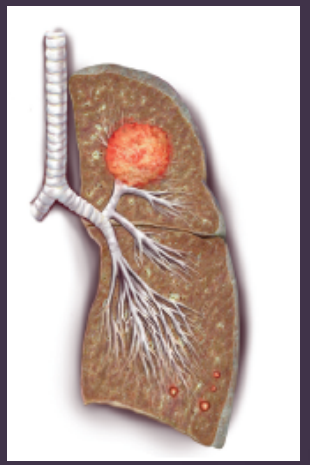
"Stage III represents a very heterogeneus group with 12 TNM classification subsets.

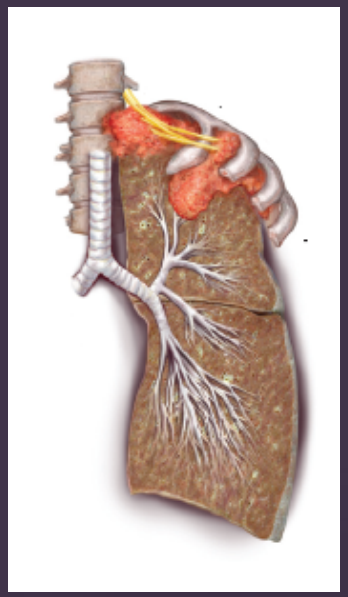
IT IS NOT SURPRISING that a single therapeutic concept cannot satisfy the needs of all subsets"





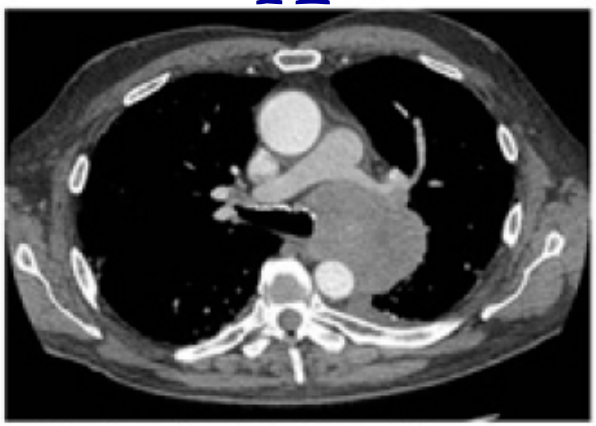






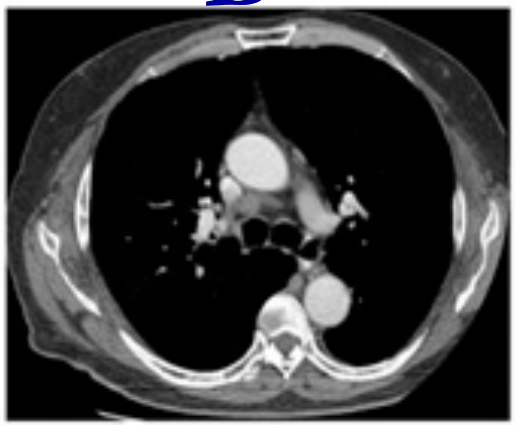
CHEST **Treatment of Stage III Non-small Cell**

A



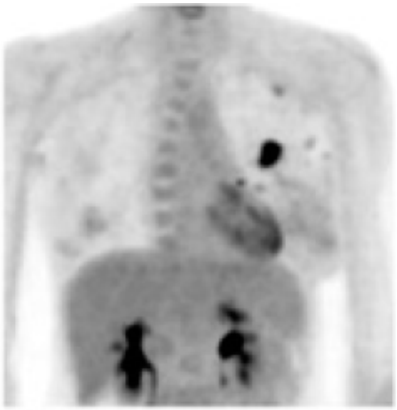
Mediastinal Infiltration

B



Discrete node enlargement

C



Clinically occult N2

TRATTAMENTO NEOADIUVANTE

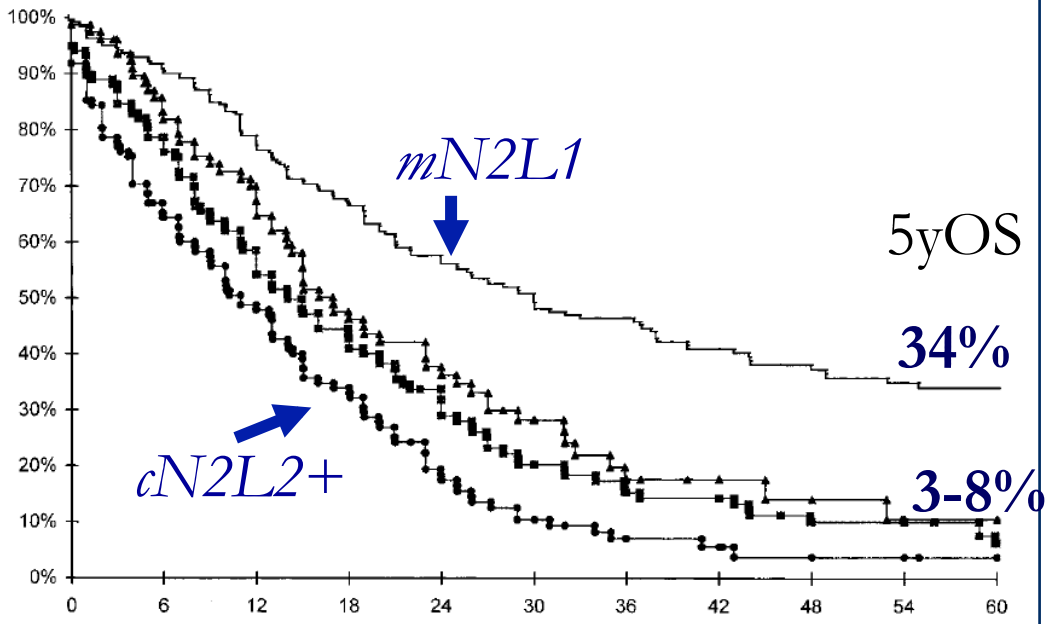
TRATTAMENTO ADIUVANTE

CHEST 2013; 143(5)(Suppl):e314S–e340S

Survival of Patients With Resected N2 Non–Small-Cell Lung Cancer: Evidence for a Subclassification and Implications

702 consecutive patients from six French centers
who underwent surgical resection of N2 NSCLC

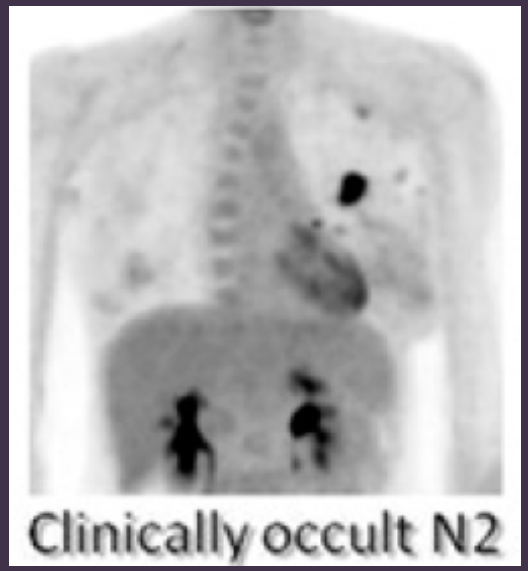
Variable	Overall Survival: Relative Risk	Overall Survival: P
Preoperative N2 status		
mN2		
cN2	1.8	< .0001
No. of levels involved		
L1		
L2+	1.6	< .0001



Andre F, J Clin Oncol 2000; 18:2981-2989

Discrete node enlargement

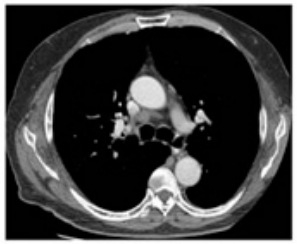
Clinical N2 (cN2)



Clinically occult N2

Pathological N2 (pN2)

CHEST 2013; 143(5 Suppl


Discrete node enlargement

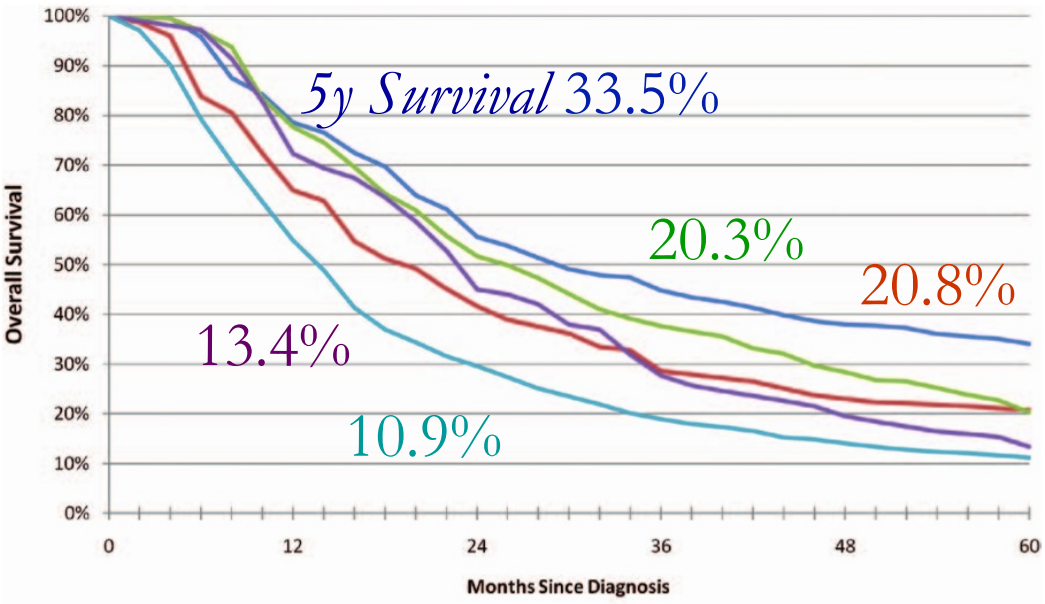
Clinical N2 (cN2)

Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

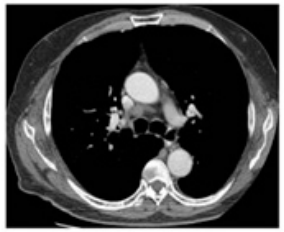
Observational data from the National Cancer Database

11.242 patients '98-'04

1. *NeoCRT* → *L*
2. *NeoCRT* → *P*
3. *L* → *adj*
4. *P* → *adj*
5. *CRT*

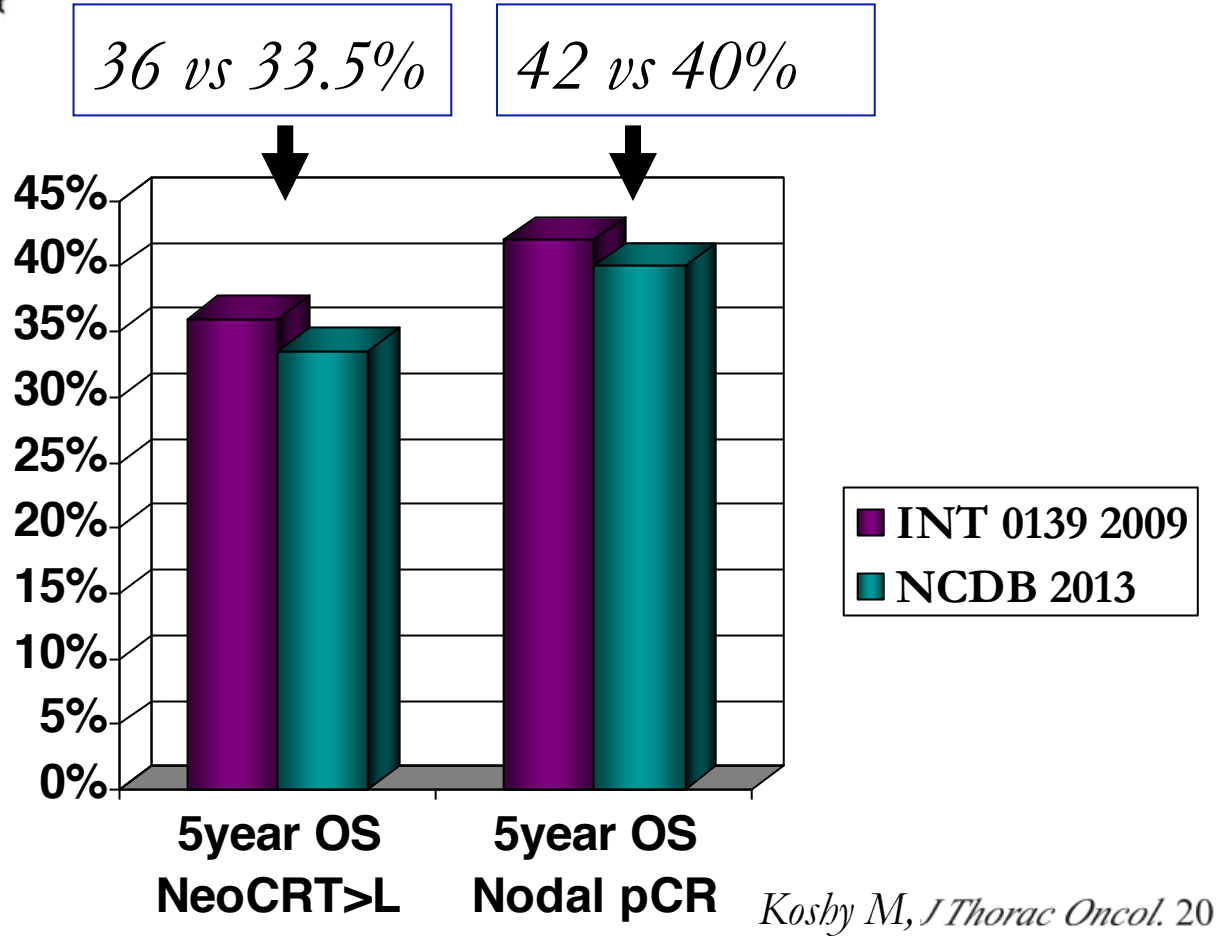


"NeoCRT>L had 49% reduced likelihood of death after adjustment fot clinical, sociodem. features" *Koshy M, J Thorac Oncol.* 2013;8: 915-922

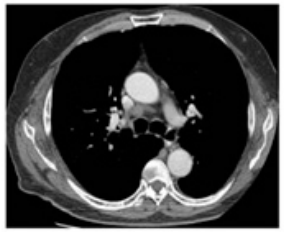


Discrete node enlargement

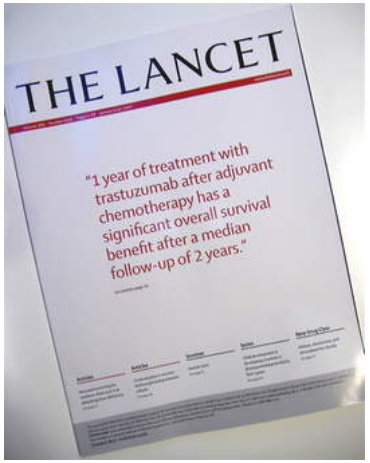
CLINICAL N2 (cN2)



Koshy M, J Thorac Oncol. 2013;8: 915-922

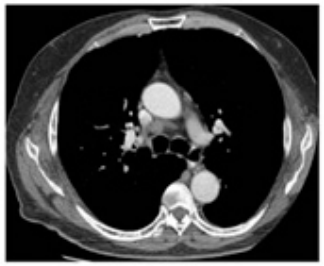

Discrete node enlargement

Clinical N2 (cN2) Neoadjuvant therapy



3 RANDOMIZED TRIALS:

- ✓ INT 0139 *(Albain Lancet 2009)*
- ✓ GERMAN study *(Thomas Lancet Oncology 2008)*
- ✓ EORTC *(Van Meerbeeck J Natl Cancer Inst 2007)*


Discrete node enlargement

Clinical N2 (cN2) Neoadjuvant Therapy

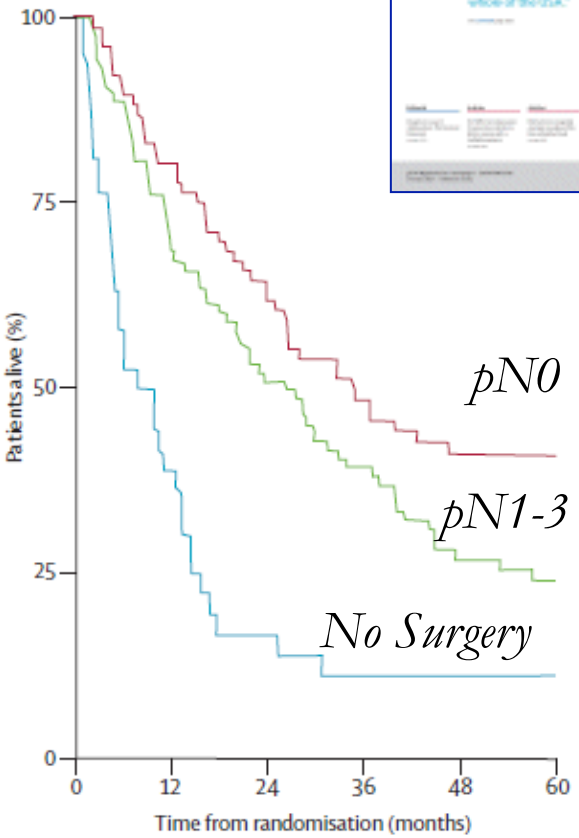
	INT 0139 CRT>S versus CRT	GERMAN study CT>CRT>S versus CT>S	EORTC CT>S versus CT>RT
Overall Survival 5year Survival			
Overall Survival pN0			
Pathological Downstaging pN0			

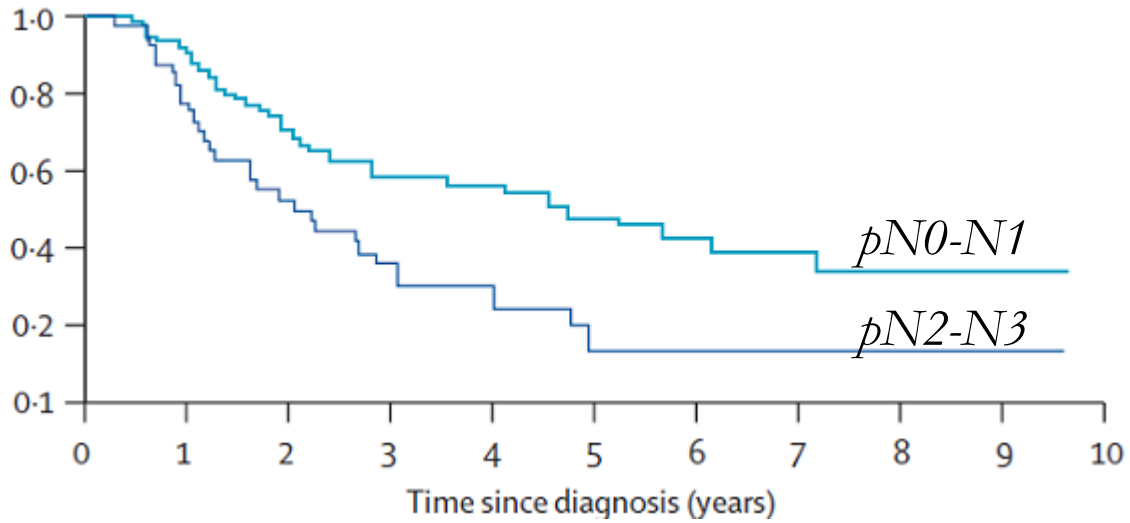
INT 0139

Albain 2009

GERMAN trial

Thomas 2008



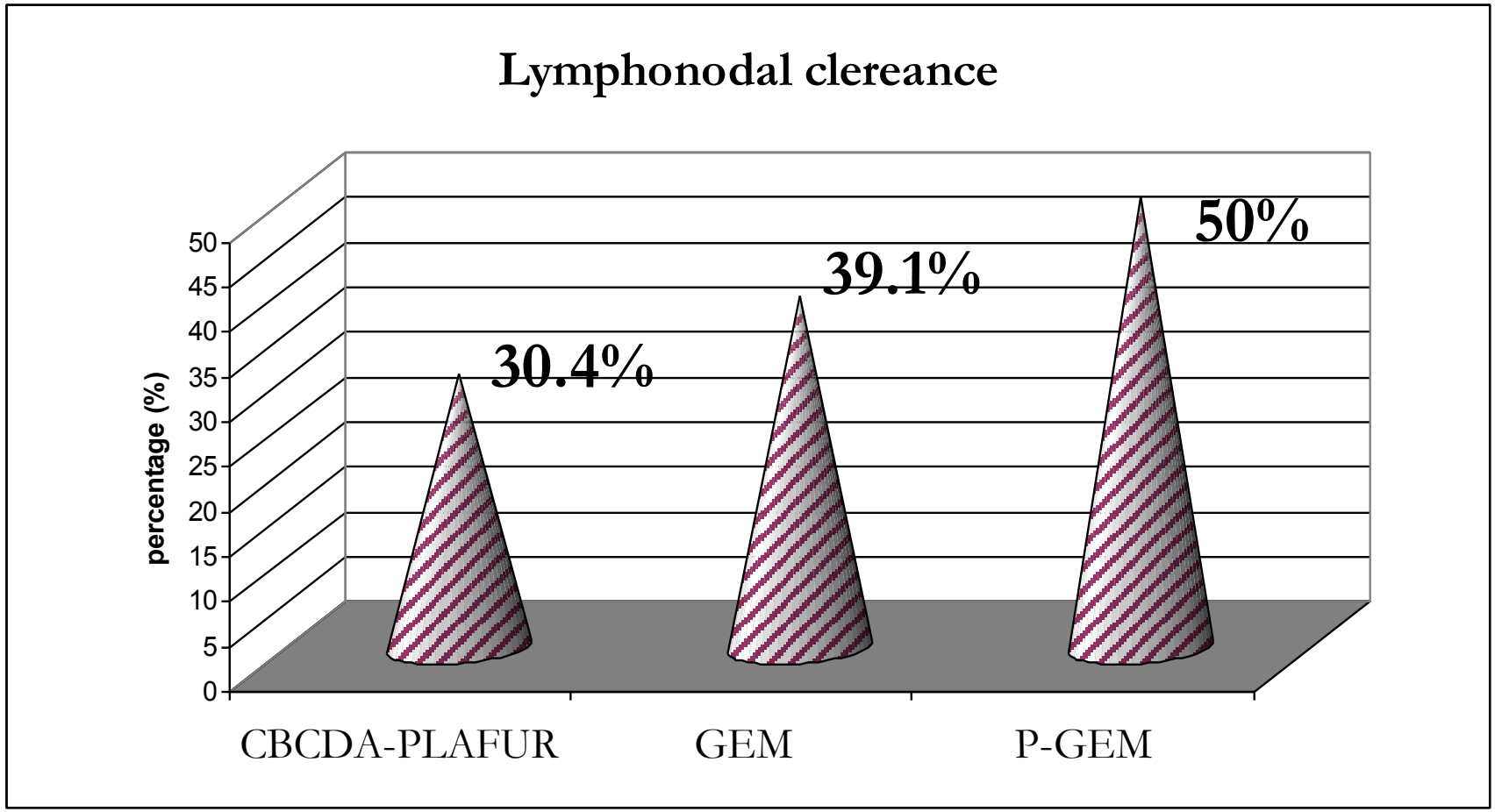


COME AUMENTARE LE RISPOSTE PATOLOGICHE ?????

L'INTENSIFICAZIONE DEL TRATTAMENTO

- ✓ Integrazione con i farmaci (*histology-driven*)
- ✓ Dose Totale
- ✓ Iperfrazionamento Accelerato

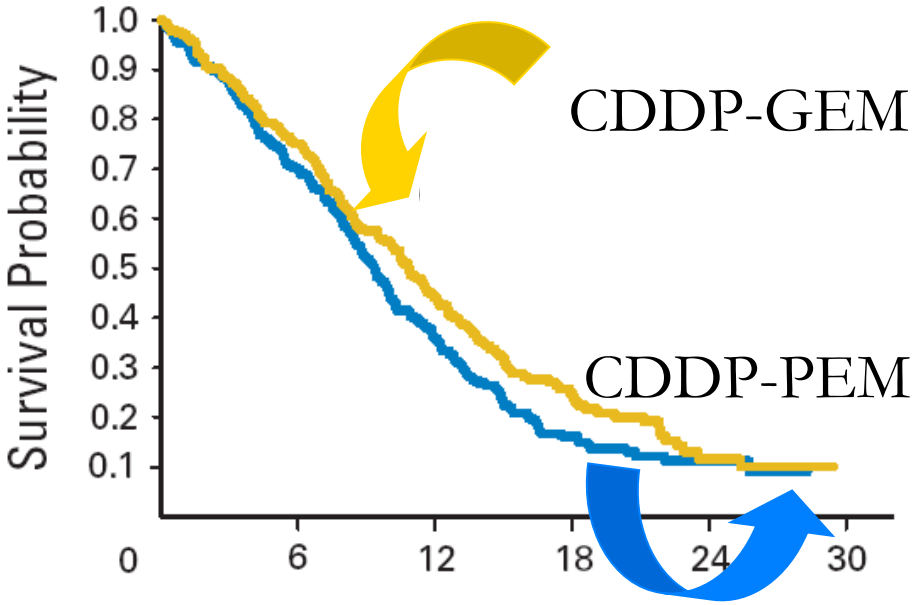
LA RADIOTERAPIA ED I FARMACI DI TERZA GENERAZIONE



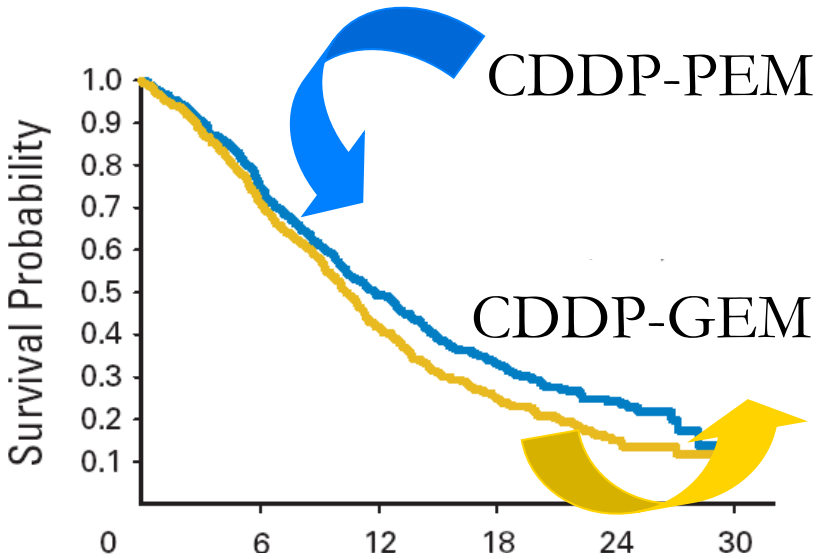
Trodella 2013

L'IMPATTO DELL' ISTOLOGIA NELLA CHEMIOTERAPIA

Squamous histology



Adenoca histology



SCAGLIOTTI G, J Clin Oncol. 2008

L'IMPATTO DELL' ISTOLOGIA NELLA RADIOCHEMIOTERAPIA

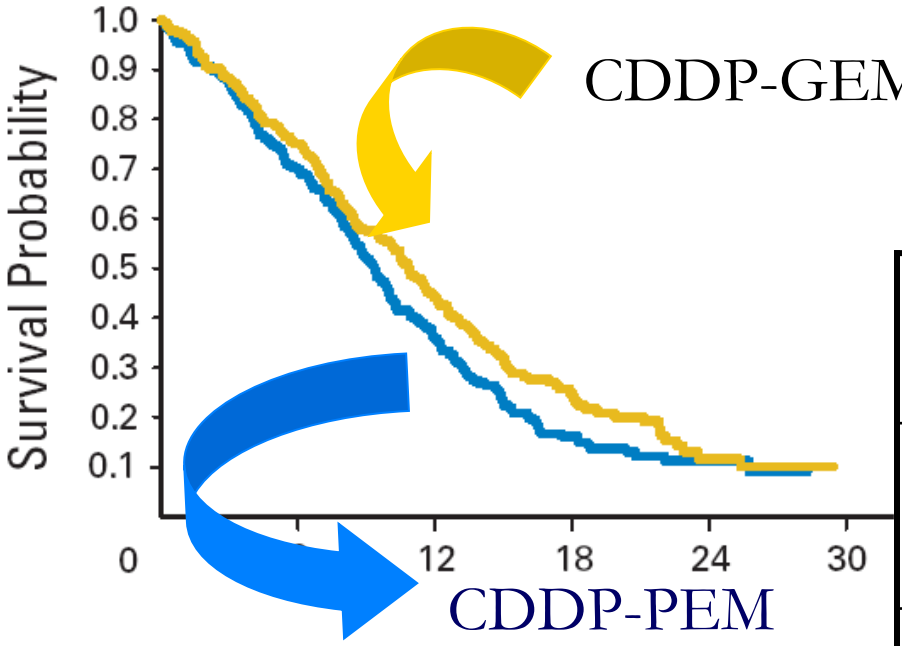
STUDI DI NEOADIUVANTE

Trials	Pts	Treatment	Stage	Resected pts	Median svv (months)	G3-4 Toxicity
A	92	CBDCART FUPLART	IIIA-IIIB	61%	17.2	Hem 5.5% No-hem 2.2%
B	46	RT + Weekly GEM	IIIA	63%	13	Hem 0% No-hem 0%
C	50	RT-CDDP + GEM	IIIA-IIIB	72%	21.8	Hem 30% No-hem 8%
D	46	IND CT followed by RT-GEM	IIIB	/	17.8	Hem 41% No-hem 13%
E	60	RT + ERLOTINIB + GEM or PEM	IIB-IV	/	14.4	Hem 33% N

A Annals of Oncology 15: 389–398, 2004
B J Thorac Cardiovasc Surg 31:314-21, 2006
C Lung Cancer 54, 331-338, 2006
D J Thorac Oncol. 4, 2009
E Biomed Res International 2013

L'IMPATTO DELL' ISTOLOGIA NELLA RADIOCHEMIOTERAPIA

Squamous histology



SCC GROUP

	GEM	NO-GEM
RESECTION RATE	74%	54% *p=0.034*
pSTAGE 0	66%	26% *p=0.001*

SCAGLIOTTI G, J Clin Oncol. 2008

Ramella S, ESTRO 2011

COME AUMENTARE LE RISPOSTE PATOLOGICHE ?????

L'INTENSIFICAZIONE DEL TRATTAMENTO

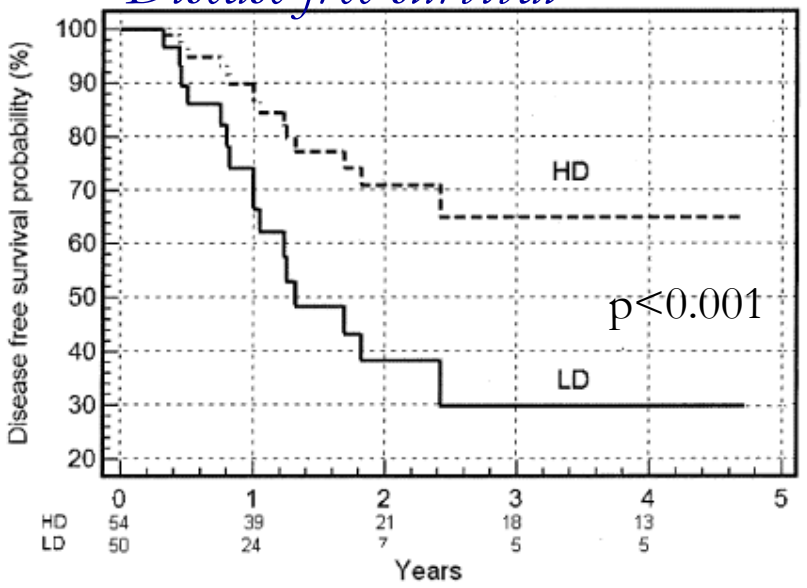
- ✓ Integrazione con i farmaci (*histology-driven*)
- ✓ *Dose Totale*
- ✓ Iperfrazionamento Accelerato

Pulmonary Resection After High-Dose and Low-Dose Chest Irradiation

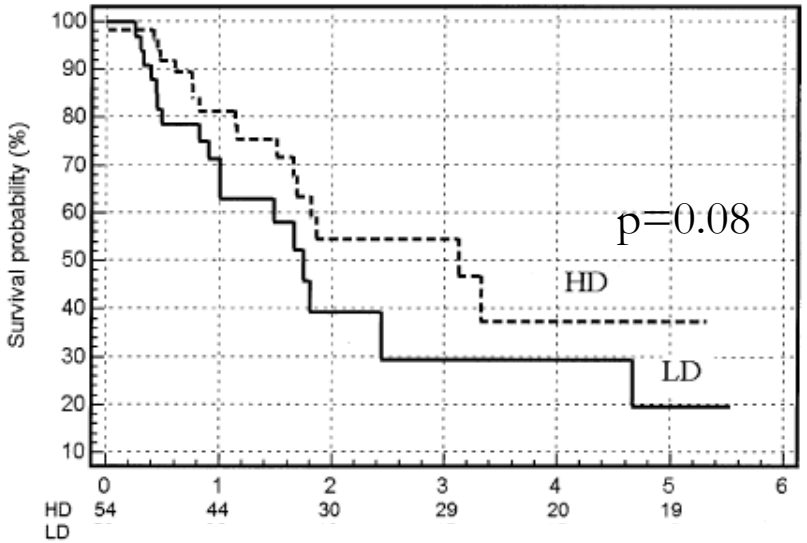
pCR group 45Gy vs 60Gy: 10% vs 28%, p=0.04

Major morbidity and mortality rates were similar: 8% vs 9% and 2% vs 3.7% for the low and high dose groups, respectively.

Disease free survival



Overall Survival



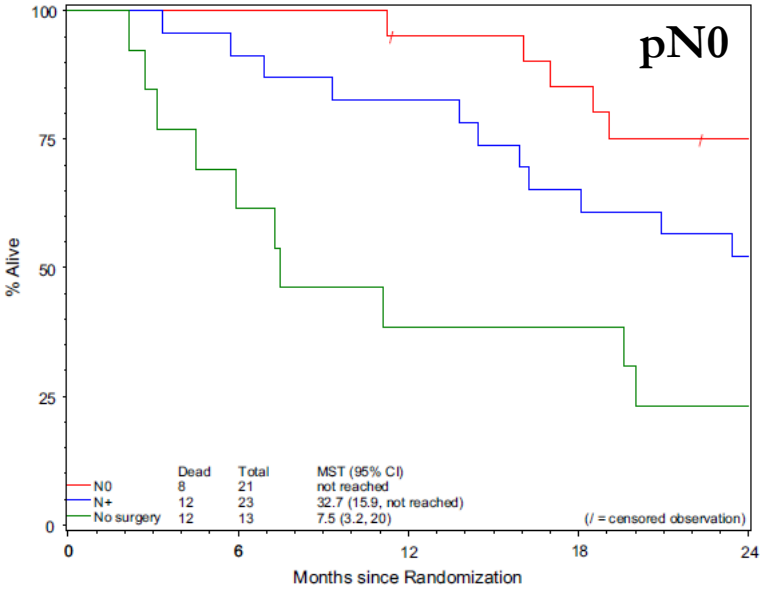
Cerfolio, Ann Thorac Surg 2005;80:1224 –30

Radiation Therapy Oncology Group Protocol 02-29: A Phase II Trial of Neoadjuvant Therapy With Concurrent Chemotherapy and Full-Dose Radiation Therapy Followed by Surgical Resection and Consolidative Therapy for Locally Advanced Non-small Cell Carcinoma of the Lung

57 patients

TREATMENT: *61.2Gy (1.8Gy/die)*
Carbo AUC2 + Taxol 50 mg/mq/w

TOXICITY
Hematologic 35%
Gastrointestinal 14%
Pulmonary 23%
Postop complicat 14%



Mediastinal Nodal Clearance 63%

Suntharalingam Int J Radiat Oncol Biol Phys 2013 84:456-463

COME AUMENTARE LE RISPOSTE PATOLOGICHE ?????

L'INTENSIFICAZIONE DEL TRATTAMENTO

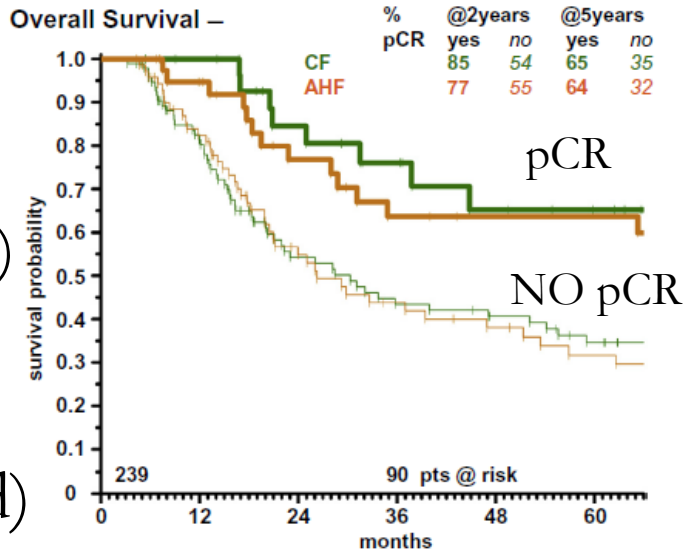
- ✓ Integrazione con i farmaci (*histology-driven*)
- ✓ Dose Totale
- ✓ *Iperfrazionamento Accelerato*

Accelerated Hyperfractionated Radiotherapy

Accelerated hyperfractionated radiotherapy within trimodality therapy concepts for stage IIIA/B non-small cell lung cancer: Markedly higher rate of pathologic complete remissions than with conventional fractionation

239 patients

CT> CRT
- Hyperfx (45gy/1.5Gy bid)
- Conventfx (46Gy/2Gy qd)



Pottgen, Eur J Cancer 2013:49:2107-2115

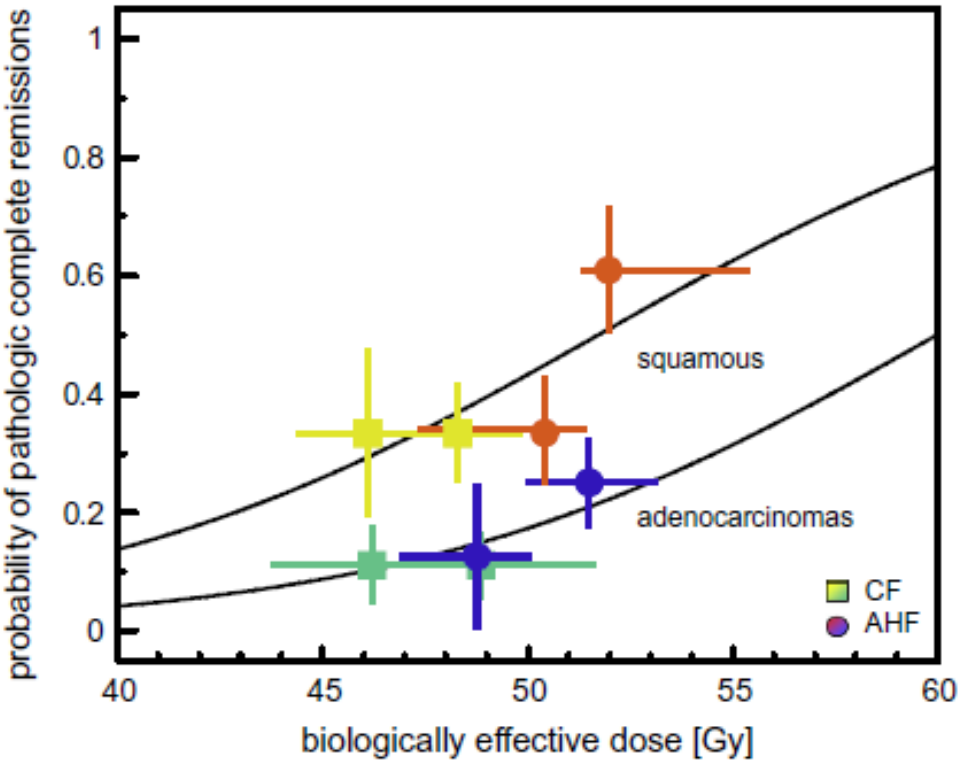
Accelerated Hyperfractionated Radiotherapy

pCR :

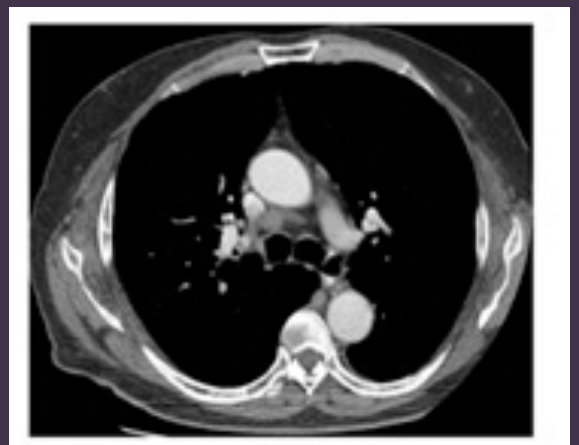
37% AHF vs 24% CF
(p=0.041)

AHF : Odds Ratio 2.11
(95%CI 1.10-4.05, p=0.025)

ADK : Odds Ratio 0.20
(95%CI 0.08-0.50, p<0.001)

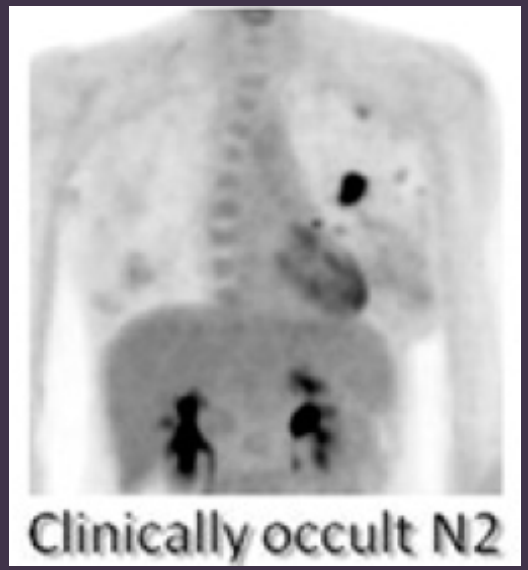


Pottgen, Eur J Cancer 2013:49:2107-2115



Discrete node enlargement

Clinical N2 (cN2)



Clinically occult N2

Pathological N2 (pN2)

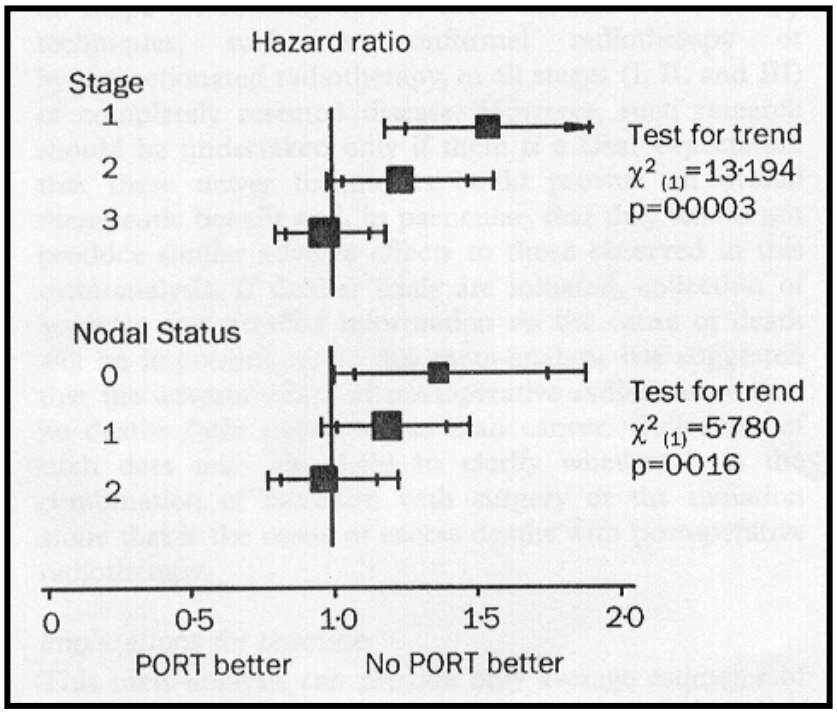
CHEST 2013; 143(

Articles

Adjuvant Radiation Therapy

Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials

*PORT Meta-analysis Trialists Group**



Critical points of trials

1. *Recruitment*
2. *Dose and fractionation*
3. *Volume*
4. *Technique*
5. *Technology*

THE LANCET • Vol 352 • July 25, 1998

Adjuvant Radiation Therapy

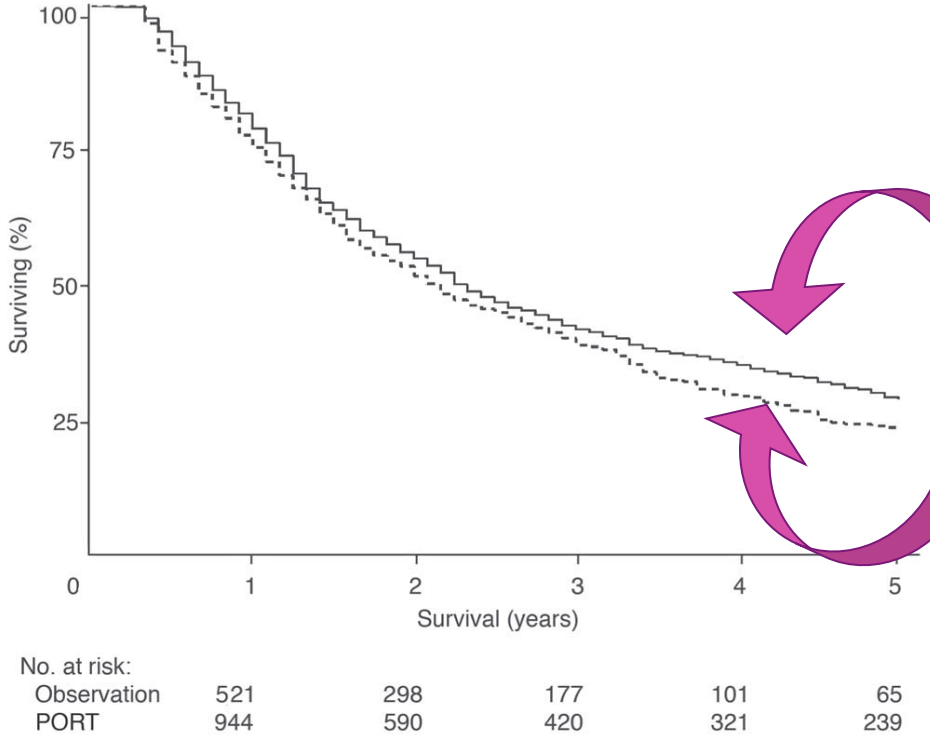
«There remains a debate as to whether data gathered some 20 to 40 years ago should have such a CRITICAL ROLE in the formation of treatment guidelines in the modern era.

This is not to question the veracity of the data, per se, but it clearly identifies a GLARING WEAKNESS and time gap in the knowledge base with respect to this important question.

Most modern cancer guidelines accept these data, BUT ALL CLAMOR FOR ADDITIONAL RANDOMIZED TRIAL»

Chest Guidelines 143: 278S-313 S 2013

Post-operative Radiotherapy for stage II or III NSCLC using the SEER database *(7465 pts)*



pN2 5y svv

PORT 27%

NOPORT 20%

HR 0.855; 95% CI, 0.762-0.959; p=0 .0077

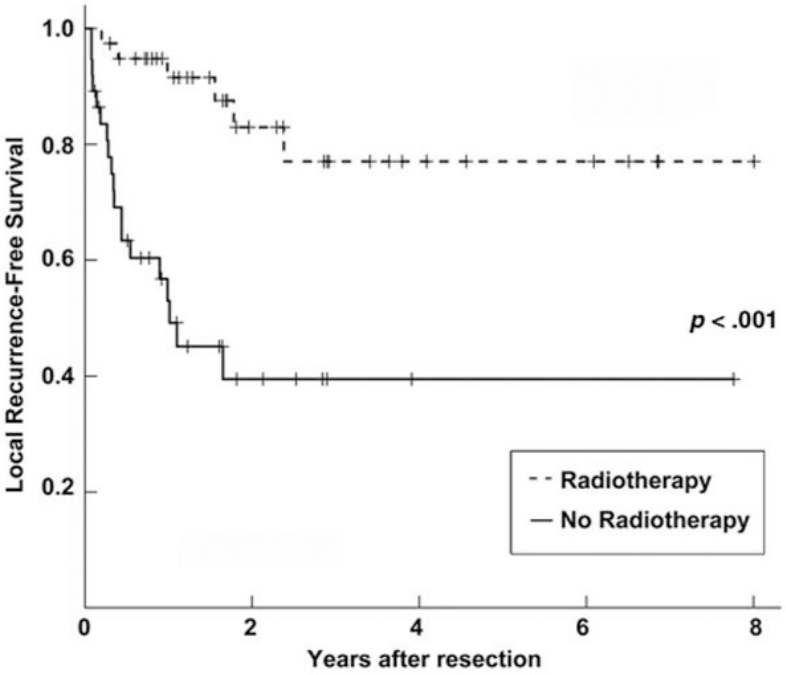
Lally BE JCO July 2006

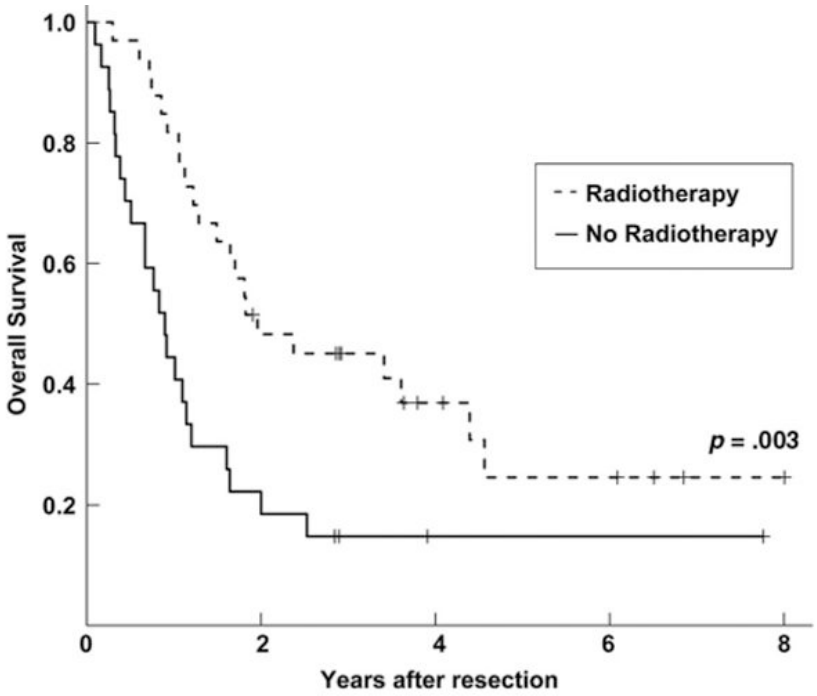
The Oncologist

Lung Cancer

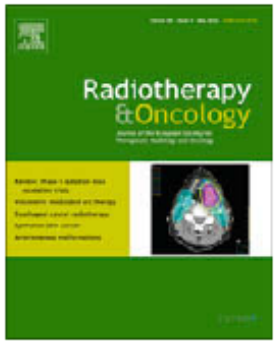
Prognostic Factors for Resected Non-Small Cell Lung Cancer with pN2 Status: Implications for Use of Postoperative Radiotherapy

Vanderbilt University Medical Center between 1994 and 2004





Moretti L, Oncologist. 2009; 14(11): 1106–1115.



ADJUVANT RADIOTHERAPY: 2010 RETROSCPECTIVE ANALYSIS

		LR		
		PORT	NO PORT	LR HR 0.45 (0.24-0.87, p=0.015
FLORENCE UNIVERSITY	175	32.1%	15.1%	OS no differences

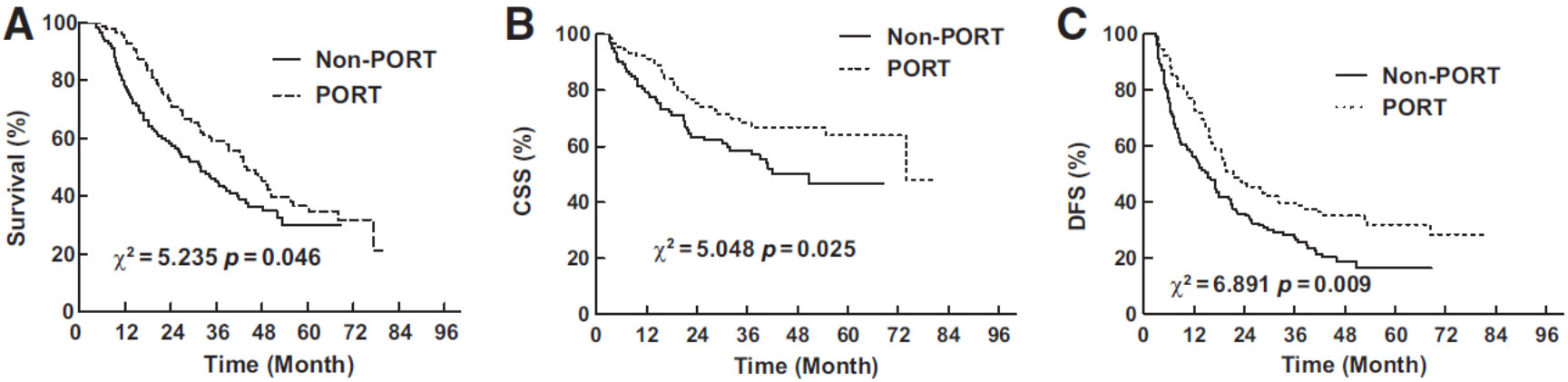
Scotti V. Radiother Oncol, 96(1):84-8, 2010

	pN2 PTS	OS		DFS	
		POCRT	POC	POCRT	POC
SICHUAN UNIVERSITY	183	30.5%	14.4% (p = 0.007)	22.2%	9.3% (p = 0.003)

Zou B, IJROBP; 77: 321–328, 2010

The Oncologist®
CME
Lung Cancer

Postoperative Radiotherapy for Resected Pathological Stage IIIA–N2 Non-Small Cell Lung Cancer: A Retrospective Study of 221 Cases from a Single Institution



Dai H, The Oncologist 2011;16:641–650

pN2 Adjuvant Radiation Therapy

	Median OS (m)		5y OS (%)	
	ANITA	***Dai 2011***	***ANITA***	***Dai 2011***
CHEMO+ PORT	47,4	48,3	47	38,2
CHEMO+ no PORT	23,8	38,1	34	31,9
NoCHEMO+PORT	22,7	38,3	21,3	33,7
NoCHEMO+no PORT	12,7	21,6	16,6	23,1

«These consistent results indicate that both patients treated with or without adj chemotherapy may benefit from PORT for pN2 disease»

Douillard Int J Radiat Oncol Biol Phys 2008, 72:695-701

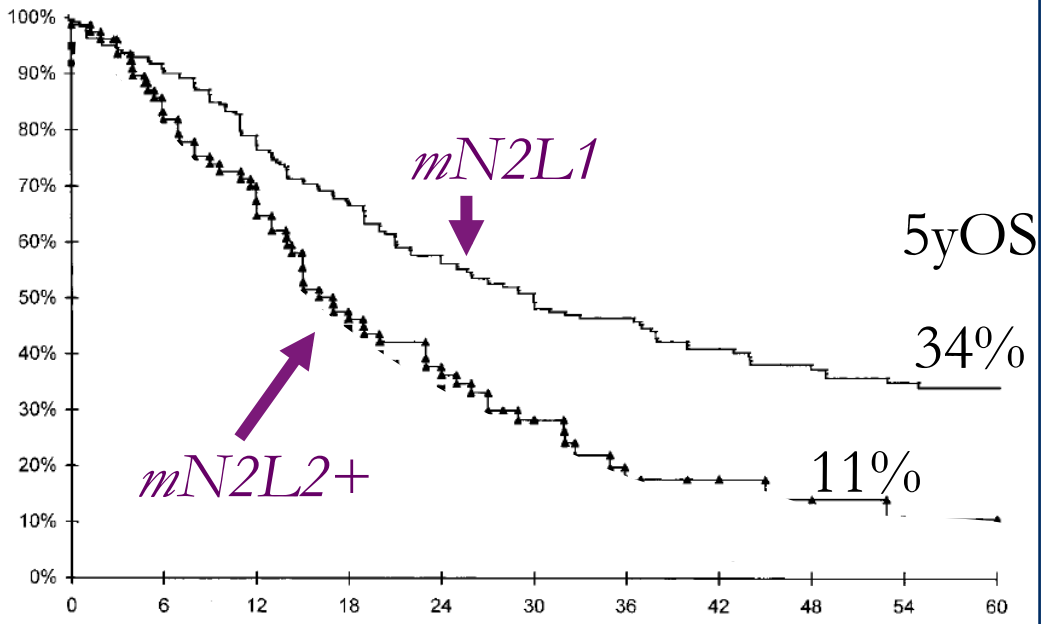
Survival of Patients With Resected N2 Non–Small-Cell Lung Cancer: Evidence for a Subclassification and Implications

FATTORI PROGNOSTICI:

I LIVELLI LINFONODALI INTERESSATI

Overall Survival

Variable	Relative Risk	P
No. of levels involved		
L1		
L2+	1.6	< .0001



Andre F, J Clin Oncol 2000; 18:2981-2989

The Oncologist® CME
Lung Cancer

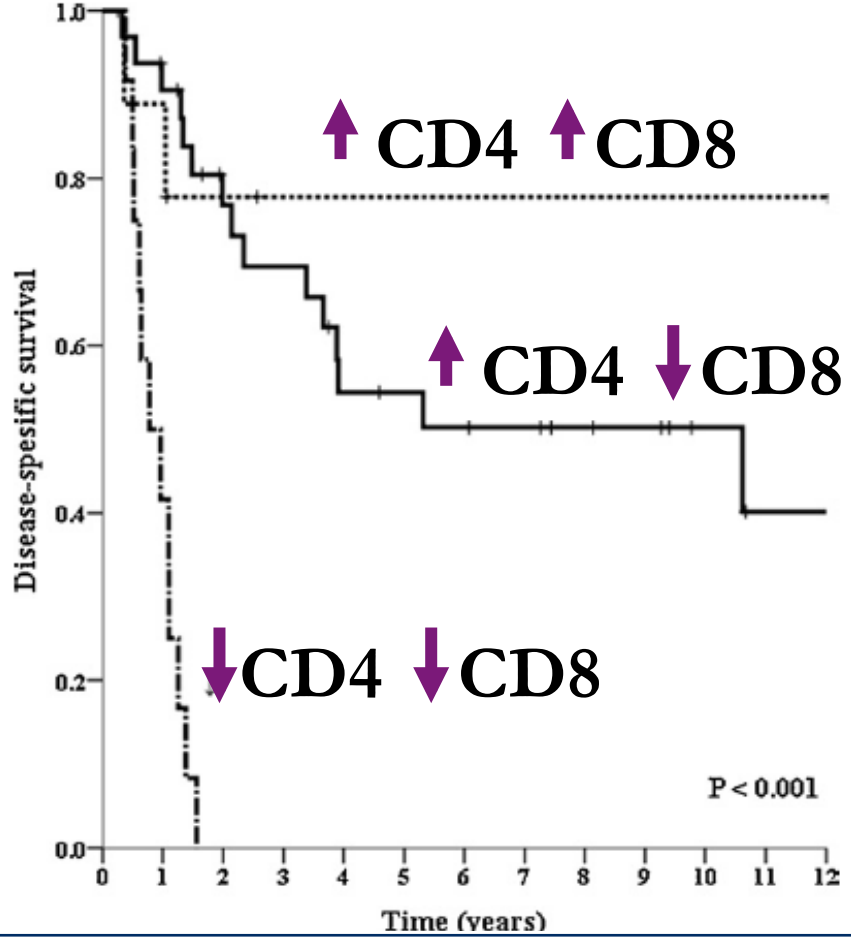
Postoperative Radiotherapy for Resected Pathological Stage IIIA–N2 Non-Small Cell Lung Cancer: A Retrospective Study of 221 Cases from a Single Institution

Table 2. Results of univariate and multivariate analyses of prognostic factors for OS

	Univariate analysis			Multivariate analysis		
Characteristic	**MST (mos)**	**5-yr OS (%)**	***p*-value**	**HR**	**95% CI**	***p*-value**
n of positive nodes			.000	1.389	1.031–1.872	.031
1–3	52.0	46.2				
4–6	39.3	35.8				
7–9	31.5	30.7				
≥10	25.8	12.2				

Dai H, The Oncologist 2011;16:641–650

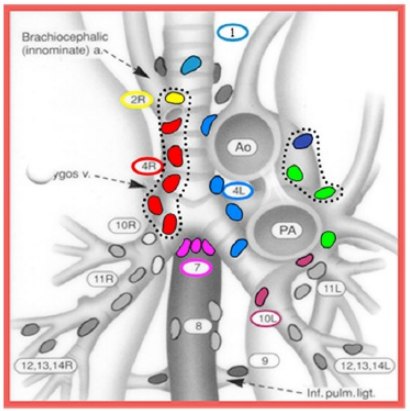
CD4/CD8 co-expression shows indipendent prognostic impact in resected NSCLC patients treated with adjuvant radiotherapy

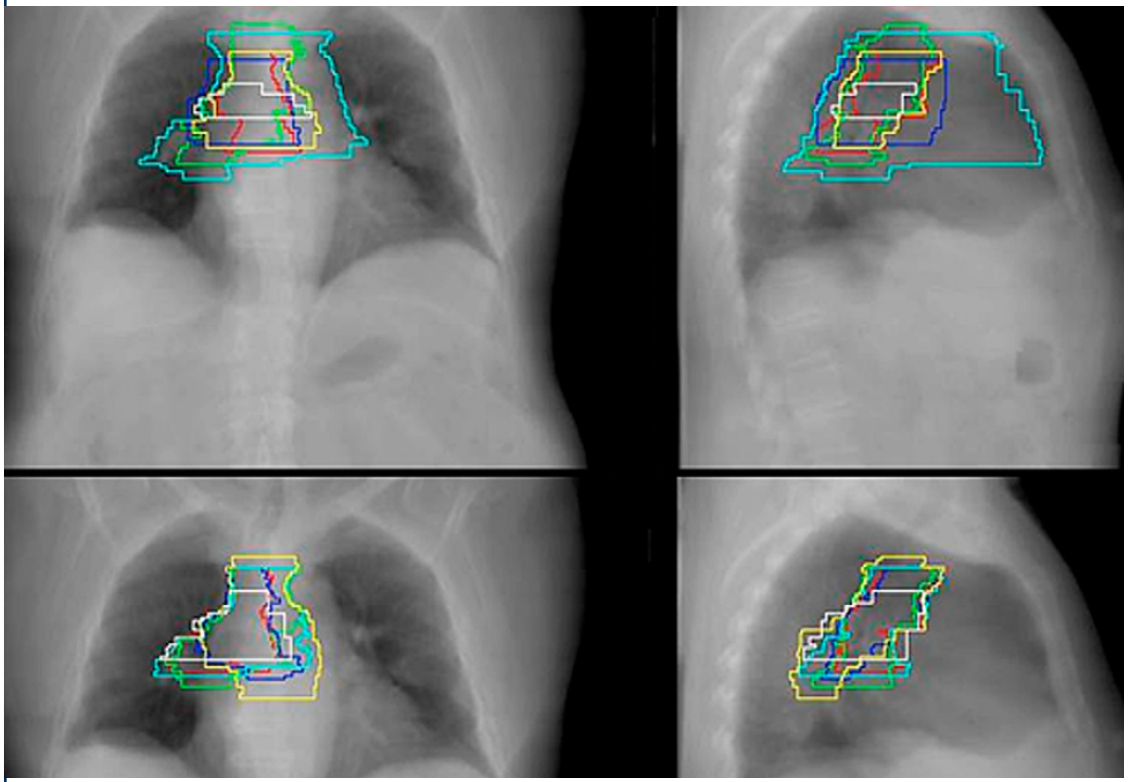


Stromal CD4CD8	HR	95% CI	pvalue
A	1.0		
B	1.84	0.4-8.3	0.430
C	*21.12*	*3.8-115*	*<0.001*

Hald SM, Lung Cancer 80 (2013) 209- 215

TARGET VOLUME DELINEATION IN PORT





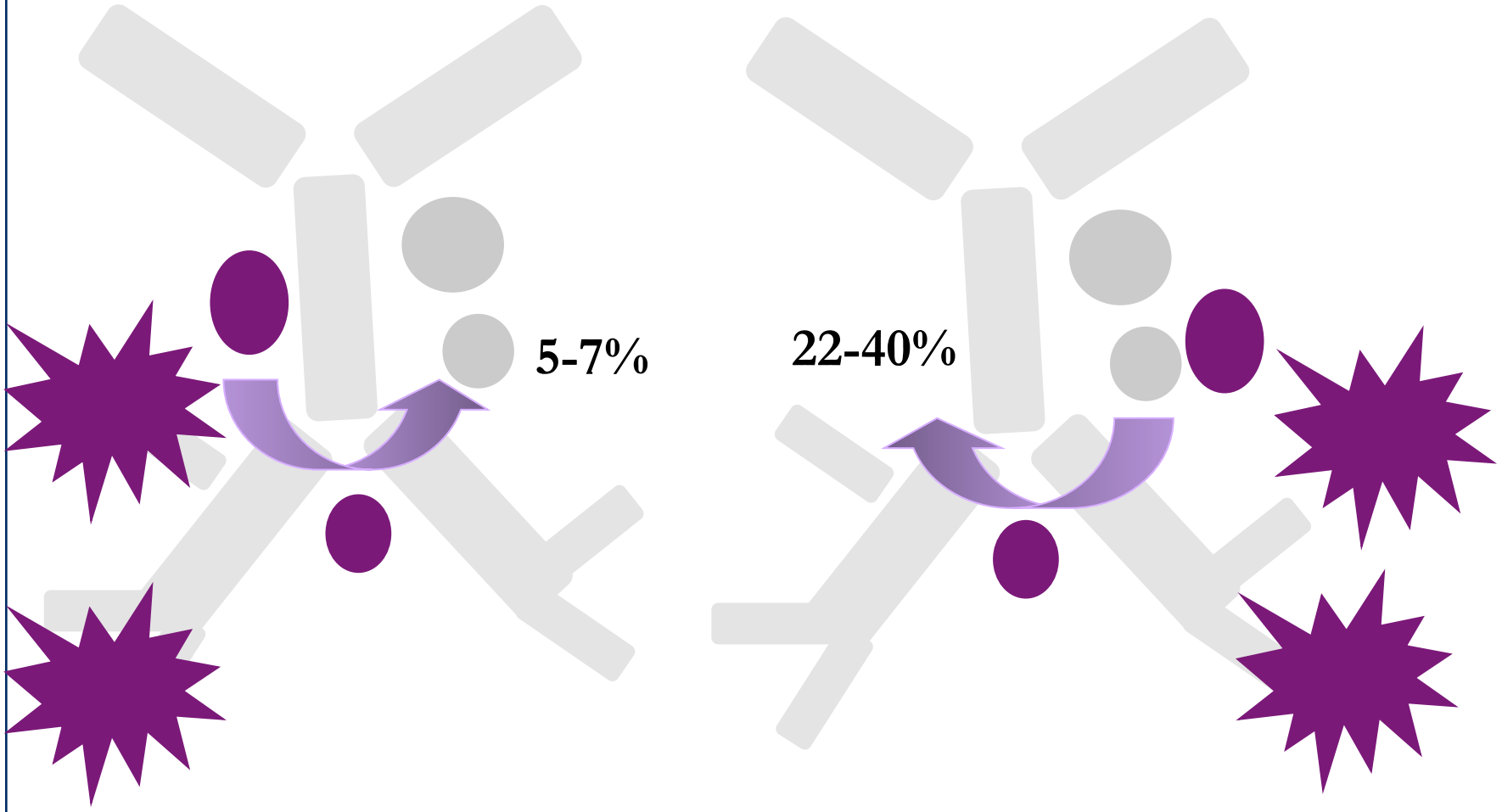
SIGNIFICANT INTERCLINICIANS VARIATIONS IN CONTURING AND IN PORT FIELDS CAN CONFOUND PORT RESULTS

MANDATORY QUALITY ASSURANCE PROCEDURES HAVE BEEN INCORPORATED IN LUNG ART

Spoelstra, IJROBP 2010.

TARGET VOLUME DELINEATION IN PORT

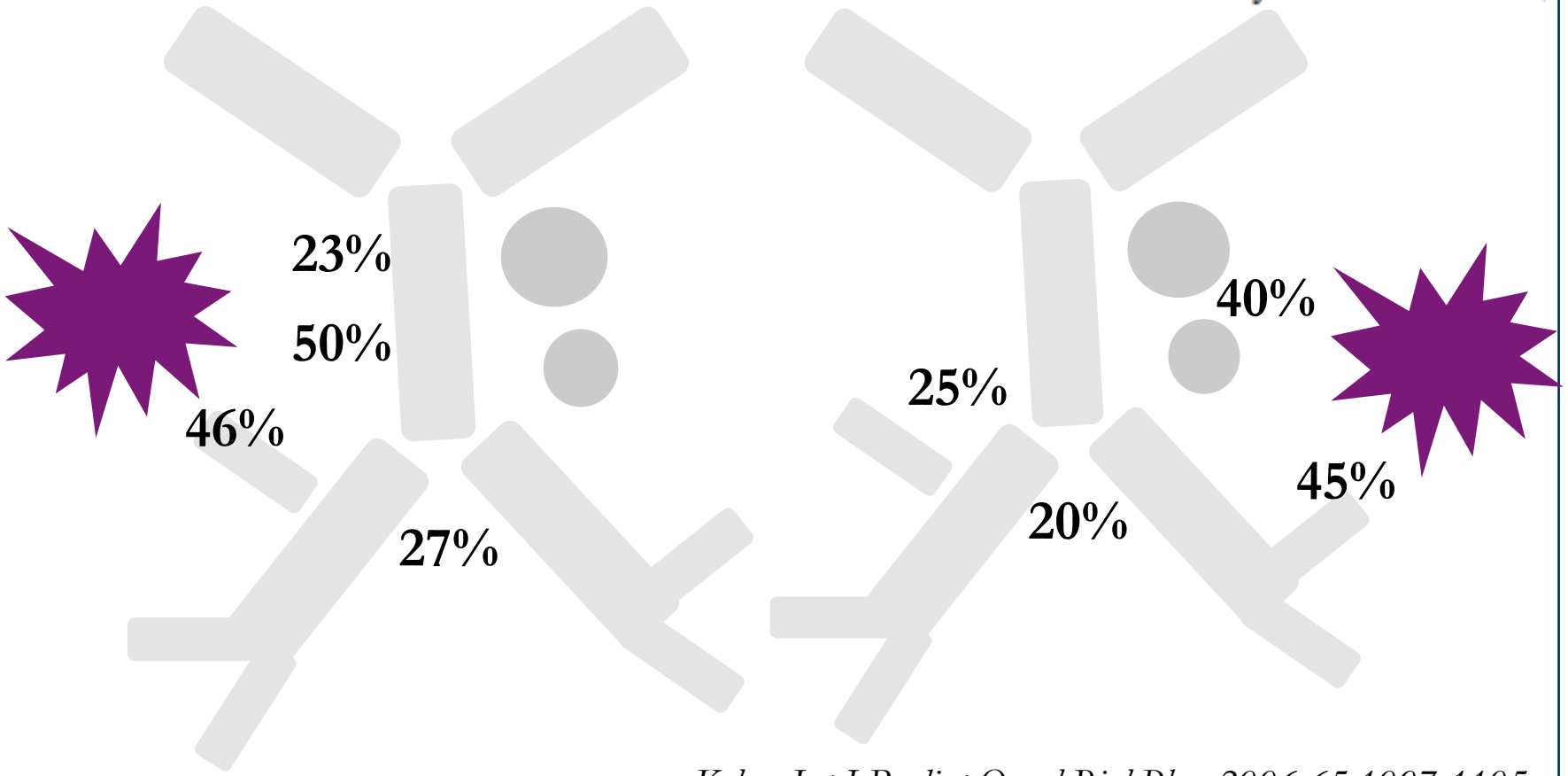
CONTRALATERAL MEDIASTINUM INVOLVEMENT



Kelsey Int J Radiat Oncol Biol Phys 2006 65:1097-1105

TARGET VOLUME DELINEATION IN PORT

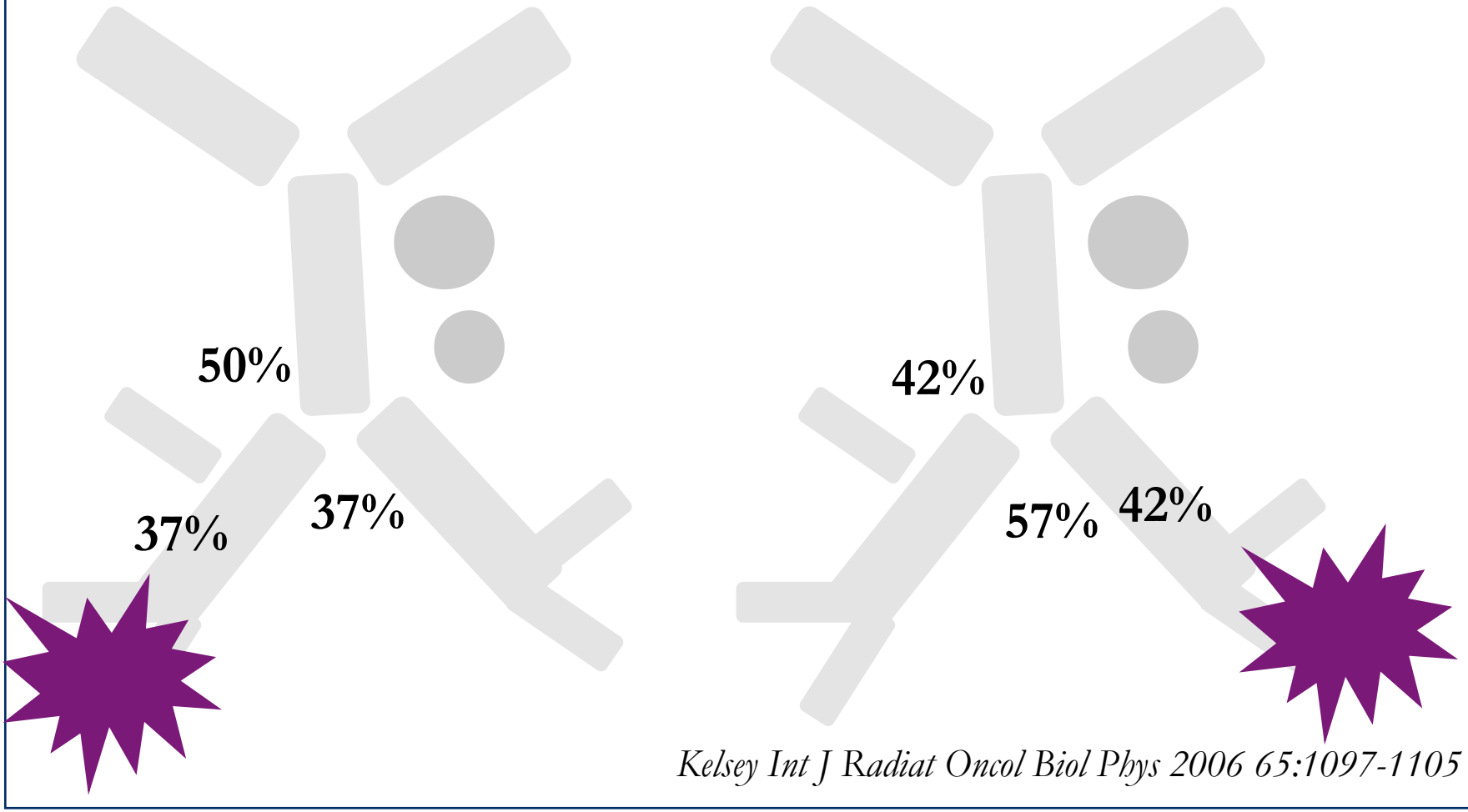
PATTERNS OF FAILURE AFTER RESECTION OF NON–SMALL-CELL LUNG CANCER: IMPLICATIONS FOR POSTOPERATIVE RADIATION THERAPY VOLUMES Duke University Medical Center,



Kelsey Int J Radiat Oncol Biol Phys 2006 65:1097-1105

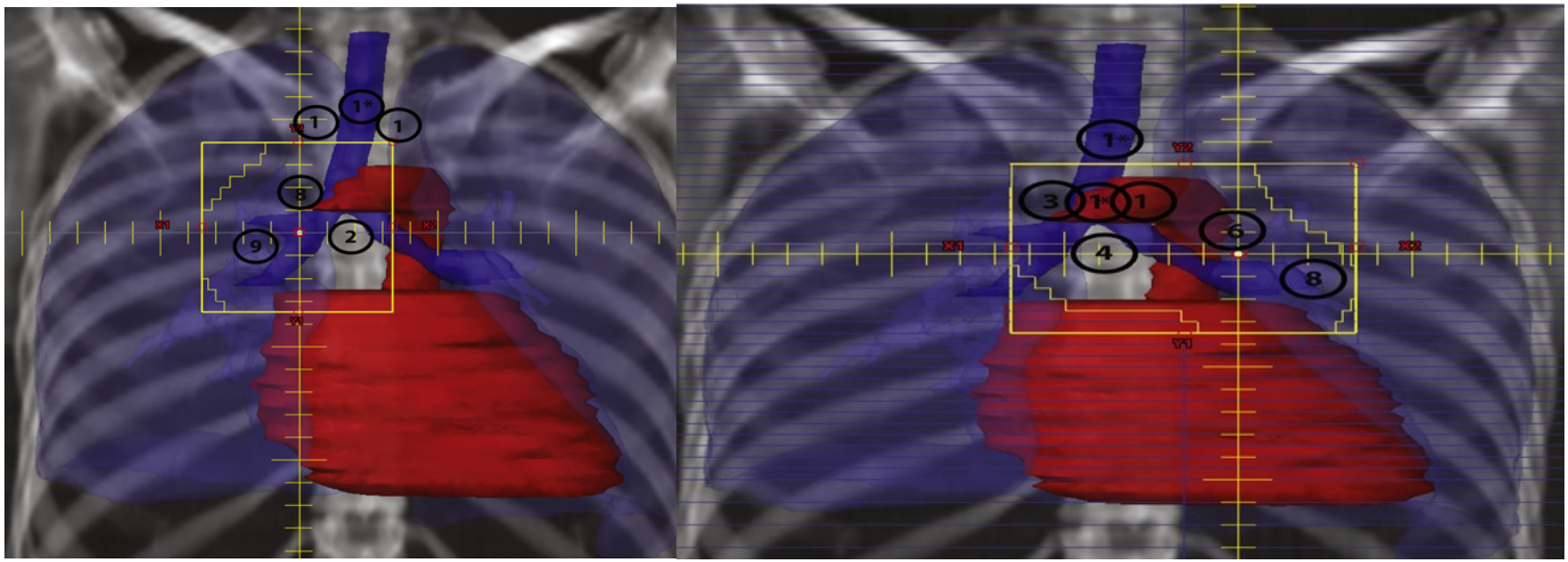
TARGET VOLUME DELINEATION IN PORT

PATTERNS OF FAILURE AFTER RESECTION OF NON–SMALL-CELL LUNG CANCER: IMPLICATIONS FOR POSTOPERATIVE RADIATION THERAPY VOLUMES



Kelsey Int J Radiat Oncol Biol Phys 2006 65:1097-1105

TARGET VOLUME DELINEATION IN PORT

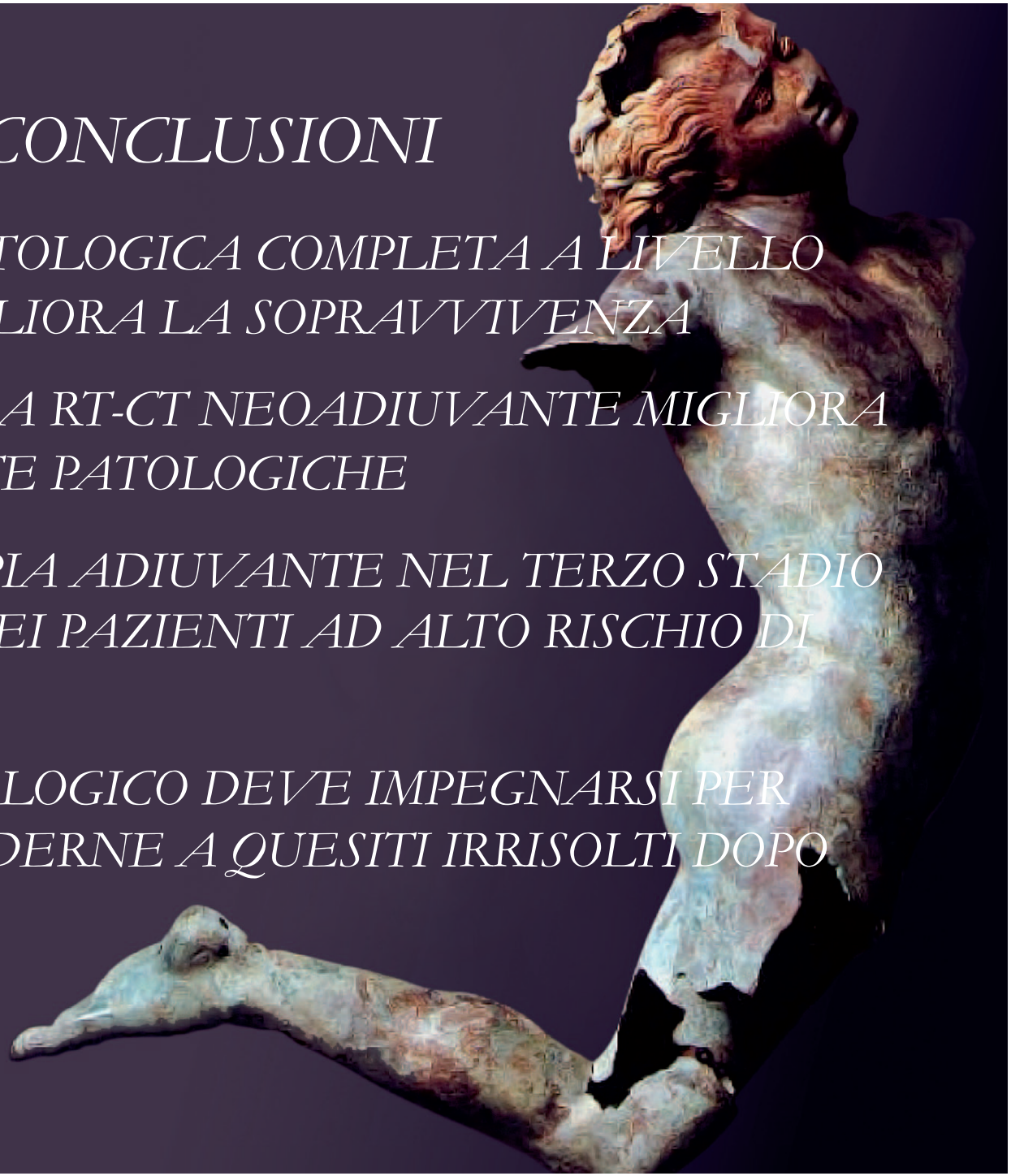


"87% of failures would have been encompassed by RT fields"

Kristin A. Higgins Int J Radiation Oncol Biol Phys, Vol. 83, No. 2, pp. 727-733, 2012

CONCLUSIONI

- ✓ *LA RISPOSTA PATOLOGICA COMPLETA A LIVELLO LINFONODALE MIGLIORA LA SOPRAVVIVENZA*
- ✓ *L'IMPIEGO DELLA RT-CT NEOADIUVANTE MIGLIORA IL TASSO DI RISPOSTE PATOLOGICHE*
- ✓ *LA RADIOTERAPIA ADIUVANTE NEL TERZO STADIO N2 E' SUGGERITA NEI PAZIENTI AD ALTO RISCHIO DI RICADUTA*
- ✓ *IL MONDO ONCOLOGICO DEVE IMPEGNARSI PER DARE RISPOSTE MODERNE A QUESITI IRRISOLTI DOPO OLTRE 20 ANNI*




GRAZIE PER
L'ATTENZIONE!!!


GRAZIE PER
L'ATTENZIONE!!!

CONCLUSIONI

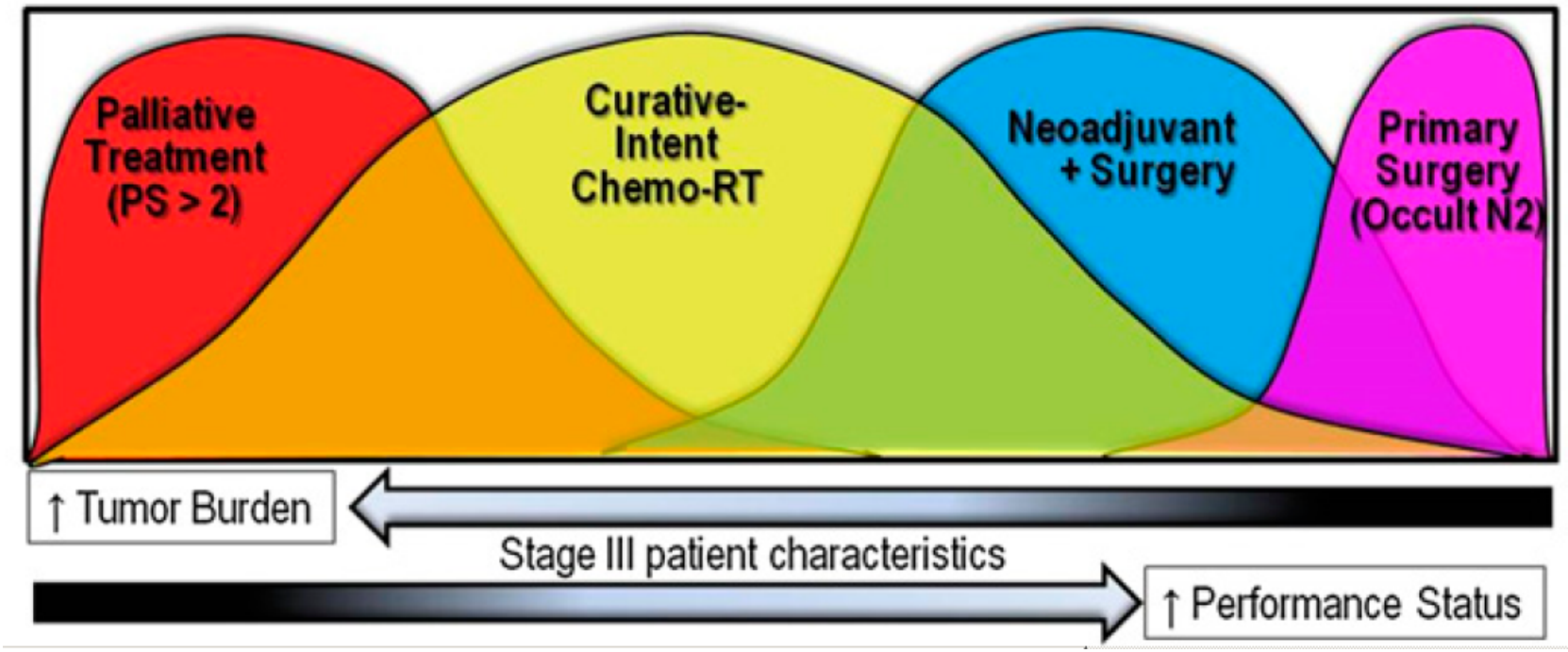
INDUCTION CHEMOTHERAPY

Authors, Ref. Year	Phase	Disease	Patients (N)	Resected (n)	Resected (%)	pCR (%)	5-y Survival (%)	N2 Downstaging
Burkes et al,[77] 1992	II	IIIA-N2	39	22	56	5	26 (3-y)	36
Sugarbaker et al,[8] 1995	II	IIIA-N2	74	46	62	NS	23 (3-y)	22
Rosell et al,[6,78] 1994, 1999	III	44/60 (N2)	60	23/27	85	3	17 (induction), 0 (no induction)	32
Roth et al,[4,5] 1994, 1998	III	IIIA	60	17/28	61	4	36 (induction), 15 (no induction)	NS
Van Zandwijk et al (EORTC),[79] 2000	II	IIIA-N2	47 (17 surgery)	16/17	94 (induction)	6 (1/17)	NS for surgical group	53
Betticher et al,[80] 2003	II	IIIA-N2	90	75	83	NS	34 (3-y)	61
Nagai et al,[81] 2003	III	IIIA-N2	62	20/31	65 (induction)	0 (0/31)	22 (induction), 10 (no Induction)	NS
O'Brien et al (EORTC),[82] 2003	II	IIIA-N2	52 (15 surgery)	12/15	80 (induction)	2	NS for surgical group	17
Garrido et al,[83] 2007	II	IIIA (N2)-B (T4N0–1)	69 (N2)	46 (N2)	67	2 (N2)	32 (N2 resected)	22

INDUCTION RADIO-CHEMOTHERAPY

Authors, Ref. Year	Phase	Disease	Patients (N)	Resected (n)	pCR (%)	5-y Survival (%)	N2 Downstaging
Albain et al (SWOG 8805),[9] 1995	II	IIIA-N2	75 (N2 patients)	57	21	27 (3-y; N2)	51
Mathisen et al,[84] 1996	II	IIIA-N2	40	35	6	43	40
Katayama et al,[85] 2004	II	IIIA-B	22	19	23	66 (3-y)	NS
Albain et al (INT 0139),[10] 2009	III	IIIA	429	155/202	14	27 (induction), 20 (no induction)	41% (N0)
Steger et al,[86] 2009	II	III-N2/3	55	55	35	49	69

CHEST Treatment of Stage III Non-small Cell



CHEST 2013; 143(5)(Suppl):e314S–e340S

Hyperfractionated Accelerated Radiotherapy

120 patients

CT 4 cycles>CRT
(45Gy/1.5Gy bid)

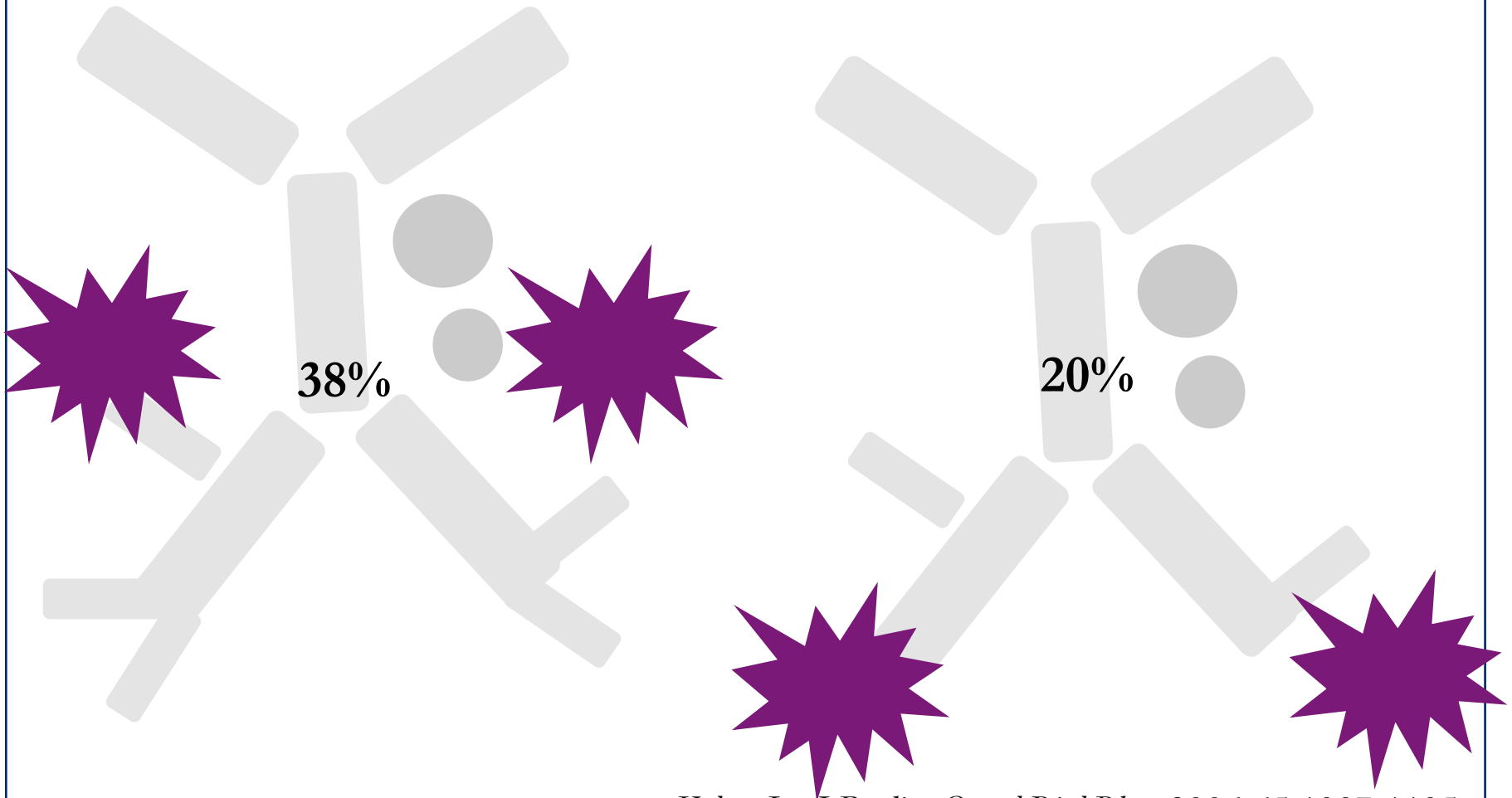
Lobect 30%
Pneumo 46%
Other Surg 24%

Variable	No. of Patients	5-Year Survival (%)	Median Survival (months)		*P*	Relative Risk
			Time	CI		
All	120	24.5	18	14.1 to 21.8		
R0	58	45.0	35	21.9 to 48.0	.000	
No resection	62	0.0	11	8.9 to 13.0		1.9
IIIA primary	30	35.6	21	9.3 to 32.6	.296	
IIIB primary	88	21.1	16	11.4 to 20.6		
R0N0	44	49.7	40	6.9 to 73.1	.254	
R0N2/3	18	33.3	28	18.2 to 37.7		
R0, stage 0	15	66.7	—		.001	
R0, stage I	13	61.5	—			1.3
R0, stage II	12	41.7	37	3.1 to 70.9		2.2
R0, stage IIIA	10	50.0	—			1.8
R0, stage IIIB	10	00.0	21	11.7 to 30.3		6.1
R0, tumor regression > 90%	29	58.6	—		.071	
Tumor regression < 90%	21	28.6	29	20.0 to 38		1.5
R0T4N0	7	57.1	—		.004	
No operation, T4N0	8	00.0	9	4.8 to 13.2		

Friedel G., J Clin Oncol 2010 28:942-948

TARGET VOLUME DELINEATION IN PORT

BYPASS HILAR NODES IS COMMON



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