Chemio (Radioterapia)

Neoadiuvante nel NSCLC

Michele Fiore

Radioterapia Oncologica

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XXV CONGRESSO NAZIONALE
AIRO 2015
PALACONGRESSI - Rimini, 7-10 novembre

DICHIARAZIONE

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)**

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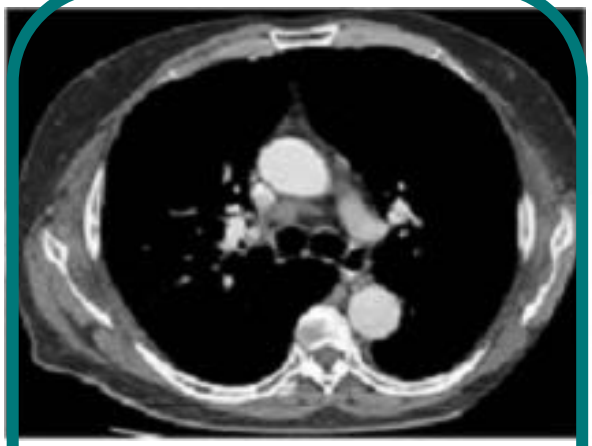
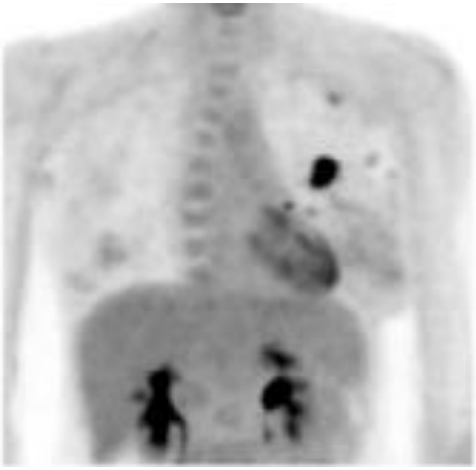
CHEST Treatment of Stage III Non-small Cell

Mediastinal infiltration



Discrete node enlargement



Clinically occult N2

Neoadjuvant therapy

CHEST 2013; 143(5)(Suppl):e314S–e340S

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

*NSCLC Meta-analysis Collaborative Group**

Lancet 2014; 383: 1561–71

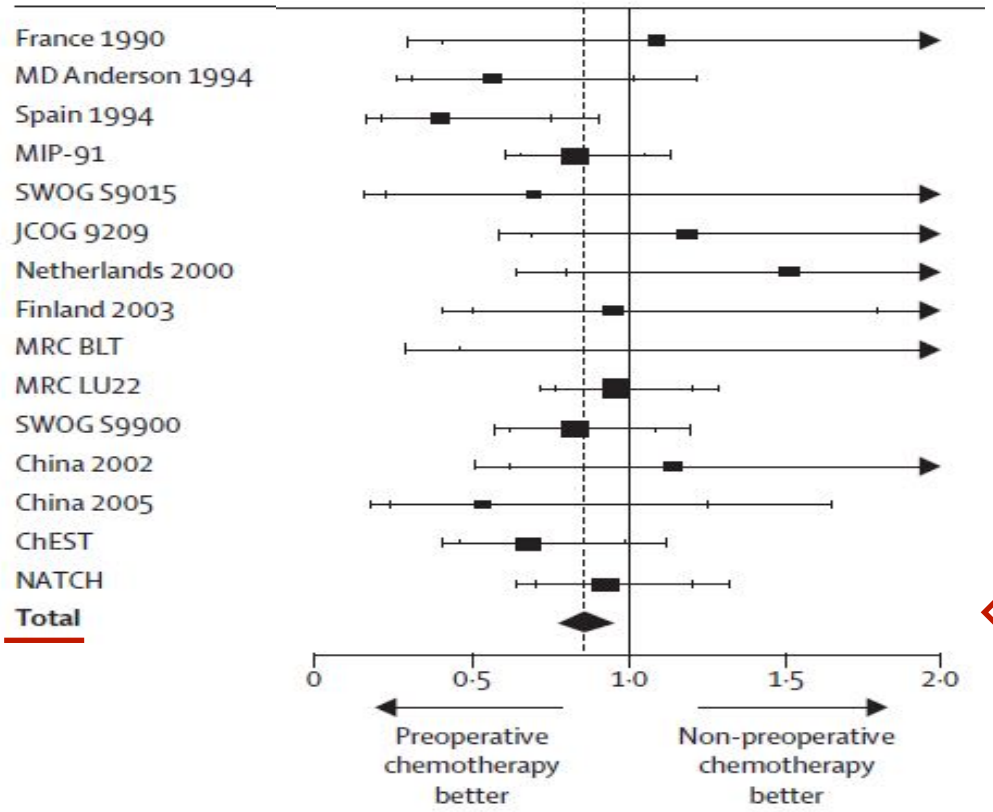
15 randomised controlled trials (2385 patients) ; mainly Stage IB–IIIA

Clinical stage		
IA	63 (5%)	71 (6%)
IB	545 (46%)	501 (43%)
IIA	21 (2%)	29 (3%)
IIB	309 (26%)	278 (24%)
IIIA	246 (21%)	270 (24%)
IIIB	4 (<1%)	9 (<1%)
IV	0 (<1%)	3 (<1%)
Unknown	6 (<1%)	4 (<1%)

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

NSCLC Meta-analysis Collaborative Group*

Lancet 2014; 383: 1561–71



SURVIVAL

HR 0.87 (0.78-0.96)
p=0.007

Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data

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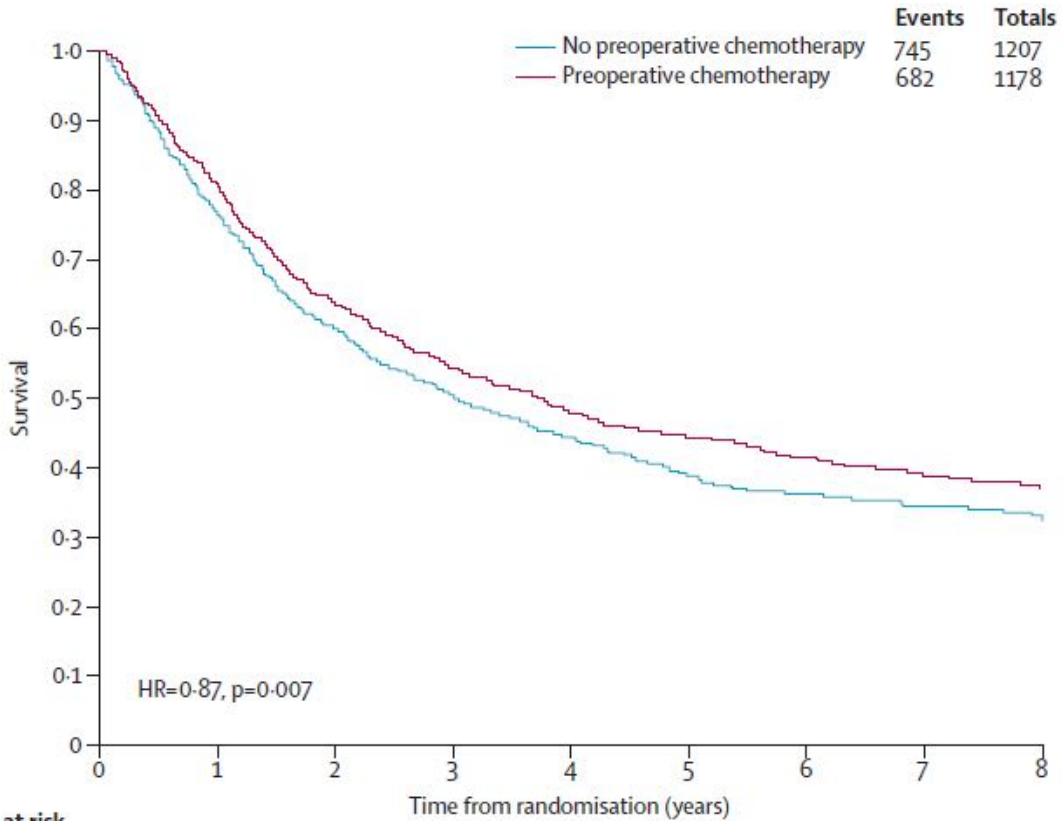
Lancet 2014; 383: 1561–71



13% reduction in the relative risk of death

Absolute survival improvement of 5% @5y

Preoperative versus Postoperative Chemotherapy in Patients with Resectable Non-small Cell Lung Cancer

Systematic Review and Indirect Comparison Meta-Analysis of Randomized Trials

32 randomized trials (22 trials: postoperative CT; 10 trials: preoperative CT)

Estimated 5-yr Survival Probability, Impact on Survival and Limits of the Difference Between Postoperative and Preoperative Administration

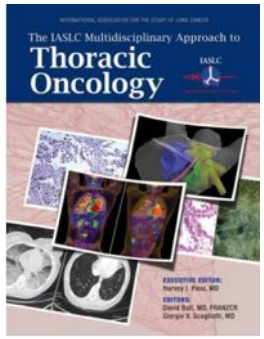
Stage	5-yr Survival Reported	Postoperative Chemotherapy			Preoperative Chemotherapy			Difference (Postoperative versus Preoperative)		
		Expected	Lower 95% CI	Upper 95% CI	Expected	Lower 95% CI	Upper 95% CI	Expected	Upper 95% CI	Lower 95% CI
IA	73	78.4	76.4	80.3	78.1	73.7	81.8	−0.30	−4.23	4.51
IB	54	63.2	59.8	66.4	62.7	55.2	69.0	−0.51	−7.20	7.68
IIA	48	58.5	54.6	62.0	57.9	49.4	64.9	−0.58	−8.14	8.68
IIB	38	50.5	45.9	54.7	49.8	39.7	58.2	−0.69	−9.71	10.35
IIIA	25	40.1	34.5	45.3	39.3	27.0	49.4	−0.84	−11.75	12.52
IIIB	19	35.3	29.3	40.9	34.4	21.2	45.3	−0.91	−12.68	13.53
IV	21	36.9	31.0	42.3	36.0	23.1	46.7	−0.88	−12.37	13.19

Lim E. J Thorac Oncol. 2009;4:1380–1388

In patients with resectable lung cancer, there was no evidence of a difference in overall and disease-free survival between the timing of administration of chemotherapy (postoperative versus preoperative).

Lim E. J Thorac Oncol. 2009;4:1380–1388

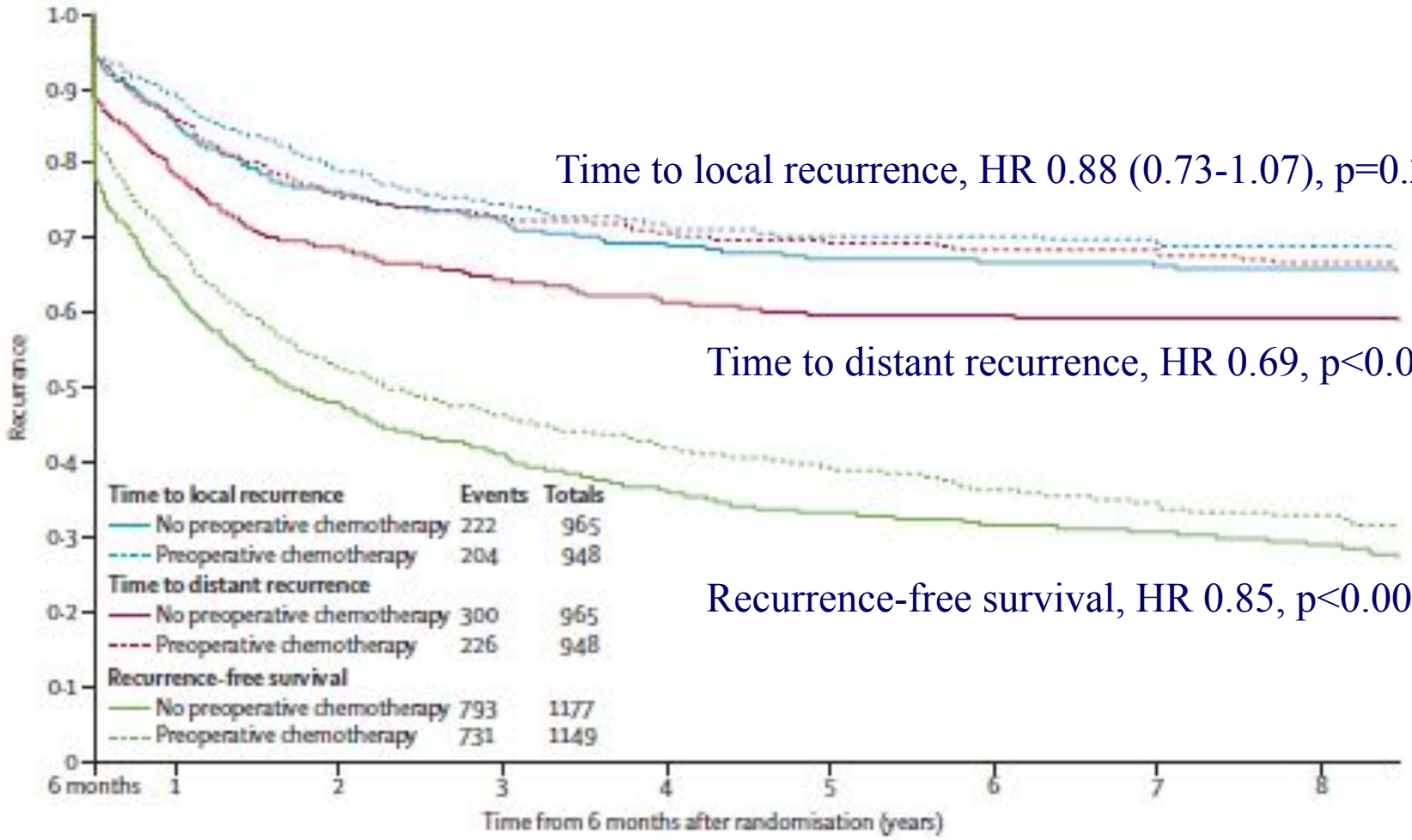
« Benefit similar between preoperative and postoperative chemotherapy »



IASLC Thoracic Oncology Textbook, Ed. 2014

NSCLC Meta-analysis Collaborative Group*

Lancet 2014; 383: 1561–71



Time to local recurrence, HR 0.88 (0.73-1.07), p=0.2

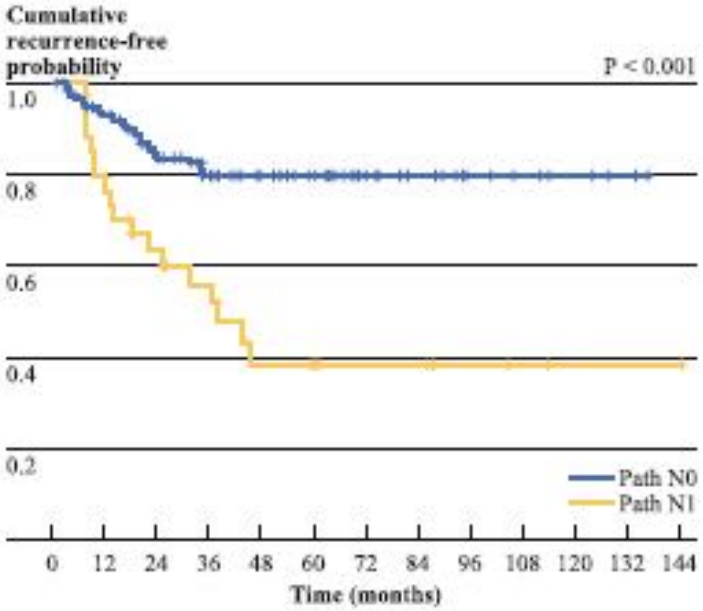
Time to distant recurrence, HR 0.69, p<0.001

Recurrence-free survival, HR 0.85, p<0.002

Predictors for Locoregional Recurrence for Clinical Stage III-N2 Non-small Cell Lung Cancer with Nodal Downstaging After Induction Chemotherapy and Surgery

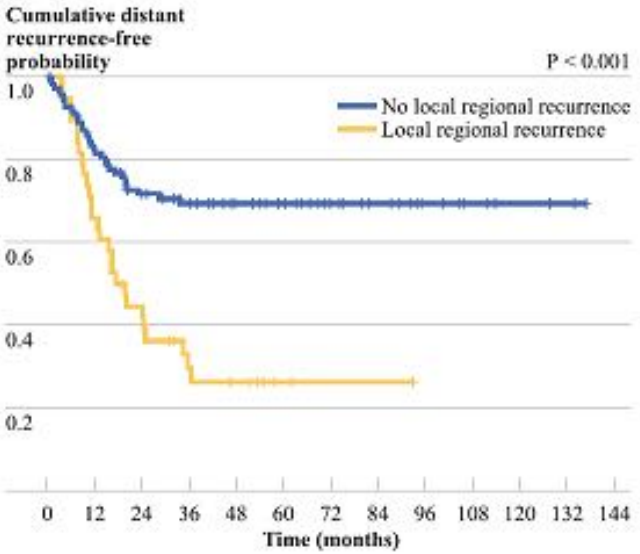
153 patients (MD Anderson Cancer Center; Memorial Sloan Kettering Cancer Center)

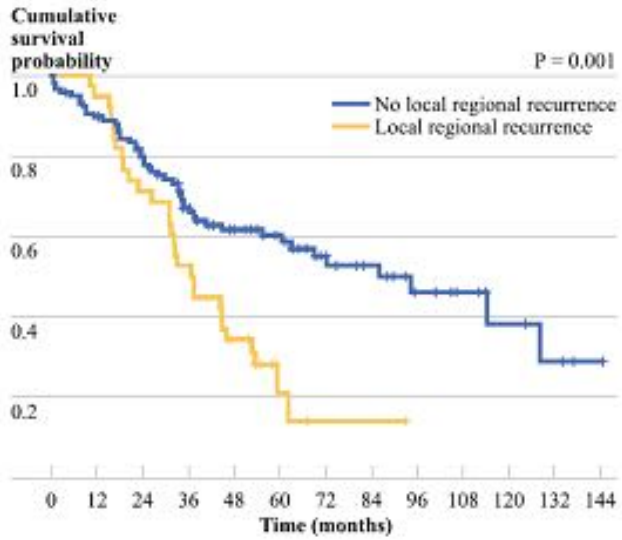
The 5-year local-regional failure (LRF) rate was 30.8 %



LRF was significantly higher in patients with pathologic N1 compared with N0 disease ($p<0.001$)

Amini A. Ann Surg Oncol 2013;20:1934-1940





Annals of SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

Patients with and without LRF had a 5-year distant recurrence-free disease of 26.3% and 69.3 %, respectively (p<0.001)

Patients with or without LRF had a 5-year OS of 21% compared with 60.1% (p = 0.001)

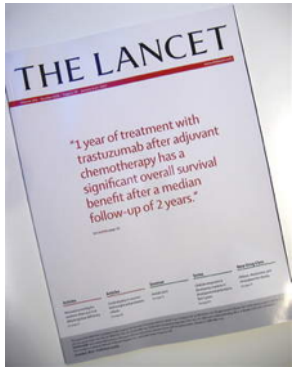
Amini A. Ann Surg Oncol 2013;20:1934-1940

Loco-regional recurrence after neoadjuvant chemotherapy

STUDY	LRR %
Rosell R, *N Engl J Med 1994*	54%
Taylor NA, *Int J Radiat Oncol Biol Phys 2003*	63%
Betticher DC, *JCO 2003*	39%
Amini A, *Ann Surg Oncol 2013*	30.8%
NSCLC Meta-analysis Collaborative Group *Lancet 2014*	33%

NEOADJUVANT THERAPY: RANDOMIZED TRIALS

- ✓ INT 0139 *(Albain KS, Lancet 2009)*
- ✓ GERMAN study *(Thomas M, Lancet Oncology 2008)*
- ✓ WJTOG 9903 *(Katakami N, Cancer 2012)*

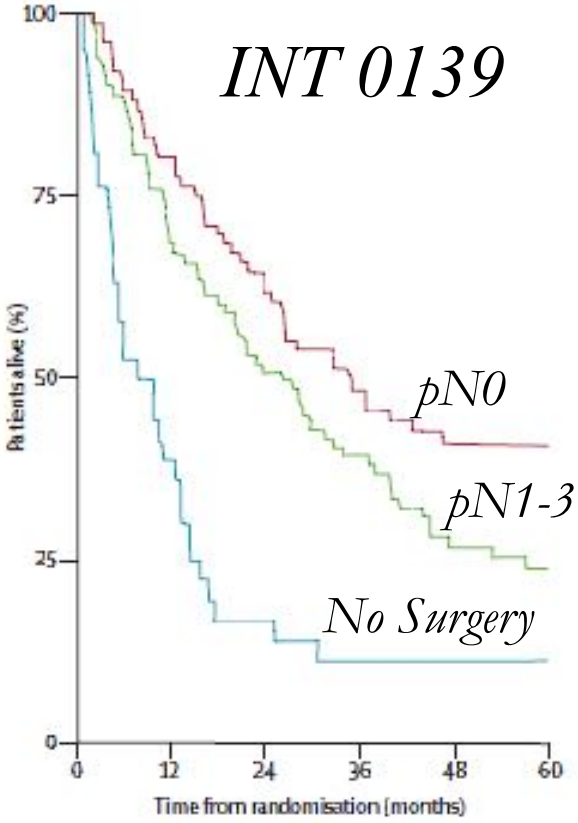


Clinical Stage IIIA (N2) NSCLC: Neoadjuvant Therapy

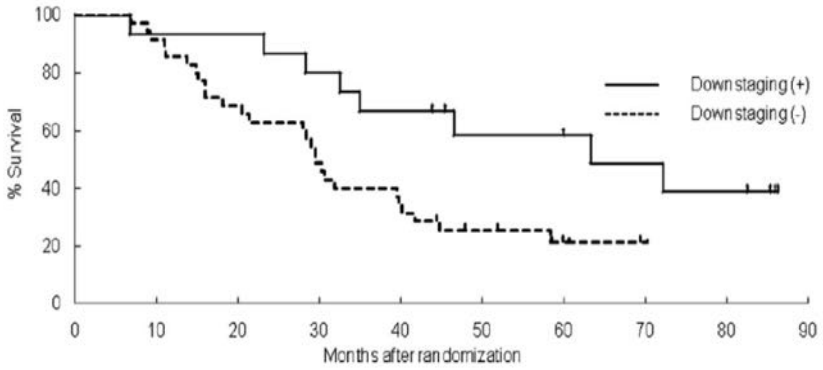
	INT 0139 ***CRT ➡S vs CRT***	***GERMAN study*** ***CT+CRT ➡S vs CT ➡S***	***WJTOG 9903*** ***CRT ➡S vs CT ➡S***
Median OS *5y-Survival*	23.6m vs 22.2m 27% vs 20%	15.7m vs 17.6m 21% vs 18%	39.6m vs 29.9m 51.7% vs 39.3%@3y
Median OS (pN0)	34.4m; 41% @5y	57.5 vs 27.1m	72.1 vs 32.6m 66.7% @3y
Pathological Downstaging pN0	42% (group1)	46% vs 29%	40% vs 21%

Neoadjuvant Therapy: Pathological Downstaging

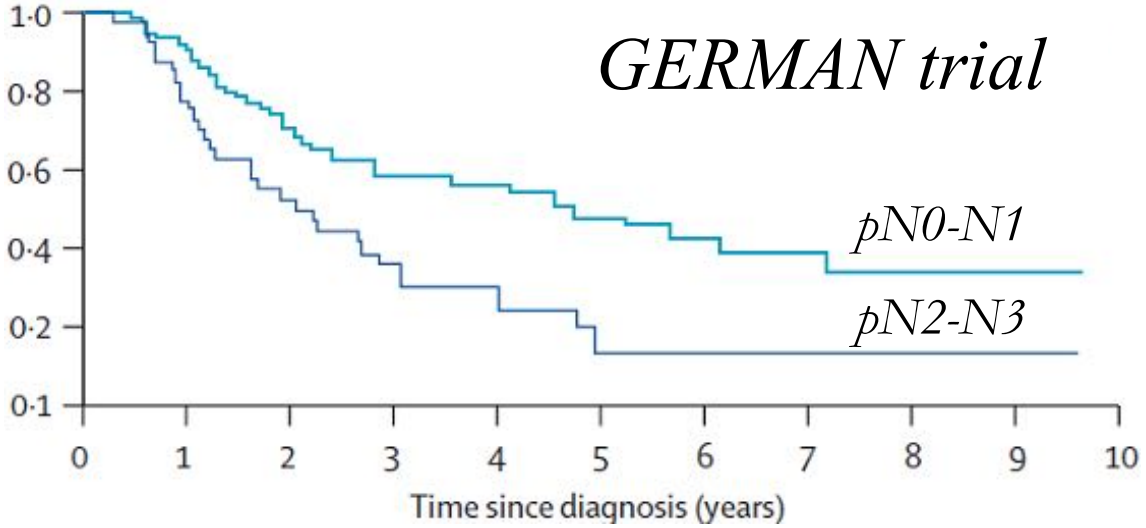
INT 0139



WJTOG 9903



GERMAN trial

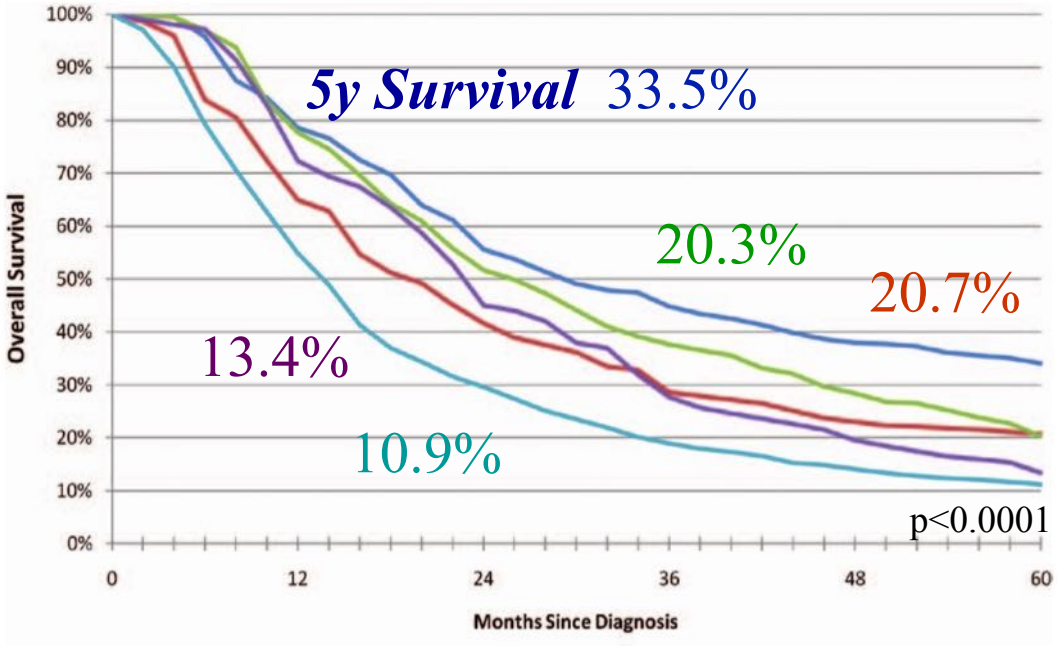


Improved Survival Associated with Neoadjuvant Chemoradiation in Patients with Clinical Stage IIIA(N2) Non–Small-Cell Lung Cancer

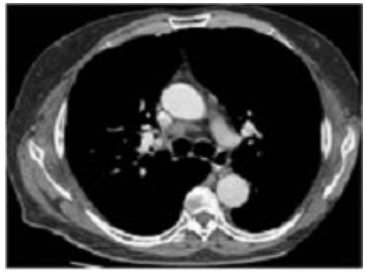
Observational data from the National Cancer Database (1998-2004)

11.242 patients

1. *NeoCRT + Lobectomy*
2. *NeoCRT + Pneumonectomy*
3. *Lobectomy + Adj therapy*
4. *Pneumonectomy+ Adj therapy*
5. *Definitive CRT*



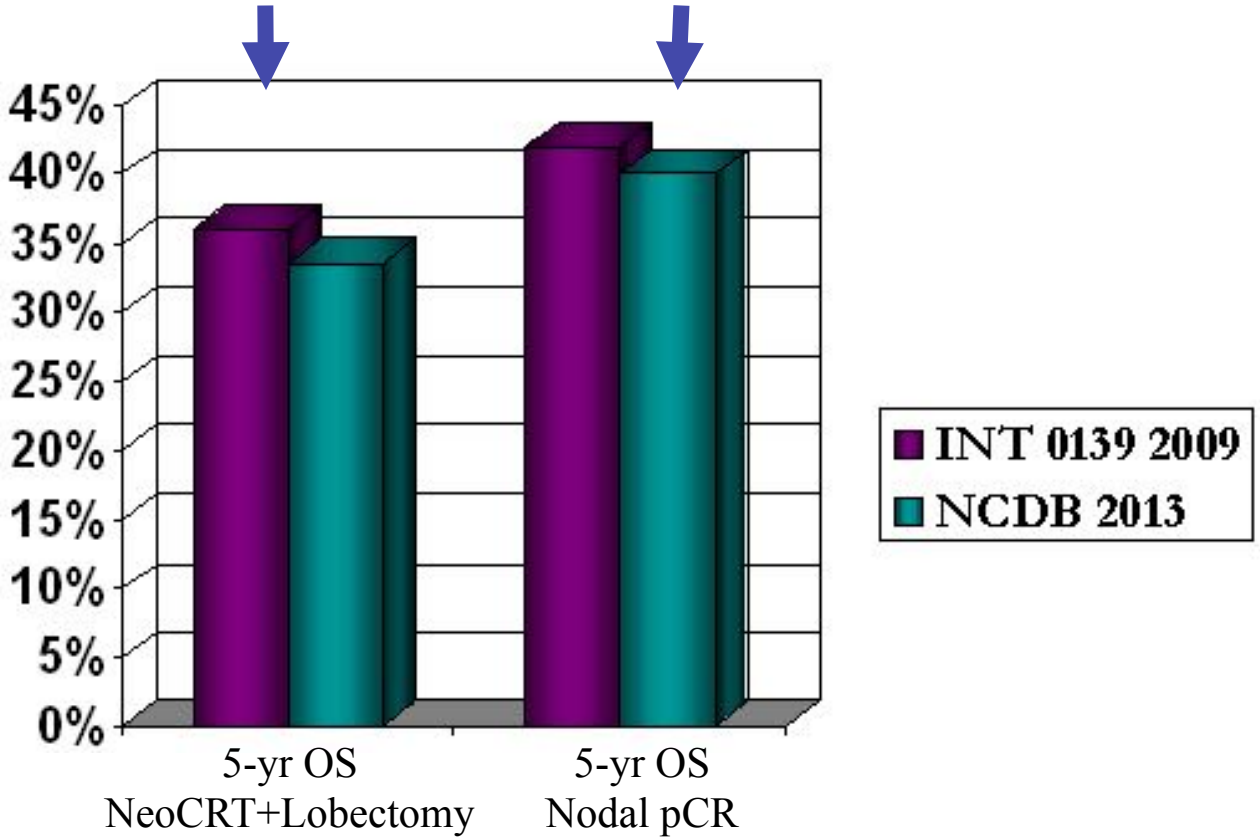
Koshy M. J Thorac Oncol. 2013;8:915-922



Clinical Stage IIIA (N2) NSCLC

36 vs 33.5%

41 vs 40%



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

Is There a Survival Benefit in Patients With Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection

A Systematic Review and Meta-analysis

Seven trials involving 1049 patients

- ✓ Randomized controlled trials (RCTs);
- ✓ Trials comparing the efficacy of neoadjuvant therapy prior to surgical resection versus neoadjuvant therapy prior to radical radiotherapy;
- ✓ Neoadjuvant chemoradiotherapy versus neoadjuvant chemotherapy alone

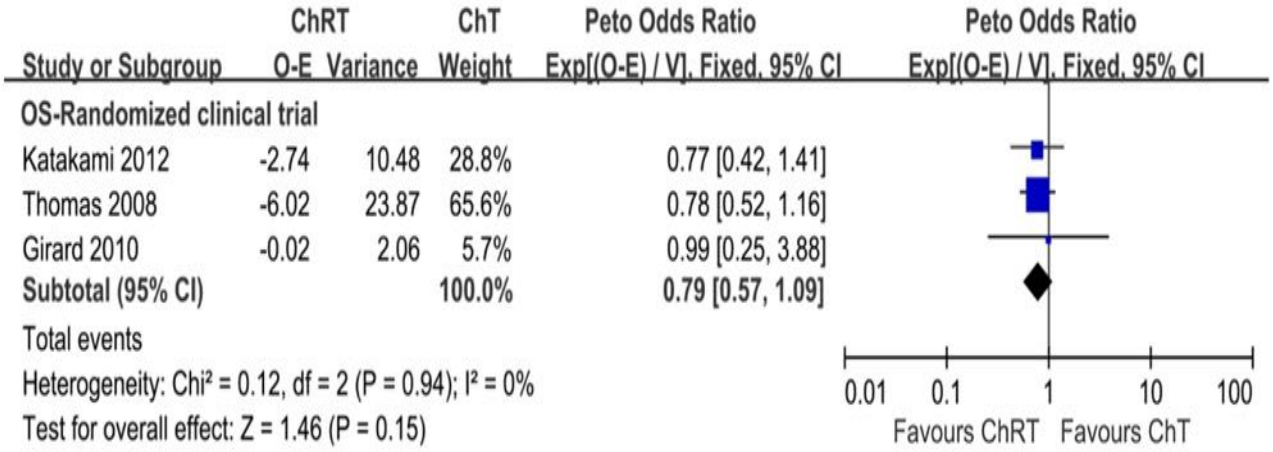
Xu XP. Medicine 2015; 4(23): e879

A Systematic Review and Meta-analysis

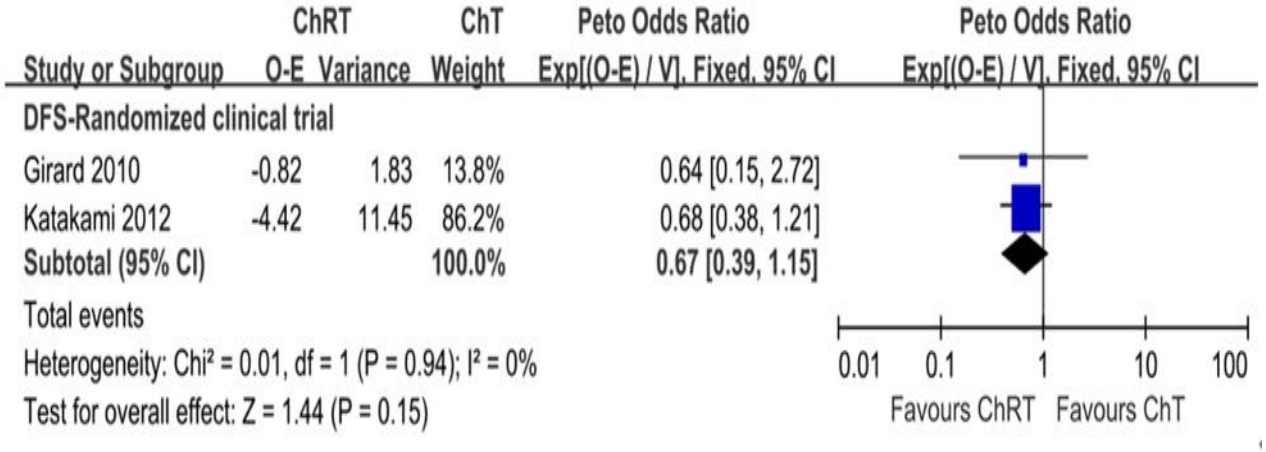
First Author	Accrual Years	Group	Treatment	Number of Patients	Median OS	3-y OS	*P*	Median DFS/PFS	3y-DFS/ PFS	*P*
Albain et al[12]	1994–2001	S	Neo-ChRT + S	202	23.6	37.9	0.24	12.8	27.3	0.017
		ChRT	ChRT alone	194	22.2	33.9		10.5	17.3	
Johnstone et al[13]	1990–1994	S	Neo-ChT + S	29	19.4	33	0.46	-	-	-
		ChRT	ChT + RT	32	17.4	22		-	-	
Van Meerbeeck et al[14]	1994–2002	S	Neo-ChT + S	167	16.4	24.9	0.596	9	17.2	0.605
		ChRT	ChT + RT	165	17.5	27.8		11.3	15.8	
Shepherd et al[15]	––	S	Neo-ChT + S	16	18.7	-	>0.05	-	-	-
		RT	RT alone	15	16.2	-		-	-	
Katakami et al[16]	2000–2006	ChRT	Neo-ChRT + S	29	39.6	51.7	0.397	12.4	34.5	0.187
		ChT	Neo-ChT + S	29	29.9	39.3		9.7	17.9	
Thomas et al[7]	1995–2003	ChRT	Neo-ChRT + S	55	19	31	0.21	9	-	0.69
		ChT	Neo-ChT + S	70	17	18		10	-	
Girard et al[17]	2003–2007	ChRT	Neo-ChRT + S	32	-	51.8	-	17.2	25	-
		ChT	Neo-ChT + S	14	24.2	25.4		12.5	38.5	

Xu XP. Medicine 2015; 4(23): e879

Neoadjuvant ChRT vs Neoadjuvant ChT



Overall Survival



DFS

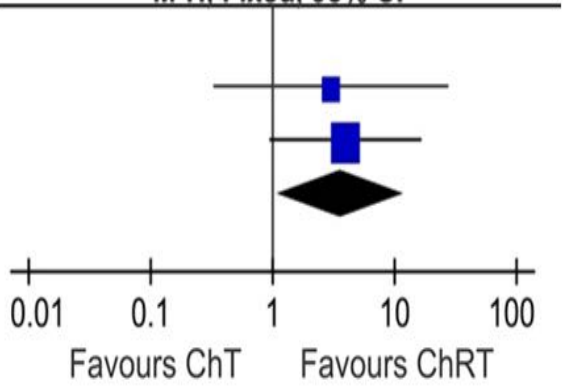
Xu XP. Medicine 2015; 4(23): e879

Neoadjuvant ChRT vs Neoadjuvant ChT

Study or Subgroup	ChRT Events	ChRT Total	ChT Events	ChT Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Mediastinal pCR-Randomized clinical trial						
Girard 2010	6	32	1	14	35.7%	3.00 [0.33, 27.60]
Katakami 2012	9	28	3	28	64.3%	3.95 [0.94, 16.60]
Subtotal (95% CI)		**60**		**42**	**100.0%**	**3.61 [1.07, 12.15]**
Total events	15		4			

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%

Test for overall effect: Z = 2.07 (P = 0.04)

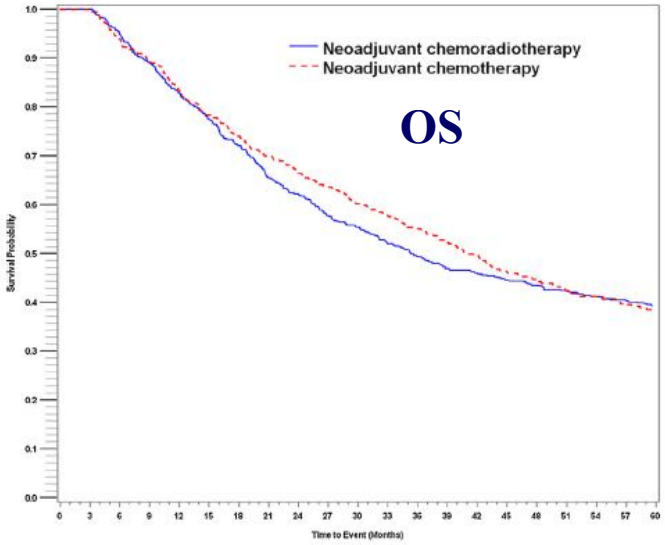


Neoadjuvant ChRT increases the mediastinal pCR significantly (p = 0.04)

Xu XP. Medicine 2015; 4(23): e879

Comparative effectiveness of neoadjuvant chemoradiotherapy versus chemotherapy alone followed by surgery for patients with stage IIIA non-small cell lung cancer

National Cancer Database
Stage IIIA NSCLC
Neoadjuvant ChRT vs Neoadjuvant CTh
1076 patients (accrual 2003-2005), 700 (65%) in NeoChRT arm



No difference in OS

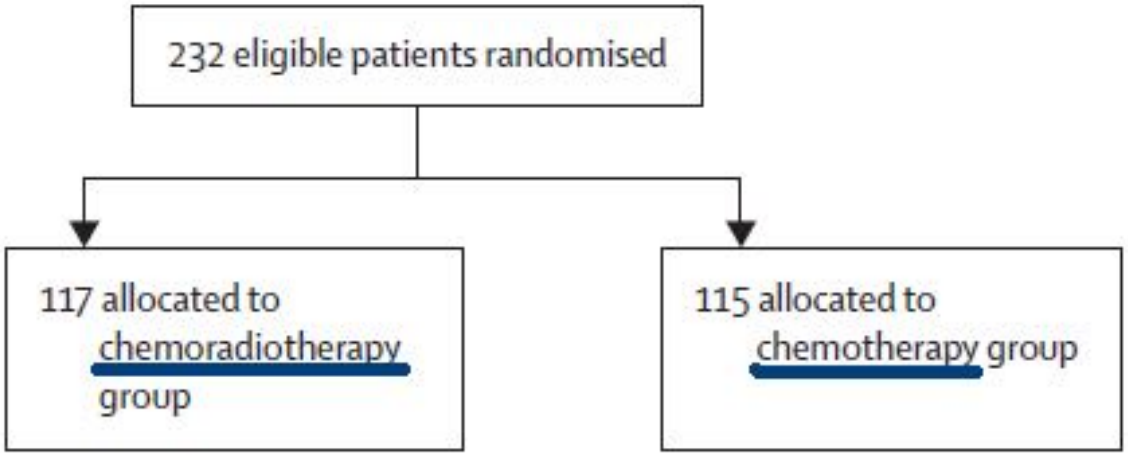
NeoChRT was associated with a lower independent risk of residual nodal disease (RND) (OR 0.75, p = 0.02) and a lower risk of adverse pathologic features (APF) (OR 0.67, p = 0.0023)

Sher DJ. Lung Cancer 2015;88:267-274

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

SAKK Lung Cancer Project Group

23 centres in Switzerland, Germany and Serbia (2001-2012)



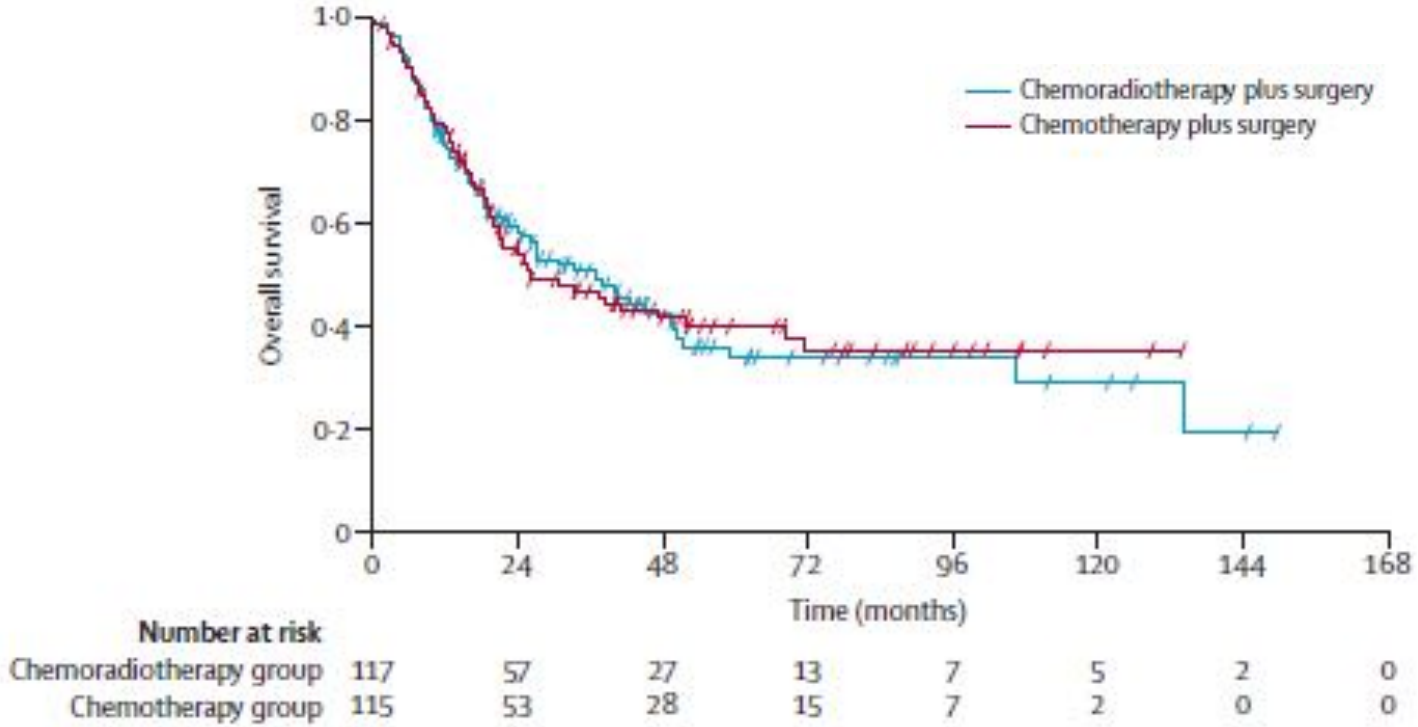
3 cycles of chemotherapy (100 mg/m² cisplatin and 85 mg/m² docetaxel) followed by radiotherapy with 44 Gy in 22 fractions over 3 weeks

3 cycles of neoadjuvant chemotherapy (100 mg/m² cisplatin and 85 mg/m² docetaxel)

Pless M. Lancet 2015;386:1049-1056

Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial

SAKK Lung Cancer Project Group



Median OS was 37.1 months in the ChRT group and 26.2 months in the ChT group

Pless M. Lancet 2015;386:1049-1056

SAKK Lung Cancer Project Group

	ChRT group (n=99)	*ChT group (n=94)*
Nodal downstaging (to N1 or N0)	63 (64%)	50 (53%)
Pathological complete remission	16 (16%)	11 (12%)

✓ The rate of toxic effects in patients who received chemotherapy was high, with 45% in ChRT group and 60% in the ChT group, having grade 3 or 4 events.

✓ 19 (16%) of the 117 patients did not start radiotherapy.

✓ Radiotherapy was delivered after surgery to 18 (16%) patients in the ChT group.

Pless M. Lancet 2015;386:1049-1056

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16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Trimodality Therapy in the Treatment of Stage IIIA Non-Small Cell Lung Cancer (NSCLC): A National Cancer Database Analysis

Madhusmita Behera[1], Conor E. Steuer[1], Felix Fernandez[1], Yuan Liu[1], Chao Fu[1], Theresa Gillespie[1], Kristin Higgins[1], Nabil Saba[1], Rathi N. Pillai[1], Seth Force[1], Suchita Pakkala[1], Dong M. Shin[1], Taofeek K. Owonikoko[1], Chandra P. Belani[2], Walter J .Curran[1], Fadlo R. Khuri[1], Suresh S. Ramalingam[1]

1.Winship Cancer Institute of Emory University, Atlanta, GA

2. Penn State Hershey Cancer Institute, Hershey, PA

EMORY | WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Abstract ID: 2962

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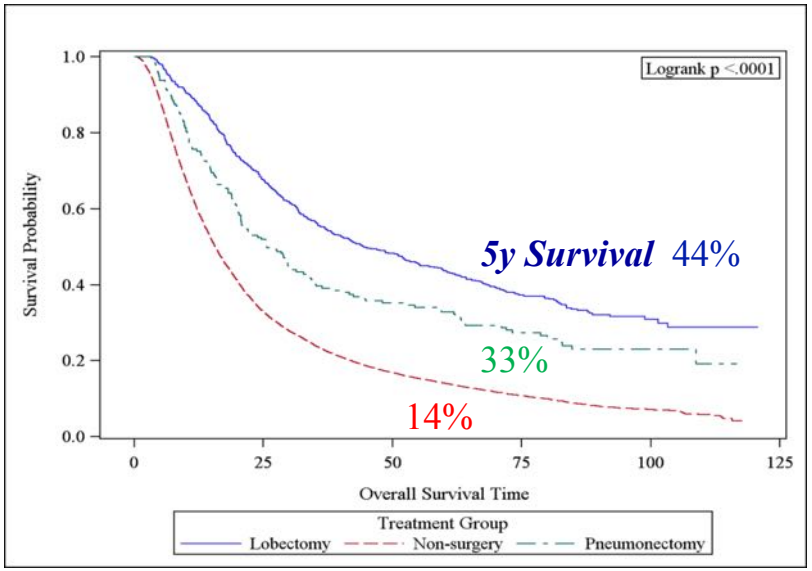
Source: National Cancer Database (Am Coll Surg, Am Cancer Soc)
Period: 2003-2011
Patient Population: 29.584 Stage IIIA-N2
Referral: 27% Academic centres
Treatment: No surgery (NS): 92%. CRT + Surgery (L or P): 2.366 pts



Results

- OS in surgical pts > than in NS (L > P)
- Prognostic factors: academic centres, surgery (all ages)
- Postop mortality factors: males, > 60 yrs, pneumonectomy (>right), comorbidity (Charlson > 2)

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16TH WORLD CONFERENCE ON LUNG CANCER
SEPTEMBER 6–9, 2015 → DENVER, COLORADO, USA

Risk Factor of Morbidity and Mortality of Surgical Resection after Induction Therapy in Patients with Stage IIIA-N2 Lung Cancer

Jong Ho Cho[1], Jhingook Kim[1], Hong Kwan Kim[1], Yong Soo Choi[1], Jae Ill Zo[1], Young Mog Shim[1], kwhanmien Kim[2]

[1]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul/Korea, [2]Seoul National University Bundang Hospital,Seoul National University College of Medicine, Seoul/Korea

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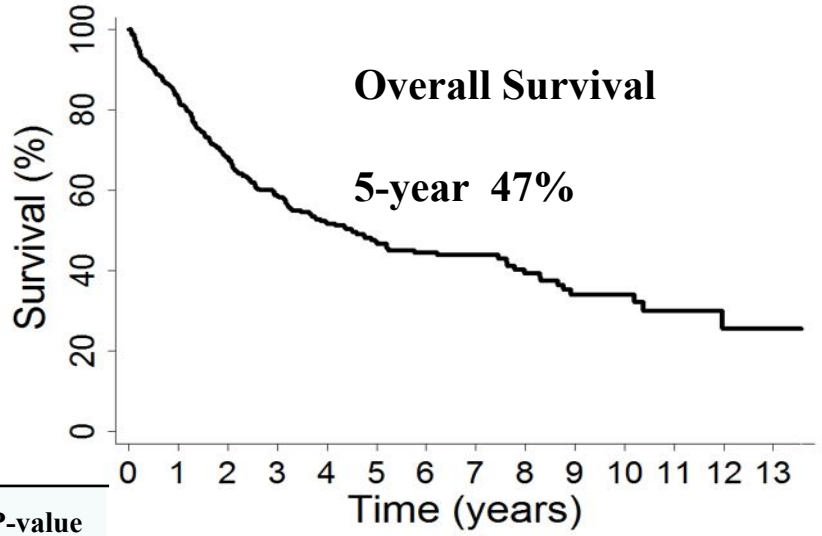
Aim of the study: to investigate the clinical outcomes and risk factor analysis for morbidity and mortality following trimodality therapy

574 pts
CT: Paclitaxel or docetaxel + platinum
RT: 44 ~ 45 Gy (concomitant)



Risk factor analysis for 90-day postoperative mortality

Variables	Catergory	No of patients	Odds ratio	95% CI	P-value
Age	<70	32/517 (6.2%)	1		
	≥70	9/57 (15.8%)	1.82	1.21-6.43	0.019
Extent of	Non-pneumonectomy	28/501 (5.6%)	1		
surgery	Pneumonectomy	13/73 (17.8%)	3.25	1.50-6.78	0.003

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

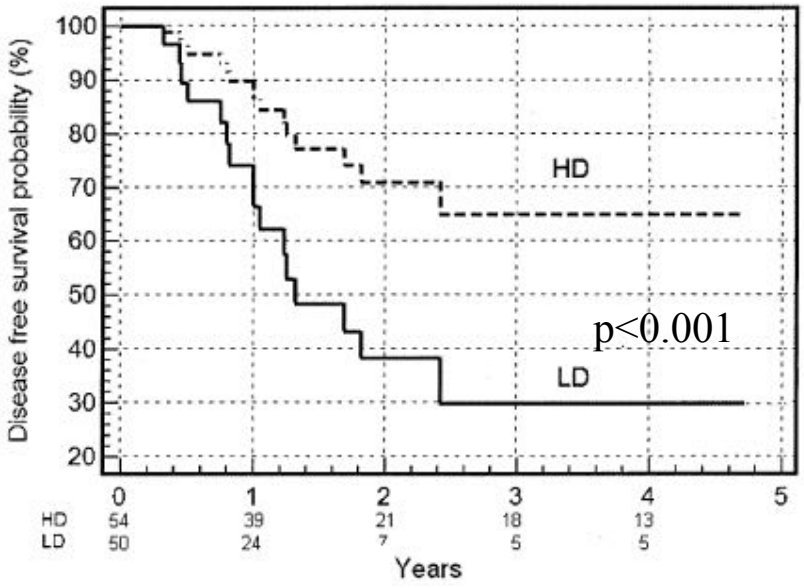
104 patients

High Dose (HD) radiotherapy > 60 Gy

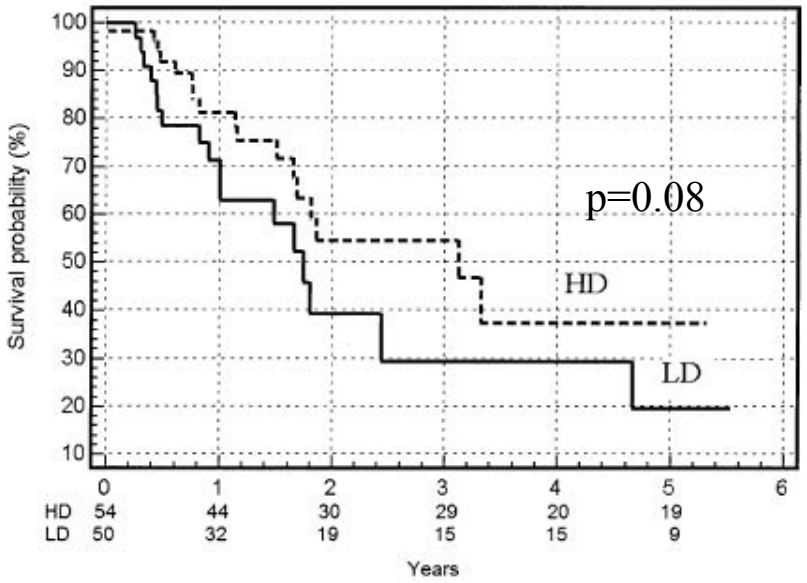
Low Dose (LD) radiotherapy < 60 Gy

pCR 28% vs 10%, p=0.04

Disease free survival



Overall Survival



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

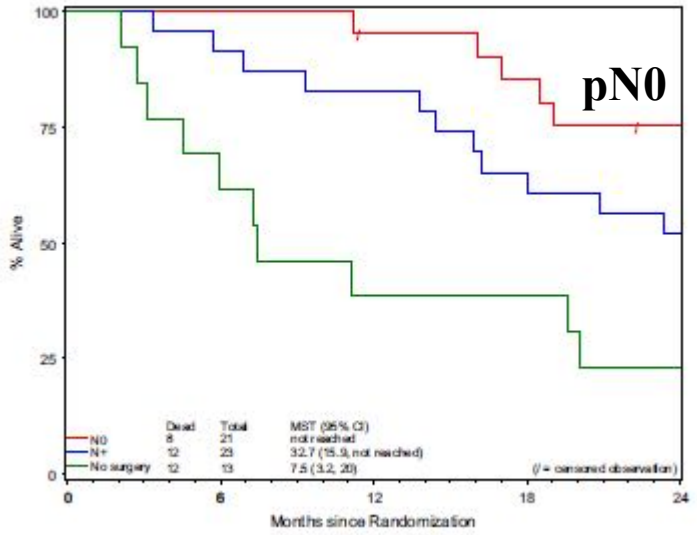
Radiation Therapy Oncology Group Protocol 02-29: A Phase II Trial of Neoadjuvant Therapy With Concurrent Chemotherapy and Full-Dose Radiation Therapy Followed by Surgical Resection and Consolidative Therapy for Locally Advanced Non-small Cell Carcinoma of the Lung

57 patients

TREATMENT:

RT: ***61.2Gy (1.8 Gy/die)***

CT: Carbo AUC2 + Paclitaxel 50 mg/mq/w



TOXICITY

Hematologic 35%

Gastrointestinal 14%

Pulmonary 23%

Postoperative complications 14%

Mediastinal Nodal Clearance 63%

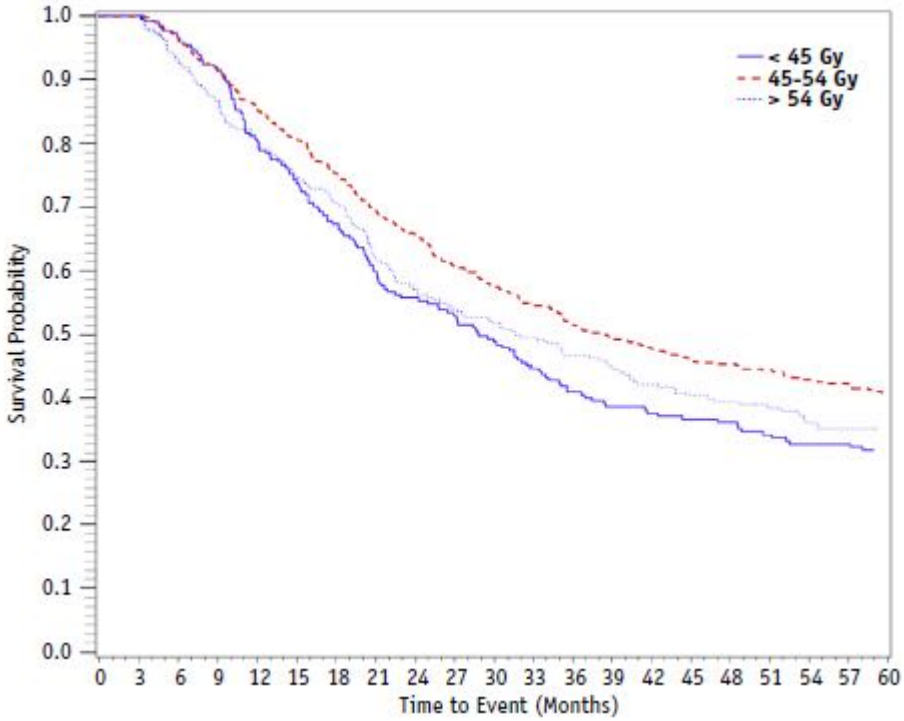
Suntharalingam M. IJROBP 2013; 84:456-463

Relationship Between Radiation Therapy Dose and Outcome in Patients Treated With Neoadjuvant Chemoradiation Therapy and Surgery for Stage IIIA Non-Small Cell Lung Cancer: A Population-Based, Comparative Effectiveness Analysis

National Cancer Database

1041 patients
- 233 (22%) : LD-RT (36 Gy to 45 Gy)
- 584 (56%) : SD-RT (45 Gy to 54 Gy)
- 230 (22%) : HD-RT (54 Gy to 74 Gy)

Sher DJ. IJROBP 2015; 92:307-316



Patients treated with preoperative SD-RT experienced superior overall survival in comparison with doses above or below this level (p=0.0089)

Residual nodal disease was seen less often after HD-RT (25.5% vs 31.8% and 37.5% for HD-RT, LD-RT, and SD-RT, respectively, p=0.0038).

There were no differences in positive surgical margin status or adverse surgical outcomes between the cohorts.

Sher DJ. IJROBP 2015; 92:307-316

Conclusions

- *The nodal clearance after neoadjuvant treatment improves survival*
- *The use of neoadjuvant radiochemotherapy improves the rate of pathological response*
- *The treatment intensification with selected drugs and higher total dose may lead to improvement of clinical results*