Chemoradiation in lung cancer

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Mini Symposium: Lung

Epidemiology of lung cancer in India: Focus on the differences between non-smokers and smokers: A single-centre experience

Noronha V, Dikshit R[1], Raut N[2], Joshi A, Pramesh CS[3], George K[3], Agarwal JP[4], Munshi A[4], Prabhash K

Department of Medical Oncology, [1]Department of Epidemiology, [3]Department of Surgical Oncology, [4]Department of Radiation Oncology, Tata Memorial Hospital, Parel, [2]Department of Medical Oncology, Seven Hills Hospital, Andheri (East), Mumbai, India

lung_cancer_epidemiology_UC.pdf (SECURED) - Adobe Reader

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	Hoarseness of voice	18.8	13.4
Histology (%)	Small-cell	10.5	5.8
	Squamous	31.8	17
	Adenocarcinoma	35.5	44.8
	Large cell	1.4	2.5
	NSCLC, NOS	15.9	19.9
	Other	5	9.9
Location of tumour (%)	Right upper	20.2	29.35
	Right middle	6.0	3.9
	Right lower	13.5	11.5
	Left upper	15.9	17.2
	Left lower	19.8	17.2
TNM stage (%)	STAGE I /II	14.6	13.7
	STAGE III	42.8	42.4
	STAGE IV	32.2	36.8
Site of metastases (%)	Bone	4.7	4.7

NSCLC

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T4 and N3!

T4 Tumour of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, oesophagus, vertebral body, carina; separate tumour nodule(s) in a different ipsilateral lobe to that of the primary.

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

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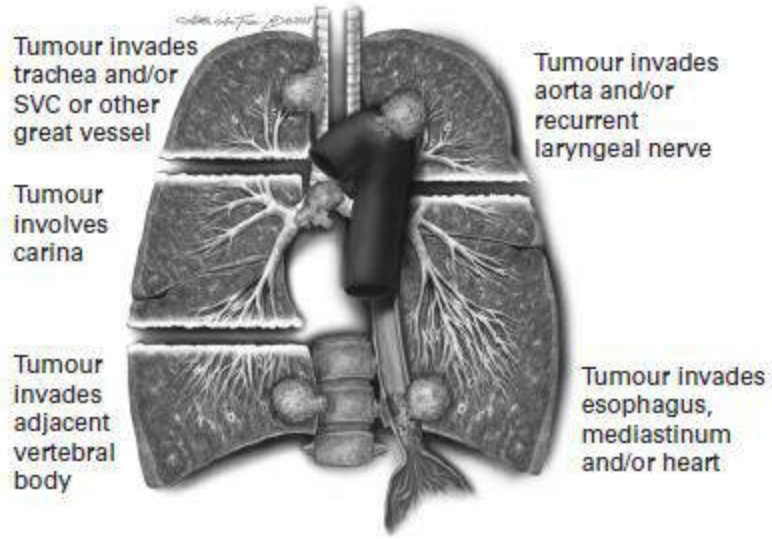
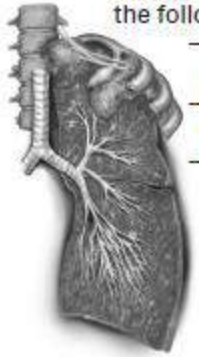
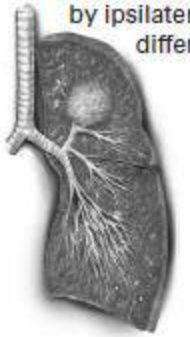
T4 and N3!

T4



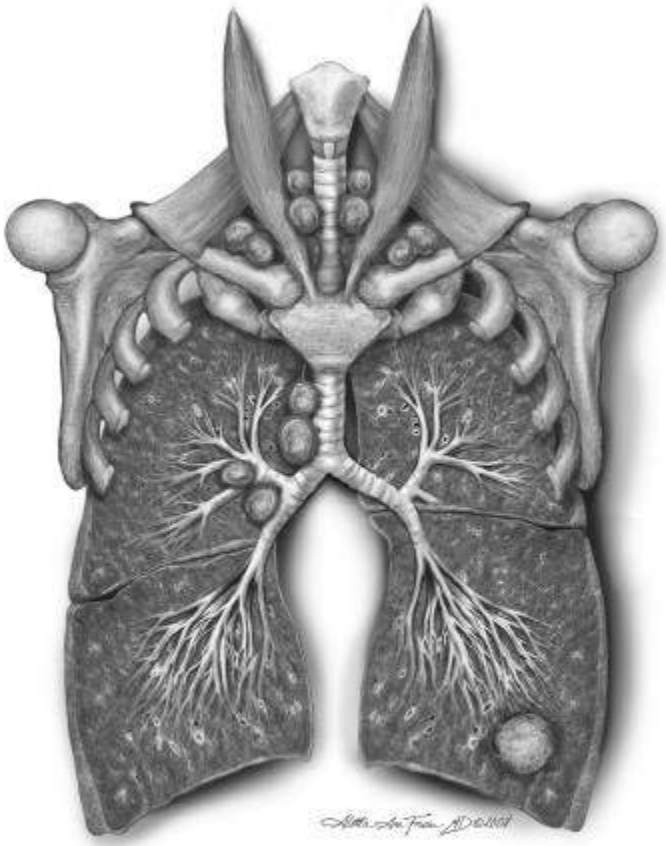


Pancoast tumours with invasion of one or more of the following structures:
- vertebral body or spinal canal
- brachial plexus (C8 or above)
- subclavian vessels



Tumour accompanied by ipsilateral nodules, different lobe

N3



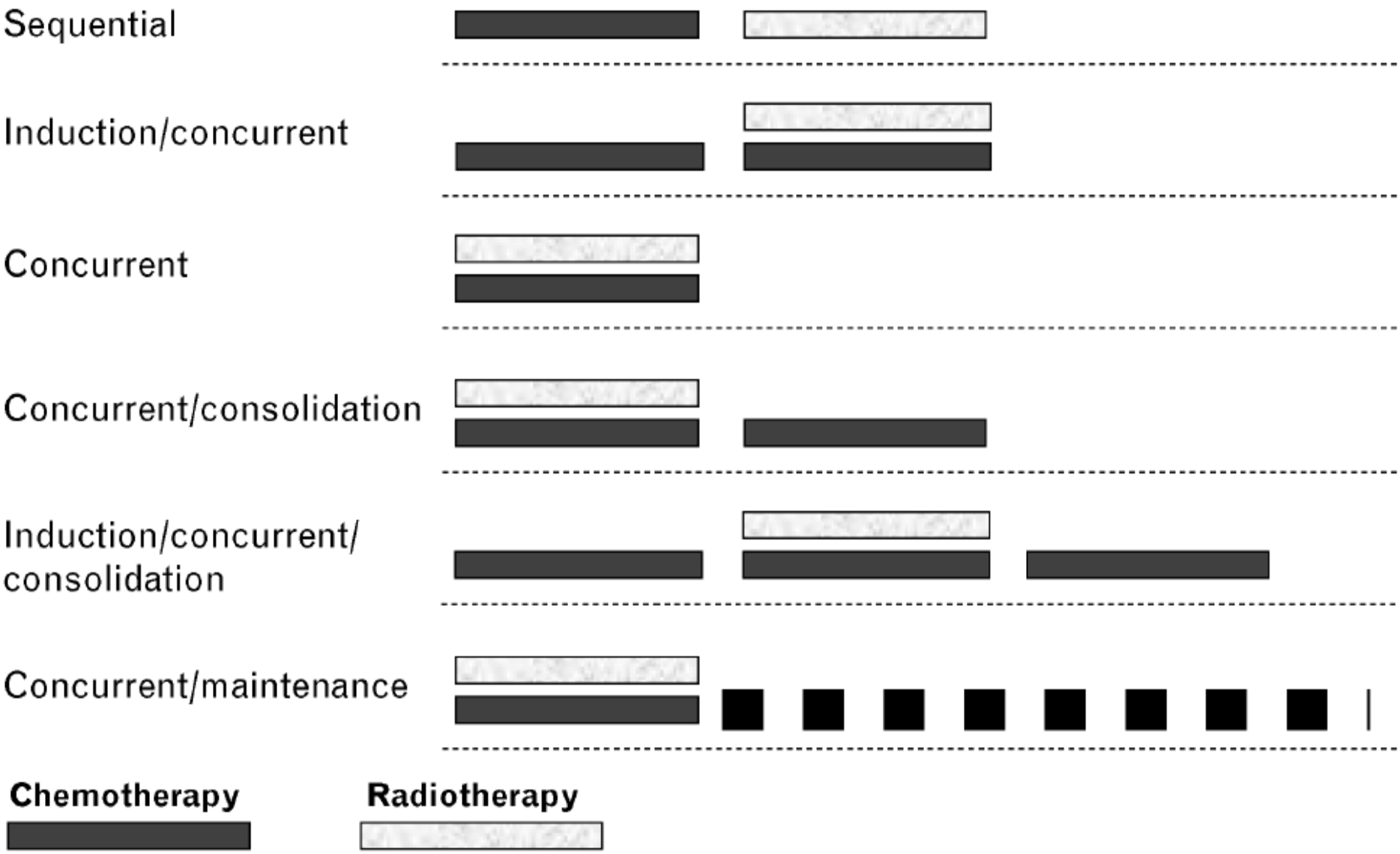
Metastasis in contralateral hilar/ mediastinal/scalene/ supraclavicular lymph node(s)

Metastasis in ipsilateral scalene/ supraclavicular lymph node(s)

Chemoradiation- Initial trials

- CALGB 8433 randomized 155 patients
- Arm 1- Chemo with cisplatin (100 mg/m2 q 4 wks X 2 doses) and weekly vinblastine followed by standard thoracic RT(60 Gy)
- Arm 2- RT alone (same dose)
- Median survival on the sequential arm 13.7 m
- Median survival RT alone arm 9.6 m (*P<0.012)*

Dillman, JNCI 1996



Baas , Curr Opin Oncol 2011

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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

Anne Aupérin, Cecile Le Péchoux, Estelle Rolland, Walter J. Curran, Kiyoyuki Furuse, Pierre Fournel, Jose Belderbos, Gerald Clamon, Hakki Cuneyt Ulutin, Rebecca Paulus, Takeharu Yamanaka, Marie-Cecile Bozonnat, Apollonia Uitterhoeve, Xiaofei Wang, Lesley Stewart, Rodrigo Arriagada, Sarah Burdett, and Jean-Pierre Pignon

Performance status				
0	309	52	297	50
1	278	46	293	49
2	13	2	9	1
Unknown	3		3	

Median follow-up 6 years

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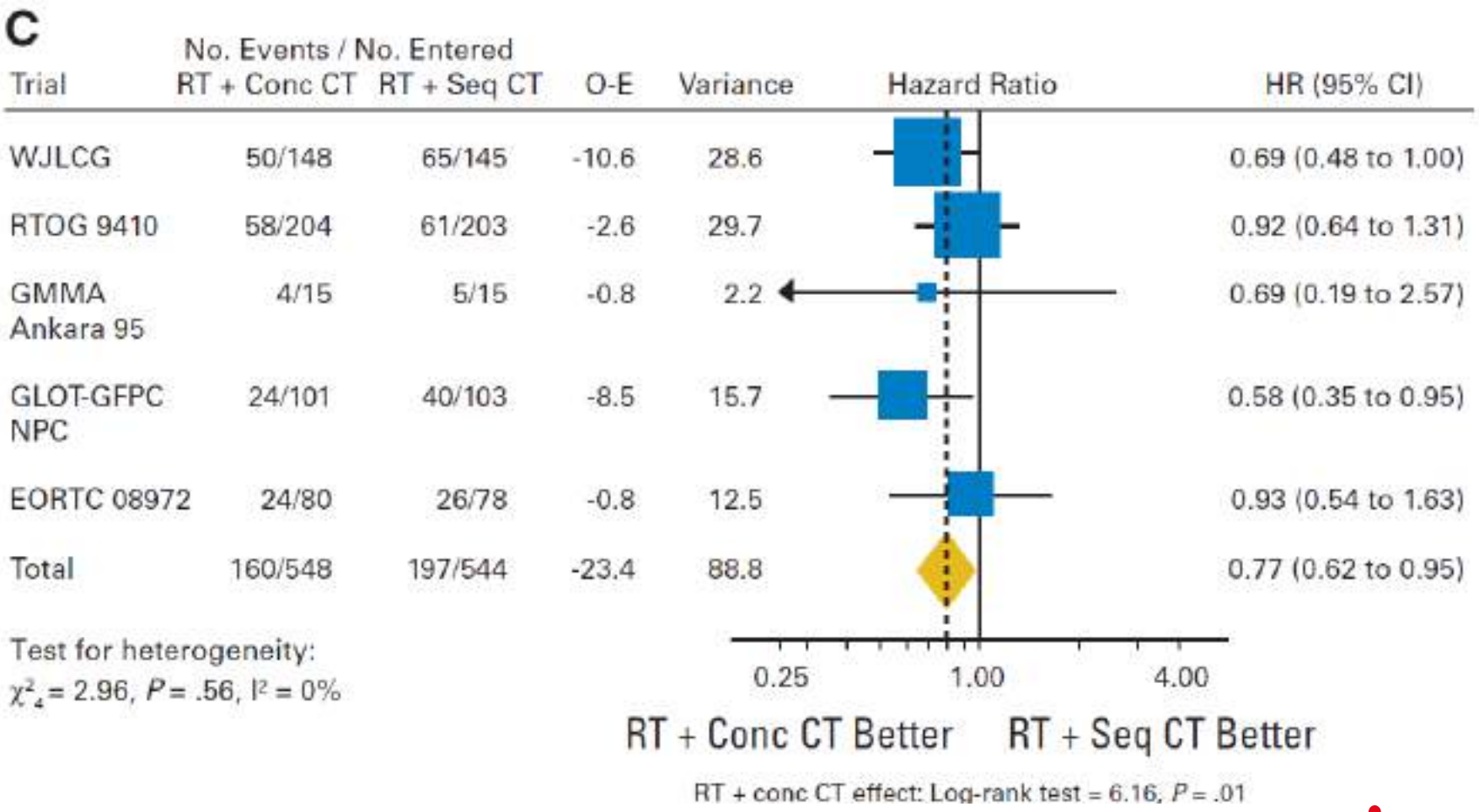
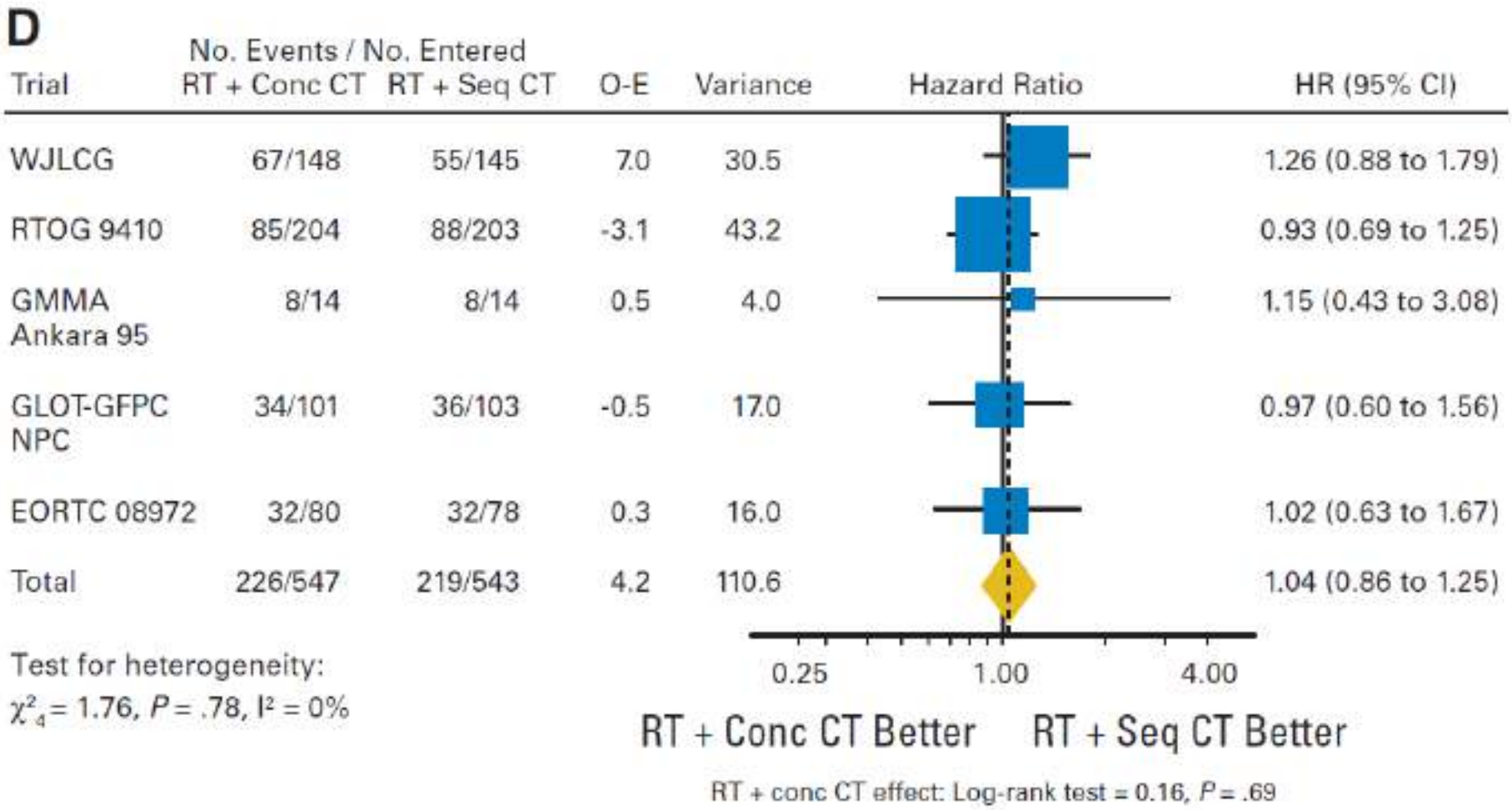
Auperin, JCO 2010.

Local progression

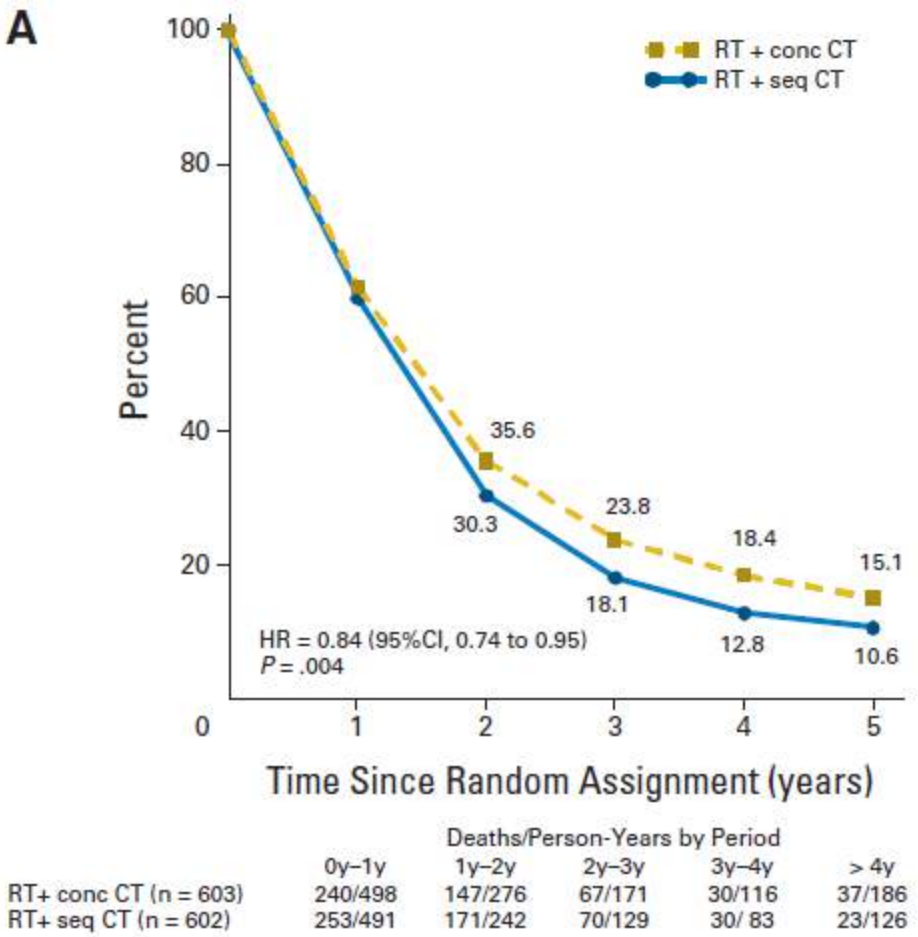


Auperin JCO 2010

Distant progression



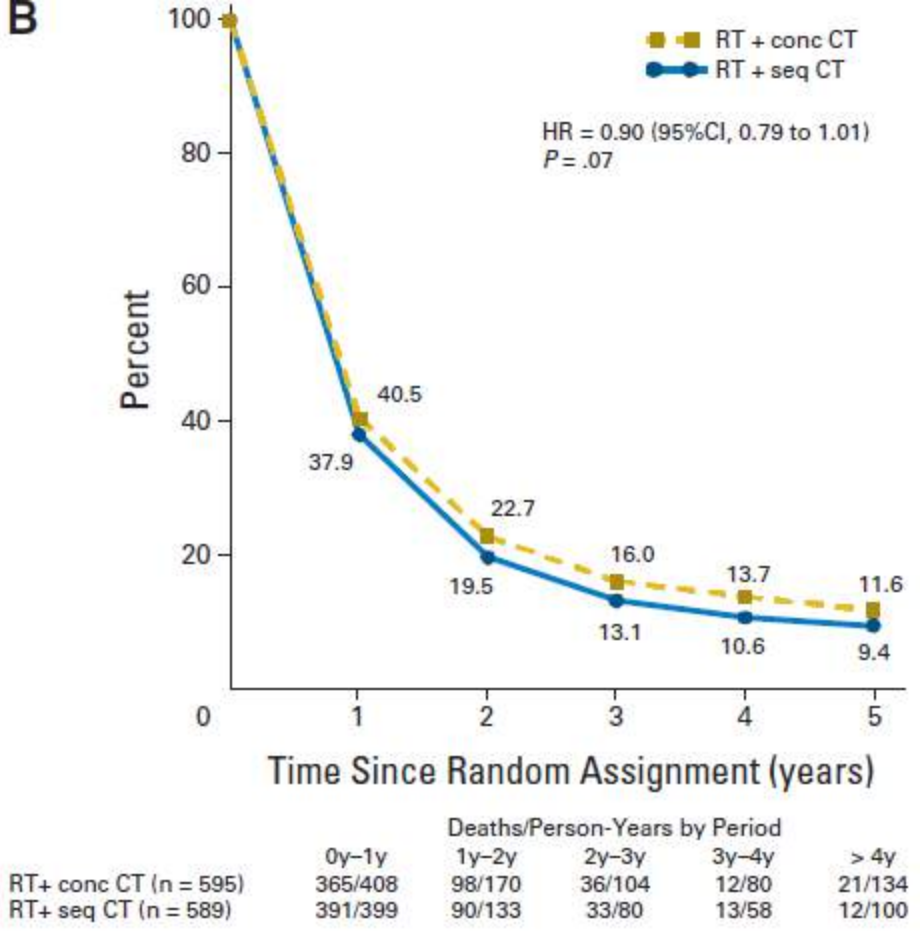
Auperin JCO 2010



Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 603)	240/498	147/276	67/171	30/116	37/186
RT+ seq CT (n = 602)	253/491	171/242	70/129	30/ 83	23/126

Overall Survival



Deaths/Person-Years by Period

	0y–1y	1y–2y	2y–3y	3y–4y	> 4y
RT+ conc CT (n = 595)	365/408	98/170	36/104	12/80	21/134
RT+ seq CT (n = 589)	391/399	90/133	33/80	13/58	12/100

Progression free Survival

- Absolute survival benefit of concomitant chemoradiotherapy 5.7% (from 18.1% to 23.8%) at 3 years and 4.5% at 5 years
- For progression-free survival, the HR was 0.90 (95% CI, 0.79 to 1.01; P .07)
- Concomitant radiochemotherapy increased acute esophageal toxicity (grade 3-4) from 4% to 18% with a relative risk of 4.9 (95% CI, 3.1 to 7.8; P .001).
- There was no significant difference regarding acute pulmonary toxicity

Auperin, JCO 2010

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Toxicity profile

Grade 3–5 toxicity recorded in trials of sequential versus concurrent chemoradiation in locally advanced non-small cell lung cancer (number cases/number assessable)

Reference	Trial arm	Treatment-related deaths	Acute oesophagitis	Acute lung toxicity	Neutropenia*	Anaemia
[9]	Concurrent	1/156	4/156	2/156	154/156	16/156
	Sequential	3/158	3/158	2/158	121/158	52/158
[10]	Concurrent	6/201	50/201	8/201	117/201	NR
	Sequential	4/201	8/201	14/201	113/201	
[19]	Concurrent /consolidation	10/100	30/93	5/93	72/93	19/93
	Sequential	3/101	3/100	11/100	88/100	28/100
[20]	Concurrent	0/51	9/51	2/51	33/51	6/51
	Sequential	0/48	4/48	1/48	19/48	3/48
[22]	Concurrent/consolidation	2/92	26/92	15/92	24/92	9/92
	Sequential	0/90	3/90	6/90	0/90	4/91
[21]	Concurrent	2/84	7/84	5/84	4/84	NR
	Sequential	2/89	0/89	2/89	0/89	
Total	Concurrent	21/684 (3%)	126/677 (19%)	37/677 (5.5%)	404/677 (60%)	50/392 (13%)
	Sequential	12/687 (1.7%)	21/686 (3%)	36/686 (5.2%)	341/686 (50%)	87/397 (22%)

Rourke, Clinical Oncology, 2012

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Int J Radiat Oncol Biol Phys. 2012 Jun 9. [Epub ahead of print]

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

Palma DA, Senan S, Tsujino K, Barriger RB, Rengan R, Moreno M, Bradley JD, Kim TH, Ramella S, Marks LB, De Petris L, Stitt L, Rodrigues G.

Department of Radiation Oncology, London Regional Cancer Program, London, Canada.

Abstract

BACKGROUND: Radiation pneumonitis is a dose-limiting toxicity for patients undergoing concurrent chemoradiation therapy (CCRT) for non-small cell lung cancer (NSCLC). We performed an individual patient data meta-analysis to determine factors predictive of clinically significant pneumonitis.

METHODS AND MATERIALS: After a systematic review of the literature, data were obtained on 836 patients who underwent CCRT in Europe, North America, and Asia. Patients were randomly divided into training and validation sets (two-thirds vs one-third of patients). Factors predictive of symptomatic pneumonitis (grade ≥2 by 1 of several scoring systems) or fatal pneumonitis were evaluated using logistic regression. Recursive partitioning analysis (RPA) was used to define risk groups.

RESULTS: The median radiation therapy dose was 60 Gy, and the median follow-up time was 2.3 years. Most patients received concurrent cisplatin/etoposide (38%) or carboplatin/paclitaxel (26%). The overall rate of symptomatic pneumonitis was 29.8% (n=249), with fatal pneumonitis in 1.9% (n=16). In the training set, factors predictive of symptomatic pneumonitis were lung volume receiving ≥20 Gy (V(20)) (odds ratio [OR] 1.03 per 1% increase, P=.008), and carboplatin/paclitaxel chemotherapy (OR 3.33, P<.001), with a trend for age (OR 1.24 per decade, P=.09); the model remained predictive in the validation set with good discrimination in both datasets (c-statistic >0.65). On RPA, the highest risk of pneumonitis (>50%) was in patients >65 years of age receiving carboplatin/paclitaxel. Predictors of fatal pneumonitis were daily dose >2 Gy, V(20), and lower-lobe tumor location.

CONCLUSIONS: Several treatment-related risk factors predict the development of symptomatic pneumonitis, and elderly patients who undergo CCRT with carboplatin-paclitaxel chemotherapy are at highest risk. Fatal pneumonitis, although uncommon, is related to dosimetric factors and tumor location.

PMID: 22682812 [PubMed - as supplied by publisher] PMCID: PMC3448004[Available on 2013/12/9]

Rationales- Why concurrent better

1

- Czech study – 30% of NACT patients did not proceed to radiotherapy

2

- Tumours that reduce with chemotherapy then proliferate at a faster rate (NS Hypothesis)

3

- Reduced efficacy of RT post chemo (anaemia, cisplat induced resistance..)

Intersting Paradox!

- In stage III NSCLC, only two cycles of full-dose chemotherapy (those given with RT) sufficient to treat micrometastatic disease
- Four to six cycles, and often maintenance, are standard for stage IV disease!

Possible Rationales

- Lesser disease load in stage III disease
- Systemic effect of local radiotherapy!

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Chemo after chemoradiation?

- Phase II trial
- 83 patients, Median age of 60 years
- 94% with PS 0-1, all with FEV1 > 1 L
- Full-dose cisplatin and etoposide concurrent with radiation therapy (61 Gy) followed by three cycles of consolidation docetaxel
- Median OS 26 months and 5-year survival 29%!

Gandara, JCO 2003

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Chemo after chemoradiation?

- Phase III study in a similar patient population
- Median age 63, performance status 0-1, 5% weight loss, FEV1 1 L
- No difference in survival in ChemoRT vs ChemoRT with consolidative chemotherapy
- 5% of patients treated with docetaxel died during consolidation therapy
- Further studies on for this issue

Hanna JCO 2007

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Chemo before chemoradiation?

- Phase III trial- CALGB 39801
- Test NACT followed by concurrent CTRT
- Arm 1 : Low-dose concurrent carboplatin (AUC 2), paclitaxel (50 mg/m2) and RT (66 Gy)
- Arm 2 : Same CTRT preceded by two cycles of full-dose induction carboplatin (AUC 6) and paclitaxel (200 mg/m2).
- Median OS concurrent CTRT (Arm 1) - 12 m
- Median OS (adding NACT)(Arm 2)-14 m (*P= 0.30).*

Vokes, JCO 2007

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Lung Cancer. 2013 Jan 25. pii: S0169-5002(13)00013-5. doi: 10.1016/j.lungcan.2013.01.006. [Epub ahead of print]

Concurrent chemoradiotherapy for large-volume locally-advanced non-small cell lung cancer.

Wiersma TG, Dahele M, Verbakel WF, van de Ven PM, de Haan PF, Smit EF, van Reij EJ, Slotman BJ, Senan S.

Department of Radiation Oncology, VU University Medical Center, De Boelelaan 1117, PO Box 7057, 1007 MB, Amsterdam, The Netherlands.

Abstract

PURPOSE: Patients with large volume stage III non-small cell lung cancer (NSCLC) are often excluded from concurrent chemoradiotherapy (CRT) protocols due to fears about excessive toxicity and poor survival. Patients with N3 nodal disease may be excluded for the same reason. We have routinely accepted fit patients in both the above groups for CRT if they met our planning parameters. We analyzed toxicity and survival outcomes for patients undergoing CRT with a planning target volume (PTV) exceeding 700cc, either with or without N3 nodal disease, or a PTV less then 700cc with N3 disease.

MATERIALS AND METHODS: Single center, retrospective study of patients with stage III NSCLC treated with CRT between 2004 and 2011.

RESULTS: 121 patients were eligible, with 81% (98/121) having a PTV>700cc (of whom 33% (32/98) had N3 nodal disease) and 19% (23/121) having N3 disease and a PTV≤700cc. Grade ≥3 esophagitis and pneumonitis were recorded in respectively 34% and 4% of all patients. Median follow-up for all patients was 37.6 months (mo). Median overall (OS) and progression-free (PFS) survivals were 15.7 mo and 11.6 mo, respectively, OS for all patients with PTV>700cc was 14.5 mo (19.5 mo with N3 and 13.2 mo without N3), compared to 26.5 mo for PTV≤700cc with N3 (p=0.009). About 1 in 4 patients with PTV>700cc died within 6 mo of starting radiotherapy (this was associated with Charlson comorbidity index [CCI]≥1), while about 18% were alive at 3 years.

CONCLUSION: Patients undergoing CRT for stage III NSCLC with a PTV>700cc, with or without N3 nodal disease, had a significantly shorter OS than patients with PTV≤700cc with N3. Patients with PTV>700cc and with CCI≥1, had a significantly higher risk of early death but longer-term survivors with PTV>700cc are observed. The PTV and CCI should be considered in clinical decision making and used as stratification factors in future trials.

PMID: 23357464 [PubMed - as supplied by publisher]

LinkOut - more resources

Chemoradiation for large volume NSCLC

Patient characteristics.

Age (y) (median, range)	62.8 (41.9–79.6)
Gender (*n*) (%)	
Male	84 (69.4%)
Female	37 (30.6%)
Stage (*n*)	
IIIA	42 (34.7%)
IIIB > 700 cc + N3	32 (26.4%)
Supraclavicular	14
Contralateral mediastinal	13
Both	5
IIIB > 700 cc without N3	24 (19.8%)
IIIB ≤ 700 cc with N3	23 (19%)
Supraclavicular	8
Contralateral mediastinal	13
Both	2
PTV[a] (cc)	
Median (mean, range)	863 (940, 334–2165)
WHO[b] performance score (*n*) (%)	
0	26 (21.5%)
1	89 (73.6%)
2	6 (5%)

Wiersma et al ,Lung Cancer 2013

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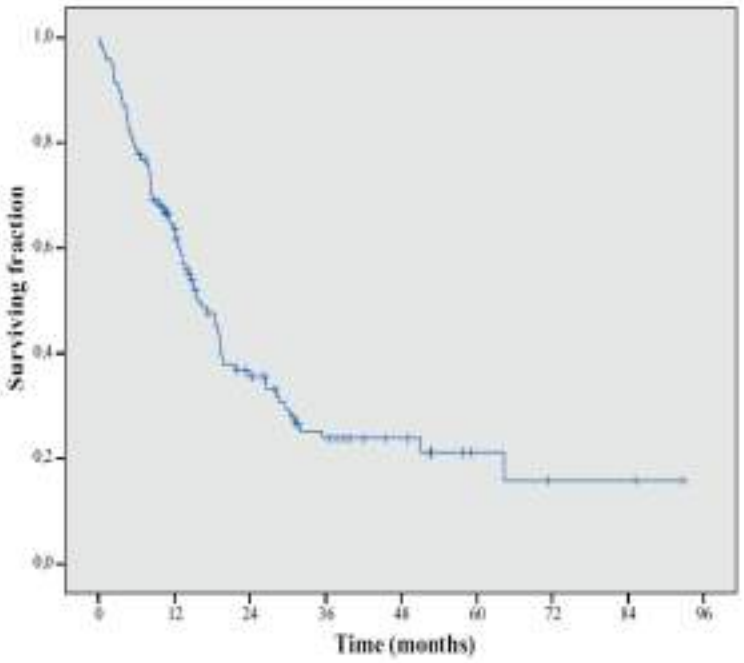
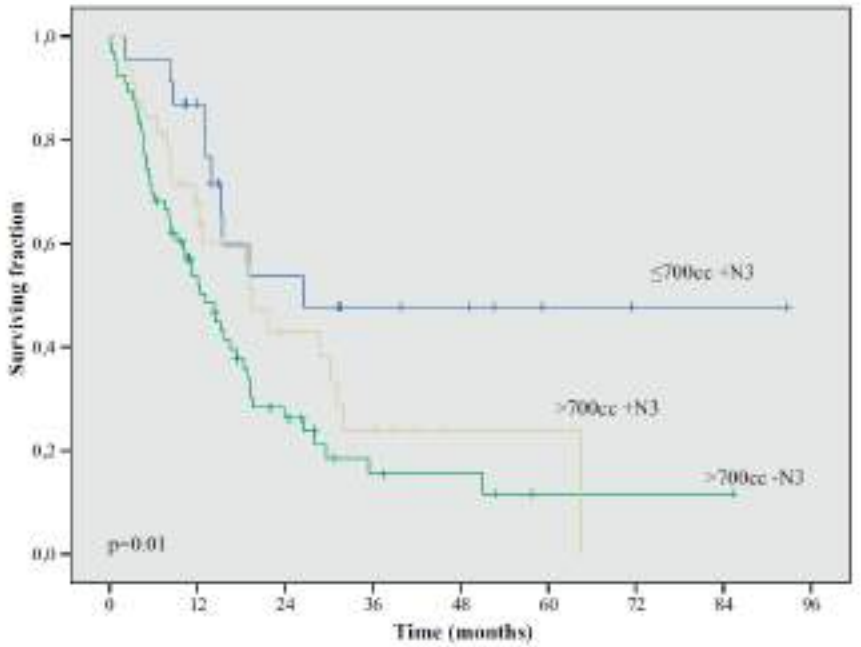
Chemoradiation for large volume NSCLC





Median survival

Subgroup ≤700 cc with N3:	26.5 m
Subgroup >700 cc with N3:	19.5 m
Sub-group >700 cc without N3 :	13.2 m

Wiersma et al ,Lung Cancer 2013

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Chemoradiation for large volume NSCLC

Characteristics of patients with PTV > 700 cc who died within 6 months after starting radiotherapy ($n = 25$) and of patients with PTV > 700 cc who lived longer than 6 months ($n = 73$).

General characteristics	<6 mo	>6 mo	Treatment characteristics	<6 mo	> 6mo
WHO[1] performance score (n) (%)			Dose		
0	3 (12.0)	18 (24.7)	Prescribed (cGy): mean, range	5882 (4500–6600)	6148 (4500–6600)
1	19 (76.0)	53 (72.6)	Delivered (cGy): mean, range	4693 (600–6600)	6234 (4600–7000)
2	3 (12.0)	2 (2.7)	Treatment completion		
Charlson comorbidity index (n) (%)			Completed (n) (%)	15 (60)	70 (95.9)
0	5 (20.0)	31 (42.5)	Lung		
1	5 (20.0)	11 (15.1)	Mean lung dose (cGy)	1691 (928–2545)	1725 (799–2641)
2	8 (32.0)	19 (26.0)	V20 (%)	28.3 (14.6–40.6)	27.6 (10–41.2)
3	6 (24.0)	8 (11.0)	V5 both lungs combined (%)	54.3 (22.1–90.7)	55.3 (23.4–85.5)
≥4	1 (4.0)	4 (5.5)	V5 contralateral lung (%)	39.0 (9.6–87.5)	39.8 (4.1–85.6)
Gender			Heart		
Male (n) (%)	15 (60.0)	54 (74.0)	Mean heart dose (cGy)	2121 (261–4976)	NA
Age (years)			V30 (%)	30.8 (1.6–77.2)	NA
Mean (range)	61.7 (45.3–79.6)	63.6 (41.8–78.9)	Spinal cord		
Esophagitis			Maximum point dose (cGy): mean (range)	4668 (711–5393)	4688 (2565–5335)
Grade ≥3 (n) (%)	7 (28.0)	23 (31.5)			

[1] WHO: World Health Organization.

- *Overall, Grade 3 esophagitis and pneumonitis were identified in 33.9% and 4.1% of all patients respectively*

Wiersma et al ,Lung Cancer 2013

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Chemoradiation lung- Criteria

1

- 0-1 ECOG PS >70

2

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4

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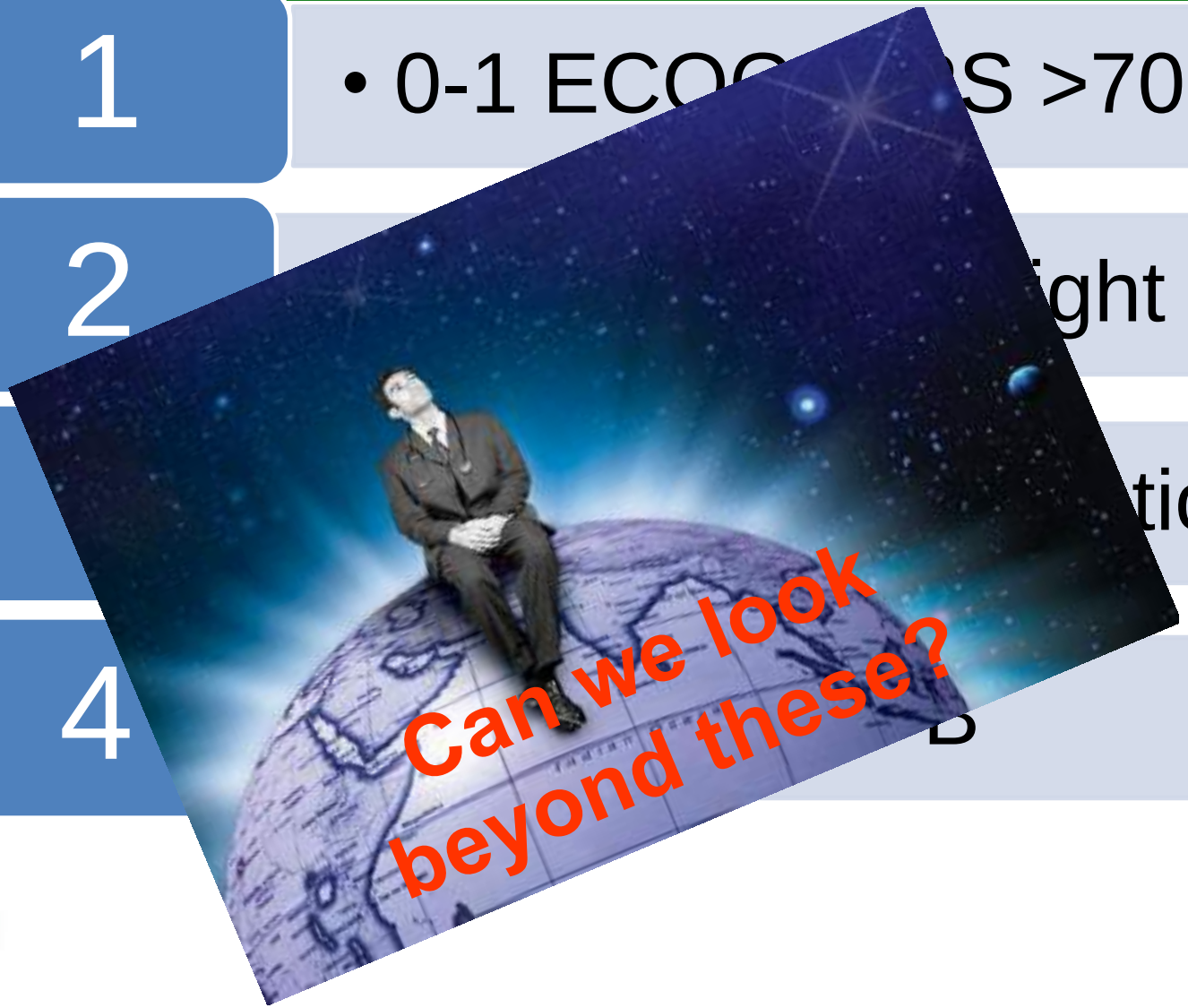

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Concurrent EGFR- TKI

Table 2. Selected Phase I/II Studies of Concurrent EGFR-TKI and Chemoradiotherapy for NSCLC

Study	No. of Patients	Concurrent	*EGFR* Inhibition	RT (Gy)	Ind/Consol	Adverse Events (%)		Response Rate (%)	OS			
						Esophagitis Grades 3-4	Neutropenia Grades 3-4		Median (months)	1-Year (%)	2-Year (%)	3-Year (%)
University of Chicago[44]	16	Cisplatin, etopside	Erlotinib MTD: 150 mg/d	66	Consol: docetaxel	19	50	65	11			20
	15	Carboplatin, paclitaxel	Erlotinib MTD: 150 mg/d	66	Ind: carboplatin, paclitaxel	40	20	59	15			16
CALGB 30106 (good risk)[43]	39	Carboplatin, paclitaxel	Gefitinib 250 mg/d	66	Consol: carboplatin, paclitaxel	31	38	81	13	53		
Zurich[45]	14	Cisplatin (optional)	Gefitinib 250 mg/d	66	Ind: cisplatin based	22	11	21	12.5		NS	
MD Anderson Cancer Center[46]	48	Carboplatin, paclitaxel	Erlotinib 150 mg/d	63	Consol: carboplatin, paclitaxel	NS	NS	90	26	84		
University of North Carolina[47]	23	Carboplatin, paclitaxel	Gefitinib 250 mg/d	74	Ind: carboplatin, paclitaxel, irinotecan	19.5	19	NS	16		20	

Postulate:
Continuous EGFR- TKI exposure results in cell cycle arrest at G1, reducing the efficacy of chemo

Salama et al , JCO 2013

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Concurrent Cetuximab

Table 3. Selected Phase II Studies of Cetuximab Delivered Concurrently With Chemoradiotherapy for NSCLC

Study	No. of Patients	Concurrent	EGFR Inhibition	RT (Gy)	Ind/Consol	Adverse Events (%)		Response Rate (%)	OS			
						Esophagitis Grades 3-4	Neutropenia Grades 3-4		Median (months)	18-Month (%)	1-Year (%)	2-Year (%)
RTOG 0324[55]	87	Carboplatin, paclitaxel	Cetuximab	63	Consol: carboplatin, paclitaxel	7	20 (all hematologic)	62	22.7			49.3%
CALGB 30407[7] (*Randomised*)	53	Carboplatin, pemetrexed	Cetuximab	70	Consol: pemetrexed	13	53	72	25.2	52		
	48	Carboplatin, pemetrexed	None	70	Consol: pemetrexed	16	50	77	21.2	58		
NKI[56]	51	Cisplatin (daily)	Cetuximab	66	None	NS	NS	NS	NS		76	
	51	Cisplatin (daily)	None	66	None	NS	NS	NS	NS		72	

Salama et al , JCO 2013

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Guidelines on chemoradiotherapy management of locally advanced non-small cell lung cancer (NSCLC)

Source	Format and process	Publication date	Recommendations	References	Level of evidence
American Society of Clinical Oncology [8]	Guideline. Literature review by expert panel	2004	Chemoradiation better than radiation alone. Consensus on two to four cycles of chemotherapy. No statement with respect to concurrent versus sequential timing of radiation.	[9,10]	Not graded
International Association for the Study of Lung Cancer [11]	Consensus report — expert opinion. No formal systematic process	2003	Chemoradiotherapy as standard of care. Two to three cycles of chemotherapy. Concurrent radiotherapy recommended, but can be at cycle 1 or later — evidence uncertain	None listed	Not graded
Australian National Health and Medical Research Council practice guidelines [14]	Guideline. Formal process of review and development	2004	Concurrent chemoradiation with cisplatin for NSCLC better than if treatment given sequentially	[9,15]	Level 2
England and Wales National Institute for Health and Clinical Excellence guidelines [16]	Guideline. Formal process of review and development	2005	Sequential chemoradiation better than radiotherapy alone. Evidence for concurrent therapy suggestive of benefit, but mature data awaited.	[5,7]	Level 1+
Scottish Intercollegiate Guidelines Network [17]	Guideline. Formal process of review and development	2005	Chemoradiation better than radiotherapy alone at standard fractionation, but issue of sequential vs concurrent radiotherapy unresolved — needs further research	[6,7]	Level 1++
Cancer Care Ontario Practice Guidelines [12]	Guideline. Literature review, formal systematic process and wide review	2006	Chemoradiation better than radiotherapy alone. Survival advantage to concurrent over sequential treatment, but with increased toxicity. Sequential treatment recommended if borderline fit.	[5,9,13]	Not graded
American College of Chest Physicians treatment of NSCLC IIIA and IIIB [18]	Guideline. Literature review. Standardised process for recommendations	2007	Concurrent chemoradiation recommended for good performance status patients	[9,10,13]	Level 1A

Rourke, Clinical Oncology, 2012

Chemoradiation lung- Tips

1. •Ensure a negative met work up
2. • Each patient has unique comorbidities
3. •All IIIA's and IIIB's not the same
4. • Borderline c… e simul… if cr… …isfactory

V20, V5, Mean lung dose…. …k out

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RT Dose escalation in chemoradiation?

- RTOG 0617 – Randomised study to see the role of dose escalation and cetuximab
- Newly diagnosed stage III NSCLC, ECOG 0-1 PS
- Nov 2007-June 2011, 464 pts accrued
- OS at 12 m 81% (60 Gy arm) vs 74% (74 Gy arm) (p=0.02)
- Median survival - 21.7 m (60 Gy arm) vs 20.7 m (74Gy arm), Toxicity nearly similar in both arms
- *To look for : Possible benefit of cetuximab once data matures*

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Altered fractionation strategies

- Hyperfractionation (smaller doses per fraction)
- Acceleration (reduced treatment time)
- CHART (smaller doses per fraction+ reduced treatment time)

Altered fractionation strategies

Clinical Oncology 24 (2012) 556–568

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Overview

Stereotactic Conformal Radiotherapy in Non-small Cell Lung Cancer — An Overview

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Received 2 August 2011; received in revised form 7 February 2012; accepted 27 March 2012

Abstract

Stereotactic conformal radiotherapy is an established technique in treating cranial lesions and has made significant inroads in the treatment of extracranial sites as well. Early stage non-small cell lung cancer is one such site. This overview assesses the results that have been achieved with stereotactic conformal radiotherapy in non-small cell lung cancer so far and compares its efficacy with surgical and other non-surgical modalities.

Key words: Carcinoma; lung; radiotherapy; stereotactic

- Moderate hypofractionation combined with concurrent chemotherapy tested in phase II studies
  - *(Cho et al, IJROBP 2009, Maguire et al, JCO 2011)*

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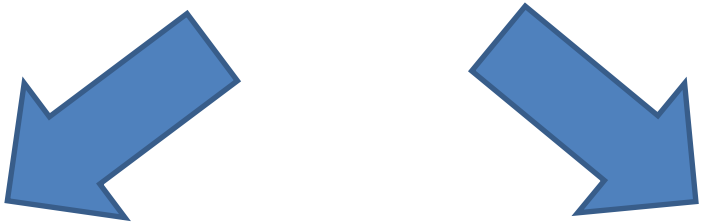
SCLC

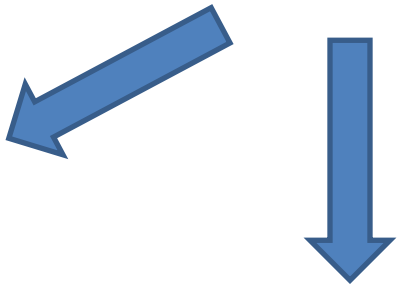


Limited Stage

Extensive disease

Limited stage disease

Options



Upfront Chemoradiation

Neoadjuvant chemotherapy followed by chemoradiation

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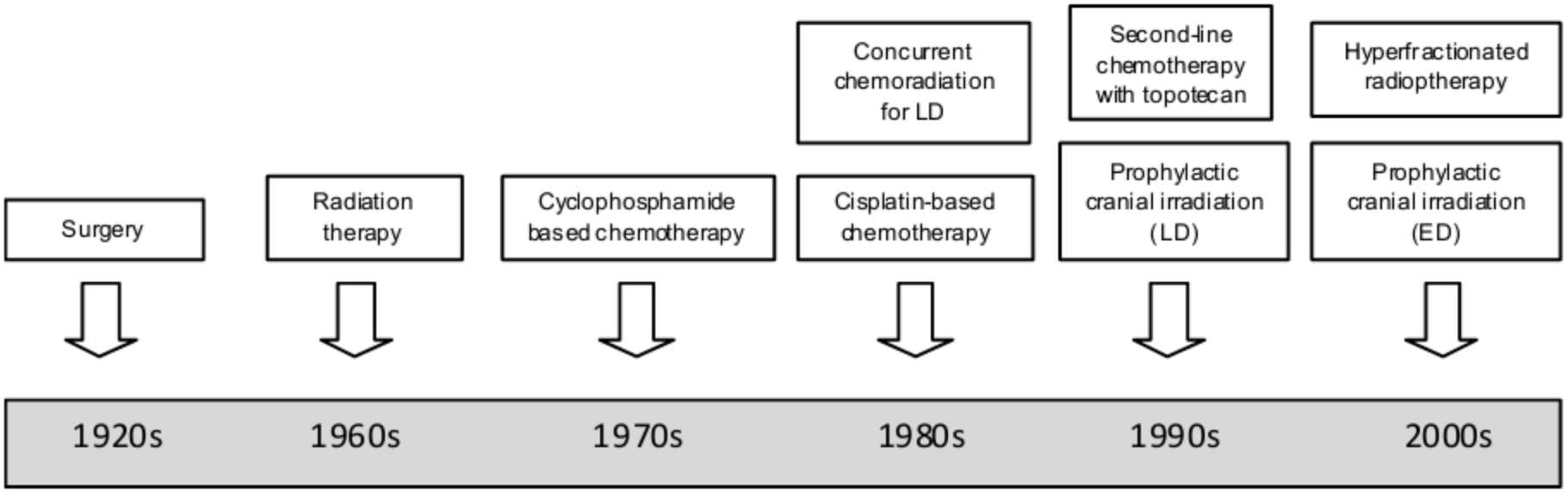
SCLC – Evolution of treatment



Limited stage disease

- Chemoradiation
- Cisplatinum/etoposide most commonly used concurrently
- Doses upto 54 Gray in conventional fractionation
- Altered fraction (hyperfractionation) tested in some randomised trials (suggestion of more benefit at the cost of increased toxicity)

CEV vs EP

Cisplatin and Etoposide Regimen Is Superior to Cyclophosphamide, Epirubicin, and Vincristine Regimen in Small-Cell Lung Cancer: Results From a Randomized Phase III Trial With 5 Years' Follow-Up

By Stein Sundstrøm, Roy M. Bremnes, Stein Kaasa, Ulf Aasebø, Reidulv Hatlevoll, Ragnar Dahle, Nils Boye, Mari Wang, Tor Vigander, Jan Vilsvik, Eva Skovlund, Einar Hannisdal, and Steinar Aamdal for the Norwegian Lung Cancer Study Group

436 eligible patients
Randomized to chemotherapy with EP (n = 218) or CEV (n = 218)

Among LD patients, median survival time was 14.5 months (EP) versus 9.7 months (CEV)

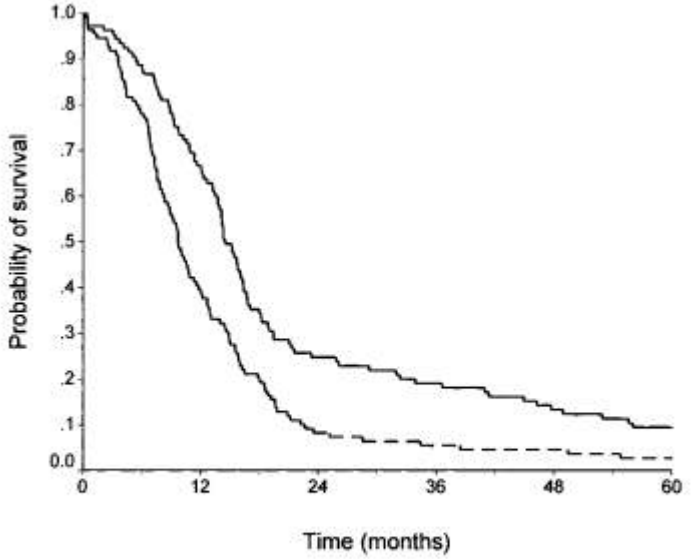


Fig 2. Overall survival of LD-SCLC patients (N = 214) according to treatment arm (P = .0001). CEV (dashed line), n = 109; EP (solid line), n = 105.

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CAV vs EP

- Three randomized trials have compared EP to CAV
  - Fukuoka M, J Natl Cancer Inst 1991;83:855
  - Roth BJ, J Clin Oncol 1992;10:282
  - Sundstrom S, J Clin Oncol 2002;20:4665
- Less myelosuppression occurred with EP
- With radiation, patients experienced less esophagitis and interstitial pneumonitis
- EP overall produced a better median (14.5 vs. 9.7 months) and 5-year (10% vs. 3%) survival for patients with limited disease
- There was no difference in survival between the arms for patients with extensive disease

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Carboplatin- or Cisplatin-Based Chemotherapy in First-Line Treatment of Small-Cell Lung Cancer: The COCIS Meta-Analysis of Individual Patient Data

Table 3. Toxicity

Toxicity	Patients With Toxicity Information	Any Grade						Severe Toxicity (grade ≥ 3)					
		Cisplatin (%)	Carboplatin (%)	Exact OR	95% CI	*P**	*P*† for Homogeneity	Cisplatin (%)	Carboplatin (%)	Exact OR	95% CI	*P**	*P*† for Homogeneity
Leucopenia	655	74	77	1.22	0.81 to 1.88	.357	< .001	34	34	0.96	0.67 to 1.37	.863	< .001
Neutropenia	458	86	90	1.53	0.81 to 2.92	.177	.397	64	73	1.74	1.07 to 2.83	.021	.999
Anemia	512	84	89	1.72	0.99 to 3.03	.049	.046	16	25	1.73	1.12 to 2.89	.011	< .001
Platelets	512	39	71	3.36	2.83 to 6.34	< .001	< .001	14	42	3.78	2.86 to 7.19	< .001	< .001
Nausea/vomiting	655	72	63	0.66	0.47 to 0.93	.013	.012	6	3	0.49	0.21 to 1.11	.066	.999
Stomatitis	655	25	21	0.78	0.52 to 1.17	.239	.065	1	< 1	0.24	0.01 to 3.32	.320	.999
Diarrhea	458	19	22	1.23	0.76 to 2.00	.415	.999	2	2	0.99	0.18 to 5.40	.999	.999
Constipation	239	39	51	1.58	0.92 to 2.73	.091	.999	3	5	1.51	0.35 to 7.48	.749	.999
Neurotoxicity	416	19	7	0.29	0.14 to 0.58	< .001	.243	1	< 1	0.35	0.01 to 7.27	.569	.999
Renal toxicity	415	25	10	0.34	0.19 to 0.61	< .001	.787	1.5	5	0.28	0.01 to 3.78	.351	.540
Toxic deaths	655	—	—	—		—	—	1.9	1.5	0.80	0.19 to 3.18	.769	.101

Abbreviation: OR, odds ratio.
*Exact test stratified by trial.
†Exact test for homogeneity of odds ratios.

- Carboplatin-containing chemotherapy is associated with more myelosuppression
- Patients treated with cisplatin had significantly more nausea/vomiting, neurotoxicity, and renal toxicity.

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Table 1. Select phase II trials of chemotherapy in LS-SCLC

Study	*n*	Chemotherapy	Thoracic radiotherapy		Median survival time (mos)	2-yr OS rate (%)
			Treatment	Start		
Levitan et al. [56]	31	EP + paclitaxel	45 Gy QD	Cycle 1	22.3	47%
Ettinger et al. [59]	53	EP + paclitaxel	45 Gy QD	Cycle 1	24.7	55%
Horn et al. [61]	61	EP + paclitaxel	63 Gy QD	Cycle 3	15.7	24%
Bremnes et al. [62]	39	EP + paclitaxel	42 Gy QD	Cycle 3	21	33%
Bass et al. [53]	37	CbE + paclitaxel	45 Gy QD	Cycle 2	19.5	47%
Woo et al. [57]	44	EP + ifosfamide	40 Gy QD	Cycle 1	22.5	NR
Hanna et al. [60]	53	EP + ifosfamide	45 Gy QD	Cycle 1	15.1	36%
Glisson et al. [58]	67	EP + ifosfamide	45 Gy BID	Cycle 1	23.7	50%
Kubota et al. [63]	30	EP + IP[a]	45 Gy BID	Cycle 1	20.2	41%
Mitsuoka et al. [64]	51	EP + IP[a]	45 Gy BID	Cycle 1	NR	51%
Miller et al. [65]	63	ET + paclitaxel → CbE	70 Gy QD	Cycle 3	20	35%
Le et al. [66]	68	EP + TPZ → EP	61 Gy QD	Cycle 1	21	NR

[a]Patients received concurrent chemoradiotherapy with EP followed by IP.
[b]Patients received two cycles of chemotherapy followed by concurrent chemoradiotherapy with Cb.
[c]Patients received concurrent chemoradiotherapy with EP plus TPZ followed by chemotherapy with EP. Trial was closed early as a result of excess toxicity for TPZ in the head and neck trial.
Abbreviations: BID, twice daily; CbE, carboplatin and etoposide; EP, cisplatin and etoposide; ET, etoposide and topotecan; IP, cisplatin and irinotecan; LS-SCLC, limited-stage small cell lung cancer; NR, not reported; OS, overall survival; QD, daily; TPZ, tirapazamine.

Radiotherapy (CT vs. CT-RT)

A META-ANALYSIS OF THORACIC RADIOTHERAPY FOR SMALL-CELL LUNG CANCER

JEAN-PIERRE PIGNON, M.D., RODRIGO ARRIAGADA, M.D., DANIEL C. IHDE, M.D., DAVID H. JOHNSON, M.D.,

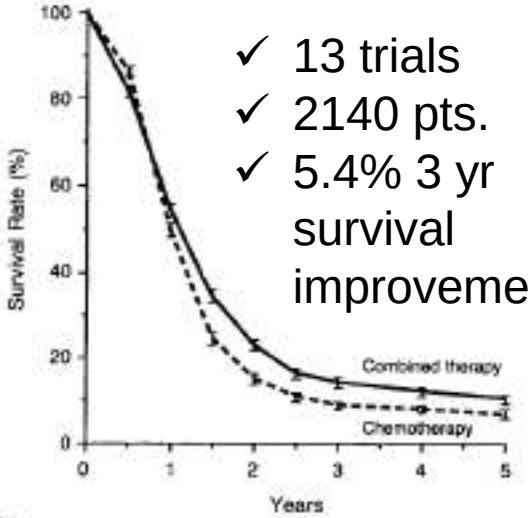
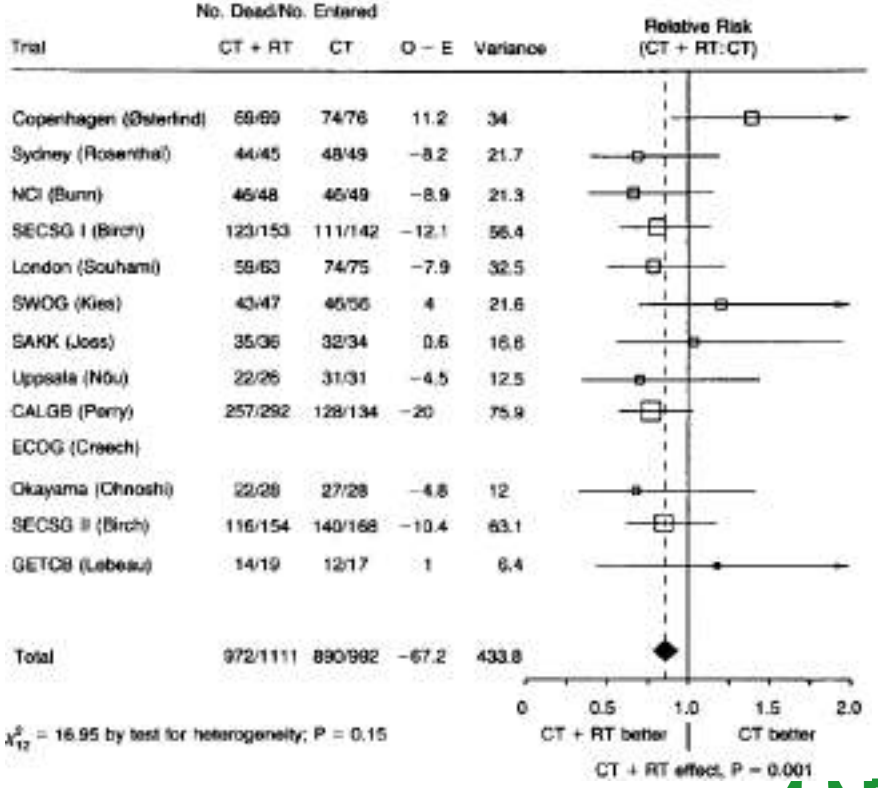


Figure 2. Survival Curves for the Combined-Therapy Group and the Chemotherapy Group.

The three-year survival rates were 14.3±1.1 percent in the combined-therapy group and 8.9±0.9 percent in the chemotherapy group (for a difference of 5.4±1.4 percent; P = 0.001 by stratified log-rank test). Each I bar denotes the standard deviation.

- ✓ 13 trials
- ✓ 2140 pts.
- ✓ 5.4% 3 yr survival improvement



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Radiotherapy (CT vs. CT-RT)

Does thoracic irradiation improve survival and local control in limited-stage small-cellcarcinoma of the lung? A meta-analysis.

Warde P, Payne D. *J Clin Oncol* 1992; 10(6):890-895.

- The risk difference method showed that RT improved 2-year survival by 5.4% (95% CI,1.1%-9.7%).
- Intrathoracic tumor control was improved by 25.3% (95%CI, 16.5%-34.1%)
- This meta-analysis shows a small but significant improvement in survival and a major improvement in tumor control in the thorax inpatients receiving TRT.
- However, this is achieved at the cost of a small increase in treatment-related mortality.

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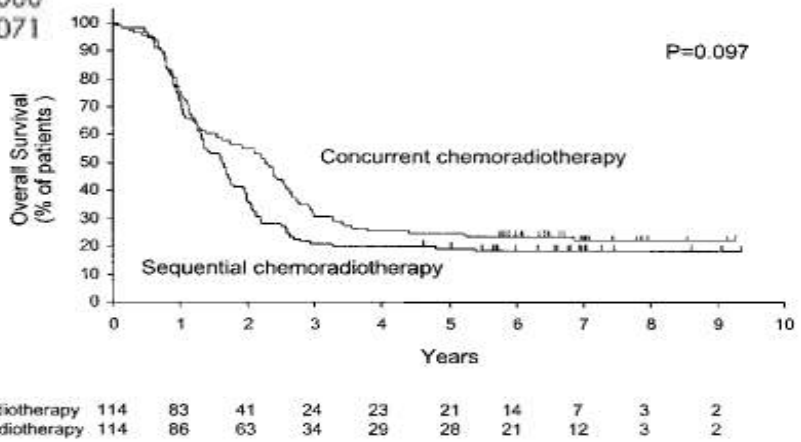
Sequential vs. Concurrent CTRT

Phase III Study of Concurrent Versus Sequential Thoracic Radiotherapy in Combination With Cisplatin and Etoposide for Limited-Stage Small-Cell Lung Cancer: Results of the Japan Clinical Oncology Group Study 9104

By Minoru Takada, Masahiro Fukuoka, Masaaki Kawahara, Takahiko Sugiura, Akira Yokoyama, Soichiro Yokota,

Journal of Clinical Oncology, Vol 20, No 14 (July 15), 2002: pp 3054-3060
DOI: 10.1200/JCO.2002.12.071

- N=231
- 4 cycles P+E with concurrent RT with cycle 1 OR sequential RT after cycle 4
- RT- 45 Gy/3 wks, 1.5 Gy b.i.d



- Underpowered
- tendency for improved survival (median 27 vs. 20 months; p< .10) with concurrent treatment.
- significant increase in Grade 3 or greater leukopenia (85% vs.54%)
- similar rates of Grade 3 esophagitis in both arms

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VOLUME 24 · NUMBER 7 · MARCH 1 2006

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Time Between the First Day of Chemotherapy and the Last Day of Chest Radiation Is the Most Important Predictor of Survival in Limited-Disease Small-Cell Lung Cancer

Dirk De Ruysscher, Madelon Pijls-Johannesma, Søren M. Bentzen, André Minken, Rinus Wanders, Ludy Lutgens, Monique Hochstenbag, Liesbeth Boersma, Bradly Wouters, Guido Lammering, Johan Vansteenkiste, and Philippe Lambin

- The SER (time from start of any intervention to end of RT) was the most important predictor of outcome.
- There was a significantly higher 5-year survival rate in the shorter SER arms (relative risk -0.62; 95% CI, 0.49 to 0.80;P<.0003),which was more than 20% when the SER was less than 30 days (upper bound of 95% CI, 90days).
- A low SER was associated with a higher incidence of severe esophagitis (RR-0.55; 95%,CI, 0.42 to 073;P<.0001).

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Remember!

- PCI to be given in all cases of SCLC (limted stage) after completion of chemoradiation
- PCI also to be given in all responders of extensive stage SCLC
- PCI has been demonstrated to have overall survival benefit in both these scenarios in randomised controlled trials

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Ancient radiotherapy

MODERN RADIOTHERAPY

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Evolution of RT

- Conventional 2 dimensional approaches
- 3DCRT (3 dimensional conformal radiotherapy)
- Intensity modulated radiotherapy(IMRT)
- Image guided radiotherapy (IGRT)
- 4 D treatments

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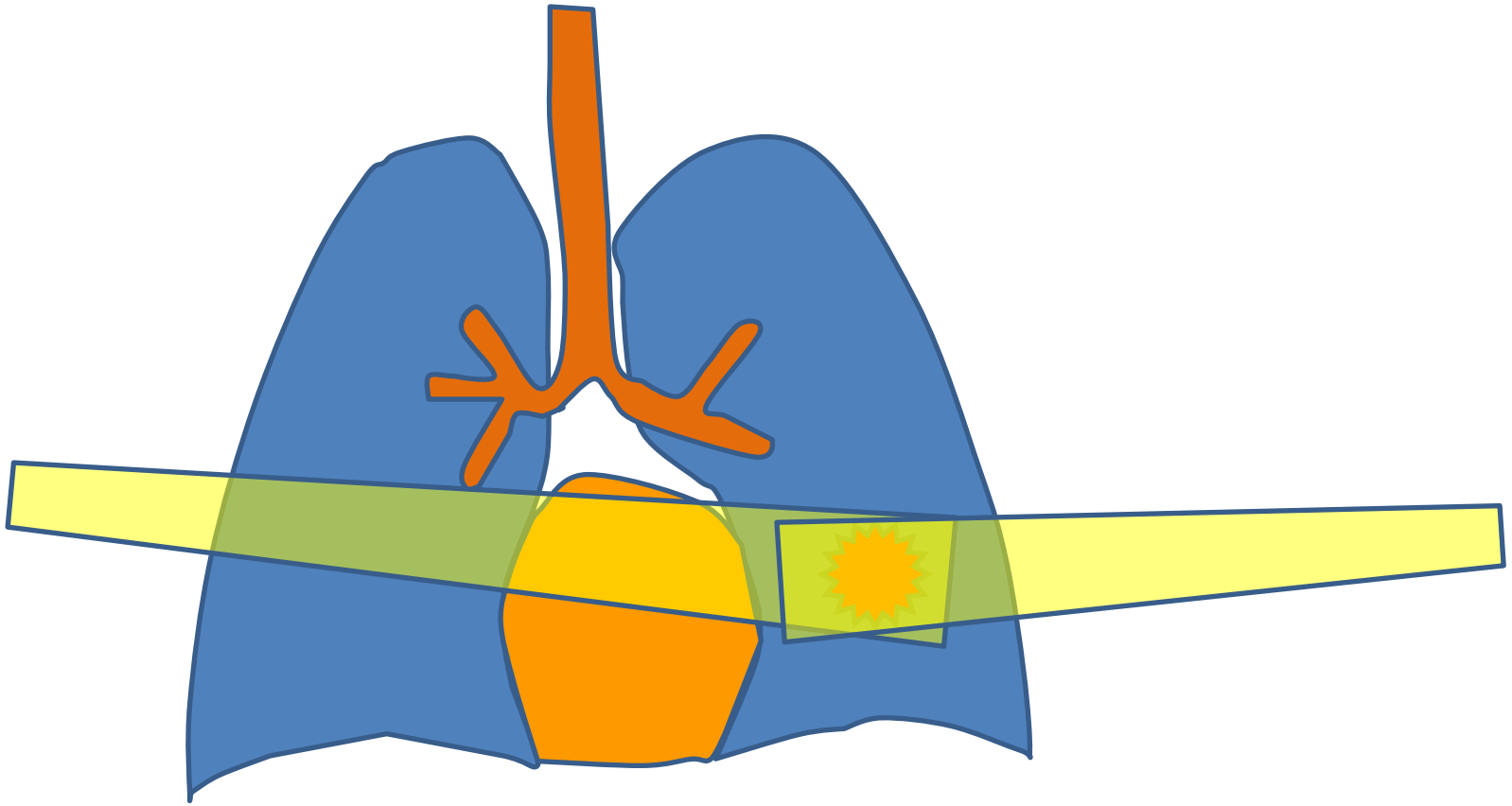
A “Normal” Treatment plan



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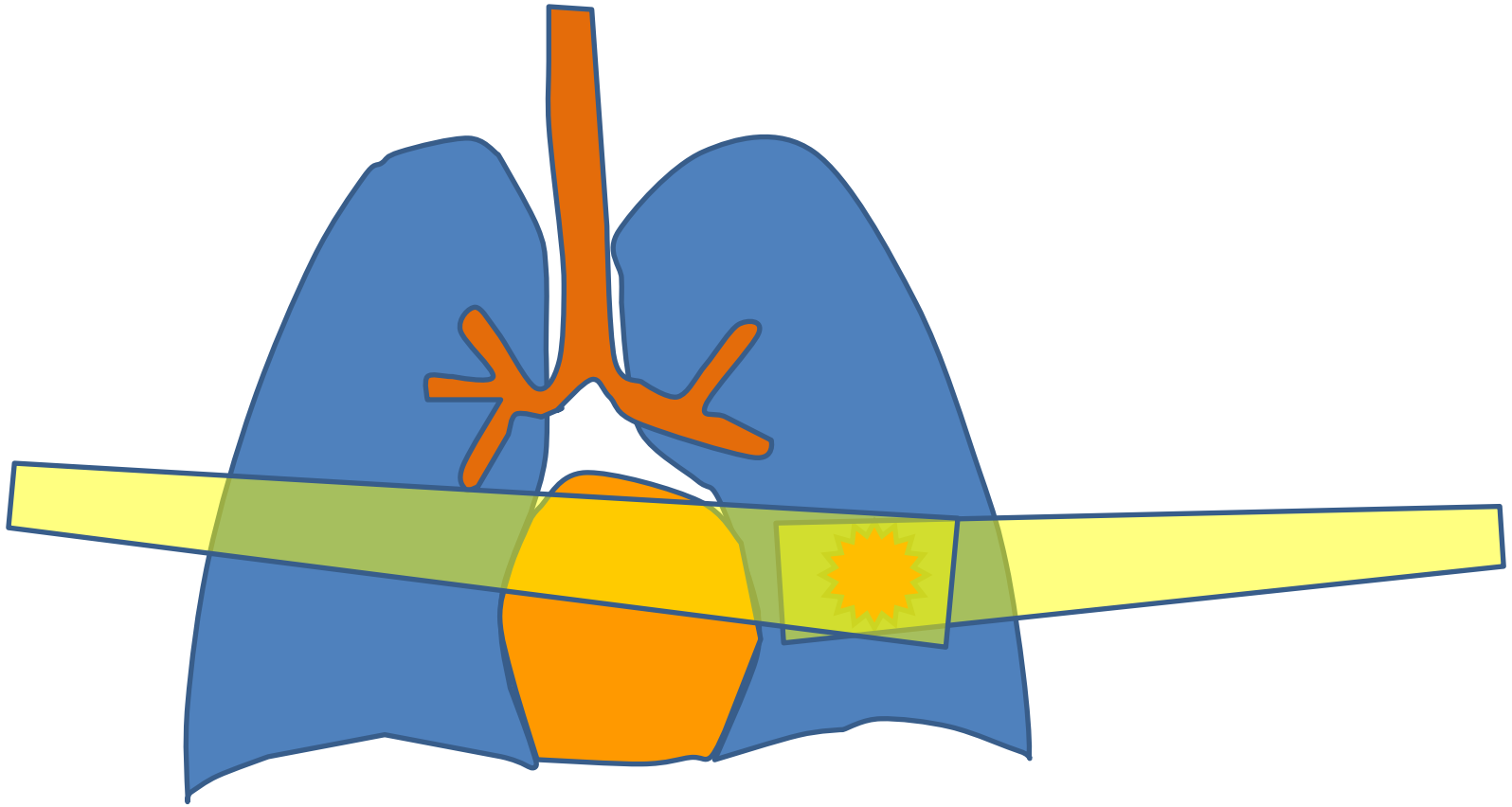
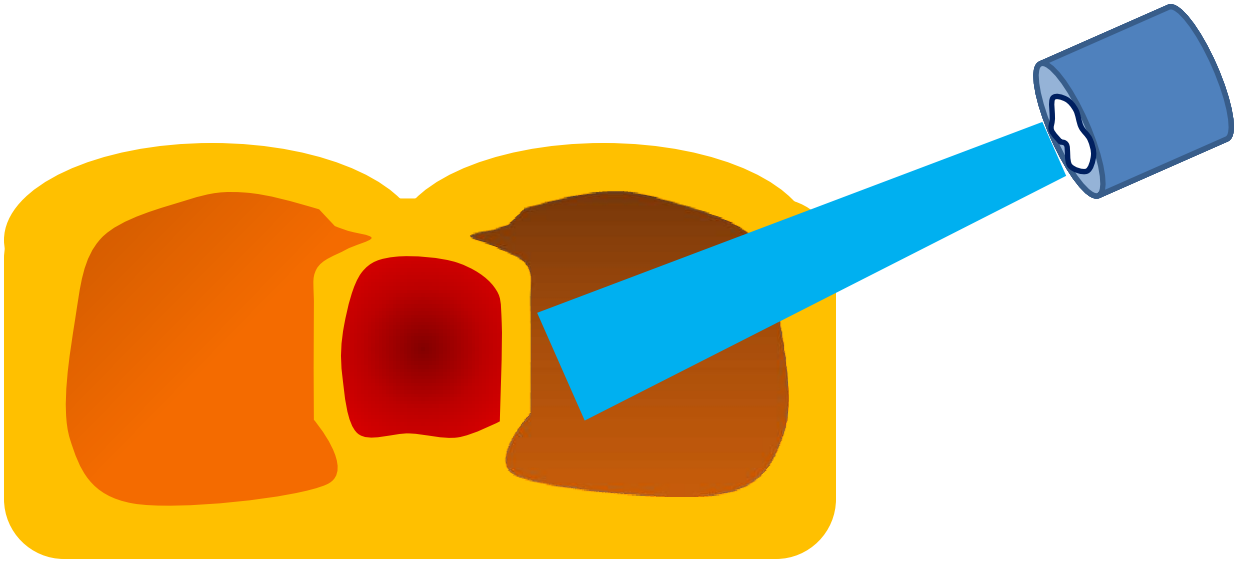
The effect of motion



The principle of Gating



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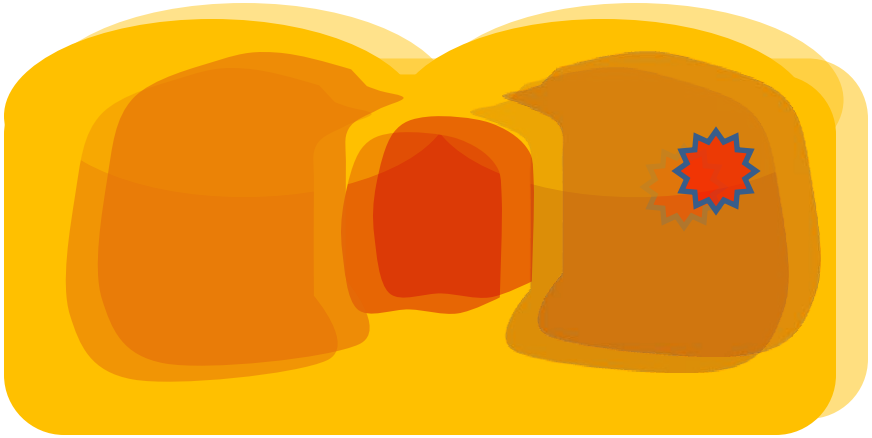
Volumetric matching (Judicious use of IGRT)



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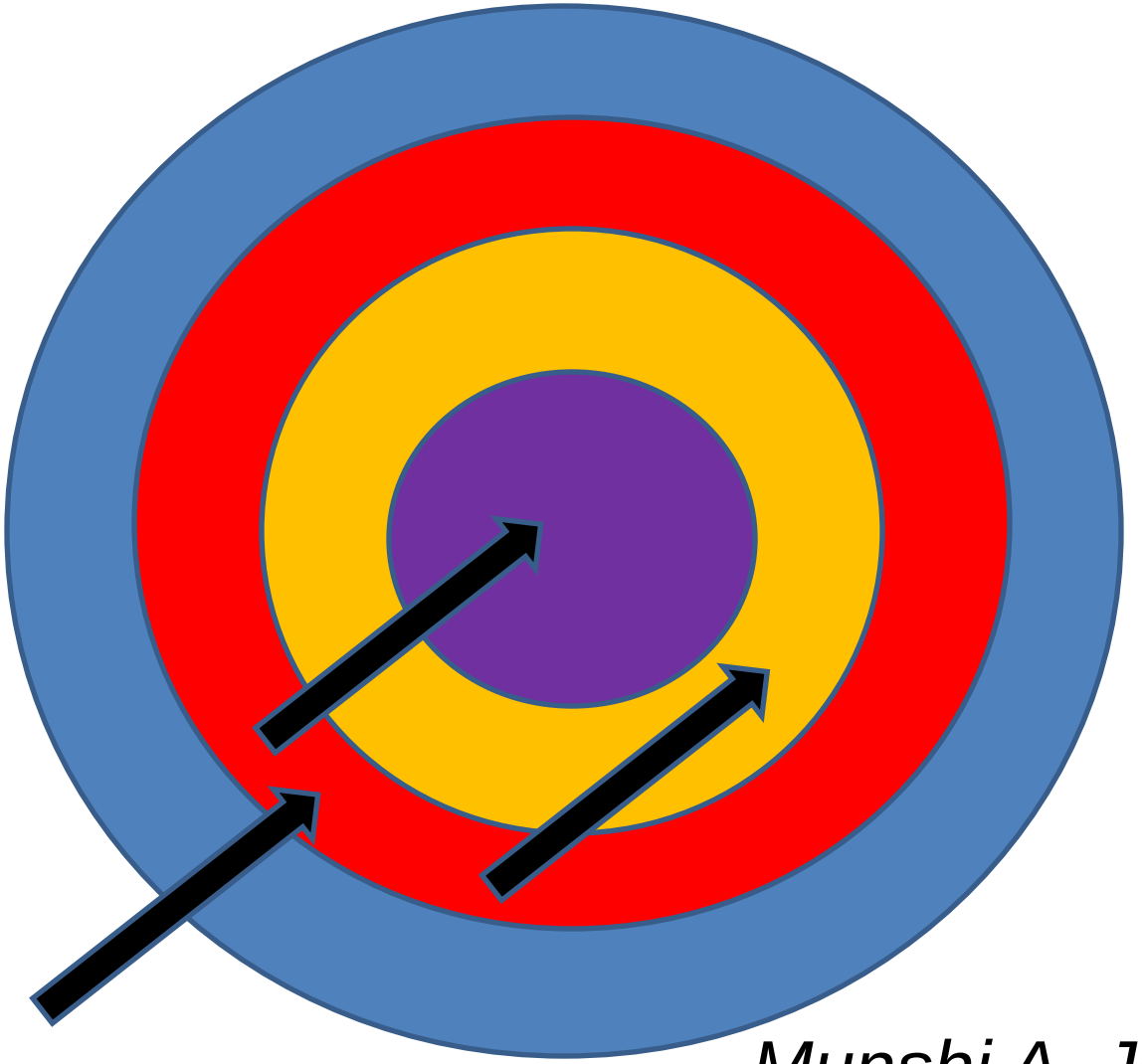
Evolution of Radiation Oncology- Sharp Gun but a blurred target



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Munshi A, JCRT 2010

Chemoradiation lung- Problems

1. Acute and delayed toxicity
2. Pneumonitis
3. Esophagitis
4. Myelosupression
5. Treatment related mortality

Critical questions for chemoradiation

- Should we dose escalate with CTRT
- Can we combine altered fractionation schedules with chemoradiation
- Can SBRT be given after NACT NACTRT in NSCLC
- How can we further reduce the side effects of RT
- What about chemoradiation in elderly/Low PS patients

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Conclusions

- Concurrent CTRT is the gold standard of care in Stage III NSCLC and Limited stage SCLC
- Treatment feasability and compliance is one of the prominent issues
- Largest evidence for cisplat/etoposide and cisplat/vinorelbine (and now pacli/carbo)
- Consolidation chemotherapy after CTRT is under further scrutinty
- Better to identify and exclude very high-risk patients from CTRT

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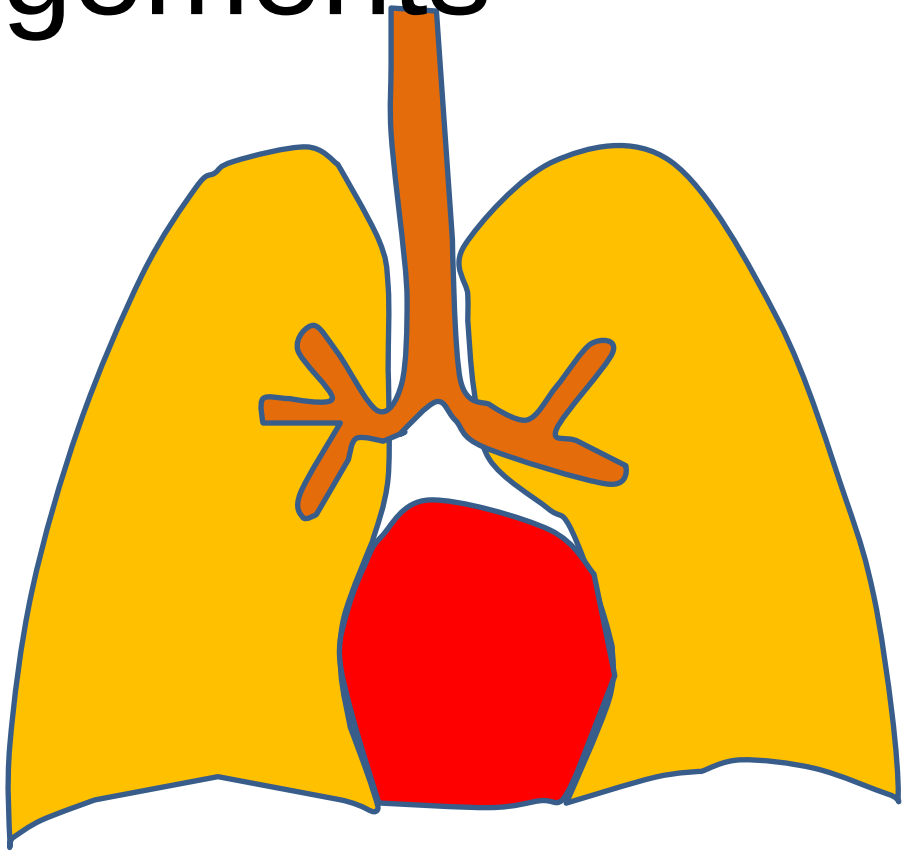
Acknowledgements

- Team Fortis Gurgaon
- The Lung working group at TMH !



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