What Dose is optimal ?
Locally Advanced NSCLC…

Dr P Vijay Anand Reddy

Director

Apollo Cancer Institute, Hyd

TNM STAGING OF LUNG CANCER

Supraclavicular	Scalene(ipsi-/contralateral)	Mediastinal (contralateral)	Mediastinal (ipsilateral)	Subcarinal	Hilar (contralateral)	Hilar (ipsilateral)	Peribronchial (ipsilateral)	LYMPH NODE (N)
+ /	+ /	+			/ +			N3
–	–	–	+ &/ +		–			N2
–	–	–	–	–	–	+ &/ +		N1
–	–	–	–	–	–	–	–	N0

Stage IV
M1 (any T, any N)

Stage III B

Stage III A

Stage II A **Stage II B**

Stage I A **Stage I B** **Stage II B**

M0

Stage 0
(Tis, N0, M0)

METASTASES (M)
M0 : Absent
M1 : Present
Separate metastatic tumor nodule(s) in the ipsilateral nonprimary-tumor lobe(s) of the lung also are classified M1

Tis : Carcinoma *in situ*

Staging is not relevant for Occult Carcinoma (Tx, N0, M0)

* Including direct extension to intrapulmonary nodes
** Including superior sulcus tumor

(& : and) (/ : or) (&/ : and /or)

T1	T2	T3	T4	PRIMARY TUMOR (T)
a&b&c	any of a,b,c,d	(a&c)/b/d	(a&c)/d	Criteria
≤ 3 cm	> 3 cm	any	any	a. Size
No invasion proximal to the lobar bronchus	Main bronchus (≥ 2 cm distal to the carina)	Main bronchus (< 2 cm distal to the carina)	–	b. Endo-bronchial location
surrounded by lung or visceral pleura	Visceral pleura	Chest wall **/ diaphragm/ mediastinal pleura/ parietal pericardium	Mediastinum/ trachea/heart/ great vessels/ esophagus/ vertebral body/ carina	c. Local Invasion
–	Atelectasis/ obstructive pneumonitis that extends to the hilar region but doesn't involve the entire lung	Atelectasis/ obstructive pneumonitis of the entire lung	Malignant pleural/peri-cardial effusion or satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung	d. Other

Locally Advanced NSCLC

- >50% of all lung cancers
- Chemo-radioth[illegible]Chemotherapy
- Po[illegible]al (5yr OS 5-20%)
- [illegible]ismal local control rates
- **Local failure a harbinger for distant metastases and survival***

How to improve the local control ?

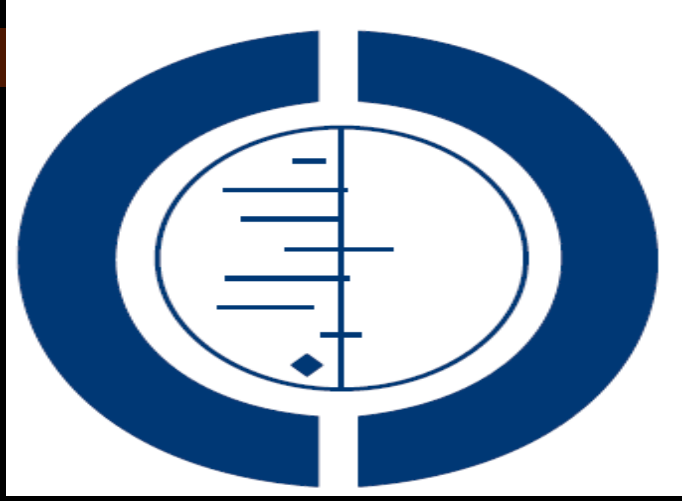
** Malissard L, IJROBP'91; Sibley GS, IJROBP'98*

Radiation Therapy in Stage III NSCLC

Therapeutic Ratio

- **Chemotherapy concurrent**
- **Dose Escalation**
  - Dose escalation - Standard fractionation
  - Altered Fractionation Schedules
  - SBRT
  - Proton Therapy
- **Modern Techniques:**
  3D Conformal RT, IMRT, IGRT, Volumatric Arc etc,

Concurrent Chemoradiotherapy in NSCLC



19 RCTs of concurrent CTRT vs RT alone:

Sig reduction in risk of death (HR.71) &
improvement in PFS (HR .69) with CTRT

6 RCTs of Concurrent vs Sequential Chemo-radiation:

10% abs survival benefit at 2yrs
Increased severe esophagitis in concurrent arm

Concurrent is even more better !

Cochrane Database of Systematic Reviews 2010

Dose Escalation…

- Dose escalation - Standard fractions
- Altered Fractionation - Hyper, Hypo #
- SBRT
- Proton Therapy

Int. J. Radiation Oncology Biol. Phys., Vol. 12, pp. 539–547
Printed in the U.S.A.

0360-3016/86 $3.00 + .00

● *Original Contribution: Clinical*

IMPACT OF TUMOR CONTROL ON SURVIVAL IN CARCINOMA OF THE LUNG TREATED WITH IRRADIATION

CARLOS A. PEREZ, M.D.,[1] MADELINE BAUER, PH.D.,[2] SHARON EDELSTEIN, B.S.,[2]
BRENDA W. GILLESPIE, M.S.,[2] AND ROBERT BIRCH, PH.D.[3]

4000 Vs 5000 vs 6000 cGy

The long-term results in tumor response, intrathoracic tumor control and survival are reported in patients with medically inoperable or unresectable non-oat cell and small cell carcinoma of the lung. In 376 patients with stages T1–3, NO-2 carcinoma of the lung tumors, accessioned to a Radiation Therapy Oncology Group (RTOG) randomized study to evaluate different doses of irradiation, a higher complete response rate (24%), intrathoracic tumor control (67%) and three year survival (15%) was observed with 6000 cGy, compared with lower doses of irradiation (4000 or 5000 cGy). Increased survival was noted in patients with complete tumor response. Three year survival in complete responders was 23%, in partial responders, 10%, and in patients with stable disease, 5%. Patients treated with 6000 cGy had an overall intrathoracic failure rate of 33% at 3 years, compared with 42% for those treated with 5000 cGy, 44% for patients receiving 4000 cGy with split course, and 52% for those treated with 4000 cGy continuous course (p = 0.02). Patients surviving 6 or 12 months exhibited a statistically significant increased

RTOG 7301, 7302

Results
376 patients

	4000 cGy, continuous	4000 cGy, split course	5000 cGy, continuous	6000 cGy, continuous
CR/PR rate	48%		53%	56%
Local rec	58%	53%	49%	35%
3-yr OS rate	10%	10%	10%	15%
5-yr OS rate	6%	6%	6%	6%

Carlos Parez et al, RTOG 7301, IJROBP 1986

Int. J. Radiation Oncology Biol. Phys., Vol. 61, No. 2, pp. 318–328, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.06.260

Dose escalation study based on vol of lung irradiated

CLINICAL INVESTIGATION **Lung**

TOXICITY AND OUTCOME RESULTS OF RTOG 9311: A PHASE I–II DOSE-ESCALATION STUDY USING THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY IN PATIENTS WITH INOPERABLE NON–SMALL-CELL LUNG CARCINOMA

JEFFREY BRADLEY, M.D.,* MARY V. GRAHAM, M.D.,† KATHRYN WINTER, M.S.,‡
JAMES A. PURDY, PH.D.,§ RITSUKO KOMAKI, M.D.,‖ WILSON H. ROA, M.D.,¶ JANICE K. RYU, M.D.,#
WALTER BOSCH, D.SC.,§ AND BAHMAN EMAMI, M.D.**

Purpose: To evaluate prospectively the acute and late morbidities from a multiinstitutional three-dimensional radiotherapy dose-escalation study for inoperable non–small-cell lung cancer.

Methods and Materials: A total of 179 patients were enrolled in a Phase I–II three-dimensional radiotherapy dose-escalation trial. Of the 179 patients, 177 were eligible. The use of concurrent chemotherapy was not allowed. Twenty-five patients received neoadjuvant chemotherapy. Patients were stratified at escalating radiation dose levels depending on the percentage of the total lung volume that received >20 Gy with the treatment plan (V_{20}). Patients with a V_{20} <25% (Group 1) received 70.9 Gy in 33 fractions, 77.4 Gy in 36 fractions, 83.8 Gy in 39 fractions, and 90.3 Gy in 42 fractions, successively. Patients with a V_{20} of 25–36% (Group 2) received doses of 70.9 Gy and 77.4 Gy, successively. The treatment arm for patients with a V_{20} ≥37% (Group 3) closed early secondary to poor accrual (2 patients) and the perception of excessive risk for the development of pneumonitis. Toxicities occurring or persisting beyond 90 days after the start of radiotherapy were scored as late toxicities. The estimated toxicity rates were calculated on the basis of the cumulative incidence method.

RTOG 9311

V 20

“V20”

Percentage of the lung volume which receives radiation doses of 20 Gy or more.
(with subtraction of the vol involved by lung cancer - PTV)

The risk for radiation pneumonitis depends on V20

V20 = 22% risk for radiation pneumonitis is nearly zero.
V 20 = 33% radiation induced pneumonitis is 10 -15%
V20 of 35%, 40% - radiation pneumonitis nearly 50%.

RTOG 9311: Trial Schema
179 pts

Phasel/II

Stage 1-3 unresectable

3DCRT, 2.15Gy fr

Group1
V20Gy<25%:

70.9Gy/33frs to 90.3Gy/42frs

Group2
V20Gy – 25-36%:

70.9Gy/33frs to 77.4Gy/36frs

Group 3:

V20>37%

Closed early

RTOG 9311 : Conclusions

- RT dose was safely escalated using the 3D CRT
- 83.8 Gy for pts with V20 values of <25% Grp I,
- 77.4 Gy for pts with V20 values 25% - 36% Grp 2,
- The 90.3 Gy dose was too toxic (deaths 2 pts)
- Using fraction size of 2.15 Gy.
- Elective nodal failure occurred in <10 pts

Jafrey Badley IJRBP vol 61, No 2, 318-328, 2005

Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 2, pp. 323–329, 1999

0360-3016/99/$–see front matter

ELSEVIER

PII S0360-3016(99)00183-2

To identify the risk factors for developing Rad Pneumonitis

CLINICAL INVESTIGATION **Lung**

CLINICAL DOSE–VOLUME HISTOGRAM ANALYSIS FOR PNEUMONITIS AFTER 3D TREATMENT FOR NON-SMALL CELL LUNG CANCER (NSCLC)

MARY V. GRAHAM, M.D., JAMES A. PURDY, PH.D., BAHMAN EMAMI, M.D., WILLIAM HARMS, B.S., WALTER BOSCH, D.SC., MARY ANN LOCKETT, M.B.A., AND CARLOS A. PEREZ, M.D.

Radiation Oncology Center, Washington University Medical Center, St. Louis, MO

Purpose: To identify a clinically relevant and available parameter upon which to identify non-small cell lung cancer (NSCLC) patients at risk for pneumonitis when treated with three-dimensional (3D) radiation therapy.
Methods and Materials: Between January 1991 and October 1995, 99 patients were treated definitively for inoperable NSCLC. Patients were selected for good performance status (96%) and absence of weight loss (82%). All patients had full 3D treatment planning (including total lung dose–volume histograms [DVHs]) prior to treatment delivery. The total lung DVH parameters were compared with the incidence and grade of pneumonitis after treatment.
Results: Univariate analysis revealed the percent of the total lung volume exceeding 20 Gy (V_{20}), the effective volume (V_{eff}) and the total lung volume mean dose, and location of the tumor primary (upper versus lower lobes) to be statistically significant relative to the development of ≥ Grade 2 pneumonitis. Multivariate analysis revealed the V_{20} to be the single independent predictor of pneumonitis.
Conclusions: The V_{20} from the total lung DVH is a useful parameter easily obtained from most 3D treatment planning systems. The V_{20} may be useful in comparing competing treatment plans to evaluate the risk of pneumonitis for our individual patient treatment and may also be a useful parameter upon which to stratify patients or prospective dose escalation trials.

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 45, No. 2, pp. 323–329, 1999

0360-3016/99/$–see front matter

PII S0360-3016(99)00183-2

CLINICAL INVESTIGATION Lung

CLINICAL DOSE–VOLUME HISTOGRAM ANALYSIS FOR PNEUMONITIS AFTER 3D TREATMENT FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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Radiation Oncology Center, Washington University Medical Center, St. Louis, MO

Factors influencing the Rad. pneumonitis

- Percent of the total Lung vol exceeding 20 Gy (V20)
- The total lung vol mean dose
- The location of the primary tumor (Upper vs Lower)

Were statistically related to Grd II pneumonitis

Multivariate analysis : V20 the single most independent predictor of pneumonitis

RTOG 0617/NCCTG N0628/CALGB 30609/ECOG R0617

A RANDOMIZED PHASE III COMPARISON OF STANDARD- DOSE (60 Gy) VERSUS HIGH-DOSE (74 Gy) CONFORMAL RADIOTHERAPY WITH CONCURRENT AND CONSOLIDATION CARBOPLATIN/PACLITAXEL +/- CETUXIMAB (IND #103444) IN PATIENTS WITH STAGE IIIA/IIIB NON-SMALL CELL LUNG CANCER

60 Gy vs 74 Gy

STRATIFY		RANDOMIZE	Concurrent Treatment	Consolidation Treatment
			Arm A Concurrent chemotherapy: → Carboplatin & Paclitaxel RT to 60 Gy, 5 x per week for 6 weeks	**Arm A** Consolidation chemotherapy: Carboplatin & Paclitaxel
	RT Technique 1. 3D-CRT 2. IMRT		**Arm B: Closed 6/17/11** Concurrent chemotherapy: → Carboplatin & Paclitaxel RT to 74 Gy, 5 x per week for 7.5 weeks	**Arm B: Closed 6/17/11** Consolidation chemotherapy: Carboplatin & Paclitaxel
	Zubrod 1. 0 2. 1			
	PET Staging 1. No 2. Yes		**Arm C** Cetuximab Loading Dose: → Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 60 Gy, 5 x per week for 6 weeks	**Arm C** Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel
	Histology 1. Squamous 2. Non-Squamous			
			Arm D: Closed 6/17/11 Cetuximab Loading Dose: → Week 1, Day 1 then Concurrent chemotherapy, Carboplatin & Paclitaxel, and Cetuximab RT to 74 Gy, 5 x per week for 7.5 weeks	**Arm D: Closed 6/17/11** Consolidation therapy: Cetuximab and Carboplatin & Paclitaxel

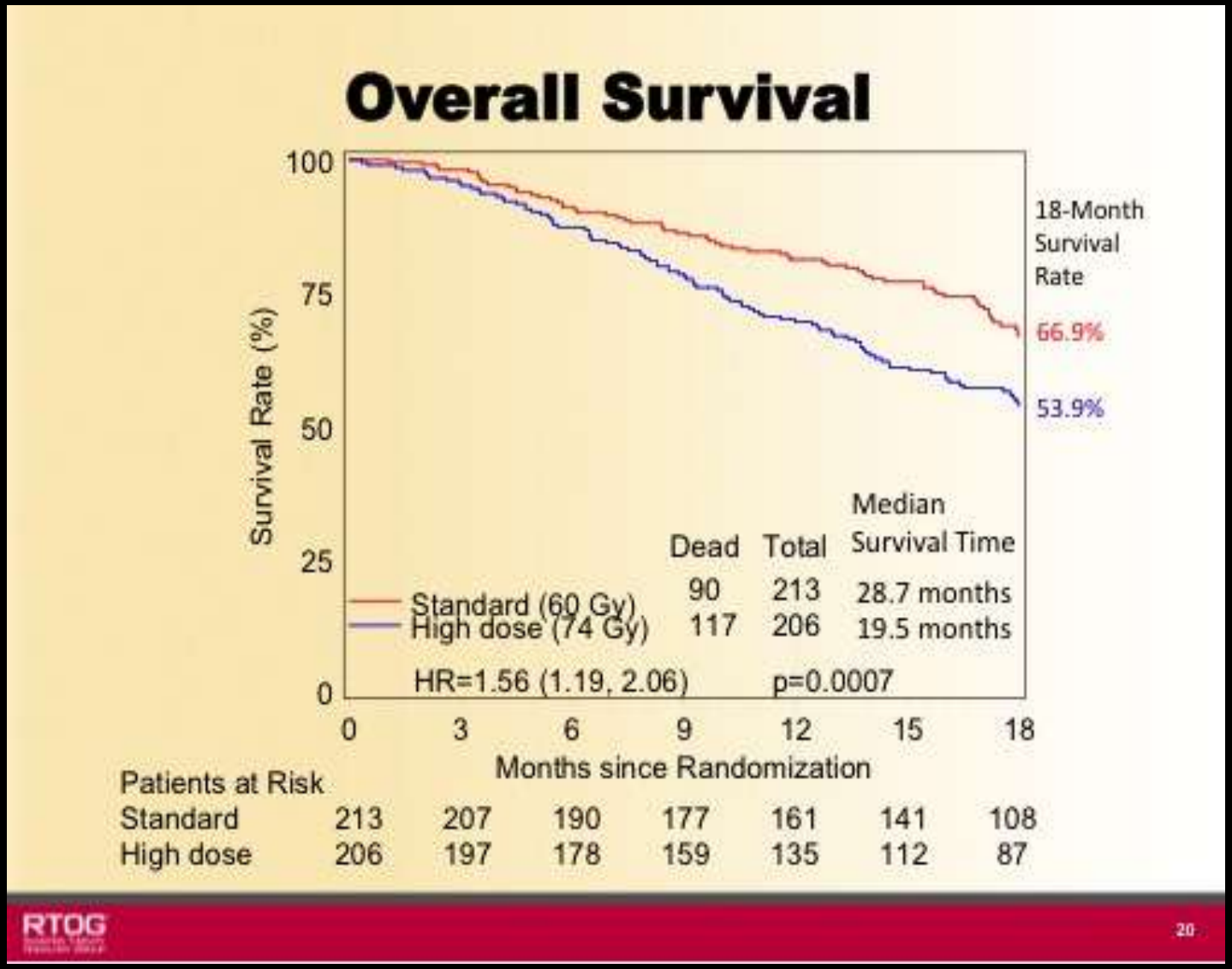
RTOG 0617: *Interim Analysis*

419 patients

Outcome	Standard Dose (60 Gy)	High Dose (74 Gy)
Med surv, months	28.7	19.5
Estimated 18-mo OS%	66.9	53.9
Local rec rates, %	25.1	34.3
Distant rec rates, %	35.3	44.0
Treatment-related deaths, n	2	10

Proc ASTRO 2011

RTOG 0617 60 Gy vs 74 Gy



RTOG 0617: 60 Gy vs 74 Gy

- Higher radiation dose is not superior to standard dose
- Outcomes better with standard dose
- High dose arms closed for further accrual

Proc ASTRO 2011

RTOG 0617:

Patient Reported QOL Outcomes

Meaningful decline in QOL

- 3mths after starting treatment in high dose arm
- Persistent decline in QOL at one year follow-up

Proc ASTRO, Sep 2013

Altered Fractionation…

- *Hyper fractionation*
- *CHART*
- *Hypofractionation*

A Randomized Phase I/II Trial of Hyperfractionated Radiation Therapy With Total Doses of 60.0 Gy to 79.2 Gy: Possible Survival Benefit With ≥ 69.6 Gy in Favorable Patients With Radiation Therapy Oncology Group Stage III Non–Small-Cell Lung Carcinoma: Report of Radiation Therapy Oncology Group 83-11

Dose escalation by hyperfrationation – RTOG 83-11

By James D. Cox, Nozar Azarnia, Roger W. Byhardt, Kyu H. Shin, Bahman Emami, and Thomas F. Pajak

A phase I_{late}/II trial of hyperfractionated (HFX) radiation therapy for non–small-cell carcinoma of the lung (NSCCL) was conducted by the Radiation Therapy Oncology Group (RTOG) between 1983 and 1987. Fractions of 1.2 Gy were administered twice daily with ≥ 4 hours between fractions. Patients were randomized to receive minimum total doses of 60.0, 64.8, and 69.6 Gy. After acceptable risks of acute and late effects were found, 74.4 Gy and 79.2 Gy arms were added, and the lowest total dose arms were closed. No significant differences in the risks of acute or late effects in normal tissues were found among the 848 patients analyzed in the five arms; risks of severe or life-threatening pneumonitis were 2.6% for 60.0 to 64.8 Gy, 5.7% for 69.6 to 74.4 Gy, and 8.1% for 79.2 Gy. Among 350 patients who had the same criteria as Cancer and Leukemia Group B (CALGB) protocol 84-33 (American Joint Committee on Cancer Staging [AJCCS], 1984, stage III; Karnofsky performance status [KPS] 70 to 100; < 6% weight loss), there was a dose response for survival: survival with 69.6 Gy (median, 13.0 months; 2 years, 29%) was significantly ($P = .02$) better than the lower total doses. There were no differences in survival among the three highest total-dose arms. Comparisons with results in similar patients treated with 60 Gy in 30 fractions of 2.0 Gy 5 days per week for 6 weeks suggest benefit from HFX radiation therapy with 69.6 Gy. Improvement in survival with HFX radiation therapy at 69.6 Gy total dose without increase in normal tissue effects, justifies phase III comparison with standard fractionation alone and combined with systemic chemotherapy in this common presentation of NSCCL.

J Clin Oncol 8:1543-1555.

RTOG 83-11… Hyperfractionation trial

- 848 pts,
- Locally advanced unresectable.
- 1.2Gy BID
- trend toward prolonged survival between 60 Gy and 69.6 Gy
- *No difference beyond!*

  69.9 Gy and 74.4 Gy and 79.2 Gy

James D Cox et al, JCO - 8, 1543-1555

Hyper # vs CT + RT

Final Results of Phase III Trial in Regionally Advanced Unresectable Non-Small Cell Lung Cancer*

Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group

William Sause, MD, FCCP; Patricia Kolesar; Samuel Taylor IV, MD; David Johnson, MD; Robert Livingston, MD; Ritsuko Komaki, MD; Bahman Emami, MD; Walter Curran, Jr., MD; Roger Byhardt, MD; A. Rashid Dar, MD; and Andrew Turrisi III, MD

RT vs CT RT vs Hyper#

Study objectives: The purpose of this phase III clinical trial was to test whether chemotherapy followed by radiation therapy resulted in superior survival to either hyperfractionated radiation or standard radiation in surgically unresectable non-small cell lung cancer.

Design: Patients were prospectively randomized to 2 months of cisplatin, vinblastine chemotherapy followed by 60 Gy of radiation at 2.0 Gy per fraction or 1.2 Gy per fraction radiation delivered twice daily to a total dose of 69.6 Gy, or 2.0 Gy per fraction of radiation once daily to 60 Gy. Patients were enrolled from January 1989 through January 1992, and followed for a potential minimum period of 5 years.

Setting: This trial was an intergroup National Cancer Institute–funded trial within the Radiation Therapy Oncology Group, the Eastern Cooperative Oncology Group, and the Southwest Oncology Group.

Patients: Patients with surgically unresectable non-small cell lung cancer, clinical stage II, IIIA, and IIIB, were required to have a Karnofsky Performance Status of ≥ 70 and a weight loss of < 5% for 3 months before study entry. Four hundred ninety patients were registered on trial, of which 458 patients were eligible.

Conclusion: Overall survival was statistically superior for the patients receiving chemotherapy and radiation vs the other two arms of the study. The twice-daily radiation therapy arm, although better, was not statistically superior in survival for those patients receiving standard radiation. Median survival for standard radiation was 11.4 months; for chemotherapy and irradiation, 13.2 months; and for hyperfractionated irradiation, 12 months. The respective 5-year survivals were 5% for standard radiation therapy, 8% for chemotherapy followed by radiation therapy, and 6% for hyperfractionated irradiation.

(CHEST 2000; 117:358–364)

Phase III trial Locally advanced NSCLC
RTOG, ECOG & SWOG
448 pts

Three Arms

RT alone 60 Gy

Chemo + RT 60 Gy

Hyperfractionation 69.6 Gy

William Sause et al, Chest 2000, 117, 358-364

RT alone vs CT=>RT vs Hyper

Phase III trial - RTOG, ECOG & SWOG

- Unresectable stg II, IIIA, IIIB, PS > 70
- 458 pts were eligible for analysis
- 1989 to 1992; 5 yrs follow up

60Gy@2Gy;	Cisp + VBN => RT;	Hyper #1.2 Gy BD 69.6Gy

William Sause et al, Chest 2000, 117, 358-364

Phase III trial
RTOG, ECOG & SWOG

	RT alone	CT => RT	Hyper fr 69.6Gy
Median Survival	11.4%	13.2%	12%
Over all survival	5%	8%	6%

William Sause et al, Chest 2000, 117, 358-364

Continuous hyperfractionated accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small-cell lung cancer: a randomised multicentre trial

CHART

*Michele Saunders, Stanley Dische, Ann Barrett, Angela Harvey, Della Gibson, Mahesh Parmar, on behalf of the CHART Steering Committee**

Summary

Background Human tumour cells can proliferate rapidly, and giving radiotherapy in many small fractions may reduce by the addition of cytotoxic chemotherapy, and by hypoxic cell radiosensitisation.

Lancet 1997; **350:** 161–65

ELSEVIER

Radiotherapy and Oncology 52 (1999) 137–148

RADIOTHERAPY & ONCOLOGY
JOURNAL OF THE EUROPEAN SOCIETY FOR THERAPEUTIC RADIOLOGY AND ONCOLOGY

www.elsevier.nl/locate/radonline

Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial

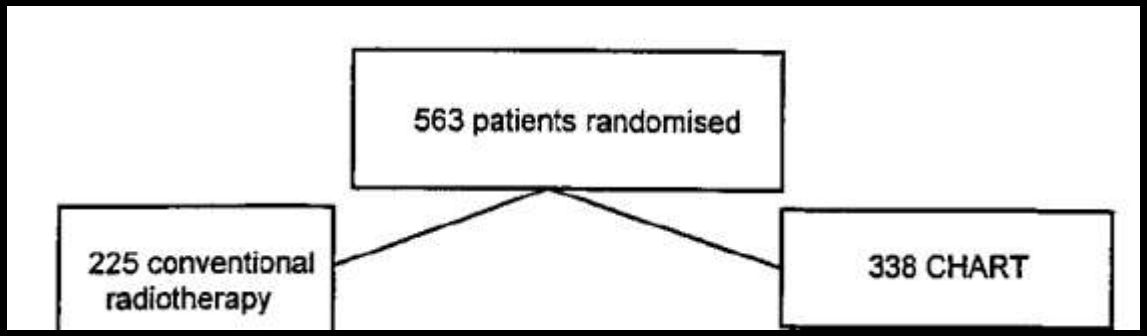
Michele Saunders[a,*], Stanley Dische[a], Ann Barrett[b], Angela Harvey[c], Gareth Griffiths[c], Mahesh Parmar (on behalf of the CHART Steering committee)[c,1]

CHART

Continuous hyper-fractionated accelerated radiotherapy

- Overcome proliferation of tumor cells during conventional RT
- Minimize long-term normal tissue toxicity by the use of multiple small #

563 patients - 13 centres



60 Gy/30# /6 weeks

54 Gy/36# - 1.5 Gy 3 tid daily in 12 consecutive days

Saunders M et al. Radiotherapy and Oncology:1999

CHART

Patient characteristics				
Total patients	CHART (338)		Conventional XRT (225)	
	No.	%	No.	%
Sex				
Male	267	79	166	74
Female	71	21	59	26
Age				
31–40	2	1	1	0
41–50	22	7	13	6
51–60	81	24	56	25
61–70	144	43	99	44
71 +	89	26	56	25
Clinical stage				
IA	22	7	11	5
IB	74	22	56	25
II	25	7	15	7
IIIA	129	38	86	38
IIIB	79	23	52	23
Unknown	9	3	5	2

Saunders M et al. Radiotherapy and Oncology:1999

CHART : Results

Results of statistical analysis of primary endpoints for all patients

Endpoints	2-Year				3-Year					
	Conventional (%)	CHART	Difference	95% C.I.	Conventional	CHART	Difference	95% C.I.	Hazard ratio	95% C.I.
All patients										
Survival	21	30	9	2, 16	13	20	7	2, 13	0.78	0.65–0.94
Local tumour control	16	23	7	1, 15	12	17	5	1, 14	0.86	0.70–1.06
Disease-free interval	13	18	5	−2, 11	9	12	3	−1, 10	0.79	0.63–0.98
Metastasis-free interval	44	48	4	−5, 13	33	40	7	−4, 14	0.89	0.69–1.14

Saunders M et al. Radiotherapy and Oncology:1999

CHART : Morbidity

Early : 3 months

	Conv.	CHART
Clinical RP	19 %	10 %
Radiological RP	65 %	56 %

Late : >6 months

Radiation Pneumonitis

1st 2 yrs - ↑ CHART

After 2 yrs - ↑ Conv.

Dysphagia @ 2 yrs

Conv. - 5 %

CHART – 7 %

Saunders M et al. Radiotherapy and Oncology:1999

Conclusion: This analysis of mature data confirms that CHART is superior to conventional radiotherapy in achieving local tumour control and survival in locally advanced NSCLC. This demonstrates the importance of cellular repopulation as a cause of failure in the radiotherapy of NSCLC. The reduction in the risk of metastasis confirms that improved local tumour control, even in lung cancer, can reduce the incidence of metastasis. This trial shows that control of local tumour can lead to an improvement in long term survival.

CHART is superior to conventional RT in achieving

- Local tumor control and
- Reduction in distant mets and
- Long term Survival

Saunders M et al. Radiotherapy and Oncology:1999

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Dose-Limiting Toxicity After Hypofractionated Dose-Escalated Radiotherapy in Non–Small-Cell Lung Cancer

Donald M. Cannon, Minesh P. Mehta, Jarrod B. Adkison, Deepak Khuntia, Anne M. Traynor, Wolfgang A. Tomé, Richard J. Chappell, Ranjini Tolakanahalli, Pranshu Mohindra, Søren M. Bentzen, and George M. Cannon

- **Prospective phase 1 trial**
- **79 pts NSCLC, all stages**
- **IMRT over 25days, 1fr/day**
- **95% pts with Tomotherapy**

Dose Levels:

57Gy	**@ 2.28Gy fr**
63.2Gy	**@ 2.53Gy fr**
69.25Gy	**@ 2.77Gy fr**
75Gy	**@ 3Gy fr**
80.5Gy	**@ 3.22Gy fr**
85.5Gy	**@ 3.4Gy fr**

Eprint, October 21, 2013

Results

No grade 3 pneumonitis was observed and an MTD for acute toxicity was not identified during patient accrual. However, with a longer follow-up period, grade 4 to 5 toxicity occurred in six patients and was correlated with total dose (P = .004). An MTD was identified at 63.25 Gy in 25 fractions. Late grade 4 to 5 toxicities were attributable to damage to central and perihilar structures and correlated with dose to the proximal bronchial tree.

Conclusion

Although this dose-escalation model limited the rates of clinically significant pneumonitis, dose-limiting toxicity occurred and was dominated by late radiation toxicity involving central and perihilar structures. The identified dose-response for damage to the proximal bronchial tree warrants caution in future dose-intensification protocols, especially when using hypofractionation.

Median f/u 17mths

Median OS 16mths

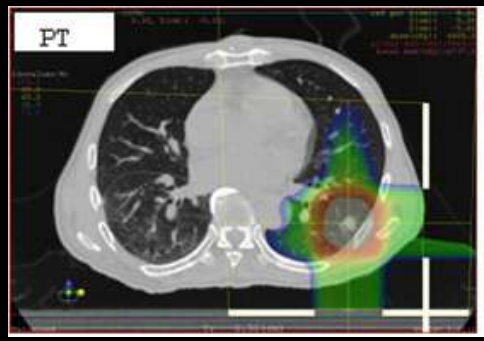
3yr OS 29%

No difference in local control

Median tolerance dose identified as 63.25 in 25 fr @ 253 cGy/fr

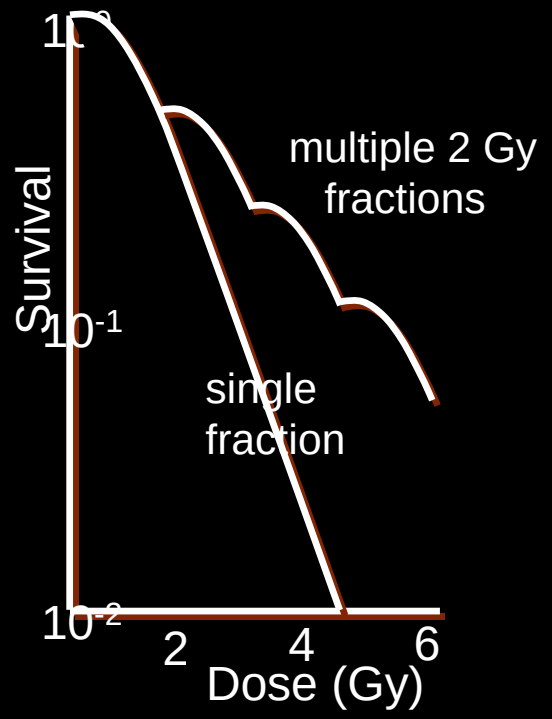
Stereotactic Body Radiation Therapy

- *Stereotactic*
  - precise positioning of the target volume in 3 dimensions.
- High dose per fraction.
- Delivery techniques
  - arcs, static fields, protons
- Technology
  - Novalis TX, Tomotherapy, Cyberknife, Proton



Stereotactic Body Radiotherapy
Radiobiology

- **High ablative dose**
  - **SRS= single Fx SBRT= 2-5 Fx**
  - **Overwhelms repair/repopulation mechanisms**
  - **BED important? (>100)**
- **Short time (1-5 treatments)**
- **Tight targets and rapid dose fall-off**
  - **Damages everything in high dose area**
  - **Critical to limit toxicity**
  - **Need target tracking or gating system**



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Clinical Investigation: Thoracic Cancer

Stereotactic Body Radiation Therapy Can Be Used Safely to Boost Residual Disease in Locally Advanced Non-Small Cell Lung Cancer: A Prospective Study

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Boost by SBRT is feasible
with no increased toxocity (Rad Pneumonitis)

to the residual primary tumor, consisting of 10 Gy × 2 fractions (20 Gy total) for peripheral tumors, and 6.5 Gy × 3 fractions (19.5 Gy total) for medial tumors using the Radiation Therapy Oncology Group protocol 0813 definitions. The primary endpoint was the development of grade ≥3 radiation pneumonitis (RP).

Results: After a median follow-up of 13 months, 4 patients developed acute grade 3 RP, and 1 (2.9%) developed late and persistent grade 3 RP. No patients developed grade 4 or 5 RP. Mean lung dose, V2.5, V5, V10, and V20 values were calculated for the SBRT boost, and none were found to significantly predict for RP. Only advancing age ($P = .0147$), previous smoking status ($P = .0505$), and high CRT mean lung dose ($P = .0295$) were significantly associated with RP development. At the time of analysis, the actuarial local control rate at the primary tumor site was 82.9%, with only 6 patients demonstrating recurrence.

Conclusions: Linear accelerator-based SBRT for dose escalation of limited residual NSCLC after definitive CRT was feasible and did not increase the risk for toxicity above that for standard radiation therapy .

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RADIATION ONCOLOGY

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Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer

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experience of dose escalation using stereotactic body radiosurgery (SBRT) following conventional cCRT for patients with LA-NSCLC.

Methods: Sixteen patients with a median age of 67.5 treated with fractionated SBRT from 2010 to 2012 were retrospectively analyzed. Nine (56%) of the patients had stage IIIB, 6 (38%) has stage IIIA, and 1 (6%) had recurrent disease. Majority of the patients (63%) presented with N2 disease. All patients had a PET CT for treatment planning. Patients received conventional cCRT to a median dose of 50.40 Gy (range 45–60) followed by an SBRT boost with an average dose of 25 Gy (range 20–30) given over 5 fractions.

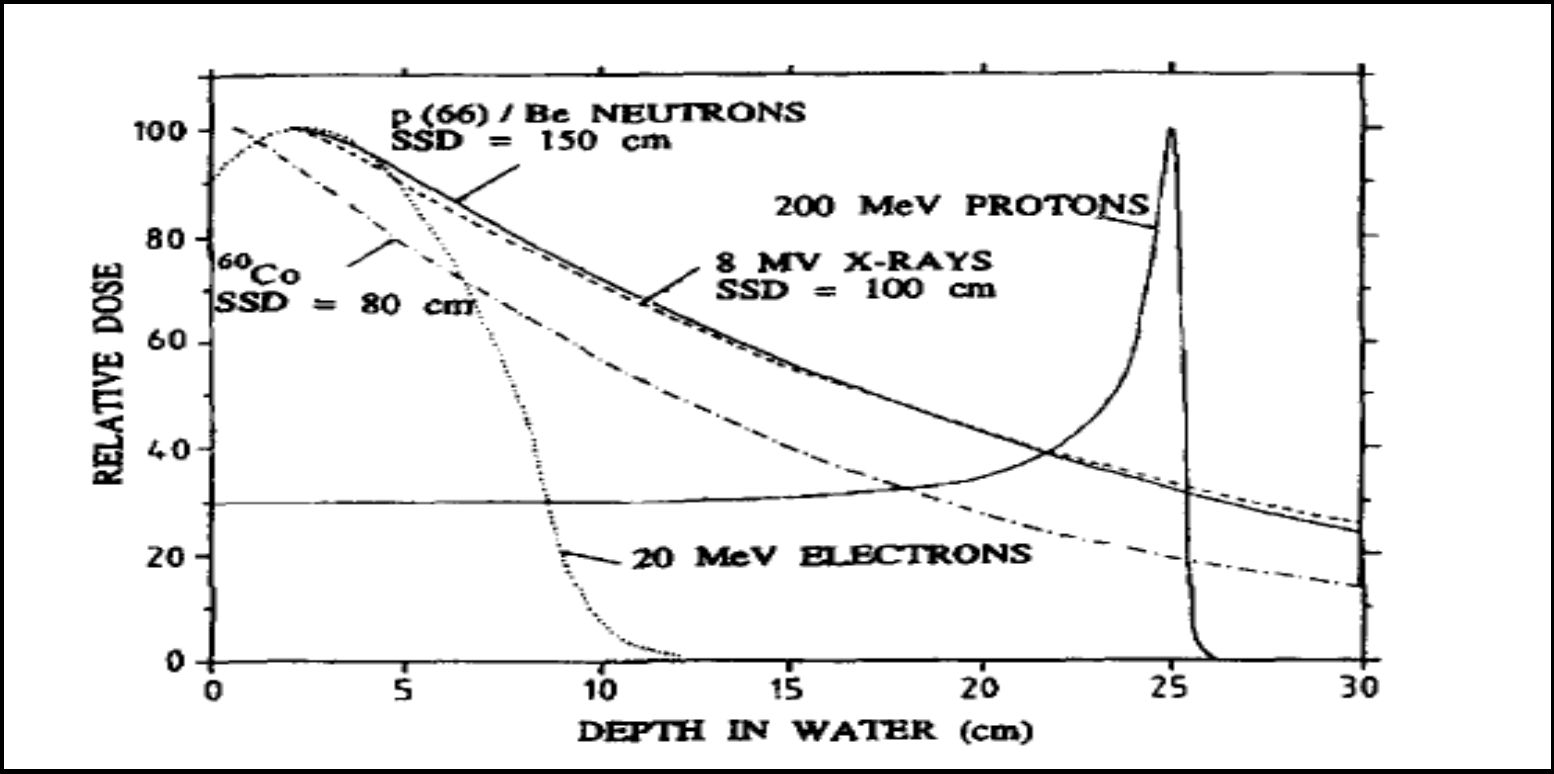
Results: With a median follow-up of 14 months (range, 1–14 months), 1-year overall survival (OS), progression free survival (PFS), local control (LC), regional control (RC), and distant control (DC) rates were, 78%, 42%, 76%, 79%, and 71%, respectively. Median times to disease progression and regional failure were 10 months and 18 months, respectively. On univariate analysis, advanced age and nodal status were worse prognostic factors of PFS ($p < 0.05$). Four patients developed radiation pneumonitis and one developed hemoptysis. Treatment was interrupted in one patient who required hospitalization due to arrhythmias and pneumonia.

Conclusion: Risk adaptive dose escalation with SBRT following external beam radiotherapy is possible and generally tolerated treatment option for patients with LA-NSCLC.

Proton Beam Therapy

Unique depth dose compared to photons, electrons

(Bragg Peak Effect)



Clinical Potential of Proton Therapy:

- Reduced side effects
- Increase tumor control probability through "dose escalation"?
- Facilitate combined modality therapy
- Re-treatment is possible

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PROTON BEAM THERAPY OF STAGE II AND III NON–SMALL-CELL LUNG CANCER

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35 patients, Median age		70.3 yrs
Median Proton dose		78.3 Gy
Local PFS		93.3% @ 1 yr, 65.9 % @ 2yrs
Overall survival		81.8% @ 1 yr, 58.9% @ 2 yrs
Toxicity	Grade I	42.9% Grd II 17.1%

a median observation period of 16.9 months. Four patients (11.4%) developed local recurrence, 13 (37.1%) developed regional recurrence, and 7 (20.0%) developed distant metastases. The progression-free survival rate for Stage II-III patients was 59.6% at 1 year and 29.2% at 2 years. The overall survival rate of Stage II-III patients was 81.8% at 1 year and 58.9% at 2 years. Grade 3 or greater toxicity was not observed. A total of 15 patients (42.9%) developed Grade 1 and 6 (17.1%) Grade 2 toxicity.

Conclusion: PBT for Stage II-III non–small-cell lung cancer without chemotherapy resulted in good local control and low toxicity. PBT has a definite role in the treatment of patients with Stage II-III non–small-cell lung cancer who are unsuitable for surgery or chemotherapy.

Conclusions

Take Home Message

- Dose Escalation appears to be safe, but with strict quality control and accuracy
- What dose?
  - Stnd # : 60Gy/30#,
  - Hyper# : 68.6Gy/1.2Gy BID,
  - ***CHART:*** *54 Gy/36#, 1.5Gy 3 tid 12d*
  - Hypo: 63.25 in 25 fr @ 253 cGy/fr
- Boost by SBRT, Proton is feasible

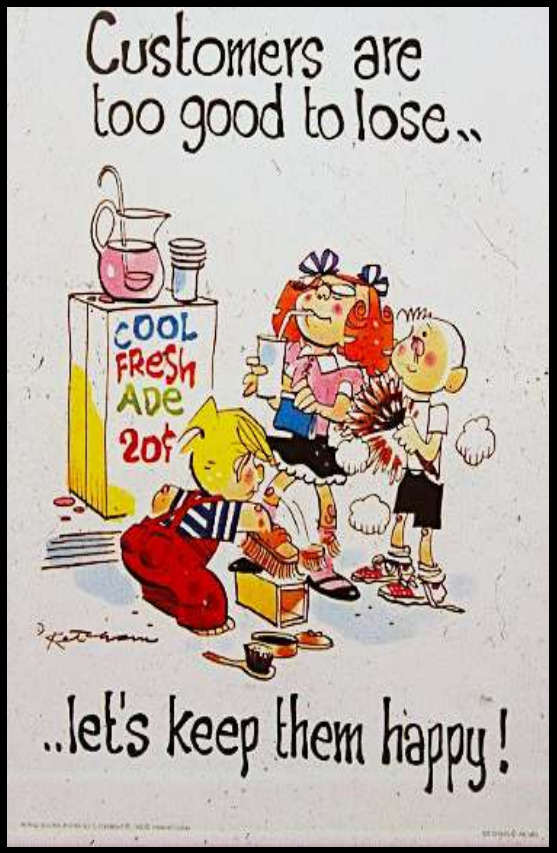
Continued..

Conclusions

Take Home Message

- Further Dose escalation with less toxicity - Whether it is going to improve surv?
- Long term follow-up imperative
- Results of RTOG 0617 surprising! needs to be thoroughly analyzed!
- CTRT more accepted than HF

Way Forward..



To improve outcome with RT

- **Dose intensification**
  - **with modern techniques, altered #, SBRT, Proton**
- **Redefining dose constraints V5, V20?**
- **Integration of CT with RT**
- **Appropriate pt. selection**

Thank you

Dr. P Vijay Anand Reddy

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