Ospedale "S. Giovanni Calibita" Fatebenefratelli

IPOFRAZIONAMENTO E TECNICHE INNOVATIVE

Ipofrazionamento in radioterapia toracica

Andrea Filippi
Dipartimento di Oncologia – Università di Torino

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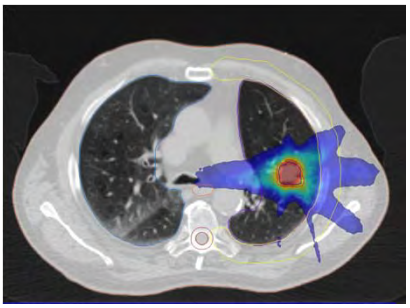
Hypofractionated Stereotactic Ablative Radiotherapy for stage I NSCLC

- Technological advances in treatment planning and delivery provide unique opportunities for improving the precision and, potentially, also the loco-regional effectiveness of RT



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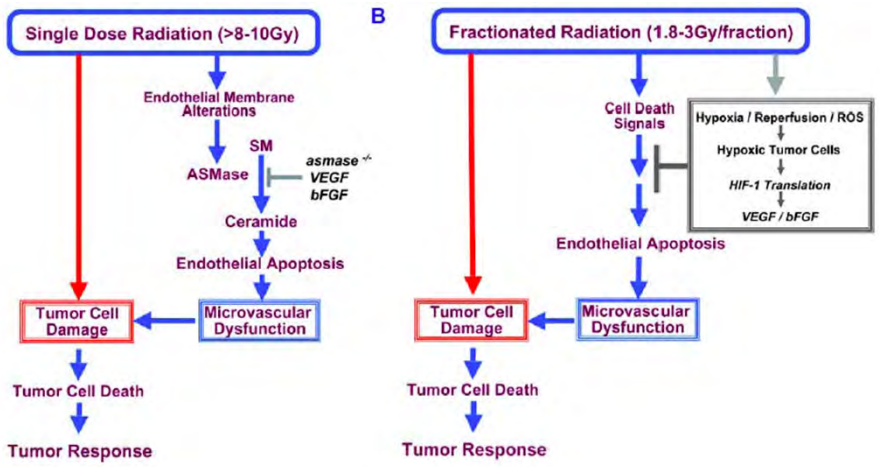
Biological mechanisms of Stereotactic Radio-Ablation



Fuks and Kolesnik, Cancer Cell 2005

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SABR in Stage I NSCLC: phase II studies

DISCOVERY MEDICINE

Table 1. Summary of Results of Recently Reported Prospective Trials of SBRT for Stage I NSCLC

Author (Year)	Type/Stage	No. of Patients	Dose	Median Follow-up	Outcomes
Fakiris (Fakiris et al., 2009)	Phase II/Medically inoperable T1-2N0M0 NSCLC	70	T1: 20 Gy x 3 T2: 22 Gy x 3	50.2 months	3-year LC: 88.1% 3-year OS: 42.7% 3-year CaSS: 81.7%
Baumann (Baumann et al., 2009)	Phase II/Medically inoperable stage I NSCLC	57	15 Gy x 3 to 67%	35 months	3-year LC: 92% 1-, 2-, and 3-year OS: 86%, 65%, and 60% 1-, 2-, and 3-year CaSS: 93%, 88%, and 88% 3-year PFS: 52%
Koto (Koto et al., 2007)	Phase II/Stage I NSCLC	31	15 Gy x 3 (45 Gy) and 7.5 Gy x 8 (60 Gy)	32 months	3-year LC: 77.9% for T1 and 40% for T2 3-year OS: 71.7% 3-year CSS: 83.5%
Ricardi (Ricardi et al., 2010)	Phase II/Stage I NSCLC	62	15 Gy x 3	28 months	3-year LC: 87.8% 3-year CSS: 72.5% 3-year OS: 57.1%
Timmerman (Timmerman et al., 2010)	RTOG Phase II/ Medically inoperable T1-2N0M0 NSCLC (peripherally located)	55	18 Gy x 3	34.4 months	3-year LC: 97.6% 3-year DFS: 48.3% 3-year OS: 55.8%

Abbreviations: LC, local control; OS, overall survival; CSS, cause-specific survival; CaSS, cancer-specific survival; DFS, disease-free survival.

Loo et al, Discovery Medicine 2011

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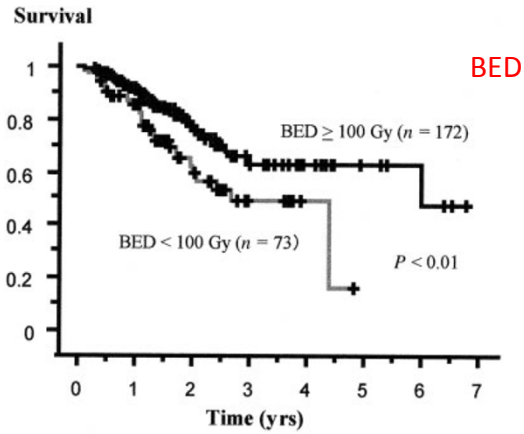
Preliminary data on dose-effect relationship in NSCLC

257 patients who received SBRT for Stage I NSCLC during the period 1995–2004 at 14 institutions in Japan



BED calculation @ isocenter

Onishi et al, Cancer 2004

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Wuerzburg University mono-Institutional study

Table 1a
Crude local control rates and biologic equivalent doses (BED) ($\alpha/\beta=10$) of different irradiation regimes applied in Wuerzburg

Regimen (dose at the PTV margin)	Tumors controlled/tumors treated (local control)	BED (PTV margin) (Gy)	BED (isocenter) (Gy)
4×7 Gy (65%)	1/2 (50%)	47.6	89.5
5×7 Gy (65%)	1/1 (100%)	59.5	111.8
8×6 Gy (80%)	2/3 (67%)	76.8	105
3×10 Gy (65%)	17/24 (71%)	60	117.2
3×12-12.5 Gy (65%)	29/31 (93%)	84.4	168.6
1×26 Gy (80%)	31/31 (100%)	93.6	138

Wulf et al, Radiother Oncol 2005

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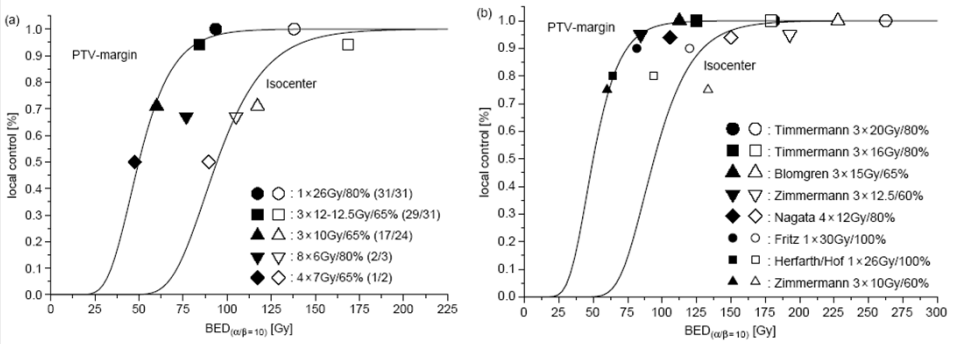
Dose at PTV margin: the only factor associated to LC



Wulf et al, Radiother Oncol 2005

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Meta-analysis of SABR trials in NSCLC: BED appears associated to OS

BED group	Pooled estimate (95% CI)	Corrected estimate (95% CI)			
	2-year OS (18–20, 22, 23, 26, 28, 31, 32, 34–36, 38, 39, 44–47, 49, 51)				
Low	0.618 (0.564–0.673)	0.623 (0.543–0.712)			
Medium	0.740 (0.685–0.795)	0.761 (0.621–0.924)			
Medium to High	0.701 (0.648–0.753)	0.683 (0.611–0.761)			
High	0.581 (0.545–0.616)	0.559 (0.497–0.627)			
Total	0.632 (0.608–0.656)				
	2-year CSS (19, 23, 32, 34, 35, 38, 44, 47, 49, 51)*				
Low	0.806 (0.730–0.882)		0.363	0.736	0.504
Medium	0.858 (0.794–0.922)			0.492	0.731
Medium to High	0.827 (0.773–0.882)				0.588
High	0.841 (0.809–0.873)				
Total	0.837 (0.813–0.863)				
	2-year LCR (18–20, 22, 23, 26, 35, 36, 38, 44, 46, 51)*				
Low	0.942 (0.871–1.000)		0.164	0.874	0.751
Medium	0.874 (0.818–0.930)			0.028	0.031
Medium to High	0.942 (0.901–0.982)				0.453
High	0.928 (0.908–0.947)				
Total	0.923 (0.907–0.940)				

Abbreviations: BED = biologically equivalent dose; CI = confidence interval'; OS = overall survival; CSS = cancer-specific survival; LCR = local control rate.
* Pooled estimates were not corrected.

Zhang et al, IJROBP 2011

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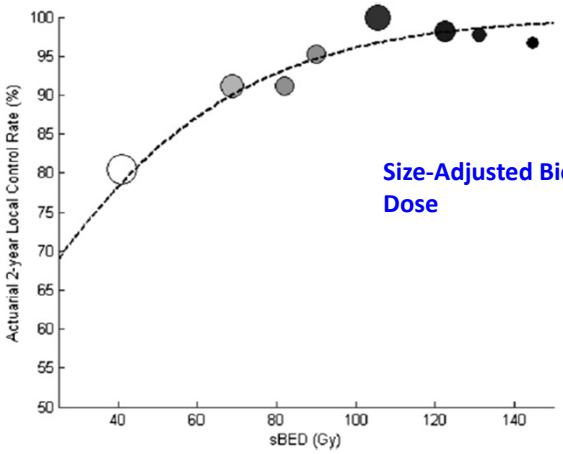
Clinical Investigation: Thoracic Cancer

Modeling Local Control After Hypofractionated Stereotactic Body Radiation Therapy for Stage I Non-Small Cell Lung Cancer: A Report From the Elekta Collaborative Lung Research Group



Size-Adjusted Biologically Effective Dose

Ohri et al, IJROBP 2012

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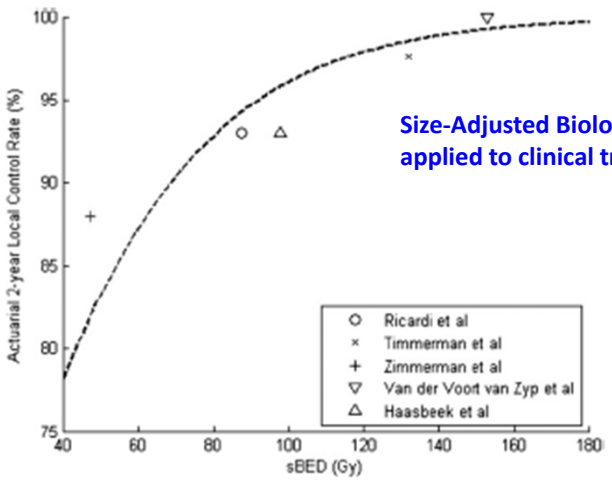

Size-Adjusted Biologically Effective Dose applied to clinical trials

Ohri et al, IJROBP 2012

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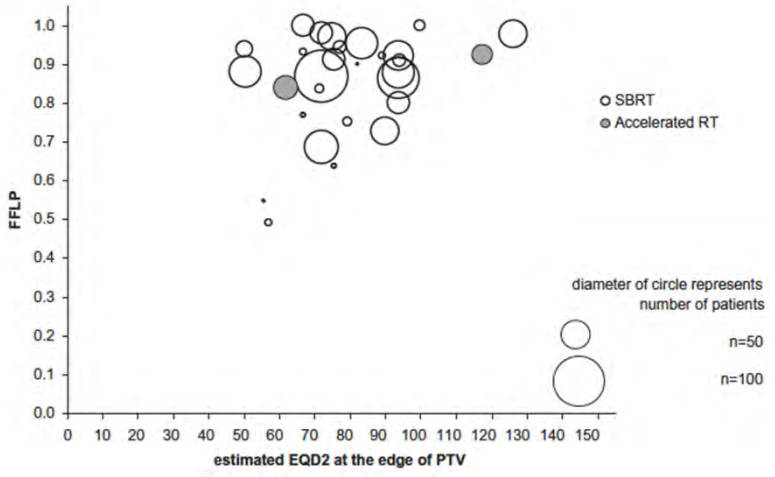
Systematic review of dose-response relationships: absence of correlation between dose and tumor control



Van Baardwijk et al, IJROBP 2012

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Dose-response relationship at medium-high doses is essential for central and large tumors

Institution	Patient population	Prescribed dose (Gy)	Fraction dose (Gy)	BED2 (Gy)	Toxicity
IndianaU.	Stage I NSCLC	60-66	20-22	219-258	11-Fold increase risk of severe-fatal toxicity
Hokkaido U	NSCLC and Mts	48	6	64	1 of 9 with severe toxicity
U. Texas, San Antonio	NSCLC and Mts	36	6-12	86-126	1 of 9 – asymptomatic airway collapse
Air Force General Hospital	Stage I-II NSCLC	60-70 40-50	6-7 4-5	120-167	No severe toxicity
VU Amsterdam	Stage I NSCLC	60	7.5	88	No severe toxicity
Technical U.	NSCLC and Mts	35	7	105	No severe toxicity

Milano et al, Radiother Oncol, 2009

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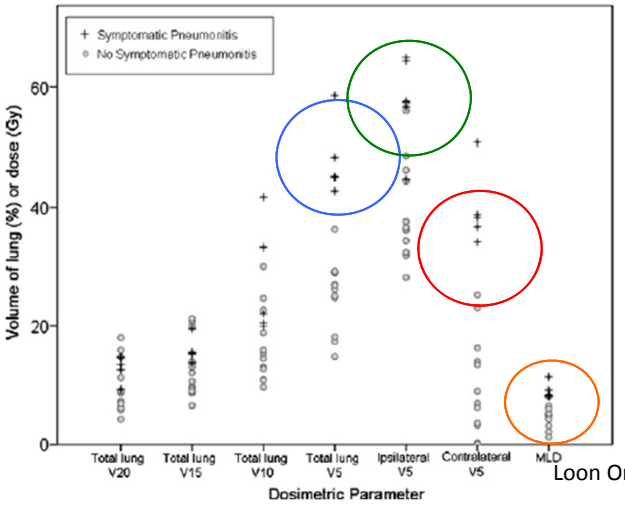
Dose-volume parameters predict toxicity in large tumors



Loon Ong et al, Radiother Oncol 2010

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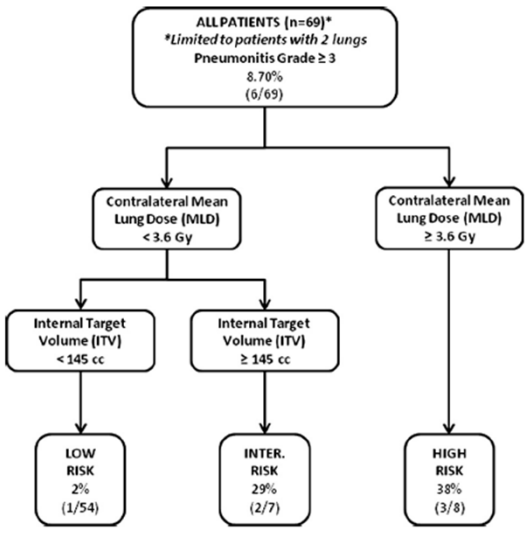
Toxicity is also dependent from contralateral Mean Lung Dose



Bongers et al, Radiother Oncol 2010

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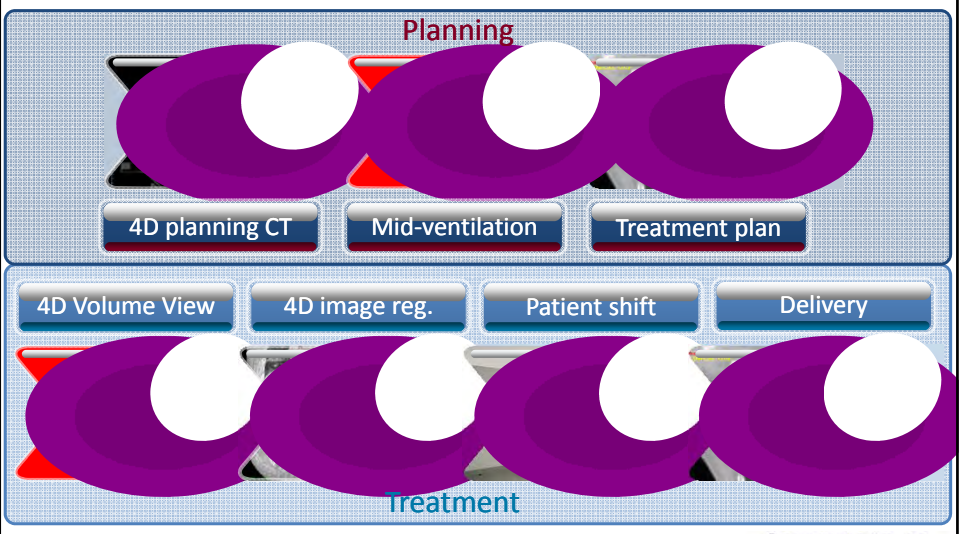
Technical Advances may have an impact on efficacy and toxicity



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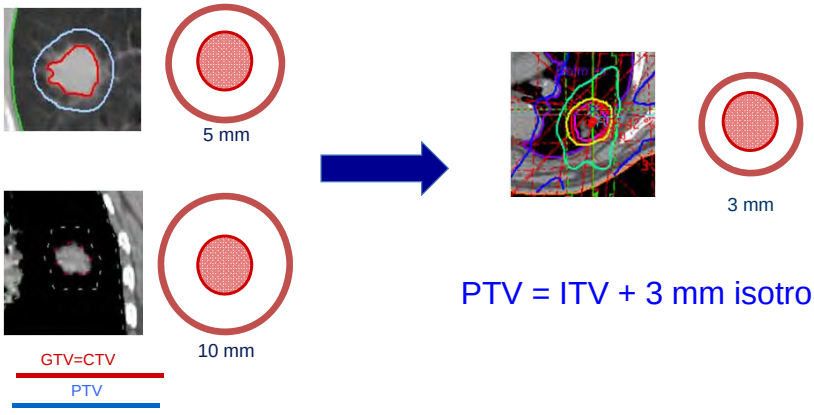
Higher accuracy should translate in less toxicity and better PTV coverage



PTV = ITV + 3 mm isotropic

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Clinical routine: "risk-adapted" SBRT protocol

- **Peripheral lesions (T1a-T1b):**

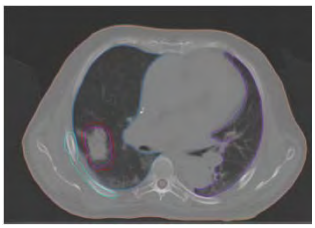
- 45-54 Gy/ 3 fractions

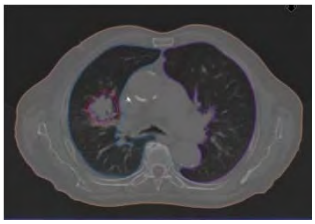
- **Peripheral lesions, with extensive contact with the chest wall, or larger tumors (T2a):**

- 55 Gy/ 5 fractions

- **Central lesions:**

- 60 Gy/ 8 fractions





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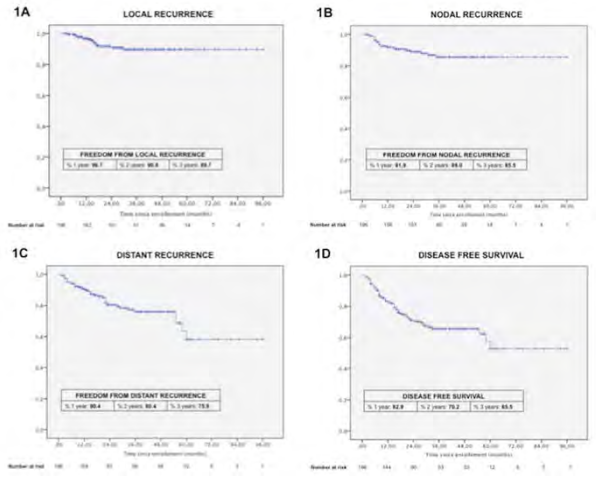
Stereotactic Ablative Radiotherapy for stage I histologically proven non-small cell lung cancer: An Italian multicenter observational study

Umberto Ricardi[a], Giovanni Frezza[b], Andrea Riccardo Filippi[a,*], Serena Badellino[a], Mario Levis[a], Piera Navarria[c], Fabrizio Salvi[b], Michela Marcenaro[d], Marco Trovò[e], Alessia Guarneri[a], Renzo Corvò[d], Marta Scorsetti[c]



Mean BED at PTV edge: 104 Gy

Ricardi et al, Lung Cancer 2014

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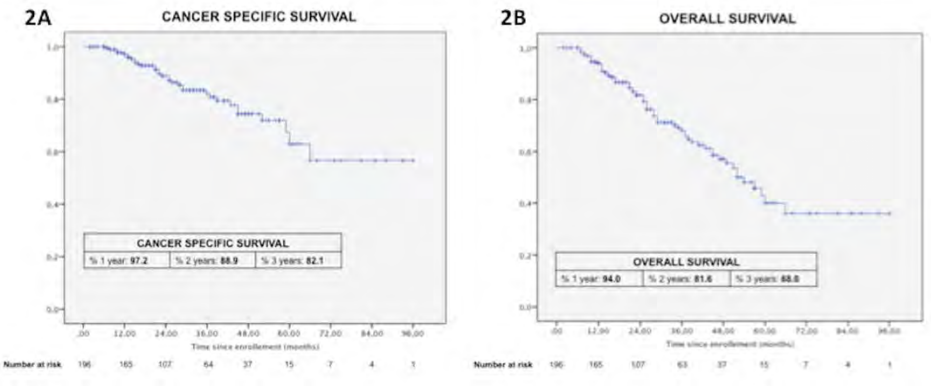

Ricardi et al, Lung Cancer 2014

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SABR in stage I NSCLC: remarks

- Radiation dose matters for local control
- Lower BED may obtain satisfactory control rates
- At moderate-high doses, the impact on survival has not been confirmed
- Design of innovative trials: systemic failures?

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The "too much" heterogeneous Stage III

Box 2
Treatment of stage III NSCLC

Standard therapy

Concurrent chemotherapy plus definitive radiotherapy

Induction chemoradiotherapy followed by surgical resection (selected patients with non-bulky mediastinal lymph nodes who do not require pneumonectomy for adequate resection)

Options in poor-risk patients

Sequential chemotherapy followed by radiotherapy

Radiotherapy alone

Pathologic stage III following surgical resection

Adjuvant chemotherapy: platinum-based, 2-drug regimen × 4 cycles

Consider adjuvant radiotherapy after completion of chemotherapy

Gadgeel SM et al, Radiol Clin N Am 50 (2012) 961–974

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Survival Results in Past 25 Years

Good PS Unresected Stage III NSCLC Survival

Co-op Group Trial	MST	3-Yr Surv
• CALGB 8433 (RT)	9.6 Mo	10%
• CALGB 8433 Seq C-RT	13.7 Mo	24%
• RTOG 9104 Conc C-RT	19.6 Mo	40%
• RTOG 9410 Seq C-RT	14.6 Mo	31%
• RTOG 9410 Con C-RT	17.1 Mo	37%
• SWOG 9504	27.0 Mo	40%
• SWOG 0023	19.0 Mo	35%

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(Un)resectable stage III NSCLC

- At present, concurrent chemotherapy with radiotherapy to a minimal dose of 60 Gy in 30 daily fractions is considered to be the standard treatment
- Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemo-radiation

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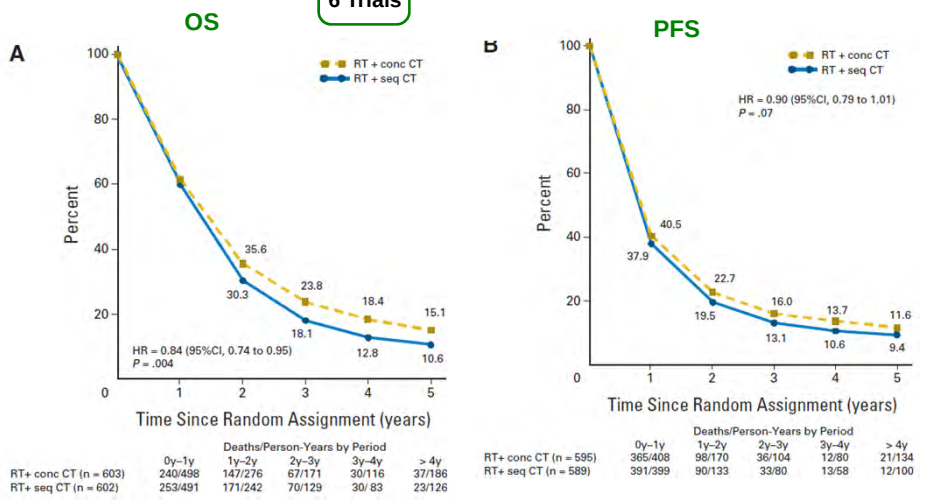
N=1205
6 Trials



Auperin et al, JCO 2010

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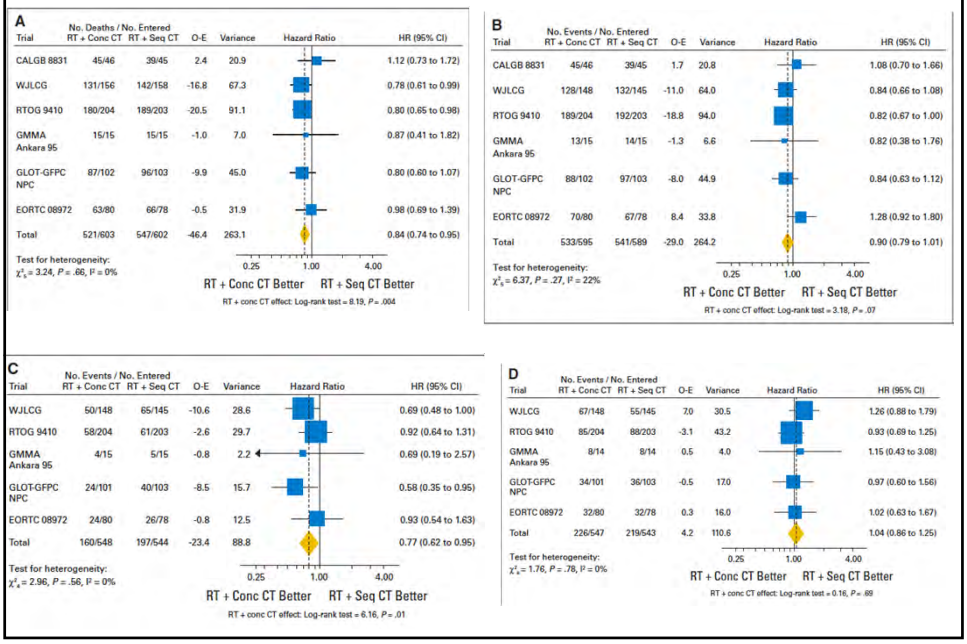
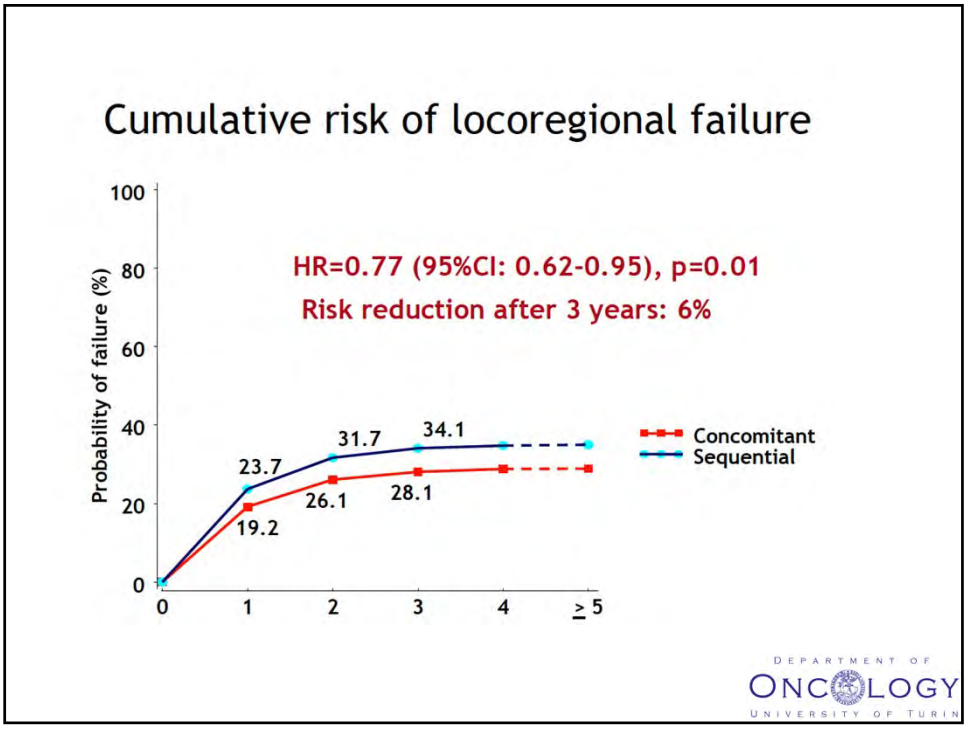
Hazard ratio (HR) plots for survival, progression-free survival, local progression, distant progression





Suboptimal local control after radiation therapy in lung cancer

- Inadequate dose to tumor
- Excessive dose to normal tissues
- Tumor extension beyond treatment volume

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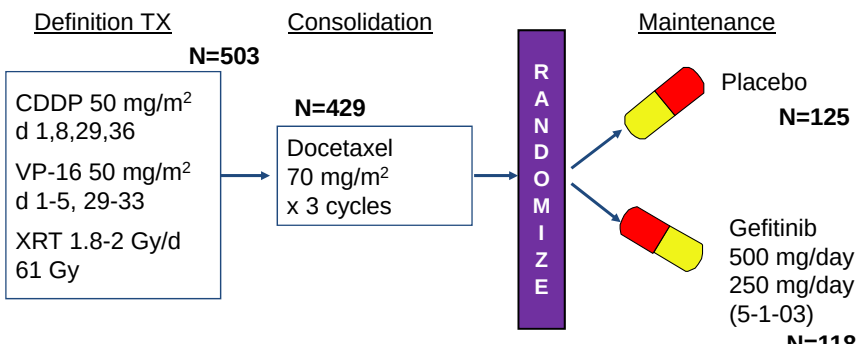
SWOG 0023: Gefitinib vs Placebo After Chemoradiation Followed by Docetaxel

Schema



1° Endpoint: overall survival; 2° Endpoint: PFS, toxicity and correlative science.
Maintenance therapy could continue for a maximum of 5 years.
Stratification factors: IIIA vs IIIB; measurable vs non-measurable disease; squamous vs nonsquamous.

Kelly K, et al. ASCO 2007. Abstract 7513. J Clin Oncol. 2008;26:2450-2456.

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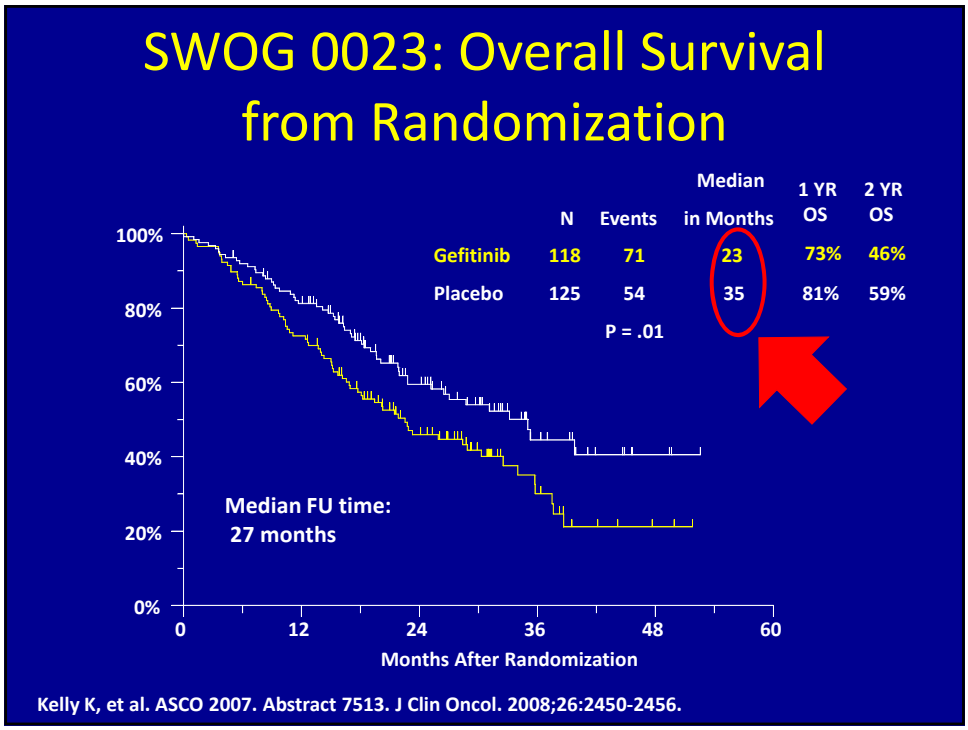
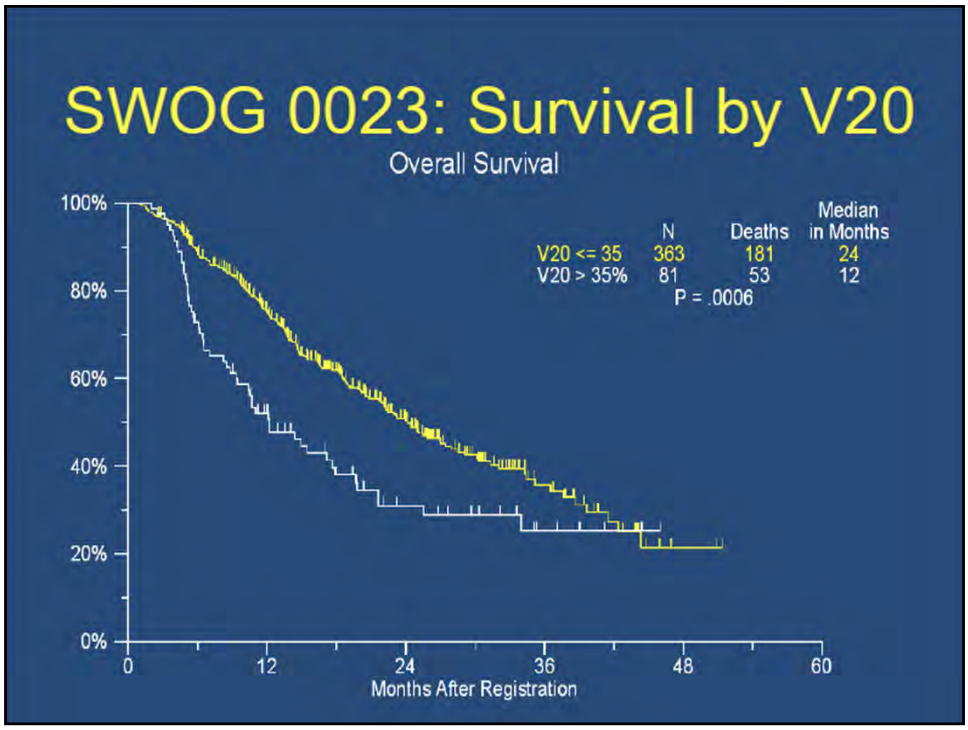


Kelly K, et al. ASCO 2007. Abstract 7513. J Clin Oncol. 2008;26:2450-2456.



Radiation pneumonitis in concurrent chemoradiotherapy

Patients treated with specific chemotherapeutic drugs:

- **Platinum**
- **Etoposide**
- **Taxanes**
- **Vinorelbine**

DO NOT appear to have a higher risk for radiation pneumonitis.

Drugs such as **Gemcitabine** are **NOT recommended** for routine use with concurrent radiotherapy in standard practice.
The same applies to targeted agents until more mature data become available

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Unresectable stage III NSCLC

- At present, concurrent chemotherapy with radiotherapy to a dose of 60 Gy in 30 daily fractions is considered to be the standard treatment

- Indirect evidence suggests that radiation dose-escalation may improve survival also in the context of chemo-radiation

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Background for high dose RT with concurrent chemo

Phase I and II Trials establishing safety and potential efficacy of 74 Gy delivered using 3D-Conformal Radiation Therapy

Study	Radiation dose (Gy)	Chemotherapy	Median survival time (months)
RTOG 0117	74	Carboplatin/paclitaxel	21.6
NCCTG 0028	74	Carboplatin/paclitaxel	37
North Carolina	74	Carboplatin/paclitaxel	24
Wake Forest	74	Gemcitabine	18
CALGB 30105	74	Carboplatin/paclitaxel	24

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Schema

STRATIFY

RT Technique
1. 3D-CRT
2. IMRT

Zubrod
1. 0
2. 1

PET Staging
1. No
2. Yes

Histology
1. Squamous
2. Non-Squamous

RANDOMIZE

Concurrent Treatment	Consolidation Treatment
Arm A Concurrent chemotherapy* RT to **60 Gy**, 5 x per wk for 6 wks	Arm A Consolidation chemotherapy*
Arm B Concurrent chemotherapy* RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm B Consolidation chemotherapy*
Arm C Concurrent chemotherapy* and **Cetuximab** RT to **60 Gy**, 5 x per wk for 6 wks	Arm C Consolidation chemotherapy* and Cetuximab
Arm D Concurrent chemotherapy* and **Cetuximab** RT to **74 Gy**, 5 x per wk for 7.5 wks	Arm D Consolidation chemotherapy* and Cetuximab

*Carboplatin and paclitaxel

RTOG

Primary Objective

- To compare the overall survival of patients treated with high-dose versus standard-dose conformal radiation therapy with concurrent chemotherapy.
- To compare the overall survival of patients treated with cetuximab versus without cetuximab with concurrent chemoradiotherapy.

RTOG 5

Pretreatment Characteristics

	60 Gy (n=216)	74 Gy (n=208)
Age (median)	64	64
Gender		
Male	127 (58.8%)	119 (57.2%)
Female	89 (41.2%)	89 (42.8%)
Race		
Other	27 (12.5%)	30 (14.4%)
White	189 (87.5%)	178 (85.6%)
RT Technique		
3DCRT	**116 (57.3%)**	**113 (54.3%)**
IMRT	**100 (46.3%)**	**95 (45.7%)**
PET Staging	**91.2%**	**88.9%**
Histology		
Adenocarcinoma	86 (39.8%)	73 (35.1%)
Squamous	86 (39.8%)	96 (46.2%)
NSCLC NOS	39 (18.1%)	33 (15.9%)
AJCC Stage		
Stage IIIA	138 (65.7%)	131 (63.6%)
Stage IIIB	72 (34.3%)	75 (36.4%)

RTOG 12

RTOG 0617: Dosimetric Data Distribution

	60 Gy (n=216) Mean (Median)	74 Gy (n=208) Mean (Median)
GTV Volume (cc)	134.9 (106.1)	122.7 (85.6)
Lung Volume (cc)	512.5 (463.4)	514.3 (440.0)
Lung V20 (%)	30.2 (30.3)	29.8 (31.5)
Esophagus Dose (Gy)	28.1 (28.1)	27.5 (27.3)
Esophagus V60 (%)	22.1 (22.1)	20.4 (20.1)
Esophagus V20 (%)	48.4 (48.7)	47.6 (46.8)
Mean Margin CTV to PTV (mm)	8.0 (7.0)	7.9 (6.6)

RTOG 13

RTOG 0617
Definitely, Probably, or Possibly Related to Treatment (Using CTCAE Version 3.0)

September 2011	Standard Dose: 60 Gy (n=192) Grade			High Dose: 74 Gy (n=183) Grade		
	3	4	5	3	4	5
Worst non-hematologic	79 (41.1%)	14 (7.3%)	4 (2.1%)	85 (46.4%)	17 (9.3%)	8 (4.4%)
Worst overall	84 (43.8%)	45 (23.4%)	4 (2.1%)	78 (42.6%)	52 (28.4%)	8 (4.4%)
Grade 5 Events		(n=4)			(n=8)	
As scored by institution		2 Pulmonary 1 Thrombosis 1 Death NOS			2 Pulmonary 1 Thrombosis 1 Upper GI Hemorrhage 1 Pulmonary Hemorrhage 1 Pneumonia NOS 1 Esophageal 1 Death NOS	
No significant difference						

RTOG 14

RTOG 0617

ASCO 2013 results

Median follow up was 17.2 months

	60 Gy	74 Gy	p-value
Median survival time	28.7	19.5	-
OS (18 months)	66.9%	53.9%	0.0007
Local-regional failure (18 months)	35.3%	44%	0.04

Bradley DJ. J Clin Oncol 31, 2013 (suppl; abstr 7501)

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Radiotherapy schedules other than conventional fractionation ones for dose intensification?

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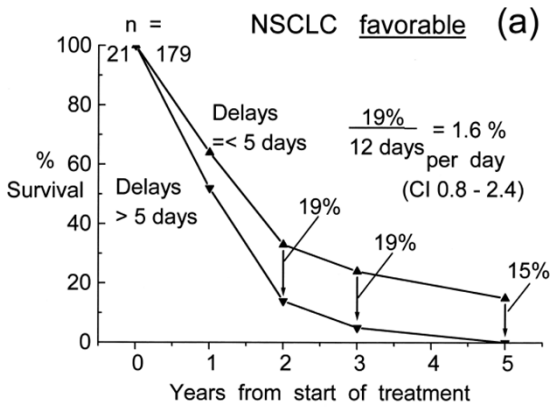
A NEW APPROACH TO DOSE ESCALATION IN NON–SMALL-CELL LUNG CANCER

MINESH MEHTA, M.D.,* RUFUS SCRIMGER, M.D.,* ROCK MACKIE, PH.D.,*†‡
BHUDATT PALIWAL, PH.D.,*† RICK CHAPPELL, PH.D.,§ AND JACK FOWLER, PH.D., D.SC.*



Rate of loss of survival with and without delays in radiotherapy

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Unresectable stage III NSCLC

- In case only radiotherapy is delivered, accelerated RT (CHART) improves survival compared to standard fractionation
- In the recent CHARTWEL trial, with the addition of chemo, accelerated RT may improve survival

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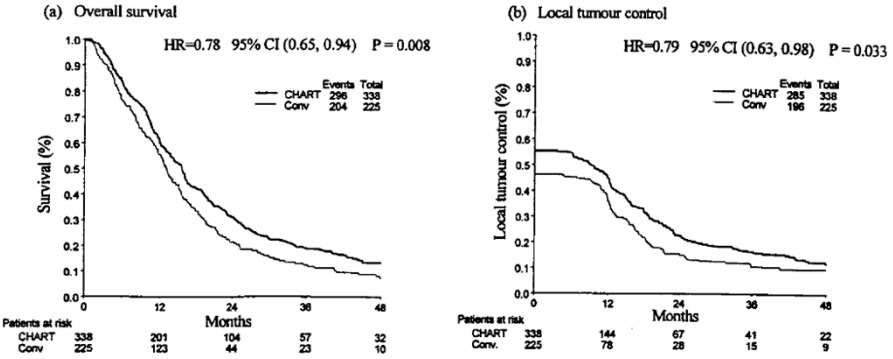
Continuous, hyperfractionated, accelerated radiotherapy (CHART) versus conventional radiotherapy in non-small cell lung cancer: mature data from the randomised multicentre trial

Radiotherapy and Oncology 52 (1999) 137–148

CHART: 54 Gy/12 days (1.5 Gy/fr TID)



Importance of cellular repopulation as a cause of failure

Unresectable stage III NSCLC

- In case only radiotherapy is delivered, accelerated RT (CHART) improves survival compared to standard fractionation
- In the recent CHARTWEL trial, with the addition of chemo, accelerated RT may improve survival

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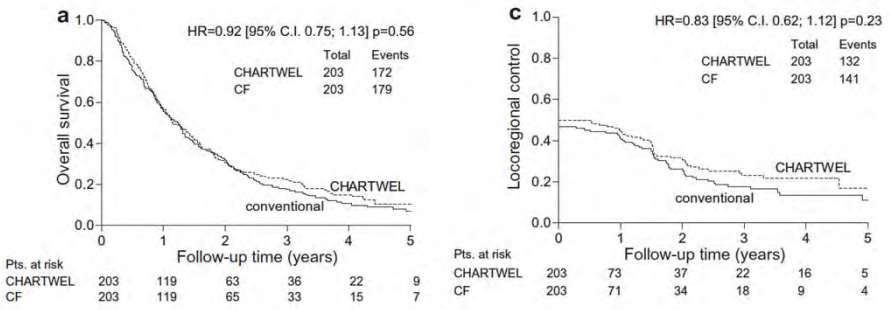
Phase III randomised trial

Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)

M. Baumann, Radiother Oncol 2011



CHARTWEL: 60 Gy/40 fr/2.5 wks

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Evaluation of modified fractionation radiotherapy effect in non metastatic lung cancer: an updated individual patients data meta-analysis on 10 randomized trials and 2685 patients

C. Le Péchoux et al.: JTO, 2011. 6: 432 (14 th World Conference on Lung Cancer, Amsterdam, 2011)

Meta-Analysis of Radiotherapy in Lung Cancer (MAR-LC)

- 2000 patients affected with NSCLC
- Modified fractionation (accelerated or hyperfractionated radiotherapy) improved overall survival as compared to conventional radiotherapy
- HR=0.88 (95% CI 0.80-0.97, p=0.009), resulting in an absolute benefit of 3% at 5 years (from 8% to 11%)

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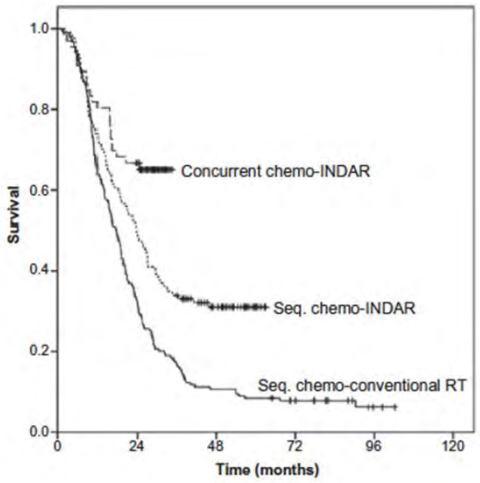
The INDAR concept:
INDividualized Isotoxic
Accelerated
Radiotherapy



De Ruysscher et al, Radiotherapy & Oncology, 2012

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Concurrent and Non-concurrent Chemo-radiotherapy or Radiotherapy Alone With Intensity-modulated Radiotherapy (IMRT) for Non Small Cell Lung Cancer (NSCLC) to an Individualised Mean Lung Dose (MLD)

This study is currently recruiting participants.
Verified January 2013 by Maastricht Radiation Oncology

Sponsor:
Maastricht **Radiation Oncology**

Information provided by:
Maastricht Radiation Oncology

ClinicalTrials.gov Identifier:
NCT01166204

First received: July 19, 2010
Last updated: January 24, 2013
Last verified: January 2013
History of Changes

- First three weeks/30 fractions: twice-daily fractions of 1.5Gy, with 8h to 10h as interfraction interval, 5 days per week. Total dose: 45Gy/30 fractions
- Thereafter: once daily fractions of 2.0Gy, 5 days per week until the target dose has been reached.

Phase II Efficacy Study
Chemotherapy: any third-generation schedule
Primary Endpoint: Overall Survival
INDAR approach: MLD < 20 Gy

Hypofractionation?

- SABR in early stage lung cancer
- Can "adapted" hypofractionation be applied to lung cancer patients with larger tumors thorugh the use of high-tech radiotherapy?

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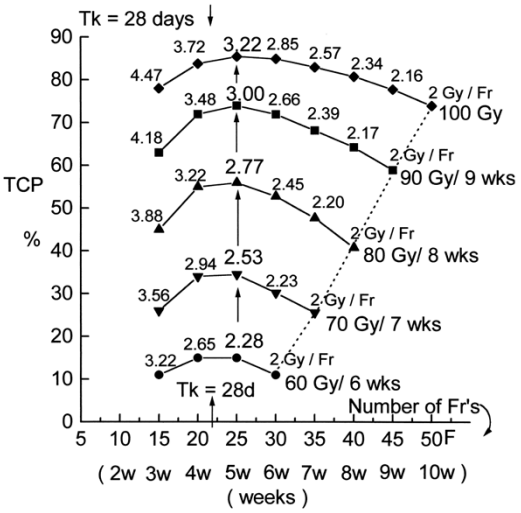
Gain in TCP from shortening overall treatment time to 5 weeks



Fewer and larger fractions calculated to deliver equal late complications also deliver higher biologic dose to tumors

Hypofractionation and Dose Escalation:

Is this possible?

Total dose	Number of fractions	Overall time	Dose per fraction	BED late α/β = 3 Gy	BED tumor		Estimated TCP*
					ignoring prolif	with prolif (Gy_{10})	
60 Gy	30	6 wk	2.00 Gy	100.0 Gy*3*	72.0	64.5	10%
56.9 Gy	25	5 wk	2.28 Gy	100.3 Gy*3*	70.0	67.5	14%

Thoracic Radiotherapy Innovations

- Imaging
- Imobilization
- Control of respiratory-induced tumor motion
- Image-guidance

Better imaging/better planning/better delivery

Filippi et al, Transl Lung Canc Res 2012

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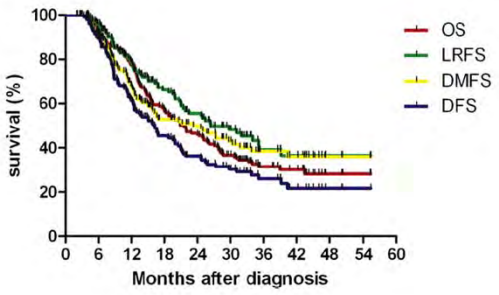
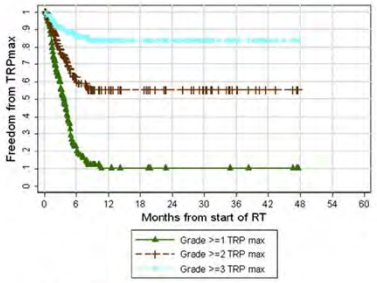
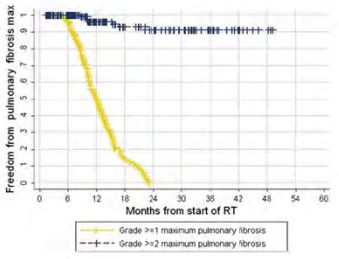
Long-Term Clinical Outcome of Intensity-Modulated Radiotherapy for Inoperable Non-Small-Cell Lung Cancer: The MD Anderson Experience



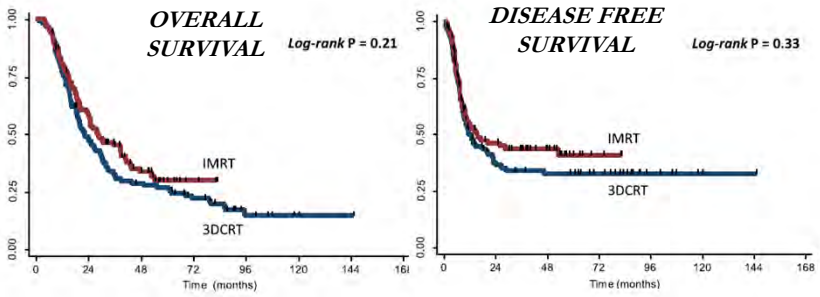




IJROBP, 2012

Clinical Investigation: Thoracic Cancer

Comparison of 2 Common Radiation Therapy Techniques for Definitive Treatment of Small Cell Lung Cancer



IMRT patients required significantly fewer percutaneous feeding tube placements (5% vs 17%, respectively, p<.005).

Shirvani, IJRBOP 2013; 87: 139-147

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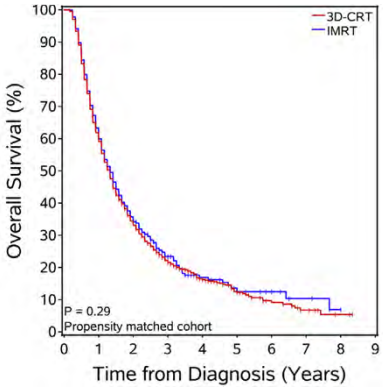
A population-based Comparative Effectiveness Study of Radiation Therapy techniques in Stage III NSCLC

Surveillance, Epidemiology and End Results (SEER-) Medicare Records
6894 patients stage III Lung Cancer 2002-2009 (716 IMRT (10%)



Summary of hazard ratios for IMRT versus 3D-CRT (reference)

	Multivariate adjusted HR (95% CI)	P
OS	0.94 (0.85-1.04)	.23
CSS	0.94 (0.85-1.05)	.28
Early UGI toxicity	1.01 (0.87-1.19)	.86
Late UGI toxicity	0.94 (0.87-1.01)	.08
Early pulmonary toxicity	1.14 (0.92-1.43)	.23
Late pulmonary toxicity	1.22 (0.82-1.83)	.33
Cardiac toxicity	0.88 (0.64-1.21)	.44

IMRT is associated with similar toxicities while maintaining good outcomes

Harris JP, IJROBP 2014 in press

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VOLUME 28 · NUMBER 14 · MAY 10 2010
JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Primary Analysis of the Phase II Component of a Phase I/II Dose Intensification Study Using Three-Dimensional Conformal Radiation Therapy and Concurrent Chemotherapy for Patients With Inoperable Non–Small-Cell Lung Cancer: RTOG 0117

Jeffrey D. Bradley, Kyounghwa Bae, Mary V. Graham, Roger Byhardt, Ramaswamy Govindan, Jack Fowler, James A. Purdy, Jeff M. Michalski, Elizabeth Gore, and Hak Choy

Table 1. Dose escalation and de-escalation

Dose level	Radiation Therapy: Original Protocol	Radiation Therapy: Amended Protocol	Cohort
1	75.25 Gy / 35 fxs (2.15 Gy per fraction)		1
2	80.5 Gy / 35 fxs (2.3 Gy per fx) (escalation dose)†	74 Gy / 37 fxs (2.0 Gy per fx) (de-escalation dose)	2 (MTD)
3	79.5 Gy / 30 fxs (2.65 Gy per fx) (escalation dose)†	70 Gy / 35 fxs (2.0 Gy per fx) (de-escalation dose)‡	
4	75 Gy / 25 fxs (3.0 Gy per fx) (escalation dose)†	N/A	

These studies were based on 3D-CRT, not IMRT

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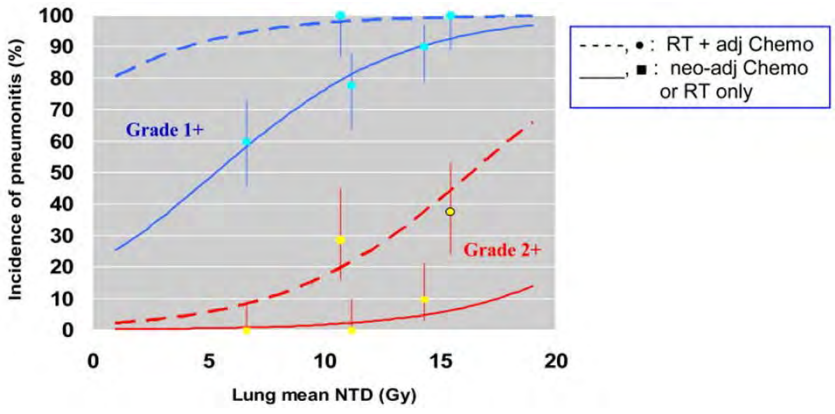
Dose Escalated, Hypofractionated Radiotherapy Using Helical Tomotherapy for Inoperable Non-Small Cell Lung Cancer: Preliminary Results of a Risk-Stratified Phase I Dose Escalation Study

Jarrod B. Adkison, MD[1], Deepak Khuntia, MD[1], Soren M. Bentzen, PhD[1], George M. Cannon, MD[1], Wolfgang A. Tome, PhD[1,2], Hazim Jaradat, PhD[1], Wendy Walker, BS[1], Anne M. Traynor, MD[2], Tracey Weigel, MD[3], and Minesh P. Mehta, MD[1,*]

46 patients: dose from 2.28 to 3.22 in 25 fractions



Tech Canc Res Treat 2008

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VOLUME 31 · NUMBER 34 · DECEMBER 1 2013

JOURNAL OF CLINICAL ONCOLOGY

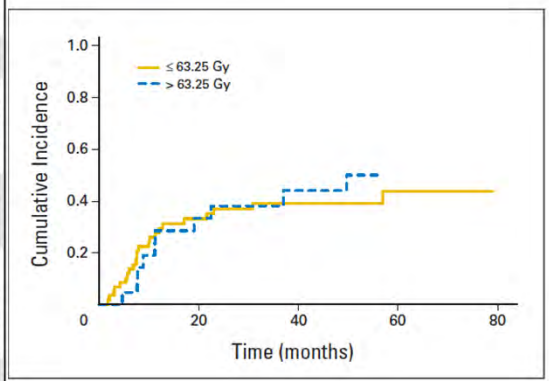
ORIGINAL REPORT

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

Table 1. Patient and Treatment Characteristics

Characteristic	No. of Patients	%
Total patients	79	100
Age, years		
< 50	6	9
50-69	47	59
≥ 70	26	32
Sex		
Female	33	42
Male	46	58
Stage		
I/II	7	9
IIIA	21	27
IIIB	35	44
IV	10	13
Recurrent	6	8
Histology		
Adenocarcinoma	24	30
Squamous cell carcinoma	26	33
NSCLC, NOS	22	28
Other NSCLC	7	9
Bin assignment, $rNTD_{mean}$		
Pilot (NA)	5	6
1 (0.00-0.119)	6	7
2 (0.12-0.179)	8	10
3 (0.18-0.239)	27	34
4 (0.24-0.309)	29	37
5 (0.31-0.410)	4	5
Performance status		
0	48	61
1	30	38
Not recorded	1	1
Prescribed radiation dose, Gy		
57	47	59
63.25	11	14
69.25	3	4
75	12	16
80.5	4	5
85.5	2	3
Chemotherapy		
Neoadjuvant	17	21
Adjuvant	33	41
Both	3	4
None	25	32
Other*	1	1



Local Failure

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Table 2. Patients With Grade 4-5 Toxicity

Age (years)	Sex	Stage	Bin	Dose (Gy)*	Grade	Interval (months)†	Toxicity
69	M	IIIB	3	63.25	5	1.2	HSV/CMV pneumonitis; history of pre-RT low-dose methotrexate
66	F	IIA	1	85.5	5	55	Fatal hemoptysis
58	M	IIIB	3	75	5	7.9	Fatal hemoptysis
63	M	IIIB	1	75	5	1.6	Lung abscess
62	M	IIIA	3	75	5	8.1	Fatal hemoptysis and abscess
61	F	IV	3	75	4	10.3	Lung abscess, bronchocavitary fistula, tracheoesophageal fistula

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INTENSITY-MODULATED RADIOTHERAPY MIGHT INCREASE PNEUMONITIS RISK RELATIVE TO THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY IN PATIENTS RECEIVING COMBINED CHEMOTHERAPY AND RADIOTHERAPY: A MODELING STUDY OF DOSE DUMPING

IVAN S. VOGELIUS, PH.D.,*†‡ DAVID C. WESTERLY, PH.D.,† GEORGE M. CANNON, M.D.,† THOMAS R. MACKIE, PH.D.,† MINESH P. MEHTA, M.D.,† CHIKAO SUGIE, M.D.,§ AND SØREN M. BENTZEN, PH.D., D.SC.†‡

IJROBP 2011

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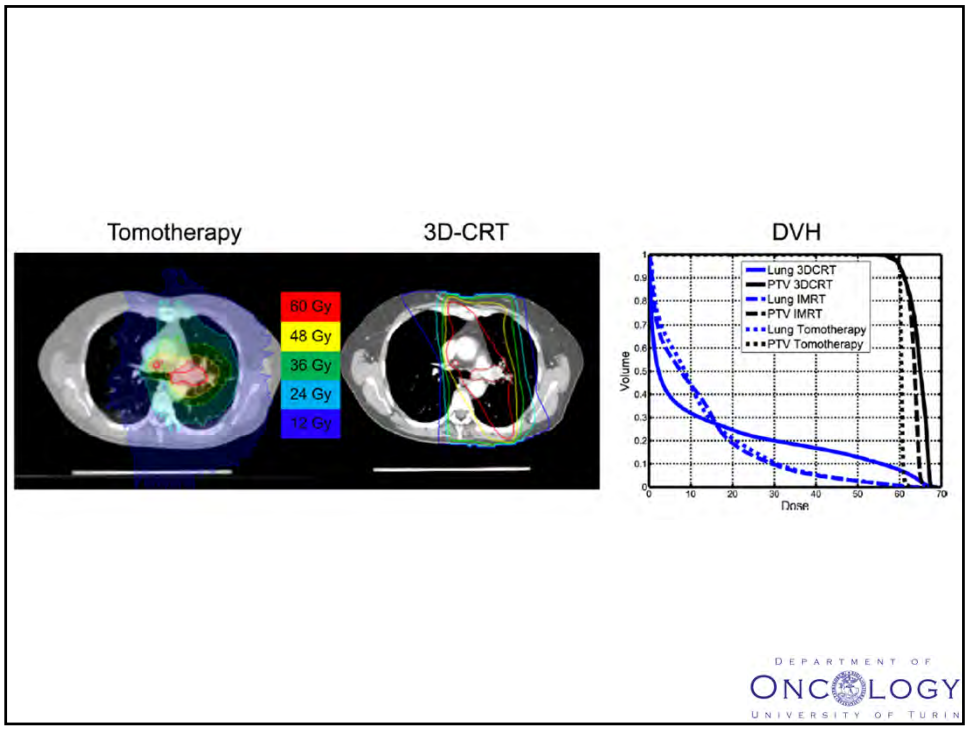
Tomotherapy
3D-CRT
DVH
60 Gy
48 Gy
36 Gy
24 Gy
12 Gy
Lung 3DCRT
PTV 3DCRT
Lung IMRT
PTV IMRT
Lung Tomotherapy
PTV Tomotherapy
Volume
Dose
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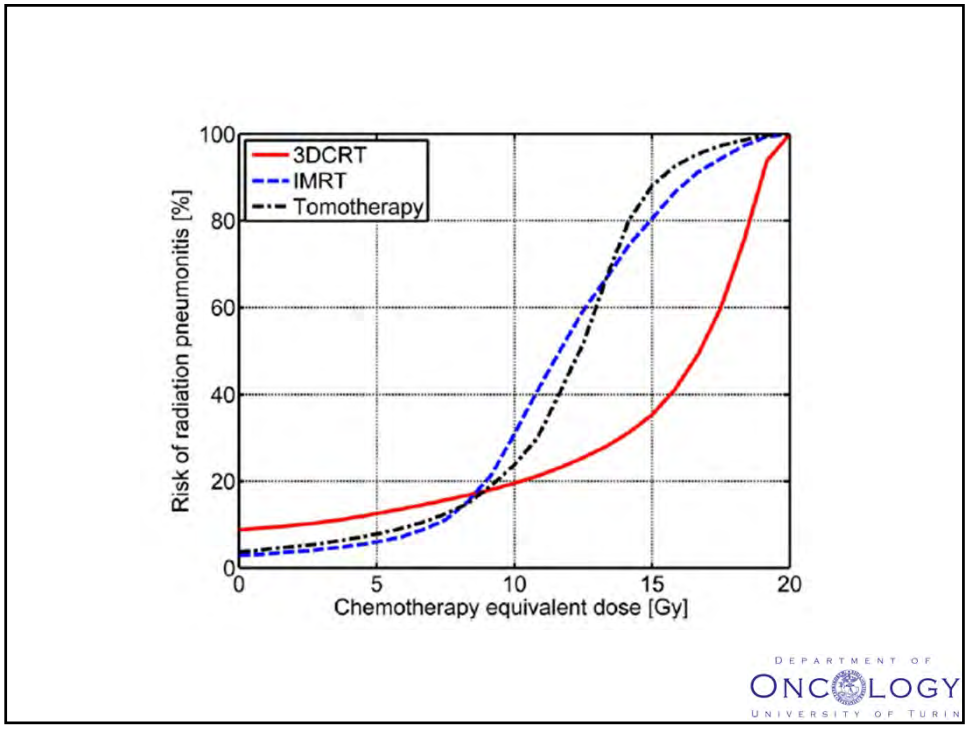
3DCRT
IMRT
Tomotherapy
Risk of radiation pneumonitis [%]
Chemotherapy equivalent dose [Gy]
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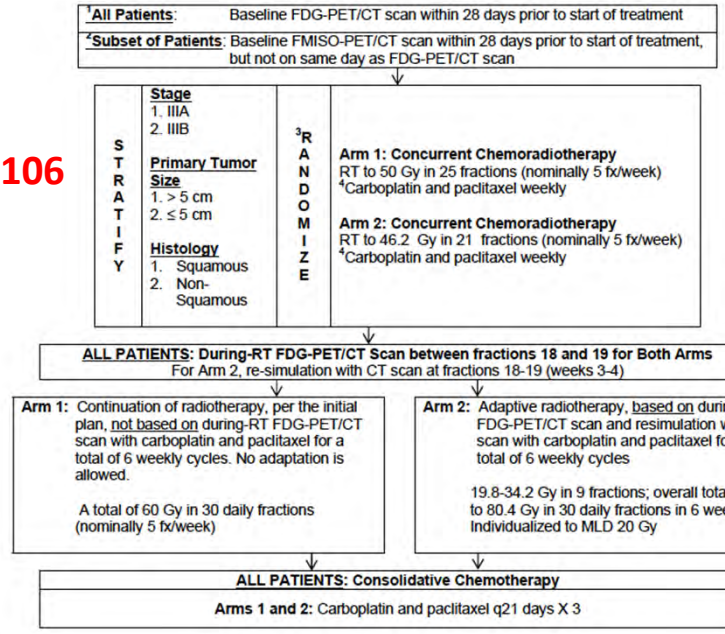
RTOG 1106



Dose Escalation by Boosting Radiation Dose Within the Primary Tumor Using FDG-PET-CT Scan in Stage IB, II and III NSCLC (PET Boost)

This study is currently recruiting participants.

Verified January 2012 by The Netherlands Cancer Institute

Sponsor:
The Netherlands **Cancer** Institute

Collaborators:
Maastricht University Medical Center
GROW

ClinicalTrials.gov Identifier:
NCT01024829

First received: December 1, 2009
Last updated: January 17, 2012
Last verified: January 2012
History of Changes

- Whole **tumor** boost

Patients in this arm will receive **radiotherapy** (66Gy) in 24 fractions of 2.75 Gy with an integrated boost to the primary **tumor** as a whole

Intervention: **Radiation**: **Radiotherapy**

Boost 50% SUV area

Patients in this arm receive **radiotherapy** (66Gy) in 24 fractions of 2.75Gy with an integrated boost to the 50% SUVmax area of the primary **tumor** (of the pre-treatment FDG-PET-CT scan)

Intervention: **Radiation**: **Radiotherapy**

Chemotherapy: concurrent or sequential
Randomized Phase II Trial
Primary endpoint: Local-Progression-Free Survival

Specialized Radiation Therapy and Chemotherapy in Treating Patients With Stage III Non-Small Cell Lung Cancer That Cannot Be Removed by Surgery

This study is currently recruiting participants.

Verified December 2012 by National Cancer Institute (NCI)

Sponsor:
Cancer and Leukemia Group B

Collaborator:
National Cancer Institute (NCI)

Information provided by:
National Cancer Institute (NCI)

ClinicalTrials.gov Identifier:
NCT01486602

First received: December 2, 2011
Last updated: December 6, 2012
Last verified: December 2012
History of Changes

Phase I study- Accelerated Hypofractionated RT with CBDCA/Paclitaxel
Primary endpoint: MTD

Image-Guided Hypofractionated Radiation Therapy With Stereotactic Body Radiation Therapy Boost and Combination Chemotherapy in Treating Patients With Stage II-III Non-Small Cell Lung Cancer That Cannot Be Removed By Surgery

This study is currently recruiting participants.

Verified February 2013 by Jonsson Comprehensive Cancer Center

Sponsor:
Jonsson Comprehensive Cancer Center

Collaborator:
National Cancer Institute (NCI)

Information provided by (Responsible Party):
Jonsson Comprehensive Cancer Center

ClinicalTrials.gov Identifier:
NCT01345851

First received: April 27, 2011
Last updated: February 11, 2013
Last verified: February 2013
History of Changes

Phase I Safety Study
Primary Endpoints: MTD
Chemotherapy: CBDCA/Paclitaxel
Secondary Endpoints: LC, PFS, OS

Stage III good PS patients: key points for future research

- Use of Any Advanced Technology RT Tools?
- Selection of Best Chemo to Give Concurrently with RT*
- Use of Functional Imaging in RT Planning/Assessment
- Higher RT Dose with a Standardized Chemo Regimen
- Use of "Targeted Agent" Concurrent with Chemo-RT

Hypofractionation in LA NSCLC should only be used in clinical trials

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