NTCP Consideration of Thoracic SBRT: What Is Safe for A Physician?

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Learning Objectives

- To understand seriousness of thoracic SBRT toxicity
- To identify simple risk factors for lung toxicity
  - To attempt modeling radiation pneumonitis
- To follow the consensus safe OAR limits

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High Dose SBRT/SABR Is Powerful

- Japanese study, 50 Gy in 4 fractions, BED>=100 Gy provides 92% tumor control
  - Onishi et al. J. Thorac Oncol, 2007 Jul;2(7 Suppl 3):S94-100.
- Germany study, confirmed tumor control plateau at BED110-140 Gy
  - Guckenberger and Wulf et al, red journal, 2009 May 1;74(1):47-54.
- Timmerman for 54-60 Gy in 3 Fx, 18Gy/Fx, BED 160-180 Gy, 98% tumor control at 2 years
  - Timmmerman et al, JAMA, 2010 Mar 17;303(11):1070-6.

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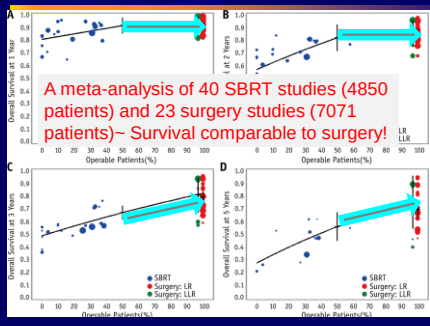
Survival of SBRT Comparable to Surgery



A meta-analysis of 40 SBRT studies (4850 patients) and 23 surgery studies (7071 patients)~ Survival comparable to surgery!

Zheng (Kong), Red Journal, in press, 2014

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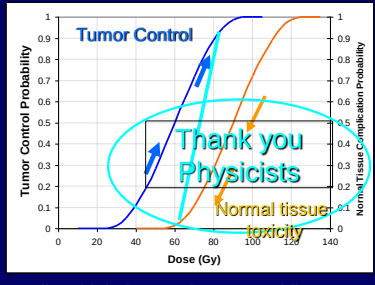
Technology Makes SBRT Possible



Deliver high dose to the tumor while minimize doses to the normal tissue

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SBRT Toxicity Is Limited

A meta-analysis comparing to 3DCRT, Proton vs Heavy Ion RT

Occurrence of adverse events grade 3–5[a] for each treatment modality in patients with stage I NSCLC.

Treatment	N events	N at risk	Proportion	(95% CI[b])	Source	N events	N at risk	Proportion	(95% CI[b])	Source
	Pneumonitis grade 3/4					*Oesophagitis grade 3/4*				
CRT	2	867	0.0023	(0.0003–0.0083)	[30,32,33,35–37,40]	1	831	0.0012	(0.0000–0.0067)	[30,32,33,35–37,40]
SBRT	16	800	0.0200	(0.0115–0.0323)	[21,23,41–44,46,47,49]	2	840	0.0024	(0.0003–0.0086)	[21,23,41–44,46–49]
Protons	1	126	0.0079	(0.0002–0.0434)	[51–53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	3	210	0.0143	(0.0030–0.0412)	[55–57]	nr	nr	-	-	
	Irreversible dyspnoea grade 3/4					*Treatment-related death (grade 5)*				
CRT	5	980	0.0051	(0.0017–0.0119)	[30–33,35–37,40]	1	980	0.0010	(0.0000–0.0057)	[30–33,35–37,40]
SBRT	6	769	0.0078	(0.0029–0.0169)	[21,23,42–44,46,47,49]	6	870	0.0069	(0.0025–0.0150)	[21,23,41–44,46–49]
Protons	0	58	0.0000	(0.0620)	[52,53]	0	126	0.0000	(0.0290)	[51–53]
Carbon-ions	0	210	0.0000	(0.0170)	[55–57]	0	210	0.0000	(0.0170)	[55–57]

Abbreviations: CRT, conventional radiotherapy; SBRT, stereotactic body radiotherapy; CI, confidence interval.
[a] Adverse events were graded in accordance with the CTCAE scoring system [19].
[b] When the number of events was 0, only the upper limit of the confidence interval was calculated.

Serious toxicity/mortality less than 1% for various strategies.

Grutters et al, Radio Oncol, 2009

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Everybody's Doing It

Courtesy of Dr. Bogart

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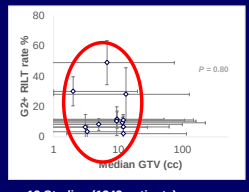
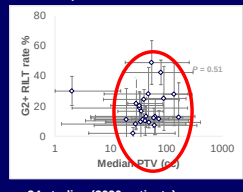
Tumors Treated with SBRT

- Majority of them are peripheral lesions
- Most of them are small tumors, ~ 2cm





13 Studies (1343 patients)

24 studies (2090 patients)

SBRT is safe with conditions!!!

Horizontal bar: range of the value
Vertical bar: 95% CI of the value

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Zhao (Kong), ASTRO, 2014

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SBRT Can Be Life Threatening

- Of 70 patients treated with 60-66 Gy in 3 fractions, 6 deaths as a result of toxicity occurred at 0.6, 3.9, 12.1, 12.8, 13.8, and 19.5 months after SBRT.
  - 4 deaths as a bacterial pneumonia
  - 1 died as a result of complications from a pericardial effusion
  - 1 death after a local recurrence next to the carina previously and subsequently had massive bleeding…

Timmerman et al, 2006, *J Clin Oncol 24:4833-4839.*

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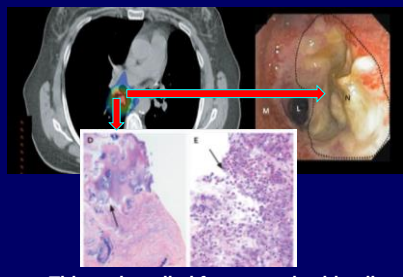
Fetal Central Airway Necrosis



This patient died from massive bleeding

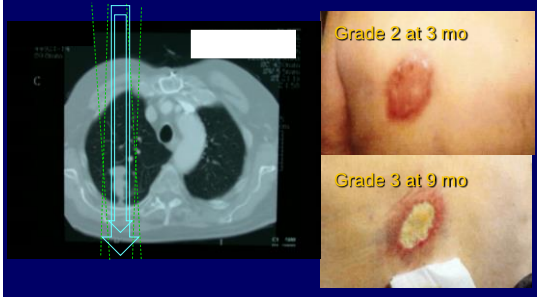
Corradetti et al, NEJM, 2012 :366:2327-2329

Massive Bleeding Is Life Threatening

- Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy.
  - 29 patients reirradiated with SBRT on 32 lung lesions (11 central, 21 peripheral).
  - Grade 3-4 toxicity was scored 14 times in eight patients.
  - 3 patients died of massive bleeding (grade 5).
  - Larger clinical target volumes (CTV) and central tumour localization were associated with more severe toxicity.
  - There was no correlation between mean lung dose (MLD) and lung toxicity.
  - Local control at 5 months after reirradiation was 52%
  - The estimated 1- and 2-year survival rates were 59% and 43%, respectively.

Peulen et al, Radiother Oncol. 2011 Nov;101(2):260-6.

Skin Reaction: Grade 2-4



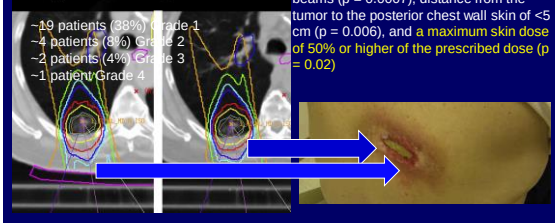
Courtesy of Dr. Timmerman

Grade 4 Skin Toxicity

MSKCC, 50 pts treated with 60 Gy in 4 fractions or 44–48 Gy in 4 fractions, multiple coplanar beams (3–7, median 4) 6 MV IMRT

~19 patients (38%) Grade 1
~4 patients (8%) Grade 2
~2 patients (4%) Grade 3
~1 patient Grade 4

Factors associated with Grade 2 or higher acute skin toxicity included using only 3 beams (p = 0.0007), distance from the tumor to the posterior chest wall skin of <5 cm (p = 0.006), and a maximum skin dose of 50% or higher of the prescribed dose (p = 0.02)



Hoppe et al, Int. J. Radiation Oncology Biol. Phys., Vol. 72, No. 5, pp. 1283–1286, 2008

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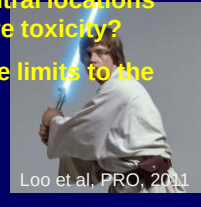
Grade 5 Radiation Pneumonitis

Radiation Is Double Edged Saw

- Can we use this SAW to larger tumors or tumors in more central locations without causing severe toxicity?
- What are the safe dose limits to the OARs?



Loo et al, PRO, 2011

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SBRT Quantec: Thoracic NTCP WG

Co-Chairs
- Feng-Ming (Spring) Kong, MD PhD
- Michael Milano, MD
- Ellen Yorke, PhD

Expert Members:
- Soren Bentzen, PhD
- Louis Constine, MD
- Shiva Das, PhD
- Andy Jackson, PhD
- Tamara LaCouture, MD
- Allen Li, PhD
- Zhongxing Liao, MD
- Lawrence Marks, MD
- Mary Martel, PhD
- Moyed Miften, PhD
- Andreas Rimner, MD
- Timothy Solberg, PhD
- Robert Timmerman, MD
- Sue Tucker, PhD

Literature search and primary reviewers:
- Lung: Jing Zhao MD PhD and Ling Li, MD PhD
- Chest wall/Rib: Chengbo Han MD PhD
- Proximal bronchial tree: Weili Wang, MD PhD
- Esophagus: Nan Bi, MD PhD
- Brachial plexus: Fang Peng, MD, MS
- Heart: Nan Bi, MD PhD

Secondary reviewers (assignment completed):
- Ellen Yorke, PhD
- Michael Milano, MD
- Shiva Das, PhD
- Allen Li, PhD
- ...
- Moyed Miften, PhD
- Andreas Rimner, MD

Team effort started at AAPM 2012, led by J Grimm, E Yorke, L Marks et al

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Thoracic Organs at Risk (OARs

- ❑ Lung
- ❑ Proximal bronchial tree
- ❑ Chest wall
- ❑ Esophagus
- ❑ Brachial plexus
- ❑ Skin
- ❑ Great vessel/Heart/pericardium
- ❑ Spinal cord (CNS)

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Grade 5 Toxicity

A total 51(36) grade 5 toxicities in 10010 cases treated in 132 Japanese hospitals in 2010 (2008)

1. Radiation pneumonitis	42 (28)
2. Pulmonary bleeding	3 (3)
3. Radiation esophagitis	1 (1)
4. Others	5 (4)

In total, grade 5 rate: 51/10010=0.5%

Nagata et al ASTRO 2013

2008 data from Nagata et al, Int J Radiat Oncol Biol Phys. 2009 Oct 1;75(2):343-7.

Courtesy of Dr. Nagata

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Grade 5 Radiation Pneumonitis

No of positive institutions: 8/16 JCOG-RTSG
Total cases: 24 in 8 institutions
Frequency: 24/1789 (1.3%) in 8 institutions

Onishi, ASTRO, 2009

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Courtesy of Dr. Onishi

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Radiation Lung Toxicity Endpoints

- ❑Functional changes
- ❑Radiographic (grade 1)
- ❑Symptomatic (grade 2-3)
- ❑Life threatening (Grade 4)
- ❑Death (grade 5)

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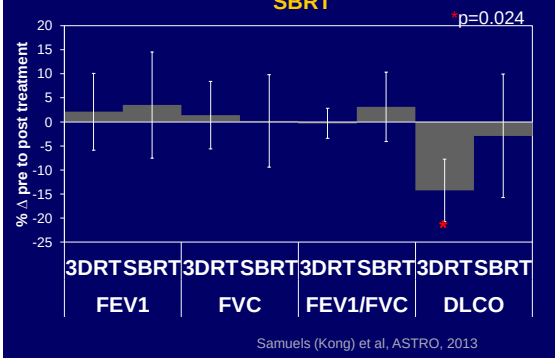
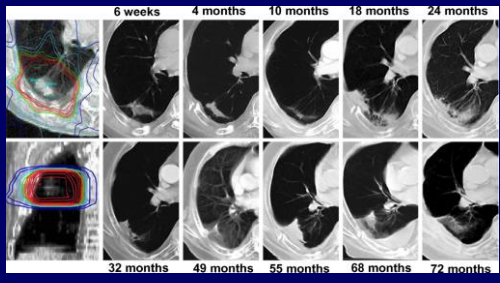
DLCO Decreases after 3DRT but not after SBRT



Samuels (Kong) et al, ASTRO, 2013

Post-SBRT Pulmonary Changes

Peripheral disease



Guckenberger et al, Green Journal, 2009

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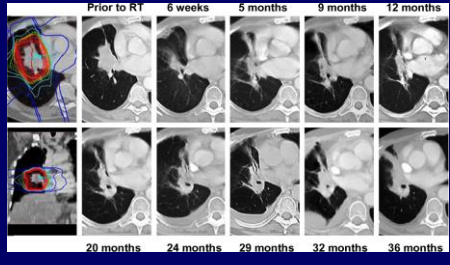
Post-SBRT Pulmonary Changes

Central Disease



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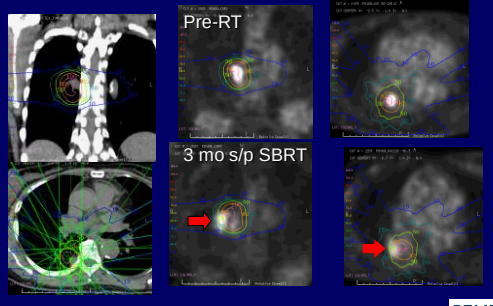
Tumor Progression vs Inflammation?



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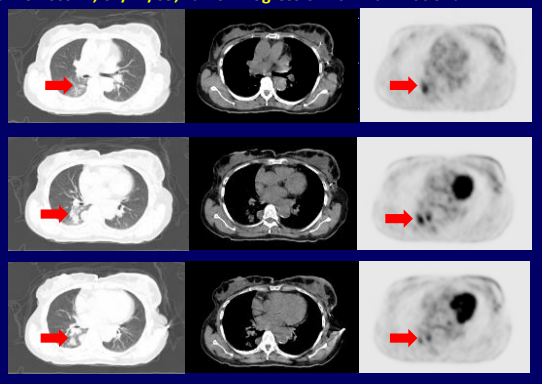
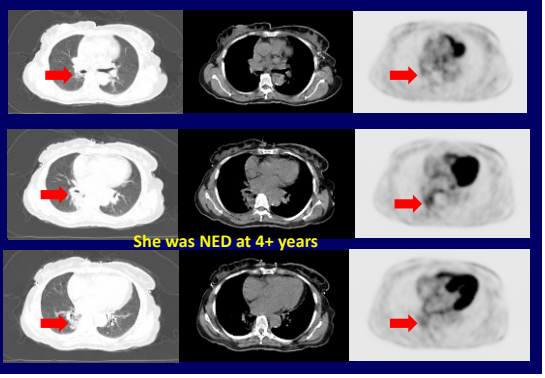
3 mo Post-RT, 04/17/09, Tumor Progression vs Inflammation?



8 mo Post-RT, Resolved Inflammation



She was NED at 4+ years

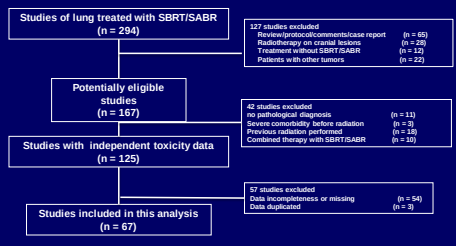
Simple Clinical Factors Associated with Symptomatic RILT after Thoracic SBRT : A Pooled Analysis of 68 Studies

J Zhao[1], L. Ling[2], E. D. Yorke[3], M. T. Milano[4], W. Liu[5], B. Kavanagh[6], A. Li[7], A Jackson[3], L. B. MarKs[8], M. Miften[6], A. Rimner[3], T Solberg[9], J. Xue[10], J. Grimm[11], FM. Kong[1]

[1]Department of Radiation Oncology, Georgia Regents University, Augusta, GA, [2]Fudan University Shanghai Cancer Center, Shanghai, China, [3]Memorial Sloan-Kettering Cancer Center, New York, NY, [4]University of Rochester, New York, NY,[5]Taian No.1 People's Hospital, Taian, China, [6]University of Colorado, Denver, CO, [7]Medical College of Wisconsin, Milwaukee, WI, [8]University of North Carolina, Wilmington, NC, [9]University of Pennsylvania, Philadelphia, PA, [10]Cooper University Hospital, Camden, NJ, [11]Holy Redeemer Hospital, Meadowbrook, PA

Will be presented as an oral at ASTRO, 2014

A Pooled Analysis of Published Studies



a total of 5631 patients

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Pooled Rates of RILT

- 67 studies 5631 patients published before 6/2014
  - G2+ RILT 12.2%
  - G3+ RILT 3.0%
  - G5 RILT 0.3%

RILT Grade	1	2	3	4	5
No. of studies	32	55	64	54	54
No. of patients	2205	4666	5456	4356	4356
No. of event	861	520	147	6	14
Rate %	38.5	11.1	2.7	0.1	0.3
95% CI of rate	29.5-52.3	8.9-13.0	2.2-4.0	0.01-0.2	0.01-0.6

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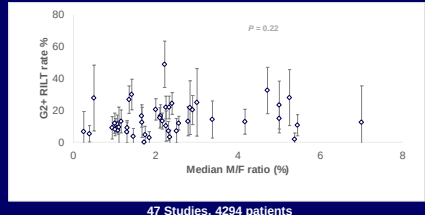
Patient Factors & G2+ RILT

- None of the patient factors such as age, gender, smoking status was significantly associated with the risk of G2+ RILT



47 Studies, 4294 patients

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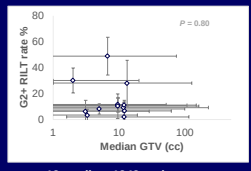
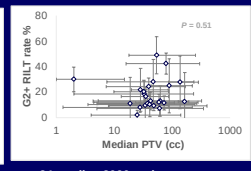
Tumor Factors & G2+ RILT

None of the tumor factors such as histology, tumor size, tumor location, GTV and PTV was significantly associated with the rate of G2+ RILT



13 studies, 1343 patients



24 studies 2090 patients

Horizontal bar: range of the value
Vertical bar: 95% CI of the value

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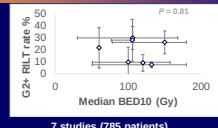
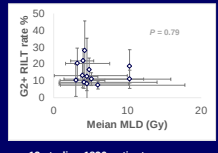
Dosimetric Factors & G2+RILT

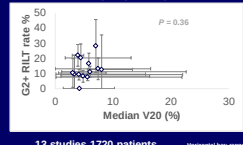
- No significant associations with median BED10, MLD or V20.



7 studies (785 patients)



13 studies 1836 patients



13 studies 1720 patients

Horizontal bar: range of the value
Vertical bar: 95% CI of the value

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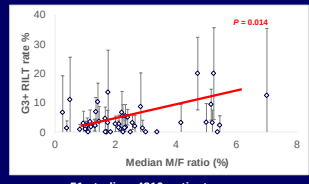
Patient Factors and G3+RILT

- Studies with greater M/F ratio had slightly higher but statistically significant higher G3+ RILT (p = 0.014)
- No significant correlation between G3+ RILT and age or smoking status



51 studies, 4810 patients

Vertical bar: 95% CI of the value

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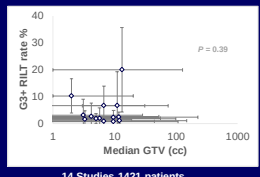
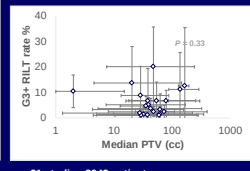
Tumor Factors and G3+RILT

- No significant correlations between G3+ RILT and GTV or PTV



14 Studies 1421 patients



21 studies 2043 patients

Horizontal bar: range of the value
Vertical bar: 95% CI of the value

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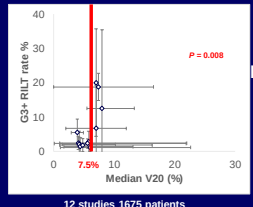
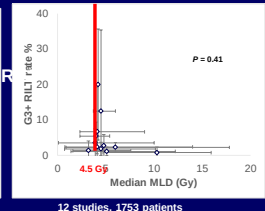
Dosimetric Factors and G3+RILT

- Median V20 was significantly correlated with G3+ RILT rate
- No significant correlation between G3+ RILT and dose or MLD



12 studies 1675 patients



12 studies, 1753 patients

Horizontal bar: range of the value
Vertical bar: 95% CI of the value

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Selected Studies Reported MLD

Author	Link	Lung definition	Toxicity grading	Median MLD	
				G0-1 RILT	G2+ RILT
Takeda A, et al	http://bir.birjour	Both lungs-GTV	CTCAE	3.5	5.0
Barriger RB, et al	http://www.scie	Both lungs-GTV	CTCAE	4.0	5.0
Takeda A, et al	http://www.scie ncedirect.com/s	Both lungs-CTV	CTCAE	3.9	4.0
Guckenberger M, et	http://www.scie	Ipisilat lung-GTV	SWOG	6.3	9.9
Yamashita H, et al	http://www.ncb	Both lungs-PTV	CTCAE	NA	NA
Matsuo Y et al	http://www.scie	Both lungs-PTV	CTCAE	NA	4.7
Chang, et al		Both lung-GTV	CTCAE	NA	5.1
Ricardi U et al	http://informah	Ipisilat lung-CTV	RTOG	5.6	10.0

DVH Factors and Radiation Pneumonitis

ASTRO 2009 Onishi H.

Comparison of SBRT dose and volume
Grade 0,1,2 vs Grade 5

min. ~ max. (mean)

RT pneumonia	Grade 0,1,2 (n=10)	grade 5 (n-24)	p
PTV	34.2~108.6 (51.3) cc	17.0~210.6 (67.9) cc	0.34
V20% (lung-GTV)*	2.8~15.4 (5.2) %	3.5~18.2 (8.3) %	< 0.01
V20 cc (lung-GTV)	124.9~294.5 (191.9) cc	66.2~410.6 (211.5) cc	0.77
V40% (lung-GTV)*	0.0~4.1 (1.4) %	1.0~6.2 (3.0) %	< 0.01
V40 cc (lung-GTV)	0.0~93.4 (50.0) cc	17.4~160.0 (77.2) cc	0.08
Mean lung-GTV dose*	2.1~7.8 (3.6) Gy	2.7~12.9 (5.5) Gy	< 0.01

* Mann- Whitney's U-test

24 G5 of 1789 patients from 8 centers (unpublished yet)

Courtesy of Dr. Onishi

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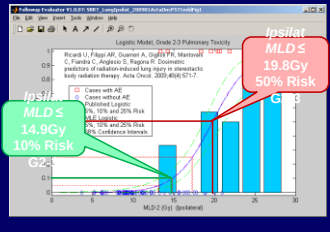
RILT After SBRT

- 67 studies (5631 patients) reported clinical data
- 15 studies (1604 patients) with partial dosimetric data
- 10 studies (1201 patients) reported complete dosimetry data
- 3 studies (247 patients) reported NTCP modeling

Modeling work in progress

WGSBRT Strategy: Independently Reproduced by Modeler 1 (Jimm Grimm)



- Reconstructed dose response model from the Ricardi 2009
- Logistic Model
- D_{50}=19.7Gy
- γ_{50}=2.19 (normalized slope)

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Ricardi U, et al. Acta Oncol. 2009;48(4):571-7.

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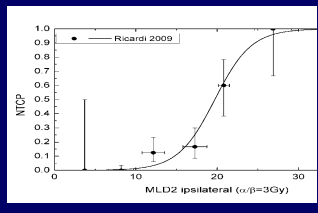
WGSBRT Strategy: Independently Reproduced by Modeler 2 (Vitali Moiseenko)



- Reconstructed dose response model
- Logistic Model
- D_{50}=19.7Gy
- γ_{50}=2.19 (normalized slope)

Almost exactly same results from two modelists !!!

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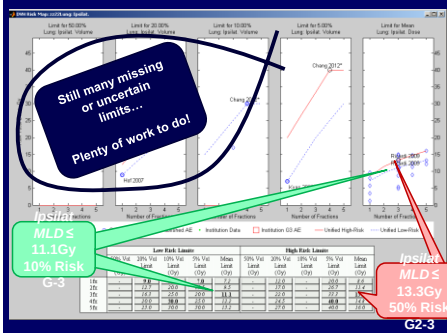

DVH Risk Map

Ipsilateral Lung

Comparison of many published dose tolerance limits

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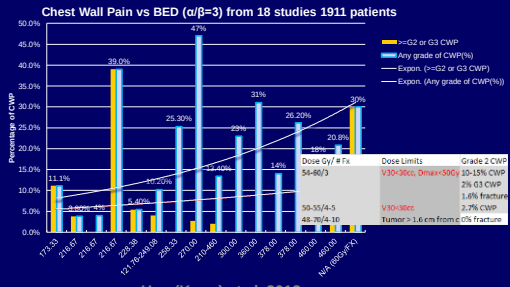
Chest Wall Pain or Rib Fracture

- 22 studies (2435 patients) reported clinical data on chest wall toxicity including 1742 CWP and 1866 rib fracture, respectively.
- 11 studies (1379 patients) with partial dosimetric data
- 5 studies (819 patients) with complete dosimetric data
- 7 studies (822 patients) reported NTCP modeling

Preliminary search and summary by Chengbo Han

Earlier Reports on Chest Wall Pain (CWP)



Han (Kong) et al, 2012

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Risk of Chest Pain after SBRT

- 22 studies including 2435 patients reported on chest pain after SBRT

Grade	CWP-1	CWP-2	CWP-3	CWP-4	CWP ≥ 2	CWP ≥ 3	Rib fracture
Involved studies	12	12	13	13	14	13	15
Enrolled patients	1097	1097	1597	1597	1242	1597	1866
Events	99	81	52	1	136	53	189
Rate %	9.0	7.4	3.3	0.0	11.0	3.3	10.1

CWP: chest wall pain

Summarized by Han 2014

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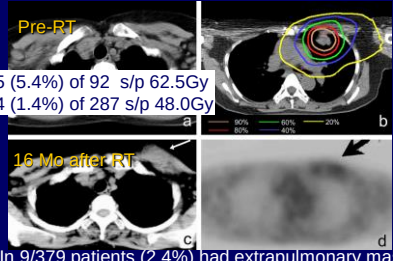
Extrapulmonary Fibrosis



5 (5.4%) of 92 s/p 62.5Gy
4 (1.4%) of 287 s/p 48.0Gy

In 9/379 patients (2.4%) had extrapulmonary masses at 3–36 months (median14) after SBRT.

Kawase et al, Red Journal, 2009

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Proximal Bronchial Tree Toxicity

- 11 studies (327 patients) reported clinical toxicity
- 4 studies (154 patients) with partial dosimetric data
- 1 study (74 patients) reported complete dosimetric data
- 1 study (17 patients) reported NTCP modeling

Preliminary search and summary by Weili Wang

Brachial Plexopathy

- University of Indiana:
  - 37 apical lesions/36 patients (epicenter above aortic arch), treated with 3 fractions
  - CTCAE v. 3.0 for ipsilateral shoulder/arm neuropathic pain, motor weakness, or sensory alteration.
  - 7 (2.5%) developed grade 2-4 plexopathy
    - 4 pts - grade 2
    - 2 pts - grade 3
    - 1 pt - grade 4

Two-year Kaplan-Meier risk of brachial plexopathy

Maximum brachial plexus dose	Risk
>26Gy	46%
<=26Gy	8% (p=0.04).

Forquer et al, Radiother Oncol, 2009 Dec;93(3):408-13

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Esophageal Toxicity

- 8 studies 873 patients
  - 44 G3+ events (G3 in 28pts, G4-5 in 16pts).
- 4 studies reported dosimetric data
- Only 1 study reported the NTCP model
- Radiation dose is the most important factor
- Systemic chemotherapy seems to be a major contributing risk factor for serious toxicity

Preliminary search and summary by Nan Bi

- QUANTEC group is working, working… and working hard…
- Model needs more and better data
- Patients are coming…
- Physician again is asking: What is safe? Can I treat larger tumors? Can I treat central tumors?

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Dose Limits of US Studies

Table 37.1. Normal Tissue Constraints Used in Major Clinical Trials[a]

Organ at Risk	One Fraction (RTOG 0915)	Three Fractions (RTOG 0618/1021)	Four Fractions (RTOG 0915)	Five Fractions (RTOG 0813)	Eight Fractions[b]
Trachea and large bronchus	D_{max} 20.2 Gy	D_{max} 30 Gy	D_{max} 34.8 Gy 15.6 Gy < 4 cc	D_{max} 105%[b] 18 Gy < 5cc[c]	D_{max} 44 Gy
Heart	D_{max} 22 Gy 16 Gy < 15 cc	D_{max} 30 Gy	D_{max} 34Gy 28 Gy < 15 cc	D_{max} 105%[b] 32 Gy < 15 cc	—
Esophagus	D_{max} 15.4 Gy 11.9 Gy < 5 cc	D_{max} 25.2 Gy 17.7 G < 5 cc	D_{max} 30Gy 18.8 Gy < 5 cc	D_{max} 105%[b] 27.5 Gy < 5 cc[c]	D_{max} 40 Gy
Brachial plexus	D_{max} 17.5 Gy 14 Gy < 3 cc	D_{max} 24 Gy 20.4 Gy < 3 cc	D_{max} 27.2 Gy 23.6Gy < 3 cc	D_{max} 32 Gy 30 Gy < 3 cc	D_{max} 36 Gy
Chest wall	D_{max} 30 Gy 22 Gy < 1 cc	30 Gy < 30 cc 60 Gy < 3 cc	D_{max} 27.2 Gy 32Gy < 1 cc	30 Gy < 30 cc 60 Gy < 3 cc	—
Spinal cord	D_{max} 14 Gy 10 Gy < 0.35 cc	D_{max} 18 Gy	D_{max} 26Gy 20.8Gy < 0.35 cc	D_{max} 30 Gy 22.5 Gy < 0.25 cc	D_{max} 28 Gy

[a]Radiation Therapy Oncology Group (RTOG) protocols can be found on the RTOG website at www.rtog.org/ClinicalTrials/ProtocolTable.aspx.
[b]Planning target volume prescription.
[c]Volume constraint for nonadjacent wall.

Senan et al, SABR chapter, Textbook of IASLC, 2013

OAR Dose Limits from Japan JCOG0403

PRV	Limited dose / fraction	Limited volume
Lung	40Gy / 4 fractions	< or = 100 mL
	Mean dose < or = 18 Gy	Lung minus GTV
	V15 < or = 25%	Lung minus GTV
	V20 < or = 20%	Lung minus GTV
Spinal cord	25Gy / 4 fractions	Max dose
Esophagus and pulmonary artery	40Gy / 4 fractions	< or = 1mL
	35Gy / 4 fractions	< or = 10 mL
Gastrointestine	36Gy / 4 fractions	< or = 10mL
	30Gy / 4 fractions	< or = 100 mL
Trachea and main bronchus	40Gy / 4 fractions	< or = 10mL
Other organs (except for chest wall)	36Gy / 4 fractions	< or = 1mL
	30Gy / 4 fractions	< or = 10 mL

Radiation Oncology PRV=OAR+3-5mm Courtesy of H Onishi

Dose Limits of OARs from EORTC

EORTC protocol 22113-08113

	α/β	allowed maximum dose (0.5 cc)	EqD2	Volume constraints
Spinal cord	2	8*4 = 32 Gy	48	No constraints specified
Oesophagus	3	8*5 = 40 Gy	64	No constraints specified
Brachial plexus	3	8*4.75 = 38 Gy	58.9	No constraints specified
Heart	3	8*7.875=63 Gy		<= 38 Gy to 15 cc One third not more than 27 Gy
Trachea/main bronchi	3	8*5.5 = 44 Gy	74.8	No constraints specified
Lungs-CTV		no restriction but recording of DVH data for toxicity evaluation		No constraints specified
Chest wall, Vertebral body, Liver		no restriction but recording of DVH data for toxicity evaluation		No constraints specified

Table 4 Maximum tolerated doses at the OAR to be used as constraints for this trial. SBRT being delivered in 8 fractions(8x 7.5 Gy i.e. BED 105 Gy to the tumor with α/β=10.)

PIs: U Nestle and C Le Pechoux

Courtesy of S Senan

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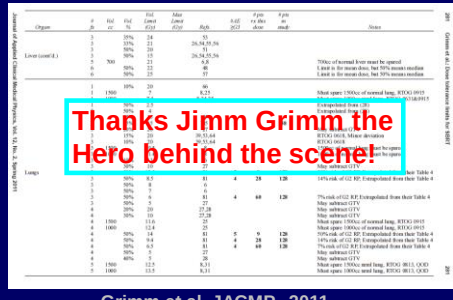
Safe Limits from All Clinical Trials



Thanks Jimm Grimm the Hero behind the scene!

Grimm et al, JACMP, 2011

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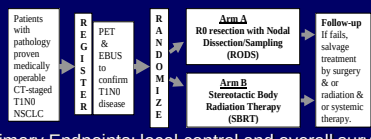
A Randomized Trial in Patients with Operable Stage I Non-Small Cell Lung Cancer: Radical Resection Vs Ablative Stereotactic Radiotherapy (POSTILV)

RTOG foundation study 3502



Primary Endpoints: local control and overall survival

Radiation oncologist PIs: J Yu, FM Kong

Surgeon PIs: Y Wu/W Mao, Chang/Orringer/D'Amico

Physicist PIs: F Yin, Y Xiao, J Yue….

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Veterans Administration Lung cancer surgery Or stereotactic Radiotherapy (VALOR) trial

- ❑SBRT vs Surgery (lobectomy)
- ❑LOI submitted to central clinical trial office
- ❑Preliminary estimates: $19.2M for 24 centers to enroll over 8 years at the cost of $100,000/ctr/yr ~ 5 truebeam linacs

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Thank You! Thoracic NTCP WG

Co-Chairs
- Feng-Ming (Spring) Kong, MD PhD
- Michael Milano, MD
- Ellen Yorke, PhD

Expert Members:
- Soren Bentzen, PhD
- Louis Constine, MD
- Shiva Das, PhD
- Andy Jackson, PhD
- Tamara LaCouture, MD
- Allen Li, PhD
- Zhongxing Liao, MD
- Lawrence Marks, MD
- Mary Martel, PhD
- Moyed Miften, PhD
- Andreas Rimner, MD
- Timothy Solberg, PhD
- Robert Timmerman, MD
- Sue Tucker, PhD

Literature search and primary reviewers:
- Lung: Jing Zhao MD PhD and Ling Li, MD PhD
- Chest wall/Rib: Chengbo Han MD PhD
- Proximal bronchial tree: Weili Wang, MD PhD
- Esophagus: Nan Bi, MD PhD
- Brachial plexus: Fang Peng, MD, MS
- Heart: Nan Bi, MD PhD

Secondary reviewers (assignment completed):
- Ellen Yorke, PhD
- Michael Milano, MD
- Shiva Das, PhD
- Allen Li, PhD
- …
- Moyed Miften, PhD
- Andreas Rimner, MD

Thank you Dr. Onishi, Dr. Nagata, Dr. Timmerman, Dr. Senan, Dr. Dr. Grimm for slides!!

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