The Evolution of SBRT and Hypofractionation in Thoracic Radiation Oncology

(specifically, lung cancer)

2/10/18

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Outline

- The history of definitive radiotherapy for lung cancer
  - Dose escalation without chemo improves local control
  - Improved technology allows further dose escalation safely
  - Benefit of extreme dose escalation is complicated
  - In modern era, we have hit a wall
  - Technology aside
  - New technologies improve accuracy, open a door
- Searching for a different path
  - Development of SBRT in Japan
  - Phase I in US
  - RTOG 0236 - Changing the game
  - Radiobiology aside
  - Population studies show survival advantage
- Future directions for SBRT
  - Towards ideal fractionation for central/ultracentral
  - Expanding the pool of pts – treating T3
  - RTOG 0915 – can we use 1 fraction?
- Applying the principles of SBRT to stage III
  - Hypofractionation without chemotherapy (60 Gy/15 fx)
  - Hypofractionation with concurrent chemotherapy (RTOG 1106)
  - SBRT boost
- Conclusion

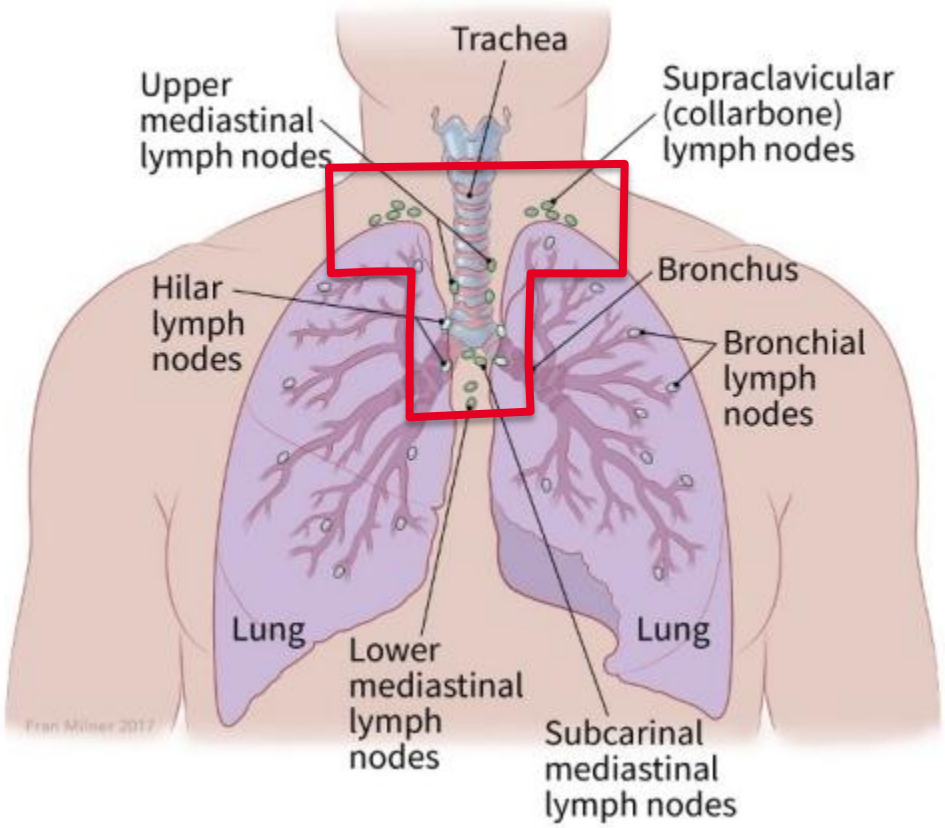
Lung Cancer Staging

- **Stage I-II**
  - **N0-N1**
- **Stage III**
  - **Any N2-3**
  - **(T3N1)**
  - **(T4N0)**

T/M	Label	N0	N1	N2	N3
T1	T1a ≤1	IA1	IIB	IIIA	IIIB
	T1b >1-2	IA2	IIB	IIIA	IIIB
	T1c >2-3	IA3	IIB	IIIA	IIIB
T2	T2a Cent, Visc Pl	IB	IIB	IIIA	IIIB
	T2a >3-4	IB	IIB	IIIA	IIIB
	T2b >4-5	IIA	IIB	IIIA	IIIB
T3	T3 >5-7	IIB	IIIA	IIIB	IIIC
	T3 Inv	IIB	IIIA	IIIB	IIIC
	T3 Satell	IIB	IIIA	IIIB	IIIC
T4	T4 >7	IIIA	IIIA	IIIB	IIIC
	T4 Inv	IIIA	IIIA	IIIB	IIIC
	T4 Ipsi Nod	IIIA	IIIA	IIIB	IIIC
M1	M1a Contr Nod	IVA	IVA	IVA	IVA
	M1a Pl Dissem	IVA	IVA	IVA	IVA
	M1b Single	IVA	IVA	IVA	IVA
	M1c Multi	IVB	IVB	IVB	IVB

Detterbeck FC et al. Chest 2017;151(1):193-203.

Lung Cancer Staging



Radiation for stage III NSCLC

- **Current standard of care for unresectable stage III:**
  - **60 Gy/30 fx with concurrent chemotherapy**
- **Management of potentially resectable stage III is controversial**
  - **Not addressed here**

How did we get here?

A (BRIEF) HISTORY OF DEFINITIVE RADIOTHERAPY FOR LUNG CANCER

Dose escalation improves LC

RTOG 73-01

- **Unresectable NSCLC**
- **Randomized**
- **40 Gy split course or 40 Gy, 50 Gy, or 60 Gy continuous**
  - **No chemo**
  - **Old radiation techniques (2D)**
- **LC rates increased with dose: 52%, 62%, and 73%, respectively**
- **No difference in OS (MS ~ 10 mos and 3 yr OS <10%)**

Perez CA et al. Cancer 1987. Jun 1;59(11):1874-81.

Improved technology allows further escalation

RTOG 93-11

- **Unresectable NSCLC**
- **Used 3D technology (CT scans!)**
- **Ph I-II dose escalation study**
- **Sequential chemotherapy**
- **Escalated to 90.3 Gy @ 2.15 Gy/fx based on dose to normal lung (V20)**
- **Maximum tolerated dose:**
  - **83.8 Gy/39 fx in low V20 group**
  - **77.4 Gy/36 fx in high V20 group**

Bradley J et al. Int J Radiat Oncol Biol Phys. 2005 Feb 1;61(2):318-28.

Modern era incorporates chemo

- **Current standard is <u>concurrent</u> chemotherapy**
  - **Concurrent > sequential > dose-escalated RT alone**

We've reached a wall

RTOG 0617

- **Stage III, unresectable pts only**
- **Ph III – 2 x 2 trial**
  - **Concurrent + consolidation carbo/paclitaxel**
  - **74 vs 60 Gy +/- cetuximab**
- **74 Gy vs 60 Gy**
  - **No improvement in LF (1 yr):**
    - **24.8% vs 16.3% (p=0.13)**
  - **Detriment to OS (1 yr):**
    - **69.8% vs 80% (p=0.004)**

Bradley JD et al. Lancet Oncol. 2015 Feb;16(2):187-99.

Where do we go from here?

- Stuck with 60 Gy in 2 Gy fractions with chemo?
- Clues from RTOG 0617
  - Allowed 3D conformal OR IMRT
    - Approx 50% each
  - IMRT:
    - Less risk of severe pneumonitis
    - Lower cardiac dose
    - No difference in outcomes – despite more advanced tumors
  - Cardiopulmonary toxicity from dose escalation may have been clinically meaningful
- Further technologic advances may open a door

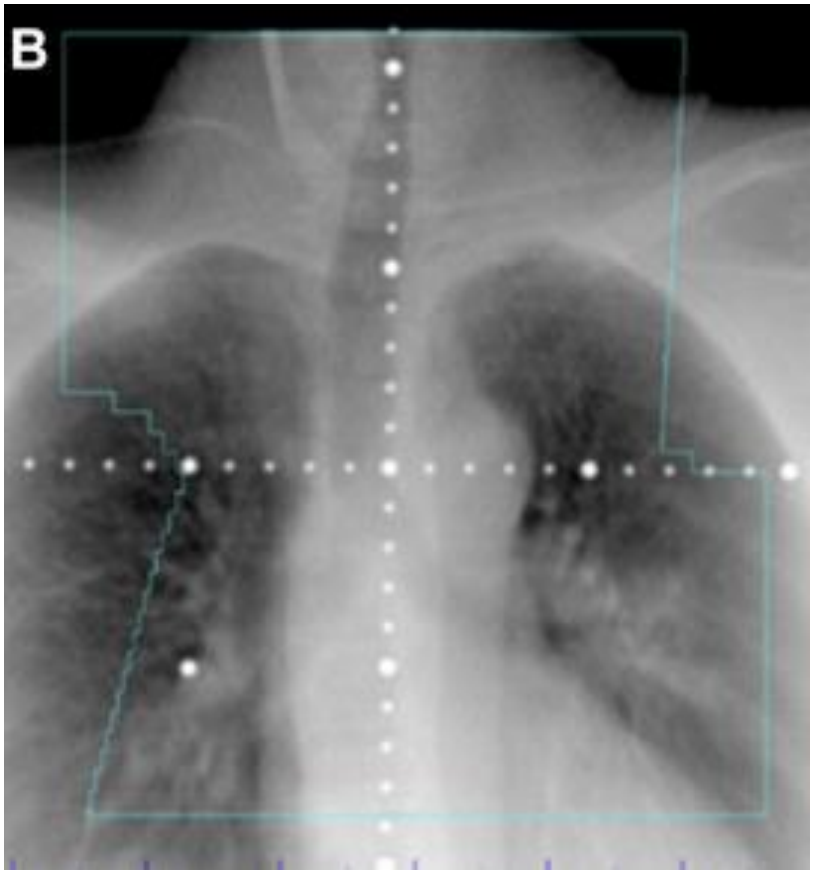
Chun SG et al. J Clin Oncol. 2017 Jan;35(1):56-62.

Quick technology aside

- 2D
- 3D
- IMRT

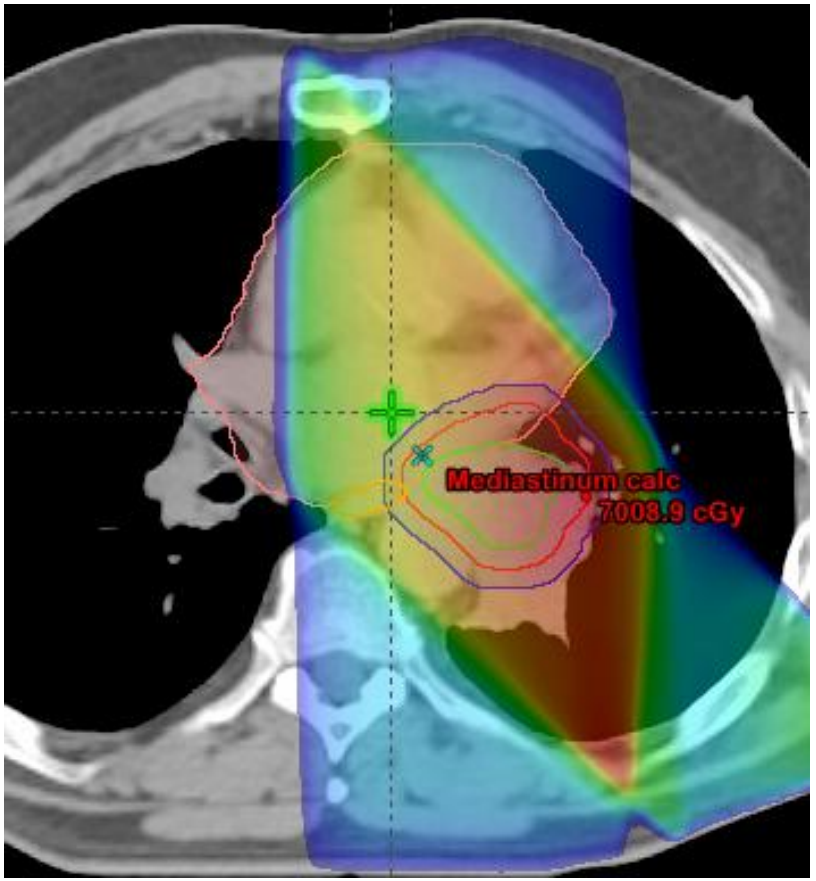
2D planning

- Oldest technique
- Radiographs are taken with fluoro
- Fields are drawn on radiographs
- Limited ability to spare normal structures



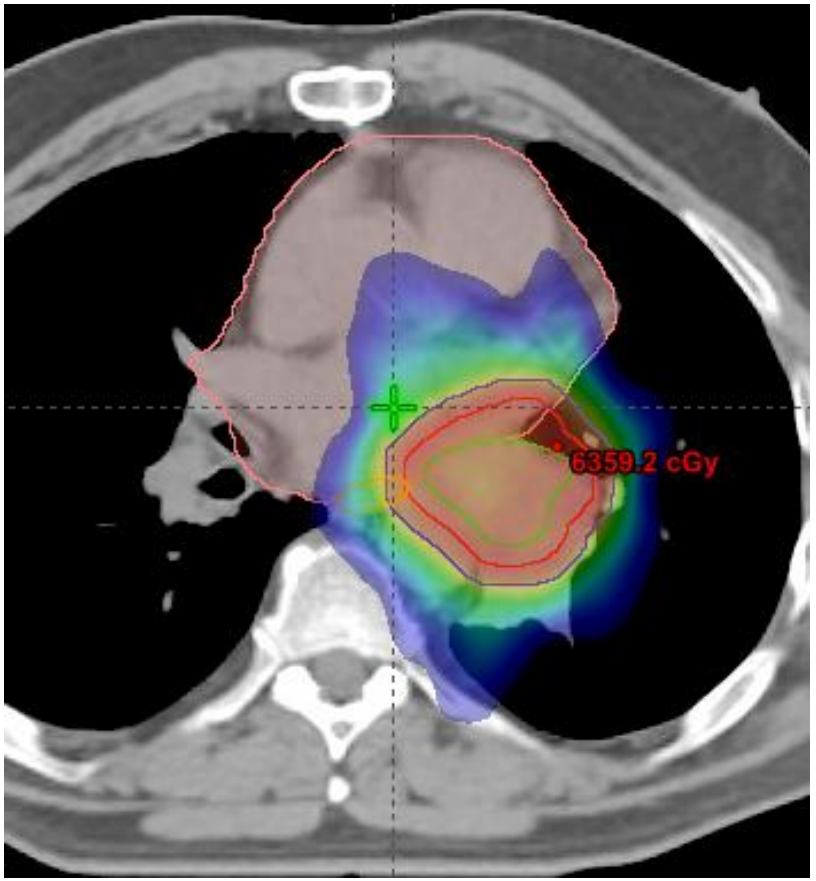
3D conformal radiation

- Uses CT for planning
- Manual planning
  - Desired dose distribution achived through trial and error
- Moderate ability to spare normal structures

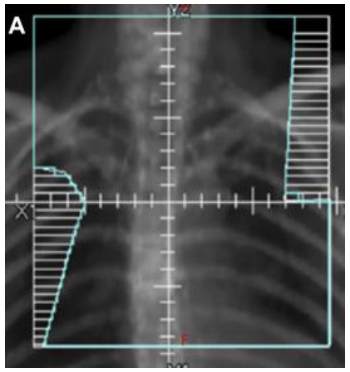


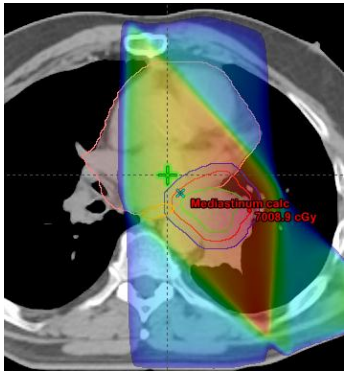
IMRT

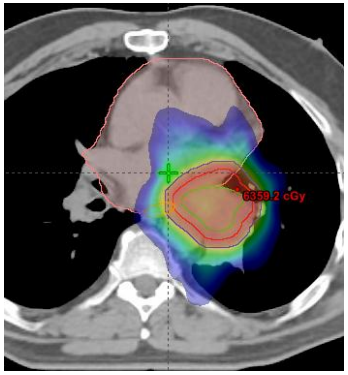
- Newest technique
- Computer algorithms try thousands of different plans to optimize dose distribution
- Significantly improves ability to spare normal structures



2D vs 3DCRT vs IMRT







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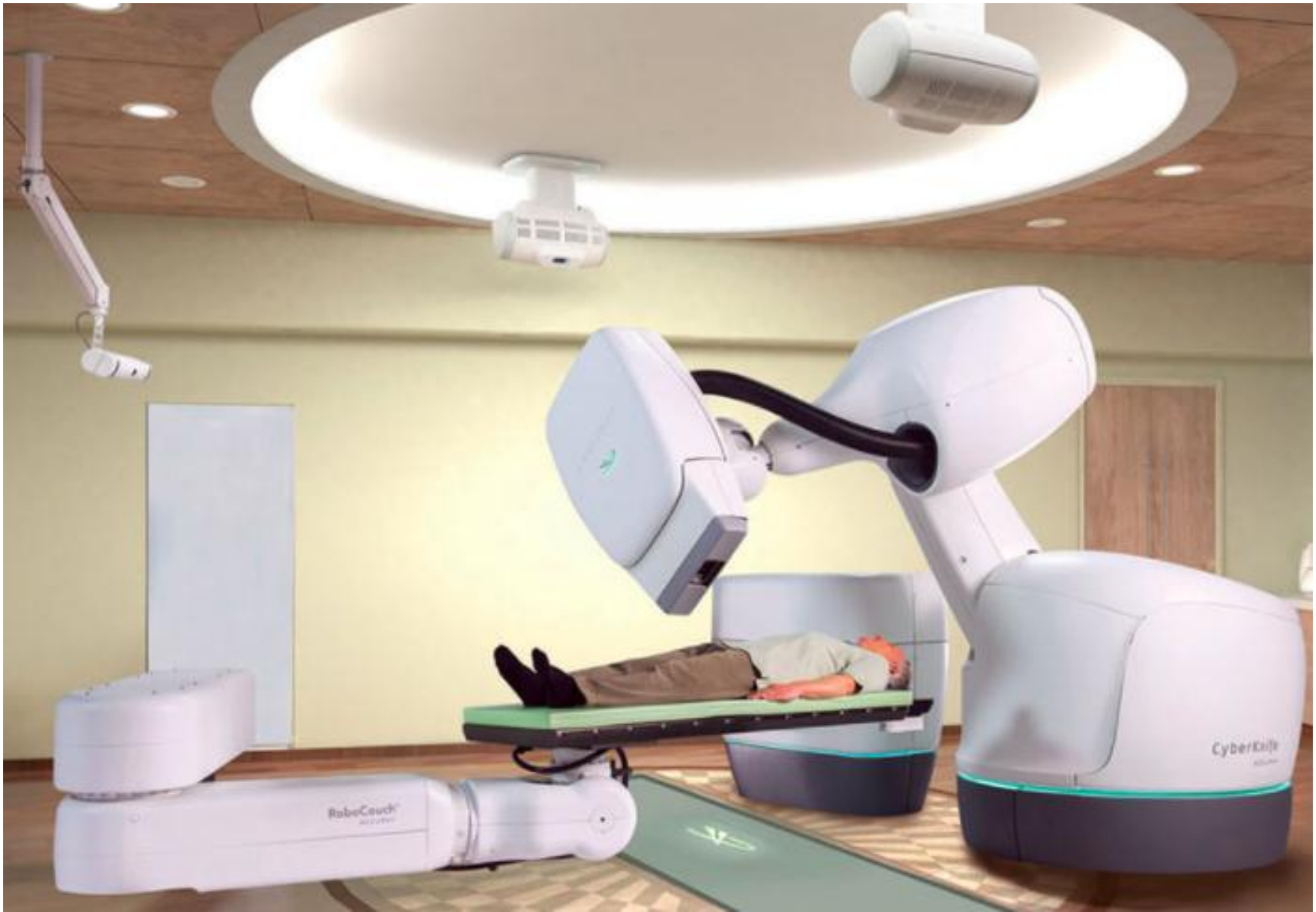
New technologies improve accuracy

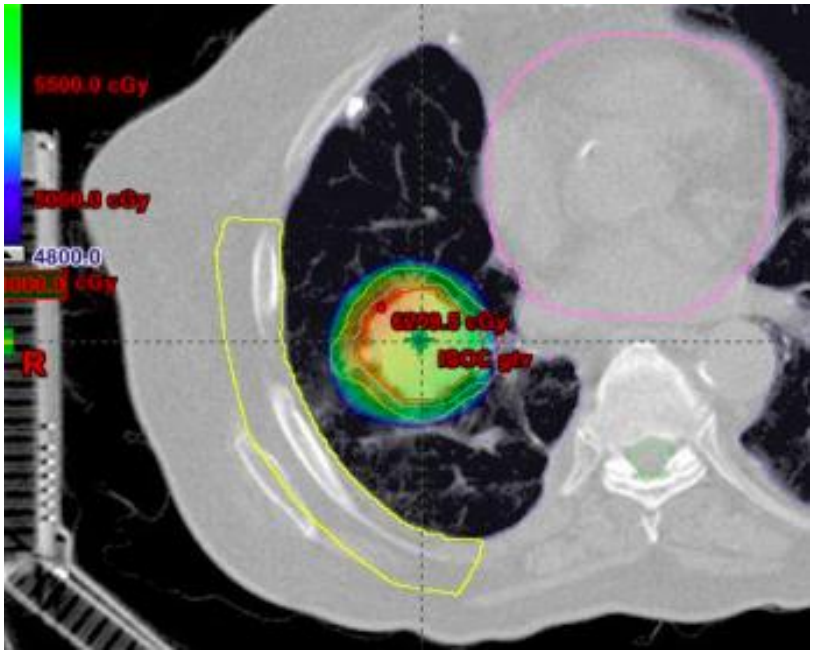


The development of SBRT

SEARCHING FOR A NEW PATH

Lung SBRT

- **“Stereotactic body radiation therapy”**
- **Developed in Japan**
- **Uses advanced planning and motion management**
- **High dose to tumor, low dose to everything else**

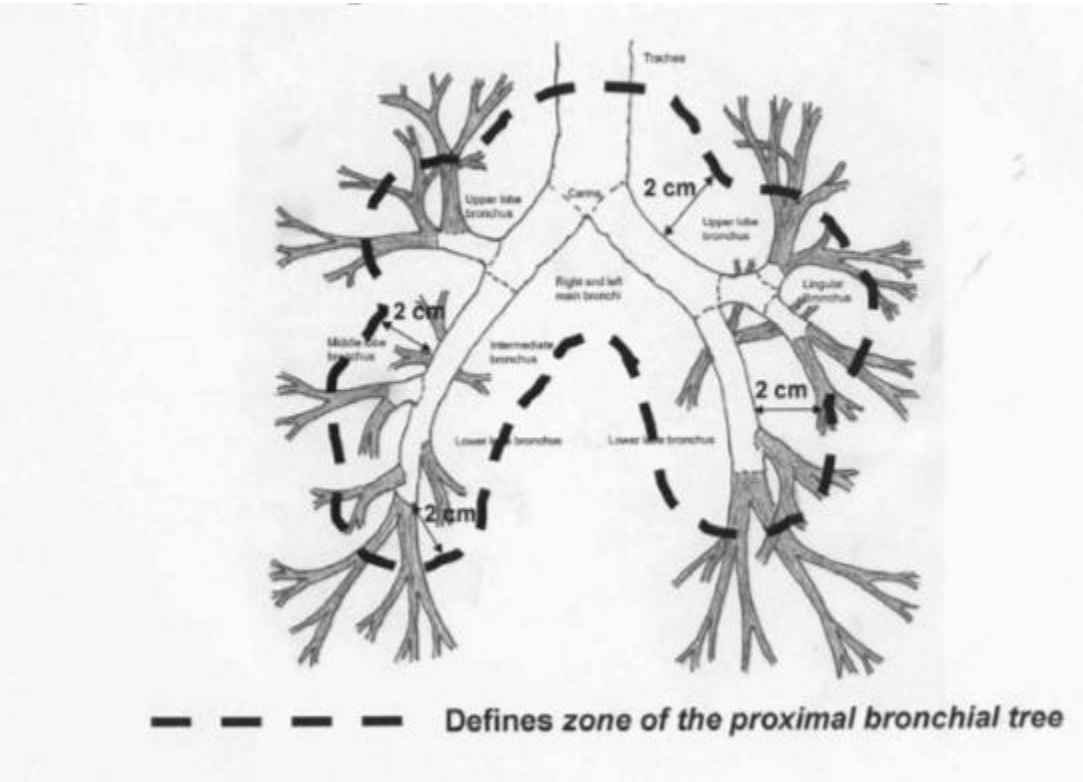


Initial US experience

- **Ph I**
  - **37 pts, medically inoperable**
  - **Dose escalation from 8 Gy x 3**
  - **Maximum dose: 20 Gy x 3**
- **Ph II**
  - **70 pts, medically inoperable**
  - **60-66 Gy in 3 fx**
  - **LC (2 yr): 95%**
  - **High toxicity for central tumors**

Timmerman R et al. Chest. 2003 Nov;124(5):1946-55.
Timmerman R et al. J Clin Oncol. 2006 Oct 20;24(30):4833-9.

Central “no fly zone”



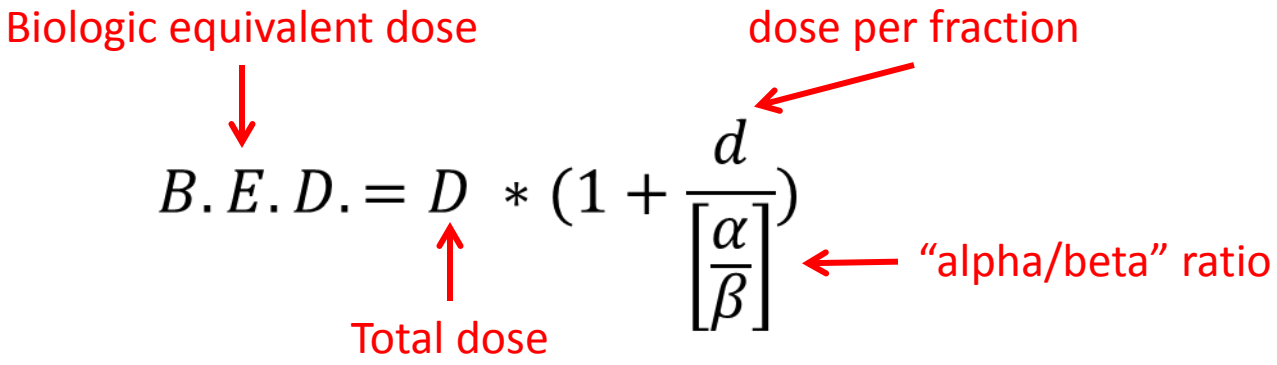
RTOG 0236 – Changing the game

- **Ph II multi-institutional**
- **55 pts**
- **Medically inoperable**
- **“Peripheral” tumors, T1-2 (≤ 5 cm) N0**
- **60 Gy in 3 fractions**
- **Results (long-term update):**
  - **Primary tumor failure (5 yr): 7%**
  - **Local failure (tumor + lobe, 5 yr): 20%**
  - **Regional failure (5 yr): 18%**
  - **Distant failure (5 yr): 31%**
  - **OS (5 yr): 40%, median OS: 4 yr**

Timmerman R et al. JAMA. 2010 Mar 17;303(11):1070-6.
Timmerman R et al. IJROBP Sept 2014 S30 Abstract #56.

High dose, greater effect

- "Biologic equivalent dose"
- "Linear quadratic equation"
  - Based on cell culture exposed to varying doses of radiation
  - Allows conversion between schedules



BED substantially increased with SBRT

BED[(α/β) =10]:

- **Conventional Fractionation**
  - 72 Gy: 60 Gy in 30 Fx
  - 84 Gy: 70 Gy in 35 Fx
  - 88.8Gy: 74 Gy in 37Fx
- **Hypofractionation/SBRT**
  - 96 Gy: 60 Gy in 10 Fx
  - 106 Gy: 48 Gy in 4 Fx (Japan Oncology Group)
  - 112.5 Gy: 50 Gy in 4 Fx (MD Anderson, PTV)
  - 119 Gy: 70 Gy in 10 Fx (MD Anderson, GTV)
  - 151.2 Gy: 54 Gy in 3 Fx (RTOG, STAR Trial)
  - 180 Gy: 60 Gy in 3 Fx (RTOG, 80% Isodose)

But why?

- **Pro-apoptotic**
- **Vascular**
- **Immunologic**

Future directions for SBRT

- **Central tumors**
  - **Initially a “no fly zone”**
    - **High rate of severe toxicity in central patients with 60 Gy/3 fx**

Timmerman R et al. J Clin Oncol. 2006 Oct 20;24(30):4833-9.

Future directions for SBRT

Central tumors

- **RTOG 0813 – Ph I-II 50-60 Gy/5 fx**
  - **Results:**
    - **3 G5 toxicities in highest dose cohorts**
    - **None in 50 Gy/5 fx cohort**
    - **High local control**
- **Adaptive: 60 Gy/8 fx, 60-70 Gy/10 fx**
  - **High BED, excellent control (90%+)**
  - **Some studies show no G5 toxicities**
  - **In contrast, other series show higher rates**
- **Still learning**
  - **Unclear what is treatment vs tumor related**
  - **Not all central created equal → "ultracentral"**

Bezjak A et al. Int J Radiat Oncol Biol Phys 2016 Oct 1;96(2):S8.
Haasbeek CJA et al. J Thorac Oncol 2011;6(12):2036-2043.

Future directions for SBRT

- **Large tumors**
  - **RR of 40 pts treated with SBRT**
  - **All had tumors > 5 cm**
  - **LC (18 mo): 91.2%**
  - **G3+ toxicity: 7.5%**

Woody NM et al. Int J Radiat Oncol Biol Phys 2015;92(2):325-331

Future directions for SBRT

- **Chest wall invasion**
  - **13 pts, RR**
  - **LC (1 yr): 89%**
  - **2 of 13 (15%) experienced new or worsening CW pain (both grade 2)**

Berriochoa C et al. Clin Lung Cancer. 2016 Nov;17(6):595-601.

Future directions for SBRT

- **Single fraction**
  - **RTOG 0915 – randomized Ph II**
  - **48 Gy/4 fx vs 34 Gy/1 fx**
  - **High local control (1 yr): 92.7 vs 97.0%**
  - **Statistically similar OS and DFS but numerical differences**
  - **Needs further study**

Videtic et al. Int J Radiat Oncol Biol Phys 2015;93(4):757-764.

Future directions for SBRT

- Central tumors can be done safely
  - Moving towards ideal fractionation for ultracentral tumors
- Large tumors (> 5 cm) – safe, effective
- Chest wall invasion – safe, effective
- Single fraction – needs further study, option in poor performing pts

The rise of hypofractionation

APPLYING THE PRINCIPLES OF SBRT TO STAGE III

Hypofractionation for stage III – a new way forward?

- Ph I dose escalation
- "Locally advanced," stage II-IV
- Pts ineligible for resection, SBRT, or concurrent chemoRT
- 55 pts, 3 dose levels: 50-55-60 Gy in 15 fx
- Used IMRT and respiratory motion management to restrict dose to normal tissues
- Results:
  - MTD not reached
  - Even higher doses well-tolerated
  - No association between dose level and toxicity
  - Median OS 6 mo, no difference between dose levels
- Randomized ph III testing OS in progress

Timmerman R et al. Int J Radiat Oncol Biol Phys 2015;93(1):72-81.

Combining paradigms – hypofractionation and chemoRT

- **RTOG 1106**
  - **Randomized ph II**
  - **Stage IIIA/IIIB**
  - **Concurrent carbo/paclitaxel + consolidation x2 cycles**
  - **60 Gy/30 fx vs up to 80.4 Gy/30 fx**
    - **Using mid-treatment PET/CT to adapt volumes**
    - **Maximum tumor dose scaled to normal tissue dose**
  - **Primary endpoint: 2 yr locoregional PFS**
  - **Closed, awaiting results**

Combining paradigms – SBRT boost

- U Kentucky ph II (37 pts)
  - Residual disease after chemoRT
  - Boost with SBRT to achieve BED 100 Gy
  - Well-tolerated, promising local control
- Brown ph I (12 pts)
  - ChemoRT to 50.4 Gy
  - Dose escalation of SBRT boost to primary and LN – 16 to 28 Gy/2 fx
  - MTD not reached, 100% 1 yr LC at higher dose levels

Kumar S et al. Int J Radiat Oncol Biol Phys 2017;99(3):652-659.
Hepel JT et al. Int J Radiat Oncol Biol Phys 2016;96(5):1021-1027.

Conclusion

- Technologic advance is allowing new approaches
- Future of thoracic radiation oncology:
  - Higher dose to tumor
  - Less dose to normal tissue
- Awaiting results of recent trials before putting into widespread practice

Thank you

Benefit of dose escalation complicated

- RTOG 93-11 showed no difference in LC or OS
- Multiple other trials showed benefit to dose escalation
  - e.g. Michigan Ph I
  - Escalated to 103 Gy
  - For 63-69, 74-84, and 92-103 Gy:
    - The 5-year control rate was 12%, 35%, and 49%
    - 5-year OS was 4%, 22%, and 28%

Bradley J et al. Int J Radiat Oncol Biol Phys. 2005 Feb 1;61(2):318-28.
Kong FM et al. Int J Radiat Oncol Biol Phys. 2005 Oct 1;63(2):324-33.

Confounding factors muddy the waters

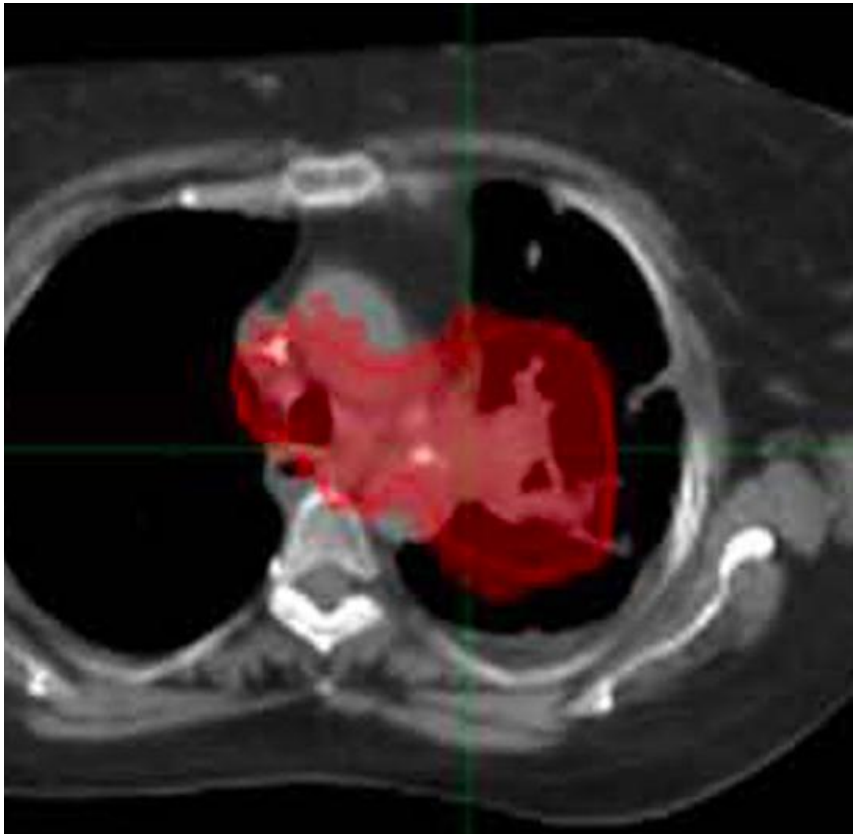
- Heterogenous trials
  - Included stage I-III
  - No PET staging
  - Small trials
  - Variable use of chemo
    - 15-20% of patients
    - Given sequentially
- Even with 3D planning, still old radiation techniques
- High rate of distant failure

Early stage lung cancer is a unique opportunity

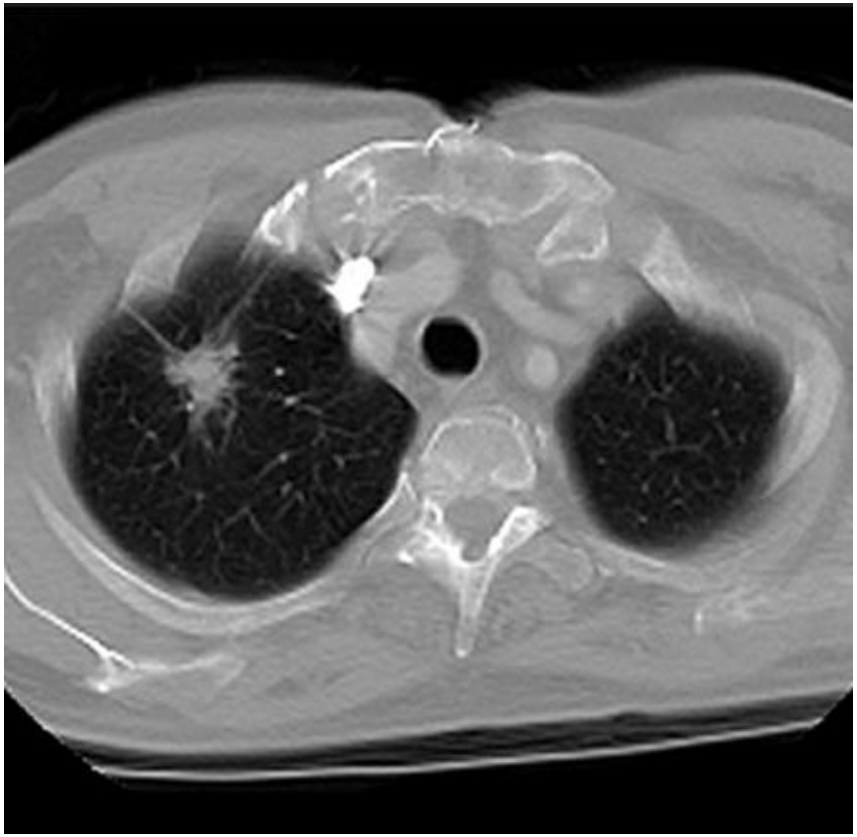
- Lower risk of distant failure
  - Local control more important
- Small tumors
- Further from critical structures

A different animal

Locally advanced NSCLC



Early stage NSCLC



Survival improvement with SBRT

- **Stage I NSCLC treated with radiotherapy**
- **VA database**
- **11,997 pts**
- **Adoption of SBRT doubled 4 yr OS (12.7% to 28.5%)**

Boyer MJ et al. J Thorac Oncol. 2017 Dec;12(12):1814-1823.

Dose threshold important for maximum control

- **LF for BED < vs ≥ 100 Gy: 42.9 vs 8.4%**
- **Sig**