The Evolution of SBRT and Hypofractionation in Thoracic Radiation Oncology

(specifically, lung cancer)

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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)

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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%)

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

Modern era incorporates chemo

- Current standard is concurrent 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)

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

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 achieved 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

The Future?
New technologies improve accuracy

- 3D motion management
  - 4DCT
  - Breath hold
- CyberKnife
SEARCHING FOR A NEW PATH

The development of SBRT
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

Central “no fly zone”

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Defines zone of the proximal bronchial tree
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. 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

\[ B.E.D. = D \times \left(1 + \frac{d}{\frac{\alpha}{\beta}}\right) \]

- Biologic equivalent dose
- Total dose
- “alpha/beta” ratio
- dose per fraction
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
  - 88.8 Gy: 74 Gy in 37 Fx
- 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

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”

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%

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)

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

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

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

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%

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%)

Dose threshold important for maximum control

- LF for BED $< 100$ Gy: 42.9 vs 8.4%
- Sigmoidal response curve

![Graph showing sigmoidal response curve with data points and fit parameters.](Image)