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

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Augusta, Georgia

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

High Dose SBRT/SABR Is Powerful

- Japanese study, 50 Gy in 4 fractions, BED≥100 Gy provides 92% tumor control
- Germany study, confirmed tumor control plateau at BED110-140 Gy
- Timmerman for 54-60 Gy in 3 Fx, 18Gy/Fx, BED 160-180 Gy, 98% tumor control at 2 years
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), Rad J, in press, 2014

Technology Makes SBRT Possible

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

SBRT Toxicity Is Limited

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

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

Grutters et al, Radiat Oncol, 2009
Everybody’s Doing It

Courtesy of Dr. Bogart

Tumors Treated with SBRT

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

SBRT is safe with conditions!!

Zhao (Kong), ASTRO, 2014

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...

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.

Skin Reaction: Grade 2-4

- Grade 2 at 3 mo
- Grade 3 at 9 mo

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

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)

Grade 5 Radiation Pneumonitis

PTV=46.9 ml
V20 (lung-GTV)=12.0%
V50 (lung-GTV)=3.3%
MLD=12.9 Gy /4f

Pre SBRT

Onishi, ASTRO 2009

90 days after SBRT

Died 112 days after

110 days after SBRT

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
SBRT Quanpec: Thoracic NTCP WG

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

Expert Members:
• Soren Bentzen, PhD
• Louis Corrinette, MD
• Shilin Dai, PhD
• Andy Johnson, PhD
• Tiziana LaCour, MD
• Allen Li, PhD
• Zhongping Liao, MD
• Lawrence Marks, MD
• Mary Marit, MD
• Moyed Miften, PhD
• Andrea Rimner, MD
• Timothy Solberg, PhD
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• Sue Tucker, PhD

Literature search and primary reviewers:
• Lung: Jing Zhao MD PhD and Ling Li, MD PhD
• Chest wall/Rib: Chengbin Nan MD PhD
• Proximal bronchial tree: Nan Bi, MD PhD
• Esophagus: Nan Bi, MD PhD
• Brachial plexus: Feng Peng, MD, PhD
• 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

Thoracic Organs at Risk (OARs)
- Lung
- Proximal bronchial tree
- Chest wall
- Esophagus
- Brachial plexus
- Skin
- Great vessel/Heart/pericardium
- Spinal cord (CNS)

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%


Courtesy of Dr. Nagata

Department of Radiation Oncology • University of Michigan Health Systems
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

Radiation Lung Toxicity

Endpoints

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

DLCO Decreases after 3DRT but not after SBRT

*p=0.024

Samuels (Kong) et al, ASTRO, 2013
Post-SBRT Pulmonary Changes

Peripheral disease

Central Disease

Tumor Progression vs Inflammation?

Department of Radiation Oncology • University of Michigan Health Systems
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 Zhao1, L. Ling1, E. D. Yorke2, M. T. Milano2, W. Liu3, B. Kavanagh3, A. Li4, A Jackson4, L. B. Marks4, M. Miften5, A. Rimner4, T Sollberg6, J. Xue7, J. Grimm8, FM. Kong9

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

Will be presented as an oral at ASTRO, 2014

Department of Radiation Oncology • University of Michigan Health Systems
A Pooled Analysis of Published Studies

Studies of lung treated with SBRT/SABR (n = 294)

Potentially eligible studies (n = 167)

Studies with independent toxicity data (n = 125)

Studies included in this analysis (n = 67)

127 studies excluded
Review/protocol/comments/case report (n = 65)
Radiotherapy on cranial lesions (n = 28)
Treatment without SBRT/SABR (n = 12)
Patients with other tumors (n = 22)

42 studies excluded
no pathological diagnosis (n = 11)
Severe comorbidity before radiation (n = 3)
Previous radiation performed (n = 18)
Combined therapy with SBRT/SABR (n = 10)

57 studies excluded
Data incompleteness or missing (n = 54)
Data duplicated (n = 3)

a total of 5631 patients

Pooled Rates of RILT

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

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

Patient Factors & G2+ RILT

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

Dosimetric Factors & G2+RILT

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

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.
Tumor Factors and G3+RILT

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

![Graphs showing no significant correlations between G3+ RILT and GTV or PTV](image)

- Median GTV (cc)
  - Horizontal bar: range of the value
  - Vertical bar: 95% CI of the value

- 14 studies 1421 patients
- 21 studies 2641 patients

Dosimetric Factors and G3+RILT

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

![Graphs showing significant correlation between G3+ RILT and median V20](image)

- Median V20 (%)
  - Horizontal bar: range of the value
  - Vertical bar: 95% CI of the value

- 12 studies 1675 patients
- 12 studies 1753 patients

Selected Studies Reported MLD

<table>
<thead>
<tr>
<th>Author</th>
<th>Link</th>
<th>Lung definition</th>
<th>Toxicity grading</th>
<th>Median MLD G0-1</th>
<th>G2+ RILT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Takeda A, et al</td>
<td><a href="http://bjr.birjournal">http://bjr.birjournal</a></td>
<td>Both lungs-GTV</td>
<td>CTCAE</td>
<td>3.5</td>
<td>5.0</td>
</tr>
<tr>
<td>Matsuo Y et al</td>
<td><a href="http://www.sciencedirect.com">http://www.sciencedirect.com</a></td>
<td>Both lungs-PTV</td>
<td>CTCAE</td>
<td>NA</td>
<td>4.7</td>
</tr>
<tr>
<td>Ricardi U et al</td>
<td><a href="http://www.sciencedirect.com">http://www.sciencedirect.com</a></td>
<td>Ipsilateral lung-CTV</td>
<td>RTDG</td>
<td>1.9</td>
<td>2.0</td>
</tr>
</tbody>
</table>
DVH Factors and Radiation Pneumonitis

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

<table>
<thead>
<tr>
<th>RT pneumonitis</th>
<th>Grade 0, 1, 2 (n=10)</th>
<th>grade 5 (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFV</td>
<td>34.2±10.6 (57.3%)</td>
<td>77.0±243 (153.7%)</td>
<td>0.04</td>
</tr>
<tr>
<td>V25% (GTV50%)</td>
<td>2.8±15.4 (12.2%)</td>
<td>13.3±7.2 (6.3%)</td>
<td>0.01</td>
</tr>
<tr>
<td>V30% (GTV50%)</td>
<td>16.9±28.3 (19.9%)</td>
<td>21.2±4.0 (21.3%)</td>
<td>0.77</td>
</tr>
<tr>
<td>V40% (GTV50%)</td>
<td>0.0±4.3 (13.4%)</td>
<td>1.0±3.1 (13.0%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Mean lung (GTV)</td>
<td>2.1±1.8 (5.0) (1.0)</td>
<td>2.5±0.3 (5.0) (1.0)</td>
<td>0.15</td>
</tr>
</tbody>
</table>

* Mann-Whitney’s U-test

24 of 1789 patients from 8 centers (unpublished yet)

Courtesy of Dr. Onishi

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
- \gamma_{50}=2.19 (normalized slope)

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

- Reconstructed dose response model
- Logistic Model
- $D_{50}=19.7\text{Gy}$
- $\gamma_{50}=2.19$ (normalized slope)

Almost exactly same results from two modelists!!

DVH Risk Map

Comparison of many published dose tolerance limits

Ipsilateral Lung

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)

<table>
<thead>
<tr>
<th>BED (α/β=3)</th>
<th>Chest Wall Pain vs BED (α/β=3) from 18 studies 1911 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% CWP &gt;= G2 or G3 CWP (%) Expon. (&gt;=G2 or G3 CWP)</td>
</tr>
<tr>
<td>80.6Gy</td>
<td>7.6%</td>
</tr>
<tr>
<td>84.0Gy</td>
<td>7.1%</td>
</tr>
<tr>
<td>85.6Gy</td>
<td>7.6%</td>
</tr>
<tr>
<td>87.6Gy</td>
<td>7.6%</td>
</tr>
<tr>
<td>90.0Gy</td>
<td>7.6%</td>
</tr>
<tr>
<td>100.0Gy</td>
<td>7.6%</td>
</tr>
<tr>
<td>108.0Gy</td>
<td>7.6%</td>
</tr>
</tbody>
</table>

Risk of Chest Pain after SBRT

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

<table>
<thead>
<tr>
<th>Grade</th>
<th>CWP-1</th>
<th>CWP-2</th>
<th>CWP-3</th>
<th>CWP-4</th>
<th>CWP &gt;= 3</th>
<th>CWP &gt; 4</th>
<th>Risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Involved studies</td>
<td>12</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>14</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Enrolled patients</td>
<td>1097</td>
<td>1097</td>
<td>1597</td>
<td>1597</td>
<td>1242</td>
<td>1597</td>
<td>1666</td>
</tr>
<tr>
<td>Events</td>
<td>99</td>
<td>81</td>
<td>52</td>
<td>1</td>
<td>136</td>
<td>53</td>
<td>189</td>
</tr>
<tr>
<td>Rate %</td>
<td>9.0</td>
<td>7.4</td>
<td>3.3</td>
<td>0.0</td>
<td>11.0</td>
<td>3.3</td>
<td>10.1</td>
</tr>
</tbody>
</table>

CWP: chest wall pain

Summarized by Han 2014

Extrapulmonary Fibrosis

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

Kawase et al, Red Journal, 2009
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 Wei Li 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

Esophageal Toxicity

- 8 studies 873 patients
  - 44 G3+ events (G3 in 28pts, G4 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>
<thead>
<tr>
<th>Organ at Risk</th>
<th>Six Fractions (Median Dose)</th>
<th>Three Fractions (Median Dose)</th>
<th>Two Fractions (Median Dose)</th>
<th>One Fraction (Median Dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trachea and bronchi</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>7.5 Gy</td>
<td>3.75 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>7.5 Gy</td>
<td>3.75 Gy</td>
</tr>
<tr>
<td>Esophagus</td>
<td>37.5 Gy</td>
<td>18.75 Gy</td>
<td>9.375 Gy</td>
<td>4.6875 Gy</td>
</tr>
<tr>
<td>Renal pelvis</td>
<td>28.75 Gy</td>
<td>14.375 Gy</td>
<td>7.1875 Gy</td>
<td>3.59375 Gy</td>
</tr>
<tr>
<td>Clot wall</td>
<td>24 Gy</td>
<td>12 Gy</td>
<td>6 Gy</td>
<td>3 Gy</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>30 Gy</td>
<td>15 Gy</td>
<td>7.5 Gy</td>
<td>3.75 Gy</td>
</tr>
</tbody>
</table>

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

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OAR Dose Limits from Japan JCOG0403

<table>
<thead>
<tr>
<th>OAR</th>
<th>PRV 40 Gy / 4 fractions</th>
<th>PRV 35 Gy / 4 fractions</th>
<th>PRV 30 Gy / 4 fractions</th>
<th>PRV 25 Gy / 4 fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Max dose &lt; 18 Gy</td>
<td>Max dose &lt; 20 Gy</td>
<td>Max dose &lt; 20 Gy</td>
<td>Max dose &lt; 20 Gy</td>
</tr>
<tr>
<td>Esophagus and pulmonary artery</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
</tr>
<tr>
<td>Trachea and main bronchi</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
</tr>
<tr>
<td>Other organs (except for chest wall)</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
<td>Max dose &lt; 10 mL</td>
</tr>
</tbody>
</table>

PRV = OAR + 3-5 mm

Courtesy of H Onishi
**Dose Limits of OARs from EORTC**

EORTC protocol 22113-08113

<table>
<thead>
<tr>
<th>OAR</th>
<th>Maximum Allowed Dose (Gy)</th>
<th>Volume constraints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal chord</td>
<td>55</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>35 – 40 Gy</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Bronchial trunk</td>
<td>35 – 40 Gy</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Liver</td>
<td>37.5 – 40 Gy</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Trachea</td>
<td>35 – 40 Gy</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Lungs-CTV</td>
<td>No maximum tolerance</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Chest wall</td>
<td>No maximum tolerance</td>
<td>No constraints specified</td>
</tr>
<tr>
<td>Lung nodules</td>
<td>No maximum tolerance</td>
<td>No constraints specified</td>
</tr>
</tbody>
</table>

**Safe Limits from All Clinical Trials**

Grimm et al, JACMP, 2011

Thanks Jimm Grimm the Hero behind the scene!

**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,...
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

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
- Shino Da, PhD
- Andy Jackson, PhD
- Tamara Lackovic, MD
- Allen Li, PhD
- Zhangbing Liu, MD
- Lawrence Marks, MD
- Mary Miften, PhD
- Moyed Miften, PhD
- Andreas Rimner, MD
- Timothy Solberg, PhD
- Stuart Timmerman, MD

Literature search and primary reviewers:
- Lung: Jing Zhou MD PhD and Ling Li, MD PhD
- Distal bronchial tree: Wei Wang, MD PhD
- Esophagus: Fang Peng, MD, MS
- Heart: Nan Bi, MD PhD

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

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

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