Recent Advances In Brachytherapy: Unconventional Applications of Brachytherapy

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Outline

• Where are we, and where are we going with clinical applications of brachytherapy?
• Role of brachytherapy as a focal technique for ablation
  – SBRT/SABR and alternative techniques of ablation
• Review of unconventional brachytherapy techniques
  – Image-guided percutaneous techniques
  – Stereotactic implantation
• Minimally invasive implantation via Electromagnetic Guidance
• EM Guided HDR for ablative treatment of lung lesions
  – Navigation and implantation
  – Dose calculation
  – Dosimetry relative to SBRT/SABR
• Discussion
  – Limitations
  – Challenges
  – Future directions
Conventional Applications of Brachytherapy

- Where are we, and where are we going with clinical applications of brachytherapy?

Conventional Applications of Brachytherapy

- Gynecological
- Genitourinary
- Breast
- Skin
- Ocular
- Unsealed Sources
“Unconventional” Applications of Brachytherapy

- Less conventional techniques

- Brachytherapy is limited by implantation access
- New forms of minimally invasive implantation may be the key forward

Focal Treatments
- Image Guided Interstitial Implantation
- Ablative dosing
Paradigms for Focal and Ablative Delivery

**External Beam**
- SABR (SBRT)
- Robotic Radiosurgery

**Alternative techniques**
- Radiofrequency Ablation
- Cryoablation
- HIFU
- Microwave Ablation
- Electroporation


Cryoablation of Renal Tumors
Alternative Techniques

Microwave ablation

- Biological mechanism of action different for thermal ablation and radiotherapy
  - DNA damage via ionizing radiation vs. thermal ablation (RFA, Microwave, Cryo)

<table>
<thead>
<tr>
<th>RFA</th>
<th>Microwave ablation</th>
<th>Cryoablation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experience regarding efficacy and safety (most widely studied and most outcome data available)</td>
<td>Compared to RF ablation: Larger tumor ablation volume. Faster ablation time. More effective ablation of cystic masses. Less “heat sink” effect. Less tissue charring. Less procedural pain. No grounding pad needed</td>
<td>Compared to RF ablation: Larger tumor ablation volume. Less procedural pain. No grounding pads needed</td>
</tr>
<tr>
<td>Not suitable for tumors in mediastinum or lung apex due to non-target injury to neuro-vasculature structures and airways. Limited by “heat sink” effect from nearby vessels. Limited by tissue charring which may prevent tumor ablation at the periphery. Potential grounding pad injury</td>
<td>Limited safety and efficacy data available</td>
<td>Limited safety and efficacy data available. Longer procedural time due to freeze-thaw-freeze cycle. Higher hemorrhage risk secondary to lack of tissue cauterization</td>
</tr>
</tbody>
</table>

Courtesy of Lee et al., Transl Lung Cancer Res 2013;2(5):340-353
Stereotactic Ablative Radiotherapy (SABR/SBRT)

Advantages
- High local control rate
- Non-invasive
- Access anywhere in lung
- Dose conformality

Challenges
- Motion management
- Potential for geometrical miss
- Substantial volume of lung can receive lower doses
- Airway and lung collapse, radiation pneumonitis, lung fibrosis, or vertebral fracture
Range of Tumor Motion for SBRT Sites

Tumor trajectories of 23 patients, using tracking of implanted fiducials.
Seppenwoolde, et al., 2002

Table II. Abdominal motion data. The mean range of motion and the (minimum-maximum) ranges in millimeters for each site and each cohort of subjects. The motion is in the superior-inferior (SI) direction.

<table>
<thead>
<tr>
<th>Site</th>
<th>Observer</th>
<th>Shallow</th>
<th>Deep</th>
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<tbody>
<tr>
<td>Pancreas</td>
<td>Surano (Ref. 57)</td>
<td>20 (10–30)</td>
<td>43 (20–80)</td>
</tr>
<tr>
<td></td>
<td>Bryan (Ref. 59)</td>
<td>20 (0–35)</td>
<td>-</td>
</tr>
<tr>
<td>Liver</td>
<td>Weiss (Ref. 66)</td>
<td>13±5</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Harauz (Ref. 67)</td>
<td>14</td>
<td>-</td>
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<tr>
<td>Surano (Ref. 57)</td>
<td>25 (10–40)</td>
<td>55 (30–80)</td>
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<td>Davies (Ref. 58)</td>
<td>10 (5–17)</td>
<td>37 (21–57)</td>
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<td>Kidney</td>
<td>Surano (Ref. 57)</td>
<td>19 (10–40)</td>
<td>40 (20–70)</td>
</tr>
<tr>
<td>Davies (Ref. 58)</td>
<td>11 (5–16)</td>
<td>-</td>
<td></td>
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<tr>
<td>Diaphragm</td>
<td>Wade (Ref. 68)</td>
<td>17</td>
<td>101</td>
</tr>
<tr>
<td></td>
<td>Korin (Ref. 64)</td>
<td>13</td>
<td>39</td>
</tr>
<tr>
<td>Davies (Ref. 58)</td>
<td>12 (7–28)</td>
<td>43 (25–57)</td>
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</tr>
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</table>
Motion Management for External Beam

• Target motion is a major complicating factor in SABR/SBRT delivery
  – Note that implanted seeds move with target
• Targets must not only be localized in space but also in time

Motion Management Techniques:
  – Motion-encompassing irradiation
  – Compression
  – Breath-hold
  – Gating
  – Dynamic tracking delivery

Videos of thoracic target motion. Courtesy of R. Li
Brachytherapy as an Ablative Adjunct to SBRT

Advantages
- Deliver ablative doses to localized volume
- Rapid dose falloff for normal tissue sparing
- Motion management issues reduced
- Enhanced dosimetry / higher ablative doses

Challenges
- Access – need for minimally invasive implantation techniques
- Dependence on quality of implant
- Optimal dosing regimens need further investigation
Image-Guided Percutaneous Techniques

• Prospective Phase II trial (Ricke, et al.)
• 30 patients with 83 singular lesions
• Mean tumor diameter was 2.5 cm (0.6–11 cm).
• 20 Gy in a single HDR fraction
• Single applicator except 2 cases with 2
• Adverse effects: nausea (n = 3, 6%), minor (n = 6, 12%) and one major pneumothorax (2%)
• 91% local control at 12 months

Figure 1. Radiation treatment planning after application of the brachytherapy catheter. Note the steep gradient with the inner isodose illustrating a dose of 30 Gy, the outer isodose of 5 Gy. The depicted myelon receives a total dose of approximately 2 Gy.
Image-Guided Percutaneous Techniques

- Number of sites including liver, renal, lung, lymph nodes
- Survey of interstitial image-guided HDR of inner organs (Bretschneider, et al., 2016)

<table>
<thead>
<tr>
<th>Author</th>
<th>Entity</th>
<th>Patients/Tumors (n)</th>
<th>Tumor size (cm)</th>
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<tbody>
<tr>
<td>Ricke et al. [16]</td>
<td>Primary and secondary liver malignancies</td>
<td>37/38</td>
<td>4.6 (2.5-11)</td>
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<tr>
<td>Ricke et al. [17]</td>
<td>Primary and secondary liver malignancies</td>
<td>20/20</td>
<td>7.7 (5.5-10.8)</td>
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<tr>
<td>Mohnike et al. [31]</td>
<td>Hepatocellular carcinoma</td>
<td>75/126</td>
<td>4.4 (1-15)</td>
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<tr>
<td>Colettini et al. [18]</td>
<td>Hepatocellular carcinoma (≥ 5 cm)</td>
<td>35/35</td>
<td>7.1 (5-12)</td>
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<tr>
<td>Colettini et al. [32]</td>
<td>Hepatocellular carcinoma</td>
<td>98/192</td>
<td>5 (1.8-12)</td>
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<tr>
<td>Schnapauff et al. [62]</td>
<td>Intrahepatic cholangiocarcinoma</td>
<td>15/15</td>
<td>5.2 (1.18)</td>
</tr>
<tr>
<td>Ricke et al. [23]</td>
<td>Colorectal liver metastases</td>
<td>73/199</td>
<td>3.6 (1-13.5)</td>
</tr>
<tr>
<td>Colettini et al. [38]</td>
<td>Colorectal liver metastases</td>
<td>80/179</td>
<td>2.8 (8-10.7)</td>
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</tbody>
</table>

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<thead>
<tr>
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<th>Entity</th>
<th>Patients/Tumors (n)</th>
<th>Tumor size (cm)</th>
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</thead>
<tbody>
<tr>
<td>Wieners et al. [39]</td>
<td>Breast cancer liver metastases</td>
<td>41/115</td>
<td>4.4 (1-11)</td>
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<tr>
<td>Collettini et al. [40]</td>
<td>Breast cancer liver metastases</td>
<td>37/80</td>
<td>2.5 (0.8-4.7)</td>
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<tr>
<td>Wieners et al. [43]</td>
<td>Pancreatic cancer liver metastases</td>
<td>20/49</td>
<td>2.9 (1.0-7.3)</td>
</tr>
<tr>
<td>Riche et al. [57]</td>
<td>Primary and secondary lung malignancies</td>
<td>15/30</td>
<td>2 (0.6-11)</td>
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<tr>
<td>Peters et al. [56]</td>
<td>Primary and secondary lung malignancies</td>
<td>30/83</td>
<td>2.5 (0.6-11)</td>
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<tr>
<td>Collettini et al. [55]</td>
<td>Primary and metastatic lung malignancies</td>
<td>22/33</td>
<td>3.3 (1-8.6)</td>
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<tr>
<td>Bretschneider et al. [61]</td>
<td>Metastases of malignant melanoma</td>
<td>14/52</td>
<td>1.5 (0.7-10)</td>
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<tr>
<td>Collettini et al. [60]</td>
<td>Lymph node metastases</td>
<td>10/10</td>
<td>3.6 (1.2-6.7)</td>
</tr>
</tbody>
</table>
Image-Guided Percutaneous Techniques

- Limited number of catheters, 1-3
- Performed under local anesthesia, conscious sedation
- Generally well tolerated, limited complications relating to catheter insertion
- CT, MR imaging with 3D planning

Bretschneider, et al., Journal of Contemporary Brachytherapy (2016/volume 8/number 3)

Fahimian, AAPM 2017, Slide: 14
Image-Guided Percutaneous Techniques

CT Guided Planning

MR Guided Planning

Images Courtesy of Bretschneider, et al., Journal of Contemporary Brachytherapy (2016/volume 8/number 3)
Frameless Stereotactic Implantation of Head and Neck Lesions

Bane, et al., Radiology 2000; 591-595

Individualized 3D-Printed Templates for Head and Neck Brachytherapy

- Huang, et al.: 25 HN patients implanted with I-125 seeds
- Entrance deviation for 619 needles was 1.18 ±0.81 mm

Established Lung Brachytherapy Techniques

**Endobronchial**
- Palliation of airway constriction, 5-7.5 Gy x 3
- Minimally invasive HDR via optical bronchoscopy with fluoroscopic verification
- Limited / no access to peripheral lesions in lung

**Intraoperative**
- Emulates classics planar implants
- Rows of I-125 seeds with 1cm spacing
- Limited as an adjunct option for operable portion of the patient population

**Focal - Percutaneous**
- Access limited by target location
- Percutaneous image guided transplantation
- Common fractionation of 20 Gy x 1

Robots-Assisted Intraoperative Approaches

- Laparoscopic robot assisted seed implantation
- Coupled with electromagnetic navigation to go beyond video assisted methods
Limitations of Optical Bronchoscopy

- Flexible optical bronoscopes range in size of outer diameter 2.8-6.9 mm
  - Provides access to primary and portions of secondary bronchus
  - In general limited or no access to tertiary bronchus and bronchiole for therapeutic scopes

- Navigation to tertiary bronchus, bronchiole, and peripheral lesions requires use of smaller probes such as electromagnetic transponders
Electromagnetic Navigation Bronchoscopy

- SuperDimension™ (Covidien) ENB system routinely utilized
  - Fiducial Placement
  - Biopsy of Peripheral Lesions
- Requires the co-registered use of
  - Thoracic CT with airway segmentation
  - Optical bronchoscopy
  - Internal EM transponder for navigation (locatable guide)

Fahimian, AAPM 2017, Slide: 22

Schwarz, et al., CHEST 2006; 129:988–994)
• Clinical experience in the diagnostic realm
  – Recent trial of 56 patients, Ozgul, et al., 2016
    • Mean procedure time was 20 ± 11.5 min.
    • Mean registration error was 5.8 ± 1.5 mm.
    • Mean navigation error was 1.2 ± 0.5 mm
    • Well tolerated
    – Pneumothorax occurred in only 1 patient (1.7%)
  – Larger study of 151 patients by Wilson, et al., 2007
    • 3 (1%) mod bleeding, 1 (0.3%) hematoma
    1 (0.3%) pneumonia

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**Electromagnetic Navigation Bronchoscopy**

### Table: Study Population and Diagnostic Yield

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Study population/patients diagnosed by EMN</th>
<th>Diagnostic yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Becker et al., 2005</td>
<td>18/30</td>
<td>60</td>
</tr>
<tr>
<td>Hautman et al., 2005</td>
<td>11/16</td>
<td>69</td>
</tr>
<tr>
<td>Gildea et al., 2006</td>
<td>32/56</td>
<td>57</td>
</tr>
<tr>
<td>Schwartz et al., 2006</td>
<td>9/13</td>
<td>69</td>
</tr>
<tr>
<td>Makris et al., 2007</td>
<td>25/40</td>
<td>63</td>
</tr>
<tr>
<td>Eberhardt et al., 2007</td>
<td>52/93</td>
<td>56</td>
</tr>
<tr>
<td>Eberhardt et al., 2007</td>
<td>23/39</td>
<td>59</td>
</tr>
<tr>
<td>Eberhardt et al., 2007</td>
<td>35/40</td>
<td>88</td>
</tr>
<tr>
<td>Wilson et al., 2007</td>
<td>151/271</td>
<td>56</td>
</tr>
<tr>
<td>Bertoletti et al., 2009</td>
<td>33/54</td>
<td>61</td>
</tr>
<tr>
<td>Lampecht et al., 2009</td>
<td>10/13</td>
<td>77</td>
</tr>
<tr>
<td>Eberhardt et al., 2010</td>
<td>38/55</td>
<td>69</td>
</tr>
<tr>
<td>Seljo et al., 2010</td>
<td>34/51</td>
<td>67</td>
</tr>
<tr>
<td>Mahajan, 2011</td>
<td>24/49</td>
<td>49</td>
</tr>
<tr>
<td>Lampecht et al., 2012</td>
<td>94/112</td>
<td>84</td>
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<tr>
<td>Pearlstein et al., 2012</td>
<td>67/101</td>
<td>66</td>
</tr>
<tr>
<td>Karnak et al., 2013</td>
<td>32/35</td>
<td>91</td>
</tr>
<tr>
<td>Loo et al., 2014</td>
<td>46/49</td>
<td>94</td>
</tr>
</tbody>
</table>

EMN: Electromagnetic navigation; EMN: Electromagnetic navigational bronchoscopy; EMN: Electromagnetic navigation
Electromagnetic Navigation Bronchoscopy

- Locatable guide: internal transponder for navigation
- Sensor 1: 1 inch below the sternal notch
  Sensors 2,3: along the mid-axillary line at the eighth rib
- Transmission frequencies: 2.5, 3.0, 3.5 kHZ
- External sensors used to account for respiratory motion

Board emits low frequency EM enabling tracking within ~40x40x30 cm box
Extended working channel containing locatable guide

Electromagnetic Navigation Bronchoscopy

Co-registration of locatable guide, CT, and optical bronchoscope

Dr. Daniel Pinkham

External Sensors
Electromagnetic Navigation Bronchoscopy

- 360 degree (8 way) steering

Figure 3. Catheter handle and locatable guide housed in blue Extended Working Channel - catheter in neutral position.

Figure 4. Squeezing of neck of catheter handle in the direction of the white arrow results in deflection of LG and EWC. The direction of deflection is controlled by turning the orange ring (black arrows) to any one of eight pre-set positions.
Electromagnetic-Guided HDR Workflow

Workflow for Electromagnetically Guided Lung HDR

- Thoracic CT simulation for electromagnetic guidance
- Navigation of catheter using SuperDimension system
- RT planning using Varian Brachyvision and Acuros Ir-192 dose calculation
- 3D rendering of navigation pathway from CT
- Flexible bronchoscope
- Peripheral lesion
- Thin electromagnetic probe
- Registration of EM transponder to the rendered 3D pathway based on CT
- Insertion of dummy wire and acquisition of CT for RT planning
- Removal of dummy, connection to HDR afterloader
- Pre-treatment image verification and delivery of treatment
First Prospective Demonstrations EM-Guided HDR

- The majority of patients (75–80%) with non-small cell lung cancer (NSCLC) are diagnosed with advanced inoperable disease resulting
- Peripheral targets present difficulties for percutaneous implantation
- Electromagnetic Navigation Bronchoscopy of a single 6F catheter, implanted with
  - CT based segmentation of the airway
  - Endobronchial Ultrasound
  - Fluoroscopic verification
- One of the first demonstrations by Harms et al. in 2006
  - 15 Gy in 3 fractions (over 5 days) after 50 Gy external beam
  - CT based planning
  - Catheter remaining in place for the fractionated treatments
    - CT verification showed <5mm variation on subsequent fractions
- Follow-up trial of feasibility and safety in 32 patients
  - Clinical results suggest optimal dosing needs further investigation

Can EM-Guided HDR Provide an Alternative to SABR?

Retrospective study

Patients formerly treated with SABR (n=10)
  – Previously treated to 50Gy with SABR
  – CT-visible airway adjacent to GTV
  – GTV ranging from 1.5 cc to 20 cc

• Replanned using single catheter HDR treatment
• Planning constraints
  – 98% min dose to GTV
  – Keep 200% dose level within original SABR PTV
• Planned with Eclipse BrachyVision (Acuros BV 1.5.0)
Grid-based Boltzmann Transport Equation Solver

\[ \Delta = \frac{D_{\text{TG43}} - D_{\text{Acuros}}}{D_{\text{TG43}}} \]

In collaboration with Dr. Marian Axente
Dosimetric Comparison of HDR Ablation vs. SABR

• Dosimetric characteristics of HDR ablation vs. SABR
  – Increased heterogeneity in the PTV, and steeper gradients in the normal tissue
  – Increased $V_{100\%}/V_{50\%}$ ratios
  – Increased $D_{\text{max}}/D_{\text{Prescription}}$ ratios
Comparative Dosimetric Analysis of HDR and SABR

<table>
<thead>
<tr>
<th>OAR</th>
<th>Median OAR $D_{\text{max}}$ Reduction Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart</td>
<td>0.72</td>
</tr>
<tr>
<td>Aorta</td>
<td>0.39</td>
</tr>
<tr>
<td>SVC</td>
<td>0.45</td>
</tr>
<tr>
<td>Cord</td>
<td>0.29</td>
</tr>
</tbody>
</table>

- For targets < 20 cc, significant reduction in OAR doses
- Concurrent escalation of dose to GTVs (83% on average) receive >200% Rx dose
Limitation in Target Size

- For single catheter approaches, study suggests dosimetric advantage for smaller targets.
- Optimal performance for lung lesions limited to tumor sizes < 20 cc.
- Potential role for treatment of multiple mets and salvage brachytherapy.

Fahimian, AAPM 2017, Slide: 33

Discussion: Limitations and Challenges

• Current study limited to single catheter approaches for lung lesions
  – Dose-shaping is limited
  – Plan quality dependent on implant placement and target size

• Registration and placement error of catheter
  – Catheter placement should ideally be through center of mass and extend beyond lesion

• Optimal dosing requires further investigation
  – Construction of ablative dose regimens analogous to SABR experience
Developmental Access (Coring) Tool

- Tools are under development to enable interstitial placement through center of mass and passed the lesion
- Workflow proposed
  - Position extended working channel (EWC) in nearby airway
  - Advance EWC into GTV using mechanical action
  - Verify with fluoro
  - Send compatible HDR catheter into EWC

**Mechanical action:**
Advance needle into tissue, then catheter, then EWC

Verify with Fluoro
Plan on CT

Confirm position with fluoroscopy
Demonstration of Coring Technology

Advance bronchoscope and extend EMG beacon

Video (Courtesy of Covidien)
Placement Accuracy and Robustness Study

- System accuracy: 3 mm for rigid simulated lung model
- Depending on quality of registration, 5 mm accuracy can be assumed
- Unlike seeds, HDR is less sensitive to positioning
  - CT-based planning based in post implant image
- Larger volume of healthy lung parenchyma will be exposed to the highest isodose levels adjacent to the HDR source.
- However even with a 5mm error isodose levels (25%,50%,75%, and 100%) compared to SABR dosimetric advantages remain (i.e. $\text{Vol}_{\text{HDR}}/\text{Vol}_{\text{SABR}} < 1$)
Optimal Dosing for HDR Ablation of Lung Mets

• Optimal dosing for EM-Guided HDR unknown, however dose escalation foreseen
• Percutaneous data:
  – Prospective Phase II trial (Ricke, et al.), 20 Gy in a single fraction for tumors up to 2.5 cm in diameter
• EM-Guided Implantation
  – Feasibility trials (Harms, et al.), 15 Gy in 3 fractions in conjunction with external beam
• Experience from SABR, e.g. Stanford iSABR protocol (Loo, Diehn, et al.)

<table>
<thead>
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<th>Peripheral</th>
<th>Central</th>
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<tr>
<td>&lt;=10 cc</td>
<td></td>
</tr>
<tr>
<td>&gt;10 &amp; &lt;=30 cc</td>
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</tr>
<tr>
<td>&gt;30 cc</td>
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</tr>
<tr>
<td>Rx dose (covering 95% PTV)</td>
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</tr>
<tr>
<td>25 Gy in 1 fxn</td>
<td></td>
</tr>
<tr>
<td>50 Gy in 4 fxns</td>
<td></td>
</tr>
<tr>
<td>54 Gy in 3 fxns</td>
<td></td>
</tr>
<tr>
<td>40 Gy in 4 fxns</td>
<td></td>
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<tr>
<td>50 Gy in 4 fxns</td>
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<tr>
<td>60 Gy in 8 fxns</td>
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• Based on experience from SABR trials, exploration of size and location dependent dose escalation for HDR techniques warranted
Summary

- Returning to the original question: Where are we, and where are we going with clinical applications of brachytherapy?
  - Ablative focal therapy important paradigm for treatment of tumors
  - Brachytherapy an ideal candidate for ablative focal therapy
  - Advanced navigation for minimally invasive implantation is key to moving forward
- Optical bronchoscopy limited in access passed secondary / tertiary bronchi
  - Electromagnetic navigation enables access passed the limitations of optical bronchoscopy to peripheral lung tumors
  - Feasibility of implantation demonstrated
- In relation to SABR/SBRT, ablative brachytherapy has the potential enhanced dosimetry and reduced motion management complications
  - Dosimetric characteristics includes steeper fall-off of dose and escalated doses to the target
  - Potential role as primary treatment of small lesions or in the setting of salvage therapy
  - Number of challenges re
    - Single catheter approaches, dose shaping is limited, optimal target size < 20 cc
    - Optimal ablative dosing primary subject of future clinical investigation
Acknowledgements

Collaborators

• Daniel Pinkham, Ph.D.
• Arthur Sung, M.D.
• Billy Loo, M.D., Ph.D.
• Michael Gensheimer, M.D.
• David Schultz, M.D.
• Maximilian Diehn, M.D., Ph.D.
• Marian Axente, Ph.D.

Special Thanks

• Antonio Damato, Ph.D.
• Mark Rivard, Ph.D.
• William Song, Ph.D.

Covidien/Medtronic

• Thomas Crowley
• Jerry McNamara