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

Head & Neck	Intracranial	Endobronchial	Intraoperative

Focal Treatments

- Image Guided Interstitial Implantation
- Ablative dosing

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

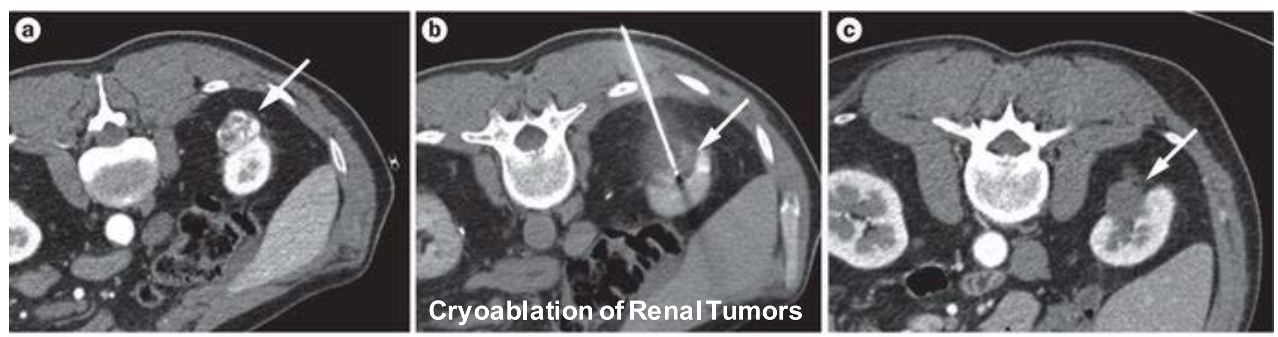
Paradigms for Focal and Ablative Delivery

<u>External Beam</u>

- SABR (SBRT)
- Robotic Radiosurgery

<u>Alternative techniques</u>

- Radiofrequency Ablation
- Cryoablation
- HIFU
- Microwave Ablation
- Electroporation

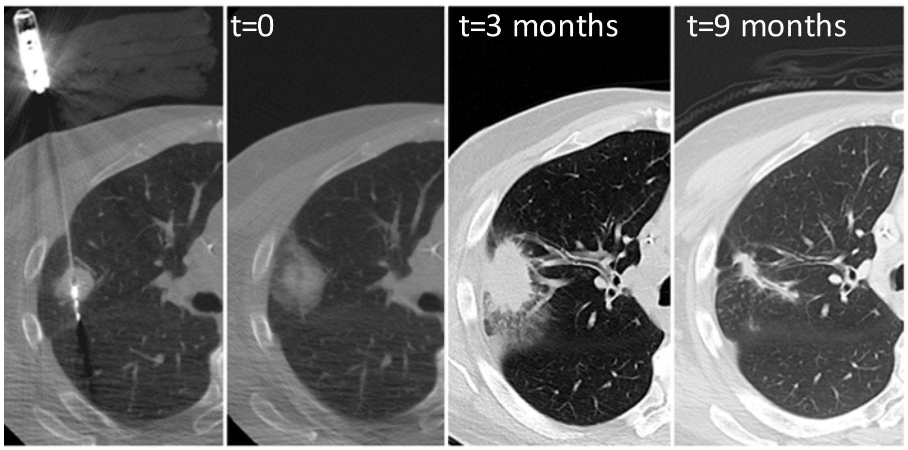


Nature Reviews Clinical Oncology 12, 175–186 (2015)

Nature Reviews | Clinical Oncology

Alternative Techniques

Microwave ablation



RFA	Microwave ablation	Cryoablation
Experience regarding efficacy and safety (most widely studied and most outcome data available)	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	Compared to RF ablation: Larger tumor ablation volume. Less procedural pain. No grounding pads needed
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	Limited safety and efficacy data available	Limited safety and efficacy data available. Longer procedural time due to freeze-thaw-freeze cycle. Higher hemorrhage risk secondary to lack of tissue cauterization

Courtesy of Lee et al., *Transl Lung Cancer Res* 2013;2(5):340-353

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

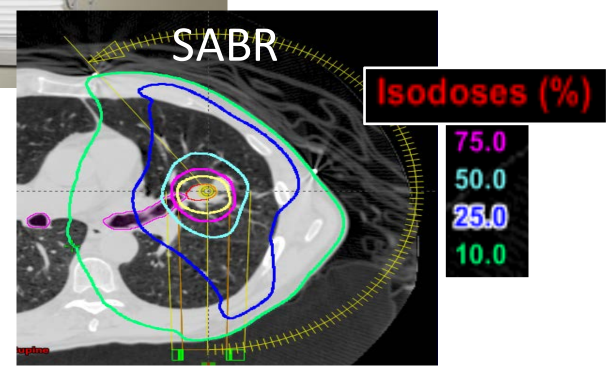
Stereotactic Ablative Radiotherapy (SABR/SBRT)

<u>Advantages</u>

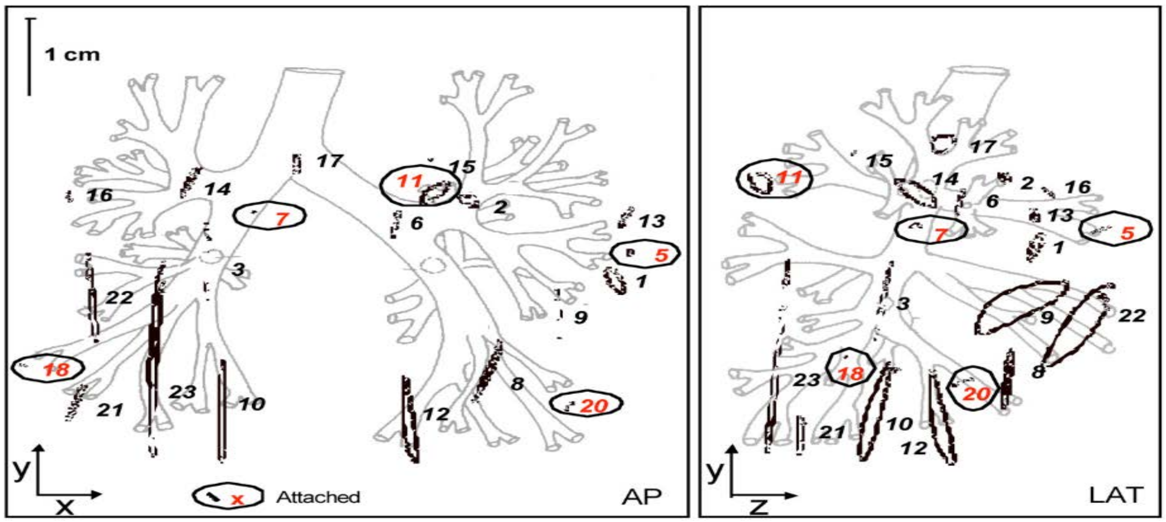
- High local control rate
- Non-invasive
- Access anywhere in lung
- Dose conformality

<u>Challenges</u>

- 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

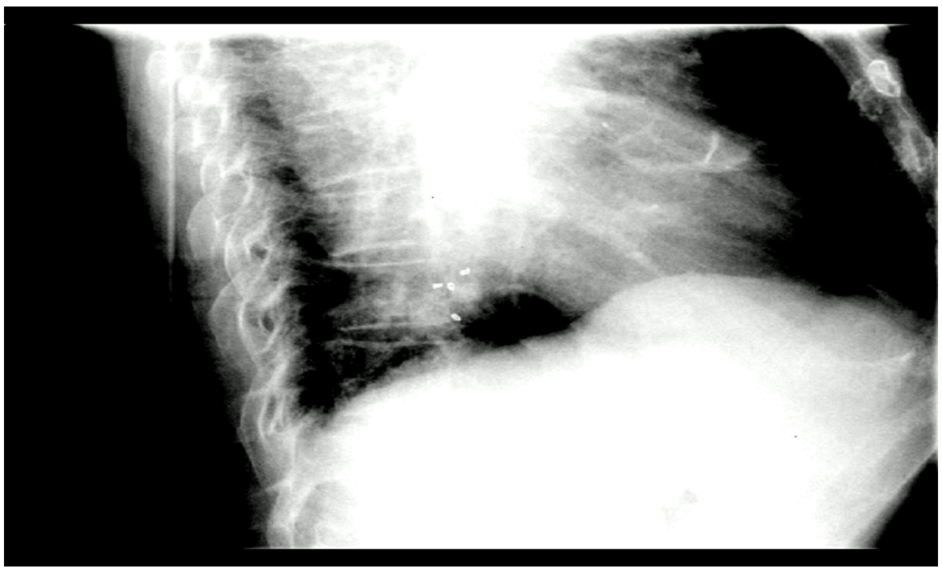
TABLE II. Abdominal motion data. The mean range of motion and the (minimum-maximum) ranges in millimeters for each site and each cohort of subjects. The motion is in the superior-inferior (SI) direction.

		Breathing mode	
Site	Observer	Shallow	Deep
Pancreas	Suramo (Ref. 57)	20 (10–30)	43 (20–80)
	Bryan (Ref. 59)	20 (0–35)	-
Liver	Weiss (Ref. 66)	13±5	-
	Harauz (Ref. 67)	14	-
	Suramo (Ref. 57)	25 (10–40)	55 (30–80)
	Davies (Ref. 58)	10 (5–17)	37 (21–57)
Kidney	Suramo (Ref. 57)	19 (10–40)	40 (20–70)
	Davies (Ref. 58)	11 (5–16)	-
Diaphragm	Wade (Ref. 68)	17	101
	Korin (Ref. 64)	13	39
	Davies (Ref. 58)	12 (7–28)	43 (25–57)

AAPM TG-76, 2006

Motion Management for External Beam

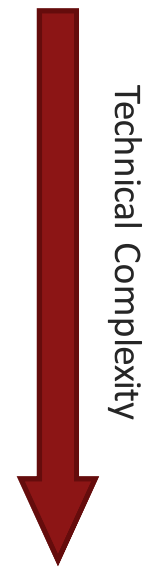
- Target motion is a major complicating factor in SABR/SBRT delivery
  - Note that implanted seeds move with target
- Targets must not only be localized in space but also in time



Videos of thoracic target motion. Courtesy of R. Li

Motion Management Techniques:

- Motion-encompassing irradiation
- Compression
- Breath-hold
- Gating
- Dynamic tracking delivery



Brachytherapy as an Ablative Adjunct to SBRT

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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

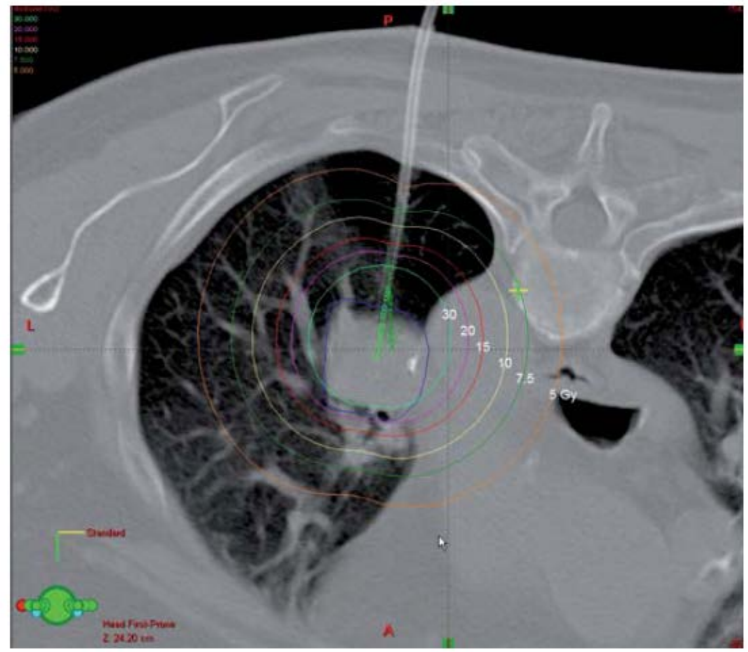

Figure 1. Radiation treatment planning after application of the brachytherapy catheter. Note the steep gradient with the inner isodose illustrating a dose of 30 Gy, the outer isodose of 5 Gy. The depicted myelon receives a total dose of approximately 2 Gy.

Strahlenther Onkol 2008 · No. 6

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)

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

Author	Entity	Patients/ Tumors (*n*)	Tumor size (cm)
Wieners *et al.* [39]	Breast cancer liver metastases	41/115	4.4 (1-11)
Collettini *et al.* [40]	Breast cancer liver metastases	37/80	2.5 (0.8-7.4)
Wieners *et al.* [43]	Pancreatic cancer liver metastases	20/49	2.9 (1.0-7.3)
Ricke *et al.* [57]	Primary and secondary lung malignancies	15/30	2 (0.6-11)
Peters *et al.* [56]	Primary and secondary lung malignancies	30/83	2.5 (0.6-11)
Collettini *et al.* [55]	Primary and metastatic lung malignancies	22/33	3.3 (1-8.6)
Bretschneider *et al.* [61]	Metastases of malignant melanoma	14/52	1.5 (0.7-10)
Collettini *et al.* [60]	Lymph node metastases	10/10	3.6 (1.2-6.7)

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

Image-Guided Percutaneous Techniques

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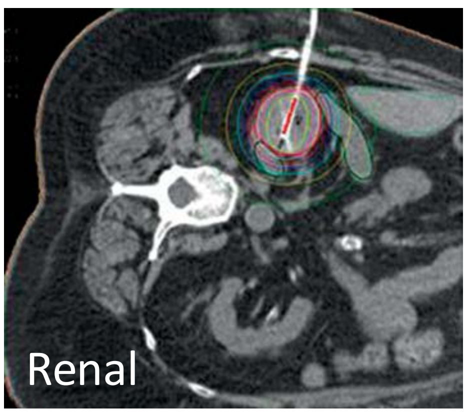
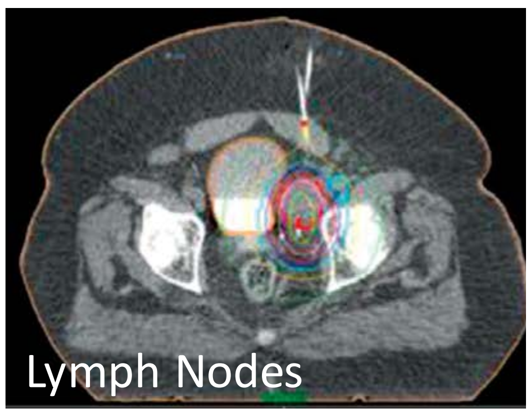
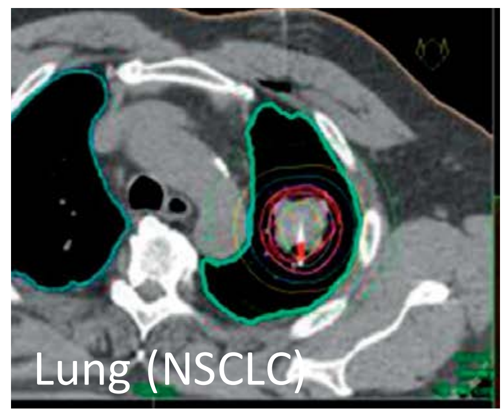
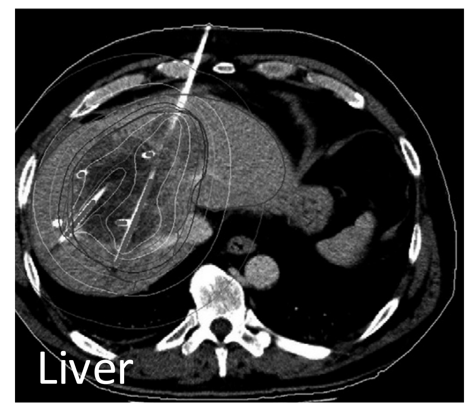
- Limited number of catheters, 1-3
- Performed under local anesthesia, conscious sedation
- Generally well tolerated, limited complications relating to catheter insertion
- CT, MR imaging with 3D planning





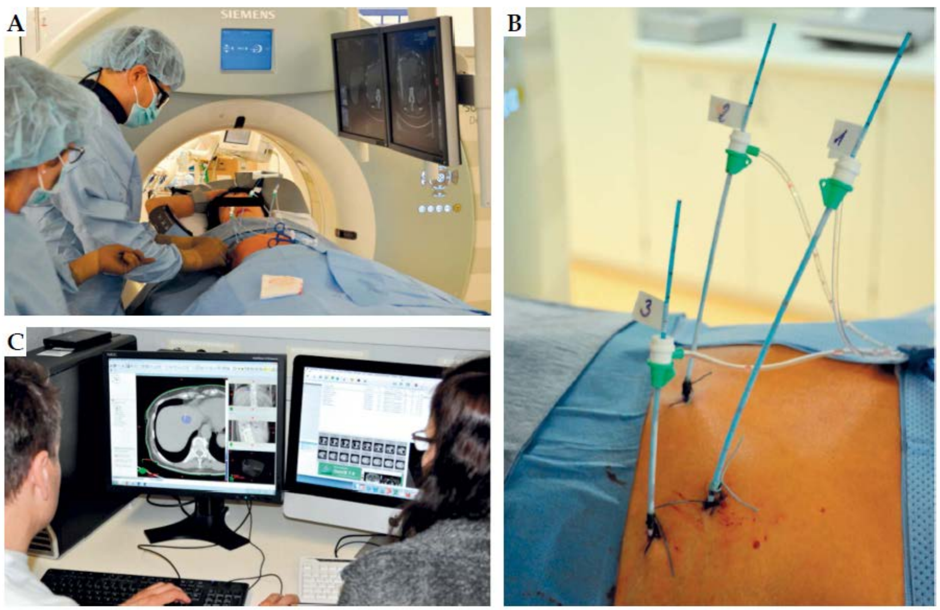




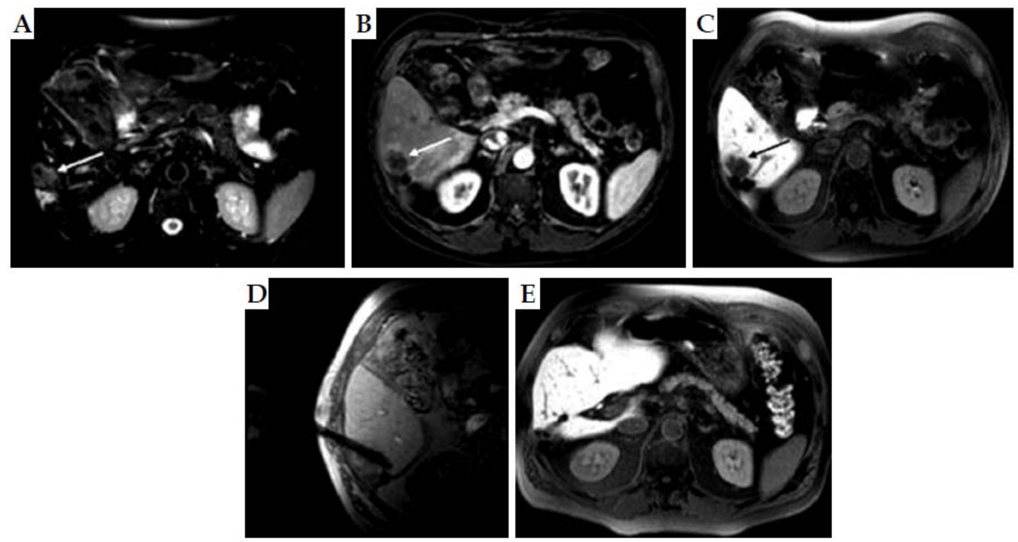
Ricke, et al., Semin Radiat Oncol, 2011, 21:287-293

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

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

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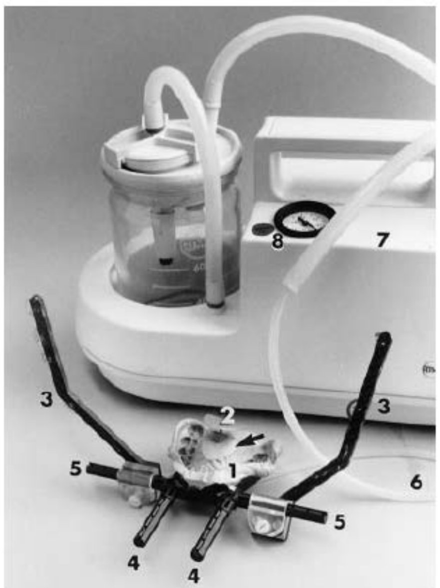


Figure 1. Modified VBH mouthpiece: dental impression (*1*) with vacuum area (arrow); vacuum spacer (*2*); registration rods (*3*); anterior extensions (*4*); lateral extensions (*5*); plastic tube (*6*), which leads to vacuum pump (*7*) with manometer (*8*).

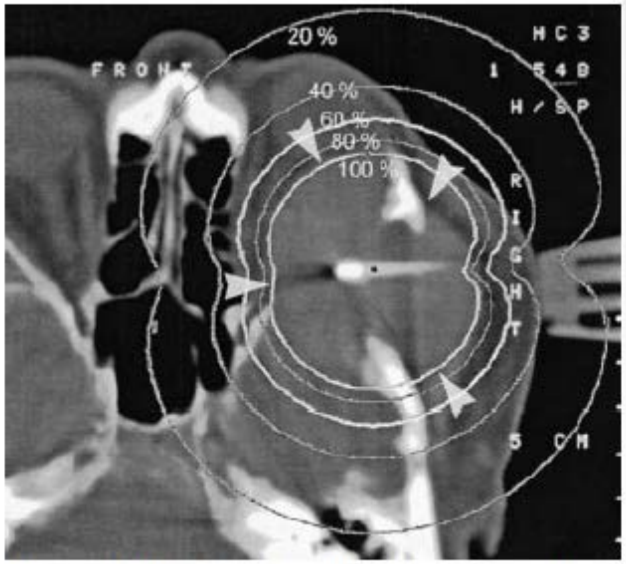
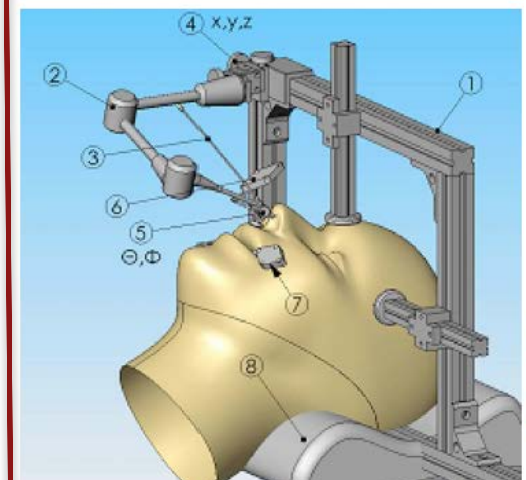


Figure 4. Patient 2. Clinical target volume (arrowheads indicate tumor) covered by 100% isodose. Note that the patient's anatomic right side is displayed on the viewer's right.

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



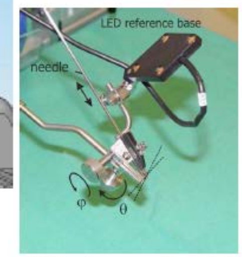


FIG. 3. The image shows a brachytherapy needle inserted in the needle holder. The needle holder has two fine-adjustable degrees of inclination (φ, θ) whose rotation axes cross (indicated with dotted lines) at the tip of the needle. To track the position and orientation of the needle a LED reference base is rigidly attached to the needle guide.

Pappas et al., Med Phys. 2005 32:6,1796-1801

Individualized 3D-Printed Templates for Head and Neck Brachytherapy

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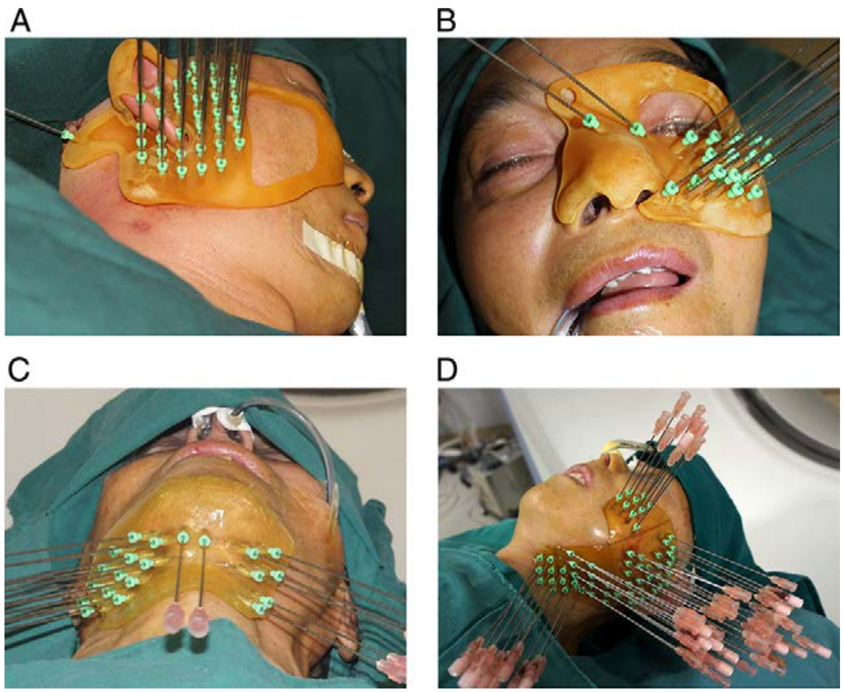

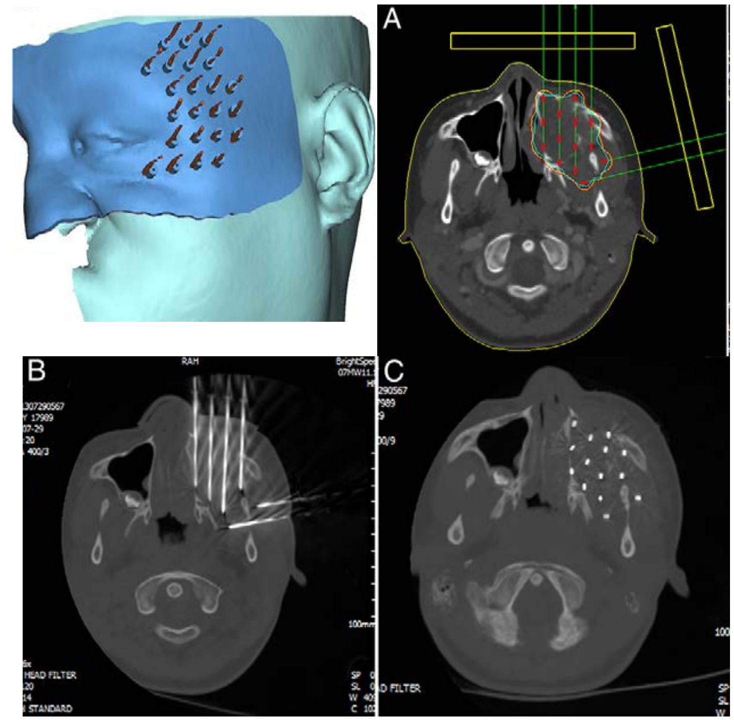

- Huang, *et al.*: 25 HN patients implanted with I-125 seeds
- Entrance deviation for 619 needles was 1.18 ±0.81 mm

Huang, et al., Journal of Radiation Research, Vol. 57, No. 6, 2016, pp. 662–667

Established Lung Brachytherapy Techniques

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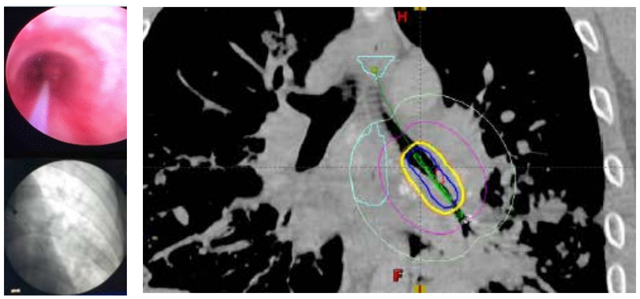
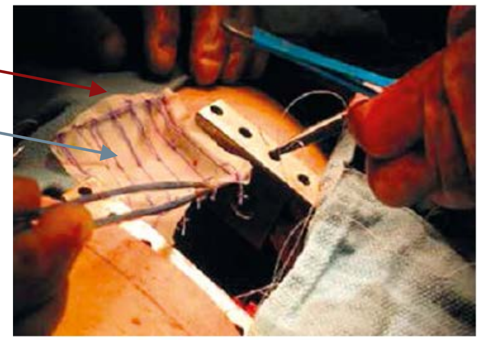
Endobronchial



- 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

Review Reference: Skowronek, Journal of Contemporary Brachytherapy 7:4 (2015)

Robotics-Assisted Intraoperative Approaches

- Laparoscopic robot assisted seed implantation
- Coupled with electromagnetic navigation to go beyond video assisted methods

Current Respiratory Medicine Reviews, 2011, Vol. 7, No. 5

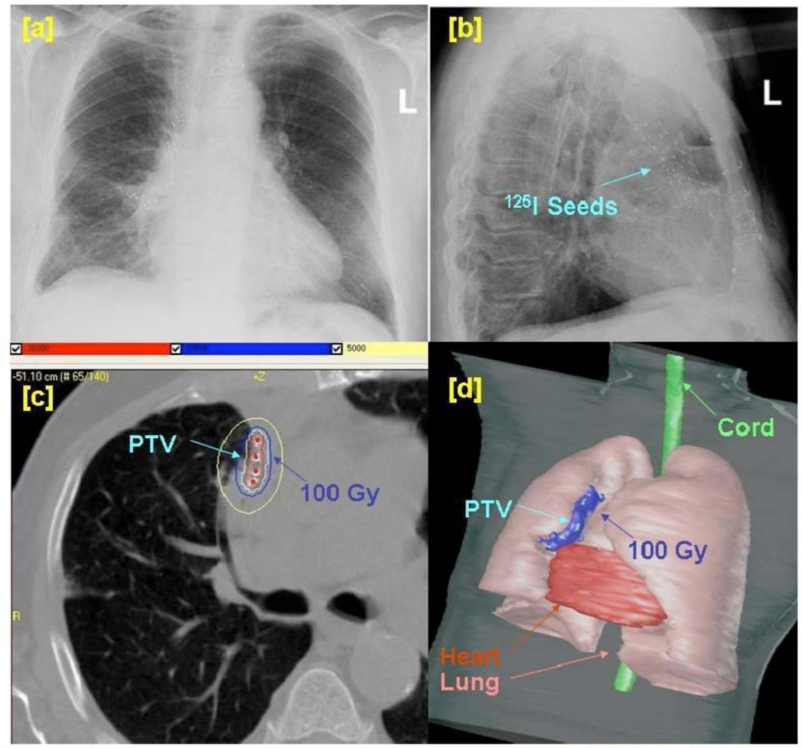
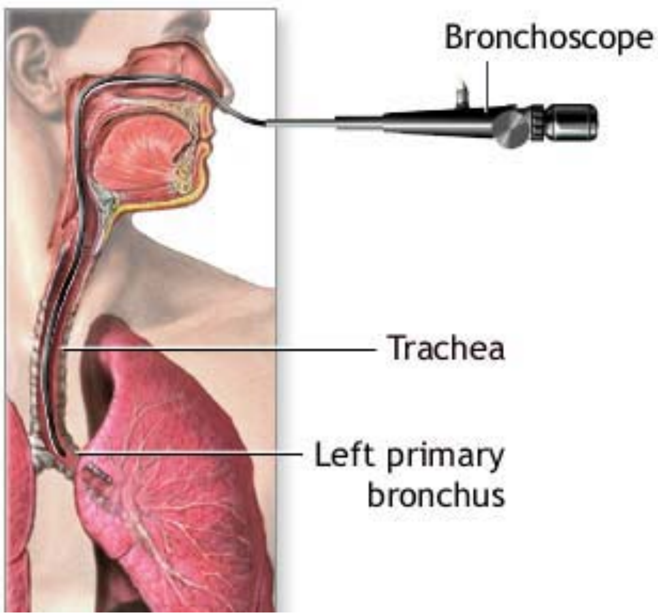
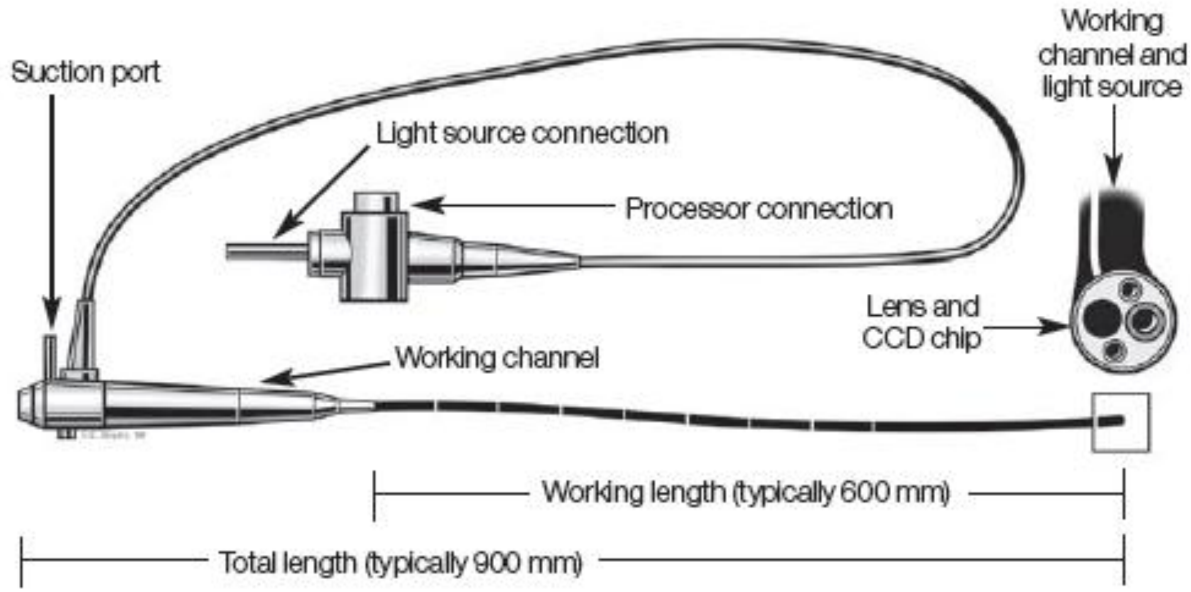


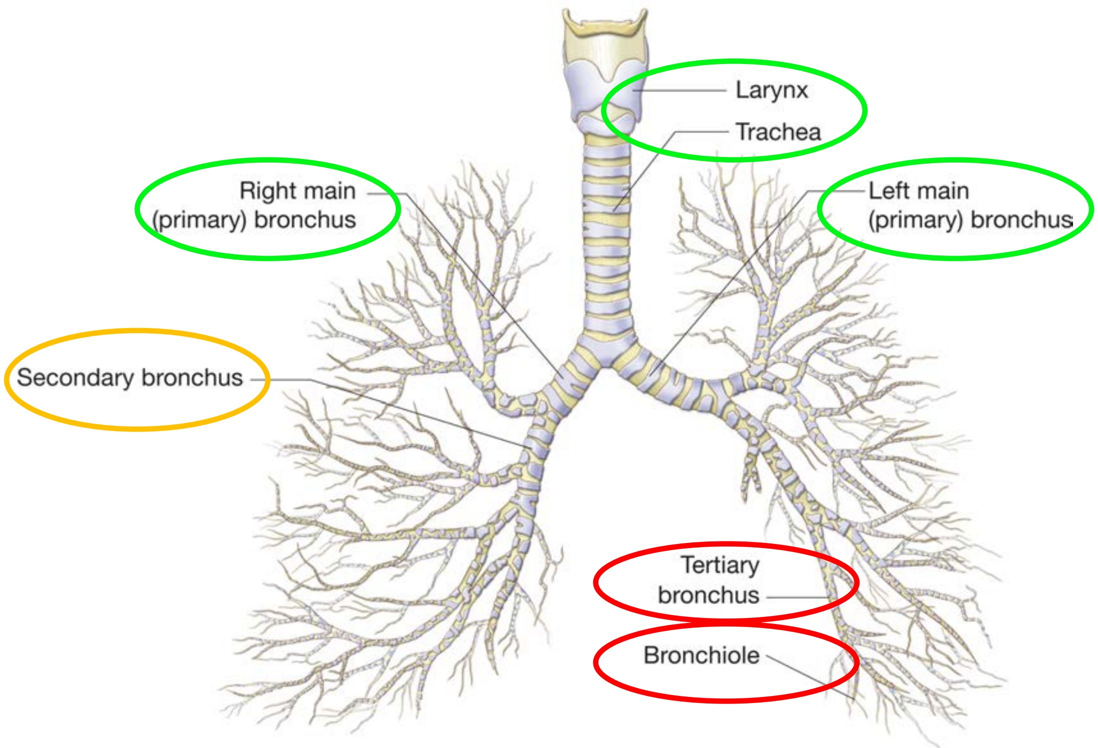
Fig. (1). Intraoperative lung brachytherapy. (**A** and **B**) Chest x-ray (PA and lateral films) of a stage I NSCLC patient with limited pulmonary capacity post sublobar resection and intraoperative brachytherapy. (**C**) Post intraoperative brachytherapy CT –simulation and treatment reveals I-125 seeds in place. Total dose prescribed was 100 Gy (blue isodose line). Isodose lines are also displayed for 50 Gy (yellow) and 200 Gy (red). (**D**) 3D display of the Planning Target Volume (PTV) demonstrating dose coverage by the 100 Gy prescription.

Optical Bronchoscopy and Endoluminal Approaches

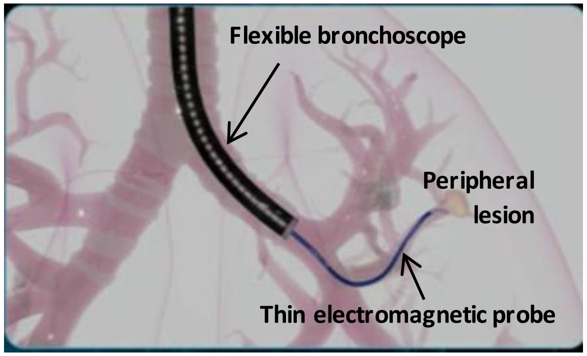




Limitations of Optical Bronchoscopy



- Flexible optical bronchoscopes 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

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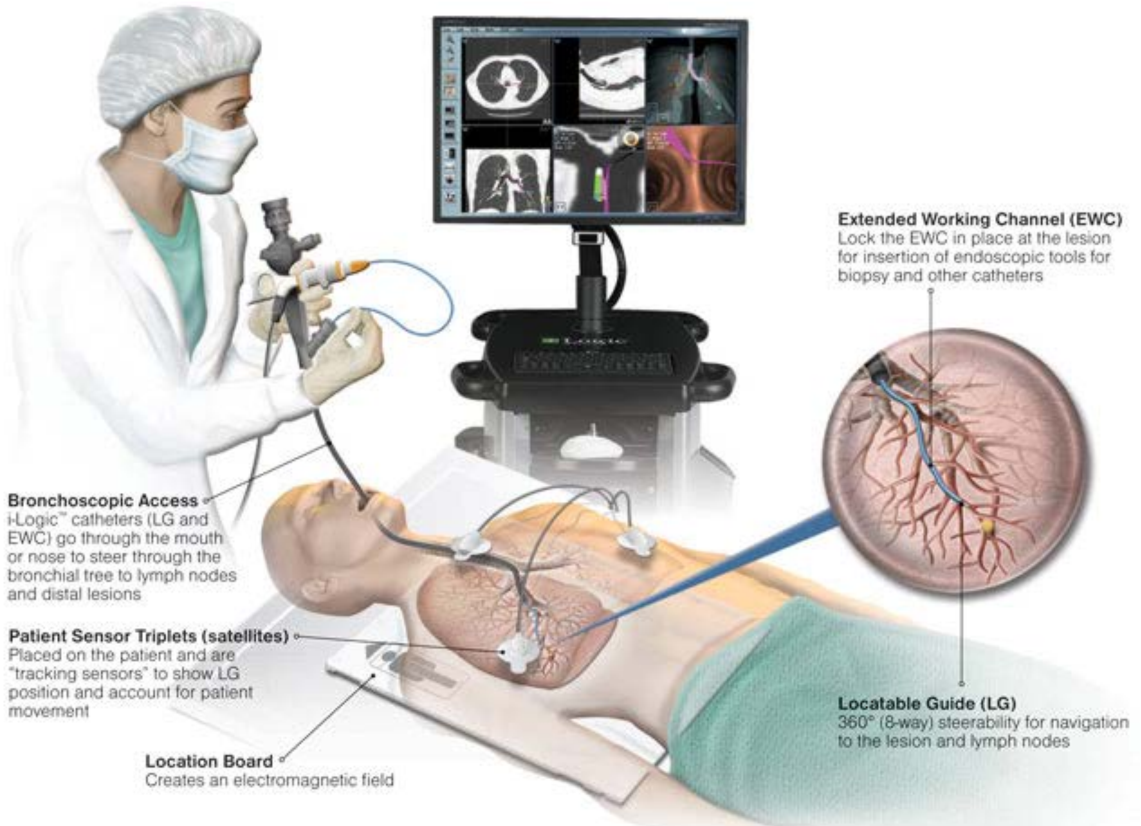
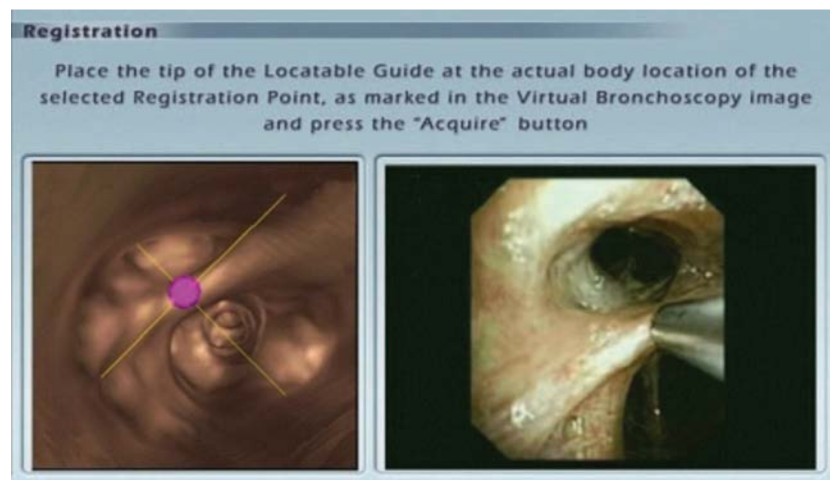


Image: Courtesy of Covidien

- 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)

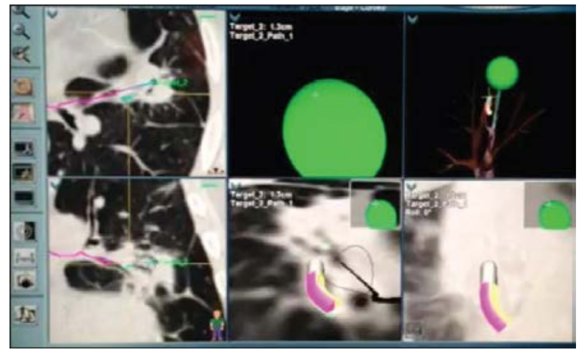


Schwarz, et al., CHEST 2006; 129:988–994)

Electromagnetic Navigation Bronchoscopy

Author, year	Study population/ patients diagnosed by EMN	Diagnostic yield (%)
Becker *et al.*, 2005[22]	18/30	60
Hautman *et al.*, 2005[34]	11/16	69
Gildea *et al.*, 2006[11]	32/56	57
Schwartz *et al.*, 2006[24]	9/13	69
Makris *et al.*, 2007[19]	25/40	63
Eberhardt *et al.*, 2007[12]	52/93	56
Eberhardt *et al.*, 2007[23]	23/39	59
Eberhardt *et al.*, 2007[23]	35/40	88
Wilson *et al.*, 2007[25]	151/271	56
Bertoletti *et al.*, 2009[35]	33/54	61
Lamprecht *et al.*, 2009[20]	10/13	77
Eberhardt *et al.*, 2010[21]	38/55	69
Seijo *et al.*, 2010[26]	34/51	67
Mahajan, 2011[36]	24/49	49
Lamprecht *et al.*, 2012[27]	94/112	84
Pearlstein *et al*, 2012[28]	67/101	66
Karnak *et al.*, 2013[37]	32/35	91
Loo *et al.*, 2014	46/49	94

ENB: Electromagnetic navigational bronchoscopy; EMN: Electromagnetic navigation



- 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

Endosc Ultrasound. 2016 May-Jun; 5(3): 189–195; J Bronchol. 2007;14:227-232

Electromagnetic Navigation Bronchoscopy

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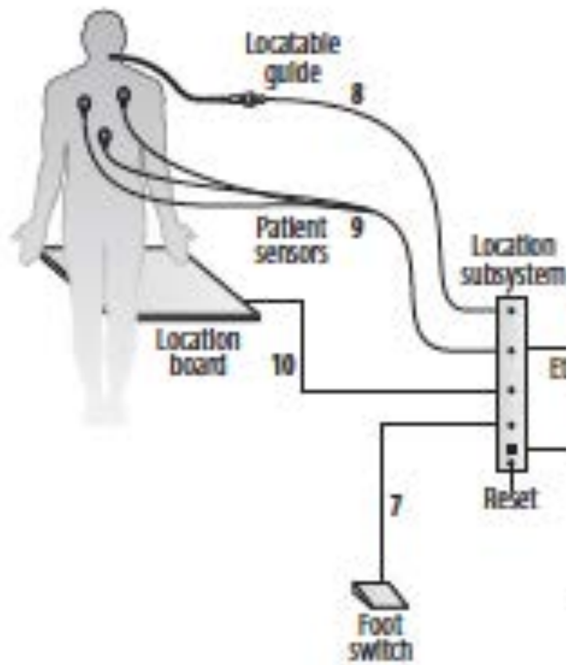
- Locatable guide: internal transponder for navigation
- Sensor 1: 1 inch below the sternal notch
  Sensors 2,3: along the mid-axillary line at the eighth rib
- Transmission frequencies:
  2.5, 3.0, 3.5 kHZ
- External sensors used to account for respiratory motion



Board emits low frequency EM enabling tracking within ~40x40x30 cm box

Extended working channel containing locatable guide

Image Reference: S. Leong et al., J. Thorac. Dis., vol **4,** pp173 (2012) and Covidien

Electromagnetic Navigation Bronchoscopy

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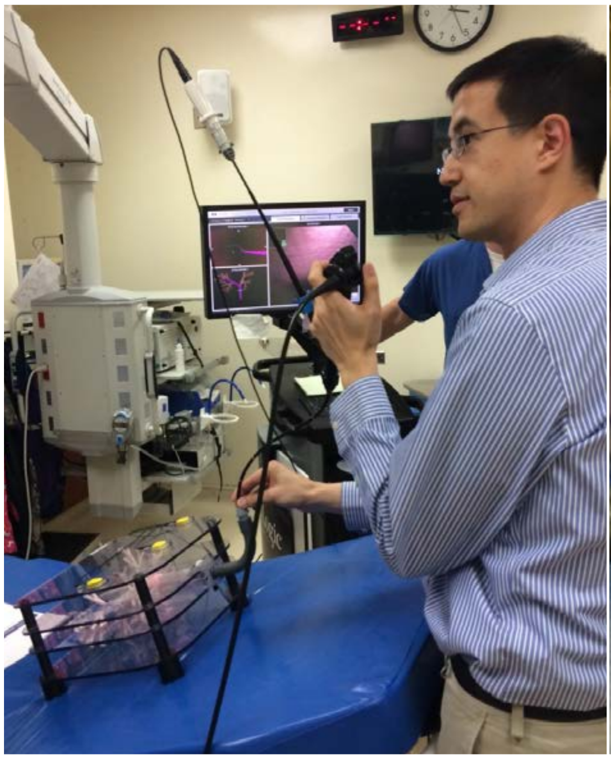
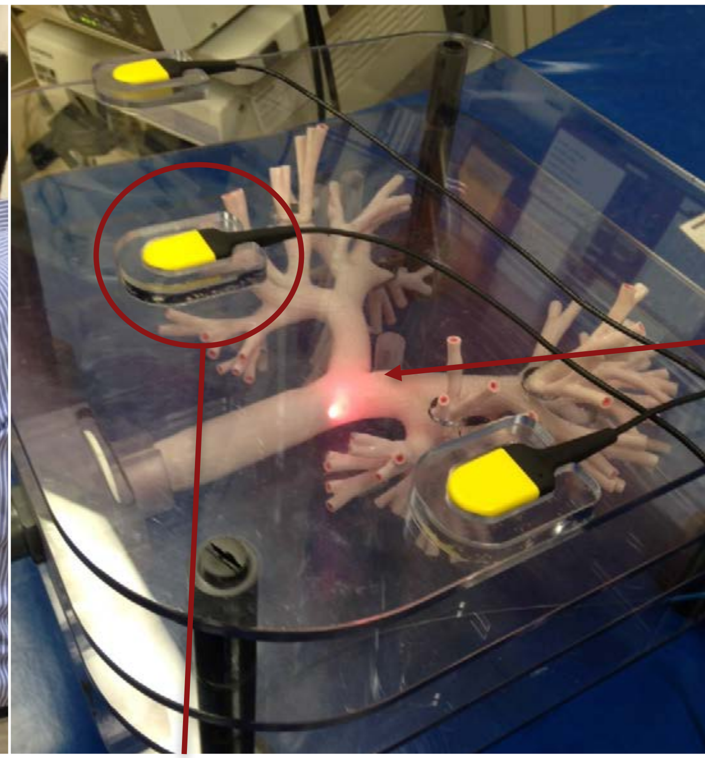
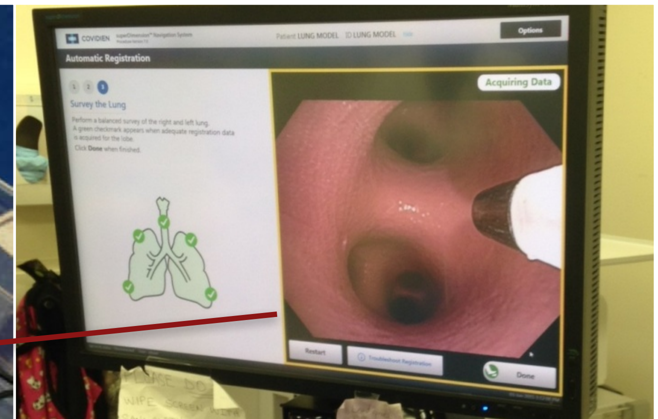


Dr. Daniel Pinkham



External Sensors



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

Electromagnetic Navigation Bronchoscopy

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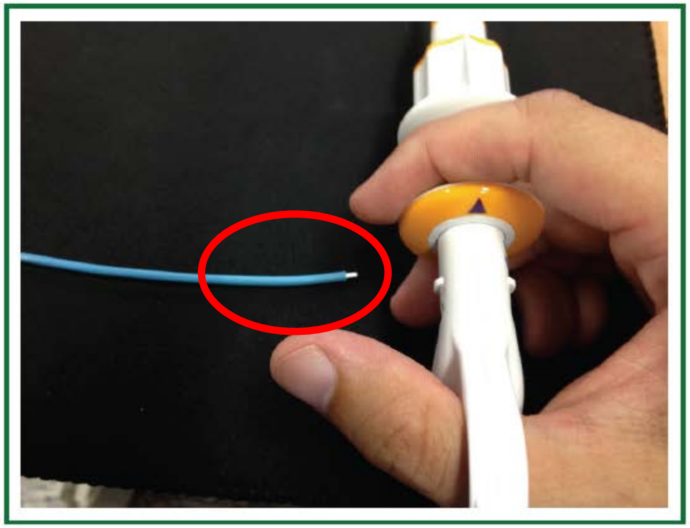

Figure 3. Catheter handle and locatable guide housed in blue Extended Working Channel - catheter in neutral position.

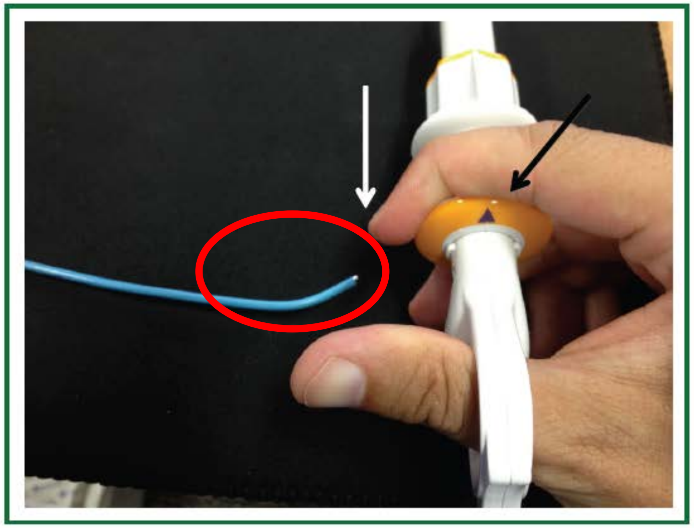

Figure 4. Squeezing of neck of catheter handle in the direction of the white arrow results in deflection of LG and EWC. The direction of deflection is controlled by turning the orange ring (black arrows) to any one of eight pre-set positions.

- 360 degree (8 way) steering

S. Leong et al., J. Thorac. Dis., vol **4,** pp173 (2012)

Electromagnetic-Guided HDR Workflow

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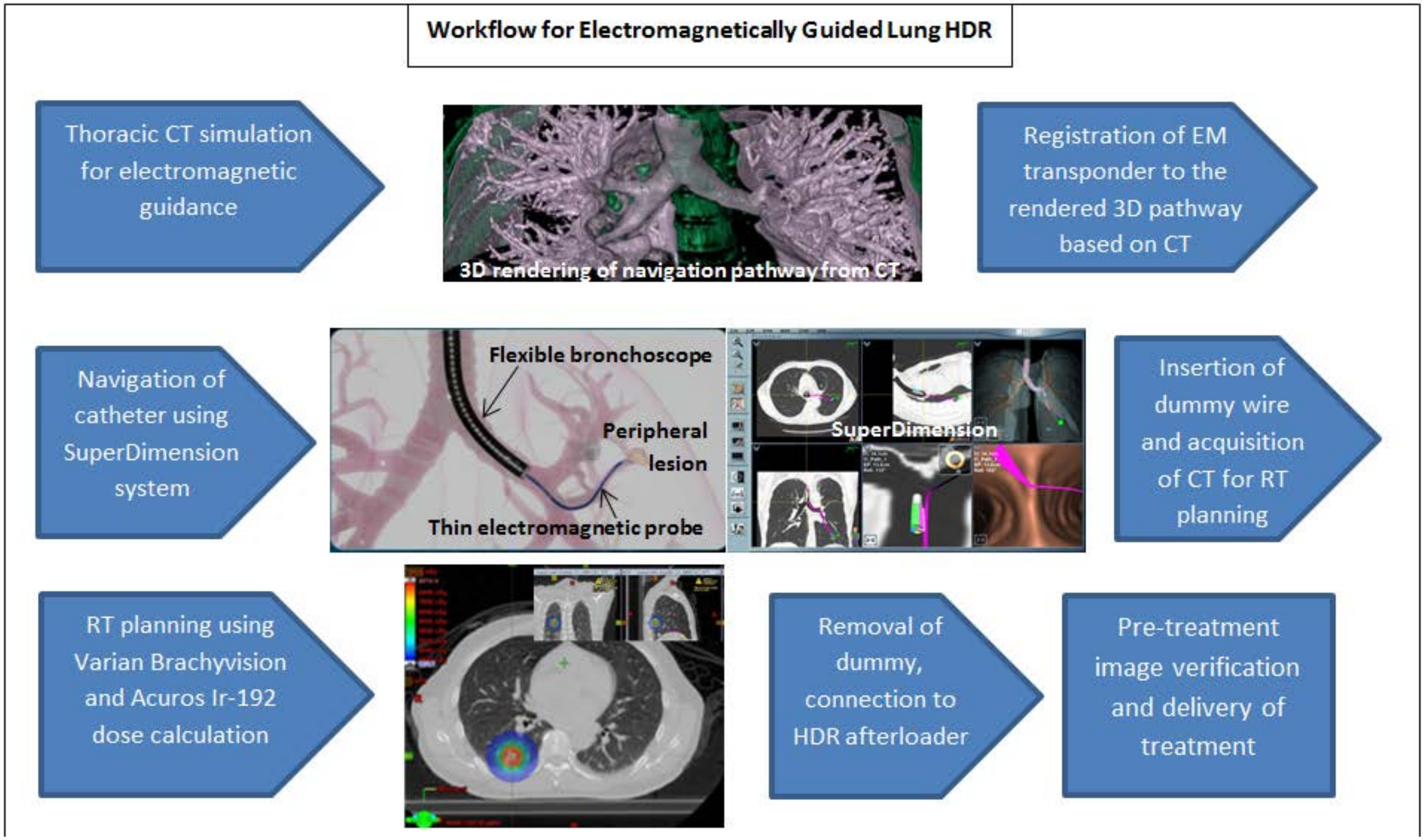
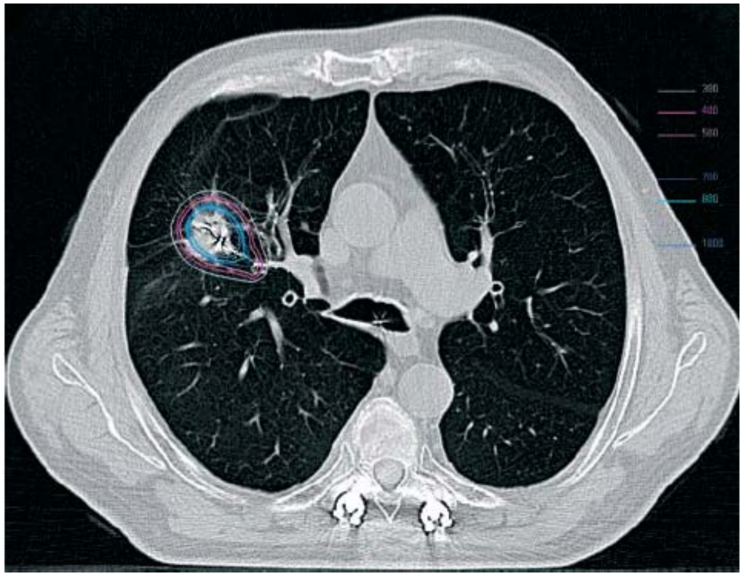
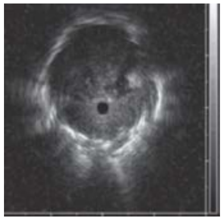


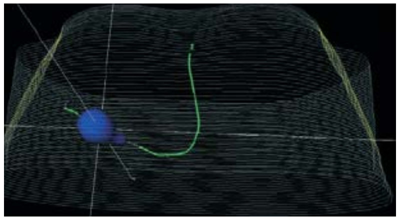
First Prospective Demonstrations EM-Guided HDR

- 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





Endobronchial US



Harms, et al. Strahlenther Onkol 2006;182:108–11

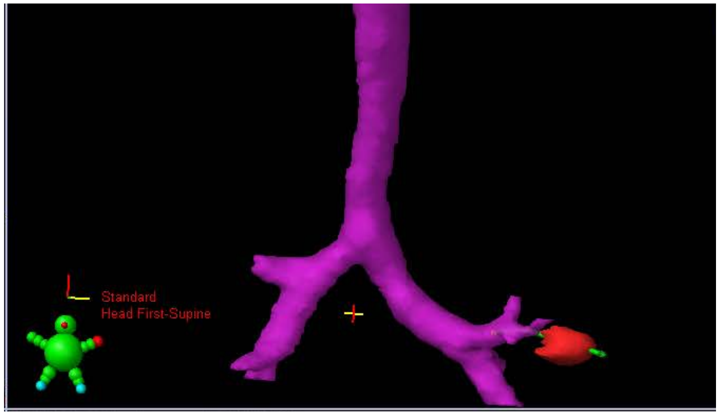
Can EM-Guided HDR Provide an Alternative to SABR?

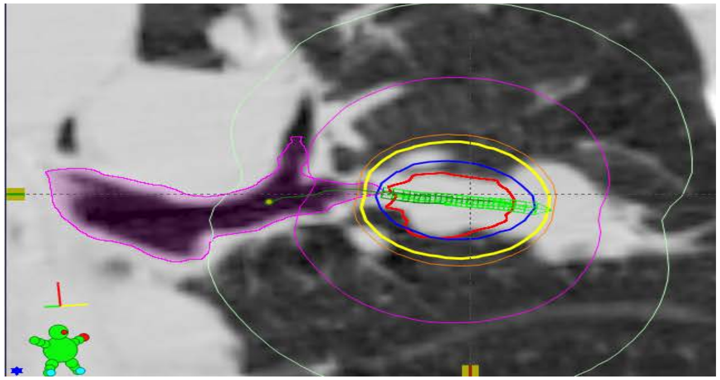
Retrospective study

Patients formerly treated with SABR (n=10)

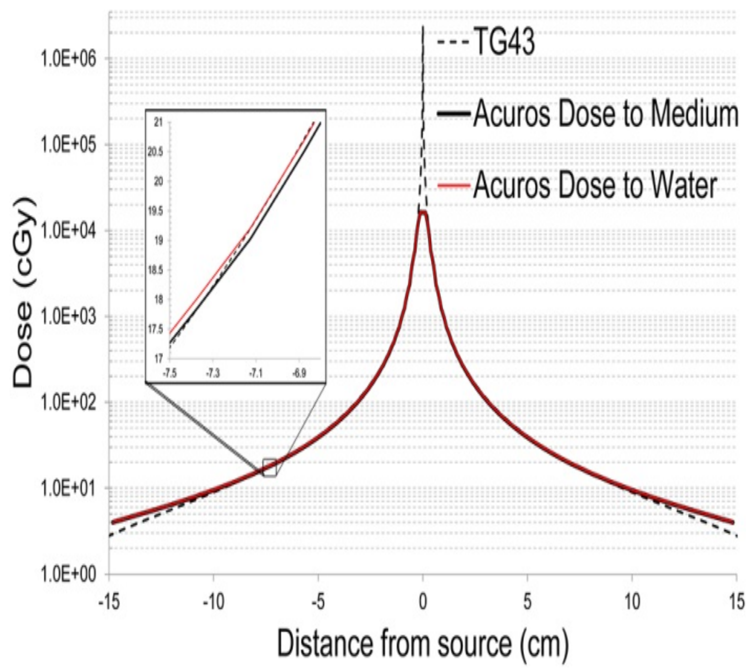
- Previously treated to 50Gy with SABR
- CT-visible airway adjacent to GTV
- GTV ranging from 1.5 cc to 20 cc

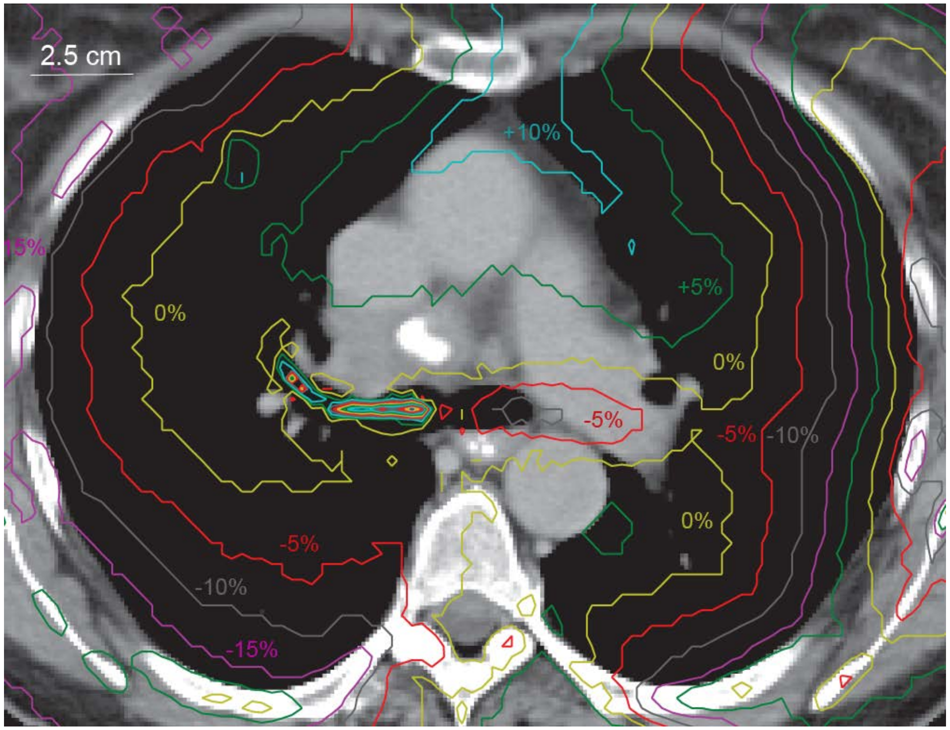
- Replanned using single catheter HDR treatment
- Planning constraints
  - 98% min dose to GTV
  - Keep 200% dose level within original SABR PTV
- Planned with Eclipse BrachyVision (Acuros BV 1.5.0)





Grid-based Boltzmann Transport Equation Solver

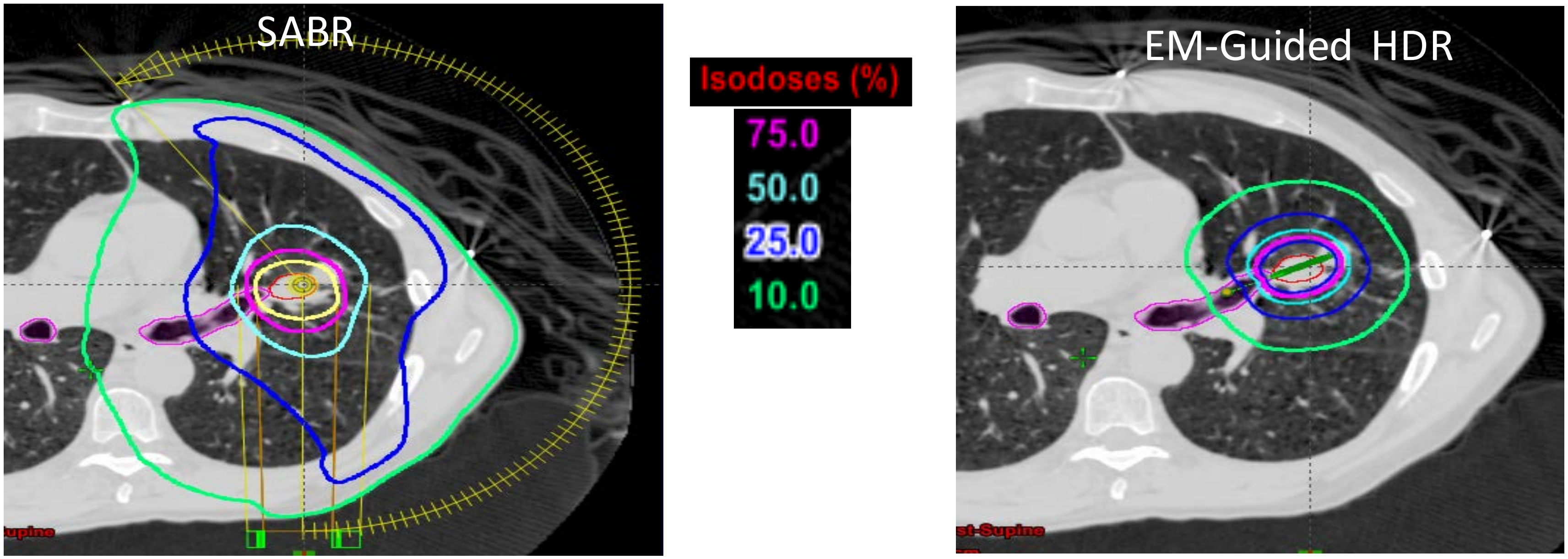




$$\Delta = \frac{D_{TG43} - D_{Acuros}}{D_{TG43}}$$

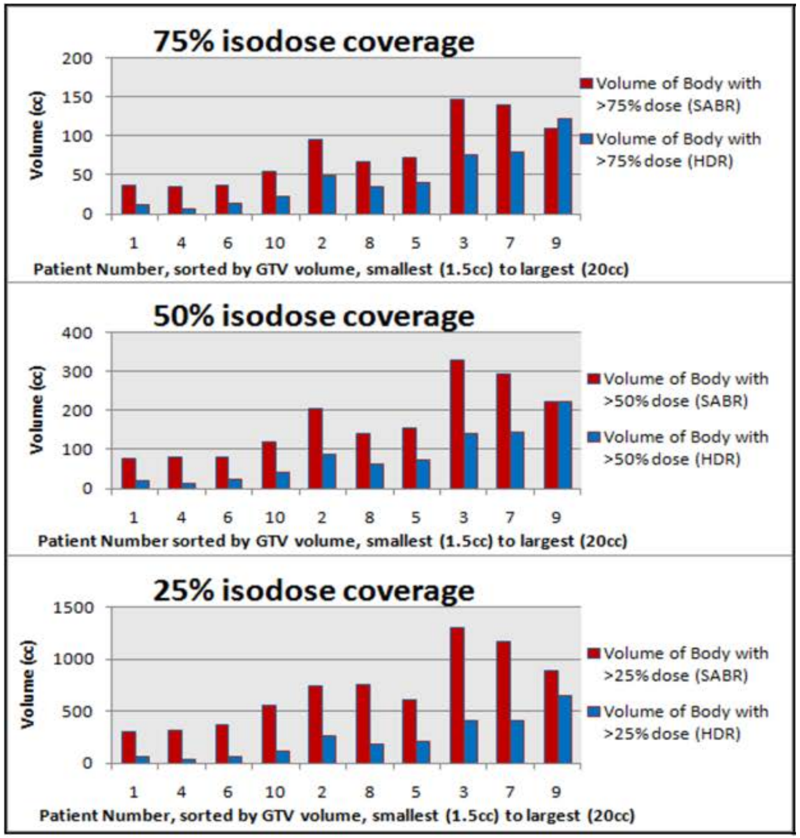
In collaboration with Dr. Marian Axente

Dosimetric Comparison of HDR Ablation vs. SABR

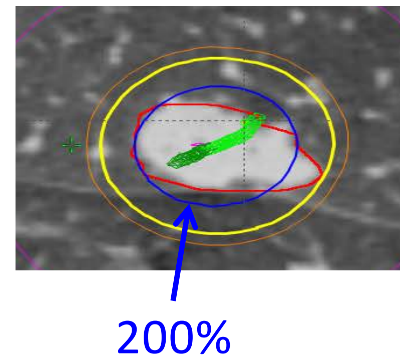


- Dosimetric charactristics of HDR ablation vs. SABR
  - Increased heterogeneity in the PTV, and steeper gradients in the normal tissue
  - Increased $V_{100\%}/V_{50\%}$ ratios
  - Increased $D_{max}/D_{Prescription}$ ratios

Comparative Dosimetric Analysis of HDR and SABR



OAR	Median OAR D_{max} Reduction Factors
Heart	0.72
Aorta	0.39
SVC	0.45
Cord	0.29



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

Pinkham, et al., Med. Phys., 42:6, 2015, 3595

Limitation in Target Size

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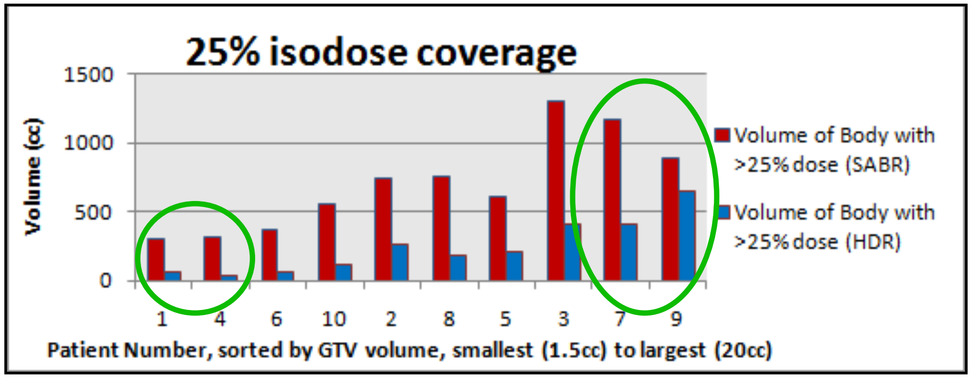
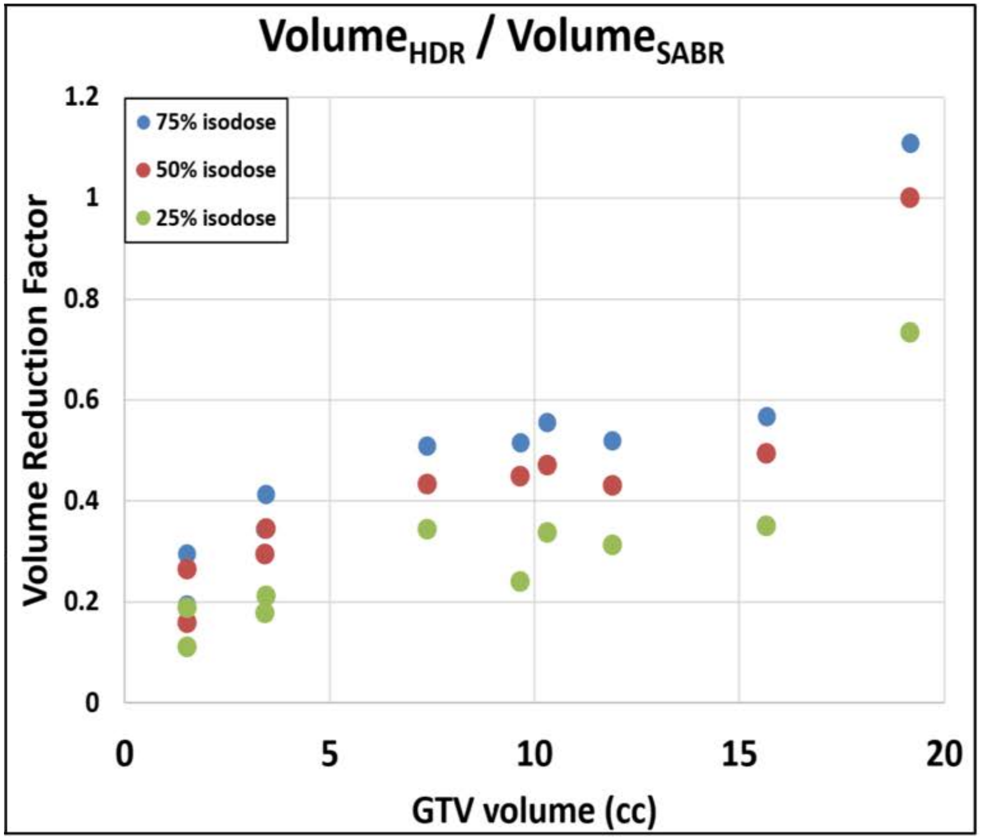
- For single catheter approaches, study suggests dosimetric advantage for smaller targets
- Optimal performance for for lung lesions limited to tumor sizes < 20 cc
- Potential role for treatment of multiple mets and salvage brachytherapy





Pinkham, et al., Med. Phys., 42:6, 2015, 3595

Discussion: Limitations and Challenges

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- 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

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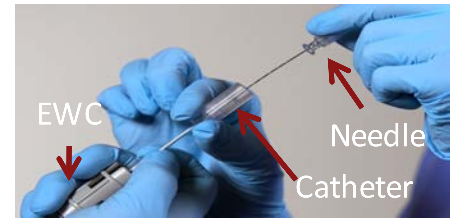
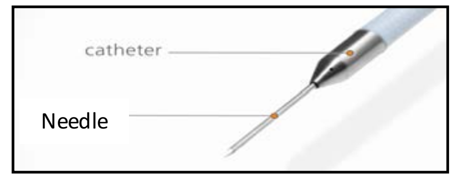
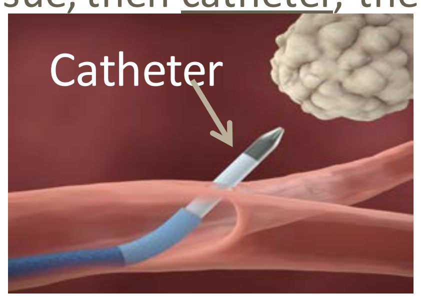
- Tools are under development to enable interstitial placement through center of mass and passed the lesion
- Workflow proposed
  - Position extended working channel (EWC) in nearby airway
  - Advance EWC into GTV using mechanical action
  - Verify with fluoro
  - Send compatible HDR catheter into EWC

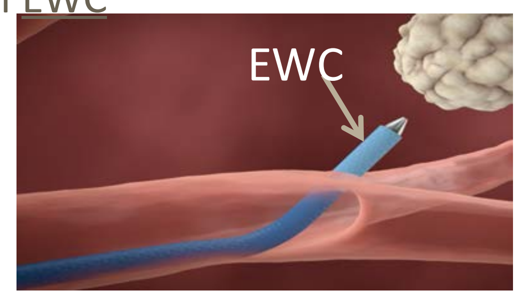




Mechanical action:

Advance needle into tissue, then catheter, then EWC





Verify with Fluoro

Plan on CT

Demonstration of Coring Technology

Video (Courtesy of Covidien)

Placement Accuracy and Robustness Study

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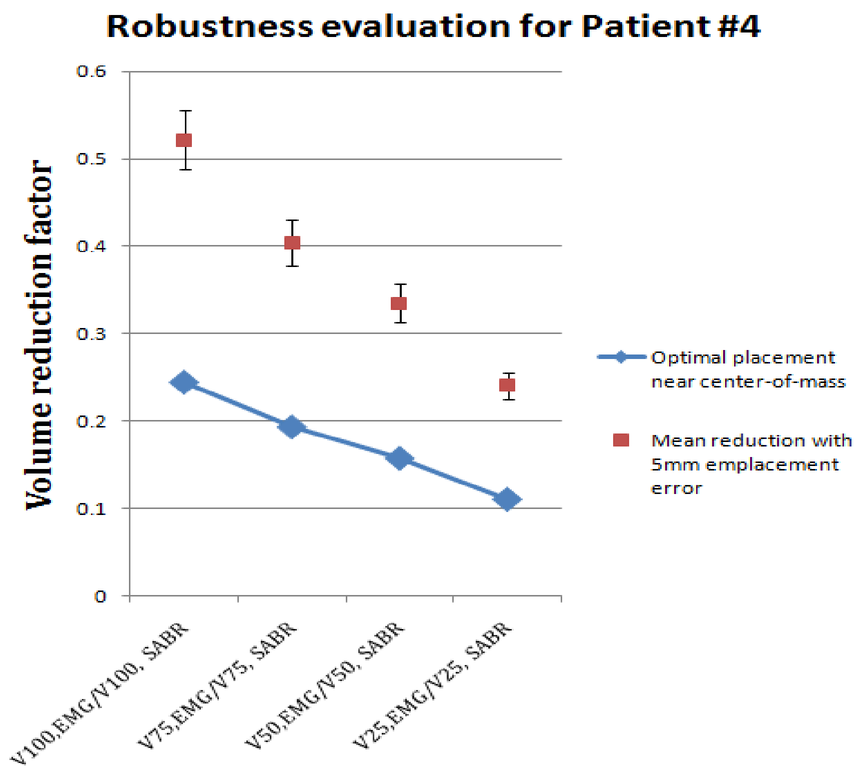
- System accuracy: 3 mm for rigid simulated lung model
- Depending on quality of registration, 5 mm accuracy can be assumed
- Unlike seeds, HDR is less sensitive to positioning
  - CT-based planning based in post implant image
- Larger volume of healthy lung parenchyma will be exposed to the highest 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. $Vol_{HDR}/VoL_{SABR}<1$)



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*.)

	Peripheral			Central		
	<=10 cc	>10 & <=30 cc	>30 cc	<=10 cc	>10 & <=30 cc	>30 cc
Rx dose (covering 95% PTV)	25 Gy in 1 fxn	50 Gy in 4 fxns	54 Gy in 3 fxns	40 Gy in 4 fxns	50 Gy in 4 fxns	60 Gy in 8 fxns

- 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

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