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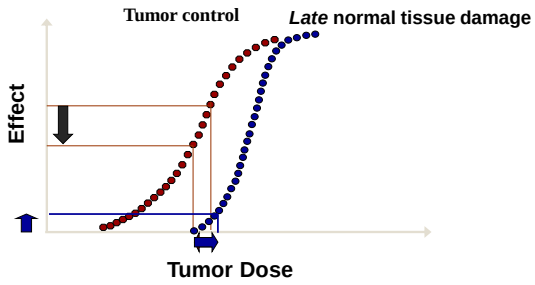
Photon versus Proton Therapy: Have we reached the limit?

American Association of Medical Physics Annual Meeting
Washington, DC

Stephen M Hahn
August 4, 2016

Effect of underdosage and overdosage



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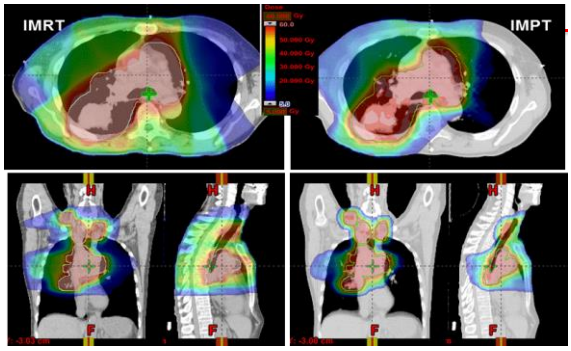

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Mohan R et al. Clin Cancer Res 19:6338, 2013

Challenges in Radiation Therapy

1. Cost & Value
2. Beam Uncertainties
   - **Protons scatter differently (charged particle) – very sensitive to tissue inhomogeneity**
   - **Range Uncertainty**
   - **Affects beam directions & introduces uncertainty about delivered dose**
   - **Accentuate the issues related to random & systematic set up errors**
3. Conformality
4. Motion & Imaging

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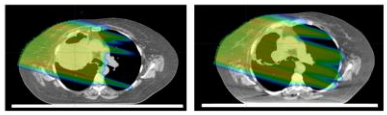

Fig.2 Comparison of dose distribution from single RAO field before and after tumor shrinkage as detected during third week of treatment. (This patient experienced the most dramatic tumor shrinkage).

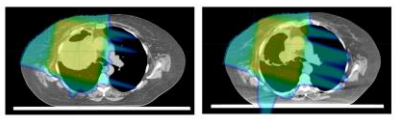

Fig.3 Comparison of total dose distribution before and after tumor shrinkage. (Same patient as Fig.2)

Amos, *et al.* Variation in dose distribution with tumor shrinkage for proton therapy of lung cancer, Poster presentation at PTCOG 46, Zibo, Shandong, China, 2007

Courtesy of Richard Amos

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Beam Uncertainties - Range Uncertainty

- **Range uncertainty has several treatment planning & clinical implications**
- **Limits field arrangements and beam weighting**
  - **Fields where the distal edge is at the interface of a critical structure (cord, optic nerve)**
  - **May limit the amount of dose delivered by any given field**
- **Affects the margin placed at the distal edge of the beam**
- **Measurement of range is likely to be important in hypofractionated regimens**

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Dose Conformality and Protons

- Protons administered with double scattering (DS) technologies, in particular, do not provide the level of dose conformality* that modern x-ray technologies do
- For many clinical situations, the high dose regions in normal tissue are higher & certainly no better than x-rays
- PBS (SFUD) and IMPT typically provide greater dose conformality compared to DS protons and perhaps modern x-ray technologies but motion is a more significant issue

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*Paddick I J Neurosurg. 2000 Dec;93 Suppl 3:219-22.

ELSEVIER

International Journal of Radiation Oncology*Biology*Physics

Volume 75, Issue 3, 1 November 2009, Pages 950–958

Physics Contribution

Proton Beam Radiotherapy Versus Three-Dimensional Conformal Stereotactic Body Radiotherapy in Primary Peripheral, Early-Stage Non–Small-Cell Lung Carcinoma: A Comparative Dosimetric Analysis

O. Kenneth Macdonald, M.D.*, Jon J. Kruse, Ph.D.*†, Janelle M. Miller, C.M.D.*, Yolanda I. Garces, M.D.*, Paul D. Brown, M.D.*, Robert C. Miller, M.D.*, Robert L. Foote, M.D.*

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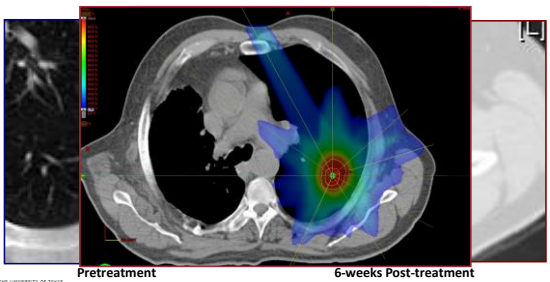
Early Stage Disease: Stereotactic Body Radiation Therapy



Pretreatment 6-weeks Post-treatment

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Hypofractionated Protons for Stage I NSCLC

- PT treatment plans were generated using single-, two-, and three-field passively scattered and actively scanned proton beams. Calculated dose characteristics were compared.
- Comparable planning target volume (PTV) median minimum and maximum doses were observed between PT and SBRT plans. Higher median maximum doses 2 cm from the PTV were observed for PT, but higher median PTV doses were observed for SBRT
- The total lung mean and V5 doses were significantly lower with actively scanned PT. The lung V13 and V20 were comparable. The dose to normal tissues was lower with PT except to skin and ribs.
- Passively scattered plans, compared with actively scanned plans, typically demonstrated higher doses to the PTV, lung, and organs at risk.

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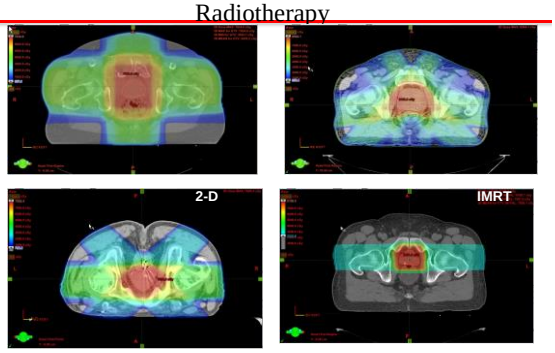
Macdonald OK et al. IJROBP 2009

Prostate Cancer: The Evolution of Radiotherapy



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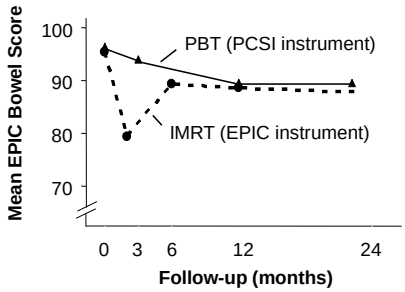
Are Protons Better than IMRT?



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Gray PJ, et al. Cancer 119:1729, 2013

Efficacy & Toxicity of IMRT and PBT

Outcome	IMRT	PBT	FU (yrs)	Evidence
OS	>80-90%	>80-90%	5	Limited
DSS8	>95%	>95%	5	Limited
FFBF	74-95%	69-95%	1.5-6	

Toxicity	Acute vs. Late	IMRT (Pooled Rate 95 CI)	PBT (Pooled Rate 95 CI)
GI	Acute	18.4 (8.3, 28.5)	0*
	Late	6.6 (3.9, 9.4)	16.7 (1.6, 31.8)
GU	Acute	30.0 (13.2, 46.7)	40.1*
	Late	13.4 (7.5, 19.2)	5.5 (4.6, 6.5)
ED		48-49**	Not reported
** 2 studies	* 1 study		

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Are Protons Better?

Proton Versus Intensity-Modulated Radiotherapy for Prostate Cancer: Patterns of Care and Early Toxicity

James B. Yu, Pamela R. Soulos, Jeph Herrin, Laura D. Cramer, Arnold L. Potosky, Kenneth B. Roberts, Cary P. Gross

Manuscript received May 15, 2012; revised September 24, 2012; accepted September 25, 2012.

Correspondence to: James B.Yu, MD, Yale University School of Medicine, Department of Therapeutic Radiology, 40 Park St, LL511-SMILOW, New Haven,

Although PRT is substantially more costly than IMRT, there was no difference in toxicity in a comprehensive cohort of Medicare beneficiaries with prostate cancer at 12 months post-treatment.
J Natl Cancer Inst 2013;105:25–32

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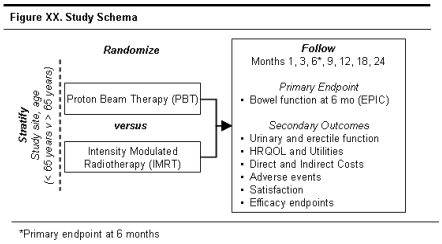
Study Schema

Figure XX. Study Schema



*Primary endpoint at 6 months

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Liao – P01 Randomized Phase II NSCLC Trial

A Bayesian Randomized Trial of IMRT vs. 3D-PSPT for Locally Advanced NSCLC

Analyses ongoing – two manuscripts in preparation

Adapted from Liao's ASCO SLides

Hypothesis

- **Proton therapy will**
  - **Reduce irradiated lung volume, hence reduce radiation pneumonitis (RP)**
  - **Achieve same local control (LC) for the same prescribed biologically effective radiation dose (RBE = 1.1)**

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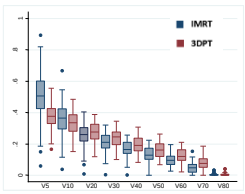
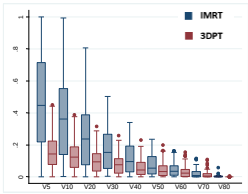
Lung and Heart V5-V80

Lung V5 – V80



Heart V5 – V80



Note: Analysis carried out using the Wilcoxon rank-sum test (also known as Mann-Whitney Two Sample Statistic)

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Radiation Pneumonitis

RP Grade	IMRT	3DPT	Total	P values
	N=92	N=57	N=149	
0	65	36	101	0.36
1	9	4	13	
2	12	11	23	
3	4	6	10	
4	0	0	0	
5	2	0	2	
Gr 0-2	86	51	137	0.54
Gr 3-5	6 (6.5%)	6 (10.5%)	12 (8.1%)	

Median Time to RP: All = 4.3 month,
IMRT= 4.5 month,
3DPT= 4.0 month (p=0.15)

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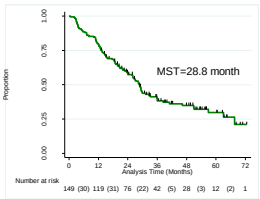
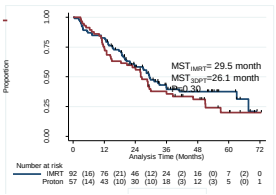
Overall Survival





Variable		HR	p-value	95% CI		Comparison
Age	Continuous	1.03	0.012	1.01	1.06	Continuous
RT Dose	>=74	0.62	0.036	0.39	0.97	<74Gy
GTV	Continuous	1.002	0.02	1.000	1.003	Continuous

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Conclusions

- Considerably fewer events occurred in both arms compared what was expected based on statistical considerations in the trial design
  - No statistically significant difference in RP or Local Failure when IMRT and 3DPT plans were required to meet identical normal tissue dose constraints and target prescription dose
- Patient enrolled after 9/27/2011 did better – learning curve and improving in techniques, but differential greater for protons

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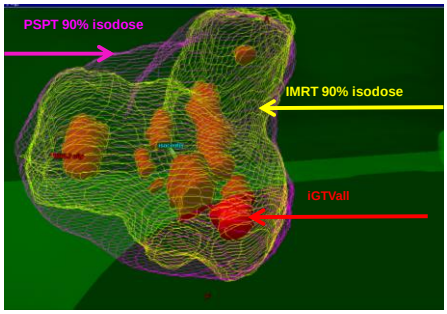
An Example of 3D Isodose Comparison for 3DPT vs. IMRT Plans: High dose volume for PSPT > for IMRT



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Understanding Factors Affecting Outcomes (Toxicities and Recurrences) for the Randomized Lung Trial

- Trial design – Requirement of the same normal tissue dose constraints and same prescription in both arms
- Greater vulnerability of proton dose distributions to intra-fractional motion and inter-fractional anatomy changes
- Larger penumbra and large spot sizes → larger higher dose volume outside the target
- State of the art of proton dose calculation algorithms
- Assumption of RBE = 1.1
- Technological state of the art insufficiently advanced (PSPT used, not IMPT; image guidance; …)
- Planning experience and expertise still evolving and lags behind IMRT

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RTOG 1308

RTOG 1308

Phase III Randomized Trial Comparing Overall Survival after Photon versus Proton Radiochemotherapy for Inoperable Stage II-IIIB NSCLC

SCHEMA

STRATIFY

Stage
1. II
2. IIIA
3. IIIB

GTV Volume
1. ≤ 130 cc
2. > 130 cc

Histology
1. Squamous
2. Non-Squamous

Neoadjuvant Chemo
1. No
2. Yes

RANDOMIZE

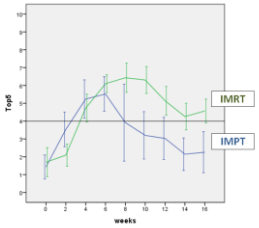
Arm 1: Photon dose—Higher achievable dose between 60-70 Gy, once daily plus platinum-based doublet chemotherapy*

Arm 2: Proton dose—Higher achievable dose between 60-70 Gy (RBE), once daily plus platinum-based doublet chemotherapy*

Both Arms: Consolidation chemotherapy x 2 is allowed*

IMPT vs IMRT for OPC
First comparative results of PROs

Symptom burden less with IMPT after treatment than IMRT based on patient reported outcomes



Symptom Burden by MDASI	IMPT	IMRT	P-value
AUC	63.9	110.4	0.0006
AUC (4-10)	8.7	36.4	0.004

Source: Sio et al. Int J Radiat Oncol Biol Phys, 2016

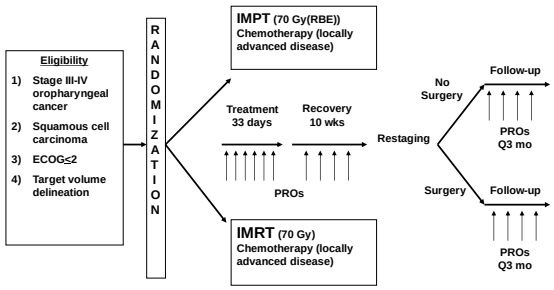
MDACC case-Matched analysis IMPT vs IMRT

- Patients with OP cancer, 50% p16+
- Using a preplanned analysis, feeding tube 3 months post RT or grade 3 weight loss (-20%)

	During RT				3-Months post RT				1 year post RT			
Endpoint	**IMPT n (%)**	**IMRT n (%)**	**OR (95% CI)**	**p**	**IMPT n (%)**	**IMRT n (%)**	**OR (95% CI)**	**p**	**IMPT n (%)**	**IMRT n (%)**	**OR (95% CI)**	**p**
G-tube presence	12 (24)	38 (38)	0.53 (0.24-1.15)	0.11	6 (12)	23 (23)	0.43 (0.16-1.17)	0.10	1 (2)	9 (10.1)	0.14 (0.02-1.16)	0.07
Weight loss >20% compared to baseline	-	-	-	-	4 (8.3)	13 (13.5)	0.64 (0.19-2.11)	0.46	3 (6.7)	17 (19.3)	0.28 (0.08-1.05)	0.06
Combined G-tube OR weight loss > 20%	-	-	-	-	9 (18)	34 (34)	**0.44 (0.19-1.0)**	**0.05**	4 (8)	24 (27)	**0.21 (0.07-0.67)**	**0.008**

Source: Blanchard et al. *Radiotherapy and Oncology* 2016 (in press)

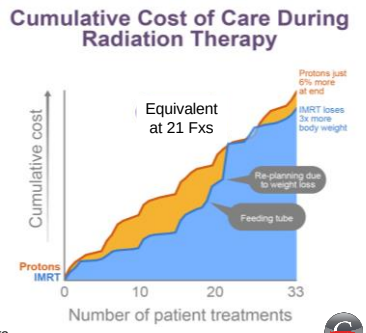
Potential Benefit for OPC
IMPT vs IMRT
A randomized controlled trial



Frank, PI: Trial Activated at MD Anderson – Sept 2013

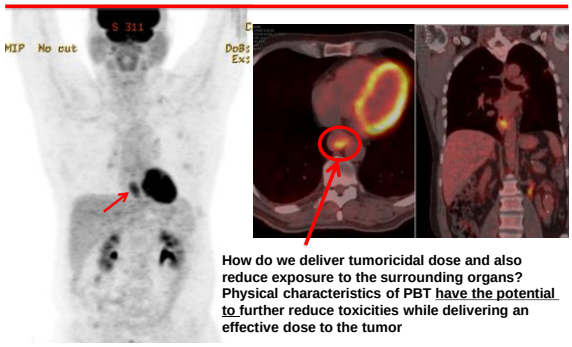
Value Proposition- H&N

$$\text{Value} \uparrow = \frac{\Sigma \text{ (Outcomes)}}{\Sigma \text{ (Costs)} \downarrow}$$



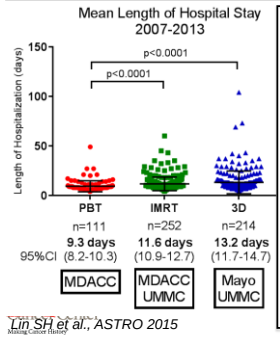
Thaker N et al. *Oncology Payers* 2014

Esophagus is surrounded by critical normal tissues (heart & lungs)



How do we deliver tumoricidal dose and also reduce exposure to the surrounding organs? Physical characteristics of PBT have the potential to further reduce toxicities while delivering an effective dose to the tumor

Length of hospitalization comparing radiation modalities



Lin SH et al., ASTRO 2015

Single institutional analysis

Clinical Investigation: Gastrointestinal Cancer

Predictors of Postoperative Complications After Trimodality Therapy for Esophageal Cancer

Jingya Wang, MD,* Caimiao Wei, PhD,† Susan L. Tucker, PhD,† Bevan Myles, MD,* Matthew Palmer, CMD, MBA,* Wayne L. Hofstetter, MD,‡ Stephen G. Swisher, MD,‡ Jaffer A. Ajani, MD,‡ James D. Cox, MD,* Ritsuko Komaki, MD,* Zhongxing Liao, MD,* and Steven H. Lin, MD, PhD*

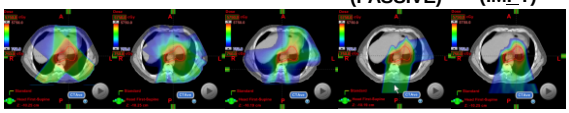
3D (N=208); **IMRT** (N=164); **PBT** (N=72)

Median length of hospital stay was significant by radiation modality

- **12 days for 3D, 10 days for IMRT, and 8 days for PBT** (p<0.0001)

Wang et al., IJROBP 2013

Mean Radiation Dose to Normal Organs Protons vs Photons

3D-CRT	IMRT	VMAT	PROTONS (PASSIVE)	PROTONS (IMPT)
				
LUNG – 1747	LUNG – 1324	LUNG – 1103	LUNG – 966	LUNG – 775
HEART – 2833	HEART – 1933	HEART – 2200	HEART – 1301	HEART – 943
LIVER – 1184	LIVER – 1141	LIVER – 986	LIVER – 218	LIVER – 235

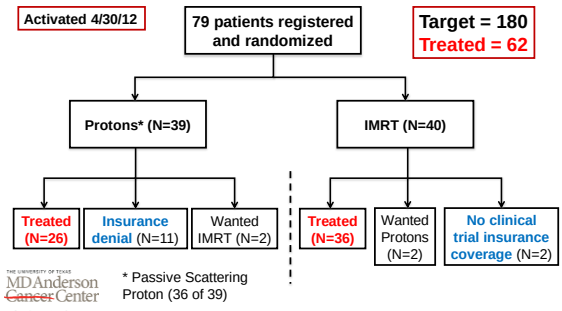
Key Question: Does reducing the unnecessary exposure of the heart and lungs to radiation using proton beam improve clinical outcomes?

ClinicalTrials.gov: NCT01512589
MDACC 2011-1036

Phase IIB Randomized Trial of Proton Beam Therapy (PBT) versus Intensity Modulated Radiation Therapy (IMRT) for the treatment of Esophageal Cancer (U19)

PI: Steven H. Lin, M.D., Ph.D. (MDACC)
Co-PI: Theodore S. Hong, M.D. (MGH)
Statisticians: Peter Thall, Ph.D., Brian Hobbs, Ph.D.
Research Nursing: Denise Erdman, RN
Activated 4/30/2012

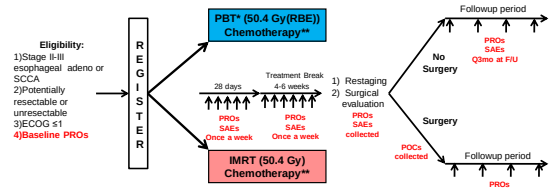
Phase IIB Randomized Trial of PBT vs IMRT for Esophageal Cancer (MDA 2011-1036)



* Passive Scattering Proton (36 of 39)

Proposed NRG Trial Schema

(Consideration to only randomize when PBT is covered)



*PBT=IMPT or Passive Scattering Proton ** Carbo/taxol or Docetaxel/5-FU

Stratification: Resectable vs. Unresectable, Induction chemotherapy (yes/no),
Stage II or III, Adenocarcinoma or SCCA, Age ≥ 65 vs. < 65

Conclusions

- Do the physical advantages of protons translate into clinical benefit? – an unanswered question
- Despite the dosimetric advantages of proton therapy, studies have yet to show a clinical benefit to proton therapy compared to IMRT.
- There are NO level 1 data published to support the use of protons over photons
- Such data are being generated – NSCLC, esophageal cancer, breast cancer, prostate cancer, OP cancer
- Encouraging early results in esophageal and OP cancers

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James Welsh, MD
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Steven Lin, MD, PhD
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Luka Milas, MD, PhD
K Kian Ang, MD,PhD

Radiation Physics
Radhe Mohan, PhD
Michael Gillin, PhD
Lei Dong, PhD
Xiaodong Zhang, PhD
Peter Balter, PhD
Richard Amos, MS
Ron. Zhu, PhD
Kazumichi Suzuki, PhD
Uwe Titt, PhD
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Frank Fossella, MD
George Blumenschein, MD
Edward Kim, MD
John Heymach, MD
Charles Lu, MD
Anne Tsao, MD
All Thoracic/GI Medical Oncologists

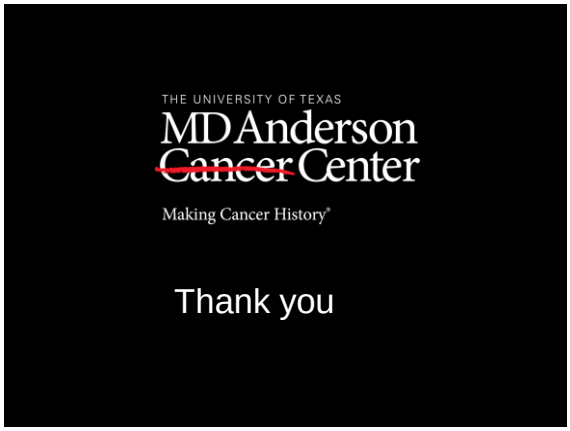
Thoracic surgery
Jack A. Roth, MD
Stephen Swisher, MD
All Thoracic Surgeons

Diagnostic images
Jeremy Erasmus, MD
All Thoracic radiologists

Molecular Pathogy
Ignacio Wistuba, PhD, MD

Biomathematics

Supported by NCI P0-1 CA 021239 & DOD : IMPACT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