Stereotactic MR-Guided Adaptive Radiation Therapy: It's the SMART thing to do!"

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SITEMAN CANCER CENTER
A National Cancer Institute Comprehensive Cancer Center
BARNES-JEWISH Hospital
Washington University in St Louis School of Medicine
NCCN National Comprehensive Cancer Network
NCI CCC

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Disclosures

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- **Research Funding**
  - –Viewray Inc

Low field MRgRT implementation

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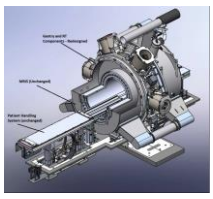

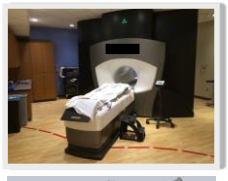

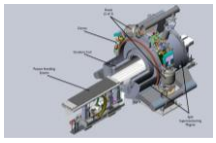

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Clinical MRgRT timeline

- 1/2014 -First patient treatment
- 9/2014 -First online adaptive treatment
- 1/2015 - First online adaptive SBRT
- 2/2015 - First online adaptive SBRT with automated MR image based gating
- 5/2018 –MR-linac comes online
- 7/2018 – First online adaptive SBRT on MR-linac

Over 10 clinical sites
Seoul National University Hospital, Seoul, South Korea
Washington University, St. Louis, Missouri, USA*
UCLA, Los Angeles, California, USA
University of Wisconsin, Madison, Wisconsin, USA*
University of Miami, Miami, Florida, USA
Heidelberg*
Miami Cancer Institute*
NYP / Weill
Sheikh Khalifa, Dubai
VUMC, Amsterdam, Netherlands
Gemelli, Rome, Italy
National Cancer Center, Tokyo, Japan
Henry Ford Medical Center, Detroit, Michigan, USA *

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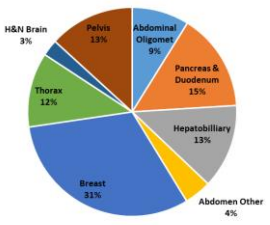
Washington University Clinical Dashboard 2014-2018



Disease Sites Treated	N	%
Adomen		
Oligomet	59	8.9
Pancreas/Duodenum	101	15.2
Hepatobilliary	87	13.1
Gastric	15	2.3
Sarcoma	7	1.1
Other	6	0.9
Pelvis & Lower extremity		
Lower GI	12	1.8
Prostate	35	5.3
Bladder	22	3.3
Oligomet	17	2.6
Extremity	2	0.3
H&N and Brain		
H&N	14	2.1
CNS	3	0.5
Thorax		
Lung & mediastinum	67	10.1
Esophagus	3	0.5
Oligomet	3	0.5
Bone	4	0.6
Breast		
APBI	203	30.5
WBRT	6	0.9

Henke, Contreras et al, Clinical Oncology, in submission

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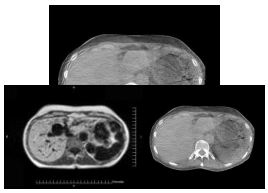
MRI imaging is better than CBCT

- Onboard CT images used for routine treatment localization were collected
  - MVCT or kVCT
  - In-plane resolution: ~1-1.5mm
  - Slice thickness: 2.5 - 4.0 mm
- 3 radiation oncologists evaluated the low-field MRI & onboard CT images side-by-side



Noel, Parikh et al, Acta Oncologica, 2015

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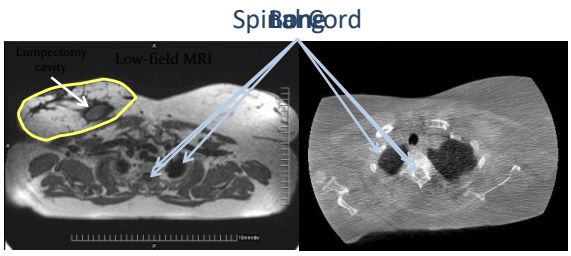
Breast Cancer Patient



Noel, Parikh et al, Acta Oncologica, 2015

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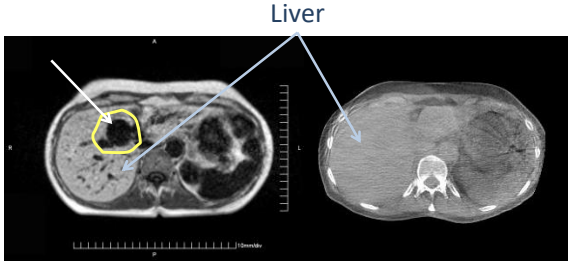
Liver Metastasis Patient



Noel, Parikh et al, Acta Oncologica, 2015

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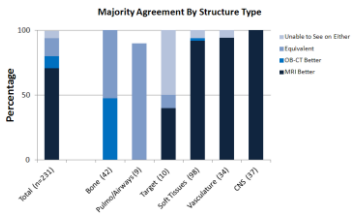
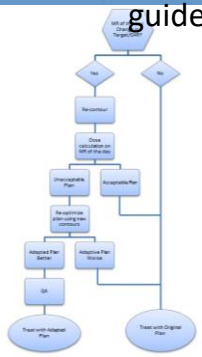
MRI vs CBCT Results

- When examined by **structure type**, there were differences in which modality offered better visualization:
  - **Bone:** OB-CT (48%) or Equivalent (52%)
  - **Pulmonary Systems/Airways:** Equivalent (90%)
  - **Target:** MRI (40%), Equivalent (10%)
  - **Soft Tissues:** MRI (92%)
  - **Vasculature:** MRI (94%)
  - **CNS:** MRI (100%)



Noel, Parikh et al, Acta Oncologica, 2015

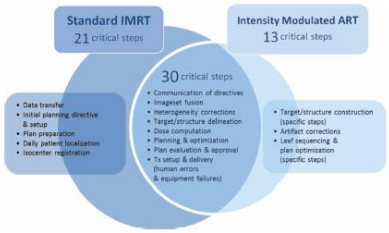
First clinical paper with adaptive MR guided radiation



Online Magnetic Resonance Image Guided Adaptive Radiation Therapy: First Clinical Applications, Acharya, et al. IJROBP Vol. 94, No. 2, pp. 394e403

FMEA analysis of QA

Noel et al, Med Phys 2014



- Found unique points of failure in ART, but some issues in standard IMRT not found. Created processes to review contours and perform virtual QA, no physical QA!

Online Adaptive SBRT Phase I Study

Radiother Oncol. 2017 Dec 22. pii:

Phase I trial of stereotactic MR-guided online adaptive radiation therapy (SMART) for the treatment of oligometastatic or unresectable primary malignancies of the abdomen.

Henke L[1], Kashani R[1], Robinson C[1], Curcuru A[1], DeWees T[1], Bradley J[1], Green O[1], Michalski J[1], Mutic S[1], Parikh P[2], Olsen J[3].

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Online Adaptive SBRT Phase I Study

- 20 patients with unresectable primary or oligometastatic disease of the liver (n = 10) & non-liver (n=10) abdomen planned for SBRT
- Prescription: 50Gy/5fx with online, adaptive MR-IGRT approach
- Isotoxicity approach, with dose escalation (or de-escalation) based on hard OAR constraints

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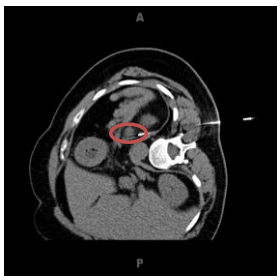
Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis

- 51yo woman, 1 year disease-free period
- Biopsy-proven, solitary 1.8cm adrenal ADC metastasis
- KPS 100%
- Preferred non-surgical option



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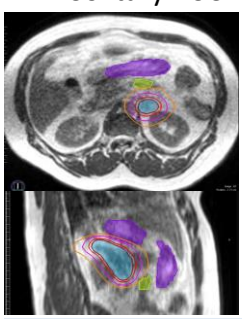
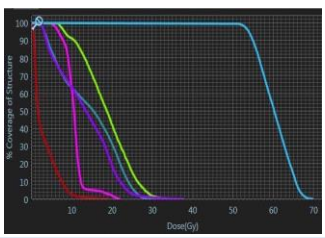
Phase I Trial Example Case

Solitary NSCLC Adrenal Metastasis



•Day 1- All OAR constraints met, including small bowel & stomach



Phase I Trial Example Case

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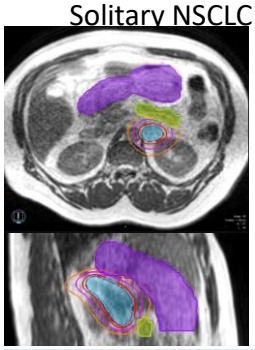
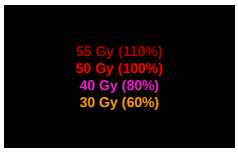
Solitary NSCLC Adrenal Metastasis



•Day 2- Application of day 1 plan violates small bowel & stomach OAR constraints



Phase I Trial Example Case

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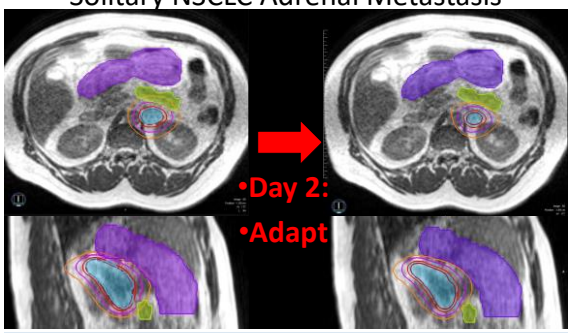
Solitary NSCLC Adrenal Metastasis



Phase I Trial Example Case

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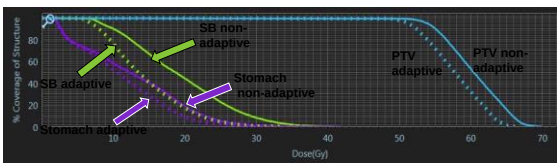
Solitary NSCLC Adrenal Metastasis



- Adaptive plan reduces small bowel and stomach dose
- PTV coverage minimally sacrificed
- PTV coverage remains at goal 50Gy

Henke et al, R&O, 2017

Phase I Trial Example Case

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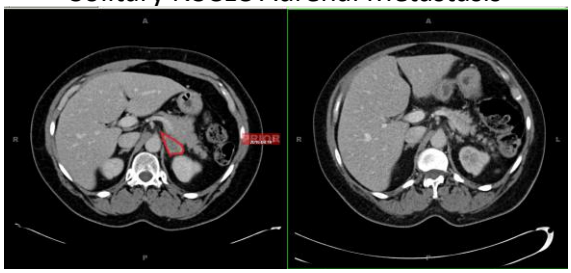
Solitary NSCLC Adrenal Metastasis



- Patient with zero reported acute or late toxicity
- Radiographic CR at 3 and 6 months

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Phase I Results—Timing

- Median on table time: 79 minutes
- Median segmentation time: 9 min
- Median re-planning time: 10 min
- Median QA time: 5 min

Henke et al, R&O, 2017

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Phase I Results—Plan Adaptation

- 83% (79/95) fx adapted—all patients had ≥1
- Plans adapted for 64% of liver & 98% of non-liver abdomen fx
- Initial plans would have violated OAR constraints in 70/95 fx
- 100% of OAR violations resolved with adaptive planning

Henke et al, R&O, 2017

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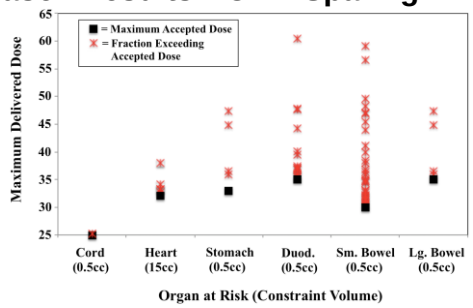
Phase I Results—OAR Sparing



Henke et al, R&O, 2017

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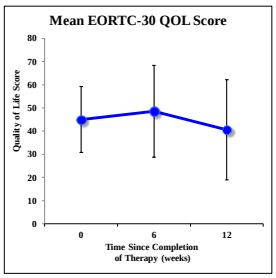
Phase I Results—Clinical Outcomes

- No Grade 3 toxicity at median 11.8 mo f/u
- Expected 20-30% using aggressive dose regimen
- No change in patient-reported EORTC-qlq 30 QOL scores (*P* = 0.29) at 0, 6, and 12wks.



Henke et al, R&O, 2017

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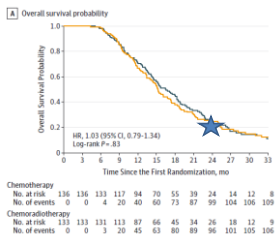
Locally Advanced Pancreatic Cancer is Bad



Hammel et al, JAMA, 2016

- "If cancer is the emperor of all maladies, then pancreatic adenocarcinoma is the ruthless dictator of all cancers" – Deborah Schrag

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Reviewing MRgRT data to date

- Reviewed five institutions' data for pancreas MRgRT (VUMC, Wisconsin, UCLA, Washington University, University of Miami)
- Locally advanced, borderline resectable and medically inoperable pancreatic cancer patients treated up to 8/2016
- Practices varied between dose, fractionation, technique between institutions
- Looked at dose as a predictor of survival

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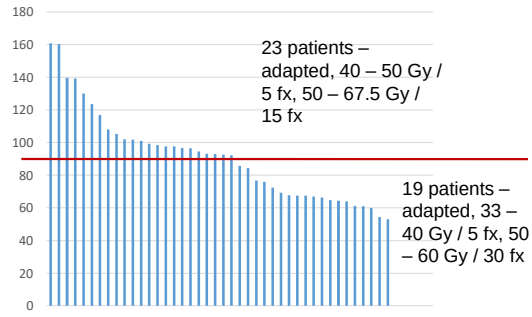
Maximum BED > 90 Gy



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Patient Characteristics	$maxBED_{10}$>90 N=23	$maxBED_{10}$<90 N=19	p-value
Age (median)	68	62	0.068
Sex:			
Male	14	12	0.879
Female	9	7	
Tumor Characteristics			
Location:			
Head	17	12	0.453
Tail	6	7	
Resectability:			
BRPC	4	6	0.409
LAPC	17	13	
Medically Inoperable	2	0	
Median CA 19-9 at diagnosis (U/mL)	263.4	82.5	0.099
Node positive	4	4	0.698

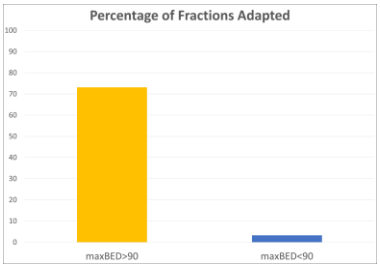
Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

Treatment Factors	$maxBED_{10}$>90 N=23	$maxBED_{10}$<90 N=19	p-value
Post – RT Surgery	3	2	1.000
Ind. Chemo:			
Gem-based	9	10	0.970
FOLFIRINOX	11	8	
FOLFOX	1	0	
None	2	1	
Conc. Chemo:			
Gem-based	4	9	0.094
Capecitabine	3	4	
None	16	6	
Radiation Factors			
BED_{10} of Rx (Gy)	72.0	59.5	<0.001
$maxBED_{10}$	101.1	66.9	<0.001
Median Fractions Adapted per patient	5	0	<0.001
GTV (cc)	38	36	0.714

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

RT Technique	Dose and Fractionation	Number of Patients
Conventional	50.4 Gy in 28 Fractions	6
	40 - 55 Gy in 25 Fractions	7
Hypofractionated	50 - 67.5 Gy in 10-15 Fractions	8
SBRT ($maxBED_{10}$ < 90)	30 – 40 Gy in 5 Fractions	6
SBRT ($maxBED_{10}$ > 90)	40 – 52 Gy in 5 Fractions	15

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017



Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

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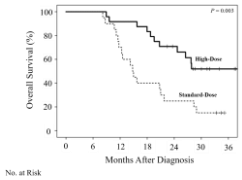
Overall Survival – median follow-up 22 months



No. at Risk

High-Dose	24	24	22	20	15	8	3
Standard-Dose	20	20	14	8	5	3	0

Updated: 7/2018 – Rudra et al, in submission

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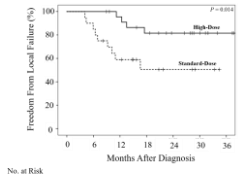
Continued high local control



No. at Risk

High-Dose	24	24	21	17	13	8	3
Standard-Dose	20	17	11	6	4	2	0

Updated: 7/2018 – Rudra et al, in submission

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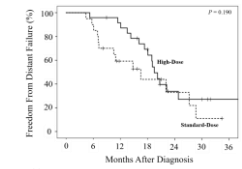
No change in distant metastases



No. at Risk

High-Dose	24	23	21	14	5	4	1
Standard-Dose	20	18	9	5	3	1	0

Updated: 7/2018 – Rudra et al, in submission

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Gr 3+ GI Toxicity	
maxBED$_{10}$>90	0%
maxBED$_{10}$<90	15.8%

Rudra S, Jiang N, Rosenberg S, Olsen J, Lagerwaard F, Bruynzeel A, Parikh P, Bassetti M, Lee P; ASTRO 2017

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Results in Context

Study	Median OS (months)
LAP07 – 3DCRT	15.2
MDACC – mostly 3DCRT	15*
MDACC – IMRT	17.8*
MRgRT – standard IMRT & SBRT	14.8
MSKCC – IMRT	23
Harvard – SBRT	20
JHU – SBRT	18.4
MRgRT – Hypofrac/High dose SBRT	**Not reached - 27.8**

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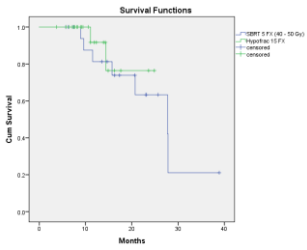
Open Questions

- Hypofractionation vs SBRT?
  - Current technology and MD time commitment at the machine makes hypofractionation difficult
  - No clear data on whether patients receiving 67.5 Gy / 15 fractions are doing better, worse or same at 50 Gy / 5 fractions
  - We don't have much surgery data after 50 Gy / 5 fractions, will need to acquire



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Open Questions

- Do the intestinal contents move during the plan adaptation process?
  - Anecdotal imaging (ie, imaging redone during treatment due to patient/machine issues) suggest some motion, but less than motion from prior fraction to today
  - This needs to be investigated formally to create action levels on plan adaptation, and engineering goals for industry

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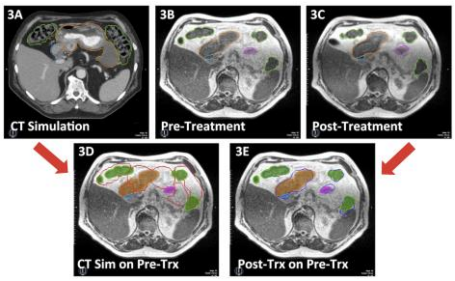
Patient example (intrafx motion)



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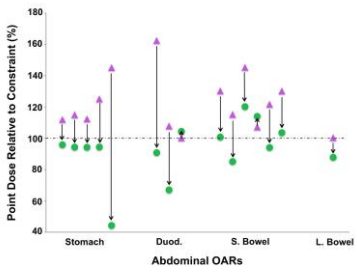
Does the adaptation work with intrafx motion?



Henke, Kashani in submission

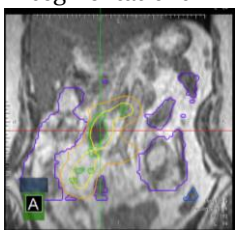
Open Questions

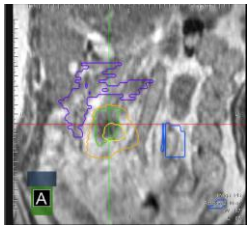
- What is the correct organ at risk constraint for GI structures at risk?
  - We do not have cumulative dose technology
  - First prospective multiinstitutional study will have more conservative dose constraints since primary aim is safety
    - 33 Gy to no more than 1 cc of stomach, duodenum, small and large bowel

Physician contouring on demand – not good at it, slows down pt flow

Changing targets

- 2 MD can mean 2 gold standard segmentations





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New Radiographer requirements

- Radiographers already had to learn MR based localization and safety
- Now learning MR based segmentation for normal tissue structures
- We created two 'Advanced Practice Radiation Therapists' who lead on-table segmentation and plan generation.
- Have increased to 8 adapted patients / day!

Idea from Europe!

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Next Step for Pancreas MRgRT

VUmc VU University Medical Center Amsterdam · UCLA · Washington University in St. Louis · WISCONSIN

Inoperable Pancreas Cancer after >= 3 months of chemotherapy → 50 Gy / 5 fractions MR guided, adapted and tracked

ViewRay Launches Clinical Trial Following Compelling Early Pancreatic Cancer Data with MRIdian System

First Initiative Based on Retrospective Study That Suggests Potential for Significantly Prolonged Survival

SNUH Seoul National University Hospital · Gemelli · University of Miami · Henry Ford Health System

Primary endpoint: Toxicity at 90 days
Secondary endpoints: Disease related outcomes
Goal: 100 patients

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Worldwide Acknowledgements

- **VUMC**
  - Frank Lagerwaard
  - Anna Bruynzeel
- **Gemelli**
  - Vincezo Valentini
- **Henry Ford Hospital**
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- **UCLA Health**
  - Percy Lee
  - Naomi Jiang

U Wisconsin
- Michael Bassetti
- Stephen Rosenberg

University of Miami
- Lorraine Portelance
- Eric Mellon

SNUH
- Eui Kyu Chie

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- Olga Green, PhD
- Lauren Henke, MD
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