US Perspectives in Radiotherapy: Robotic, Functional, and Molecular Image Guidance

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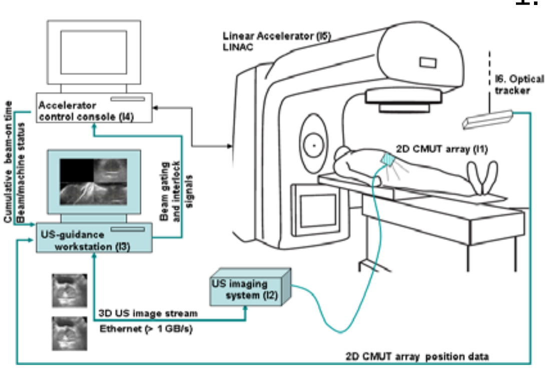
Stanford: Radiation Oncology Seed Grant,
Bio-X Interdisciplinary Initiatives Program
Cancer Institute Translational Award

NIH: R41 CA174089R01, R01 CA195443-02

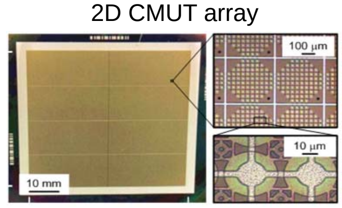
Industry: Philips Healthcare

Hand-free anatomical ultrasound imaging



2D CMUT array

1.



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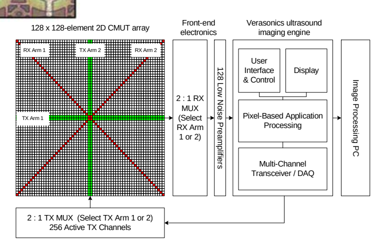
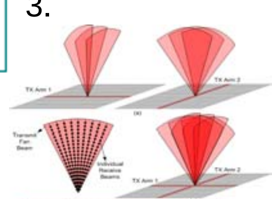


US system architecture

3.



Beamforming and imaging

Hristov et al, Real-Time Image Guidance for Radiation Therapy Symposium, AAPM Annual Meeting, July 18-22, Philadelphia, 2010.

Robotic/Manipulator-assisted hand-free ultrasound imaging

Stanford University, USA

Schlosser et al, Med. Phys. (2010)

Institute of Cancer Research, UK
MAASTRO, Netherlands

Johns Hopkins University

Su, L. et al, J Appl Clin Med Phys., (2017).
Sen, H et al, IEEE Trans. Biomed. Eng (2017)

University of Luebeck, Germany

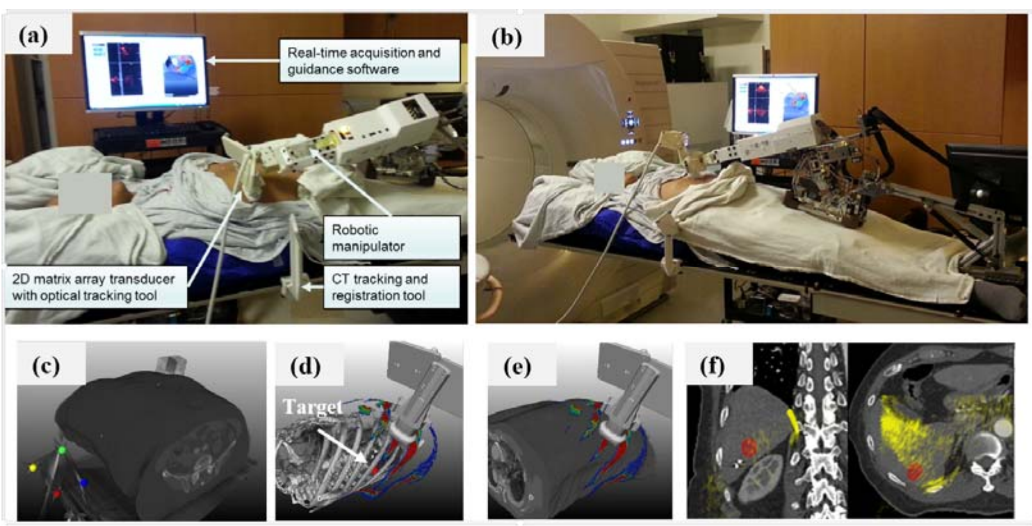
Gerlach et al, IJCARS (2017)

Medical College of Wisconsin, USA

Omari et al, Med. Phys. (2016)

UT Southwestern, USA

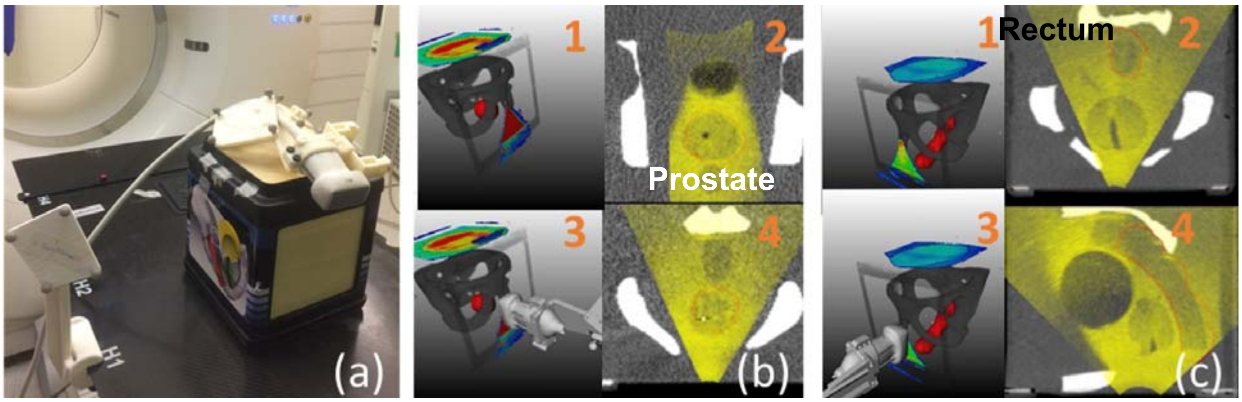
Robotic Ultrasound Image Guidance System



Schlosser J, Gong RH, Bruder R, Schweikard A, Jang S, Henrie J, Kamaya A, Koong A, Chang DT, Hristov D. Robotic intrafractional US guidance for liver SABR: System design, beam avoidance, and clinical imaging. *Med Phys* 2016;43:5951-5963.

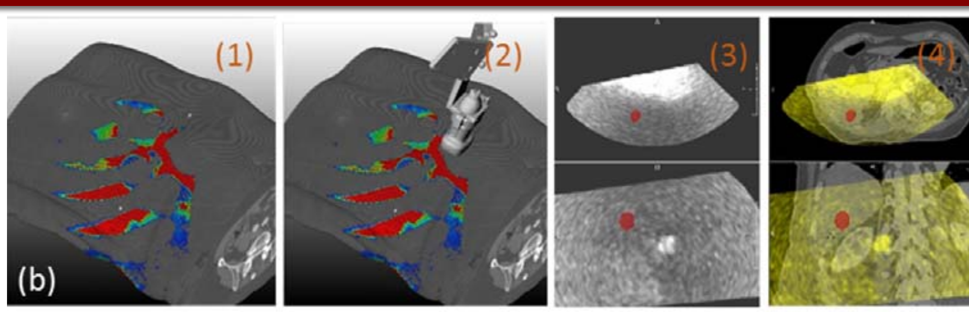
Probe placement guidance and validation

Map reflects maximum ultrasound attenuation from a given position to all points within a structure

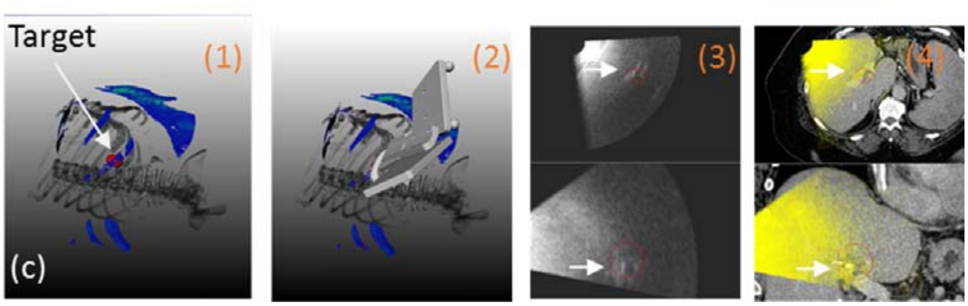


- **Map validated with multiple targets and positions**
- **Reflects attenuation, <u>neither contrast nor visibility.</u>**

Probe placement evaluation in patients

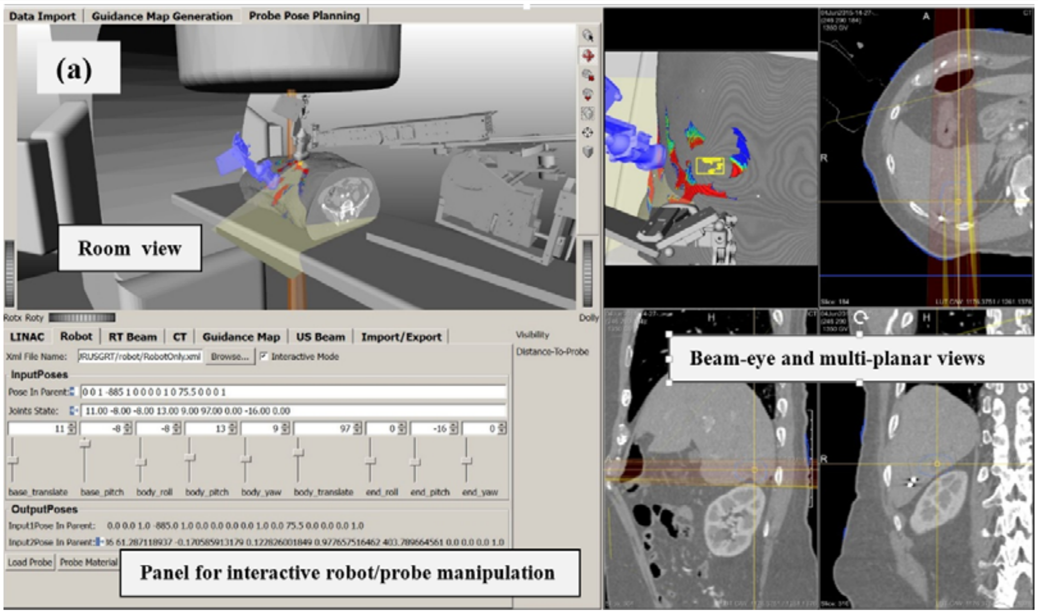


- Acoustic shadow from bowel gas

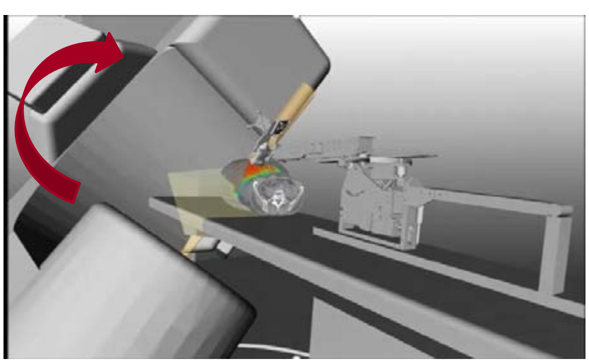


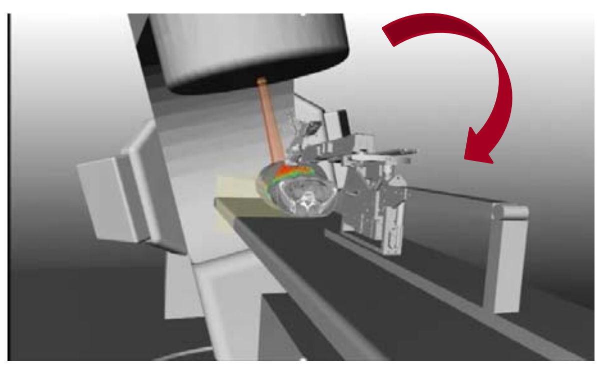
- Large attenuation
- Visible landmark

Collision interference evaluation



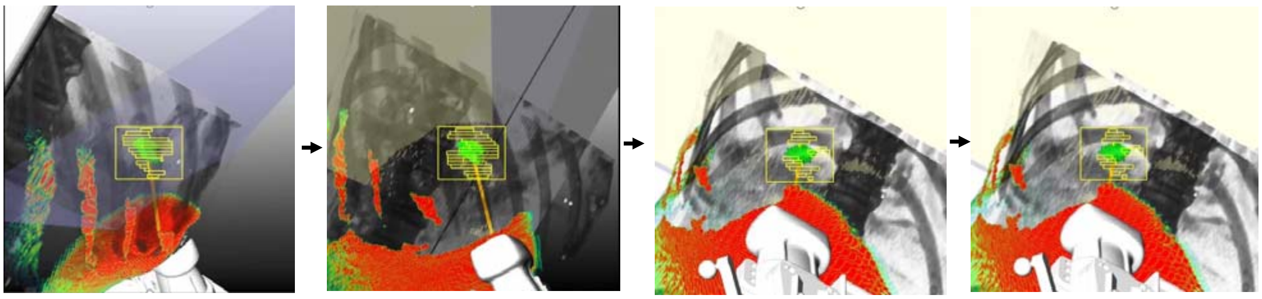
Collision interference evaluation





Room eye-view to monitor mechanical collisions: can be automated

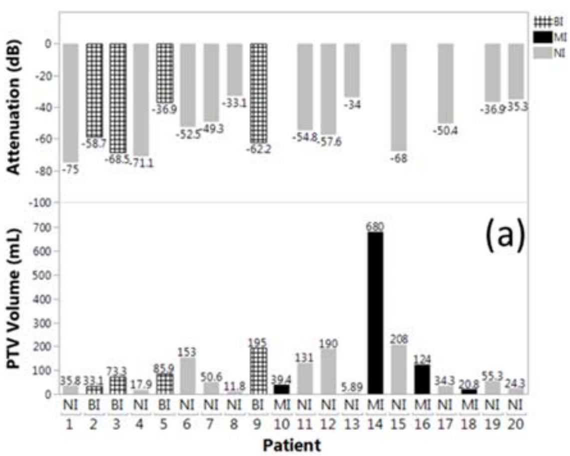
Beam interference evaluation



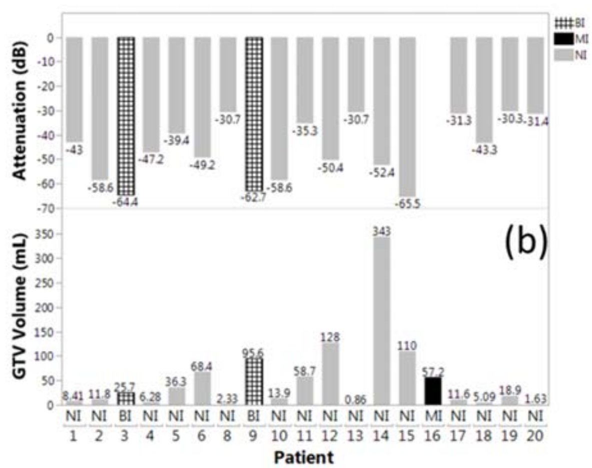
Beam eye-view to monitor entrance through probe/robot

Interference evaluation

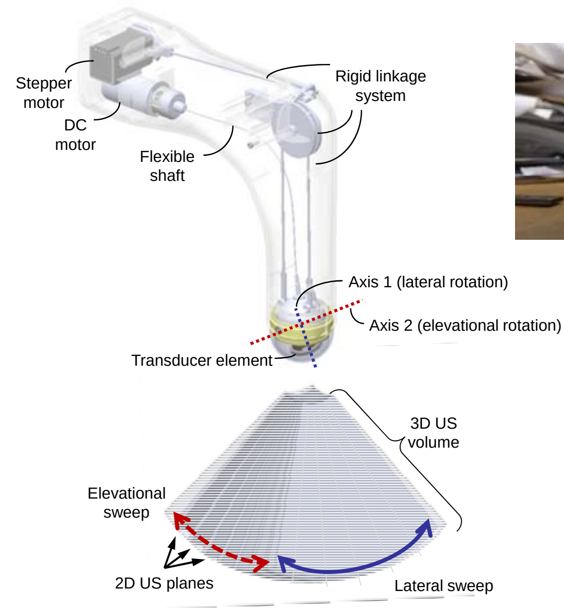
PTV: 12/20 (60%) no re-planning

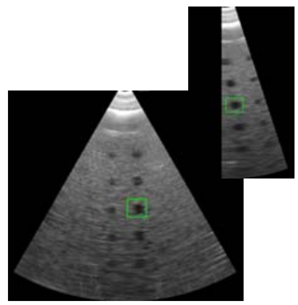


GTV: 17/20 (85%) no re-planning

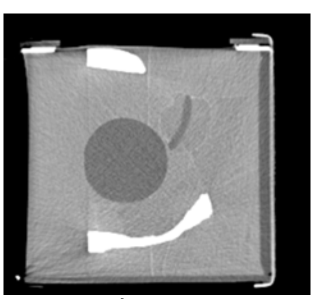


3D US Acquisition with the Remotely-Actuated Ultrasound Scanning (RUSS)

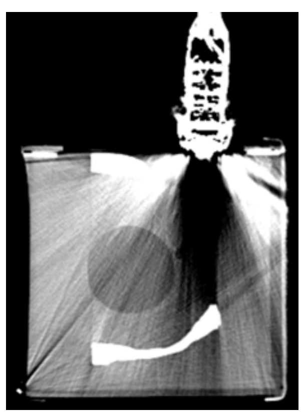




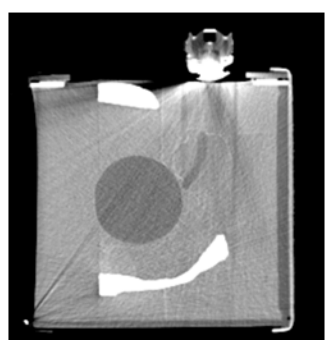
CT Compatibility



No probe present



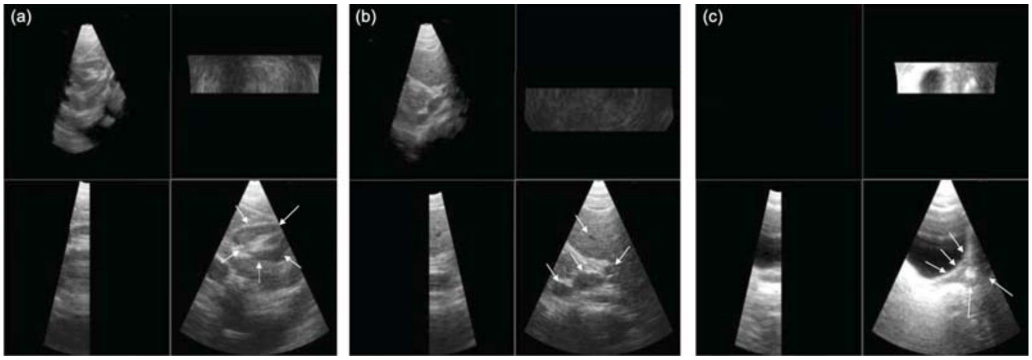
Philips X6-1 3D/4D matrix array probe



RUSS probe

Schlosser J, Hristov D. Radiolucent 4d ultrasound imaging: System design and application to radiotherapy guidance. IEEE Trans Med Imaging 2016 Oct;35(10):2292-2300

RUSS in-vivo examples



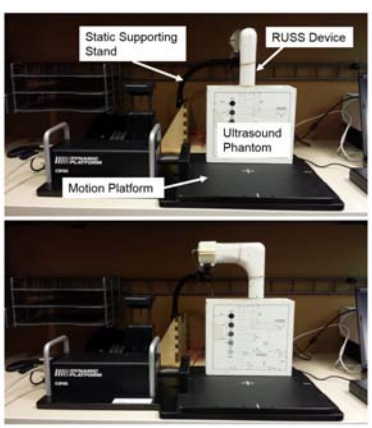
@ 10 cm depth: 5.0 cm x 4.0 cm FOV, 2.2 Hz volume rate, 48 Hz plane rate

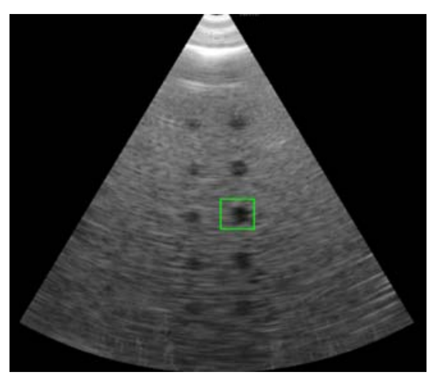
Resolution at depth	Axial	Lateral	Elevational
Resolution @ **5 cm**	**1 mm**	**5.1 mm**	**3.7 mm**
Resolution @ **10 cm**	**1 mm**	**7.9 mm**	**5.7 mm**

Schlosser J, Hristov D. Radiolucent 4d ultrasound imaging: System design and application to radiotherapy guidance. IEEE Trans Med Imaging 2016 Oct;35(10):2292-2300

Tracking Resolution

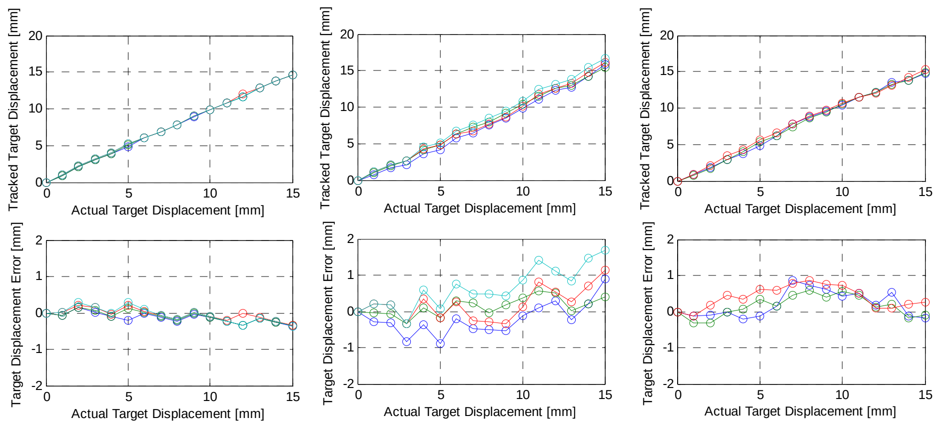
- US phantom placed on motion platform
- Targets automatically tracked using normalized cross correlation





Schlosser J, Hristov D. Radiolucent 4d ultrasound imaging: System design and application to radiotherapy guidance. IEEE Trans Med Imaging 2016 Oct;35(10):2292-2300

Tracking Resolution: Results



	Axial	Lateral	Elevational
Mean Target Tracking Error	**0.2 mm**	**0.4 mm**	**0.3 mm**
Max Target Tracking Error	0.4 mm	1.7 mm	0.9 mm

RUSS summary

Metric	Target: Intrafractional Liver Radiotherapy Guidance	Result with RUSS probe
Framerate and Field of View (FOV)	6.5 cm x 4 cm FOV at 5-15 cm depth; 1 volume per second	**@ 10 cm depth: 5.0 cm x 4.0 cm FOV, 2.2 Hz volume rate, 48 Hz plane rate**
Tracking Resolution	2 mm in each direction	**≤0.4 mm mean resolution**
Spatial Distortion	2 mm in each direction	**≤0.6 mm mean distortion**
CT Compatibility	No statistically significant difference in contouring	***Contour 1: p=0.86*** ***Contour 2: p=0.98***
Imaging during radiation delivery	No statistically significant difference between tracking performance with beam on/off	***p=0.52***
Radiotherapy planning compatibility	±3.0% / 2.0 mm agreement between computed and measured dose distributions	**All points agree within ±3.0% / 2.0 mm**

- **RUSS performance meets requirements for intrafractional radiotherapy motion management**
- **Low CT artifacts, beam compatibility, and low cost**

Significance of vascular damage

RADIATION RESEARCH 177, 311–327 (2012)
0033-7587/12 $15.00

DOI: 10.1667/RR2773.1

REVIEW

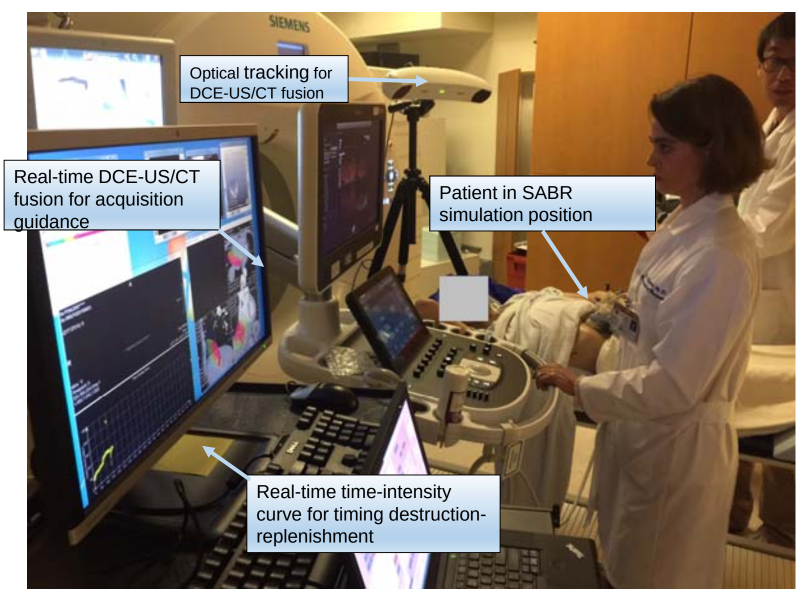
Radiation-Induced Vascular Damage in Tumors: Implications of Vascular Damage in Ablative Hypofractionated Radiotherapy (SBRT and SRS)

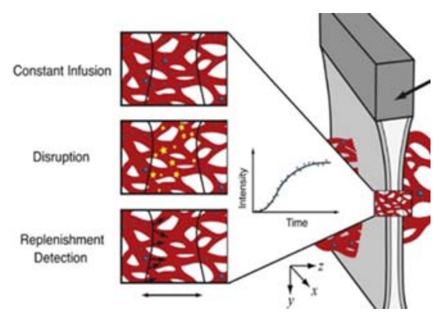
Heon Joo Park,[a,b] Robert J. Griffin,[c] Susanta Hui,[a] Seymour H. Levitt[a,d] and Chang W. Song[a,1]

[a] *Department of Therapeutic Radiology-Radiation Oncology, University of Minnesota Medical School, Minneapolis, Minnesota;* [b] *Department of Microbiology, Center for Advanced Medical Education by BK21 Project, College of Medicine, Inha University, Inchon, Korea;* [c] *Department of Radiation Oncology, University of Arkansas for Medical Sciences, Little Rock, Arkansas; and* [d] *Department of Oncology-Pathology, Karolinska Institute, Stockholm, Sweden*

"Little is known about the vascular changes in human tumors treated with high-dose hypofractionated radiation such as stereotactic body radiotherapy (SBRT) or stereotactic radiosurgery (SRS)"

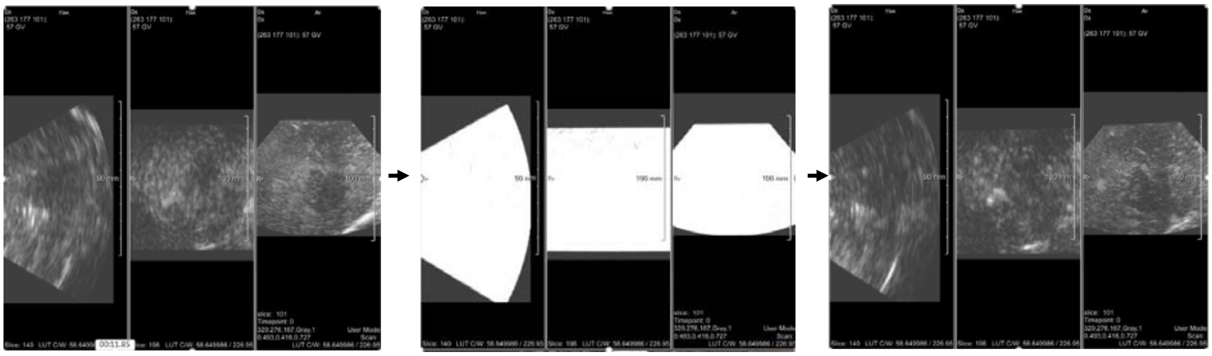
Contrast enhanced US for RT planning and response evaluation



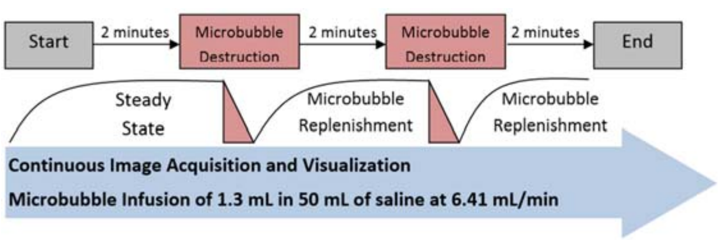


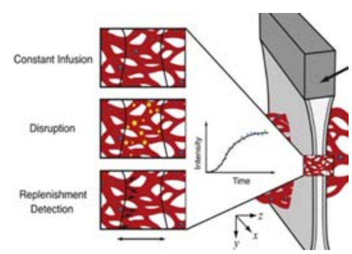
Hudson et al, Ultrasound in Medicine and Biology Volume 35, Issue 12 2009

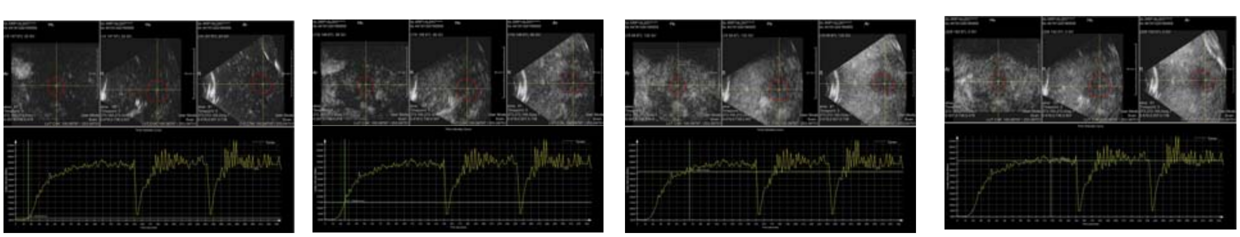
Video: Contrast enhanced US for RT planning and response evaluation



Feasibility of 3D DCE-US for SABR planning and response evaluation







Evaluation with regard to dose distribution enabled by fusion

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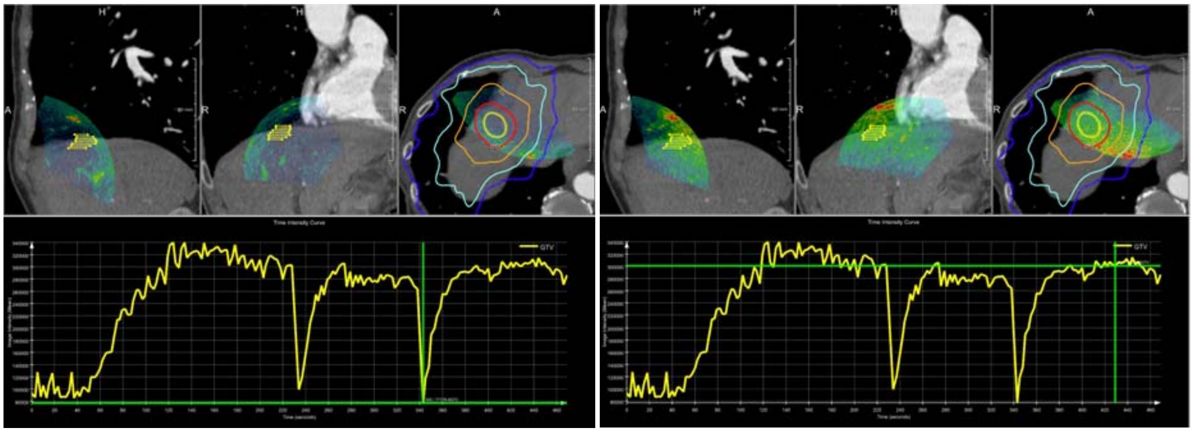

Quantification

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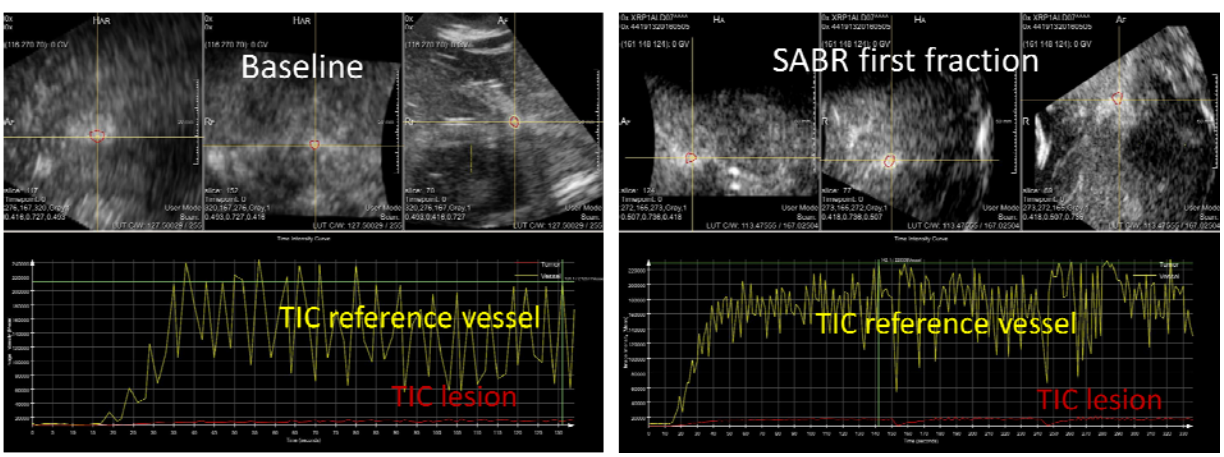


Challenges: partial occlusions, respiratory motion, low volume rates.

Molecular US imaging with targeted microbubbles

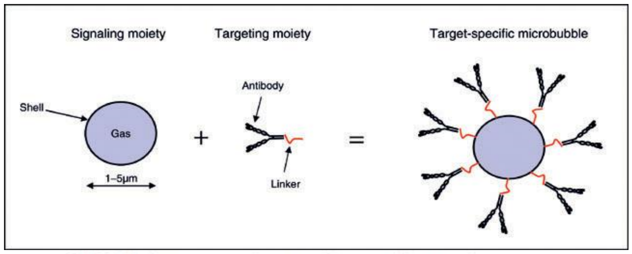
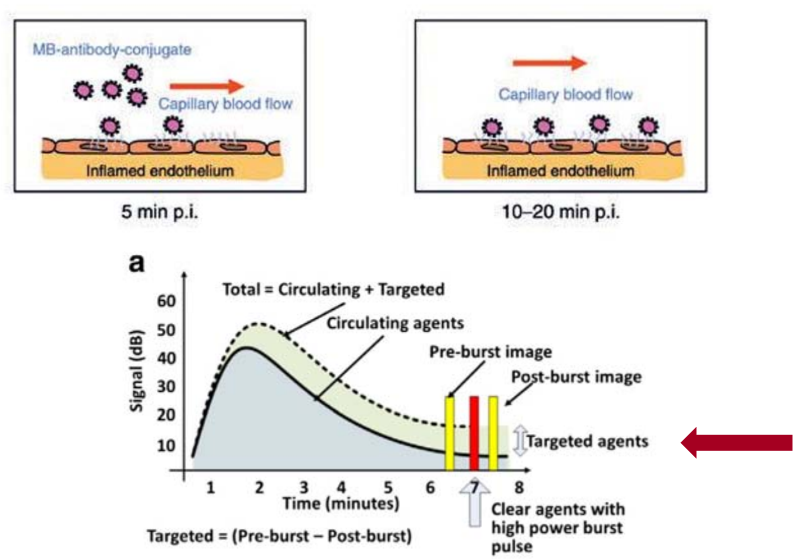


TABLE II. COMMERCIALLY AVAILABLE TARGETED CONTRAST AGENTS.

Name	Manufacturer	Linker	Ligand	Target	Possible application
Sonazoid	Amersham Health	NA[1]	NA[1]	Kupffer cells and macrophages	Liver tumors, ischemia/reperfusion injury
Micromarker	Bracco SpA	streptavidin	Biotinylated ligand of choice	biomarker of choice	depends on ligand
Targestar	Targeson Inc.	streptavidin	Biotinylated ligand of choice	biomarker of choice	depends on ligand
Visistar Integrin	Targeson Inc.	covalent to PEG-lipid	cyclic RGD peptide	$\alpha_v\beta_3$ integrin	angiogenesis
Visistar VEGFR2[2]	Targeson Inc.	covalent to PEG-lipid		VEGF-like protein	angiogenesis
YSPSL-MB[2]	Oregon Health & Science University	covalent to PEG-lipid	PSGL-1	P and E selectin	ischemia/reperfusion injury transplant rejection
BR55[3]	Bracco SpA	covalent to PEG-lipid	Heterodimer peptide	VEGFR2	angiogenesis
Selectin agent[2]	Bracco SpA	streptavidin	biotinilated PSGL-1 analog	P and E selectin	Inflammatory disease

[1]Passive targeting, phagocytic uptake of the bubbles by cells.
[2]In development.
[3]In clinical development.

Targeted microbubbles imaging



C.F. Caskey, et al., Leveraging the power of ultrasound for therapeutic design and optimization, J. Control. Release (2011), doi:10.1016/j.jconrel.2011.07.032

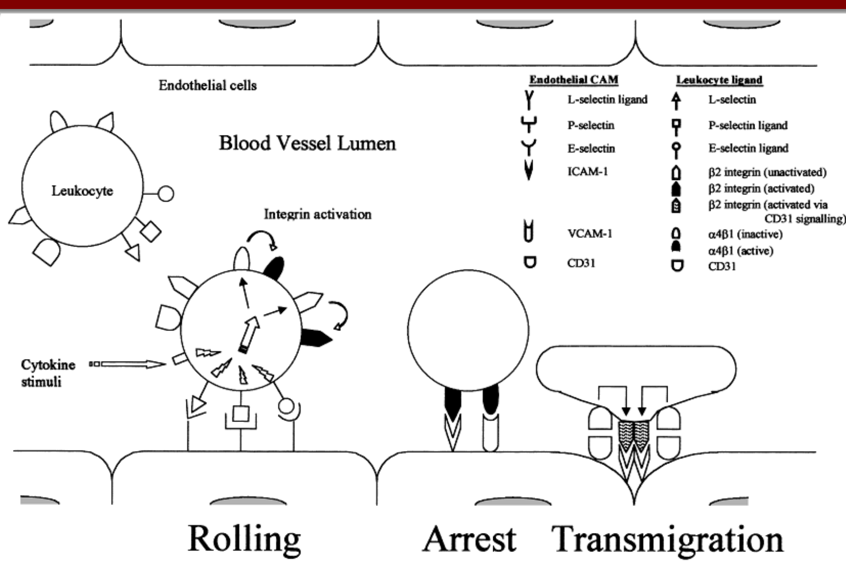
Radiation-induced adhesion molecules

Effect of Ionizing Radiation on Adhesion Molecule Expression

Cell line/tissue	Immunoglobulin superfamily: ICAM-1	VCAM-1	PECAM-1	N-CAM	Selectins: E-	L-	P-	Integrin: LLFA-1	MMac-1	Reference(s)
Endothelial cells										
HUVEC	↑	→			→		↑			*9, 17, 23–25*
HUVEC	↑				↑					*17, 26*
HMEC	↑	→			↑		→			*27, 28*
HMEC	↑				→					*9, 29*
HMEC	→				↑					*30*
HDMEC	↑	↑			↑		↑			*15, 16, 26*
HDMEC	↑	→	↑							*9, 31–33*
BMEC	↑	→			→					*34*
mlEND-1	→	→			→		→			*35*
microglia	↑				→					*36*
Leukocytes										
PBMC						↓				*35*
alveolar macrophage	↑	↑						↑		*37, 38*
oral mucosa								↑	↑	*14, 39*
Other cells										
hepatoma	↑									*40*
cervical cancer	↑									*41*
astrocytes	↑									*42*
lens cells	↑									*43*
Vessels										
lung	↑	↑	↑				↑			*20, 27, 38, 44, 45*
oral mucosa	↑	→			↑					*14, 39*
intestine	↑	↑					↑			*12, 17, 46, 47*
brain	↑	↑			↑		→		↑	*36, 42, 48–50*
glioma							↑			*50*
fetal brain				↓						*51, 52*
skin	↑	↑			↑					*15*
liver	↑									*53*

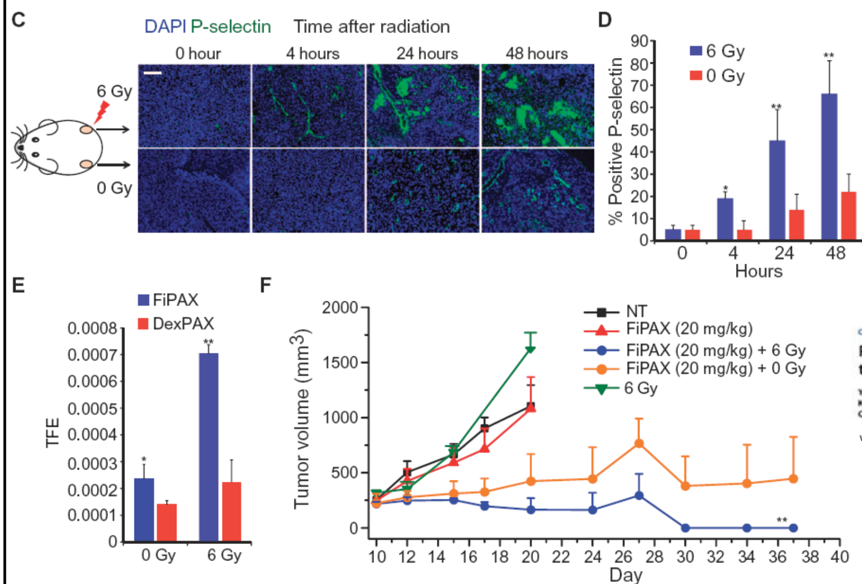
Adhesion Molecules in Radiotherapy, Roxana G. Baluna, Tony Y. Eng, and Charles R. Thomas, Jr. RADIATION RESEARCH **166**, 819–831 (2006)

Radiation-induced normal tissue injury: Role of adhesion molecules in leukocyte–endothelial cell interactions



International Journal of Cancer, Steven Quarmby, Pat Kumar and Shant Kumar
Volume 82, Issue 3, pages 385-395, 10 NOV 1999 DOI: 10.1002/(SICI)1097-0215(19990730)82:3<385::AID-IJC12>3.0.CO;2-5
http://onlinelibrary.wiley.com/doi/10.1002/(SICI)1097-0215(19990730)82:3<385::AID-IJC12>3.0.CO;2-5/full#fig2

Radiation-induced P-selecting as a therapeutic target



CANCER

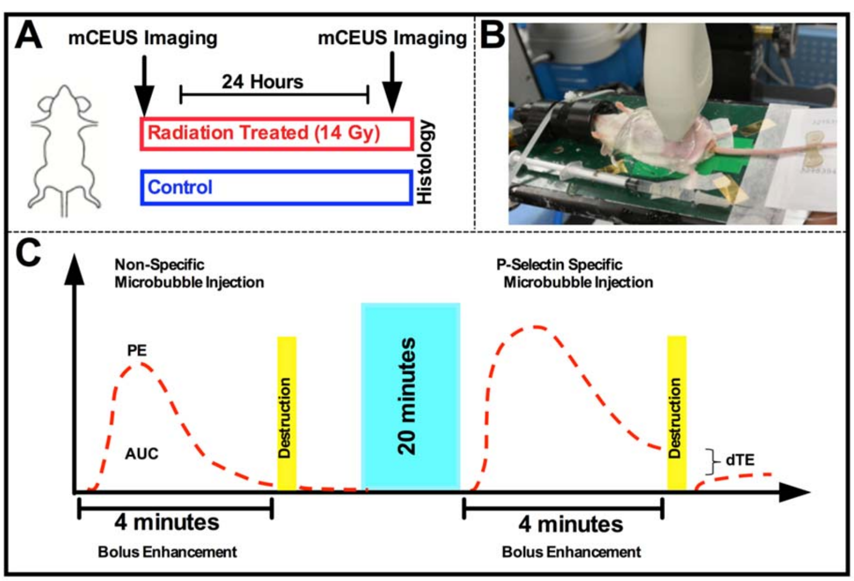
P-selectin is a nanotherapeutic delivery target in the tumor microenvironment

Yosi Shamay,[1] Moshe Elkabets,[2,3] Hongyan Li,[4] Janki Shah,[1] Samuel Brook,[2] Feng Wang,[4,5] Keren Adler,[1,6] Emily Baut,[1,7] Maurizio Scaltriti,[2,8] Prakrit V. Jena,[1] Eric E. Gardner,[1,9] John T. Poirier,[1,7,10] Charles M. Rudin,[1,7,10] José Baselga,[2,10] Adriana Haimovitz-Friedman,[4] Daniel A. Heller[1,7]*

www.ScienceTranslationalMedicine.org 29 June 2016 Vol 8 Issue 345 345ra87

27

Study design

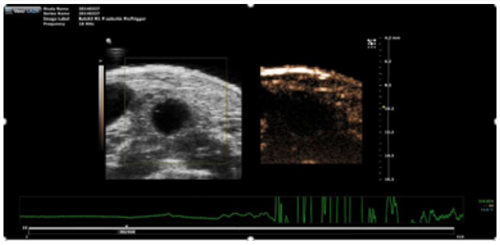


Molecular Contrast-Enhanced Ultrasound Imaging of Radiation-Induced P-Selectin Expression in Healthy Mice Colon.

El Kaffas A, Smith K, Pradhan P, Machtaler S, Wang H, von Eyben R, Willmann JK, Hristov D., Int J Radiat Oncol Biol Phys. 2017 Mar 1;97(3):581-585

Perfusion Video: bolus

1.



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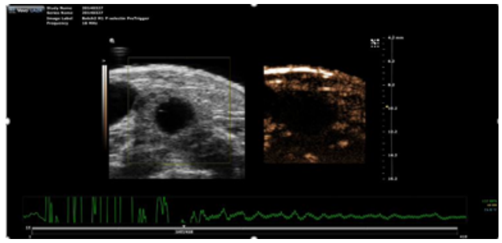

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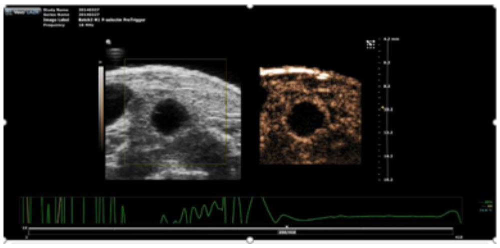
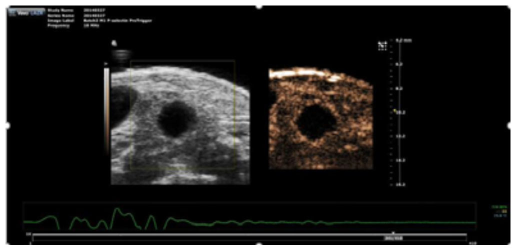


4.



Selectin-targeted Ultrasound Signals before and after Destruction Pulse

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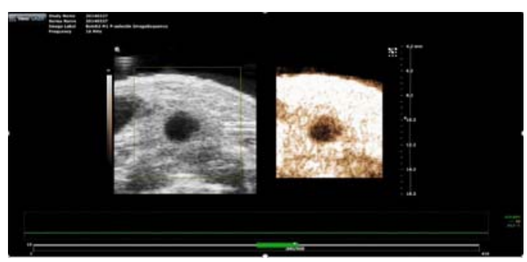
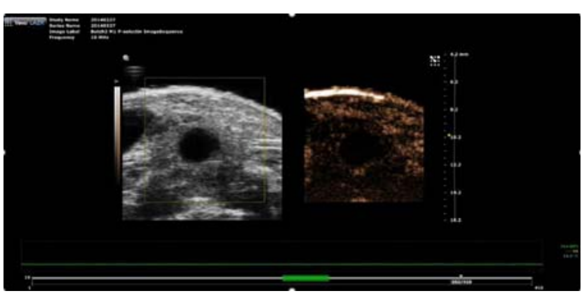
Stanford University Medical Center

1. P-selectin Attached Microbubbles and Freely Circulating Microbubbles

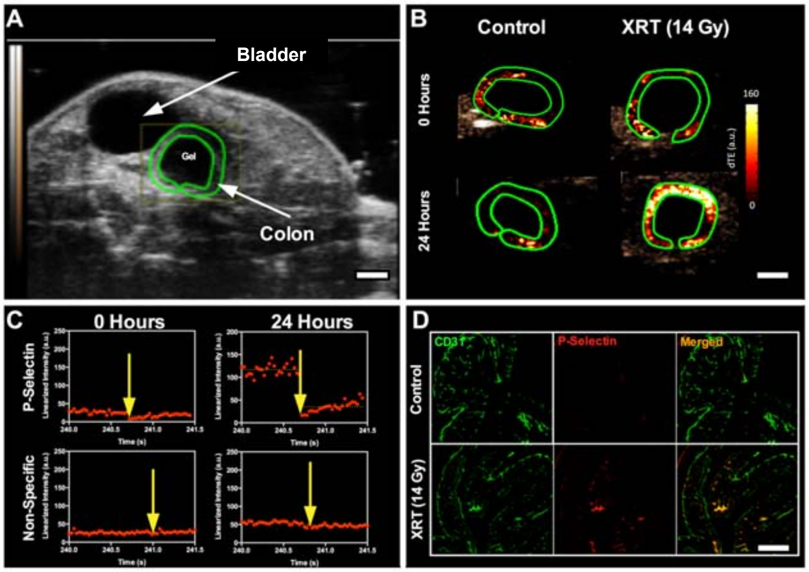
2. Destruction Pulse



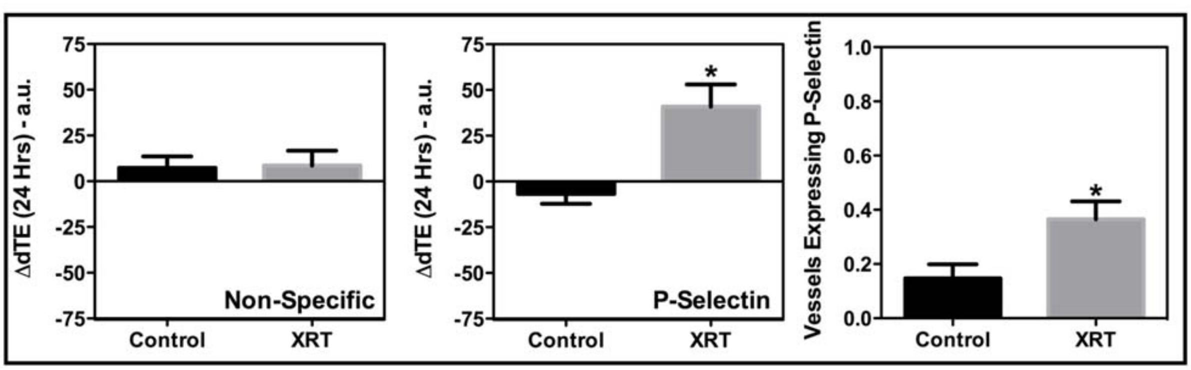


3. Freely Circulating Microbubble Only

Example of changes in targeted ultrasound signal



Changes in US signal after irradiation



- Immunohistochemistry confirms P-selectin expression in mouse colon following XRT.
- P-selectin expression is detectable with P-selectin targeted microbubbles.

US Perspectives in Radiotherapy

- Robot/Manipulator US opens a venue for intra-fractional soft-tissue imaging and guidance but dedicated low cost US devices likely needed

- Contrast enhanced US imaging with non-targeted and targeted microbubbles provides non-ionizing means of imaging processes relevant to radiation therapy.