Normal Tissue Imaging Biomarkers

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UCDAVIS COMPREHENSIVE CANCER CENTER
Radiation Oncology

2020 Joint AAPM/COMP Virtual Meeting | 7/12-16
SAM Therapy Educational Course

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Learning Objective

- To recognize the strengths and limitations of existing normal tissue imaging biomarkers (IBs) used in the routine care of cancer patients and emerging IBs at various stages of development.

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Outline

- Introduction
- IBs used in routine clinical care
  - Heart: Left ventricular ejection fraction
- IBs used as clinical research tools
  - Brain: choline-creatine ratio
  - Lung: ventilation or perfusion
  - Pelvis: ^{18}F-FDG uptake in bone marrow
  - Limitations, challenges and opportunities
- Summary

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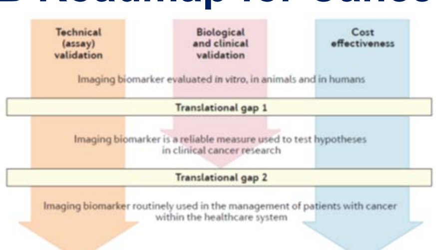
IB Roadmap for Cancer



O'Connor *et al.* (*Nat Rev Clin Oncol* 2017)

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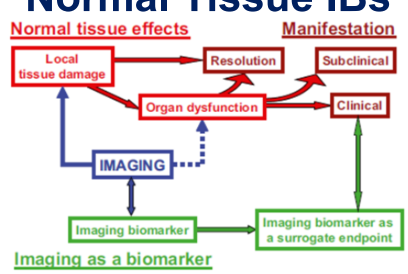
Normal Tissue IBs



Jeraj *et al.* (*IJROBP* 2010)

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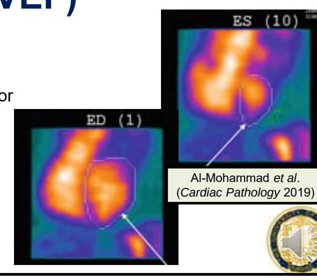
Left ventricular ejection fraction (LVEF)

- The volumetric fraction of blood ejected from the left ventricle with each contraction
- The most widely used IB to monitor the changes in cardiac function during/after chemotherapy and to detect cardiac toxicity
- Modalities: Echocardiography, scintigraphy/SPECT, MRI



Al-Mohammad *et al.* (*Cardiac Pathology* 2019)

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HERCEPTIN® (trastuzumab)
Intravenous Infusion
Initial U.S. Approval: 1998

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning
Cardiomyopathy: Herceptin can result in sub-clinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Herceptin for cardiomyopathy. (5.1, 2.2)

Infusion reactions, Pulmonary toxicity: Discontinue Herceptin for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to Herceptin during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death.

fda.gov

Assess left ventricular ejection fraction (LVEF) prior to initiation of Herceptin and at regular intervals during treatment. Withhold Herceptin dosing for at least 4 weeks for either of the following:

- ≥ 16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

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EXPERT CONSENSUS STATEMENT

Expert Consensus for Multimodality Imaging Evaluation of Adult Patients during and after Cancer Therapy: A Report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging

Juan Carlos Plana, MD, FASE, Chair, Maurizio Galderisi, MD, FESC, Co-Chair, Ana Barac, MD, PhD, Michael S. Ewer, MD, JD, Bonnie Ky, MD, FASE, Marielle Scherrer-Crosbie, MD, PhD, FASE, Javier Ganame, MD, PhD, FASE, Igal A. Sebag, MD, FASE, Deborah A. Agler, RCT, RDCS, FASE, Luigi P. Badano, MD, PhD, FESC, Jose Banchs, MD, FASE, Daniela Cardinale, MD, PhD, FESC, Joseph Carver, MD, Manuel Cerqueira, MD, Jeanne M. DeCara, MD, FASE, Thor Edvardsen, MD, PhD, FESC, Scott D. Flamm, MD, MBA, Thomas Force, MD, Brian P. Griffin, MD, Guy Jerusalem, MD, PhD, Jennifer E. Liu, MD, FASE, Andreia Magalhães, MD, Thomas Marwick, MBBS, PhD, MPH, Liza Y. Sanchez, RCS, FASE, Rosa Sicari, MD, PhD, FESC, Hector R. Villarraga, MD, FASE, and Patrizio Lancellotti, MD, PhD, FESC, *Cleveland, Ohio; Naples, Padua, Milan, and Pisa, Italy; Washington, District of Columbia; Houston, Texas; Philadelphia, Pennsylvania; Boston, Massachusetts; Hamilton, Ontario and Montreal, Quebec, Canada; Chicago, Illinois; Oslo, Norway; Liege, Belgium; New York, New York; Lisbon, Portugal; Hobart, Australia; Rochester, Minnesota*

Plana *et al.* (*J Am Soc Echocardiogr* 2014)

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Consensus Recommendations for Detection of Cardiac Toxicity

- Cancer therapeutics-related cardiac dysfunction is defined as a decrease in LVEF of >10% to a value <53% (normal reference value for 2D echocardiography).
- Different techniques use different normal reference values.
- The same imaging technique should be performed for baseline and follow-up studies.
- LVEF has low sensitivity for detection of small changes in LV function.

Plana *et al.* (*J Am Soc Echocardiogr* 2014)

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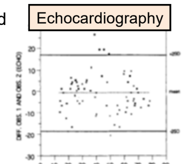
LVEF: Inter-Observer Variability

Comparison and Reproducibility of Visual Echocardiographic and Quantitative Radionuclide Left Ventricular Ejection Fractions

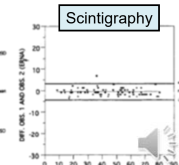
Niels van Royen, Carl C. Jaffe, MD, Harlan M. Krumholz, MD, Kevin M. Johnson, MD, Patrick J. Lynch, MS, Donna Natale, CNMT, Patricia Atkinson, Paul Deman, RTNM, and Frans J. Th. Wackers, MD

- A 73-patient study quantified inter-observer variability in LVEF measured by echocardiography and scintigraphy.

Echocardiography



Scintigraphy



van Royen *et al.* (*Am J Cardiol* 1996)

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LVEF: Inter-Modality Variability

Original Investigation | Cardiology

Variability in Ejection Fraction Measured By Echocardiography, Gated Single-Photon Emission Computed Tomography, and Cardiac Magnetic Resonance in Patients With Coronary Artery Disease and Left Ventricular Dysfunction

- International multisite study for 2,032 patients
- There was substantial inter-modality variability in LVEF between echocardiography, SPECT and MRI
- Only 43-54% of LVEF measurements agreed within 5%

Pellikka *et al.* (*JAMA Network Open* 2018)

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LVEF vs. Cardiac Toxicity

VOLUME 23 · NUMBER 31 · NOVEMBER 1 2005

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Assessment of Cardiac Dysfunction in a Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Paclitaxel, With or Without Trastuzumab As Adjuvant Therapy in Node-Positive, Human Epidermal Growth Factor Receptor 2–Overexpressing Breast Cancer: NSABP B-31

Tan-Chiu *et al.* (*J Clin Oncol* 2005)

- 2,043 patients enrolled
- 31 of 850 trastuzumab-treated patients experienced congestive heart failure
- Congestive heart failure was more frequent in patients with a reduced LVEF at baseline or after anthracyclines

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LVEF: Key Points

- LVEF has crossed the two translational gaps and is widely used in routine clinical care of cancer patients.
- There is an extensive literature on precision and associations with clinical outcomes of chemotherapy.
- There is little or no evidence for associations with outcomes of radiotherapy (RT).
- 2D echocardiography and scintigraphy/SPECT are more widely available and cheaper compared with 3D echocardiography and MRI.

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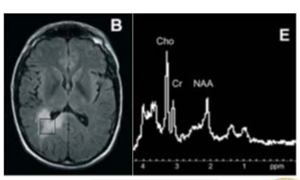
Brain MR Spectroscopy Choline-Creatine (Cho/Cr) Ratio

- Increased Cho level in brain tumors
- Decreased Cho level in RT-induced brain injury
- Cr, a marker of energy metabolism, is stable under most conditions



Plotkin *et al.* (*J Neurooncol* 2004)

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Cho/Cr: Sensitivity/Specificity

European Journal of Radiology

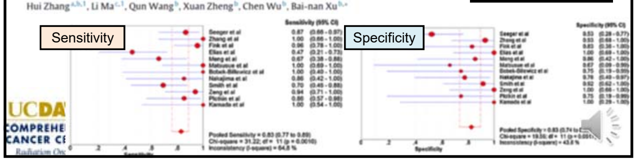
ELSEVIER

Review

Role of magnetic resonance spectroscopy for the differentiation of recurrent glioma from radiation necrosis: A systematic review and meta-analysis

Hui Zhang, Li Ma, Qun Wang, Xuan Zheng, Chen Wu, Bai-nan Xu

Zhang *et al.* (*Eur J Radiol* 2014)



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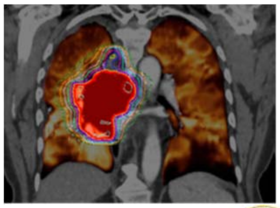
Lung Ventilation or Perfusion

- Can be used to guide functional avoidance RT and to monitor the changes in lung function during/ after RT
- Modalities
  - Ventilation: Biphasic/4D CT, dual-energy CT, SPECT, PET, MRI
  - Perfusion: Dual-energy CT, SPECT, PET, MRI



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Ventilation vs. Pulmonary Toxicity

International Journal of Radiation Oncology biology • physics

Evaluating the Toxicity Reduction With Computed Tomographic Ventilation Functional Avoidance Radiation Therapy

Austin M. Faught, PhD, Yuya Miyasaka, BS, Noriyuki Kadoya, PhD, Richard Castillo, PhD, Edward Castillo, PhD, Yevgeniy Vinogradskiy, PhD, and Tokihiro Yamamoto, PhD

Dose metric	P value	AUC
fV5 Gy	<.01	0.693
V5 Gy	.05	0.637
fV10 Gy	<.01	0.718
V10 Gy	.13	0.614
fV20 Gy	<.01	0.707
V20 Gy	.36	0.545
fV30 Gy	<.01	0.682
V30 Gy	.75	0.508
fMLD	<.01	0.723
MLD	.12	0.584

- A 70-patient study quantified predictive power of dose-volume and 4D CT ventilation-based dose-function metrics for grade ≥2 pneumonitis
- Dose-function metrics had greater AUC values

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Faught *et al.* (*IJROBP* 2017)

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Perfusion vs. Pulmonary Toxicity

Contents lists available at ScienceDirect

ELSEVIER

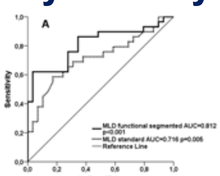
Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Radiation induced lung damage

Inclusion of functional information from perfusion SPECT improves predictive value of dose–volume parameters in lung toxicity outcome after radiotherapy for non-small cell lung cancer: A prospective study

Katherina P. Farr, Jesper F. Kallehauge, Ditte S. Møller, Azza A. Khalil, Stine Kramer, Henrik Bluhme, Anni Morsing, Cai Grau



- A 58-patient study quantified predictive power of dose-volume and SPECT perfusion-based dose-function metrics for grade ≥2 pneumonitis
- Functional MLD had greater AUC value

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Farr *et al.* (*Radiother Oncol* 2015)

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Functional Avoidance RT Clinical Trials for Lung Cancer

Institution	Endpoint	# of participants	Allocation	Modality	ClinicalTrials.gov ID
London Health Sciences Centre	QOL	27	Randomized	MR ventilation	NCT02002052
University of California Davis	Grade ≥3 adverse events	34	Single arm	4D CT ventilation	NCT02308709
University of Colorado	Grade ≥3 pneumonitis	87	Single arm	4D CT ventilation	NCT02528942
University of Washington	Overall survival	60	Single arm	SPECT perfusion	NCT02773238
University of Wisconsin	Ventilation changes	120	Randomized	4D CT ventilation	NCT02843568

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^{18}F-FDG Uptake in Pelvic Bone Marrow

- ^{18}F-FDG PET allows for measurement of metabolic activity of bone marrow
- ^{18}F-FDG uptake in the skeleton is caused by active hematopoietic bone marrow
- Uptake pattern and amount vary with age and level of marrow function

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Blebea *et al.* (*Semin Nucl Med* 2007)

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Bone Marrow-Sparing RT Clinical Trial for Cervical Cancer

- Endpoint: Grade ≥3 neutropenia or clinically significant GI toxicity
- 83 patients enrolled at 8 sites
- 48 patients underwent CT-based IMRT
- 35 patients underwent PET-based active bone marrow-sparing IMRT

International Journal of Radiation Oncology biology • physics

Bone Marrow-sparing Intensity Modulated Radiation Therapy With Concurrent Cisplatin For Stage IB-IVA Cervical Cancer: An International Multicenter Phase II Clinical Trial (INTERTECC-2)

Loren K. Mell, MD, Igor Sirák, MD, PhD, Lichun Wei, MD, Rafal Tarnawski, MD, PhD, Umesh Mahantshetty, MD, Catheryn M. Yashar, MD, Michael T. McHale, MD, Ronghui Xu, PhD, Gordon Honerkamp-Smith, PhD, Ruben Carmona, MD, Mary Wright, BS, Casey W. Williamson, MD, Linda Kasaová, PhD, Nan Li, PhD, Stephen Kry, PhD, Jeff Michalski, MD, Walter Bosch, PhD, William Straube, MS, Julie Schwarz, MD, PhD, Jessica Lowenstein, PhD, Steve B. Jiang, PhD, Cheryl C. Saenz, MD, Steve Plaxe, MD, John Einck, MD, Chonlakiet Khorprasert, MD, Paul Koonings, MD, Terry Harrison, MD, Mei Shi, MD, and A.J. Mundt, MD, for the INTERTECC Study Group

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Mell *et al.* (*IJROBP* 2017)

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Bone Marrow-Sparing RT Clinical Trial for Cervical Cancer

Variable	CT IMRT (n=48)	PET IG-IMRT (n=35)	P value
Pelvic bone marrow dose (%)			
Mean V_{10}	86.9 ± 2.8	78.5 ± 6.9	<.01*
Mean V_{20}	70.8 ± 3.5	56.4 ± 9.2	<.01*
Mean V_{30}	44.8 ± 6.9	38.4 ± 7.4	<.01*
Mean V_{40}	21.9 ± 7.3	18.1 ± 6.1	.01*
Overall mean	27.6 ± 1.6	24.2 ± 2.3	<.01*
Toxicity events			
Any primary event	17 (35.4)	5 (14.3)	.031*
Clinically significant GI toxicity†	8 (16.7)	2 (5.7)	.13
Grade ≥3 neutropenia	13 (27.1)	3 (8.6)	.035*
Grade ≥2 GI toxicity	18 (37.5)	18 (51.4)	.30
Grade ≥3 GI toxicity	1 (2.1)	2 (5.7)	.38
Grade ≥3 hematologic toxicity	21 (43.8)	11 (22.9)	.25

Mell *et al.* (*IJROBP* 2017)

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Limitations and Challenges

- Little evidence from adequately powered, randomized controlled trials specifically designed to test an IB
- Limited statistical power
- Limited data on precision
- Variations in endpoints, treatment modalities, imaging modalities, image acquisition and analysis across studies

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Opportunities for Progress

- Multisite reproducibility
- Standardization/harmonization to improve precision
- Multisite randomized controlled trials
- Data sharing/pooling

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Summary

- There are many published normal tissue IBs in the literature, but only a few are widely used.
  - LVEF has been used in routine clinical care.
  - There are many emerging normal tissue IBs that have great potential to improve cancer therapy or detection/ monitoring of toxicity.
- Key steps for successful clinical translation include large-scale validation studies through collaboration.

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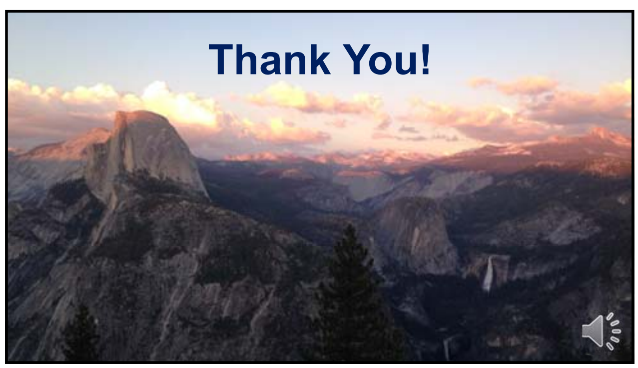
Thank You!



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