Imaging Modalities to Diagnose Cardiovascular Toxicities with Immunotherapy

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Outline

- Potential Imaging Modalities for Immunotherapy Cardiotoxicity Evaluation
  - Echocardiography
  - Positron emission tomography/computed tomography (PET/CT)
  - Cardiac magnetic resonance (CMR) imaging

- Necessary Advances in Research

What are Our Diagnostic and Prognostic Imaging Targets?

- Myocardial Inflammation
- Cardiomyocyte Injury
- Contractile dysfunction and remodeling
- Establish disease severity
- “Rule-out” other disease states

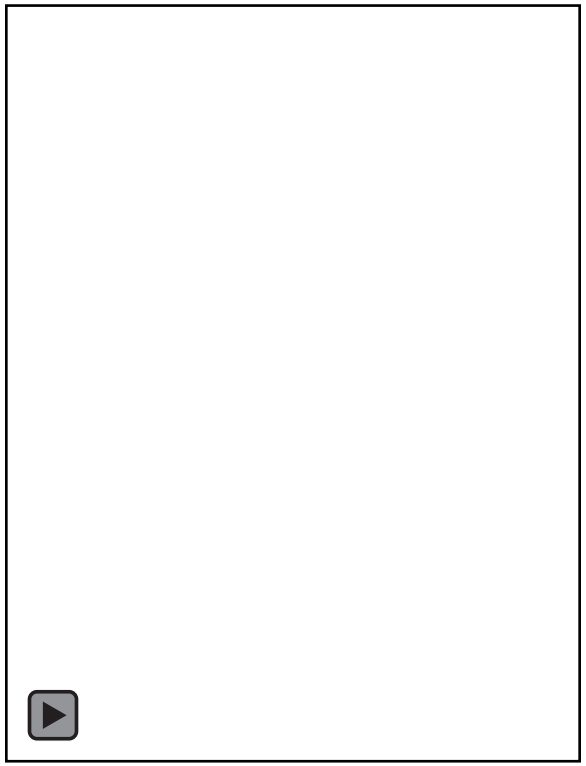
Acute: Diagnosis

- Myocardial fibrosis
- Recovery of function/resolution of injury

Chronic: Prognosis

Quantitative Echocardiography Provides Detailed Phenotypic Characterization

Echocardiographic Measure	Phenotypic Characterization
2D/3D RA, RV, LA, & LV size, shape	Cardiac structure
2D/3D LV & RV strain, strain rate, ejection fraction	Systolic function
E/a, e', a', E/e'	Diastolic function, filling pressures
Ea, E_{es}, Ea/E_{es}, wall stress	Ventricular & vascular Stiffness
Twist, torsion	Systolic & diastolic deformation
Regurgitation, stenosis	Valvular disease
Pericardium	Pericardial effusion
Cardiac output, pulmonary pressures	Hemodynamics



Echocardiography

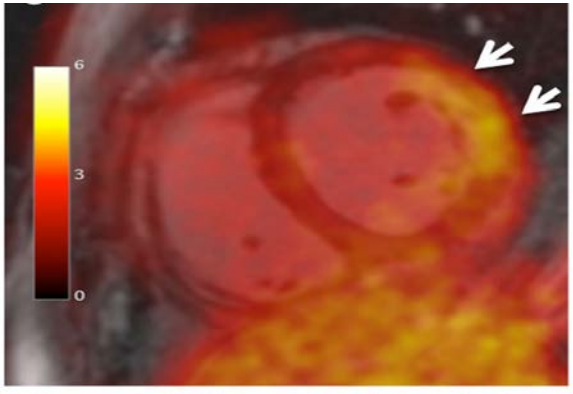
- Advantages: Safe, versatile, widely and readily available
- Disadvantages: Not sensitive or specific for the diagnosis of myocarditis or biologic disease activity
- Potential role: Screening tool, post-diagnosis for serial assessment of cardiac function and remodeling

Myocardial PET Can Be Used to Detect Inflammation

- Positron Emission Tomography (PET): Tool to evaluate myocardial perfusion, cardiac function, inflammation, metabolism, or cell death

- ^{18}F-fluorodeoxyglucose (^{18}F-FDG): Quantitatively and qualitatively evaluate inflammation; increased glucose uptake hallmark of inflammatory activity

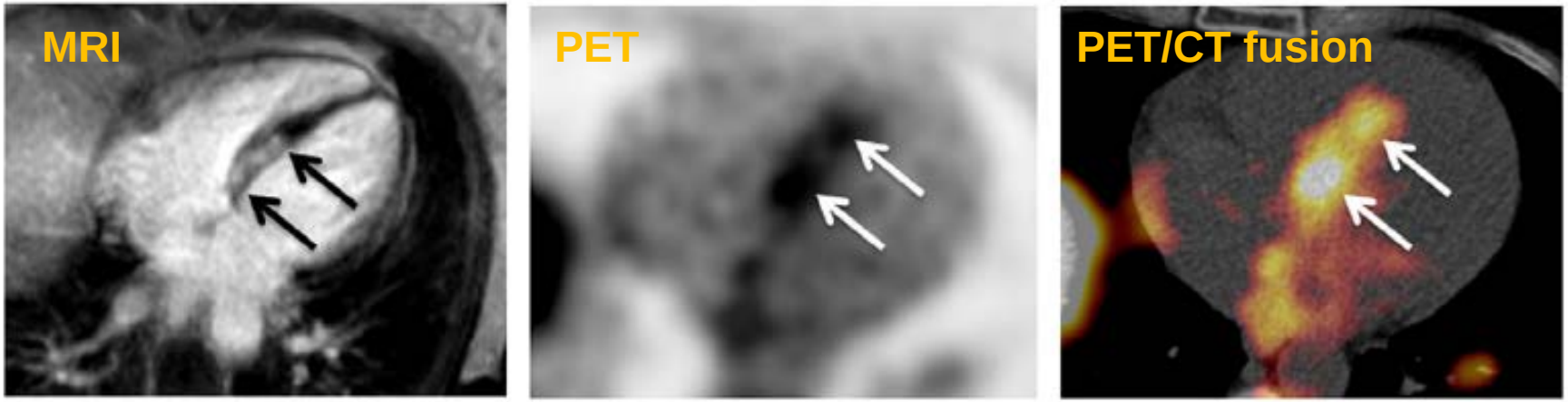
- Agreement with CMR for myocarditis diagnosis (N=55):
  - Kappa 0.73
  - Sensitivity 74% and Specificity 97%



Nensa, et al. J Nucl Cardiol. 2016.
Kircher, et al. Curr CV Imaging Rep. 2017.

Myocardial PET: Research Advances

- Small in vivo animal and human studies report the use of novel tracers in myocarditis diagnosis:
  - ^{11}C-methionine: increased uptake in macrophages, T cells and B cells; no uptake in healthy myocardium
  - Somatostatin receptor based radiotracer: activated macrophages overexpress somatostatin receptor subtypes 1 and 2; concordance with CMR 85.3% (n=12)



Increased somatostatin receptor uptake in septum in acute myocarditis

Lapa, et al Int'l J Cardiol. 2015.
Maya, et al. J Nucl Med. 2016.

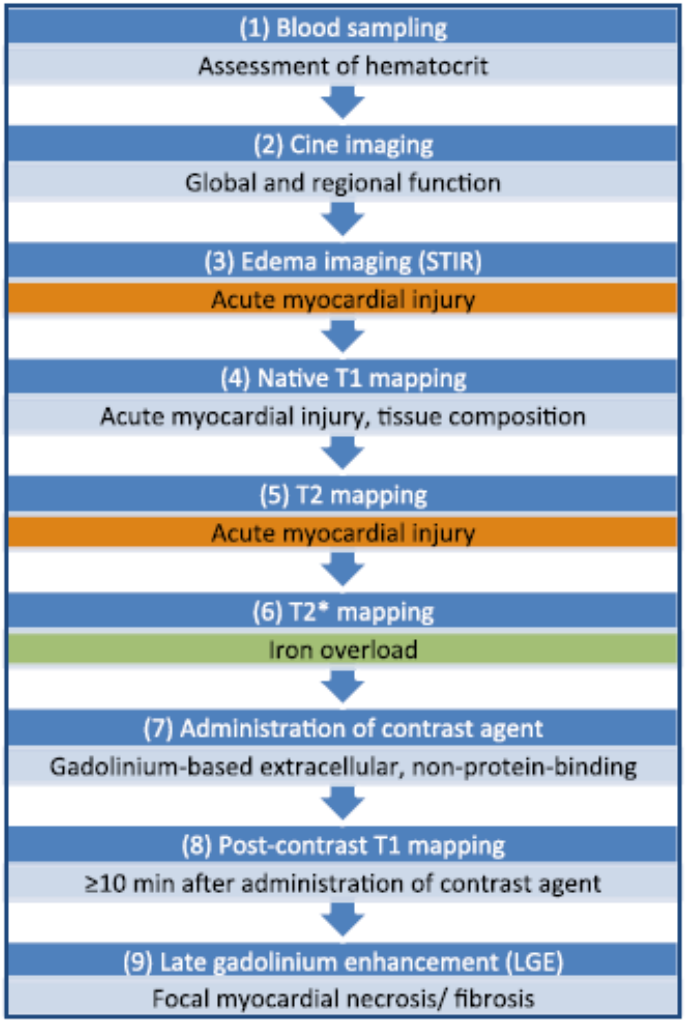
Myocardial PET

- Advantages: Insight into ‘active’ myocarditis
- Disadvantages: Radiation exposure, critical to ensure inhibition of physiological myocardial glucose uptake (~12% failed in one study), limited specificity
- Potential (future) role: Monitor response to therapy, localization of disease to guide biopsy, complement to CMR to enhance sensitivity

Nensa, et al. J Nucl Cardiol. 2016.
Kircher, et al. Curr CV Imaging Rep. 2017.

CMR Provides Detailed Characterization of Structure and Function

- Characterize with high reproducibility cardiac size and function
  - LVEF, volumes, mass, strain
- Gain unique qualitative and quantitative insight into intracellular and extracellular abnormalities
  - T1/T2 mapping, extracellular volume, delayed enhancement
  - Edema, inflammation, fibrosis



General Imaging Protocol for Myocardial Tissue Characterization

Messroghli, et al. JCMR. 2017.

CMR and Myocarditis Diagnosis

- Lake Louise criteria (2 of 3):
  - Hyperemia (T1-weighted imaging w/*early* gadolinium enhancement)
  - Edema (T2-weighted imaging w/high signal intensity*)
    *Patchy, subepicardial/septal, transmural, global
  - Necrosis/cell injury and fibrosis (*late* gadolinium enhancement*)
  - Repeat CMR in 1-2 weeks if no findings are present but clinical suspicion high

- Additional supportive findings: LV dysfunction – regional or global; pericardial effusion

- Sensitivity 67%, Specificity 97% (pooled), although features can also observed in non-inflammatory cardiomyopathy

Caforio, et al. EHJ. 2013.
Friedrich, et al. JACC. 2009.

Advances in CMR to Improve Diagnostic Accuracy

- 129 patients with suspected myocarditis → CMR, biopsy (MyoRacer-Trial)
- ↑ T1 Native, ECV – elevated in acute group (edema, hyperemia, myocardial fibrosis/necrosis)
- ↑ T2 – Elevated in acute & chronic groups (free water content, edema); findings corroborated by others

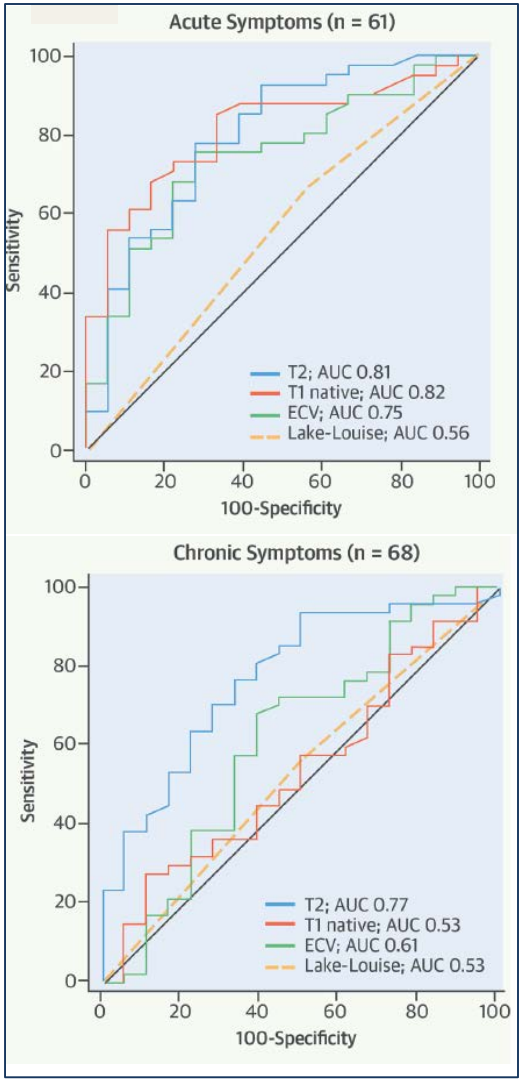


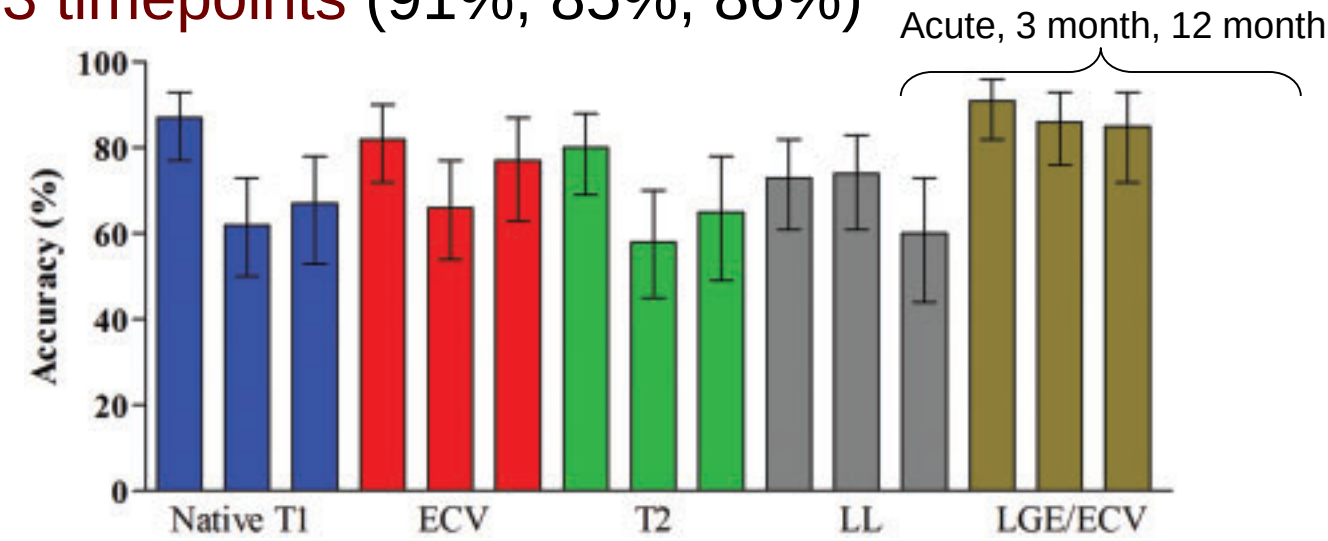
TABLE 3 CMR Imaging Techniques

	<14 days symptoms Acute Group			>14 days symptoms Chronic Group		
	Acute Myocarditis	No Myocarditis	p Value	Acute Myocarditis	No Myocarditis	p Value
1.5-T						
Edema ratio	1.97 ± 0.37	1.81 ± 0.42	0.225	1.94 ± 0.44	1.80 ± 0.40	0.19
Early enhancement	4.63 ± 2.23	5.69 ± 4.45	0.762	7.69 ± 15.99	6.99 ± 4.70	0.82
Presence of LE	77	63	0.430	69	63	0.84
LLC	66	53	0.394	64	53	0.42
Native T_1	1,113 ± 67	1,044 ± 42	<0.001	1,096 ± 64	1,080 ± 79	0.46
ECV	37.2 ± 6.5	31.8 ± 4.9	0.001	35.8 ± 5.3	33.8 ± 10.8	0.45
T_2	62.2 ± 4.5	56.9 ± 7.2	0.007	62.8 ± 4.5	59.4 ± 2.9	0.001

Lurz, et al. JACC. 2016; von Knobelsdorff-Brenkenhoff, et al. Circ CV Img. 2017.

Advances in CMR to Improve Diagnostic Accuracy

- 48 patients with myocarditis underwent repeated assessment by CMR (acute, 3 months, and 12 months)
- Initially increased, but native T1 and T2 decreased over time, potentially indicative of ability to differentiate “acute” versus “healed”
- LGE/ECV* parameter had highest diagnostic accuracies at all 3 timepoints (91%, 85%, 86%)



*LGE/ECV = Late gadolinium enhancement or ECV ≥27%

Bohnen, et al. EHJ-CV Imaging. 2017.

CMR

- Advantages: Structural and functional characterization, potential to differentiate acute versus healed
- Disadvantages: Less readily available, highly dependent upon adequate image quality, reproducibility/variability of T1, T2 derived parameters
- Potential role: Diagnosis, prognosis, response to cardiac therapy and/or to immunotherapy

CV Phenotyping with Imaging: Needs and Opportunities

- Improve upon the sensitivity, specificity, and diagnostic accuracy of imaging modalities

- Define subgroups and settings of highest utility for imaging--- diagnosis or prognosis (guide further diagnostic testing, response to cardiac therapy, likelihood of recovery, or safety of immunotherapy)

- Establish an efficient infrastructure to ask impactful imaging questions of interest (Cancer Moonshot Initiative, Provocative Questions RFA)

- Develop evidence-based, consensus guidelines specific to immunotherapy and cardiotoxicity (White Paper)

THANK YOU

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