

Detecting Cardiac Amyloidosis

Cardiac bone scan procedurals

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None

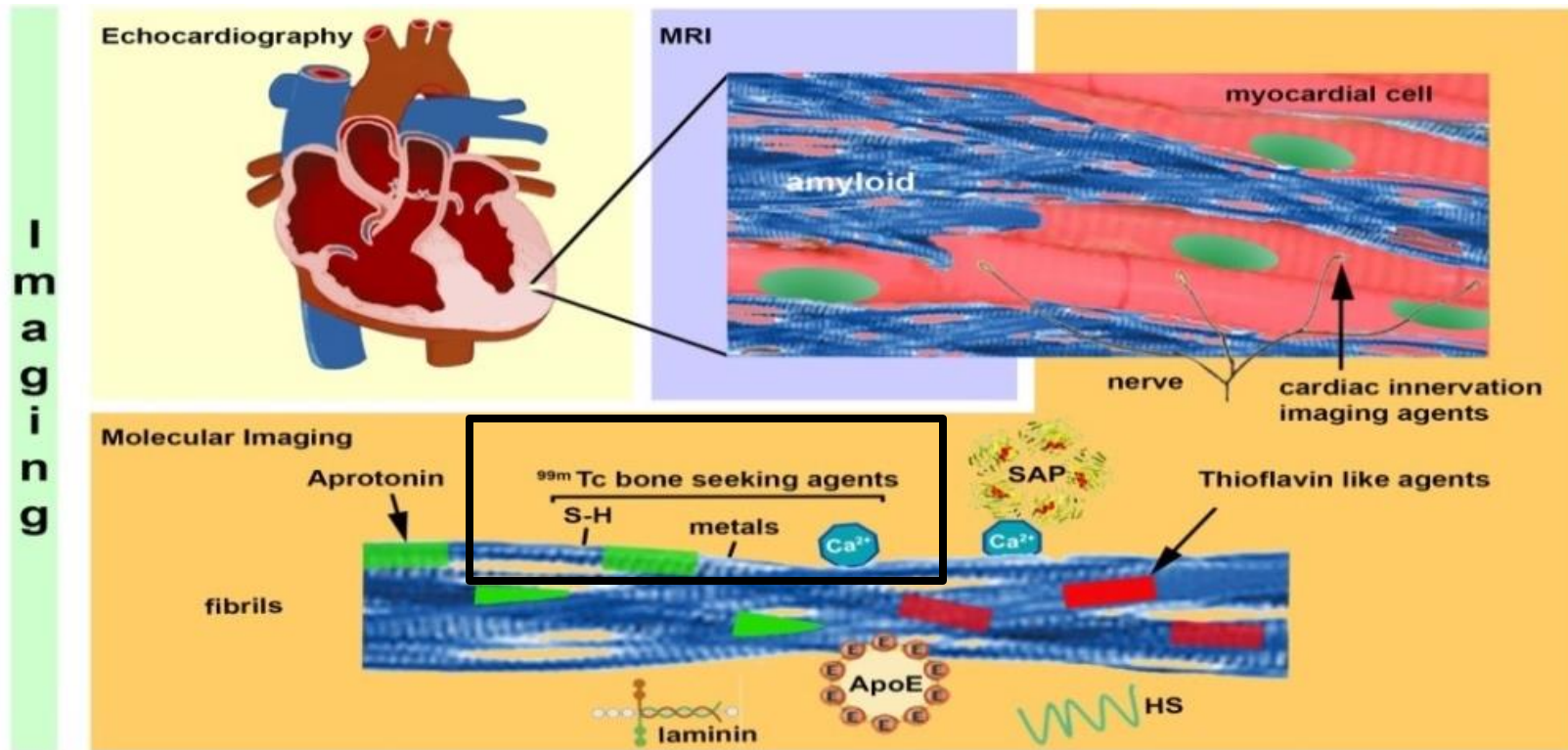


CONTENT lecture

- Background bone tracers +procedurals:
 - How to perform bone scanning?
 - How to interpret bone scanning?
 - How to report bone scanning?
- Accuracy bone scanning in ATTR (vs AL)
- Cases
- Work-flow CA suspicion
- Conclusion(s)



Cardiac amyloidosis imaging



Nuclear Medicine modalities for CA

- Serum amyloid P component (^{123}I -SAP)
- Aprotinin ($^{99\text{m}}\text{Tc}$ -Aprotinin)
- Antibodies (^{111}In -Antimyosin)
- β -amyloid (^{11}C -PiB, ^{18}F -Florbetapir)
- Metaiodobenzylguanadine (^{123}I -MIBG)
- Bone-seeking tracers: $^{99\text{m}}\text{Tc}$ -HMDP/(MDP)/DPD/PYP
 ^{18}F -NaF?



Bone seeking tracers

- ^{99m}Tc -HMDP/ ^{99m}Tc -DPD:



- ^{99m}Tc -pyrophosphate (PYP):



Bone seeking tracers

- Background
- In which patients?
- Bone tracers
- Imaging procedure
- Imaging interpretation
- Reporting

<https://www.asnc.org/guidelinesandstandards>

<https://www.eanm.org/publications/guidelines>



ASNC AND EANM CARDIAC AMYLOIDOSIS PRACTICE POINTS

^{99m}Techetium-
3,3-diphosphono-
1,2-propanodicarboxylic
acid (DPD) and ^{99m}Techetium
hydroxymethylene diphosphonate
(HMDP) Imaging for Transthyretin
Cardiac Amyloidosis



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How to PERFORM ^{99m}Tc -bone tracer images?



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Table 4. Recommendations for standardized acquisition of ^{99m}Tc -PYP/DPD/HMDP for cardiac amyloidosis

Imaging procedures	Parameters	Recommendation
Preparation	No specific preparation. No fasting required.	Required
Scan	Rest scan	Required
Dose	^{99m}Tc -PYP: 10-20 mCi (370-740 MBq) intravenously ^{99m}Tc -DPD: 10-20 mCi (370-740 MBq) intravenously ^{99m}Tc -HMDP: 10-20 mCi (370-740 MBq) intravenously	Recommended
Time between injection and acquisition: ^{99m}Tc -PYP	1 hour 3 hours	Recommended Optional, recommended if excess blood pool activity noted on 1-hour images
Time between injection and acquisition: ^{99m}Tc -DPD/HMDP	2 or 3 hours	Recommended

General imaging parameters		
Field of view	Heart	Required
	Chest	Optional
Image type	Planar	Recommended
	SPECT if planar is positive	Required
Position	Supine	Required
	Upright	Optional
Energy window	140 keV, 15–20%	Required
Collimators	Low energy, high resolution	Recommended
Matrix-Planar	256 x 256	Recommended
Matrix-SPECT	128 x 128 (at least 64 by 64 is required)	Recommended
Pixel size	3.5–6.5 mm	Recommended
Planar imaging specific parameters		
Number of views*	Anterior and lateral	Required
Detector configuration	90°	Recommended
Image duration (count based)	750,000 counts	Recommended
Magnification	1.46	Recommended

<https://www.eanm.org/publications/guidelines>

<https://www.asnc.org/guidelinesandstandards>



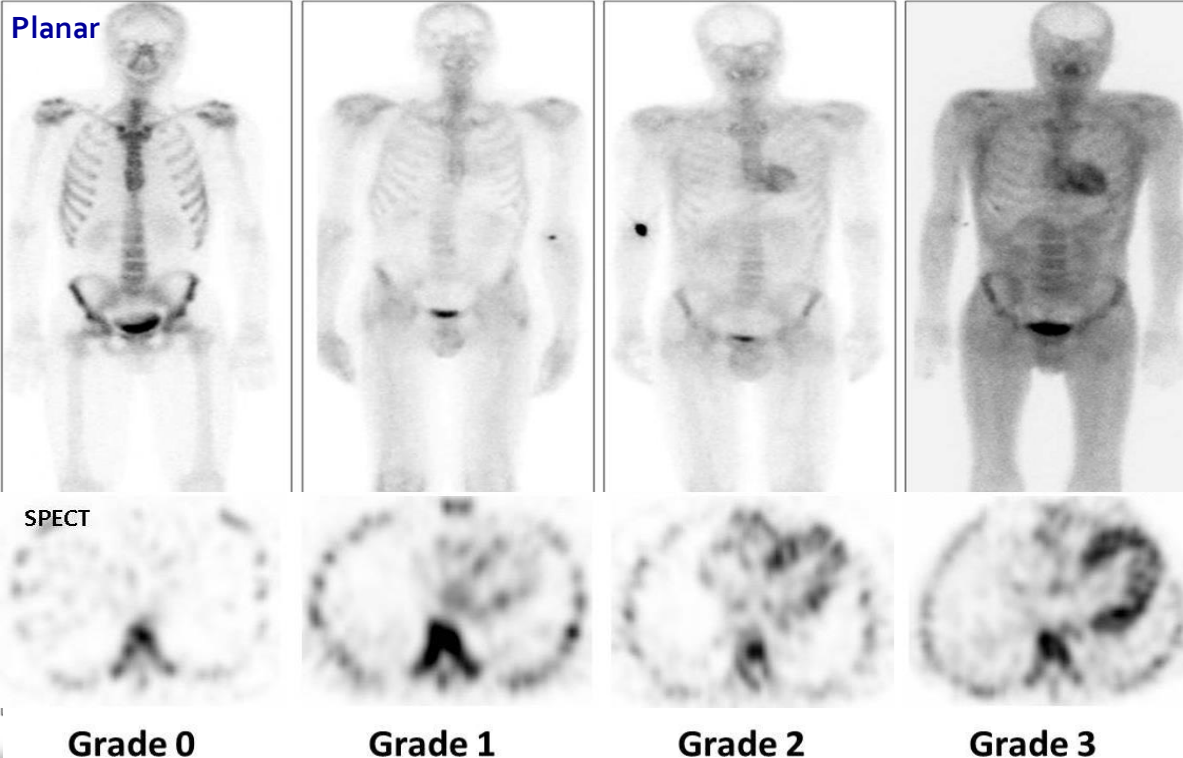
How to INTERPRET ^{99m}Tc -bone scans?



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Grading of ^{99m}Tc -bone tracer on Planar and SPECT



Perugini grade

Grade	Myocardial ^{99m}Tc -PYP Uptake
Grade 0	no uptake and normal bone uptake
Grade 1	uptake less than rib uptake
Grade 2	uptake equal to rib uptake
Grade 3	uptake greater than rib uptake with mild/absent rib uptake

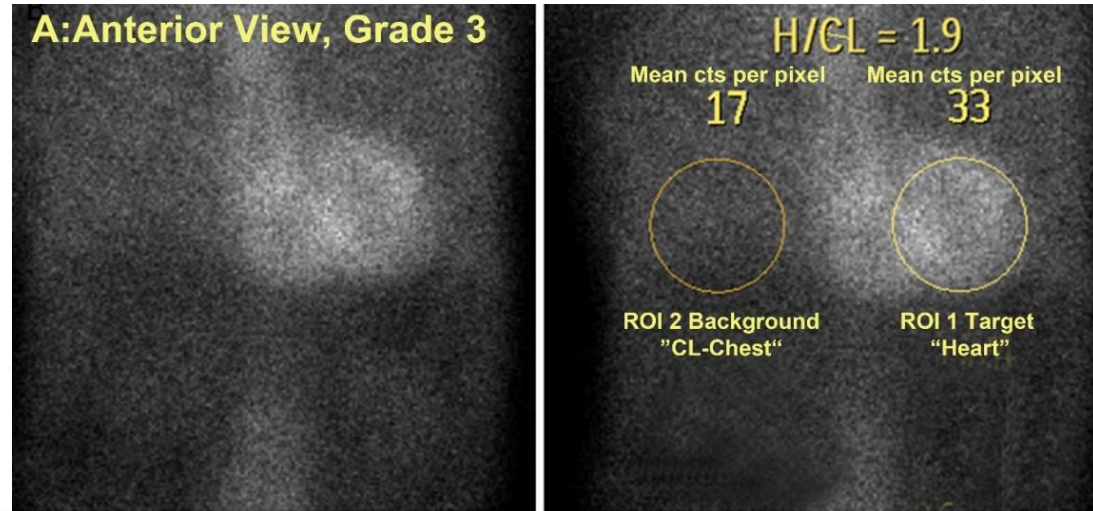


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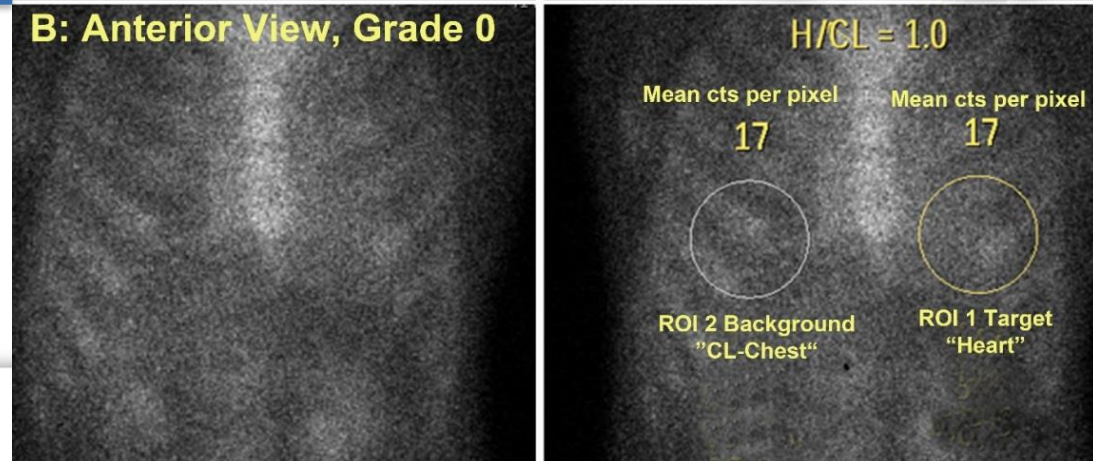
Positive scan

A: Anterior View, Grade 3



Negative scan

B: Anterior View, Grade 0



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Quantification of myocardial ^{99m}Tc -labeled bisphosphonate uptake with cadmium zinc telluride camera in patients with ATTR CA

Table 2 Heart-to-background uptake ratio according to the Perugini grade

Heart-to-background ratio	Perugini 1	Perugini 2	Perugini 3
Whole-body	$1.45 \pm 0.04^*$	$1.65 \pm 0.22^{+/\ddagger}$	$2.42 \pm 0.67^{\ddagger}$
SPECT anterior projection	$1.51 \pm 0.36^{\ddagger\ddagger}$	$1.63 \pm 0.24^{+/\ddagger}$	$2.27 \pm 0.67^{\ddagger}$
SPECT LAO projection	$1.24 \pm 0.06^*$	$1.77 \pm 0.29^{+/\ddagger}$	$2.35 \pm 0.70^{\ddagger}$
SPECT 3D	$1.96 \pm 0.88^*$	$3.07 \pm 0.63^{\ddagger}$	5.01 ± 1.85

* $p < 0.01$. ‡ $p < 0.0001$ and ‡‡ $p < 0.05$ vs. Perugini grade 3. ‡ $p < 0.0001$ vs. SPECT 3D



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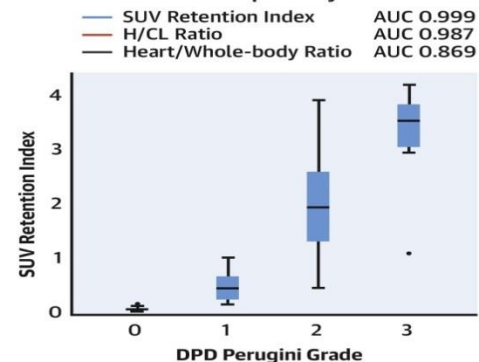
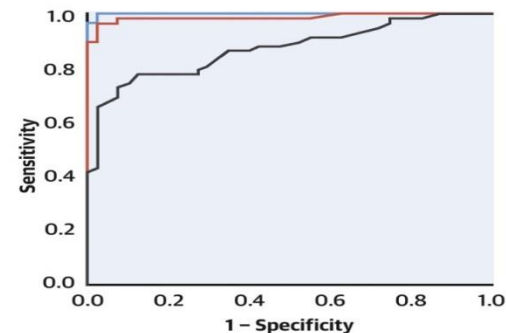
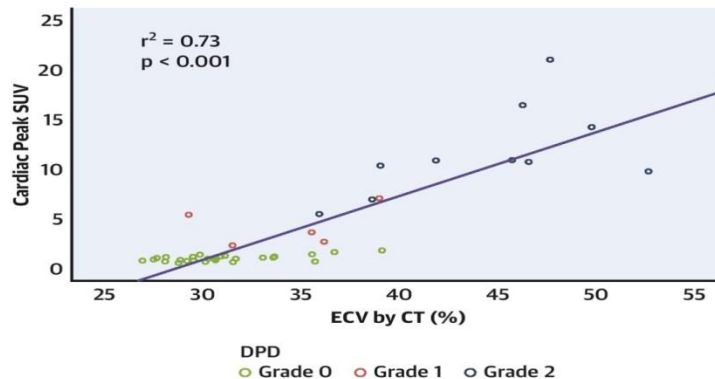
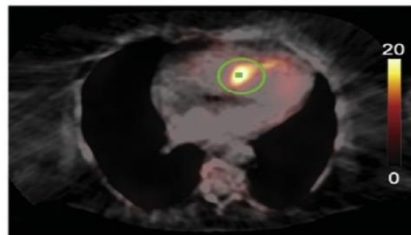
SUV SPECT in bone scintigraphy

- Injected activity, residual dose, height, weight, and timing data input.
- Recorded counts per voxel converted into activity per unit volume and displayed as an SUV = a parameter representing the concentration of the radiopharmaceutical in the respective tissue.



CENTRAL ILLUSTRATION: Planar and SPECT/CT Quantification in DPD Scintigraphy

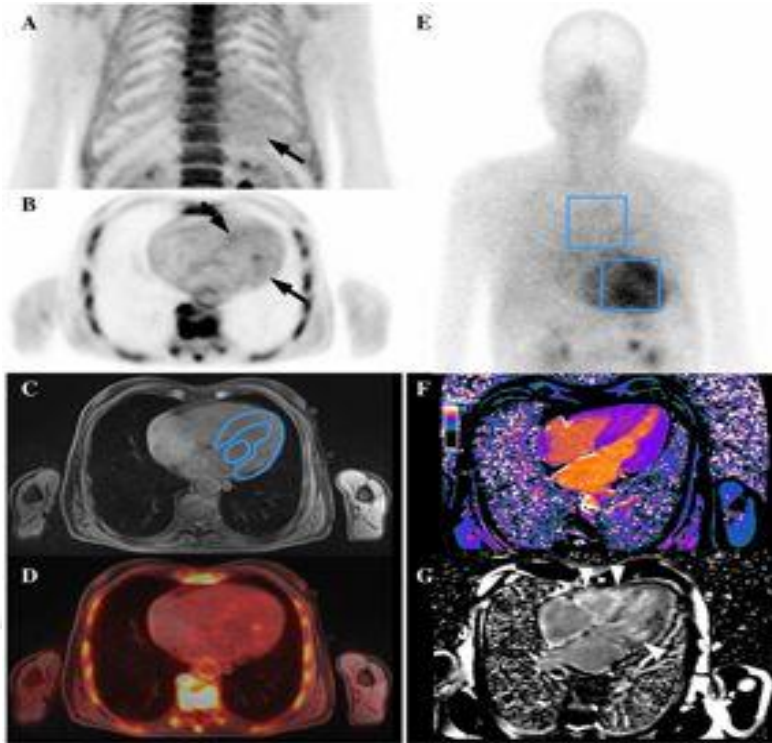
Retrospective, single-center study
100 DPD Scans
40 grade 0, 12 grade 1, 41 grade 2, 7 grade 3
Planar vs. SPECT/CT Quantification



SPECT/CT outperforms planar quantification and correlates with ECV_{CT}
SUV retention index likely to provide better discrimination between higher grades
Potential for diagnosis and therapeutic monitoring



^{18}F -NaF PET/MRI



- 16 ATTR CA, 7 AL CA, 4 no-CA
- 3 (mild) positive ATTR on ^{18}F -NaF
- $^{99\text{m}}\text{Tc}$ -HMDP uptake : ATTR > AL > no-CA
- MRI T1, LE Gd, ECV in CA > controls



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How to REPORT $^{99\text{m}}\text{Tc}$ -bone scans?

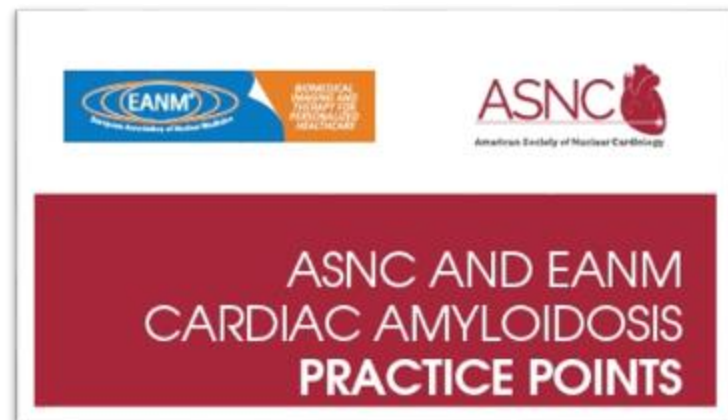


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Table 6. Recommendations for standardized reporting of ^{99m}Tc -PYP/DPD/HMDP imaging for cardiac amyloidosis

Parameters	Elements
Demographics	Patient name, age, sex, reason for the test, date of study, prior imaging procedures, biopsy results if available (Required)
Methods	Imaging technique, radiotracer dose and mode of administration, interval between injection and scan, scan technique (planar and SPECT) (Required)
Findings	Image quality Visual scan interpretation (Required) Semi-quantitative interpretation in relation to rib uptake (Required) Quantitative findings H/CL lung ratio (Optional; recommended for positive scans)
Ancillary findings	Whole-body imaging if planar whole-body images are acquired (Optional) Interpret CT for attenuation correction if SPECT/CT scanners are used (Recommended)
Conclusions	1. An overall interpretation of the findings into categories of 1) not suggestive of ATTR cardiac amyloidosis; 2) strongly suggestive of ATTR cardiac amyloidosis or 3) equivocal for ATTR cardiac amyloidosis a. Not suggestive: A semi-quantitative visual grade of 0. b. Equivocal: If myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 1 or H/CL ratio 1-1.5. c. Strongly suggestive: If myocardial uptake of ^{99m}Tc-PYP/DPD/HMDP is visually confirmed, a semi-quantitative visual grade of 2 or 3 2. Interpret the results in the context of prior cardiac evaluation and evaluation for systemic AL amyloidosis using serum-free light chain assay, serum immunofixation, and urine immunofixation studies. A ^{99m}Tc-PYP/DPD/HMDP scan does not exclude AL cardiac amyloidosis. Therefore: a. If echo/CMR are strongly suggestive of cardiac amyloidosis, and ^{99m}Tc-PYP/DPD/HMDP is negative or equivocal, consider further evaluation for AL amyloidosis by serum FLCs, serum, and urine immunofixation and referral to a hematologist or an amyloidosis expert. Endomyocardial biopsy may be considered. b. A positive ^{99m}Tc-PYP/DPD/HMDP scan with abnormal FLC evaluation, consider referral to a hematologist or an amyloidosis expert.



Pitfalls

- Large myocardial infarction (FP, FN)
- Severe renal dysfunction (moderate quality, FP)
 - SPECT(/CT)



Diagnosis of Cardiac Amyloidosis Tc-99m DPD

Highly sensitive and specific for TTR

10 familial mutant TTR and 5 senile wild type TTR

Table 2. Scintigraphic Findings in the Patient Population and Control Group

	Group A TTR-Related CA (15 Patients)	Group B AL CA (10 Patients)	Unaffected Control Patients (10 Patients)	p Value (Kruskal-Wallis Test/ Contingency Tables)
Heart tracer retention (%)				
Median	7.3*†	3.8‡	2.9	0.0001
Interquartile range	6.7–8.4	3.4–4.05	2.7–3.5	
Whole-body tracer retention (%)				
Median	70.1†	67.6‡	56	0.010
Interquartile range	63.6–77.3	61.8–71.3	52–60	
Heart/whole-body ratio				
Median	10.0*†	5.4	5.4	0.0001
Interquartile range	8.9–11.2	5.2–5.5	5.0–5.7	
Visual cardiac score				
0	0 (0%)	10 (100%)	10 (100%)	0.0001
1	0 (0%)	0 (0%)	0 (0%)	
2	3 (20%)	0 (0%)	0 (0%)	
3	12 (80%)	0 (0%)	0 (0%)	

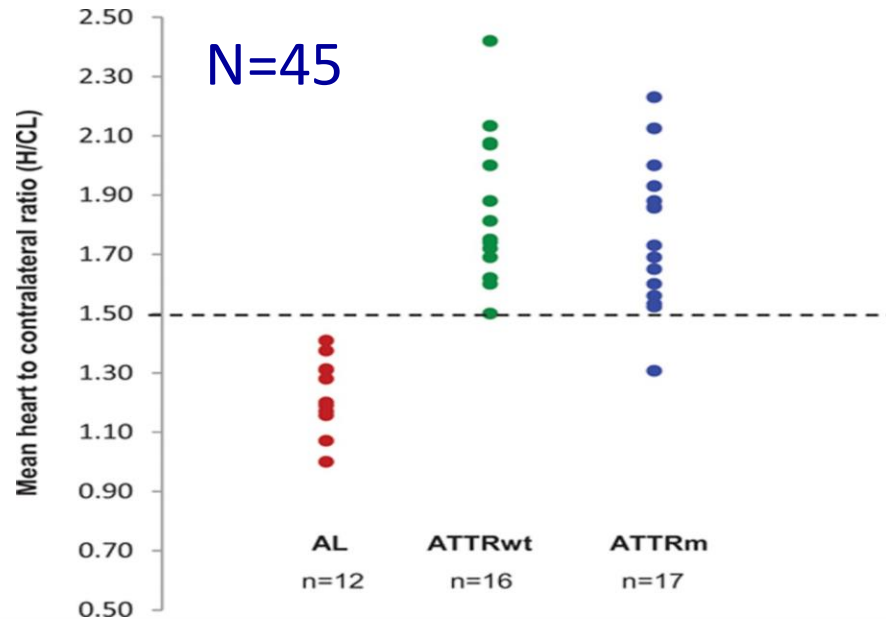
*p < 0.05 group A vs. B. †p < 0.05 group A vs. control group. ‡p < 0.05 group B vs. control group.
CA = cardiac amyloidosis; TTR = transthyretin.



Diagnosis of Cardiac Amyloidosis Tc-99m PYP

Mean heart-to-contralateral PYP ratio ATTR > AL

Mean H/CL ratio of 1.5 separates ATTR from AL

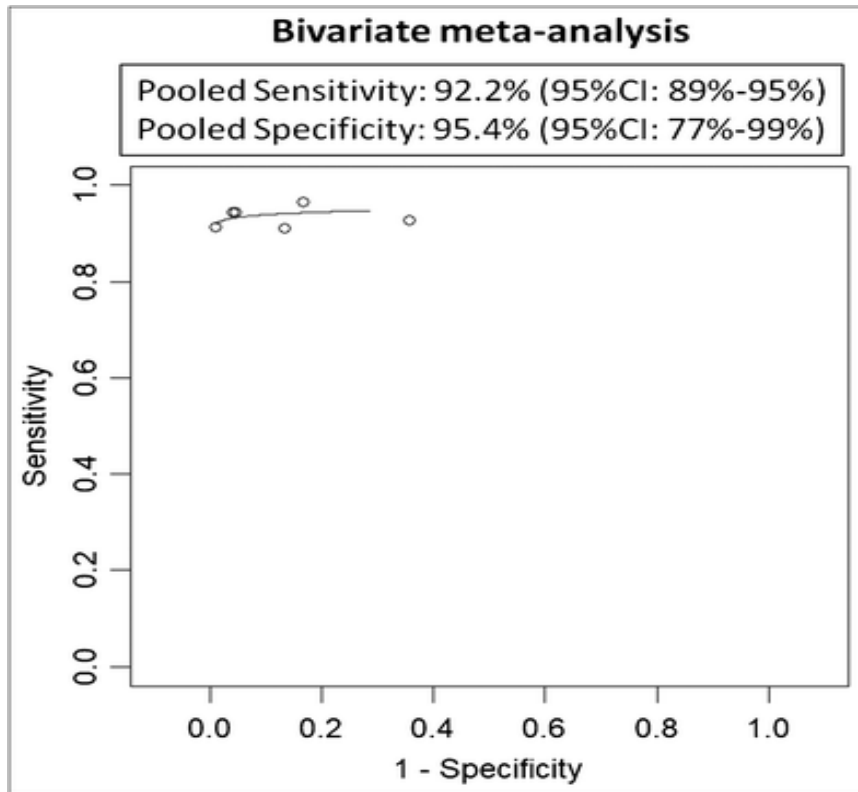


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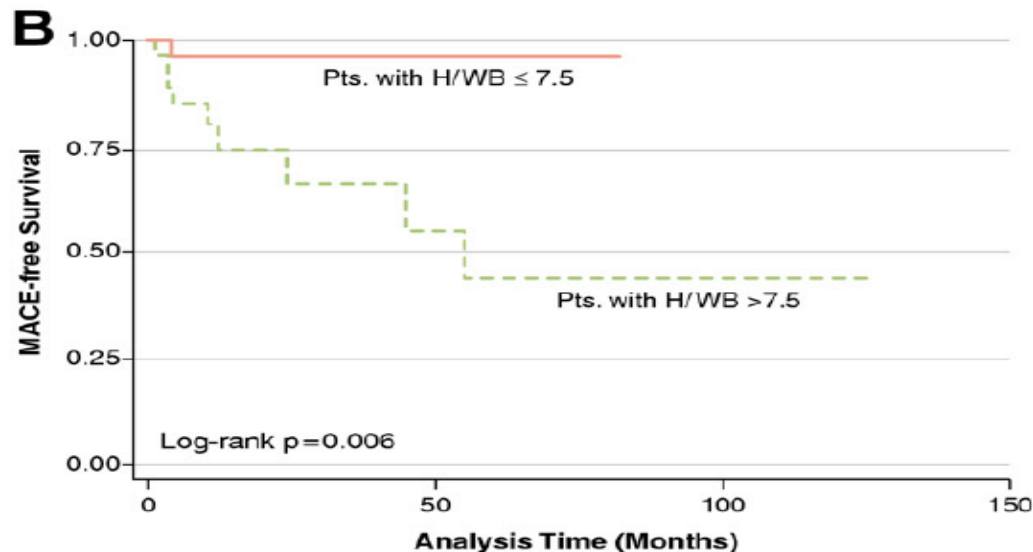
- 6 included studies
- ^{99m}Tc -DPD/HMDP/PYP
- N=529 patients
- Sens. 92%, Spec. 95% ATTR CA
- Highest for ^{99m}Tc -HMDP (NS)



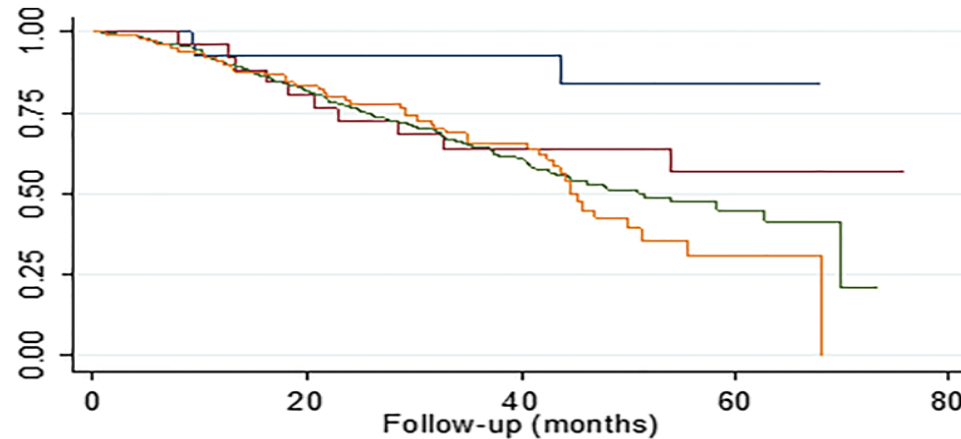
Prognosis of Hereditary TTR Cardiac Amyloidosis ^{99m}Tc -DPD:

High ^{99m}Tc -DPD uptake worse prognosis

63 patients with ATTR: 40 with and 23 without echo CMP;
14 month median FU



Survival in ATTR amyloidosis stratified by Perugini grade on ^{99m}Tc -DPD



Number at risk					
PeruginiGrade = 0	28	22	12	3	0
PeruginiGrade = 1	28	20	13	7	0
PeruginiGrade = 2	436	272	109	14	0
PeruginiGrade = 3	110	74	40	7	0

— PeruginiGrade = 0	— PeruginiGrade = 1
— PeruginiGrade = 2	— PeruginiGrade = 3

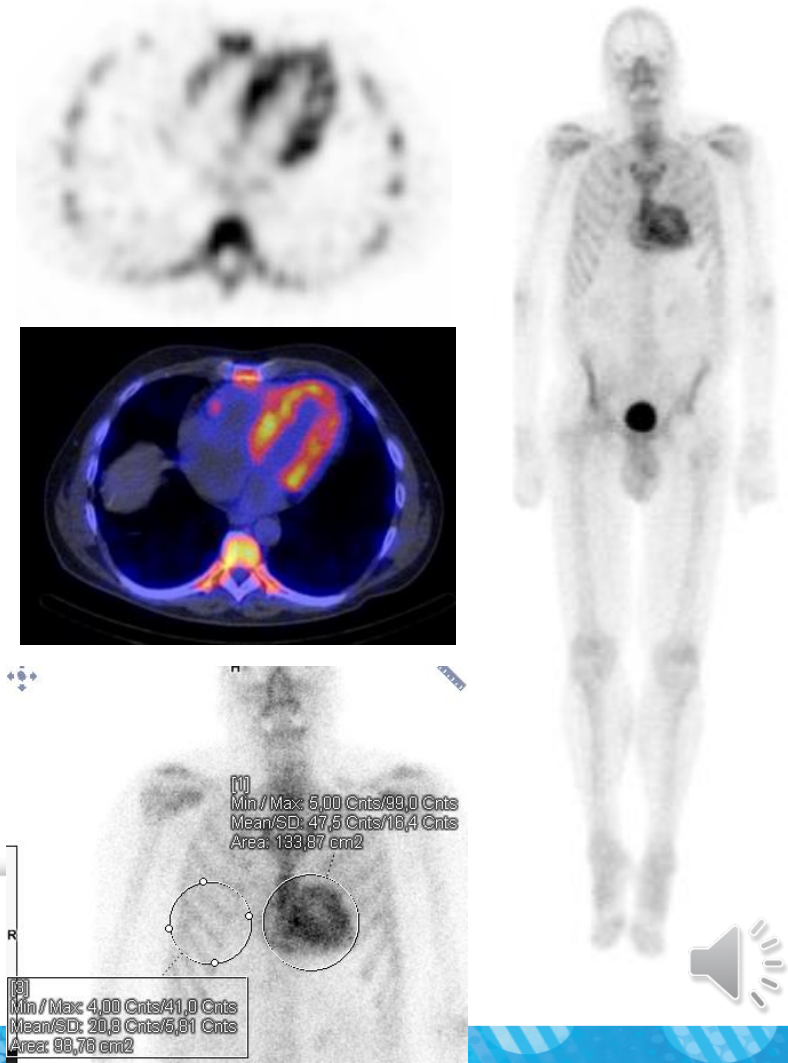


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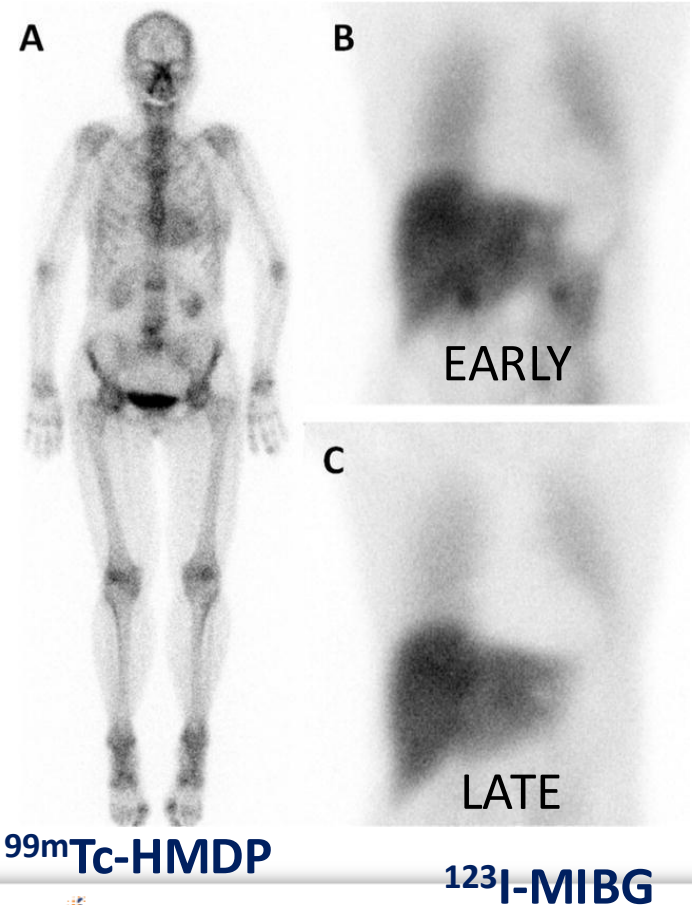
Case 1

- **ATTR-WT**
- Male 64 yrs
- Echo heart: LVEF 50%, hypertrophy
- Bone scan (HMDP)
- Heart/ribs ratio assessment
- SPECT/CT helpful



Case 2

- **ATTR-mutate**
- Female 70 yrs
- Echo heart: LVEF 45%
- Bone scan (HMDP) + MIBG (innervation)
- Late HMR MIBG = 1.38 (normal > 2)



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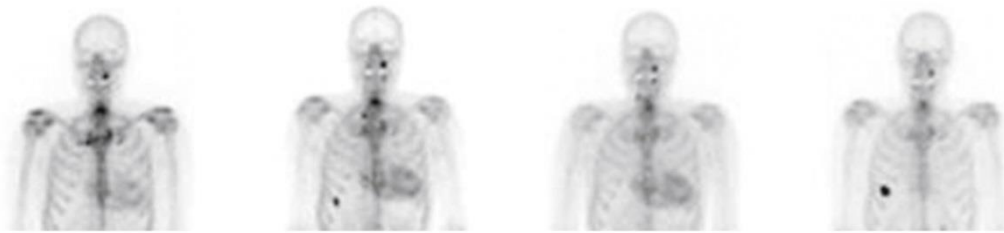
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Regression of Bone-Tracer Uptake in Cardiac Transthyretin Amyloidosis: CASE 3

- A 68-year-old white man was diagnosed with ATTRv amyloidosis, caused by the *TTR* p.Val50Met variant
- Echocardiography did not suggest cardiac involvement (< 10 mm) (2009)
- ^{99m}Tc -HDMP bone scintigraphy 2012:





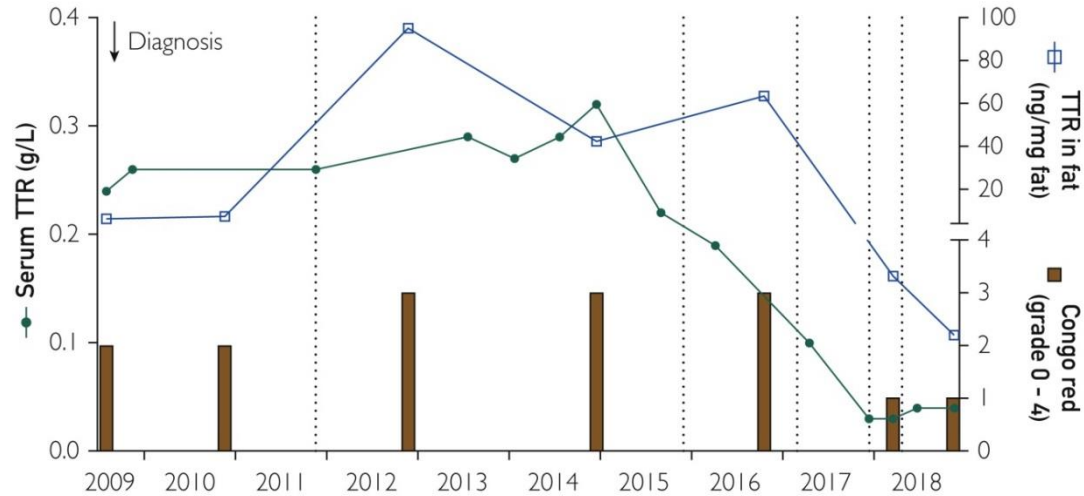
2012 2014 2016 2018

Perugini grade
H/B ratio

I	2	2	0
1.20	1.62	1.60	0.92

- Echo: diastolic dysfunction in 2014

A



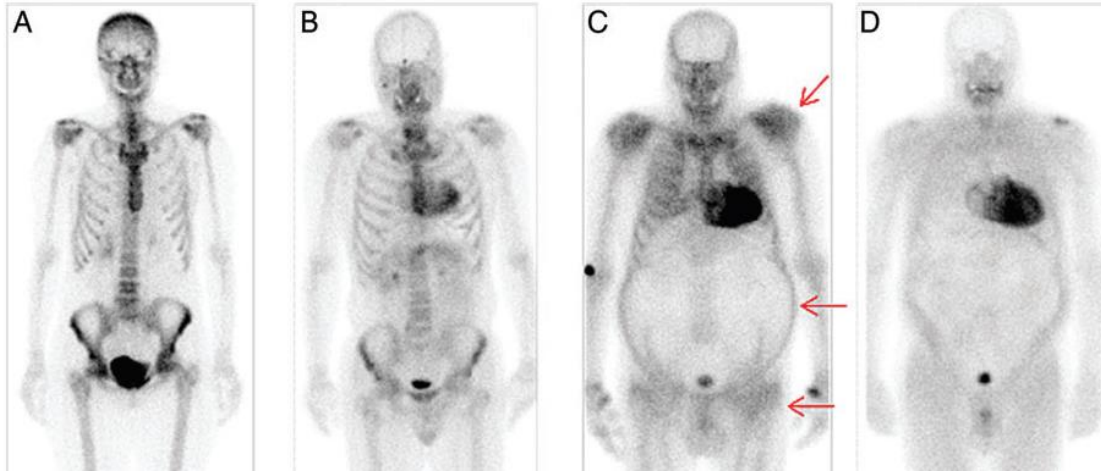
B



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Extra-cardiac findings



ATTR

- N= 158 patients
- ATTR-wt + mutate variants
- ^{99m}Tc -DPD

Heart failure, syncope, or bradyarrhythmia, with echocardiogram and/or cardiac magnetic resonance imaging (CMR) suggesting/indicating cardiac amyloid

Bone scintigraphy with ^{99m}Tc -DPD/HMDP/PYP

Grade 0

Grade 1

Grade 2 to 3

Serum immunofixation + Urine immunofixation + serum free light chain assay (Freelite)
Monoclonal protein present?

No

Yes

Yes

No

Yes

No

Cardiac
AL/ATTR
amyloidosis
unlikely

Review/request
CMR

Need specialized assessment
for Diagnosis :
Histological confirmation
and typing of amyloid

Cardiac ATTR
amyloidosis

TTR
genotyping

Cardiac amyloidosis
(AL/ApoA1/ATTR/other)

Variant ATTR
amyloidosis

Wild-Type ATTR
amyloidosis

The “imaging specialist” in the Cardiac Amyloidosis Team: it's role and a learning process



Multidisciplinary approach



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Conclusions

- ^{99m}Tc -bone seeking agents:
 - ^{99m}Tc -DPD/HMDP, ^{99m}Tc -PYP should be used
 - Early diagnosis of ATTR CA: high accuracy
 - grade ≥ 2 /no light chain clone: ATTR
 - SUV?
 - Prognosis/survival of ATTR CA
 - Extra-cardiac findings
- Use the ASNC and EANM practical points/expert consensus
- Multidisciplinary & patient-related approach



Thank you



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