99mTechnetium-pyrophosphate scintigraphy: a practical guide for early diagnosis of transthyretin amyloid cardiomyopathy

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Abstract

Transthyretin amyloid cardiomyopathy (ATTR-CM) is caused by the cardiac deposition of insoluble amyloid fibrils formed by misfolded transthyretin proteins and is associated with various cardiac symptoms, such as progressive heart failure, conduction disturbance, and arrhythmia. The implementation of 99mtechnetium (99mTc)-labelled bone radiotracer scintigraphy for diagnosing ATTR-CM has enabled accurate diagnosis of the disease with high sensitivity and specificity and positioned this diagnostic modality as an integral part of disease diagnostic algorithms. In 2020, 99mTc-pyrophosphate scintigraphy received exceptional approval for Japanese national health insurance reimbursement as a diagnostic method of ATTR-CM. Nevertheless, the utility of 99mTc-labelled bone radiotracer scintigraphy and the importance of an early diagnosis of suspected ATTR-CM using this technique have yet to be internalized as common practice by general cardiologists, and guidance on daily clinical scenarios to consider this technique for a diagnosis of suspected ATTR-CM is warranted. In this review, we discuss the utility of 99mTc-labelled bone radiotracer scintigraphy and the importance of an early diagnosis of suspected ATTR-CM using this technique have yet to be internalized as common practice by general cardiologists, and guidance on daily clinical scenarios to consider this technique for a diagnosis of suspected ATTR-CM is warranted. In this review, we discuss the utility of 99mTc-labelled bone radiotracer scintigraphy for the early diagnosis of ATTR-CM based on published literature and the outcomes of an advisory board meeting. This review also discusses clinical scenarios that could support early diagnosis of suspected ATTR-CM as well as common pitfalls, correct implementation, and future perspectives of 99mTc-labelled bone radiotracer scintigraphy in daily clinical practice. The clinical scenarios to consider 99mTc-labelled bone radiotracer scintigraphy in daily practice may include, but are not limited to, patients with a family history of the hereditary type of disease; elderly patients (aged ≥60 years) with unexplained cardiac findings (e.g. cardiac hypertrophy associated with abnormalities on an electrocardiogram, heart failure with preserved ejection fraction associated with unexplained left ventricular hypertrophy, and heart failure with reduced ejection fraction associated with atrial fibrillation and left ventricular hypertrophy); and patients with cardiac hypertrophy associated with diastolic dysfunction, right ventricular/interatrial septum/valve thickness, left ventricular sparkling, or apical sparing. Cardiac hypertrophy and persistent elevation in cardiac troponin in elderly patients are also suggestive of ATTR-CM. 99mTc-labelled bone radiotracer scintigraphy is also recommended in patients with characteristic cardiac magnetic resonance findings (e.g. diffuse subendocardial late gadolinium enhancement patterns, native T1 increase, and increase in extracellular volume) or patients with cardiac hypertrophy and bilateral carpal tunnel syndrome.

Keywords Amyloidosis; Cardiomyopathy; Heart failure; 99mTechnetium-pyrophosphate scintigraphy; Transthyretin

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**Introduction**

Transthyretin (TTR) amyloidosis is a systemic disorder involving various organs and tissues and is caused by the systemic deposition of insoluble amyloid fibrils formed by misfolded TTR proteins. TTR amyloidosis may present as various phenotypes, among which the disease resulting from the deposition of amyloid fibrils in the heart is specifically referred to as TTR amyloid cardiomyopathy (ATTR-CM). ATTR-CM is associated with various cardiac symptoms, such as progressive heart failure, conduction disturbance, and arrhythmia.

The introduction of non-invasive techniques and the emergence of disease-modifying therapies (DMTs) have changed the diagnostic methods and treatment outcomes of ATTR-CM. Developments in non-invasive diagnostic modalities, such as 99mTc-labelled bone radiotracer scintigraphy, in addition to the historical gold-standard endomyocardial biopsy, have enabled the accurate diagnosis of ATTR-CM. Society guidelines and expert consensus documents now recommend 99mTc-labelled bone radiotracer scintigraphy for the diagnosis of ATTR-CM, and in 2020, 99mTc-pyrophosphate (99mTc-PYP) scintigraphy received exceptional approval for Japanese national health insurance reimbursement as a diagnostic method of ATTR-CM. As DMTs, several novel options, including the oral TTR stabilizer, gefitinib, and TTR silencers patisiran and inotersen, are now available for clinical use in many countries. The introduction of 99mTc-labelled bone radiotracer scintigraphy as a routine diagnostic test and treatment with a DMT at the National Amyloidosis Centre in the United Kingdom in 2012 resulted in the diagnosis of ATTR-CM at an earlier stage of the disease and a significant improvement in the survival of diagnosed patients. In addition, the use of bone-avid radiotracer cardiac imaging allowed physicians to increasingly recognize that ATTR-CM is an underdiagnosed cause of heart failure in several populations; specifically, ATTR-CM has been identified in a significant subgroup of patients with heart failure with preserved ejection fraction (HFpEF), aortic stenosis, or hypertrophic cardiomyopathy. Nevertheless, the utility of 99mTc-labelled bone radiotracer scintigraphy as a diagnostic modality and the importance of early ATTR-CM diagnosis have not yet been internalized as common practice by general cardiologists. Moreover, the procedures for 99mTc-labelled bone radiotracer scintigraphy are highly variable among institutions. These findings indicate a need for guidance on daily clinical scenarios to consider 99mTc-labelled bone radiotracer scintigraphy for a suspected diagnosis of ATTR-CM, as well as a standardized protocol for imaging.

This review aims to provide an up-to-date understanding of ATTR-CM and 99mTc-labelled bone radiotracer scintigraphy by summarizing recent findings in the literature. This review also discusses clinical scenarios that could support the early identification of suspected ATTR-CM cases in daily clinical practice as well as the appropriate use of 99mTc-labelled bone radiotracer scintigraphy imaging. Clinical scenarios provided in this review are based on the clinical experience of the authors, as discussed in a virtual medical advisory board meeting held in September 2020.

**Wild-type and variant TTR amyloidosis: similarities and differences**

Transthyretin amyloidosis may occur in individuals with either a wild-type or mutated TTR gene [variant TTR (ATTRv) amyloidosis]. Wild-type TTR (ATTRwt) amyloidosis is commonly associated with cardiac involvement and is thus also referred to as wild-type ATTR-CM (ATTRwt-CM; formerly known as senile systemic amyloidosis). Dissociation of the TTR protein and misfolding and aggregation as amyloid fibrils (Figure 1) are pathological mechanisms common to ATTRwt and ATTRv amyloidosis. In the variant type of the disease, TTR destabilization is caused by point mutations in the TTR gene, and more than 130 TTR mutations have been identified worldwide. Some TTR gene mutations, including the replacement of valine with methionine at position 30 (Val30Met or p.Val50Met) with a late onset of disease, are commonly associated with various symptoms, including cardiac symptoms.

In patients with ATTR-CM, clinical symptoms such as carpal tunnel syndrome (CTS) and left ventricular hypertrophy (LVH) commonly present months to years before diagnosis, indicating the importance of clinicians’ understanding of the most prevalent clinical manifestations of ATTR-CM. As patient characteristics and pathologies overlap between ATTRwt-CM and late-onset ATTRv-CM, a differential diagnosis aided by genetic testing is necessary.

**Epidemiology of ATTRwt-CM and applicability of non-invasive diagnostic techniques for early patient identification**

**Epidemiology and natural history of ATTRwt-CM**

Although the true prevalence of ATTRwt-CM remains unclear, previous research has reported that ATTRwt-CM was found in 3.1–25% of autopsied elderly cases. 1,2,13,16 13% of elderly patients (aged ≥60 years) with heart failure with preserved ejection fraction and 16% of elderly patients with severe aortic stenosis. The median survival for patients with ATTRwt-CM is approximately 5 years from diagnosis, and the disease may be associated with unexpected deaths among the elderly.
Approximately 85% of patients with biopsy-proven ATTRwt-CM have New York Heart Association (NYHA) functional Class ≥II symptoms.29,30 These findings indicate that amyloid deposition in the heart does occur in patients at NYHA functional Class I or II stage. With the use of non-invasive scintigraphy, identification of patients with an early-stage (NYHA functional Class I or II) disease is occurring with increasing frequency.31 A conceptual diagram representing the pathophysiology of ATTR-CM and applicability of non-invasive diagnostic techniques is shown in Figure 1.

**99mTc-labelled bone radiotracer scintigraphy**

For non-invasive, disease-specific diagnosis of ATTR-CM at an early stage of the disease (NYHA functional Class I or II), the utility of cardiac scintigraphy using 99mTc-labelled tracers, including 99mTc-PYP, 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (99mTc-DPD), and 99mTc-hydroxymethylene diphosphonate (99mTc-HMDP), has been suggested in the literature.32,33 In a previous study involving patients with suspected cardiac amyloidosis, Grade 2 or 3 myocardial uptake along with the absence of monoclonal gammopathy on serum and urine analysis demonstrated a specificity and positive predictive value of 100% for ATTR-CM.34 In a multicentre study that applied planar 99mTc-PYP scintigraphy to patients with ATTR-CM (including both ATTRwt-CM and ATTRv-CM), the heart-to-contralateral (H/CL) ratio (ratio of heart regions of interest mean counts to contralateral chest region of interest mean counts35) in patients with NYHA functional Class I or II symptoms showed no difference from that in patients with Class III or IV symptoms.32 Moreover, a follow-up study of 11 asymptomatic individuals carrying a TTR gene mutation (i.e. asymptomatic carriers of ATTRv-CM) revealed that 99mTc-DPD scintigraphy measurement successfully detected cardiac involvement earlier than electrocardiogram (ECG), echocardiography, or biomarkers, although the number of subjects was low.33 Subjects with Grade ≥1 cardiac 99mTc-DPD uptake showed a statistically significant increase in interventricular septal thickness (IVST) on echocardiography vs. subjects without cardiac uptake (12.2 ± 2.3 mm vs. 9.1 ± 0.9 mm; \(P = 0.001\)) as well as a statistically significant increase in left ventricular wall thickness (11.6 ± 1.7 mm vs. 8.9 ± 0.8 mm; \(P = 0.0001\)).33

**Cardiac magnetic resonance, echocardiography, and ECG**

Cardiac magnetic resonance (CMR) helps differentiate cardiac amyloidosis from other causes of LVH, such as hypertension and hypertrophic cardiomyopathy,36 and can identify patients with cardiac amyloidosis, independent of the type of amyloid protein. However, the results are not specific to ATTR-CM, and there is no consensus as to whether this diagnostic modality is suitable for early detection of the disease. In a pilot study that assessed the phenotypes of 49 patients (aged >65 years) with HfPpEF, including 26 (53%) patients with NYHA functional Class II symptoms, 15 (31%) patients showed a characteristic infiltrative pattern on CMR.37 Of these 15 patients, 9 had cardiac uptake in 99mTc-DPD scintigraphy and were diagnosed with ATTRwt-CM by genetic testing, while the remaining 6 had no significant cardiac 99mTc-DPD uptake and were diagnosed with biopsy-proven or suspected light-chain (AL) amyloidosis (amyloidosis characterized by the deposition of misfolded monoclonal immunoglobulin light chains38). Late gadolinium enhancement (LGE) is an...
Utility of $^{99m}$Tc-labelled bone radiotracer scintigraphy in the diagnosis of ATTR-CM, guideline recommendations, and limitations

Evidence has been established regarding the utility of cardiac scintigraphy using $^{99m}$Tc-labelled tracers for the diagnosis of ATTR-CM. A meta-analysis of six studies on $^{99m}$Tc-labelled bone radiotracer scintigraphy for ATTR-CM ($^{99m}$Tc-PYP, $^{99m}$Tc-DPD, and $^{99m}$Tc-HMDP) yielded a pooled sensitivity of 92.2% (95% confidence interval, 89–95%) and specificity of 95.4% (95% confidence interval, 77–99%) and found no statistically significant differences in diagnostic performance among the radiotracers used. The risk of developing future cancer attributable to $^{99m}$Tc-PYP scintigraphy is low and estimated to be <1% of total future cancers. By using positive cardiac uptake of the $^{99m}$Tc-labelled tracer as an indicator, suspected ATTRwt-CM was found in 2.8% of individuals (aged ≥75 years; no prior clinical suspicion of ATTR-CM) visiting a university hospital in Spain. 0.36% of individuals aged ≥65 years (estimated to be up to 1.4% of men in the ninth decade) and 0.06% of individuals (aged >30 years) who underwent scintigraphy for non-cardiac reasons at a university hospital in South Korea. In an Australian general population, the prevalence of positive $^{99m}$Tc-HMDP cardiac uptake increased with age and reached 6.15% in men and 1.69% in women aged ≥85 years.

$^{99m}$Tc-labelled bone radiotracer scintigraphy is now included in the diagnostic algorithms in the Japanese Circulation Society (JCS) guidelines for the diagnosis and treatment of cardiac amyloidosis and in expert consensus recommendations assembled by the American Society of Nuclear Cardiology (ASNC), Amyloidosis Research Consortium, and European Society of Cardiology. A detailed approach for planar $^{99m}$Tc-PYP scintigraphy with visual grading assessment and H/CL ratio-based quantitative assessment is described in the JCS guidelines and ASNC expert consensus recommendations for multi-modality imaging in cardiac amyloidosis.

The assessment of planar $^{99m}$Tc-PYP scintigraphy is performed on the basis of 1- or 3-h imaging (imaging assessed 1 or 3 h after radiotracer injection). Imaging should be followed by an H/CL ratio assessment and visual grading assessment. The cardiac uptake results are categorized as: Grade 0 (no uptake), 1 (mild uptake, less than rib uptake), 2 (moderate uptake, equal to rib uptake), or 3 (high uptake, greater than rib uptake). Grades 2 and 3 are deemed positive for ATTR-CM. An H/CL ratio of >1.5 on 1-h images or >1.3 on 3-h images in $^{99m}$Tc-PYP scintigraphy has a high diagnostic accuracy in distinguishing ATTR-CM from AL amyloidosis. The 1-h imaging has advantages in terms of patient comfort, fast throughput, and sensitivity of visual assessment, which is higher than that of the 3-h imaging (95% vs. 58%); however, the specificity is relatively low (79%), requiring single-photon emission computed tomography (SPECT) or SPECT/computed tomography (CT) imaging to differentiate true myocardial uptake from radiotracer activity associated with myocardial infarctions, rib fractures, or blood pools. By contrast, the 3-h imaging requires a longer interval between the radiotracer injection and imaging but enables reduction in blood pools and myocardial radiotracer activity, leading to an enhanced specificity (100%) in visual assessment. Discordance between the 1- and 3-h planar imaging results can be minimized by additionally obtaining SPECT or SPECT/CT images. The authors recommend further planar imaging at 3 h, as visual grading is easy to use, and SPECT imaging is not feasible in all institutions across Japan.

Of note, however, it is advisable to not rely solely on $^{99m}$Tc-PYP scintigraphy results for the diagnosis of ATTR-CM. As patients with AL amyloidosis may also test positive with $^{99m}$Tc-PYP scintigraphy, the serum free light chain assay and serum and urine protein electrophoresis with immunofixation to confirm the absence of monoclonal protein, concurrently with bone-avid tracer imaging, are essential for a non-invasive, accurate diagnosis of ATTR-CM.
endomyocardial, abdominal fat pad, surgical skin, gastrointestinal, or salivary glands biopsy followed by amyloid typing and genetic testing may also be required. Caution is advised for the selection of the biopsy site in patients with ATTRwt-CM, as the sensitivity of fat pad biopsy (14–15%) is not as high as that of endomyocardial biopsy (approximately 100%) for detecting ATTR deposits.\textsuperscript{55,56}

**Clinical scenarios to consider \(99mTc\)-PYP scintigraphy for a diagnosis of suspected ATTR-CM**

Presenting scenarios in daily clinical practice where \(99mTc\)-PYP scintigraphy should be considered for suspected ATTR-CM helps cardiologists further understand the recommendations provided in existing guidelines or expert consensus documents.\textsuperscript{6–9} This section summarizes the clinical scenarios to consider \(99mTc\)-PYP scintigraphy for suspected ATTR-CM, as discussed in the virtual advisory board meeting.

Typical indicators for suspected ATTR-CM are summarized in Figure 2, and representative images of patients with ATTR-CM are depicted in Figure 3A–3F. Detailed clinical scenarios for considering \(99mTc\)-PYP scintigraphy in daily clinical practice are shown in Table 1. \(99mTc\)-PYP scintigraphy should be considered in patients with a family history of ATTRv amyloidosis or elderly patients (aged \(\geq 60\) years) with unexplained cardiac findings. Typical unexplained cardiac findings in elderly patients include cardiac hypertrophy on echocardiography,\textsuperscript{57} abnormal ECG findings (e.g., progressive conduction disturbance, low QRS voltage or low voltage-to-mass ratio, and poor R-wave progression),\textsuperscript{43,58,59} HFrEF associated with LVH,\textsuperscript{14} and heart failure with reduced ejection fraction (HFrEF) associated with atrial fibrillation and LVH. \(99mTc\)-PYP scintigraphy should be also considered in patients showing cardiac hypertrophy on echocardiography associated with diastolic dysfunction, right ventricular/interatrial septum/valve thickness,\textsuperscript{43} left ventricular sparkling, or apical sparing.\textsuperscript{60,61} Advanced age (\(\geq 60\) years) associated with cardiac hypertrophy and persistent elevation in high-sensitivity cardiac troponin (hs-cTn)\textsuperscript{62,63} and characteristic CMR findings, such as diffuse subendocardial LGE,\textsuperscript{39} increased native T1,\textsuperscript{40} and increased ECV, are also suggestive of ATTR-CM. Moreover, \(99mTc\)-PYP scintigraphy should be considered in elderly patients with cardiac hypertrophy and CTS (especially bilateral CTS).\textsuperscript{28,64,65}

However, deviations from these clinical scenarios do not always exclude suspected ATTR-CM. For example, the absence of a restrictive pattern or low QRS voltage on ECG should not rule out the diagnosis of ATTR-CM, as these findings were not commonly observed in patients with moderate-to-severe increase in IVST (restrictive pattern, 18%; low QRS voltage, 33%).\textsuperscript{43}

\(99mTc\)-PYP scintigraphy can be considered with a high priority when a patient presents with an elevated level (\(\geq 0.0308\) ng/mL) of hs-cTnT, increased left ventricular posterior wall thickness (\(\geq 13.6\) mm), and wide QRS (\(\geq 120\) ms); the \(99mTc\)-PYP positivity rates were 96%, 63%, 21%, and 13% when 3, 2, 1, and no criteria were met, respectively (Kumamoto criteria).\textsuperscript{66} In another study that aimed to validate the Kumamoto criteria, the \(99mTc\)-PYP positivity rates were 89%, 69%, 39%, and 4% when 3, 2, 1, and none of the aforementioned criteria were met, respectively.\textsuperscript{67}

**Data interpretation and common pitfalls of \(99mTc\)-PYP scintigraphy**

Cardiologists may face difficulties in data interpretation and diagnosis of ATTR-CM while implementing \(99mTc\)-PYP scintigraphy in daily clinical practice. In this section, guidance on the correct implementation and data interpretation of \(99mTc\)-PYP scintigraphy and common pitfalls of this diagnostic modality are discussed in detail.

**Figure 2** Typical indicators to suspect transthyretin amyloid cardiomyopathy (ATTR-CM) and consider \(99mTc\)-PYP scintigraphy in daily clinical practice. CMR, cardiac magnetic resonance; CTS, carpal tunnel syndrome; ECV, extracellular volume; ECG, electrocardiogram; LGE, late gadolinium enhancement; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide; HFpEF, heart failure with preserved ejection fraction.
Diagnostic algorithm for patients with Grade 1 myocardial tracer uptake and a negative monoclonal protein detection test

In daily clinical practice, patients sometimes present with Grade 1 myocardial tracer uptake (mild uptake less than rib uptake) and a negative monoclonal protein detection test. To distinguish cardiac blood pool activity from true myocardial uptake, not only planar images but also SPECT or SPECT/CT images should be evaluated (Figure 4A). Figure 4B depicts our proposed algorithm for diagnosing patients with Grade 1 myocardial tracer uptake and a negative monoclonal protein detection test. The next step after the SPECT or SPECT/CT image evaluation is to review CMR data (LGE, native T1, and ECV) or order CMR tests if no data are available. After

| Serial number | Clinical scenario |
|---------------|-------------------|
| 1             | Family history of ATTRv amyloidosis |
| 2             | Age ≥60 years; cardiac hypertrophy on echocardiography associated with conduction disturbance, low voltage, or poor R-wave progression on ECG |
| 3             | Age ≥60 years with HFrEF associated with unexplained LVH |
| 4             | Age ≥60 years with HFrEF associated with atrial fibrillation and LVH |
| 5             | Cardiac hypertrophy on echocardiography associated with diastolic dysfunction, right ventricular/interatrial septum/value thickness, left ventricular sparkling, or apical sparing |
| 6             | Age ≥60 years; cardiac hypertrophy on echocardiography associated with persistently elevated hs-cTn |
| 7             | Cardiac hypertrophy with diffuse subendocardial LGE patterns, native T1 increase, or increased ECV on CMR |
| 8             | Cardiac hypertrophy with CTS |

99mTc-PYP, 99mTc-technetium-pyrophosphate; ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant transthyretin; CMR, cardiac magnetic resonance; CTS, carpal tunnel syndrome; ECG, electrocardiogram; ECV, extracellular volume; HFrEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; hs-cTn, high-sensitivity cardiac troponin; LGE, late gadolinium enhancement; LVH, left ventricular hypertrophy.
thorough review of the available CMR data, ECG, echocardiography, and clinical findings, if ATTR-CM is suspected, ATTR deposition should be evaluated with a biopsy. An endomyocardial biopsy is recommended when ATTR-CM is strongly suspected; however, other sites (e.g. abdominal fat pad and upper gastrointestinal tract) can also be considered for a biopsy depending on the patient’s condition, as a diagnosis of ATTR-CM can be formed in Japan if amyloid deposition is detected in non-cardiac biopsies. As the sensitivity of non-cardiac biopsies is low (14–15%), the JCS guidelines recommend performing biopsies at multiple sites other than the endocardium. In view of the progressive nature of the disease (median survival of approximately 5 years from diagnosis), a follow-up with scintigraphy after 6 months–1 year is advisable in patients without ATTR deposition on biopsy or those not (or weakly) suspected of ATTR-CM.

Figure 4 (A) Representative planar (top) and single-photon emission computed tomography/computed tomography (SPECT/CT; bottom) images of patients with Grade 1 myocardial tracer uptake and negative monoclonal protein test. White and red arrows indicate cardiac blood pools and positive cardiac uptake, respectively. (B) Flow chart of transthyretin amyloid cardiomyopathy (ATTR-CM) diagnosis in patients with planar $^{99m}$Tc-PYP scintigraphy Grade 1 and a negative monoclonal protein detection test. Endomyocardial, abdominal fat pad, or upper gastrointestinal tract biopsy is recommended. For patients who test negative with a biopsy, it is advisable to schedule regular follow-up with scintigraphy after 6 months–1 year. Grade 1 in $^{99m}$Tc-PYP scintigraphy refers to mild uptake less than rib uptake.

False positives, false negatives, and inconsistencies between $^{99m}$Tc-PYP scintigraphy and biopsy findings

False-positive cases in $^{99m}$Tc-PYP scintigraphy for ATTR-CM may include Grade 2 or 3 myocardial uptake; a recent history of acute myocardial infarction; AL amyloidosis; apolipoprotein AI amyloidosis (ApoAI), apolipoprotein AI amyloidosis (ApoAII), apolipoprotein A-IV amyloidosis (ApoAIV), or β2-microglobulin amyloidosis (β2M); hypertrophic cardiomyopathy; hydroxychloroquine toxicity; and cardiac blood pools. Case reports on false-positive myocardial uptake following intravenous iron injections have been published for $^{99m}$Tc-DPD and $^{99m}$Tc-HMDP scintigraphy. In contrast, Grade 0 or 1 myocardial uptake, an insufficient amount of amyloid deposits, rib fractures, valvular/annular calcifications, recent myocardial infarction, delayed or premature acquisition in $^{99m}$Tc-PYP scintigraphy, ATTRv-CM with a low sensitivity for $^{99m}$Tc-labelled bone radiotracer scintigraphy (Ser77Tyr or Phe64Leu mutation), and initial diagnosis of cardiac pools with myocardial deposits are examples of possible false-negative cases (Table 2). In case of inconsistencies between planar $^{99m}$Tc-PYP scintigraphy results and biopsy findings, potential causes should be suspected and investigated, such as errors in scintigraphy imaging time or interpretation, errors in biopsy sampling or pathological diagnosis, deposits of proteins other than TTR (e.g. AL), and ATTRv-CM with a low sensitivity in $^{99m}$Tc-PYP scintigraphy (Table 3).

Guide for appropriate implementation of $^{99m}$Tc-PYP scintigraphy in daily clinical practice

For appropriate implementation of $^{99m}$Tc-PYP scintigraphy, in addition to planar imaging, SPECT or SPECT/CT fusion imaging is necessary to differentiate myocardial uptake from blood pools or overlying bone uptake. A standardized protocol (practice points document) for planar $^{99m}$Tc-PYP scintigraphy and SPECT data acquisition has been published by the ASNC. In brief, the dose of $^{99m}$Tc-PYP intravenous injection is set at 10–20 mCi, a rest scan is recommended for data acquisition, and the time between $^{99m}$Tc-PYP injection and data acquisition is set at 1 or 3 h. If persistent blood pool activity is noted on 1-h SPECT and planar images, 3-h images may also be obtained.

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Future perspectives

Recent clinical research has positioned 99mTc-labelled bone radiotracer scintigraphy as a highly sensitive and specific diagnostic tool for ATTR-CM and suggests its potential as a quantitative diagnostic tool for ATTR-CM. For example, the use of quantitative metrics for 99mTc-PYP imaging (SPECT/CT or SPECT) showed a higher diagnostic accuracy compared with the traditional visual grading approach as well as its potential as a non-invasive marker for prognosis. Nevertheless, challenges remain in terms of appropriate implementation of this technique in daily clinical practice. A low level of familiarity with 99mTc-labelled bone radiotracer scintigraphy and standardization of imaging procedures, such as tracer compound dose, time from injection to imaging, and data interpretation and quantification, are challenges that need to be overcome by cardiologists. Despite its high sensitivity and specificity, 99mTc-labelled bone radiotracer scintigraphy is not suitable to form a diagnosis of ATTR-CM as a stand-alone technique, and exclusion of monoclonal protein components through a careful haematological assessment is required for a definitive diagnosis to avoid misdiagnosis and inappropriate treatment. Moreover, research is warranted to elaborate the mechanism of myocardial 99mTc-labelled tracer uptake in patients with ATTR-CM. Lastly, the cost-effectiveness of 99mTc-labelled bone radiotracer scintigraphy needs further investigation in the era of treatment with DMTs.

Conclusions

The ATTR-CM remains an under-recognized disease owing to its non-specific clinical manifestation. Cardiac changes are not disease specific, which makes differential diagnosis challenging. Awareness of the disease has been low, but is expected to increase with advances in the treatment strategy. Moreover, a highly accurate diagnosis is warranted as ATTR-CM is a progressive and fatal disorder. The introduction of 99mTc-labelled bone radiotracer scintigraphy as a non-invasive diagnostic modality with high sensitivity and specificity and the coverage of 99mTc-PYP scintigraphy by

| Table 2 | Typical false-positive and false-negative cases in planar 99mTc-PYP scintigraphy for the diagnosis of ATTR-CM |
| --- | --- |
| Planar 99mTc-PYP scintigraphy results | Potential causes of false results |
| False positive |  |
| Positive |  |
| Negative |  |
| False negative |  |
| Positive |  |
| Negative |  |

A positive 99mTc-PYP scintigraphy result refers to Grade 2 (moderate cardiac uptake equal to rib uptake) or Grade 3 (high cardiac uptake greater than rib uptake), and a negative result refers to Grade 0 (no cardiac uptake) or Grade 1 (mild cardiac uptake less than rib uptake). 99mTc-PYP, 99mtechnetium-pyrophosphate; AL, light chain; ATTR-CM, transthyretin amyloid cardiomypathy; ATTRv-CM, variant ATTR-CM.

| Table 3 | Potential causes of inconsistencies between planar 99mTc-PYP scintigraphy and biopsy findings in suspected ATTR-CM |
| --- | --- |
| Planar 99mTc-PYP scintigraphy | Biopsy | Potential causes of inconsistencies |
| Positive | Negative |  |
| False positive |  |
| False negative |  |

A positive 99mTc-PYP scintigraphy result refers to Grade 2 (moderate cardiac uptake equal to rib uptake) or Grade 3 (high cardiac uptake greater than rib uptake), and a negative result refers to Grade 0 (no cardiac uptake) or Grade 1 (mild cardiac uptake less than rib uptake). 99mTc-PYP, 99mtechnetium-pyrophosphate; AL, light chain; ATTR-CM, transthyretin amyloid cardiomypathy; ATTRv-CM, variant ATTR-CM.
the Japanese health insurance have enabled an early and de-
finite diagnosis of ATTR-CM. We anticipate that the clinical
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cardiovascular centers of excellence. In addition to the pivotal 99mTc-PYP scintigraphy imaging discussed in this review will help cardiologists establish an early and accurate diagnosis of ATTR-CM in daily clinical practice.

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Conflict of interest

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