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Review Article

Cardiac imaging techniques for the assessment of immune checkpoint inhibitor-induced cardiotoxicity and their potential clinical applications

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Abstract: Immune checkpoint inhibitors (ICIs) have encouraged a paradigm shift in the clinical management of patients with cancer. Despite the dramatically improved tumor response and patient prognosis, ICIs have been associated with ICI-related myocarditis, which has a high fatality rate. Cardiac imaging plays a critical role in the assessment of cardiac injury. Echocardiography, cardiac magnetic resonance imaging, and targeted tracer-based cardiac molecular imaging techniques alone or in combination reflect pathophysiology and depict different aspects of lesions at different clinical stages, i.e., they have potentially complementary value. Imaging techniques for identifying ICI-induced cardiotoxicity at the early stage may reduce the incidence of adverse cardiovascular events. Particularly in planned ICI therapy among patients with cancer, improved monitoring approaches to identify patients who are at the highest risk of ICI-related myocarditis may help in refining clinical decisions, allowing treatment to be more accurately targeted toward patients who are most likely to benefit. In this study, we systematically reviewed the studies on cardiac imaging techniques for assessing ICI-induced cardiotoxicity. We elaborated about the potential applications of cardiac imaging techniques for the optimized management of patients with ICI-related myocarditis, including risk stratification, diagnosis, and prognosis.

Keywords: Immune checkpoint inhibitors, cardiac imaging, cardiotoxicity, cancer, myocarditis

Introduction

Harnessing the defense ability of the immune system has revolutionized the management of patients with cancer [1-3]. With the discovery of immune checkpoint inhibitors (ICI), there has been a major shift in the paradigm of cancer treatment [4]. ICIs are monoclonal antibodies that antagonize the signaling pathways for immune checkpoints and strengthen the immune system-mediated attack on cancer cells [5, 6]. At present, ICI therapies are approved for various cancers, and the application spectrum of ICIs has rapidly expanded from the advanced form of the disease to the first-line metastatic and adjuvant settings [7].

However, despite excellent outcomes in tumor response, immune checkpoint inhibitors are associated with a series of specific side effects termed immune-related adverse events (irAEs) [8]. Among cardiovascular toxicities, despite the lack of prospective studies on the evaluation of myocarditis, retrospective literature has shown that the incidence of ICI-related myocarditis is in the range of 1%-2% [9, 10]. Although cardiotoxicity is uncommon, the case mortality rate of ICI-related myocarditis is high (40%-50%) [10, 11]. Cardiovascular irAEs are higher in patients treated with ICI in combinations than in those undergoing monotherapy. Therefore, clinicians need to recognize and be aware of these extreme adverse situations to appropriately guide patient management.

No standard is available at present for the diagnosis and treatment of patients with ICI-induced cardiotoxicity. The diagnosis of patients with ICI-related myocarditis is often challenging owing to the heterogeneity of clinical symptoms

and signs, with cardiac biomarkers and electrocardiograms (ECGs) having limited specificity for the assessment of myocarditis [12]. Endomyocardial biopsy represents the gold standard for the diagnosis of ICI-related myocarditis, but it may not be used frequently because of its complications. The diagnostic difficulties have led to the increasing importance of the use of different imaging techniques in the assessment of ICI-induced cardiotoxicity. In this review, we discuss the role of imaging techniques in optimizing the management of ICI-induced cardiotoxicity, including risk stratification, early toxicity identification, myocarditis assessment, and prognosis of biomarkers.

Diagnostic criteria of ICI-related myocarditis

Clinical manifestations of myocarditis, including the signs of acute heart failure, differ from each other [13]. A systematic review showed that the most frequently found symptoms of ICI-related myocarditis are dyspnea, weakness, and chest pain [14]. In ICI-related myocarditis, serum cardiac markers are always elevated, although the positive predictive value of each marker varies [9]. Growing evidence has indicated that patients manifesting an irAE can eventually be diagnosed with acute myocarditis without any information of clinical cardiac symptoms [15].

The diagnosis of acute myocarditis depends on the combined algorithm of typical clinical manifestations and laboratory tests, including inflammatory markers, serum cardiac markers, and imaging criteria. Given the inconsistency in clinical presentations, the assessment of ICI-induced cardiotoxicity currently presents a challenge. For early monitoring of myocardial injury induced by ICIs, serial laboratory tests, ECG, and echocardiography can be beneficial for patients with cancer. For the accurate assessment of ICI-related myocarditis, further diagnostic approaches, such as cardiac magnetic resonance (CMR) or an endomyocardial biopsy, are also required [16]. Endomyocardial biopsy should be performed when the treatment course is affected by suspected ICI-induced cardiotoxicity.

Histological characteristics and potential mechanism

Histological analyses of patients and animal models have showed that the infiltration of T lymphocytes and macrophages is the primary cause of ICI-related myocarditis [17, 18]. The change in the expression of various inflammatory cytokines and reactions further demonstrates the activation of T cells. Tumor necrosis factor-α, granzyme B, and interferon-γ are produced and secreted by activated T cells, thereby inducing cardiomyocyte toxicity and death. This excessively fierce inclination toward an inflammatory reaction may contribute to cardiac injury and dysfunction [19].

The potential mechanism of ICI-induced cardiotoxicity has not been clarified. The most likely explanation is that the T cells target an antigen shared between the tumor cells and cardiac muscle cells [20]. Another possible explanation is that the same T-cell receptor targets a tumor cell antigen and a different cardiac muscle cell antigen that is homologous [20]. Under this condition, hyperproliferative T lymphocytes and macrophages aberrantly infiltrate the myocardial tissue following ICI treatment through a series of inflammatory reactions, thereby inducing cardiac injury. ICIs unblock the immune cell suppression by tumor cells and may induce the same manner of inhibition by cardiomyocytes, leading to T-cell over-activation in the myocardium [21].

Imaging techniques for the assessment of ICI-related myocarditis

Echocardiography remains an essential and the most frequently used preliminary assessment tool in cases of suspected myocarditis. CMR is widely accepted as a fundamental diagnostic tool for acute myocarditis owing to its high accuracy and spatial resolution [22]. Current guidelines have established the “Lake Louise Criteria” on CMR as the diagnostic criteria for myocarditis in patients with suspected acute or active myocardial inflammation [22, 23]. It also has a substantial prognostic and predictive value as a negative CMR, which is associated with a low risk of cardiovascular events, in the setting of possible acute myocarditis [24]. Molecular imaging improvement has shed light on the mechanisms underlying different etiological factors mediating cardiotoxicity. Molecularly targeted tracers may help monitor the earliest stages of myocardial inflammation. In addition, medical imaging modalities have raised considerable interest for their promising characteristic cardiac features in vivo as markers of potential risks

Table 1. Characteristics of different imaging techniques and their applications

Technique	Advantages	Disadvantages	Applications
Echo	Noninvasive; no radiation; real-time; wide availability; low costs; bedside examination	Low resolution; operator dependency; high variability; low reproducibility	Cardiac structure; wall motion; myocardial strain; EF
CMR	Noninvasive; no radiation; high resolution; high sensitivity and specificity; high reproducibility	Time consuming; high price; contrast agent dependency; complicated operation	Cardiac structure; wall motion; myocardial strain; myocardial edema; myocardial necrosis/fibrosis; EF
PET-CT	Noninvasive; high resolution; high reproducibility; inflammation assessment	Radiation; time consuming; high costs; radiotracers dependency	Inflammation; fibrosis; protein expression

Abbreviations: CMR = cardiac magnetic resonance; PET-CT = positron emission tomography-computed tomography; EF = ejection fraction.

induced by ICI. We will briefly review the features and potentials of the primary imaging modalities used for the detection of ICI-related myocarditis (**Tables 1** and **2**).

Diagnostic accuracy of echocardiography

Echocardiography is a technique that can be easily performed for assessing the cardiac structure and function. It is frequently used for the assessment of myocarditis and monitoring the response to treatment. Echo findings of myocarditis include left ventricular enlargement, diffused left ventricular systolic dysfunction, and segmental wall motion abnormalities [25]. In the early stage of the disease, the cardiac usually presents normal dimensions; the chronic stage of this condition usually involves cardiac enlargement and remodeling [26]. Regional wall motion abnormality, pericardial effusion, and strain changes have also been reported in the acute stage of this condition [27].

Data available at present on echocardiography assessment in regard to ICI-related myocarditis are limited. A recent review focusing on the echo characteristics of ICI-related myocarditis revealed that 32.5% of the cases showed a normal left ventricular ejection fraction (LVEF). However, 61.5% of these patients passed away, which indicated that a preserved systolic function did not predict a high survival rate [14]. In a cohort study of 35 patients with ICI-related myocarditis, more than half of the cases presented with preserved LVEF, whereas the average internal dimensions of the left ventricle during diastole were within the normal range [9]. In addition, the lack of correlation between preserved systolic function and major adverse cardiac events (MACE) was reported in this observational study [9]. A newly emerging pericardial fluid, which can be easily detected using echocardiography, is evidence that supports the echocardiography of myocarditis. A baseline echocardiography assessment is beneficial to monitor individual therapeutic responses, including changes in systolic and diastolic function, ventricular-wall motion abnormalities, or pericardial fluid volume, which can provide an indication for the diagnosis of ICI-related myocarditis. However, echocardiography lacks specificity for myocarditis and shows insufficient sensitivity in cases with no evident changes in cardiac structure and function [28].

Prognosis and follow-up biomarkers of echocardiography

Clinical evidence on prognostic biomarkers with respect to ICI-related myocarditis is extremely scarce. The global longitudinal strain (GLS) of feature tracking was first used in echocardiography to assess the predictive value of subsequent cardiomyopathy in several recent studies involving patients with cancer, thereby shedding light on cardiotoxic chemotherapy [29, 30]. In a large retrospective case-control study, which compared echocardiography GLS using speckle tracking at manifestation with ICI-related myocarditis (cases, n = 101) with patients receiving an ICI and who did not develop myocarditis (controls, n = 92), the results showed that the risk of MACE was higher with a lower GLS among patients with either a reduced or preserved EF [31]. After adjusting with LVEF, each percent decrease in GLS was associated with an increased risk of subsequent MACE among cases with a reduced ejection fraction (EF) (hazard ratio (HR): 1.5; 95% confidence interval (CI): 1.2-1.8) and cases

Table 2. Published research on cardiac imaging of ICI-associated cardiotoxicity

Technique	Study type	Study population	Variable analyzed	Outcomes	Findings
Echo [31]	Retrospective cohort study	101 patients with ICI-related myocarditis and 92 patients without ICI myocarditis	Global longitudinal strain (GLS)	MACE	Significant decrease in GLS 20.3% ± 2.6% to 14.1% ± 2.8% ($p < 0.001$). GLS was independently associated with MACE in patients with a reduced EF (HR 1.5, 95% CI: 1.2-1.8) and patients with a preserved EF (HR 4.4, 95% CI: 2.4-7.8).
CMR [35]	Retrospective cohort study	103 patients with ICI-related myocarditis	LGE, T2-weighted STIR	MACE	LGE was present in 48%, and elevated T2-weighted STIR was present in 28% overall. The presence of LGE, LGE pattern, or elevated T2-weighted STIR were not associated with MACE.
CMR [38]	Retrospective cohort study	136 patients with ICI-related myocarditis, 86 cases had T1 maps, 79 cases had T2 maps	T1/T2 mapping	MACE	Significant increase in native T1 (1079.0 ± 55.5 ms vs. 1000.3 ± 22.1 ms; $p < 0.001$) and T2 (56.2 ± 4.9 ms vs. 49.8 ± 2.2 ms; $p < 0.001$) values. Native T1 values had excellent discriminatory value for MACE (AUC = 0.91, 95% CI: 0.84-0.98). Native T1 values (HR: 1.44; 95% CI: 1.12-1.84) were independently associated with MACE.
CMR [39]	Prospective study	22 participants planned ICI therapy	Multiparametric cardiac MRI	NA	Significant increased features of diffuse myocardial edema (T1, 972 ms ± 26 vs. 1006 ms ± 36 [$P < 0.001$]; T2, 54 ms ± 3 vs. 58 ms ± 4 [$P < 0.001$]). Significant decrease in GLS (-23.4% ± 4.8% vs. -19.6% ± 5.1%, $P = 0.005$). Small pericardial effusions were more evident (4.5% vs. 45.5%; $P = 0.004$).
CMR [40]	Retrospective cohort study	33 patients with ICI-related myocarditis and 21 patients without ICI myocarditis	T1/T2 mapping, LGE, ECV	MACE	Significant increase in native T1, ECV, and T2 z-scores (0.03 ± 0.85 vs. 1.79 ± 1.93 [$P < 0.001$]; 1.34 ± 0.57 vs. 2.59 ± 1.97 [$P = 0.03$]; and -0.76 ± 1.41 vs. 0.88 ± 1.96 [$P = 0.002$]). LGE was more frequently observed (81.8% vs. 9.5%; $P < 0.001$). Septal LGE was independently associated with MACE (adjusted HR, 2.7, 95% CI: 1.1-6.7; $P = 0.03$).
CMR [41]	Retrospective cohort study	52 patients with ICI-related myocarditis	GLS, GCS, GRS	MACE	The GLS was independently associated with MACE (adjusted HR: 2.12; 95% CI: 1.38-3.25; $p = 0.001$). GLS was independently associated with MACE among patients with a preserved EF (adjusted HR: 1.36; 95% CI: 1.01-1.83; $p = 0.045$).
PET-CT [48]	Retrospective study	26 patients received ICI therapy, 3 patients with suspected myocarditis, and 23 patients without myocarditis	standardized uptake values (SUV)	NA	^{68}Ga-FAPI was found to be a potential early marker of ICI myocarditis with a median SUV of 1.79 (IQR 1.65-1.85) in myocarditis patients vs. 1.15 (IQR 0.96-1.52) in non-myocarditis patients.
PET-CT [49]	Retrospective study	11 patients had clinically suspected ICI-related myocarditis, 9 underwent ^{68}Ga-DOTATOC PET/CT	myocardium-to-background ratio (MBRpeak)	NA	All nine patients with ^{68}Ga-DOTATOC PET/CT presented with pathological myocardial uptake in the LV (MBRpeak of 3.2 ± 0.8, range 2.2-4.4). In 5/6 (83%) patients presented with concomitant myositis, pathological uptake was seen on whole-body images in the skeletal muscles.

Abbreviations: HR = hazard ratio; CI = confidence interval; AUC = area under the curve; LGE = late gadolinium enhancement; STIR = short tau inversion recovery; GLS = global longitudinal strain; CMR = cardiac magnetic resonance; PET-CT = positron emission tomography-computed tomography; ICI = immune checkpoint inhibitor; MACE = major adverse cardiac events; EF = ejection fraction; ECV = extracellular volume fraction; GCS = global circumferential strain; GRS = global radial strain.

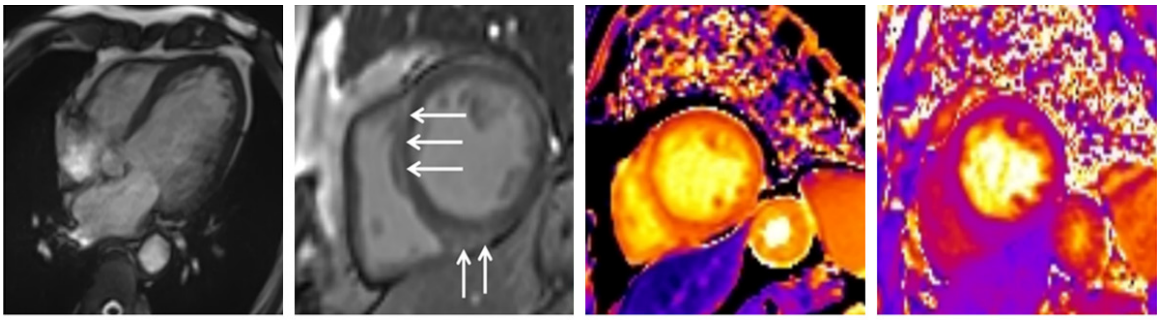

Figure 1. Multiparameters of CMR imaging in a patient with confirmed ICI-related myocarditis. Cine showed decreased LVEF (28.3%) and RVEF (40.6%). LGE revealed patchy areas of enhancement in the septal and inferior walls. Mapping sequences showed an overall value of 1413 ms on T1 mapping and an overall value of 43 ms on T2 mapping. ICI = immune checkpoint inhibitor, LVEF = left ventricle ejection fraction, RVEF = right ventricle ejection fraction, LGE = late gadolinium enhancement.

with a preserved EF (HR 4.4, 95% CI: 2.4-7.8). These findings suggested that feature-tracking GLS is a useful marker of poor prognosis in patients with cancer having ICI-related myocarditis.

Diagnostic accuracy of CMR

CMR is the primary imaging technique for the diagnosis of myocarditis, and it provides multiple unique advantages compared with echocardiography. Thus, CMR is an important tool for the assessment of patients with clinically suspected myocarditis. The advances in CMR tissue characterization techniques can be used as a surrogate for monitoring changes in myocardial tissue characteristics under different phases of myocardial injury. Comprehensive study findings on CMR have been described as the "Lake Louise Criteria" for the diagnosis of acute myocarditis [22, 23]. Since the advent of this standard, considerable progress has been achieved in the application of quantitative tissue characterization means such as T1 and T2 mapping [32, 33].

CMR is a critical detection tool in patients with suspected ICI-induced cardiotoxicity. Higgins et al. observed that despite the lack evidence regarding left ventricular impaired function, abnormalities in the T2 signal, left ventricular strain, and the presence of late gadolinium enhancement (LGE) can identify ICI-induced cardiotoxicity [34]. An international registry study enrolled 103 participants with ICI-related myocarditis [35]. LGE was found in 48% of all cases; elevated T2-weighted short tau inversion recovery (STIR) was reported in overall 28% of cases; myocardial edema evaluated using T2-weighted STIR was observed in 28% of all cases. The anteroseptal, inferoseptal, inferior, and inferolateral segments were the main distribution segments of LGE. The mean value of extracellular volume fraction (ECV) was 34.3% ± 2.1% in patients with ICI-related myocarditis, which was higher than normal ECV values of 25.3% ± 3.5% [35, 36]. However, a normal CMR with normal T1 and T2 values and negative LGE signs cannot be excluded from the diagnosis of ICI-related myocarditis [35, 37]. Another retrospective study from an international registry enrolled 136 patients with ICI-related myocarditis [38]. Native T1 (1,079.0 ± 55.5 ms vs. 1,000.3 ± 22.1 ms) and T2 (56.2 ± 4.9 ms vs. 49.8 ± 2.2 ms) values were higher than normal T1 and T2 values. Increased T1 and T2 values were noted in 78% and 43% of all cases, respectively. Following the revised Lake Louise Criteria, 95% fulfilled the diagnostic criteria of nonischemic myocardial injury, and 53% fulfilled the diagnostic criteria of myocardial edema [23, 38]. These findings indicated that the detection of abnormalities by employing tissue characterization techniques can help elucidate the underlying myopathic process, highlighting the application of CMR in conducting this challenging diagnosis and management (**Figure 1**).

CMR can also be used to detect the extent of subclinical cardiac effects associated with ICI treatment. In a prospective study involving 22

patients who were to undergo ICI therapy, CMR was applied to evaluate cardiac characteristics, including myocardial edema, myocardial strain, LGE, and T1 and T2 relaxation times [39]. After a median follow-up time of 3 months, the participants presented with elevated markers of diffuse myocardial edema (T1 relaxation time, 972 ms ± 26 vs. 1006 ms ± 36 [P < 0.001]; T2 relaxation time, 54 ms ± 3 vs. 58 ms ± 4 [P < 0.001]). Left ventricular mean systolic longitudinal strain declined at follow-up CMR (-23.4% ± 4.8% vs. -19.6% ± 5.1%, P = 0.005). New emerging nonischemic LGE lesions were noted in two (9%) participants. These findings suggested a high load of acute cardiac response in patients with cancer treated using ICI, indicating the requirement of careful cardiologic surveillance during ICI therapy, which may help prevent severe fulminant courses of ICI-induced cardiotoxicity. The monitored high load of subclinical acute myocardial toxicity may also have important indications for appropriate treatment-related decision-making.

Prognosis and follow-up biomarkers of CMR

The characteristic findings on CMR were potentially assessed as prognostic markers in patients with cancer having ICI-related myocarditis. After a median follow-up of 149 days, Zhang et al. observed that the presence of LGE, LGE pattern, or elevated T2-weighted STIR signal did not correlate with subsequent MACE [35]. In a multivariate model, a decreased LVEF was significantly associated with a higher risk of subsequent MACE (HR: 2.07; 95% CI: 1.10-3.93). However, in a review of 88 cases with ICI-related myocarditis, LVEF was not a marker of poor prognosis [14]. After a median follow-up of 158 days, Thavendiranathan et al. found that native T1 values had significant predictive value for subsequent MACE, with an area under the receiver operating characteristic curve (AUC) of 0.91 (95% CI: 0.84-0.98) [38]. Native T1 values (HR: 1.44, 95% CI: 1.12-1.84) were independently associated with subsequent MACE. In a retrospective study of 33 patients with ICI-related myocarditis, CMR was used to evaluate cardiac LGE patterns, T1/T2 mapping, and ECV [40]. After a median follow-up of 1 year, septal LGE was found to be the only CMR marker of subsequent MACE after adjusting for peak troponin (adjusted HR: 2.7; 95% CI: 1.1-6.7). In a recent retrospective study involving 52 patients with ICI-related myocarditis, GLS assessed by CMR was also reported as an independent factor associated with the increased risk of subsequent MACE (adjusted HR: 2.115; 95% CI: 1.38-3.25) [41]. The above findings indicated that CMR markers help predict the prognosis of ICI-related myocarditis. However, their clinical utility should be validated by large prospective studies.

Molecular imaging aided the early identification of ICI-induced cardiotoxicity

Molecular imaging has attempted to investigate distinctive biological processes occurring in the heart in vivo and holds the promise of early and specific diagnoses [42, 43]. Emerging molecularly targeted tracers in molecular imaging can help in the evaluation of processes such as inflammation, fibrosis, and protein expression [44]. These processes may aid in the early recognition of ICI-induced cardiac signs.

Identification of primary inflammatory cell changes, such as those in macrophage and T lymphocyte, prior to cardiac injury can help prevent the morbidity and high mortality associated with ICI-induced cardiotoxicity. Molecular targeted probes for specific detection and assessment of T cells status may be a potential approach to identify an inflammatory response at the earliest stages of the disease, which can encourage patients to undergo a more appropriate treatment earlier and therapeutic efficacy monitoring [45, 46]. The expression of fibroblast activating protein (FAP), another potential warning marker of early stages of myocarditis, is significantly upregulated in patients with cancer, inflammation, and fibrosis [47]. ^{68}Ga-FAPI was an early radiotracer of ICI-related myocarditis with a median standardized uptake value (SUV) of 1.79 in patients with myocarditis (interquartile range (IQR): 1.65, 1.85) vs. a median SUV of 1.15 (IQR: 0.955, 1.52) in patients with myocarditis [48]. FAP imaging showed a promising capability in identifying the disease. However, its expression level in the myocardium of patients treated with ICIs remains unclear. In recent studies, positron emission tomography (PET)/CT showed a high sensitivity to assess ICI-related myocarditis, particularly at the early stage of the disease because patients may show negative CMR findings at this stage [49, 50] (**Figure 2**).

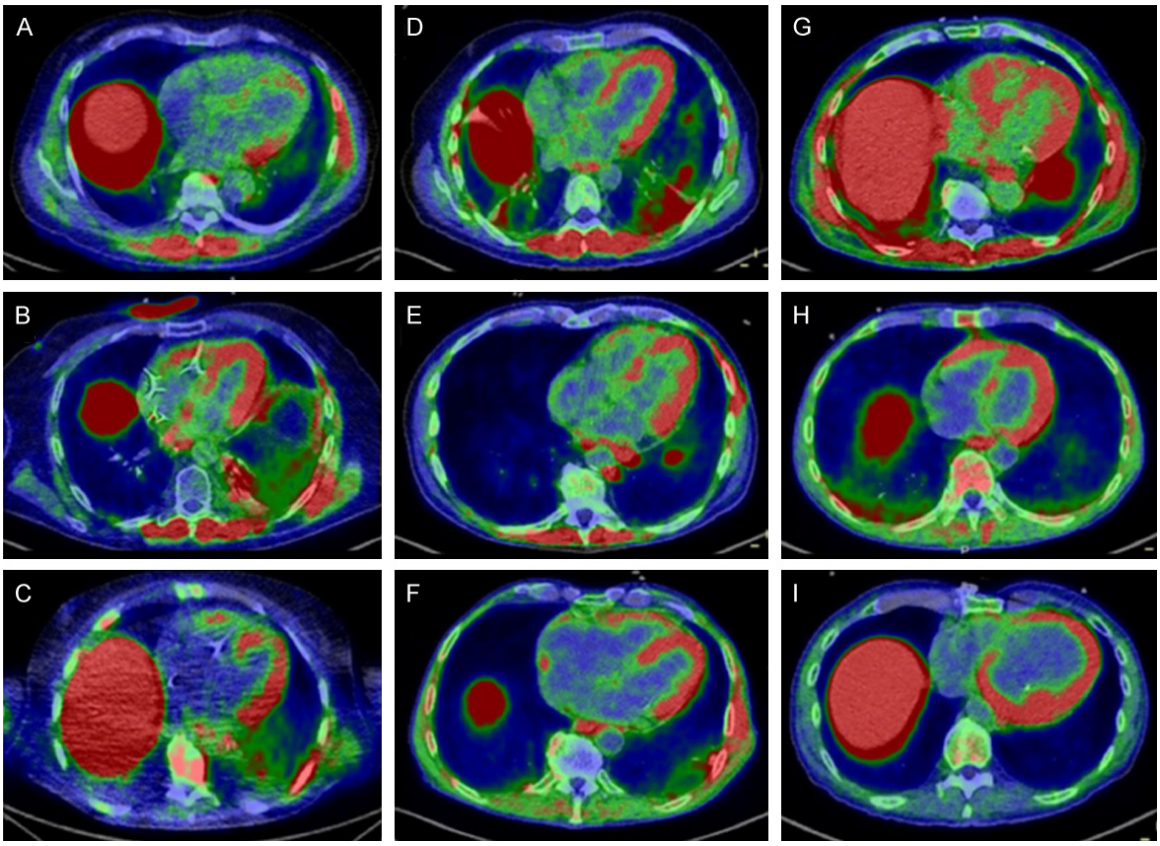

Figure 2. Fused ^{68}Ga-DOTATOC PET/CT images of patients with ICI-induced cardiotoxicity. Images show pathological uptake in the myocardium on the long axis of the LV. Picture published with permission from [49].

Molecular imaging aided risk stratification of ICI-related myocarditis

Another challenge associated with ICI-related myocarditis is the identification of patients who are at increased risk. PD1 as a molecular target of ICIs and its expression in the myocardium requires further research as a potential risk marker. ^{64}Cu-DOTA-pembrolizumab, as a PET radiotracer, can be used to evaluate the expression of PD1 in rodent hearts and on the surface of human blood cells and may be a potential avenue in such studies [51]. In addition, the expression of PD-L1 on the surface of a cardiomyocyte is upregulated in cardiac injury, indicating that the PD-L1 signaling pathway has a protective effect on cardiac immunologic regulation [52]. Therefore, tracers targeting PD-L1 may be useful for identifying potential patients having a myocardial risk of ICI [53].

Clinical insight

From a clinical standpoint, a multitude of techniques can assess cardiac changes, which correlate with the histologic construct of ICI-related cardiac injury (**Figure 3**). Regardless of this, the diagnosis of ICI-related myocarditis is still challenging, and the primary objective is to conduct an early assessment because no predictive markers are currently available to discriminate between patients prone to this disease and those who are not. Clinicians should be aware of potential advantages and findings derived from every single methodology and their costs and potential side effects. They should also be aware of the largely anecdotal correlation of such disparate techniques with clinical events. Most of the proposed approaches are limited to small-sample, single-center experience or retrospective research and to center preferences in the use of available information for practical decision-making. Based on a head-to-head comparison of the specific features of different techniques, CMR-based techniques have the potential for gathering information on most of the physical, biological, and histopathological changes of ICI-related myocarditis. In contrast, molecular imaging has the

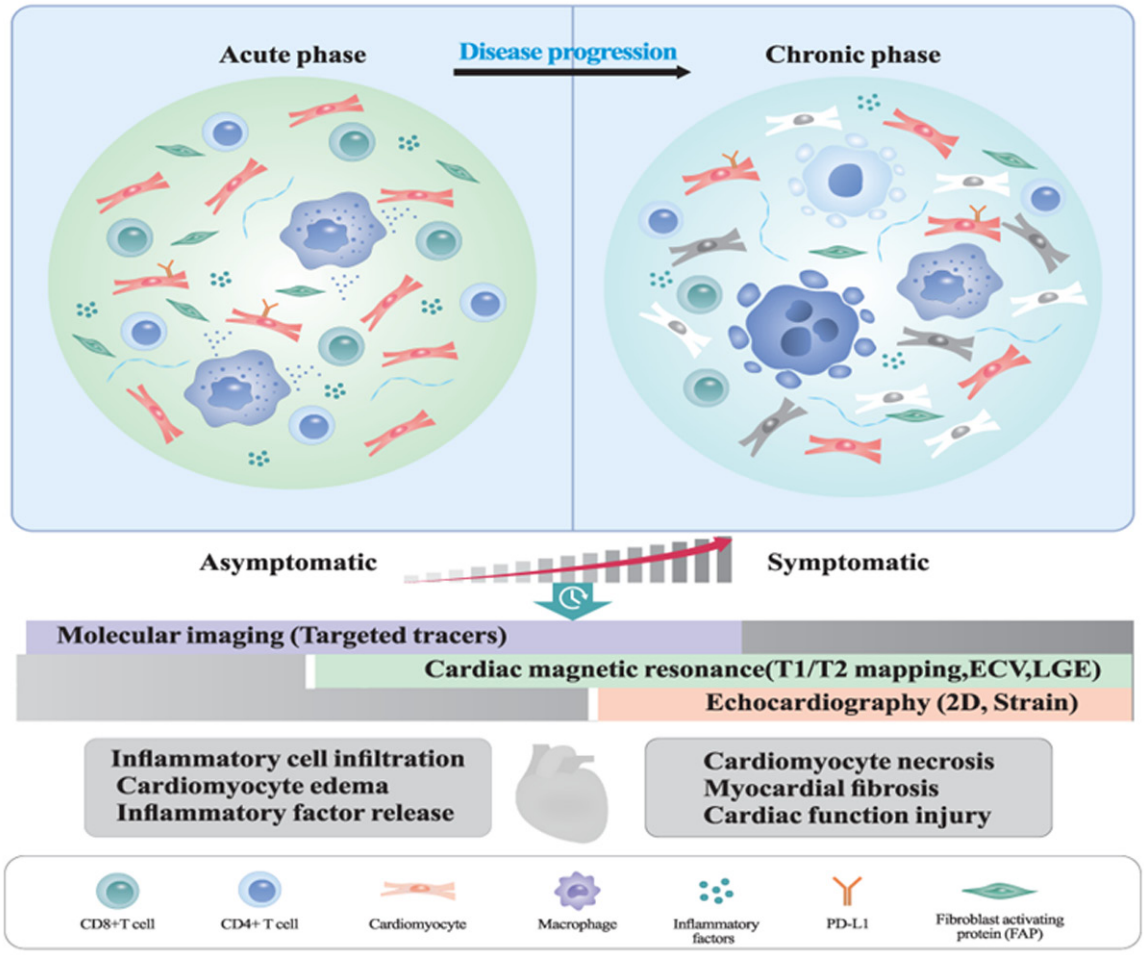

Figure 3. Medical imaging techniques in the assessment of ICI-related cardiotoxicities. At the early stage of this condition, the main changes in the myocardium were predominantly CD4+/CD8+ T lymphocytes and a few macrophages infiltration and increased the release of inflammatory factors. Molecular imaging techniques, based on molecularly targeted probes, facilitate the assessment of early cardiotoxicities, and may reflect increased risk of ICI-related myocarditis. As it progresses, the disease involves cardiomyocyte necrosis, myocardial fibrosis, and impaired cardiac function. CMR uses tissue characterization assessments, such as T1/T2 mapping, ECV, LGE, and cine, to evaluate myocardial fibrosis patterns and cardiac function. In addition, CMR biomarkers can be used predict the prognosis of ICI-related myocarditis. Echocardiography can be used to evaluate regional and global strains to assess signs of ICI-related myocarditis. ICI = immune checkpoint inhibitor; ECV = extracellular volume fraction; LGE = late gadolinium enhancement.

potential to identify cases at high risk of experiencing ICI-related cardiac injury at the earliest stages. The advantage of ultrasound-based techniques, compared with CMR and molecular imaging and owing to radiation exposure of molecular imaging and their costs, is their real-time repeatability in a clinical setting where serial assessments are an extremely frequent need for clinical decision-making.

Future research directions

Either monotherapy or combination immunotherapy can result in adverse effects on the heart. Although the incidence of ICI-related myocarditis remains relatively infrequent, clinicians must be aware of this adverse condition because of its high mortality rate. The assessment of ICI-related myocarditis depends on a combination of the clinical syndrome, ECG, myocardial enzyme test, and imaging criteria. Among these diagnostic methods, medical imaging significantly contributes to optimizing clinical decision-making, including diagnosis, treatment, and outcomes. However, recently published American and European guidelines dealing with the management of this condition do not depict any diagnostic procedures [54,

55]. Echocardiography, CMR, and molecular imaging are the commonly used techniques for the assessment of myocarditis and evaluation of the extent and severity of myocardial lesions [56]. Given the high mortality associated with ICI-related myocarditis, studies should seek the development of scientifically proven clinical/imaging algorithms to specifically identify small cohorts of patients at a high risk of this condition. In addition, a better capability to predict the development of ICI-related myocarditis using one or several imaging techniques would eventually allow a scientifically proven diagnostic path and possibly more focused systemic (drugs) or local therapeutic approaches. Here, multiparametric imaging in prospective studies comparing the yield of complementary but also inevitably expensive, techniques variously proposed in the literature should be undertaken, possibly including recent advances from machine learning [57, 58]. In this respect, artificial intelligence has a significant potential role after improvements in this field have paved the way for creating novel modeling and forecasting disciplines for clinical application [59]. By unbiased creation of risk models that incorporate multiple parameters from different imaging techniques without a priori selection of those features, deep learning may provide the capability to identify patterns of imaging information that improve risk stratification [60-62].

Conclusions

Echocardiography remains an easily available preliminary assessment that can offer important cardiac structural and functional information on acute myocarditis. Speckle tracking has improved the early detection of echocardiography. Advances in CMR have strengthened its utility as a high accuracy technique for detection in this setting. Except for routine evaluation for cardiac edema, fibrosis, and necrosis, novel emerging quantitative tissue characterization techniques have significantly improved the overall sensitivity and specificity for assessing acute myocardial injury. Advances in molecular imaging may help in determining the underlying causes and help guide targeted treatments. However, the imaging biomarkers of early identification, differential diagnosis, and prognosis prediction of ICI-related myocarditis still need to be clarified and validated using additional research. In addition, promoting the translation from basic to clinical studies may further help improve cardiovascular prognosis in patients with cancer having ICI-induced cardiotoxicity.

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Disclosure of conflict of interest

None.

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