ORIGINAL ARTICLE Cardiac Imaging

MRI in cardio oncology: a two years' experience, preliminary results

Marousa Ntouskou, Rebecca Dobson*, Jay Wright*
Department of Radiology, Liverpool Heart and Chest Hospital, Liverpool, UK
**Department of Cardiology, Liverpool Heart and Chest Hospital, Liverpool, UK*

SUBMISSION: 14/02/2022 - ACCEPTANCE: 15/03/2022

ABSTRACT

Cardio oncology is a new subspecialty, already counting three years of massive expansion following the amazing improvements in the field of cancer treatments.
Imaging is the key part in the diagnosis and follow up of the oncologic patient.
The role of MRI in cardiac imaging is well-known and established. MRI is the gold standard for functional analysis but also the only method providing a non-invasive tissue characterization.
The impact of anthracycline therapy in the heart is well known. Long term myocardial fibrosis and left ventricular functional impairment appears to be irreversible and heart failure difficult to respond to treatment if it is diagnosed in a late stage. Early detection can alter and improve patient's prognosis.
Immune check -point inhibitors [ICI] induced myocarditis is a life-threatening complication, which requires early diagnosis and urgent treatment.
Sometimes clinical signs and biomarkers are not sufficient to provide a definite diagnosis.
Primary cancers of the chest or heart, direct invasion of the heart or metastasis in the myocardial muscle need an accurate diagnosis.
MRI can be the key imaging modality for risk assessment, diagnosis and follow up of cardiotoxicity related to treatment, and in oncologic patients with types of cancers affecting the heart, primarily or secondary.
The established T2 weighted images can detect myocardial oedema, the use of Late Gadolinium Enhancement sequences and recently the use of mapping can offer an intrinsic view of the changes in the myocardial muscle in patients under cancer treatment.
More data are required to define the imaging protocols and further analysis and correlation of the imaging with the clinical history of the disease and the histological findings.

KEY WORDS: Cardiac MRI; immune check-point inhibitors [ICI]; cardiotoxicity; cardiac mapping; anthracycline cardiotoxicity

CORRESPONDING AUTHOR, GUARANTOR
Marousa Ntouskou
E-mail: Marousa.ntouskou@lhch.nhs.uk

Introduction

In the last 10 years there is a massive expansion in the oncologic imaging.

New cancer treatments and new strategies in the management of the heart failure have contributed to a significant improvement in the surveillance of the oncologic patients, and the prolongation of their life expectancy.

Imaging always plays an important role in the diagnosis and follow up of the oncologic patient.

Cancer treatments, including radiotherapy in the chest can be cardiotoxic and result in permanent impairment of the cardiac function or in acute and potentially fatal inflammatory reaction of the cardiac muscle.

Anthracyclines is used as a treatment to a wide spectrum of carcinomas, including breast, small cell lung, oesophagus, stomach, liver and thyroid, in leukaemia, lymphoma and sarcomas.

The anthracycline related cardiotoxicity is well known and can present as symptomatic heart failure or an asymptomatic decline in the functionality of the left ventricle [1].

The extension of the cardiac impact is related to the dose of treatment and concomitant use of radiotherapy and trastuzumab is known to increase the risk of adverse cardiac events.

Anthracycline induced cardiotoxicity was thought to be irreversible. But recent studies have shown that early medical therapy for heart failure can improve outcomes and prevent progressive left ventricular dysfunction [2].

Immune checkpoint inhibitors [CIs] are novel therapies and according to recent data can be used in up to 36% of the cancer patients. The use of ICI therapies is rapidly expanding, combination of treatments is under investigation and the use of ICI in earlier stages of certain types of cancer has been already approved [3].

ICI induced myocarditis is a known complication, it should be suspected in any new cardiac symptoms, and prompt investigation should start as soon as possible [4].

The results of many studies have suggested that ICI-induced myocarditis presents early after starting treatment, but there is a wide variation from 2-454 days.

Risk factors for ICI-induced myocarditis are the age of the patient, the cancer type (renal, lung cancer), comorbidities like diabetes and liver disease.

The risk of myocarditis increases when a combination of therapies is used compared to monotherapies [5].

Cardiotoxicity requires an accurate assessment of the functionality of the ventricles and detection and characterization of the changes in the composition of the myocardial muscle.

Electrocardiogram and cardiac biomarkers are the initial tests in cardiac assessment.

Echocardiography with global myocardial strain assessment (GLS) is the first imaging modality and when available can be used as a baseline scan but also for the follow up of the patients [6,7].

Unfortunately, echocardiography depends on the user and the body habitus of the patient.

A variability of 10% between the users is confirmed by many studies and a bad echo window is not so rare.

MRI is the only non-invasive imaging tool to provide functional assessment of the heart, flow studies and tissue characterization. The intrinsic characteristics make MRI a unique tool for diagnosis and follow up of the oncologic patient.

Assessment of cardiomyopathy induced by cancer treatment should include [8]:

a. Functional evaluation and volumetry of the left ventricle

Cardiac MRI is the reference standard in the assessment of the functionality and the volumetry of the left ventricle.

Cardiotoxicity has as a result reduced contractility of the wall of the left ventricle, and reduced end systolic volumes.

An increase of the end diastolic volume can happen as a response and remodelling of the left ventricle to preserve the ejection fraction and the cardiac output.

In end stage cases of cardiotoxicity an increase in the end diastolic volume of the left ventricle can appear in 16%-19% of the patients under chemotherapy and is a sign of exhaustion of the cardiac muscle.

b. Characterization of the tissue composition of the myocardial muscle.

Definite diagnosis of a primary cardiac tumour or a cardiac metastasis or a direct invasion of the cardiac muscle by a chest tumour can only be done by a myocardial biopsy.

Cardiac biopsy can confirm or exclude the presence of chemotherapy and ICI -induced cardiotoxicity.

Cardiac biopsy is an invasive, not easy and sometimes not available method and can be reserved for non-conclusive cases.

MRI can be the alternative diagnostic imaging ap-

proach. Tissue characterization is the intrinsic strength of the MRI.

Cardiac MRI allows the use of dedicated sequences to detect myocardial oedema, focal or diffuse fibrosis.

T2 weighted images, STIR and T2FS sequences, ECG triggered, are designed to detect myocardial oedema.

Cardiac mapping is one of the emerging techniques in cardiac MRI, allowing a non-invasive quantitative analysis of the myocardial diseases.

Mapping sequences offer a reliable pixel-based measurements of myocardial longitudinal and transverse relaxion time.

Specific mapping parameters, T1, T2, T2*can detect diffuse myocardial pathologies [11].

T2 mapping is used to assess myocardial oedema and infiltrative pathologies like deposition of siderosis that reduce the myocardial T2 time.

Extensive research has proved that there is correlation between T1 mapping values and the presence and degree of diffuse interstitial myocardial fibrosis [12].

Materials and methods:

In the last two years we examined 54 oncologic patients. 21 of them had a clinical and biochemical suspicion of ICIs myocarditis.

Patients presented with symptoms of new chest pain, palpitations, fatigue, breathlessness, ECG changes and elevation of troponin and BNP.

27 patients had a history of treated cancer in the past with use of anthracyclines and /or radiotherapy or had been under chemotherapy for a long time and were diagnosed with ventricular functional impairment. 10 of them needed further chemotherapy and MRI was requested as a base line assessment for further treatment decisions.

8 patients were referred for an MRI scan to assess their disease progression. These cases included a primary sarcoma of the right cavities, 2 patients with stage 4 lung cancer and 5 patients with metastatic disease in the chest. The primary tumours were sarcoma, renal and oesophageal cancer and lymphoma.

Two MRI scanners were used: 1.5Tesla MAGNETOM Aera and 3Tesla MAGNETOM Vida, Siemens Healthineers.

We used a multi-channel cardiac coil. All sequences were ECG triggered. In cases of inability to get sufficient ECG signal, a peripheral pulse was used.

The imaging protocol followed the update to the 2013 publication of the Society for Cardiovascular Magnetic Resonance (SCMR) Board of Trustees Task Force on Standardized Protocols.

We performed a functional and structural assessment of the heart which was followed by tissue characterization.

The protocol to assess myocarditis was based on the 2018 Lake Louise Criteria (LLC) [9,10].

Our imaging protocol included:

1. cine SSFP images in 2ch, 4ch, 3ch and short-axis views

2. T2 STIR (short inversion time inversion-recovery sequence) in short-axis view, 2ch and 4ch using the 1.5Tesla scanner and T2 weighted fat suppression (T2FS) images using the 3Tesla scanner.

3. Intravenous administration of gadolinium-based contrast agent, early and late gadolinium enhancement (LGE) sequence, 2D PSIR in all planes. Inversion time (IR) was determined by a TI scout sequence.

A bolus injection of 0.2mmol/kg of body weight of gadoburrol, (Gadovist; Bayer Healthcare, Germany) was administered.

4. T2 mapping, GRE single shot FLASH sequence in short axis and 4ch view.

5. T1 mapping I, using a single shot True FISP IR sequence in short axis and 4ch view.

Images were analysed using Syngo via, the dedicated software for cardiac analysis.

For the assessment of the STIR and T2FS images apart from visual assessment for the presence of myocardial oedema, we calculated the T2 -ratio. A region of interest was drawn in the myocardial muscle and in a skeletal muscle. The subsequent signal intensity of the myocardial magnetic signal was divided by the signal of a skeletal muscle.

Oedema was diagnosed when the T2 ratio was ≥2.

In cases where there were artifacts in the T2W images we measured the signal in many segments of the wall of the left ventricle and we compared the values to the signal of the segments that appeared normal.

Myocardial T2 time was derived by multiple ROIs. T2 values above 52msec for the 1.5T scanner and 44msec for the 3T scanner were considered abnormal and an indication for myocardial oedema.

The normal ranges of the native T1 myocardial time for our scanners were:

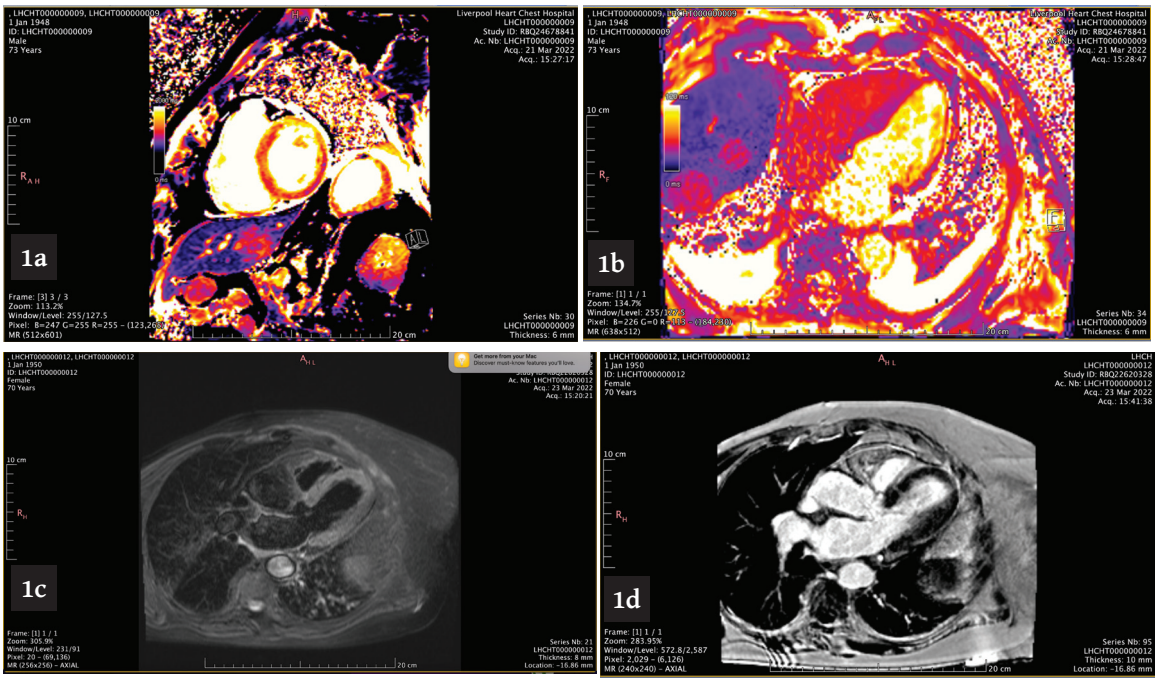

Figure 1a, b, c, d. *Metastatic renal cancer, immunotherapy induced myocarditis. Increased native myocardial T1 time in the anterior and lateral wall. Increased myocardial T2 time , indicative of oedema and acute inflammation correlated well with the increased magnetic signal in STIR images. Mild delayed enhancement and focal pericardial enhancement.*

1.5T scanner :947-1055msec, 3T scanner :1136-1263msec

Results

The present study included 54 patients. 21 patients were referred with the clinical suspicion of acute myocarditis.

In 12 patients the diagnosis of myocarditis was confirmed.

Myocardial oedema was patchy and did not follow a specific distribution.

The T2 maps correlated well with the morphological T2FS and T2 STIR images.

In cases where there were artifacts in the morphological images, we used the myocardial T2 time to confirm or exclude myocardial oedema.

The native T1 myocardial time was elevated in all myocarditis cases.

All oedematous areas showed diffuse mild early enhancement of the myocardium.

In the LGE images enhancement was patchy, mild and showed different patterns of distribution. The enhancement was mid wall or subepicardial, or both. **(Figure 1a, b, c)**

Only in one patient a subendocardial lesion was detected. The pattern was like a small myocardial infarct, the reason of this lesion of ischemic type was unclear.

In one patient treated for metastatic melanoma, myocarditis lesion was focal and showed rim enhancement and central necrosis.

In two of the myocarditis cases, a small amount of pericardial fluid was detected. This was associated with a smooth enhancement of the pericardial layers, confirming the involvement of the pericardium.

In two patients with the clinical suspicion of myocarditis the first MRI scan was normal but after a week a follow up scan confirmed the presence of acute myocarditis. **(Figure 2 a, b)**

The second patient, with strong suspicion of ICI-induced myocarditis and a negative MRI scan, deteriorated rapidly and died without any further imaging assessment.

In 8 patients with the suspicion of myocarditis, no acute pathology was detected. The MRI scan was normal in 6 patients, in 2 cases there were findings of previous myocardial infarcts, and in 1 patient the appearances of the left ventricle could be related to a not well controlled hypertension.

27 patients were referred having a history of previous

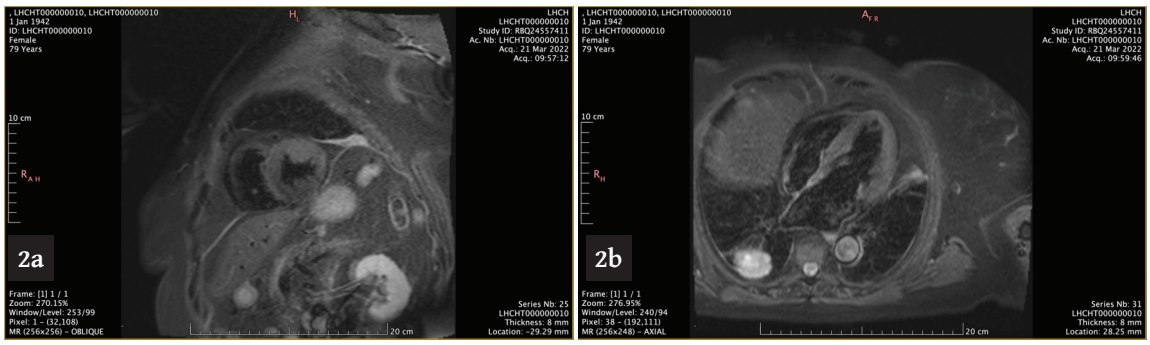

Figure 2a,b. *Metastatic lung cancer. STIR images showed increased myocardial signal related to oedema. Mild patchy areas of delayed enhancement and the enhancing primary mass are seen in the LGE images.*

treatment for a cancer and signs of functional impairment in echocardiography.

Functional analysis showed mild to moderate functional impairment in 20 patients.

Fibrosis was confirmed in these 20 patients. This was confirmed by an elevation of the native T1 time. LGE images showed enhancement and fibrosis in 15 cases. The pattern of enhancement was non ischemic, mid wall or subepicardial. **(Figure 3a, b)**

No myocardial oedema was seen in the STIR and T2 FS images, the myocardial T2 time was within the normal limits in all patients referred for post treatment cardiac assessment.

The remaining 8 patients were referred for an MRI scan for assessment of the extend of their disease. The borders of the tumour, the relation to the cardiac cavities and compression phenomena were accurately assessed.

In three patients an intracavitary thrombus was detected.

We extended the scanning protocol in patients referred for the assessment of their intrathoracic disease involving the cardiac structures. We added T1 weighted images before and after contrast.

The cardiac deposits were accurately assessed and there was clear differentiation of the tumour from the healthy myocardium and any concomitant thrombus. **(Figure 4 a, b, c)**

In a sarcoma case the compression of the cardiac cavities was confirmed, and myocardial infiltration was excluded.

The stability, regression or progression of the disease was accurately reported in all cases.

Discussion

Cardiac MRI is the gold standard in the functional evaluation of the left ventricle.

We obtained diagnostic images in all patients we examined.

We found diffuse cardiac fibrosis in 74% of the patient referred with a history of previous cancer treatment with anthracyclines and functional impairment of the left ventricle in the echocardiography.

None of these patients showed myocardial oedema or pathologic myocardial T2 time.

In these cases, functional parameters, derived from the cardiac MRI, were used as the baseline for future assessment predominantly in the patients who will get more treatment due to ongoing disease, progression or recurrence.

Management and optimization of the treatment protocols were based on the results of the cardiac MRI.

Unfortunately, there was no previous imaging, and this did not allow to differentiate between cardiotoxicity from other causes of myocardial fibrosis as valvular disease, coronary disease or previous episode of myocarditis.

57% of patients examined with the clinical question of ICIs induced myocarditis showed imaging findings of acute myocarditis.

High magnetic signal was detected on STIR and T2FS images in all patients.

There were three cases where T2 morphological images suffered from severe motion artifacts and diagnosis of oedema relied on the increased myocardial T2 time.

STIR images are very sensitive to motion artifacts and cardiac arrythmia which is not so uncommon in patients with suspected ICIs induced myocarditis.

In two cases STIR and T2FS images were abandoned as

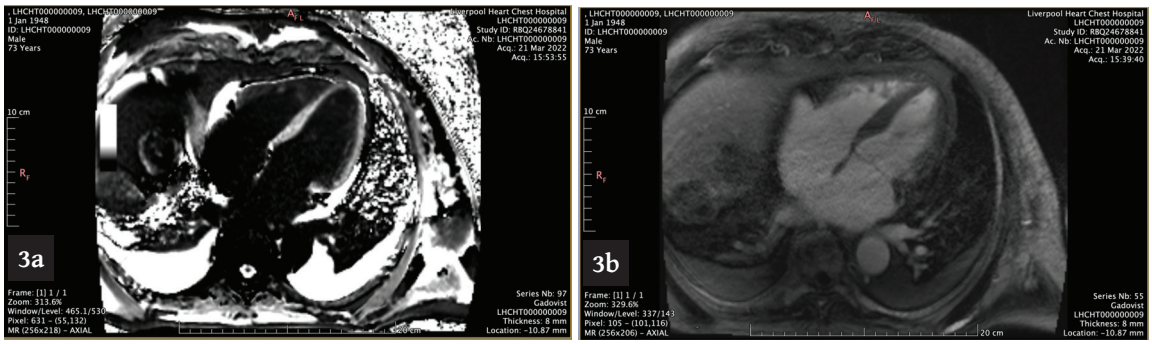

Figure 3a,b *Immunotherapy in 2020 for colonic cancer. Non ischemic, mild subepicardial fibrosis in the lateral wall, no myocardial oedema.*

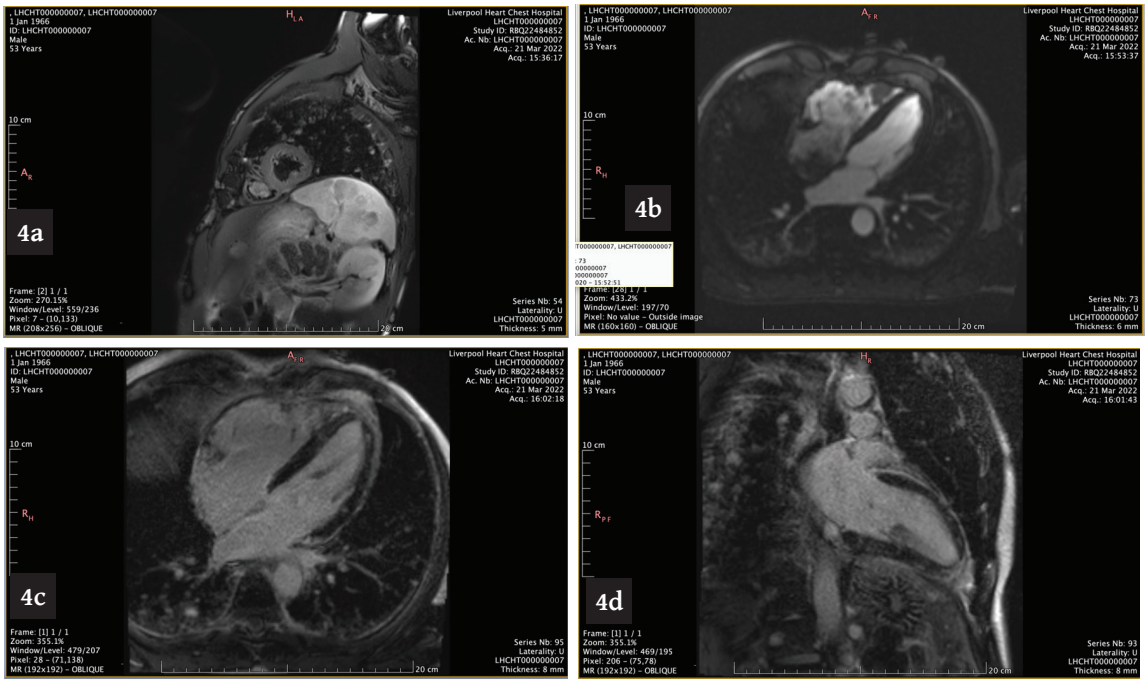

Figure 4a,b,c,d. *Metastatic melanoma. Extensive invasion of the wall of the right ventricle, associated with late gadolinium enhancement and a neoplastic thrombus in the apex of the right ventricle. Areas of enhancement in the wall of the left ventricle.*

patient could not comply with the breath hold requirement.

We used T2FS sequence for patients scanned in the 3T scanner and in some of the patients scanned in the 1.5T, as they are less prone to artifacts [13,14].

None of the positive for ICI associated myocarditis showed diffuse increased T2 magnetic signal. There were segments where the signal of the myocardium was visually normal.

Parametric mapping images were diagnostic in all patients. Increased native T1 and T2 myocardial time was used to confirm the diagnosis of acute myocarditis irrespectively of the presence or absence of LGE. As per the updated Lake Louise Criteria requirements, at least one T2 based and one T1 based positive finding are sufficient to establish the diagnosis of acute myocardial inflammation [15].

In 3 patients with clinical suspicion of ICI induced myocarditis and a negative MRI scan, we found signs of coronary artery disease and old myocardial infarcts.

In one patient there was hypertrophy of the left ventricle and diffuse fibrosis which could be related to an uncontrolled hypertension.

No further imaging was required in the 8 patients with negative MRI scan for myocarditis.

This study is a preliminary one and we did not per-

form any correlation between the level of the cardiac biomarkers and the time the MRI scan was performed.

Moreover, there was no correlation with the type of therapy, monotherapies or a combination of treatment.

A highly skilled radiographer, a robust protocol and a patient able to comply with the requirements of the scan are needed to perform a cardiac MRI scan.

All sequences of a cardiac MRI scan require a cooperative patient who can hold his breath for many times and stay still through the whole scan. The whole scan takes approximately 45minutes.

The quality of a cardiac scan depends massively upon the patient. Oncologic patients, who require a cardiac MRI scan can have symptoms from their primary and in many cases metastatic disease as well as symptoms from the cardiac involvement, like breathlessness.

They cannot lie down for long and they cannot hold their breath for less than 10 seconds.

This is a major challenge for a cardiac MRI in these cases.

The preparation of the patient is very important. Analgesia is necessary in cases of pain, optimised therapy before the scan to reduce the oedema, the symptoms of the heart failure and control as better as possible an unstable cardiac rhythm.

Oncologic patient is very sensitive. Spending some more minutes to explain the procedure and make them feel comfortable can massively help to increase the quality of the scan.

Cardiac scanning in 3T is challenging. The higher T1 values of the tissues at 3T are beneficial in angiography, perfusion and delayed enhancement images. But the reduction in the main field homogeneity and the increase in the susceptibility artifacts can reduce the quality of the STIR and fat suppression images.

On the opposite having two scanners available you can reduce the wating time for an MRI scan, which is crucial for an oncologic patient. The clinical situation can change within a few days and early diagnosis plays a major role.

Limitations

Limitations are the small number of the patients, the stage of the disease and the lack of any baseline imaging evaluation.

Our cohort of patients included clinically confirmed cases or highly suspicious for myocarditis.

Only one patient was scanned in a very early stage and no abnormality was identified.

In chronic cases the lack of a baseline assessment did not allow certain conclusions about the abnormalities noted in the scans.

None, apart from one, of our patients had any follow up scan.

Conclusion

MRI is a powerful tool in oncology, due to the high sensitivity and specificity to detect alterations in the tissues.

Cardiac imaging MRI is the only non -invasive method to assess the myocardial muscle. Cardiac MRI can accurately assess the functionality of the left ventricle and detect myocardial oedema and diffuse or focal myocardial fibrosis.

Myocardial oedema which is a common finding in the late stages of an inflammatory process as the ICIs induced myocarditis or cardiomyopathies is present in cases of acute myocardial inflammation as it happens in cases of ICI induced myocarditis.

Functional impairment and myocardial fibrosis are common findings in cases of cardiotoxicity due to chemotherapies.

Imaging protocols should be agreed and studies with a large number of patients and multicentric studies are needed to find ways to depict the patients at risk to develop cardiotoxicity, to explore ways to detect the early stage of the disease and provide an accurate follow up.

Histological approach is essential to understand the exact pathophysiology and how this is correlated with the imaging findings. ICIs induced myocarditis is an emergency and time plays an important role in the prognosis and the future of the patient.

Imaging of the oncologic patient requires dedication and combined skills in cardiac and oncologic imaging. Accurate diagnosis is needed to guide the cardiologist and oncologist to the right decision.

There are multiple publications, but we are still in the beginning of a very interesting and challenging field. **R**

Conflict of interest

The authors declare no conflict of interest

Abbreviations:

ICI =immune checkpoint inhibitors, LLC=Lake Louise criteria, BNP=B-type natriuretic peptide,
ROI=region of interest, LGE=Late Gadolinium Enhancement, GLS=Global Longitudinal Strain

References

1. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. *Heart* 2017. http://dx.doi.org/10.1136/heartjnl-2017-312103
2. Narezkina A., Nasim K., Anthracycline Cardiotoxicity. One step closer to reversing the irreversible. Circulation: Heart Failure, vol 12, No 3: e005910
3. Zhang L, Reynolds KL, Lyon AR, et al. The Evolving Immunotherapy Landscape and the Epidemiology, Diagnosis, and Management of Cardiotoxicity: JACC: CardioOncology Primer. *JACC CardioOncol*. 2021 Mar;3(1):35-47.
4. Arbune A., Soufer A., Baldassarre L.A. Clinical and Advanced MRI Techniques for Detection of Checkpoint Inhibitor Associated Myocarditis, *Current Cardiovascular Imaging Reports*, 2020, DOI: 10.1007/s12410-019-9521-5
5. Jain P., Jahir Guiterrez Bugarin, Guha A. et al., Risk factors for myocarditis associated with immune checkpoint inhibitors using real-world clinical data. *Journal of Clinical Oncology*, 2020;38 (15), e15100
6. Kang Y, Scherrer-Crosbie M. Echocardiography Imaging of Cardiotoxicity. *Cardiol Clin*. 2019 Nov;37(4):419-427
7. Kamphuis, J.A.M., Linschoten, M., Cramer, M.J. et al. Early- and late anthracycline-induced cardiac dysfunction: echocardiographic characterization and response to heart failure therapy. *Cardio-Oncology* 6, 23 (2020). https://doi.org/10.1186/s40959-020-00079-3
8. Kramer C.M., Barkhausen, J., Bucciarelli-Ducci, C. et al. Standardized cardiovascular magnetic resonance imaging (CMR) protocols: 2020 update. *J Cardiovasc Magn Reson* 22, 17 (2020). https://doi.org/10.1186/s12968-020-00607-1
9. Cundari, G., Galea, N., De Rubeis, G. et al. Use of the new Lake Louise Criteria improves CMR detection of atypical forms of acute myocarditis. *Int J Cardiovasc Imaging* 37, 1395–1404 (2021). https://doi.org/10.1007/s10554-020-02097-9
10. Luetkens L., Faron A., Isaak A. et al., Comparison of Original and 2018 Lake Louise Criteria for diagnosis of Acute Myocarditis: Results of a Validation Cohort. *Radiology: Cardiothoracic Imaging* 2019;1(3) e190010
11. Messroghli DR, Moon JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). *J Cardiovasc Magn Reson*. 2017 Oct 9;19(1):75.
12. Nakamori S, Dohi K, Ishida M, et al. Native T1 Mapping and Extracellular Volume Mapping for the Assessment of Diffuse Myocardial Fibrosis in Dilated Cardiomyopathy. *JACC Cardiovasc Imaging*. 2018 Jan;11(1):48-59.
13. Oshinski, John N et al. "Cardiovascular magnetic resonance at 3.0 T: current state of the art." *Journal of cardiovascular magnetic resonance*: official journal of the Society for Cardiovascular Magnetic Resonance vol. 12,1 55. 7 Oct. 2010, doi:10.1186/1532-429X-12-55
14. Prabhakar Rajiah, Michael A. Bolen. Cardiovascular MR Imaging at 3T: Opportunities, Challenges, and Solutions. Radiographics 2014; 34:1612-1635
15. Varricchi G., Galdiero M.R., Tocchetti C. Cardiac Toxicity of Immune Checkpoint Inhibitors, *Cardio oncology Meets Immunology Circulation* 2017 Nov; 136, (21): 1989-1992

Ready - Made Citation

Ntouskou M, Dobson R, Wright J. MRI in cardio oncology: a two years' experience, preliminary results. *Hell J Radiol* 2022; 7(1): 18-25.