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MINI REVIEW

Molecular Imaging in Oncocardiology

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Summary

Cancer and Cardiovascular Disease (CVD) are the most common causes of death and disability in many countries. Cancer and CVD are closely related in terms of both scientific and clinical perspectives. Oncocardiology has recently gained attention by oncologists, cardiologists, and radiologists for mutual work on pathophysiology analysis and treatment strategy [1-3]. In various clinical settings, these specialists may collaborate in the diagnosis and treatment of cancer patients with cardiovascular disease.

There are number of drugs applied to oncology therapy which may cause a variety of cardiotoxic effects. Significant progress in the development of new drugs, such as anthracycline and HER2 has led to the increasing use of cancer targeted therapy. Such new therapy has shown great improvements in prognosis in cancer, but also increased risk of severe cardiovascular toxicities. While wide application with new progress in the field of targeted therapeutics together with the growing number of long-term survivors after oncology therapy, the cardiotoxic side effects has become essential for the best possible oncocardiology treatment.

Immune Checkpoint Inhibitor (ICI) therapy has been developed as a new therapy by blocking immune-inhibitory signaling via the programmed death 1, or T lymphocyte associated protein 4 pathways [4]. The survival rate of various cancers has been greatly improved, particularly in melanoma and non-small cell lung cancer. But, ICI therapy is associated with the risk of immune-related adverse events (irAEs), including ICI-related myocarditis, which may cause cardiogenic shock and severe arrhythmia [4]. Increasing use of ICI therapy has unmasked further cardiotoxic side effects, including subclinical LV dysfunction or elevations in cardiac troponin, takotsubo syndrome, and pericardial disease [5]. Cardiac irAEs are commonly treated by immunosuppressive therapy.

Side effects on cardiovascular system should also been considered for radiation therapy. Intensified follow-up care of cancer patients is particularly important after radiotherapy after combined therapeutic approaches. Radiotherapy is associated with significant cardiovascular complications, such as pericarditis and long-term complications, such as restrictive or constrictive pericarditis, and therefore, it is important to realize that approximately 35% of cancer patients undergo radiotherapy within 1 year after diagnosis [6,7].

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Suitable diagnosis and assessment of cardiovascular toxicities has been the most important challenge for oncocardiology. There are number of techniques which has been used for detecting CVD and assessing its severity after cancer treatment. Measurement of serum biomarker, such as troponin, is valuable for detection of early signs of cardiotoxic effect during chemotherapy [8]. There are a number of non-invasive imaging modalities in oncocardiology which provide predominantly structural information of the heart. Including, echocardiography, CT, and thermally polarised MRI, and which provide information on the molecular level such as nuclear medicine and hyperpolarised MRI [9].

Echocardiography has been used as a gold standard in oncocardiology field [10]. Left Ventricular Ejection Fraction (LVEF) is often used as the main parameter for detecting changes in LV function. In addition, advanced assessment of Right Ventricular (RV) function by 3D-echocardiography is valuable for cardiotoxicity analysis [11]. New imaging techniques such as longitudinal strain on echocardiography, cardiac MRI, and nuclear imaging has recently gained attention in this field. Myocardial strain is expected to use for detecting early changes before heart function deteriorates. Recent meta-analysis study confirms a good prognostic performance of global longitudinal strain for subsequent LV dysfunction from anthracycline therapy [12].

Cardiac MRI is valuable for myocardial tissue characterization and it may depict structural changes in the myocardium, including signs of edema and inflammation, possibly prior to the LV dysfunction [13]. Cardiac MRI may be useful to identify perfusion defects similar to CT perfusion and radionuclide perfusion techniques. However, the main advantage of cardiac MRI is myocardial tissue characterization by using multiparametric imaging, such as late gadolinium enhancement to detect gross scar, T1 mapping to define interstitial fibrosis, and extracellular matrix expansion and T2 mapping to assess myocardial edema [14].

Nuclear medicine imaging has also been commonly applied for quantitative assessment of cardiovascular damages after cancer therapy [15,16]. Among various nuclear cardiology techniques, Positron Emission Tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) as a marker of glucose utilization shows oxidative stress and alterations in cardiac metabolism. In particular, accumulation of FDG is associated with an active inflammatory process, thus allowing for the activity of the inflammatory disease to be evaluated under fasting condition [17,18]. Patient preparation should be carefully done before the FDG administration, depending on the purposes of in-vivo functional imaging [19,20]. Post-prandial, glucose loading, or insulin clamp condition is applied for myocardial viability assessment where FDG is accumulated both in normal and ischemic but viable myocardium. On the other hand, long fasting condition with or without heparin administration is required for identifying active inflammatory lesions with suppressing physiological myocardial FDG uptake. The activation of granulocytes and macrophages during inflammation enhances the FDG uptake, and therefore, FDG PET is valuable for detecting active cardiovascular inflammation [21,22].

In oncocardiology field, FDG-PET has been used for identifying active myocarditis and vasculitis after chemotherapy, immunotherapy, and radiation therapy. Distinct patterns of FDG uptake, particularly in the RV, have been associated with anthracycline cardiotoxicity [23]. Furthermore, FDG-PET/CT provides an elegant approach for a simultaneous assessment of cardiovascular involvement and tumor response to therapy as well [23]. While cancer therapy-related cardiotoxicity remains the prime concern in patients suffering from cancer, the increased risk of vascular disease already posed by the cancer itself is further increased by those therapies. Vascular toxicities are the second most common cause of death in patients with cancer undergoing outpatient therapy. Number of studies suggested chemotherapy-related vascular side effects and radiotherapy-related vascular side effects [24]. Recent studies nicely suggested that FDG-PET/CT can identify unstable atherosclerosis and active vasculitis [25-27]. FDG-PET to apply for those with arteritis has recently been approved for insurance coverage in Japan [22]. While there remain limited clinical reports at present, FDG-PET should play an important role for identifying and managing active vasculitis after cancer therapy.

Another exciting molecular imaging biomarker is ^{123}I-meta-iodobenzylguanidine (^{123}I mIBG), a radiolabeled norepinephrine analogue. Cardiac neuronal function is compromised in various cardiac diseases, such as congestive heart failure, ischemia, arrhythmia, and some types of cardiomyopathy [28]. Tracer approaches are considered uniquely suited for radionuclide imaging-based in vivo characterization of neuronal function in the myocardium. The myocardial ^{123}I mIBG imaging is considered as a novel approach for assessing dysregulated presynaptic norepinephrine homeostasis which is a prognostic marker in heart failure [29-31]. Cardiac innervation imaging is preferable, which may accurately identify cardiotoxicity at a subclinical stage, before decrease in LVEF occurs. Early evidence suggests increasing ^{123}I mIBG washout as a marker for myocardial compensation to cardiotoxic injury from anthracycline exposure [32].

Oncocardiology represents an important new area that should be covered by multiple specialist teams. Imaging analysis can provide important insights in the early detection and monitor cardiotoxicity. Among them, molecular imaging should play an important role for precise assessment its pathophysiology and future treatment strategy of cardiovascular dysfunction after cancer therapy. Future studies are warranted to assess the promising potential of molecular imaging in oncocardiology.

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