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State-of-the-art modalities in cardio-oncology: insight from a nuclear medicine approach

Narges Jokar[1], Abdullatif Amini[2], Mohammadreza Ravanbod[3], Maryam Barekat[4], Hossein Shooli[1], Ali Gholamrezanezhad[5], Majid Assadi[1]

[1]The Persian Gulf Nuclear Medicine Research Center, Department of Molecular Imaging and Radionuclide Therapy (MIRT), Bushehr Medical University Hospital, Bushehr University of Medical Sciences, Bushehr, Iran
[2]Medical Heart Center, Faculty of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran
[3]Department of Internal Medicine, Persian Gulf Tropical Medicine Research Center, Bushehr University of Medical Sciences, Bushehr, Iran
[4]Department of Regenerative Medicine, Cell Science Research Center, Royan Institute for Stem Cell Biology and Technology, ACECR, Tehran, Iran
[5]Department of Radiology, Keck School of Medicine, University of Southern California, Los Angeles, United States

Abstract

Cancer and cardiovascular disease are the most significant causes of morbidity and mortality worldwide. Although the cancer survival rate has increased due to improved treatment approaches, especially targeted therapy, some side effects such as cardiotoxicity decrease the efficiency of the clinical outcome. Radiation therapy and chemotherapy have a long-established history of potential cardiotoxic effects. A new multi-disciplinary and translational field known as cardio-oncology has been developed for the identification, prevention, and treatment of cardiovascular dysfunctions associated with cancer treatment approaches. One of the important tools for detecting and monitoring cardiotoxic effects is non-invasive nuclear cardiac imaging techniques. Cardiac nuclear imaging modalities especially recent findings positron emission tomography (PET) tracers have a quintessential role in the early detection of cardiovascular disorders. Moreover, comprehensive studies are required to investigate novel nuclear medicine treatment approaches such as peptide receptor radionuclide therapy (PRRT), fibroblast activation protein (FAP), and chemokine receptor (CXCR) targeting probes for possible cardiac side effects that play important roles in the treatment of malignancies.

KEY words: cardiotoxicity; cardio-oncology; PRRT-related cardiotoxicity; nuclear medicine; FAPI; CXCR4; [^{99m}Tc]Sestamibi; [^{18}F]MitoPhos; [^{68}Ga]Galmydar

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Background

Cancer and cardiovascular disease are the most significant causes of morbidity and mortality worldwide [1]. Significant advances have been made in the early detection, treatment, and long-term survival of cancer patients. Importantly, each new therapeutic development has encountered specific challenges such as multi-organ adverse events [2]. Therefore, cardiovascular diseases and malignancies may coexist in these patients because of using combination treatment approaches in molecular oncology for better patient management [3].

Cardiotoxicity as acute and occasionally lethal cardiac events (chronic) related to cancer therapeutic methods occurs either during or immediately following treatment in patients exposed to mediastinal radiation therapy (RT) and anti-cancer drugs as well as decreases the efficiency of the patient's health outcomes. It is categorized into different subtypes (Type I and II) including cardiomyopathy, thrombosis, hypertension, left ventricular dysfunction, QT prolongation, oedema, arrhythmias, metabolic abnormalities, and capillary leak syndrome, which might lead to cardiovascular abnormalities, especially in elderly patients with pre-existing cardiovascular disease [4–9]. Some chemotherapy agents such as vinblastine, anthracyclines, ramucirumab,

Correspondence to: Majid Assadi
The Persian Gulf Nuclear Medicine Research Center, Department of Molecular Imaging and Radionuclide Therapy (MIRT), Bushehr Medical University Hospital, Bushehr University of Medical Sciences, 45654775 Bushehr, Iran
e-mail: assadipoya@yahoo.com

trastuzumab, cyclophosphamide, and 5-fluorouracil, can increase the risk of cardiovascular diseases in patients with different malignancies (breast, sarcoma, lung, bladder, gastric, prostate, leukaemia, lymphoma, etc.) [10]. Moreover, there are different reasons for radiation-induced cardiovascular dysfunction such as damage to cardiomyocytes as well as stimulating an inflammatory process in cardiac cells leading to the acceleration of atherosclerosis [11].

Cardio-oncology is a multidisciplinary clinical approach that improves awareness of monitoring and treatment methods in patients with cardiovascular complications related to cancer treatment [12]. According to The American Society of Echocardiography and the European Association of Cardiovascular Imaging, cardiotoxicity defines as a 10–15% early reduction in global longitudinal strain index [13].

One of the important tools for early detection and monitoring cardiotoxic effects are non-invasive imaging techniques. These techniques also give opportunities for the classification of therapeutic choices to improve patient management. Among these techniques, cardiac nuclear imaging modalities including planar multi-gated acquisition or multi-gated radionuclide angiography (MUGA), single-photon emission computed tomography (SPECT), and PET scans have demonstrated a significant role in the detection, screening during treatment, and monitoring of cancer treatment-related cardiotoxicities [14, 15].

Heretofore, chemotherapeutic agents were extensively assessed for cancer-therapy-related cardiotoxicity [9, 16]. On the other hand, recent developments in the field of nuclear medicine resulting in the introduction of new treatment modalities along with other common approaches require extensive investigations for probable side effects, including cardiotoxicity.

In this state-of-the-art review, the authors briefly present cancer treatment techniques that may induce cardiotoxicity and discuss nuclear cardiac imaging modalities used for detecting cardiotoxicity related to cancer treatment. New treatment modalities in the field of nuclear medicine are also evaluated in terms of potential cardiotoxic effects.

Cancer treatment approaches inducing cardiotoxicity

One of the unexpected adverse events of mediastinal RT is cardiotoxicity. The most important risk factors for radiation-associated heart failure include a delivered dose of more than 30–35 Gray (Gy), hyper-fractionated regimens including multiple dose fractions per day, exposure of an extensive volume of the heart to radiation, younger age, long-term survival, and some other patient characteristics such as obesity, family history of heart problems, diabetes, inactive lifestyle, dyslipidaemias, hypertension, and smoking [17]. Radiation-induced heart disease commonly occurs in patients with Hodgkin lymphoma, lung cancer, and breast cancer involving cardiac structures [18]. For many years, Hodgkin lymphoma patients used a traditional radiation therapy technique, known as the mantle technique, that induced cardiac disease and cardiotoxicity [19]. However, more developments resulted in less cardiac exposure to ionizing radiation, but cardiotoxicity remains a major concern in Hodgkin lymphoma [20]. Moreover, radiation therapy, as an adjuvant or neoadjuvant technique, has been used in more

than 50% of patients with breast cancer. In a meta-analysis carried out in 2005, the researchers found that cardiovascular-related mortality increased significantly (27%) in patients with combined treatment modalities including surgery and radiation therapy versus surgery as the only treatment modality [21]. Advanced modalities of high-precision RT techniques including intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), helical tomotherapy, prone and isocentric lateral decubitus (ILD) positions, breath-hold techniques, and proton therapy result in dose homogeneity, less cardiac exposure, and delivering lower doses to the heart and reduce adverse effects. The suitable selection of these techniques (alone or in combination) is based on the patient's characteristics, RT regions, and accessibility [22–33]. Although long-term follow-ups are needed to confirm the definitive role of these new techniques, clinical findings have been confirmed the positive effects of new radiation therapy techniques resulting in more precise treatment plans and decreased life-threatening effects including cardiotoxicity [34, 35].

Additionally, cardiac dysfunctions occur in a significant proportion of patients who receive chemotherapy. The pathophysiology of chemotherapeutic drug-induced cardiotoxicity is complex that involves multiple biochemical pathways and results in considerable efforts that have been made for early detection of cardiotoxic events. The most common drug classes that induce cardiotoxicity are anthracyclines (such as doxorubicin), alkaline agents (such as cyclophosphamide, ifosfamide), antimetabolite agents (such as 5-Fluorouracil (5-FU), and vinblastine [36]. Cardiac abnormalities mostly reduce left ventricular ejection fraction (LVEF) in more than 20% of the patients, which may not be detected until the final chemotherapy session [37, 38].

Monoclonal antibodies were developed as a basis for biological therapeutics for many cancers by Kohler and Milstein [39]. The main strategy of these drugs is anti-angiogenic treatment methods involving many factors such as vascular endothelial growth factor (VEGF). Bevacizumab, trastuzumab, ramucirumab, interleukin-2 (IL-2), and interferon-Alpha (INF) are the most common biological treatment agents for cancer patients that may cause cardiovascular toxicity (Tab. 1) [36, 40–43]. Some studies reported significant cardiotoxicity induced by bevacizumab in patients with breast cancer, renal cell carcinoma, and glioma [44–47]. Trastuzumab regimen is another monoclonal antibody that blocks the human epidermal growth factor receptor-2 (HER2 or ErbB2) in breast and gastric cancers including HER-2 positive receptors. In addition to improved disease-free survival, this drug induces acute cardiac disorders such as congestive heart failure and LV dysfunction as well as result in partial impairment in mitochondrial function and increased levels of oxidative stress (Fig. 1) [43, 48, 49].

Systematic studies and evidence-based recommendations are required to determine the early biomarkers of toxicity, risk-assessment models, monitoring, survivorship, prognostication of cardiotoxicity, and suitable treatment options for elderly people with malignancy that receive potentially cardiotoxic regimens.

Specifically, non-invasive and cost-effective diagnostic tools such as imaging have a high priority in detecting early cardiovascular disorders and play an important role in risk stratification and accurate management of elderly patients with cancer.

Table 1. Common anticancer agents with potential cardiotoxicity

| Agent	Drug class	Cancer clinical use	Type of cardiotoxicity
Doxorubicin	Anthracyclines (Chemotherapeutic agent)	Breast, sarcoma, lung, bladder, gastric, prostate, leukemia, lymphoma, others	LV dysfunction
Cyclophosphamide	Alkylating (Chemotherapeutic agent)	Sarcoma, SCT, lymphoma, myeloma, breast	Myopericarditis, arrhythmias
Ifosfamide	Alkylating (Chemotherapeutic agent)	Testicular, sarcoma, lymphoma	Arrhythmias, LV dysfunction
5-Fluorouracil (5-FU)	Antimetabolites (Chemotherapeutic agent)	Colon, pancreatic, breast, head and neck	Coronary vasospasm, ischemia, arrhythmias
Vinblastine	Antimicrotubule (Chemotherapeutic agent)	Lymphoma, testicular, lung, melanoma	Ischemia, hypertension
Bevacizumab	Antibody VEGF (Biologic agents)	Colon, rectal, cervical, glioblastoma, ovarian, renal, endometrial, sarcoma	Hypertension, LV dysfunction
Trastuzumab	Antibody HER-2 (Biologic agents)	Breast, gastric, gastro-esophageal	LV dysfunction
Ramucirumab	Antibody VEGFR-2 (Biologic agents)	Colon, rectal, gastric, lung	Hypertension, thromboembolism
Interleukin-2 (IL-2)	Immune agent	Melanoma, renal	Capillary leak syndrome, hypotension, myocardial toxicity
Interferon-Alpha (INF)	Immune agent	Melanoma, renal, lymphoma	Arrhythmias, ischemia
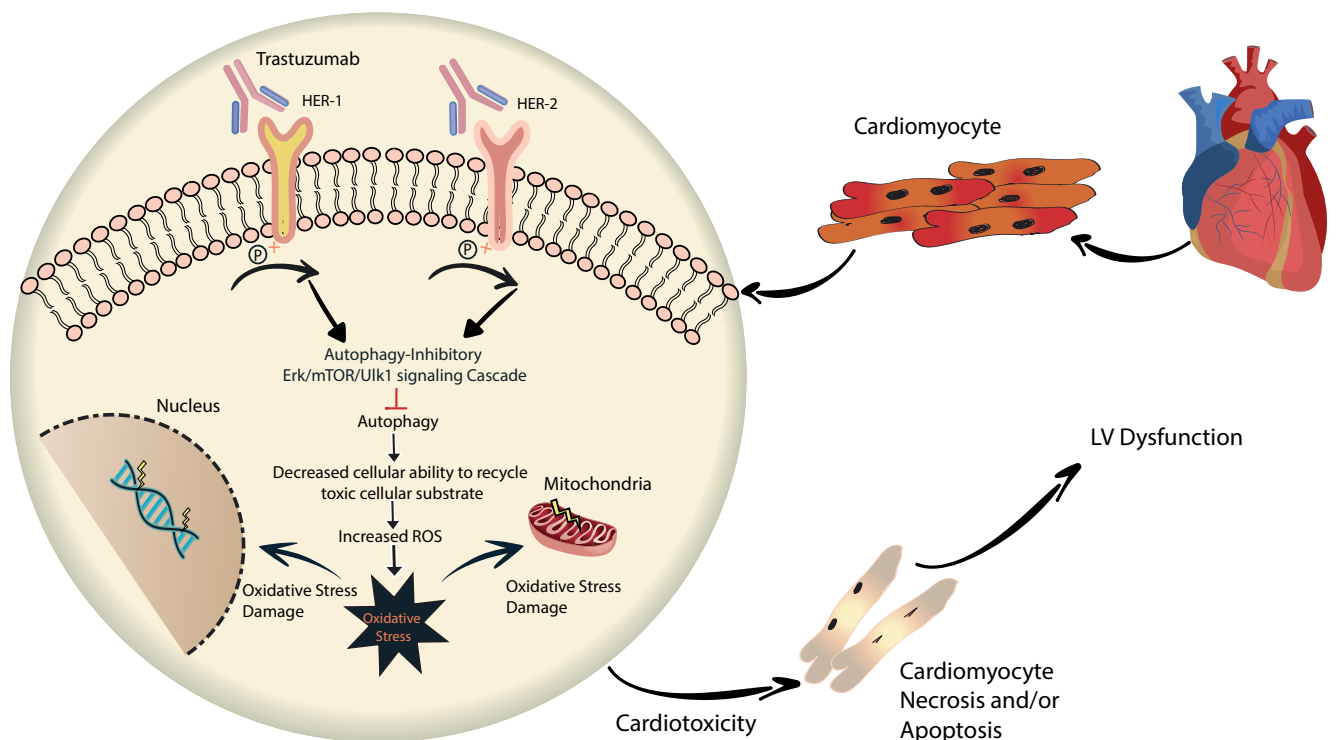
Figure 1. Trastuzumab is directed against the extracellular part of HER2 in HER-2 positive breast cancer patients. This agent causes the phosphorylation of tyrosine 845 (Y845) and 1248 (Y1248) at HER-1 and HER-2, respectively. This process activates the Erk/mTOR/ Ulk1 signalling cascade that inhibits autophagy in the primary cardiomyocytes. Subsequently, autophagy inhibition increases the intracellular level of reactive oxygen species (ROS) leading to oxidative stress in cardiomyocytes, resulting in apoptosis or necrosis of cardiomyocytes. Additionally, trastuzumab alters ultrastructural formation, and also expression profile of genes and DNA repair. These structural and genetic changes increase myocardial increased myocardial oxidative and nitrative stress and potentially activates apoptotic pathways in cardiomyocytes

Nuclear cardiac imaging in cardio-oncology

Cardio-oncology balances correct patient-centred treatment procedures and cardiovascular disorders. Therefore, it needs a multi-disciplinary team including cardiologists, oncologists, and nuclear medicine specialists for the best efficiency in understanding, treating, and preventing cardiovascular disease [10, 50].

Non-invasive cardiovascular imaging modalities with their versatility have caused a revolution in this field. There are many imaging techniques, but the most common practical procedures are two-dimensional echocardiography and multi-gated acquisition imaging, which evaluate resting left ventricle ejection fraction. Nuclear medicine using different radiotracers has a long history in the identification and management of myocardial cardiotoxicity (Tab. 2) [15].

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Table 2. Important radiotracers in cardiac nuclear imaging for cardiotoxicity

Imaging modality	Radiotracer	Advantages	Disadvantages
Planar MUGA Scintigraphy	[^{99m}Tc]erythrocyte	Superior accuracy and highly reproducibility versus 2D echo	Limited structural and functional information beyond LVEF/radiation exposure
SPECT	[^{111}In]antimyosin [^{123}I]MIBG [^{99m}Tc]Sestamibi [^{111}In]Tz [^{99m}Tc]annessin V [^{123}I]BMIP [^{99m}Tc]tetrofosmin	Well-validated accuracy/Reproducibility/ High sensitivity and specificity/No inter- and intra-observer variability	Low sensitivity of EF for early diagnosis/ /less information about diastolic function
PET	[^{18}F]FDG [^{11}C]HED [^{11}C]phenylephrine [^{18}F]FDA [^{18}F]MitoPhos [^{18}F]12 [^{18}F]DHMT [^{68}Ga]Galmydar [^{11}C]HED [^{11}C]EPI [^{11}C]CGP12177 [^{11}C]CGP12388 [^{11}C]GB67	Quantification/ Sensitivity/ Reproducibility/ 3-dimensional pharmacokinetic analysis Spatial resolution/ Myocardial metabolic and perfusion evaluation	Limited availability/ High cost

[^{99m}Tc]Multi-Gated Acquisition Scan (MUGAs)

A multi-gated acquisition scan is reproducible and provides the most accurate radionuclide ventriculography to visualize the cardiac blood pool. [^{99m}Tc]erythrocyte camera scintigraphy, also known as equilibrium radionuclide angiocardiography, assesses cardiac blood pool and its function for treatment response and collects prognostic information for patients with cardiac haemorrhage. One of the accepted cost-effective methods for cardiac monitoring of patients undergoing trastuzumab treatment is MUGAs. The results of the MUGA scan indicate cardiotoxicity if the LEVF decreases more than 10% (to a final ejection fraction of less than 50%) [51].

A study by Schwartz et al found the superiority of MUGA for monitoring cardiotoxicity and identifying cognitive heart failure in cancer survivors [52]. Additionally, MUGA is considered a promising choice for detecting the asymptomatic reduction of LVEF.

A serial cross-sectional study compared the use of three conventional cardiac imaging methods for chemotherapy-related cardiotoxicity. The major disadvantages of MUGA were high radiation exposure and the inability to provide information about the right ventricular, valvular, or pericardial disease [13]. The use of the MUGA scan decreased between 2011 and 2014 and two imaging methods including echo and cardiovascular magnetic resonance imaging were used instead. These results may be due to increased knowledge of patients and physicians about radiation risks associated with serial radionuclide ventriculography scans. Moreover, the findings of serial radionuclide ventriculography are similar to the findings of echocardiography and cardiac magnetic resonance imaging [53].

Single-photon emission computed tomography (SPECT)

Three-dimensional gated blood pool SPECT is similar to the previous method, but it has the potential to differentiate cardiac chambers better than planar radionuclide ventriculography. Automatic measurement of the LVEF by [^{99m}Tc]gated blood-pool SPECT (GBPS) provides accurate segmental wall motion analysis and estimates the cavity volume in a single examination [54, 55]. Nevertheless, there is a good agreement in the rough calculation of LVEF between MUGA and GBPS methods [56].

Anthracycline drugs are used to treat many different malignancies such as lymphoma, leukaemia, myeloma, breast carcinoma, lung, ovarian, and gastric. They are also induced cardiotoxicity inducing cardiomyopathy, valvular heart disease, coronary heart disease, and heart failure [57, 58]. Two important mechanisms correlated with anthracycline-cardiotoxicity are mitochondrial dysfunction and elevated oxidative stress [58, 59]. [^{99m}Tc]Sestamibi SPECT imaging is important in vivo molecular scan approach that enables interrogation of mitochondrial dysfunction and detection of doxorubicin-induced cardiotoxicity [60].

Moreover, myocardial abnormalities can be detected through ^{123}I-labeled metaiodobenzylguanidine ([^{123}I]MIBG) scan before causing permanent excessive left ventricular impairment. [^{123}I]MIBG is a norepinephrine analog radiotracer. This radiotracer shows appropriate reproducibility and sensitivity for the evaluation of myocardial adrenergic disorders.

In a study using myocardial perfusion imaging with [^{123}I]MIBG and [^{123}I]BMIPP for patients undergoing anthracycline treatment agents, the results showed early detection of anthracycline-related

cardiotoxicity through [123I]MIBG. Early diagnosis results in a lower incidence and intensity of heart damage in these patients [61–63].

Indium-111 labelled antimyosin antibody as the main marker of myocardial cell necrosis has been introduced for direct visualization of myocyte damage. The myocardial uptake of this radiotracer correlates with the LVEF decrease in patients treated with an anthracycline. Additionally, 111In-antimyosin SPECT imaging can identify cardiotoxicity associated with anthracycline chemotherapy regimens in breast cancer patients as well as the doxorubicin regimen in leukaemia, lymphoma, and other solid tumours [64–66].

Several preclinical results using the [99mTc]Annexin V scan confirmed the significant role of this radiotracer in the detection of myocardial apoptosis. [99mTc]Annexin V scintigraphy successfully detected apoptotic cells in myocarditis, acute myocardial infarction, the curative effect of anti-apoptosis medications in heart ischemia patients, unstable atherosclerotic plaque, cardiac transplant rejection, and a cardiotoxicity-related anthracycline [67–72]. Additional clinical studies are needed to assess the common use of this radiotracer, especially for early detection of myocardial damage associated with anticancer drugs.

Long-chain fatty acids, as a vital nutrient for the myocardium, are metabolized by β-oxidation. These fatty acids or related analogues can be used in specific imaging probes ([123I]labelled fatty acids) to assess oxidative differentiation in multiple cardiac diseases [73]. Nevertheless, this radiotracer has not been used in SPECT imaging due to its instability in vivo. Therefore, novel tracers such as 123I-15-(p-iodophenyl)-3-methyl pentadecanoic acid (BMIPP) have emerged, which have demonstrated promising results in nuclear cardiology [74, 75].

Some studies examined 111In-DTPA-trastuzumab imaging techniques to visualize the human epidermal growth factor receptor 2 (HER2) expressed by myocytes in breast cancer patients. Trastuzumab has been used as a monoclonal antibody to bind to HER2 for curative purposes. This radiotracer has been used to detect patients potentially subject to trastuzumab-related cardiotoxicity. This technique may be helpful, especially in patients with high-risk cardiac failure [76–80]. Regardless of the predictive role of this radiotracer, the data are limited, and this method has not yet been used in conventional clinical practice.

Positron emission tomography (PET)

More common imaging procedures, such as computed tomography (CT) scan, nuclear magnetic resonance (NMR), and magnetic resonance imaging (MRI), define anatomic and physiological functional properties; nonetheless, they cannot determine the autogenetic myocardial biochemistry. Positron emission tomography (PET) assesses both myocardial metabolism and perfusion with a better resolution and higher sensitivity [81, 82]. Moreover, PET myocardial tracers provide an extensive and detailed evaluation of early and reversible cardiotoxic effects of anticancer treatment regimens. The uptake of fluorine-18-fluorodeoxyglucose ([18F]FDG) increases in cardiomyocytes before the LVEF decrease in patients treated with anthracyclines [83].

Reactive oxygen species (ROS) have been involved in cell signalling, homeostasis. However, a high number of ROS causes pathogenesis of a high number of human diseases and drug toxicities, so the development of imaging tools that able to characterize

ROS biology in vivo has been recently considered and turned into a big challenge [84]. The 18F-12 microPET imaging of the heart in mice with Doxorubicin-induced cardiac inflammation indicated 2-fold higher oxidation of this tracer compared to the control group. These findings showed that compound 12 is a suitable PET tracer for in vivo imaging of ROS [85]. Another PET tracer that evaluated superoxide production for early detection of doxorubicin-induced cardiotoxicity is 18F-DHMT. This tracer detected excessive production of reactive oxygen species before a decrease in LVEF that may give a good chance for early cardiotoxicity detection in patients with malignancies [86]. Moreover, [68Ga]Galmydar is also evaluated as a potential radiotracer to monitor Doxorubicin-induced cardiomyopathy in different situations. MicroPET/CT scan showed a high-resolution non-invasive assessment of metabolic changes related to Doxorubicin treatment using 68Ga-Galmydar at the earliest stages. Single-cell imaging and quantitative biodistribution demonstrated that Galmydar localized precisely in mitochondria of treated cells with Doxorubicin [87].

18F-MitoPhos as radiolabelled lipophilic cations was used for early detection of imaging cardiotoxicity in acute doxorubicin in the rat model. [18F]MitoPhos PET imaging demonstrated appropriate pharmacokinetic parameters for cardiac imaging and was introduced as a promising radiopharmaceutical for imaging chemotherapy-induced cardiotoxicity [88].

It has been recently demonstrated that [82Rb]PET imaging could be a potential radiotracer for quantitative assessment of the myocardial blood flow in patients that are at high risk for anthracycline cardiotoxicity [15, 89]. Several studies are investigating nuclear cardiac imaging for the early detection of cardiotoxicity-related cancer therapy modalities. Important radiotracers used for investigating cardiotoxicity in cardiac nuclear imaging are summarized in Table 2.

Can treatment nuclear medicine modalities stimulate cancer therapy-related cardiotoxicity?

Another important modality for the treatment of malignancies is using injectable radiopharmaceuticals, which, similar to other treatment methods, require the assessment of possible side effects including cardiotoxicity.

One of the important approaches in nuclear medicine is theranostics, which combines diagnostic imaging and therapeutic methods through labelling the same molecule or the same agent with distinct radionuclides. More knowledge in genomics led to detecting theranostic biomaterials to diagnosis and treatment of malignancies along with molecular imaging tools. Cancer lesions are heterogeneous and therefore common treatment approaches may not provide favourable results. Nevertheless, these lesions can be detected through theranostics. Therefore, this characteristic can be used to determine which patient will benefit from therapy and which patient may not receive conventional treatments.

Theranostics is currently considered as the recommended modality not only for diagnosis and treatment of malignancies but also for staging, follow-up, monitoring response to treatment, and restaging. An important characteristic of this approach is delivering high doses to tumours while sparing non-targeted tissues.

Different theranostic probes have been developed from clinical experiments of radioactive iodine for evaluation of physiologic

metabolism and thyroid disorders to recent applications in neuroendocrine tumours and prostate cancer. Some pairs of radionuclides that have been used in theranostics include diagnostic gamma or positron emission radionuclides such as ^{123}I ($t_{1/2}$ = 13.22 h), ^{124}I ($t_{1/2}$ = 4.2 d), ^{68}Ga ($t_{1/2}$ = 68 min), ^{99m}Tc ($t_{1/2}$ = 6h), ^{111}In ($t_{1/2}$ = 2.81 d), and therapeutic high-dose radioactive materials such as ^{177}Lu ($t_{1/2}$ = 6.71 d) and ^{90}Y ($t_{1/2}$ = 64.02 h). Therapeutic radionuclides emit beta and alpha particles, causing damage to double-stranded DNA and death in cancer cells. The most common available pairs of theranostic radiopharmaceuticals include [^{68}Ga]PSMA/[^{177}Lu]PSMA for prostate cancer and [^{68}Ga]DOTATATE/[^{177}Lu]DOTATATE for neuroendocrine (NETs) (Fig. 2 and 3).

Theranostics is a form of systemic endo-radiotherapy that delivers toxic radiation to target cells but some side effects including severe hematotoxicity and nephrotoxicity have been reported. Many studies evaluated early and late side effects of radioligand therapy, especially peptide receptor radioligand therapy (PRRT), and found that side effects were almost entirely limited, predictable, and/or reversible [90–96]. Nonetheless, a recent case-report study found cardiotoxicity related PRRT in patients with metastatic neuroendocrine tumours.

Different radiotracers have been used in nuclear medicine to visualize and treat neuroendocrine tumours. These tumours develop in many tissues including the lungs, stomach, small intestine, appendix, colorectal tissue, and heart [97–99]. Somatostatin analogues are an inseparable component of diagnostic and treatment policies in metastatic carcinoid tumours. Neuroendocrine tumours have the potential to be targeted with radiopeptides due to peptide receptor expression. Peptide receptor radionuclide therapy using [^{90}Y]DOTATAC and [^{177}Lu]DOTATATE have successful results in the treatment of inoperative and metastases liver cancers. PRRT can cause renal or haematological adverse effects, but the timely application of appropriate precautionary measures and safe dose administration decrease these toxicities [100, 101].

More than 50% of patients with advanced carcinoid tumours are prone to carcinoid heart disease [102]. At the time of carcinoid cardiac metastases, due to the expression of somatostatin receptors in the cardiac tissue (sst1, sst2, sst4, and sst5), caution should be practised to target neuroendocrine tumour cells with somatostatin-radioisotope compounds. [^{177}Lu]DOTATATE is confirmed as an effective option in inoperative metastases of neuroendocrine tumours with symptomatic cardiovascular impairment [103].

In a case report study, a 51-year-old-man was diagnosed with neuroendocrine tumour lesions and received somatostatin analogue therapy. After a while, a [^{68}Ga]DOTATATE scan was used to evaluate the patient. Imaging demonstrated that metastatic lesions spread in the axial skeleton, liver, and spleen as well as the right and even the left myocardium. The ejection fraction was normal (62%) in the beginning. After receiving two cycles of [^{177}Lu]labeled PRRT, an echocardiogram showed a serious decrease in the left ventricular systolic function and left ventricular ejection fraction (34%). Therefore, PRRT stopped but it started again because the cardiac function continued to decline. In this case, the cardiac function was normal before treatment, but the patient developed cardiotoxicity after treatment due to the delivery of the radioactive isotope to metastatic lesions. This cardiotoxic effect should be considered as a precaution in a patient with neuroendocrine tumour and cardiac metastases receiving PRRT [104].

Moreover, recent advances in nuclear medicine imaging and therapy have shown that fibroblast activation protein (FAP) and chemokine receptor (CXCR) are promising targets for nuclear-labelled tumour probes. Different reports have indicated an effective role of [^{68}Ga]pentixafor chemokine-directed imaging in some solid tumours such as glioblastoma, ovarian cancer, renal cell cancer, small cell lung cancer, and adrenocortical carcinoma. However, a study by Vag et al. questioned its possibility in other tumours including pancreatic cancer, sarcoma, and breast cancer [105–109].
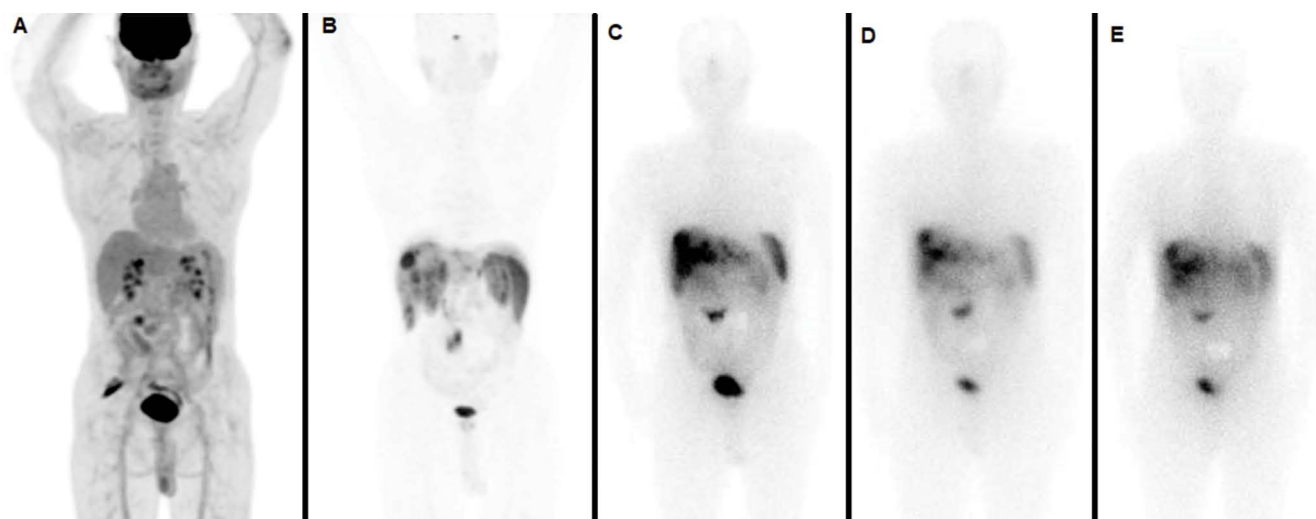

Figure 2. A 68-year-old man with metastatic neuroendocrine tumours refractory to chemotherapy presented for PRRT. Pre-treatment FDG PET (**A**) showed no abnormal radiotracer uptake, while all lesions in the liver and mid-abdomen revealed significant SSTR expression on pre-treatment 68Ga-DOTATATE PET/CT (**B**). The patients underwent 3 cycles of PRRT (22.2 GBq). The post-treatment scintigraphy after the 1st cycle (**C**) indicated intensive uptake of radiotracer in the above regions, which decreased significantly in number and size in post-treatment scintigraphy after the 3rd cycle (**D, E**)
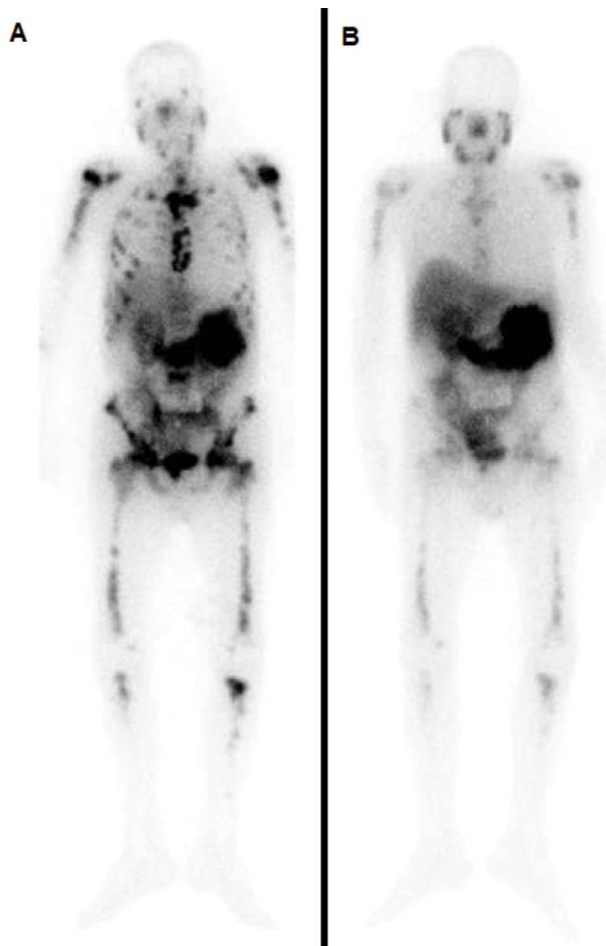
Figure 3. A 58-year-old man with metastatic castration-resistant prostate cancer refractory to different regimes of hormone therapy and chemotherapy presented for lutetium-177-labelled prostate-specific membrane antigen radioligand therapy. The patients underwent 3 cycles of [^{177}Lu]PSMA therapy (22.2 GBq). Post-treatment scintigraphy after the 1st cycle (**A**) indicated widespread uptake of radiotracer throughout the entire body which decreased significantly in number and size in post-treatment scintigraphy after the 3rd cycle (**B**)

^{177}Lu-pentixather has demonstrated outstanding CXCR4-targeting properties and a favourable pharmacokinetic profile. Additionally, [^{68}Ga]pentixafor/^{177}Lu-pentixather based CXCR4-targeted theranostic approach delivers high doses to the tumour sparing healthy non-targeted cells [110]. Several malignant cells including head and neck, breast, lung, pancreatic, and oesophageal, colorectal cancer have a high uptake of [^{68}Ga]FAPI that can be used for non-invasive molecular imaging, locating the primary site of unknown malignancies, and staging of tumours. On the other hand, [^{68}Ga]FAPI tracers contain universal DOTA chelators. This property makes it possible to label the ligand with a suitable therapeutic radionuclide for a theranostic approach [106, 111].

However, although no life-threatening side effects have been reported for these radioligands, concise studies should be performed to evaluated probable side effects and cardiotoxicity.

Conclusion

Cardio-oncology as a multi-modality approach has become a valuable strategy for improving treatment outcome and patient management through screening cardiotoxicity during cancer treatment. Several studies investigated cancer treatment cardiotoxicity in chemotherapy and external radiation therapy. In addition to the significant role of nuclear cardiac imaging procedures for early detection of cardiovascular changes, it is required to perform more comprehensive studies to investigate cancer treatment options such as PRRT, fibroblast activation protein, and chemokine receptor targeting probes for possible cardiac side effects that play important roles in the treatment of malignancies. Finally, it is required to establish a network of collaboration between oncologists, nuclear medicine specialists, and cardiologists to obtain optimal patient outcomes and decrease life-threatening cardiotoxicity.

Ethics approval and consent to participate

Not applicable.

Availability of data and materials

Not applicable.

Conflict of interests

The authors declare that they have no competing interests.

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