Molecular Imaging Biomarkers in Cardiooncology: A View on Established Technologies and Future Perspectives

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Novel therapeutic options have significantly improved survival and long-term outcomes in many cancer entities. Unfortunately, this improvement in outcome is often accompanied by new and increasingly relevant therapy-related cardiovascular toxicity. In this context, cardiooncology has emerged as a new field of interdisciplinary individual patient care. Important tasks are pretherapeutic risk stratification and early detection and treatment of cardiotoxicity, which comprises cardiac damage in relation to cardiovascular comorbidities, the tumor disease, and cancer treatment. Clinical manifestations can cover a broad spectrum, ranging from subtle and usually asymptomatic abnormalities to serious acute or chronic complications. Typical manifestations include acute and chronic heart failure, myo- and pericarditis, arrhythmias, ischemia, and endothelial damage. They can be related to almost all current cancer treatments, including cytotoxic chemotherapy, targeted therapy, immunotherapy, hormonal therapy, and radiotherapy. Molecular imaging biomarkers can aid in pretherapeutic cardiooncologic assessment for primary prevention and personalized surveillance, detection, and differential diagnosis of cardiotoxic complications. Potential advantages over conventional diagnostics are the higher detection sensitivity for subtle changes in cardiac homeostasis, higher reproducibility, and better observer independence. Hybrid imaging with highly sensitive PET/MRI may be particularly suited for early diagnosis. Important technologies that are encouraged in current multidisciplinary guidelines are equilibrium radionuclide angiography for evaluation of ventricular function and chamber morphology, as well as myocardial perfusion imaging for additional detection of ischemia. Novel modalities that may detect even earlier signs of cardiotoxicity comprise 123I-metaiodobenzylguanidine SPECT to visualize sympathetic innervation, [18F]-FDG and somatostatin receptor (68Ga-DOTA-TOC/DOTATATE) PET to indicate a metabolic shift and inflammation, and [68Ga]-fibroblast activation protein inhibitor PET to monitor cardiac remodeling. In addition, PET imaging of mitochondrial function has recently been introduced in preclinical models and will potentially broaden the field of application through higher sensitivity and specificity. By enabling higher individualization of diagnostic concepts.

Key Words: molecular imaging; cardiotoxicity; nuclear cardiology; cardiooncology

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This review provides insight into cancer therapies and their cardiotoxic potential, discusses underlying mechanisms, and introduces molecular imaging biomarkers for nuclear medicine physicians, oncologists, and cardiologists in the evolving field of nuclear cardiooncology.

CARDIOTOXICITY OF CANCER THERAPIES

Cardiooncology is a mainstay in oncologic treatment since cancer therapy–related cardiovascular toxicity (CTR-CVT) can affect up to 50% of oncologic patients—depending on the therapy and its administered dose (1). The first and best-studied example of culprit agents in CTR-CVT is that of anthracyclines, which belong to the most important and most applied cytotoxic chemotherapeutics with a wide spectrum of indications. Since the 1970s, they have been known to induce heart failure (HF) in a dose-dependent manner (2), and they are a major reason why cardiooncologic monitoring has found its way into various clinical guidelines. Radiotherapy is another established cancer treatment with an already well-known cardiotoxic profile (2).

Over the last few years, cancer treatment has experienced a rapid development with the availability of novel options leading to a significant increase in long-term survival and improvement in the quality of life of patients (3). However, almost all new forms of oncologic treatment are included in the list of therapies that can cause CTR-CVT by both common and novel pathophysiological mechanisms. In addition, because of improved survival, many oncologic diseases can now be considered chronic rather than acute life-threatening conditions, and as a result, treatment side effects and involvement of other organ systems are of increasing clinical importance (2). Typical clinical manifestations of CTR-CVT include not only impairment of systolic and diastolic ventricular function and, as a result, acute or chronic HF but also myo- and pericarditis, ischemic heart disease, valvulopathies, thromboembolisms, arrhythmias and QT prolongation, peripheral and cerebral arterial occlusive disease, pulmonary hypertension, arterial hypertension, and endothelial damage (4). The spectrum of the most common cardiotoxic side effects for each category of cancer treatment and their typical time of occurrence are presented in Table 1.

Of these, HF and myocardiitis are among the most clinically significant complications with the greatest impact on patient morbidity and mortality (5–7). Therefore, current oncologic consensus statements and guidelines recommend considering all patients...
under potentially cardiotoxic cancer therapy as at risk of HF, even those without structural heart disease or symptoms of HF (8). The likelihood of cardiac complications is determined not only by the type of anticancer drug administered but also by each patient’s unique risk profile and medical history. For example, up to 37.5% of high-risk patients according to the prospective CARDIOTOX registry trial (9) experience any form of cardiotoxic complications. Therefore, each patient requires an initial evaluation of cardiovascular risk factors and preexisting cardiovascular disease before therapy starts (8,10). Typical risk factors for CTR-CVT are shown in Table 2. On the basis of this risk stratification, a customized cardiooncologic monitoring, prevention, and therapy plan can be developed (11,12).

Although the stratification for risk of CTR-CVT in hematono-logic patients is not standardized yet, the cardiooncology study group from the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society developed baseline cardiovascular risk stratification proformas for the most commonly used cancer drug categories to be applied before initiation of potentially cardiotoxic cancer therapies (8). Baseline parameters for risk assessment are derived from medical history, physical examination, electrocardiography, cardiac serum biomarkers (e.g., high-sensitivity troponin and N-terminal pro–brain natriuretic peptide), and imaging. The same diagnostic tools are also recommended for cardiooncologic monitoring during therapy (3).

Typically, echocardiography is the first-line imaging approach for the assessment of global left ventricular function. The cardiooncologist may turn to other imaging modalities in cases of unfavorable sonographic conditions or when ultrasound findings necessitate further investigation. In this case, cardiac MRI can provide detailed images of the heart and its structures, as well as information on blood flow and function. Thus, cardiac MRI not only can assess left ventricular ejection fraction (LVEF) and strain but also can provide tissue characterization (the most relevant parameters are displayed in Table 3) to detect subtle alterations in early phases of developing cardiotoxicity (13). In patients with contraindications to cardiac MRI (implanted cardiac devices such as pacemakers and defibrillators that are not or not fully MRI-compatible), in cases of technical limitations (cardiac arrhythmias), or in patients who cannot tolerate the procedure (inability to lie flat or claustrophobia), nuclear imaging can be of value. For example, the 2022 European Society of Cardiology guidelines on cardiooncology recommend equilibrium radionuclide angiography, also known as multigated acquisition nuclear imaging, as a third-line modality for assessing LVEF (3,14).

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### TABLE 1
Common Cardiotoxic Side Effects for Typical Categories of Cancer Treatment and Indication of Typical Time of Occurrence

<table>
<thead>
<tr>
<th>Agent</th>
<th>HF</th>
<th>Myocarditis</th>
<th>Arrhythmias</th>
<th>Acute pericarditis</th>
<th>Arterial hypertension</th>
<th>Atherosclerosis/coronary artery disease</th>
<th>Thromboembolic events</th>
<th>Early stage*</th>
<th>Late stage†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthracyclines</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Bleomycin</td>
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<tr>
<td>Alkylating agents</td>
<td>X</td>
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<tr>
<td>Platin</td>
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<td>Taxanes</td>
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<td>Fluoropyrimidines</td>
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<tr>
<td>Proteasome inhibitors</td>
<td>X</td>
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<td>HER2/neu antibodies</td>
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<td>Tyrosine kinase inhibitors</td>
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<td>X</td>
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<td>Mitogen-activated protein kinase/BRAF inhibitors</td>
<td>X</td>
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<td>X</td>
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<tr>
<td>Immunomodulatory drugs</td>
<td>X</td>
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<td></td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
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<tr>
<td>Vascular endothelial growth factor inhibitors</td>
<td>X</td>
<td></td>
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<td></td>
<td>X</td>
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<tr>
<td>Immune checkpoint inhibitors</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Chimeric antigen receptor T-cell therapy</td>
<td>X</td>
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</tbody>
</table>

*Onset of CTR-CVT early after initiation of treatment.
†Onset of CTR-CVT during or after discontinuation of treatment.
In-depth information is covered in current guidelines (3).
Various molecular imaging techniques enable the visualization of specific pathophysiologic mechanisms at an earlier stage. In an integrative approach with established blood test–derived and echocardiography or cardiac MRI–derived diagnostic parameters, molecular imaging biomarkers have the potential to visualize individual development of CTR-CVT. Even subtle changes in cardiac homeostasis can be detected before any clinical manifestation and, furthermore, can be used in conjunction with the precision medicine approaches of genomics, metabolomics, and proteomics for personalized pathophysiologic phenotyping (15).

In the following, we review the most important cardiotoxic cancer therapies and their pathophysiology that may be relevant for molecular imaging targeting. Figure 1 provides an overview of important CTR-CVT–inducing treatments, pathologic effects, and molecular imaging biomarkers.

**Cytotoxic Chemotherapy**

Not only anthracyclines but almost all classes of cytotoxic chemotherapy are long known to trigger CTR-CVT. The most important clinical manifestations of anthracycline-related CTR-CVT are acute or chronic HF, arrhythmias, and pericarditis. Anthracycline-induced HF occurs in 0.2%–8.7% of patients and shows a dose-dependent incidence. It can develop both during and after treatment, with a possible onset of up to years after discontinuation. A cumulative dose of at least 250 mg of doxorubicin per square meter body surface area or an equivalent dose of other anthra- cyclines is supposed to increase the risk of cardiotoxicity by a factor of about 5 (16). Therefore, current cardiooncologic guidelines recommend closer surveillance of cardiac function in this patient group.

Moreover, anthracyclines are the class of CTR-CVT–inducing therapies whose pathophysiologic mechanisms are best elucidated, with most findings being derived from preclinical models using doxorubicin as a representative drug. Doxorubicin interacts with both topoisomerase 2 variants: topoisomerase 2α and topoisomerase 2β. In consequence, the topoisomerase 2β–doxorubicin complex can cause DNA double-strand breaks, activating DNA damage response that leads to death of cardiomyocytes. In addition, many cytotoxic drugs induce mitochondrial damage by disrupting the electron transport chain, resulting in the mitochondrial membrane potential uncoupling and metabolic dysregulation. For example, the doxorubicin metabolite doxorubicinol has been shown to target the CREB-regulated transcription coactivator (CRTC) to casquestrin 2, resulting in an elevated cytoplasmic Ca^{2+} concentration and reduced Ca^{2+} uptake in the sarcoplasm. These Ca^{2+} alterations can lead to a temporary cardiomyocyte dysfunction and to cell death (17).

Other classes of frequently used cancer drugs with a cardiotoxic profile are fluoropyrimidines (e.g., 5-fluorouracil), alkylating agents, and antimicrotubule agents (e.g., taxanes). These are applied to various solid malignancies, for example, in the first- and second-line treatment of gastrointestinal and pancreatobiliary cancers. However, the pathophysiology of CTR-CVT is not as well investigated for these drugs as for anthracyclines.

The incidence of 5-fluorouracil–related CTR-CVT ranges from 1% to 19%, mainly occurring at the beginning of treatment (18). Preclinical studies suggest that pathophysiology is based on endothelial damage, which activates apoptosis and autophagy pathways in both endothelial cells and myocytes. This activation contributes to accumulation of vasoconstrictors, platelets, and fibrin, resulting in a procoagulant effect (19). Alkylating agents evoke HF with an incidence of up to 28% and atrial fibrillation with an incidence of up to 22.5%. This cardiotoxic profile is attributed to DNA damage, endothelial dysfunction, and thrombogenicity (20). Antimicrotubule agents are also associated with cardiac arrhythmia, which typically manifests within the first few weeks of chemotherapy. Up to one third of patients treated with paclitaxel have been reported to develop bradycardia, and, rarely, other types of arrhythmias (21). One special pathophysiologic mechanism is direct damage to the Purkinje system, which dysregulates autonomic nervous system control. Moreover, the incidence of taxane-induced HF ranges

### TABLE 2
Risk Factors for CTR-CVT in Oncologic Patients According to Lyon et al. (3)

<table>
<thead>
<tr>
<th>Factor no.</th>
<th>Factor description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Age</td>
</tr>
<tr>
<td>2</td>
<td>Previous cardiovascular disease, with 10-y risk score &gt; 20%</td>
</tr>
<tr>
<td>3</td>
<td>Cardiovascular risk factors: hyperlipidemia, diabetes mellitus, chronic kidney disease proteinuria, hypertension</td>
</tr>
<tr>
<td>4</td>
<td>Current smoker or significant smoking history</td>
</tr>
<tr>
<td>5</td>
<td>Current cancer therapy with anthracycline (cumulative dose and concomitant administration with trastuzumab)</td>
</tr>
<tr>
<td>6</td>
<td>Previous exposure to anthracycline, trastuzumab, radiation therapy to left chest or mediastinum, nonanthracycline chemotherapy</td>
</tr>
<tr>
<td>7</td>
<td>Obesity (body mass index &gt; 30 kg/m²)</td>
</tr>
<tr>
<td>8</td>
<td>Elevated baseline NT-proBNP, elevated troponin, abnormal cardiac imaging results</td>
</tr>
</tbody>
</table>

NT-proBNP = N-terminal pro-brain natriuretic peptide.

### TABLE 3
Advanced Cardiac MRI Techniques for Tissue Characterization with Relevance for Diagnosing CTR-CVT

<table>
<thead>
<tr>
<th>Tissue</th>
<th>MRI parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edema and inflammation</td>
<td>T2-weighted cardiac MRI; T1/T2 parametric mapping</td>
</tr>
<tr>
<td>Diffuse fibrosis</td>
<td>T1-weighted cardiac MRI; pre- and postcontrast T1 mapping; extracellular volume fraction</td>
</tr>
<tr>
<td>Focal fibrosis and scarring</td>
<td>Late gadolinium enhancement</td>
</tr>
</tbody>
</table>
from 1% to 8%. Furthermore, taxanes can rarely cause hypertension and acute coronary syndrome due to vasoconstriction (22).

Radiotherapy and Radionuclide Therapies

Like cytotoxic chemotherapy, radiation therapy has a long history in unspecific treatment of cancer and can evoke CTR-CVT (2) if the heart is partly involved in the irradiation volume. This situation occurs in, for example, mediastinal lymphoma, breast cancer, or lung cancer. Pathophysiologically, irradiation can induce cellular damage by generation of free radicals, which disrupt the integrity of the DNA double helix (23). Thoracic radiation therapy has been shown to carry a significant risk of long-term cardiovascular complications, particularly when the mean heart dose exceeds 15 Gy (3). Moreover, radiation therapy predisposes for atypical, accelerated atherosclerosis and thrombosis. These are risk factors for acute coronary artery syndrome, pulmonary hypertension, and cardiac fibrosis (14).

Target-specific systemic radionuclide therapies are gaining popularity in clinical oncologic settings. This increased popularity was underlined by the Food and Drug Administration approval of peptide receptor radionuclide therapy using the somatostatin receptor agonist $^{177}$Lu-DOTATATE in patients with gastroenteropancreatic neuroendocrine tumors and the prostate-specific membrane antigen inhibitor $^{177}$Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer. Thus far, published data on cardiotoxicity arising from radionuclide therapy are limited. In a retrospective analysis of 24 patients who underwent $^{177}$Lu-DOTATATE or $^{177}$Lu-PSMA therapy, no changes in troponin I levels were detected (24). Therefore, for certain indications, systemic radionuclide therapies can provide a safe alternative to potentially cardiotoxic chemotherapy, especially in patients at high cardiovascular risk. Special attention should be given to the rare case of heart metastases (25), when effects comparable to those of external radiation therapy may be evoked because of high accumulated activities close to the myocardium.

Targeted Therapy

The introduction of targeted therapy options broadened the spectrum of available cancer drugs and opened the possibility of personalized treatment concepts, leading to improved survival rates. However, this increased survival was likewise accompanied by new forms of CTR-CVT. The best-studied paradigm of targeted therapy is the class of tyrosine kinase inhibitors. Their toxicity is related mainly to the inhibition of numerous tyrosine kinases beyond those stated by drug manufacturers and studied in clinical trials. These off-target actions can be responsible for cardiotoxic effects and may be aggravated in combined therapies, depending on the selectivity of the involved growth-signaling pathways (2).

Human epidermal growth factor receptor 2 (HER2/neu, also known as ERBB2) inhibitors such as trastuzumab are applied in a broad spectrum of indications, for example, in breast cancer in combination with anthracyclines and in HER2/neu–positive gastric cancer. The incidence of cardiotoxicity is estimated to be 2%–20% and depends greatly on the previous treatment with other cardiotoxic cancer drugs, especially anthracyclines (26). Trastuzumab-related cardiotoxicity typically occurs during its administration or late after oncologic treatment. The cardiotoxic effects are—unlike for the anthracyclines—often reversible when treatment with trastuzumab is stopped (20). CTR-CVT is, for example, explained by inhibition of neuroregulin-HER2/neu signaling. Neuroregulin is a ligand to the HER2/neu receptors, and neuroregulin-HER2/neu signaling is involved in cardiac development and stress response. If HER2/neu signaling is inhibited, the heart fails to respond adequately to potential damage or other stress stimuli (27).

Tyrosine kinase inhibitors revolutionized the treatment of many cancer types. For example, inhibitors of breakpoint cluster region–Abelson murine viral oncogene homolog (BCR-ABL) kinase are a standard treatment in hematologic malignancies and gastrointestinal tumors (3,28,29). Inhibitors of vascular endothelial growth factor are used in many malignancies to impede the angiogenesis, survival, and metastatic potential of tumors. Brunt tyrosine kinases interfere in B-cell development after immunoglobulin heavy-chain rearrangement. Arterial hypertension, HF, arrhythmias, acute coronary syndromes, pulmonary hypertension, and venous thrombosis are the most common off-target cardiac complications of these drugs (20). Most frequently, arterial hypertension can occur within the first treatment cycles and is related to increased levels of endothelin 1 and activation of the renin–angiotensin–aldosterone system. Monitoring of patients during the initial treatment phase may prevent the development of serious complications. The incidence of CTR-CVT ranged from 4% (for imatinib) to 68% (for lenvatinib) (30). In addition, the risk of HF was over 2.5 times higher among patients receiving a combination therapy with vascular endothelial growth factor–targeting tyrosine kinase inhibitors (20).
Another important side effect of tyrosine kinase inhibitors is QT prolongation, whose incidence varies from 0.2% (for bosutinib) to 8% (for vandetanib) (31). Moreover, Bruton tyrosine kinase inhibitors interact with the phosphoinositide 3-kinase pathway in cardiomyocytes, affecting the conduction of electric signals and leading to arrhythmias (32). Precapillary pulmonary hypertension is a serious but reversible complication of tyrosine kinase inhibitor treatment, affecting 11% of patients treated with dasatinib and occurring 8–40 mo after treatment (31). Ponatinib is a multikinase inhibitor targeting BCR-ABL, vascular endothelial growth factor receptor, fibroblast growth factor receptor, and their effector proteins extracellular signal-regulated kinase and protein kinase B. The pathway of rapidly accelerated fibrosarcoma and mitogen-activated protein kinase comprises tyrosine and serine-threonine kinases. Their phosphorylation can induce cell cycle entry and promote the development of cardiac cells into terminally differentiated cardiomyocytes (33). Therefore, these kinases play an important role in cell growth and proliferation (3). Their inhibition can be correlated with myocyte hypertrophy, cardiac remodeling, and myocardial cell death (28).

Immunotherapy

The introduction of immunotherapy was a breakthrough in oncologic treatment options, and its range of indications is rapidly expanding. Immunotherapy can evoke various forms of CTR-CVT, including myocarditis, arrhythmias, and acute HF. Myocarditis is considered one of the most severe complications, with a median onset time of 18–39 d after application of the first therapeutic dose (34) and an incidence of about 1.4% (16). Moreover, these drugs can promote rapid growth of atherosclerotic plaques through plaque-mediated T-cell reactivation, leading to a 3-fold higher risk for cardiovascular diseases (35). Immunotherapy-related myocarditis seems to be evoked by shared antigens of tumor and myocardium, which lead to processes of molecular mimicry (36). It is hypothesized that dysregulated immune cells recognize mitochondrial receptors, such as cardiolipin, as antigens and initiate an immune response. The involvement of other mechanisms has yet to be determined (36,37). Clinical manifestations vary from asymptomatic elevation of cardiac biomarkers to fulminant and fatal manifestation of HF. In the long term, it is also assumed that chronic inflammation and remodeling procedures due to the myocardial infiltration of lymphocytes may evoke fibrosis and chronic HF (26).

Immunomodulatory drugs, dexamethasone, proteasome inhibitors (such as bortezomib, carfilzomib, and ixazomib), and monoclonal antibodies (e.g., daratumumab) exert their anticancer effect by regulating the ubiquitination of key proteins for tumor growth and enhancing their immunogenicity. Thus, they activate proapoptotic signaling cascades and inhibit autophagy (38). These mechanisms of action have already been reported to be involved in off-target cardiotoxic complications such as ischemia, arrhythmia, HF, and peripheral arterial vascular disease (39).

Chimeric antigen receptor T-cell (CAR T-cell) therapy is a novel modality that uses T-cells engineered with chimeric antigen receptors to make them recognize and target cancer cells. This therapeutic approach is associated with cytokine release syndrome, a serious multiorgan manifestation of systemic inflammatory response syndrome. It can induce immune hyperactivation with subsequent release of proinflammatory cytokines leading to microvascular and mitochondrial dysfunction, alterations of calcium metabolism in cardiomyocytes, and, thus, decreased response to catecholamines and myocardial ischemia. Its most severe form, capillary leakage, results in distributive shock hemodynamics and multiorgan dysfunction (40). The incidence of these complications in the form of arrhythmia, HF, and cardiac death was reported as 12 (41).

**NOVEL BIOMARKERS IN NUCLEAR CARDIOONCOLOGY**

In the field of novel cancer therapies, which are associated with various forms of CTR-CVT, different molecular imaging biomarkers support cardiooncologic assessment in various ways. On the one hand, molecular imaging techniques used for oncologic staging or restaging can also depict biomarkers of myocardial and vascular CTR-CVT in a single examination. On the other hand, novel modalities of molecular imaging for CTR-CVT that specifically visualize pathophysiologic mechanisms are increasingly being introduced.

**Cardiac Glucose Consumption and Inflammation**

The most common molecular imaging tool for oncologic assessment is 18F-FDG PET for imaging of glucose metabolism. However, it is also a valuable tool for imaging of myocardial glucose consumption and activated inflammatory cells. Imaging of inflammation relies on the expression of high levels of glucose transporters by activated inflammatory leukocytes such as macrophages and lymphocytes. When the concentration of infiltrating inflammatory cells in the inflamed tissue is high enough, 18F-FDG accumulation generates a PET signal that can be externally detected.

In a mouse model, immunotherapy was shown to promote myocardial infiltration of immunocompetent cells (42). This explains case reports describing increased 18F-FDG uptake in immune checkpoint inhibitor–associated myocarditis (43), which was, in one case, detected well before a decline in LVEF and also before cardiac MRI showed pathologic reactions (44). A different pathophysiologic characteristic that can be visualized by 18F-FDG PET is a therapy-related metabolic shift of cardiomyocytes. Anthracyclines can disturb oxidation of free fatty acids in cardiac mitochondria and evoke a metabolic shift toward glucose consumption, which can be a very early sign of cardiotoxicity (45). In this context, several preclinical and retrospective clinical investigations have documented increasing myocardial 18F-FDG uptake while LVEF decreased after anthracycline therapy (46).

Not only myocardial but also vascular inflammatory processes can be visualized by 18F-FDG PET (47). A relevant cancer-therapy complication that is related to vascular inflammation is coronary artery disease (48). Vascular 18F-FDG uptake is typically detected in atherosclerotic lesions and plaques, as these are large enough and show sufficient concentrations of inflammatory cells to generate a focal detectable PET signal. A possible application might be imaging of aggravated atherosclerosis by immune checkpoint inhibitor therapy. Measurable changes in coronary 18F-FDG uptake evoked by inflammatory reactions to radiation of the heart itself (e.g., in breast cancer patients) were not yet documented and are, thus, unlikely.

Another molecular imaging biomarker that can be beneficial for early assessment of cardiotoxicity is cardiac uptake of somatostatin receptor agonists. Somatostatin receptor PET using 68Ga-DOTATOC/DOTATATE is well established for staging or restaging of patients with neuroendocrine tumors but can also visualize myocardial macrophage infiltration (49). This visualization might enable earlier detection of myocardial inflammation than does cardiac MRI in patients with pericarditis, myocarditis, or subacute myocardial...
infarction and serve as a potential predictor of cardiac remodeling processes (49). Recent reports describe first applications of somatostatin receptor PET also in immunotherapy-induced myocarditis (50,51). Nevertheless, comprehensive analyses within the context of CTR-CVT remain absent in the current literature. The use of molecular imaging to assess expression of C-X-C chemokine receptor type 4 by 68Ga-pentixafor (as a possible indicator of myocardial inflammation (52)) or of matrix metalloproteinase activity (which could potentially serve as an alternative marker for vascular inflammation (53)) has not yet been documented in the field of CTR-CVT.

**Cardiac Remodeling**

A novel target structure for specific imaging of remodeling processes is fibroblast-activating protein (FAP), which can be targeted by 68Ga-labeled FAP inhibitors (68Ga-FAPI). 68Ga-FAPI PET is increasingly applied in a broad spectrum of indications. FAP is expressed in the microenvironment of many solid tumors (54), a reason why 68Ga-FAPI PET is increasingly used in staging and restaging of various oncologic diseases, but is also an indicator of activated fibroblasts which occur in tissue remodeling and fibrosis (55). In this context, fibroblast activation is also detectable in myocardial remodeling after cardiac injuries. Thus far, identification of FAP-positive cardiac myofibroblasts through 68Ga-FAPI PET imaging has been documented predominantly after myocardial infarction (56), in which fibrosis is not limited to the injured myocardium but also affects adjacent noninfarcted areas (57). 68Ga-FAPI PET imaging in the early phase of myocardial infarction has potential to prognosticate left ventricular remodeling after a follow-up time of 12 mo (58). Recent reports extend the field of application of cardiac 68Ga-FAPI PET toward other diseases, such as hypertrophic cardiomyopathy (59). In a murine model, cardiac uptake in 68Ga-FAPI PET reached its highest point during the initial stages of HF progression, reflecting the activation of myofibroblasts. Subsequently, this uptake gradually declined as the degree of fibrosis and the severity of HF increased (60).

First reports also mention that myocardial uptake seen on 68Ga-FAPI PET is a possible molecular imaging biomarker of early cardiac damage in patients under cytotoxic chemotherapy (61) and with immunotherapy-induced myocarditis (51,62). However, currently, the understanding of the pathophysiologic connection between the administration of cardiotoxic cancer drugs and the emergence of FAP-positive cells in noninfarction remodeling remains incomplete. Notably, a potential role of mitochondrial dysfunction as an inducer of cardiac fibrosis is a subject of discussion in the context of cytotoxic chemotherapy–induced effects (63). In this context, anthracyclines might exert their effects not only on cardiomyocytes but also on cardiac fibroblasts and endothelial cells (64). Moreover, crosstalk with immune cells leading to activation of fibroblasts, collagen deposition, and cardiac fibrosis is a key factor in the pathophysiology of myocarditis (65), and fibrosis was detected in endomyocardial biopsy samples of patients with immune checkpoint inhibitor myocarditis (66). However, we still lack systematic analyses to fully elucidate the processes that induce 68Ga-FAPI uptake in patients with CTR-CVT. Figure 2 shows example 68Ga-FAPI and 18F-FDG PET images of a patient with chemotherapy-induced cardiotoxicity.

PET imaging that targets αβγ integrin, such as 18F-galacto-arginine-glycine-aspartate, has the potential to serve as an additional molecular imaging biomarker for cardiac remodeling. This integrin is expressed by activated cardiac fibroblasts and serves as an indicator of angiogenesis, thus offering a promising possibility for evaluating changes in the cardiac tissue (67). However, it has not yet been clinically used in the context of CTR-CVT.

**Sympathetic Innervation**

Cardiac sympathetic innervation can be visualized by 123I-metaiodobenzylguanidine (MIBG) scintigraphy, which is also used for oncologic imaging of neural crest tumors. 123I-MIBG shows adrenergic uptake and storage and release patterns similar to those of norepinephrine and can, thus, be used to draw a picture of the efferent cardiac adrenergic innervation system (68). As molecular imaging biomarkers of the cardiac adrenergic system, the heart-to-mediastinum ratio and the washout rate between early and late images can be used (69). Alternatively, 123I-MIBG SPECT can be performed for derivation of quantitative or semiquantitative biomarkers from higher-quality and 3-dimensional images.

Dysregulation of the adrenergic innervation system, which contributes to the pathophysiology of CTR-CVT (68,70), can indicate HF at subclinical stages, and 123I-MIBG imaging is an approved diagnostic option in patients with HF (71). In conditions of cardiac damage, a compensatory sympathetic drive may be released to increase contractility, conduction, and heart rate (68). In a preclinical study of chemotherapy-induced cardiotoxicity, a decrease in 123I-MIBG uptake preceded a decrease in LVEF (72). Moreover, several clinical

**FIGURE 2.** (Left) 18F-FDG and 68Ga-FAPI PET (top) and PET/CT (bottom) images of 61-y-old patient with dedifferentiated chondrosarcoma of left radius with lung metastases. Dilated cardiomyopathy was diagnosed after chemotherapy (EUROBOSS protocol). 68Ga-FAPI PET images show increased uptake of left inferior wall (arrow), whereas 18F-FDG uptake cannot be evaluated because of high 18F-FDG uptake of left ventricular myocardium (no specific patient preparation for cardiac imaging was performed). (Right) Follow-up 18F-FDG and 68Ga-FAPI PET (top) and PET/CT (bottom) images 9 mo later still show increased 68Ga-FAPI uptake (arrow); 18F-FDG uptake (arrow) is discernable after suppression of myocardial glucose consumption. In these oncologic examinations, no specific patient preparation for cardiac 18F-FDG imaging was performed. Therefore, observed myocardial 18F-FDG uptake may be evoked by inflammatory processes of developing CTR-CVT but may also be consequence of incomplete suppression of myocardial glucose consumption. (Created with Biorender.com.)
studies showed promising results for $^{123}$I-MIBG imaging to detect early cardiotoxicity (73).

Molecular imaging of cardiac adrenergic innervation can also be performed with PET to benefit from improved image quality and the possibility of absolute quantification. One complementary PET tracer to $^{123}$I-MIBG is $^{124}$I-MIBG. Alternatively, the noradrenaline analog $^{11}$C-methylephedrine can be used. However, these tracers are available at only a few centers. A novel $^{15}$F-labeled alternative for imaging of sympathetic cardiac innervation is $^{18}$F-flurobenguane, which is expected to be approved soon (74). The availability of an approved highly specific tracer labeled with the standard radionuclide $^{18}$F will probably extend the clinical acceptance and application of molecular imaging of cardiac innervation in the context of cardiooncologic assessments.

**Mitochondrial Function and Regulated Cell Death Pathways**

Although most molecular imaging approaches indirectly visualize impairment of myocardial function, some radiotracers aim to directly indicate myocardial or even subcellular cardiac damage. With the growing awareness of the prominent role of mitochondrial dysfunction in the pathogenesis of CTR-CVT, mitochondria-targeted molecular imaging may arise as a ubiquitous biomarker of cardiac damage. One indicator of mitochondrial damage is a change in the mitochondrial membrane potential. In a preclinical setting, $^{18}$F-(4-fluorophenyl)triphenylphosphonium PET has been used to measure mitochondrial depolarization after anthracycline infusion (75). Other novel radiotracers that can indicate mitochondrial damage and were applied in preclinical models of CTR-CVT are $^{18}$F-mitopos (76) or $^{68}$Ga-gelmydar (77). Another novel radiotracer of interest in this field is $^{18}$F-DHMIT, which is a marker of reactive oxygen species and was shown to detect cardiac superoxide production as an effect of anthracycline-related cardiotoxicity before impairment of LVEF in a rat model (78).

Furthermore, indicators of necrosis or apoptosis can be examined and were, historically, applied in scintigraphy imaging. For example, $^{111}$In-antimyosin can show myocardial necrosis by binding to intracellular myosin if the sarcolemma is damaged (5). It was used in some patient studies for visualization of CTR-CVT (79). For imaging of apoptosis, $^{99m}$Tc-annexin V can be applied. $^{99m}$Tc-annexin V binds to phosphatidylserine, which is a membrane marker of apoptotic cells (5). In preclinical experiments, $^{99m}$Tc-annexin V imaging was used for visualization of doxorubicin-induced cardiotoxicity (80). In recent years, only a few studies have used imaging of the regulated cell death pathway in the context of CTR-CVT, but these techniques might find revival if PET imaging tracers become available.

**Biodistribution of CTR-CVT—Inducing Pharmaceuticals**

Some novel approaches use PET imaging to depict the biodistribution of cancer therapeutics. They can be used for both therapy planning and response assessment. Examples include studies with $^{89}$Zr-trastuzumab (81) and immuno-PET with radioactively labeled antibodies or small molecules targeting immune receptors (82). These examinations also offer the potential to assess cardiac accumulation of cancer therapeutics as a possible risk factor for the later occurrence of CTR-CVT. Similar approaches have also been applied in the development of peptide drug candidates for the treatment of cardiovascular diseases (83). The possibility of deriving prognostic factors from tracer uptake in off-target organs has also been demonstrated for $^{18}$F-FDG PET in response assessment of lymphoma patients to CAR T-cell therapy (84). However, applications in the field of CTR-CVT have not yet been described.

**Ventricular Function and Myocardial Perfusion**

Different molecular imaging techniques for ventricular function and myocardial perfusion have a long history in evaluating the cardiac function of patients with CTV. Equilibrium radionuclide angiography for assessing ventricular function has already been introduced. Moreover, gated myocardial perfusion imaging (MPI) can assess myocardial perfusion while also evaluating left ventricular function (including ventricular volumes, ejection fractions, wall motion, and phase analysis) in a single examination (85). This ability makes MPI a valuable tool in patients with adequate pretest probability. Like equilibrium radionuclide angiography, MPI has the advantage of high reproducibility and observer independence (86). Stress and rest MPI can also be used to assess ischemia, making MPI suitable for symptomatic patients before and after the use of cardiotoxic cancer therapies (87). In this context, MPI can play a unique role in the diagnosis of characteristic adverse effects, such as in assessing the exacerbation of atherosclerosis, which could result in acute coronary syndrome after treatment with immune checkpoint inhibitors (88,89). Additionally, MPI is relevant for evaluation of myocardial viability and remains a pillar for primary prevention in patients with chronic coronary syndrome, as well as being used for secondary prevention in patients with detectable myocardial perfusion defects after radiotherapy (90,91).

Because $^{18}$F-labeled perfusion tracers (e.g., $^{18}$F-flurpiridaz) will soon become available and PET scanners are becoming more widely accessible because of the success of PET in oncologic imaging, PET MPI is likely to gain importance—particularly outside the United States. This growing importance of PET MPI will make it a valuable tool for cardiooncologic surveillance, providing improved image quality and absolute quantification (92), which are essential for kinetic modeling approaches to quantify myocardial blood flow (93). Additionally, PET MPI enables evaluation of the integrity of the microvascular circulation and the epicardial vessels, which may be impaired by specific cancer therapy, particularly by radiotherapy (94).

**CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES**

Because of compensatory cardiac mechanisms, subtle myocardial changes evoked by CTR-CVT can occur even before a significant decrease in LVEF or strain imaging becomes evident. Therefore, monitoring additional biomarkers can improve pretherapeutic assessment, stratify patients to risk groups more precisely, and detect cardiotoxicity earlier, which may benefit timely initiation of therapy (68,95). In addition, investigation of additional biomarkers may help to unravel the underlying pathophysiology of CTR-CVT in each individual. Molecular imaging offers unique novel possibilities to detect even subtle changes in cardiac homeostasis.

On the one hand, additional information about CTR-CVT can be derived from oncologic investigations performed for staging or restaging—such $^{18}$F-FDG, $^{68}$Ga-FAPi, or $^{68}$Ga-DOTATOC/DOTATATE PET—and cardiac biodistribution of therapeutics could be evaluated from imaging studies within theranostic concepts. For example, cardiac uptake may be evaluated on $^{18}$F-FDG PET performed for oncologic staging or restaging. Figure 3 provides example $^{18}$F-FDG PET images of a patient with Hodgkin lymphoma showing differences in cardiac tracer accumulation before, during, and after chemotherapy. However, prospective studies to
evaluate the efficacy of $^{18}$F-FDG PET as a screening tool for CTR-CVT have not yet been performed. Additionally, retrospective analyses are often limited by the absence of heart-specific patient preparation (46), which may limit the value of the examination and is a potential disadvantage of $^{18}$F-FDG PET in comparison to other molecular imaging techniques. On the other hand, various specific molecular imaging biomarkers can represent specific pathophysiologic processes in the development of CTR-CVT and the beginning of changes at the subcellular level and along multiple pathways. These might be beneficial for clarification of results and to elucidate pathophysiologic mechanisms. Figure 4 provides an overview of the nuclear–cardiologic modalities used in cardiooncology.

**CONCLUSION**

Even if the establishment of a general molecular imaging biomarker for simultaneous oncologic assessment and evaluation of CTR-CVT is difficult to realize because of the diversity of pathologic processes, the different molecular imaging biomarkers may contribute to new personalized approaches to individual early detection, prevention, and timely initiation of treatment. Given the increased clinical relevance of CTR-CVT, in conjunction with multiomics data and other established imaging techniques, therapeutic strategies may be developed according to pathophysiologic phenotypes. All PET-derived molecular imaging biomarkers can be combined with PET/MRI to derive additional features for tissue characterization (96). Given the complex pathologic changes that are not fully understood, these concepts have the potential to enable a better scientific understanding of patient- and therapy-specific pathophysiologic processes through in vivo assessment of molecular interactions. Since clinical cardiooncologic monitoring has shown limited evidence of benefit in terms of mortality and survival, a deeper understanding is even more important.

Until now, evaluations of various novel molecular imaging biomarkers in larger patient cohorts have been missing. Prospective clinical trials will be essential to determine the role of molecular imaging in cardiooncology, to optimally harness its potential, and to decide which modalities are best suited to be integrated into multimodality approaches. Because of the clinical significance of CTR-CVT, these efforts appear crucial to achieve optimal personalized antitumor therapy while individually minimizing the risk of cardiovascular side effects.

**DISCLOSURE**

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