Curr. Treat. Options in Oncol. (2021) 22: 70
DOI 10.1007/s11864-021-00868-7

Cardio-oncology (MG Fradley, Section Editor)

Cardiotoxicity of Radiation Therapy: Mechanisms, Management, and Mitigation

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Published online: 10 June 2021

This article is part of the Topical Collection on *Cardio-oncology*

Keywords Cardiotoxicity · Radiation therapy · Cardio-oncology · Coronary calcification · Prevention

Opinion Statement

Radiation therapy is a key component of modern-day cancer therapy and can reduce the rates of recurrence and death from cancer. However, it can increase risk of cardiovascular (CV) events, and our understanding of the timeline associated with that risk is shorter than previously thought. Risk mitigation strategies, such as different positioning techniques, and breath hold acquisitions as well as baseline cardiovascular risk stratification that can be undertaken at the time of radiotherapy planning should be implemented, particularly for patients receiving chest radiation therapy. Primary and secondary prevention of cardiovascular disease (CVD), as appropriate, should be used before, during, and after radiation treatment in order to minimize the risks. Opportunistic screening for subclinical coronary disease provides an attractive possibility for primary/secondary CVD prevention and thus mitigation of long-term CV risk. More data on long-term clinical usefulness of this strategy and development of appropriate management pathways would further strengthen the evidence for the implementation of such screening. Clear guidelines in initial

cardiovascular screening and cardiac aftercare following radiotherapy need to be formulated in order to integrate these measures into everyday clinical practice and policy and subsequently improve post-treatment morbidity and mortality for these patients.

Introduction

Over the last three decades, we have seen a dramatic improvement in cancer survival, predominantly driven by better and earlier detection and improvements in therapeutic modalities. Alongside surgery and systemic therapies, radiotherapy (RT) plays an important part in the multidisciplinary optimization of longer-term cancer control. However, these improvements in cancer-specific outcomes come at a cost. Mortality, and especially cardiovascular (CV) mortality, among people with cancer who are alive at least 5 years after diagnosis is higher than for the general population [1]. Breast cancer, alongside lung cancer, and mediastinal lymphoma are the most commonly treated malignancies with RT that are in close proximity to the heart and have high probability of being enclosed in the RT field. In 2020, breast cancer accounted for approximately 14% of all cancer diagnoses in Australia and 6.3% of all cancer deaths [2]. The majority of patients who are diagnosed with breast cancer survive long after their treatment, and as such toxicity, especially CV disease, becomes an important issue. We have long had well-established risk stratification models for patients who are at risk of cardiac disease in the general population; and we now have emerging tools and models to help us further risk stratify and manage the oncology population.

Mechanisms of radiation-related cardiac damage

RT can have deleterious effects on several key tissues within the heart. Mechanisms of cardiac injury from RT are mainly related to microvascular changes and inflammation leading to longer-term fibrotic changes [3, 4]. Changes in the endothelium following RT result in reduced capillary-to-myocyte ratio, damage to the epicardial vessels leading to a prothrombotic state, and activation of inflammatory proteins leading to sustained inflammation [4]. Sustained inflammation is thought to accelerate atherosclerosis via increased recruitment of monocytes and macrophages to sites of active inflammation as well as vessel lumen occlusion secondary to prothrombotic environment and formation of fatty streaks within the vessels [3, 4]. Risk factors such as hyperlipidemia appear to shorten the time to atherosclerosis development, with studies showing multiplicative effect of irradiation and other risk factors in producing RT-induced atherosclerosis [5]. In studies using mouse models with established atherosclerosis, RT tends to cause structural changes in plaques leading to intraplaque hemorrhage, infiltration of macrophages leading to an unstable plaque that is vulnerable to thrombosis [6].

Myocardial changes following RT include myocardial fibrosis as a consequence of endothelial cell degeneration of myocardial capillaries [7]. This direct myocardial injury is further potentiated by endothelial injury leading to collagen deposition in the capillary walls and vascular stenosis resulting in worsening myocardial blood supply [8]. Cardiac valves, pericardium, and conducting system are generally spared in modern radiotherapy delivery, although these structures were frequently affected with older RT regimens.

Another increasingly recognized cardiovascular complication of RT is autonomic dysfunction (AD), presenting as abnormal heart rate recovery times and elevated resting heart rates. The incidence of AD has not been well described, mainly owing to the confounding variables and etiologies, such as pre-existing neuropathy, paraneoplastic effect, tumor invasion, cancer-related deconditioning, or an underlying autoimmune disease [9]. Additionally, a number of chemotherapeutic agents (e.g., platinum compounds, vinca alkaloids, taxanes, and anthracyclines) that are administered to patients receiving RT can cause AD [10], further complicating assessment of incidence of RT-related AD. The mechanism of RT-mediated injury to the components of the autonomic nervous system is postulated to be similar to the mechanism of its myocardial or endothelial damage descried above [9]. It is also important to note that AD has been reported after cranial, neck, and mediastinal RT [10]. Clinically, in addition to the obvious effects on the quality of life [4], presence of AD has also been shown to lead to worse outcomes in cancer patients [11].

Interaction of traditional cardiac risk factors and radiation

Armstrong et al. [5] performed a longitudinal study of 10,724 participants, evaluating the interplay between traditional cardiac risk factors such as hypertension, dyslipidemia, smoking, and diabetes mellitus and thoracic RT with matched siblings who did not undergo thoracic RT serving as controls. In that study, patients had a significantly increased risk of all cardiovascular events (CVE) compared to their matched siblings. Those patients who underwent RT in combination with anthracycline-containing chemotherapy had an even higher risk of cardiac events in their lifetime, than RT alone. Furthermore, patients treated with thoracic RT who developed two or more CV risk factors of which one was hypertension demonstrated a statistically significant increased relative excess risk for development of coronary artery disease, heart failure, valvular disease, and arrhythmia (27.9%, 18.3%, 60.9%, and 8.6% respectively) suggesting potentiation of risk for major cardiac events. However, when survivors had multiple CV risk factors that did not include hypertension, the excess CVE risk was not observed.

Timeline of radiation-related cardiac sequelae

Large case-control series have strongly suggested a cause and effect link between increasing radiation dose to the heart and subsequent major coronary events [12]. For every 1 gray (Gy) increase of dose to the heart measured by the mean heart dose, the relative risk of subsequent events increased by 7.4%. This shows that both baseline risk and extent of exposure to radiation are potentially modifiable risk factors which can be targeted.

Recently, the interval of time between the RT exposure and cardiac morbidity has come into question. Previously, the assumption was made that this time interval was measured in decades [13–17]; however, recent evidence has shown that this lag time is more likely to be months to years. A study examining risk of ischemic heart disease after radiation exposure in breast cancer patients [12] showed that there was a 16.3% increase in major cardiac events in the first 4 years after exposure and a 15.5% increase in cardiac events 5–9 years after

radiation exposure compared to controls who did not receive RT. Wang et al. performed a post hoc pooled analysis of 6 studies undertaking dose escalated RT to the thorax for non-small cell lung cancer [18]. In this study, 23% of patients had at least 1 cardiac event at a median of 26 months post RT, which included pericardial effusion, acute coronary syndrome, pericarditis, arrhythmias, and heart failure.

There are a number of clear paths towards improving CV outcomes for patients receiving chest RT: (i) technical innovations to reduce RT dose to cardiac structures; (ii) identification of patients undergoing RT, who are at high risk of CVE with a view to risk factor modification; and (iii) development of new models of care for cardiac care during and after RT.

Interventions to reduce the risk of cardiac disease

Increasing recognition that incremental cardiac RT dose increases the risk of cardiac events led to the development of a number of strategies to reduce cardiac dose [19], and some of these strategies have become standard of care today. Deep inspiration breath hold (DIBH) is a technique where the patient is asked to take a deep breath during delivery of dose, which reduces cardiac dose by displacing the heart away from the anterior chest wall with some intervening expanded lung. This results in significant reduction in cardiac tissue receiving radiation dose [20]. DIBH can be used for the majority of patients provided that they have sufficient respiratory function and a reasonable understanding and tolerance of the technique itself. Multiple studies have found that mean heart dose (MHD) and other cardiac dosimetric parameters have been significantly reduced by this technique [21, 22]. A retrospective study of 319 patients showed that DIBH significantly reduced the MHD from 5.2 to 2.7 Gy, V20Gy (the volume of heart receiving a dose of 20Gy) from 7.8 to 2.3%, and V40Gy (the volume of heart receiving a dose of 40Gy) from 3.4 to 0.3% [23]. Critically, DIBH reduces left anterior descending coronary artery dose [24]. A modelling study estimated that DIBH could reduce the radiation-induced cardiac death probability from 4.8% with free breathing to 0.1%, based on the dose reduction achieved with this strategy [25]. A number of studies have also examined respiratory gating, where treatment is coordinating with the breathing cycle, for patients undergoing breast cancer treatment [26, 27]. These studies have shown that respiratory gating can also significantly reduce cardiac dose compared to free breathing with comparable target volume coverage.

Alternative patient positioning has been extensively investigated as a method of decreasing cardiac exposure [19, 28, 29]. Prone patient positioning is often used in clinical practice for patients who have large pendulous breasts and has been shown to reduce cardiac dose [30]. It must be noted however that this does not apply to all patients: Obese patients receive significantly higher dose to the left anterior descending artery and to the heart when treated in the prone position [31]. A number of studies have also found that treating patients in a lateral decubitus position also decreases heart doses when compared to the traditional supine position [32, 33]. Bonsart et al. [32] reported mean heart doses ranging from 0.5 to 1.5 Gy for left-sided breast cancers and 0.25 to 0.52 Gy for right-sided breast cancers.

Improvements in techniques to deliver RT such as the evolution from 3D conformal RT (3DCRT) to the use of rotational techniques such as intensity modulated RT (IMRT) and volume modulated arc therapy (VMAT) have heralded an improvement in the ability to cover complex volumes while limiting dose to nearby organs at risk. Static forms of IMRT have been shown to significantly reduce mean heart dose compared to classical 3DCRT techniques while still achieving good coverage of specified target volumes [19, 33, 34]. Static forms of IMRT have also been shown to have equivalent locoregional control and overall survival from an oncological perspective [35]. More complex forms of IMRT such as VMAT or tomotherapy have proven dosimetric benefit in cases of complex anatomy; however, due to the low radiation dose wash, there is concern that late cardiotoxic sequelae may be increased and further long-term studies are needed to asses this [36].

Newer treatment modalities such as the use of proton therapy for treatment of breast cancer [19] have demonstrated improved coverage of target volumes while ensuring that organ at risk (e.g., heart) dose remains low [37]. A single-arm phase II trial examining the use of proton beam RT in patients who were otherwise considered suboptimal candidates for the technique demonstrated an excellent tolerance profile and no cardiac adverse events after 5 years of follow-up [38]. The radiobiologically equivalent MHD was 0.5 Gy, and the median dose to the left anterior descending coronary artery was 1.16 Gy. Of course, further evidence is needed in this space as this was a single-arm study with small patient numbers: This evidence may come from the RADCOMP breast cancer trial, which will be a phase III randomized trial comparing photon beam RT to proton therapy [39].

A number of studies have shown that in context of thoracic RT, traditional CV risk factors compound the risk of CVE [40]. Yet, both preclinical and clinical data examining the role of preventative measures in reducing the risk of modifiable CV risk factors in patients undergoing thoracic RT is scarce. The use of statins has been studied in 5718 cardiovascular patients undergoing thoracic or head and neck RT [41, 42], with results showing a strong trend towards reduction in cardiovascular and cerebrovascular events. After adjusting for age, sex, prior history of stroke/transient ischemic attack or myocardial infarction, diabetes mellitus, dyslipidemia, atrial fibrillation, chronic kidney disease, heart failure, and hypertension, statin use post-RT was associated with a non-statistically significant 15% relative risk reduction in CVE.

Although aggressive management of modifiable cardiac risk factors has not been extensively researched in the RT population, using evidence extrapolated from the general and high CV risk populations, it can be assumed that reducing these modifiable risk factors will also lead to a reduction in cardiac morbidity in the RT population. It is well established that aggressive management of hypertension in patients who have a high CV risk reduces further CVE and all-cause mortality [43, 44]. In both primary and secondary prevention, lipid lowering therapy has been shown to reduce the risk of CVE in the general population [45–47]. Aspirin use in the general population for primary prevention of CVE is not beneficial, mainly due to the offset of said benefit by the risk of bleeding [48]; however, the role of aspirin is well established in secondary prevention for patients with established CVD [49]. Modification of lifestyle factors such as increasing exercise, improvement of diet, and reduction of obesity also plays a significant role in reduction of cardiovascular risk in the general population

[50]. Another important avenue of reducing the risk of cardiac disease in breast cancer patients undergoing RT is incorporating mitigation of cardiac morbidity in survivorship programs.

Emerging strategies for identification of high-risk patients

A correlation between coronary artery calcium (CAC) scores and atherosclerosis has been known for many decades after a correlation was noted between CAC on fluoroscopy and adverse cardiovascular events [51, 52]. CAC refers to the deposited calcium in the coronary vessels that occurs as a result of chronic inflammation in atherosclerotic lesions [52]. A number of studies have noted that this can be assessed on computer tomography (CT) imaging to help quantify cardiovascular risk [53]. Importantly, CAC scoring has been shown in a number of large prospective trials, including the multi-ethnic study of atherosclerosis (MESA) [54], to be an independent predictor of cardiac risk, including coronary events, myocardial infarction, and all-cause cardiac mortality [52, 55, 56]. Another benefit of CAC scoring is its utility as a negative risk marker in circumstances where no CAC is present as shown in a number of studies [52]. A meta-analysis of 71,595 asymptomatic people showed that the event rate for cardiovascular events was 0.47% for those with a CAC score of zero, compared to 4.14% in those with a non-zero CAC score over a follow-up period of 50 months [57]. Studies have also shown that CAC score can improve the overall accuracy of CV risk assessment on top of the traditional risk calculators, such as the Framingham risk calculator [54, 58, 59]. This improvement is most marked in asymptomatic patients who are classified as intermediate risk on such traditional risk calculators [52].

Traditionally in the studies, CAC score has been performed on an electrocardiogram (ECG) gated non-contrast CT scan with 3-mm slice thickness, and scoring has been placed into groups based on a linear nominal score as per the Agatston method [52, 60]. However, studies examining the use of non-dedicated CAC scoring CTs, such as those used in RT planning, have shown them to be a reliable method of assessing CAC risk scores [61]. One such study compared the use of automated CAC scoring on planning CTs in patients undergoing breast cancer RT planning with that performed manually by an expert radiologist [62]. This study showed that automated CAC scoring on planning CTs was a reliable method of assessing CAC score, especially when a CT with breath hold technique was used for assessment. A meta-analysis by Xie et al. [63] found that the correlation between non-ECG triggered and ECG triggered CT scans was excellent ($r = 0.94$) with the false negative rate of 8.8% and no false positives. Incidental findings of positive CAC score is a common occurrence on non-contrast CT scans with one study finding a 24% positive [62] and another showing 78% positive [64]. This evidence highlights the potential utility in using RT planning chest CT scans as tools for opportunistic CV screening in patients with cancer. Figure 1 demonstrates typical appearance of coronary calcification on a routine planning CT. Recent guidelines from the British Society of Cardiovascular Imaging and the British Society of Cardiac Computed Tomography recommend the reporting of incidental coronary artery calcification on all non-gated thoracic CT [64].

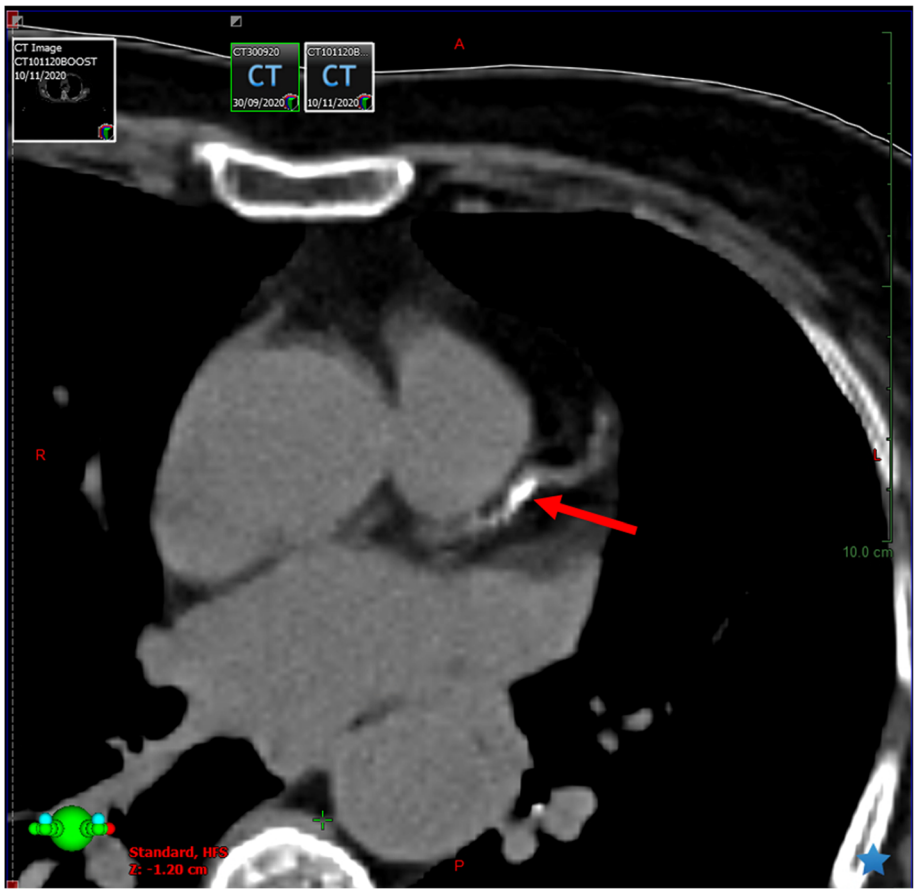

Fig. 1. Coronary calcification observed on routine planning CT performed as part of radiation therapy planning for breast cancer. Arrow (red) indicates significant left anterior descending coronary artery calcification

Some evidence has suggested that incidental finding of CAC is very common [64]. In a study reviewing RT planning CT scans for early stage lung cancer, 78% had a positive CAC score, and 61% of those patients had no pre-existing diagnosis of coronary artery disease; hence, many of these patients were not on any therapy aimed at primary CVD prevention [64]. A number of studies in the non-oncology population have shown that CAC scoring may have the ability to be a significant aid in decision-making for consideration of commencement of pharmacotherapy for primary prevention of CAD [65–67]. CAC scoring has been shown to be very useful in guiding who will benefit most from statin therapy, with one study showing that the number needed to treat (NNT) to prevent one coronary event was 549 for individuals with CAC score = 0 and 24 for those with a CAC score > 100 [66]. Another large long-term study has verified these results showing a significant reduction in risk of major coronary events in the general (non-oncology) population [67]. CAC scoring has also aided in identifying a subgroup of patients (CAC score > 100), in whom prophylactic aspirin may be of benefit in primary prevention [65]. In this study, the NNT with aspirin to prevent one coronary event was significantly less than the number needed to harm for significant bleeding [65].

The most appropriate group of patients to undergo CAC assessment for prognostication are those who fall into the intermediate risk category by Framingham criteria [52]. Evidence has shown that the net reclassification improvement of CAC scoring in addition to the Framingham risk equation was 52% for those initially in the intermediate risk Framingham group, 12% in the low risk group, and 34% in the high risk group [68]. Cardiac Society of Australia and New Zealand (CSANZ) position statement on CAC scoring [69] suggest that CAC scoring is not appropriate for symptomatic patients and it must also be noted that CAC scoring does not report the burden of non-calcified plaques [70]. This, of course, adds to the complexity of using opportunistic CAC screening in the oncology setting, as detailed CV assessments, and even more so, Framingham risk scores are seldom performed during oncological management and follow-up.

Some other issues surrounding the use of CAC scoring in the oncology clinic include (i) psychosocial issues such as whether patients can handle this complex information at or near the time of diagnosis of a new malignancy and subsequent to that; (ii) will this significantly increase the time spent in the initial consultation in oncology clinic; (iii) risks associated with other incidental findings when investigating after the diagnosis of a non-zero CAC score and then risks associated with their investigation; and (iv) how do we synthesize this information into conversation with the patient as such that the patient understands the risks and benefits and can participate in reasonable informed consent. The answers to these questions may take some debate to answer in the oncology setting.

Current guidelines

At present, there is a notable paucity of guidelines regarding the management of RT-related cardiac complications in patients undergoing RT for breast cancer. Many of the guidelines focus on risk management after systemic therapy, as cardiac effects of anthracyclines, HER2 directed agents, and other agents are becoming increasingly more recognized. Only recently has there been an emergence of recognition of the need for such guidelines. In 2013, the European Society of Cardiovascular Imaging and the American Society of Echocardiography released a consensus statement regarding the recommended screening for cardiovascular complications of RT in adults [71]. The key recommendations in this statement are as follows:

- Referral of all patients receiving anterior or left-sided thoracic irradiation for cardio-oncology review
- Comprehensive cardiovascular history and examination as well as baseline echo at the initial presentation with the radiation oncologist
- Yearly history and examination focusing on controlling risk factors by treating radiation oncologist
- If patient is asymptomatic and not high risk, echo at 10 years and then 5 yearly thereafter
- If the patient is asymptomatic and high risk, echo at 5 years and 5 yearly thereafter and stress echo at 5–10 years and 5 yearly thereafter

High-risk patients are defined in the above document as those receiving anterior or left-side chest irradiation with one or more of the following risk factors:

- Age < 50 years at time of treatment
- High prescribed dose to tumor >30 Gy
- High dose of radiation fractions >2Gy/day
- Previous or planned chemotherapy with anthracyclines
- Presence of one or more of the traditional risk factors (obesity > 30 BMI, smoker, hypertension, dyslipidemia, diabetes, pre-existing CVD)

Improving cardiovascular outcomes—way forward

Cardiovascular disease-related mortality among people with cancer who are alive at least 5 years after diagnosis is consistently shown to be higher than for the general population [1]. Thus, every effort needs to be made to reduce this excess cardiovascular disease burden for patients living with and beyond cancer.

Improvements in long-term cardiac outcomes in patients who have undergone thoracic RT for breast cancer can only be achieved if we are armed with the correct tools and knowledge to identify the patients at risk, detect abnormalities reliably and early, and have management plans and means to alter the adverse outcomes. Throughout medicine, shifts in focus and changes in practice have been led by research, creation of consensus statements from expert bodies, and creation of structured care tools to allow for this new information to become part of everyday practice. All clinicians involved in the care of cancer patients play a key role in their overall long-term care and management either by actively managing these issues or facilitating referrals to those who can; thus, it is pivotal that they are aware of the RT-related CV risks as well as monitoring and mitigation strategies. Education and raising awareness of these complications among patients and physicians are vital to achieve this goal. Reporting of cardiac radiation dose on end of treatment summaries so that physicians have a record for future is another such strategy that should become everyday practice.

Opportunistic screening has been employed in a variety of other settings for early detection of malignant and non-malignant diseases. Recent evidence has now highlighted another potential avenue for opportunistic screening: CAC scoring on RT planning CT scans to screen for asymptomatic coronary artery disease. In the future, this may lead to an opportunity where an automated screening tool can be built into planning systems to allow for an easier referral pathway for risk stratification and cardiology review.

Care plans and survivorship programs have always been a vital part of oncology practice. They allow for automation and verification that all parts of the aftercare and the referral process have been adequately completed. Simple tools acting as a reminder or as an automated way of generating a referral can be built into our record keeping system to be done at the completion of treatment. Another vital part to the success of cardiac screening in patients undergoing RT to the thorax is the involvement of oncology clinical nurse consultants as a way of ensuring that all parts of the aftercare are completed and any referrals are made in a timely manner.

Funding

This work is supported in part by the National Heart Foundation Future Leader Fellowships (DTMN [104814] and ALS [101918]), NSW Health EMCR Fellowship (DTMN), NSW Health Cardiovascular Capacity Building

EMC Grant (ALS), Hunter Cancer Research Alliance New Strategic Initiatives Grant (ALS and DTMN), and John Hunter Charitable Trust Grants (DTMN and ALS).

Compliance with Ethical Standards

Conflict of Interest

Philippa Ell declares that she has no conflict of interest. Jarad Martin is a contractor and shareholder for GenesisCare. Daniel A. Cehic declares that he has no conflict of interest. Doan T.M. Ngo declares that she has no conflict of interest. Aaron L. Sverdlov has received an equipment loan for research support from Roche Diagnostics Pty Ltd., an unrestricted educational grant from Celgene Pty Ltd., and a conference sponsorship grant from Bristol-Myers Squibb Australia Pty Ltd.

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