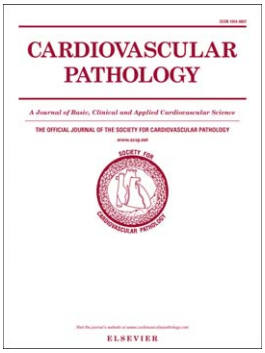

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Winning the Battle, but Losing the War: Mechanisms and Morphology of Cancer Therapy-Associated Cardiovascular Toxicity

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Introduction

In the United States, the lifetime risk of a cancer diagnosis is nearly 40%; in 2016 that represents almost 1.6 million new patients, and despite advances in early diagnosis and treatment, roughly 35% will ultimately die of their malignancy. Fortunately, the number of patients living with a cancer diagnosis also continues to expand, anticipated to be more than 19 million in less than a decade [1]. In calculating the relative risks and benefits of therapy it is therefore important to consider the morbidity and mortality associated with anti-tumor therapy itself. Significantly, excluding demise due to the cancer itself, treatment-induced adverse cardiovascular events are the leading cause of death in affected patients [2-4]. Chemotherapy, targeted therapies, immune check-point inhibition, and radiation therapy can all adversely impact cardiac function, and their effects can be synergistic. Consequently, it is important that possible side-effects of therapy be recognized and effectively controlled. To address this burgeoning clinical need, several institutions have established cardio-oncology divisions to manage the cardiac complications of therapy in cancer patients and survivors. As of 2015, there were at least 49 such Cardio-Oncology Centers in the United States [5]. Patients are often followed presumptively based on total dosing (e.g., for anthracycline therapies), or by non-invasive biomarkers or imaging (e.g., troponins and echocardiogram). In other circumstances, cardiac biopsy and histologic evaluation may be required, typically to confirm or exclude other causes of acute or chronic heart failure.

The goal of this review is to highlight the mechanisms and morphology of the cardiac injury associated with the more common forms of cancer therapy. Although for many cases the histologic findings are non-specific, in the appropriate clinical context, therapeutic cardiotoxicity can be inferred and the treatment approach refined appropriately.

Cancer Therapy-Associated Cardiotoxicity

Chemotherapy-induced cardiotoxicity can be categorized into five basic pathophysiologic categories: 1) cardiac systolic dysfunction, 2) ischemia, 3) arrhythmias including repolarization abnormalities such as QT prolongation, 4) pericardial disease and 5) thrombophilia (Table 1). Radiation therapy can also induce cardiac disease,