



Cardiac MRI for Detecting Early Cardiac Toxicity after Proton Therapy for Hodgkin Lymphoma

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Dear Editors:

During the past several decades, substantial improvements in the treatment of Hodgkin lymphoma (HL) have led to improved prognosis after diagnosis [1]. Focus has shifted to mitigating the late toxicities associated with treatment. Both anthracycline chemotherapy and thoracic radiotherapy (RT), mainstays of HL treatment, are known cardiotoxic agents [2, 3]. Although modern treatment techniques, such as intensity-modulated radiotherapy and proton therapy (PT), have allowed radiation oncologists to drastically reduce RT doses to the heart, even small RT doses can increase the risk for late cardiac disease in long-term survivors [4–7]. Subclinical changes associated with RT-related cardiac disease likely precede the development of symptomatic disease [8]. There has been substantial interest in identifying noninvasive methods to determine patients at greatest risk for developing cardiac disease after RT and/or chemotherapy [9]. We report the results of a small, prospective study investigating the value of cardiac magnetic resonance imaging (MRI), at 5 years after RT, in identifying patients with RT-associated cardiac damage.

We conducted an institutional review board–approved prospective study of 5 patients treated with chemotherapy and PT for mediastinal HL. Patients were treated with PT between October 2009 and December 2010, and cardiac MRI scans were performed between June 2015 and October 2015. The PT was delivered via passive-scatter techniques. Free breathing or deep inspiration breath holds were used at the treating physician's discretion to minimize heart dose [10]. Demographic data and initial treatment details of the 5 patients are summarized in **Table 1**.

All patients had pretreatment echocardiograms reporting left ventricular ejection fraction (LVEF); all were within reference range. No patient had any diagnosis of cardiac disease at the time of treatment. Patients were treated with doxorubicin, bleomycin, vinblastine, and dacarbazine–based (ABVD) chemotherapy, followed by involved-site proton RT [11, 12]. Radiation dose distributions to the heart were calculated before treatment.

At 5 years, no patients had cardiac symptomatology. Gadolinium-enhanced cardiac MRIs were performed approximately 5 years after treatment, along with a transthoracic echocardiogram (TTE) and a serum brain natriuretic peptide (BNP). No patients had MRI evidence of cardiac dysfunction. The median LVEF on cardiac MRI (LVEF_{MRI}) was 60% (range, 52%–61%), which generally agreed with the LVEF calculated by TTE (**Table 1**). Two patients did experience a decline in the LVEF_{MRI} > 5% in the 5 years after treatment compared with their initial LVEF, as calculated by TTE. Those 2 patients were the only 2 patients to receive a mean cardiac RT of ≥ 10 Gy and a cumulative anthracycline dose

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Editorial

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Table 1. Demographic and treatment characteristics of studied patients treated for Hodgkin lymphoma.

Patient No.	Age at diagnosis,			RT prescription dose, Gy (RBE)	Cumulative anthracycline dose, mg/m ²	Mean heart RT dose, Gy (RBE)	Mean LAD RT dose, Gy (RBE)	Mean LV RT dose, Gy (RBE)	Mean RV RT dose, Gy (RBE)	Pretherapy LVEF TTE, %	LVEF		
	y	Sex	Stage								on 5-y cardiac MRI, %	LVEF on 5-y TTE, %	5-y Pro-BNP, pg/mL
1	19	F	IIB	39.6 ^a	350	19.7	32.2	10.1	27.9	60	53	50	182.4
2	25	F	IIB	36	300	13.8	33.4	20.1	12.4	72	61	60-65	95.4
3	40	F	IIB	30.6	175	2.1	9.0	0.1	0.5	54 ^b	60	60-65	120.0 ^c
4	37	M	IIB	36	200	10.1	2.9	2.1	3.4	51	52	55-60	29.1
5	22	M	IB	30.6	300	7.6	4.6	0.0	14.4	59 ^d	54	50-55	22.0

Abbreviations: RT, radiotherapy; RBE, relative biological effectiveness; LAD, left anterior descending artery; LV, left ventricle; RV, right ventricle; LVEF, left ventricular ejection fraction; TTE, transthoracic echocardiogram; MRI, magnetic resonance imaging; BNP, brain natriuretic peptide; ABVD, doxorubicin, bleomycin, vinblastine, dacarbazine.

^aTreated with deep inspiration breath hold.

^bAfter third cycle of ABVD.

^cDrawn 6 y after treatment completion.

^dAfter sixth cycle of ABVD.

exceeding 250 mg/m², both known risk factors for the development of late cardiac disease [13]. Interestingly, the patient who received the most cardiotoxic therapy (patient 1) was the only one who also had an elevated BNP (182.4 pg/mL; the upper limit of the reference range at the testing laboratory was 125 pg/mL).

In this small, prospective analysis, we show that cardiac MRI, as performed at our institution, at 5 years after treatment, did not identify significant cardiac changes, even in patients who received a relatively high burden of cardiotoxic therapy. Two patients with normal cardiac MRI findings did have a decline in LVEF_{MRI}, although both patients' LVEF_{MRI} remained within reference range. Because the 2 patients with LVEF_{MRI} decline had the highest mean cardiac radiation dose and cumulative anthracycline dose—predictive factors for late cardiac disease—it is possible that these early LVEF_{MRI} declines will predict later cardiac dysfunction. Symptomatic cardiac disease may take many years to develop when the heart is only exposed to modest RT doses. A Japanese study evaluating late-gadolinium enhancement on cardiac MRI, as a marker of RT-induced myocardial damage in survivors of esophageal cancer, found that at approximately 2 years after treatment, no evidence of myocardial damage was seen in areas receiving doses < 40 Gy [14].

The burden of cardiac disease in survivors of HL is significant. Compared with the general American population, children and adolescents treated for HL have a 29.6-fold increased risk of death from cardiac disease [15]. With long-term follow-up, a high incidence of subclinical cardiac disease has also been documented. A German study of 20-year survivors of HL, treated with mediastinal RT, showed reductions in LVEF in 23% of patients and perfusion deficits in 68% on cardiac MRI [9]. An analysis of 1820 American, adult survivors of childhood cancer showed that echocardiography could identify either abnormal LVEF or other evidence of cardiac dysfunction in 37% of patients treated with either anthracycline chemotherapy, chest-directed RT, or both. These analyses clearly exemplify the need to optimize screening methodologies to detect cardiac disease at its earliest stages in survivors of HL because early detection and treatment may improve cardiac function in these patients [16]. Current screening guidelines for cardiomyopathy in survivors of childhood cancer recommend echocardiography as the primary method of detection, with MRI (or radionuclide angiography) used only in those for whom echocardiography is not feasible or optimal; however, an acknowledged evidence gap is the prognostic utility of cardiac changes identified by cardiac MRI [17].

There are several limitations in this analysis. Foremost, only a small sample of patients was evaluated in this pilot study. Another is the inherent intraobserver and interobserver variability in the measurement of LVEF by cardiac MRI as the primary method of evaluation for cardiac effects; prior studies have estimated that variability at approximately 4% [18]. We attempted to ameliorate that variability by correlating to TTE results. Future studies will likely require the evaluation of other endpoints beyond LVEF, including global longitudinal strain and measures of diastolic dysfunction, to best identify survivors at the greatest risk of treatment-related toxicity in the most expeditious manner possible.

We report a small study regarding the use of cardiac MRI to detect early evidence of cancer therapy-related cardiotoxicities in survivors of HL. We show that, despite ample evidence of the frequency of imaging abnormalities with > 20 years of follow-up, at 5 years, cardiac MRI is not of substantial utility in the detection of such abnormalities. Early declines in LVEF_{MRI} were seen in patients receiving large burdens of cancer therapy (≥ 250 mg/m² of anthracycline and ≥ 10 Gy mean cardiac RT

dose), which may be a harbinger of further dysfunction. Larger prospective investigations will be necessary to identify methods capable of demonstrating early changes predictive of late effects in patients who may benefit from early detection.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Nancy P. Mendenhall, MD, is Editor-in-Chief of the *International Journal of Particle Therapy*. Bradford S. Hoppe, MD, MPH, is an Associate Editor of the *International Journal of Particle Therapy*. Additionally, Bradford S. Hoppe, MD, MPH, is on the scientific council for Merck & Co., Inc. The authors have no additional conflicts of interest to disclose.

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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