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Natural History of Myocardial Deformation in Children, Adolescents and Young Adults Exposed to Anthracyclines: Systematic Review and Meta-Analysis

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Abstract

Objective: Anthracyclines are widely used to treat solid and hematologic malignancies, but are known to cause cardiotoxicity. As more childhood cancer survivors reach adulthood due to improvements in oncologic treatments, they become susceptible to late and progressive anthracycline-induced cardiotoxicity. Nonetheless, diagnostic criteria for early detection of cardiac dysfunction are not well defined in children, adolescent, and young adult group (CAYA, ages 1 to 40 years). We present a natural history of the changes in myocardial deformation in CAYA patients after anthracycline therapy.

Methods: We performed a literature review search between 2001 and 2016 using Pubmed with the following search terms: strain (or deformation), torsion (or twist), children (or adolescent or young adult), cardiotoxicity (or dysfunction), and anthracyclines (or doxorubicin). A total of 23 articles were reviewed. Fourteen articles were incorporated in the meta-analysis.

Results: Strain abnormalities are observed at both short-term and long-term follow-up. Global longitudinal strain (GLS) abnormalities are common during or early after chemotherapy, whereas changes in global circumferential strain (GCS) are more significant and consistent on long-term follow-up. Although global radial strain and torsional parameters are also often abnormal late after chemotherapy, there are few studies evaluating these parameters.

Conclusion: There are significant abnormalities in GLS and GCS following anthracycline therapy acutely and late after treatment. The prognostic value of these strain abnormalities warrants further investigation.

Keywords

Cardiac toxicity; myocardial strain; transthoracic echocardiography

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1. INTRODUCTION

Anthracyclines have been used since the 1950's to treat many solid and hematologic malignancies, and are known to cause cardiotoxicity [1–3] in a dose-dependent relationship [4]. The risk of cardiovascular disease-related morbidity and mortality is 8 times higher in anthracycline-treated cancer survivors than in the general population, and persists up to 45 years after treatment [5]. As increasing numbers of childhood cancer survivors reach adulthood due to improved cancer treatments, more of these survivors will be affected by the long-term cardiac consequences of anthracycline therapy. As of 2008, there were 619,000 cancer survivors under the age of 40 in the United States, a number which is likely to increase with improvements in diagnosis and treatment protocols [6,7]. Despite the burden of cardiovascular morbidity and mortality in childhood cancer survivors, especially in the children, adolescent, and young adult group (CAYA – 1 to 40 years of age), sensitive diagnostic tools for evaluating subclinical dysfunction are not well defined.

Classification of cardiotoxicity can be based on chronology: acute (during treatment), early chronic (<1 year after treatment), and late chronic (>1 year after treatment). Subclinical myocardial dysfunction can develop during or after anthracycline treatment and is estimated to occur in 20 to 75% of survivors [8]. Acutely, anthracyclines cause transient electrophysiological changes and mild changes in myocardial contractility, which may be reversible after treatment [9,10]. Early- and late-onset cardiotoxicity are defined by heart failure, pericardial effusions, or dilated cardiomyopathy [9]. Children tend to present with asymptomatic restrictive and dilated cardiomyopathy [10].

The current paradigm for detection of chemotherapy-related cardiotoxicity is symptomatology of congestive heart failure or >10% decline in echo-derived left ventricular ejection fraction (LVEF) [11]. This practice has significant limitations because subclinical myocardial damage often occurs in the presence of a stable LVEF. The deterioration in LVEF is frequently only seen late when irreversible damage has already occurred [12]. Myocardial strain (or deformation) imaging has been proposed as a more sensitive surrogate for assessing myocardial function of cancer survivors [2].

Because large-scale studies to assess the natural history of anthracycline-related cardiotoxicity in the CAYA group are lacking, we aim to systematically summarize the effect of anthracyclines on myocardial deformation in CAYA with cancer or survivors of childhood cancers classified by timing of echocardiographic evaluation.

2. METHODS

2.1 Data sources and searches

A literature search was performed based on recommendations from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews [13]. Various combinations of the following terms were searched using PubMed: strain (or deformation), torsion (or twist), children (or adolescent or young adult), cardiotoxicity (or dysfunction), and anthracyclines (or doxorubicin). The time frame was limited to 2001–2016. The last date searched was April 25, 2016. For one article,

unpublished data was obtained directly from the author [14]. Data was estimated from figures if numerical values were not provided.

2.2 Data selection, abstraction, synthesis, and analysis

The studies were limited to those focusing on the effects of anthracyclines on myocardial strain in subjects between 1 and 40 years of age, both during and after treatment. Two authors reviewed the titles and abstracts for appropriateness. The articles include observational, cross-sectional, and case-control studies. Studies of anthracycline exposure in CAYA were divided into three groups based on the duration of anthracycline exposure: during or less than one year after treatment (acute and early-chronic), 1–10 years after treatment (intermediate-late chronic), and ≥10 years after treatment (late-chronic). Because studies of anthracycline toxicity in the CAYA group described the risk of cardiotoxicity as a function of cumulative doxorubicin dosages, the total cumulative anthracycline dose was derived by taking the sum of the calculated doxorubicin-isotoxic dose equivalents [15]: [doxorubicin × 1] + [daunorubicin × 0.833] + [epirubicin × 0.67] + [idarubicin × 5] + [mitoxantrone × 4]. Cutoffs for anthracycline cardiotoxicity are as follows: doxorubicin >500 mg/m^2, liposomal doxorubicin >900 mg/m^2, epirubicin >720 mg/m^2, mitoxantrone >120 mg/m^2, and idarubicin >90 mg/m^2. The meta-analysis portion was used to increase population size for two measures of myocardial deformation, GLS and GCS, which have been shown to be feasible and reproducible markers of myocardial injury [16] in adult patients. A meta-analysis was performed to evaluate the consistency of the change in GLS and GCS after chemotherapy across the available studies in the literature. Studies included in the meta-analysis were weighted based on the inverse of the reported standard error (and therefore indirectly to the sample size). Studies with smaller standard error and larger sample size were given more weight in calculating the pooled effect size. The heterogeneity among studies was determined using Cochran's Q [17], which is based on Chi-square test with significance defined as $p<0.10$ [18]. Heterogeneity was also quantified using I^2 [19]. Low, moderate, and high degree of inconsistency corresponds to I^2 values of 25%, 50%, and 75%, respectively. A random-effects model was chosen to assess for standard mean difference (SMD) of global longitudinal strain (GLS) in two groups (pre- versus post-treatment and post-treatment versus normal controls) and global circumferential strain (GCS) in one group (post-treatment vs normal controls).

2.3 Myocardial deformation imaging parameters

Strain, defined as the percentage of change in myocardial wall length, was measured by using tissue Doppler imaging (TDI), speckle tracking echocardiography (STE) in both 2D and 3D, or velocity vector imaging (VVI) [16,20,21]. Longitudinal (LS) and circumferential (CS) strain describe active strain or shortening of the fibers while radial strain (RS) measures passive strain or thickening of the myocardium [16]. Global strain represents the average strain of the entire myocardium for each respective direction [16], whereas segmental strain refers to shortening or lengthening of a specific portion of the myocardium based on the 16- or 17-segment model [22]. Strain rate (Sr) is the rate of change in strain (reported as strain per second). Rotational mechanics represent myocardial rotation around the axis of the LV at the base and apex [16]. Twist is the absolute apex-to-base difference in rotation reported in degrees while torsion is the base-to-apex difference of the rotation angle

divided by the axis of the LV and is reported in degrees per centimeter. Rotation and twisting velocity, reported in degrees per second, are calculated by dividing by the time-in-systole [16,23,24].

3. RESULTS

The search returned 131 articles, 23 of which were included in this review (Figure 1). Fourteen papers provided quantitative strain data and were used for the meta-analysis (Figures 2 and 3). Figure 2 illustrates the standardized mean difference (SMD) and 95% confidence intervals (CI) of GLS between patients pre- and post-anthracycline therapy. The pooled data in Figure 2 suggest that GLS is a suitable biomarker and can detect a change in myocardial function across a wide spectrum of anthracycline dosages with good agreement among the included studies. Figure 3 and figure 4 illustrate the SMD and 95% CI of GLS and GCS respectively in patients post-anthracycline therapy versus control subjects. Compared to the data in Figure 2, pooled data in Figure 3 and 4 show less agreement because of variations in the average anthracycline doses, time-to-evaluation, and technique for strain quantification.

3.1 Reference values for myocardial deformation in CAYA

Differences in strain between groups are described as absolute changes in the strain magnitude with the convention that LS and CS are negative and RS is positive. The following values were used as reference ranges for strain [25] (mean [95% CIs]): GLS (−20.2 [−20.8 to −19.6]), global CS (GCS) (−22.3 [−24.6 to −19.9]), global RS (GRS) (45.2 [38.8 to 51.7]). Levy et al [25] further separated the strain values by age (0–1, 2–9, 10–13, and 14–21 years-of-age), and age-specific values were used as reference when appropriate. For young adults older than 21 years of age, adult strain reference values were applied [26] (mean [95% CIs]): GLS (−19.7 [−20.4 to −18.9]), GCS (−23.3 [−24.6 to −22.1]), and GRS (46.3 [43.6 to 51.0]).

3.2 Acute and early (<1 year post-treatment) evaluation of strain

Seven studies [27–33] investigated strain during or less than 1 year after anthracycline exposure (Table 1). All studies assessed strain at baseline and over the course of chemotherapy [27–31,33], except Pignatelli et al [32] who measured myocardial strain only post-treatment. Several studies (3 of 7 studies) compared post-treatment patients to healthy controls [31,33] or reference values in healthy children [32]. Ganame et al [27] used TDI while 2D-STE was used in the other studies. The average anthracycline dose in the seven studies was below conventional and established thresholds for high-risk of cardiotoxicity (normalized to doxorubicin, <500 mg/m^2). One study evaluated the relationship between change in strain with respect to patient age [32].

3.2.1 Longitudinal Strain.—The decrease in GLS during or immediately following treatment compared to baseline values ranged from 8.2% to 19% [27,28,30,31,33]. Post-treatment GLS was 6.7% to 20% lower compared to control values [31–33]. All post-treatment GLS values fall outside the reference range [25] except for the 1–4 year-old and 10–14 year-old groups in Pignatelli et al's paper [32]. The majority of segmental LS values

were significantly decreased as well. The left-ventricular (LV) basal LS decreased by 14% [27] to 16% [33], mid LS decreased by 11% [27] to 12% [33], and apical LS decreased by 11% [28]. Three papers [27,28,31] showed significant changes in GLS rate (GLSr) from 12% [28] to 18% [27], though most post-treatment values remained within reference range [34]. Two studies [29,30] showed that severity of LS abnormalities after chemotherapy varies based on the echocardiographic view; the most significant reduction was seen in the apical long axis view (40% decrease) with more modest changes in the apical 4 chamber and apical 2 chamber views (8.7%, and 13% decrease, respectively).

3.2.2 Circumferential Strain.—All post-treatment values of GCS [31,32] were outside the reference range [25], indicating that GCS in cancer survivors can deteriorate as early as 1 year after treatment. Mavinkurve-Groothuis et al [31] reported a 13% decrease in GCS and a 12% decrease in GCS rate (GCSr) from baseline to post-treatment in patients. Pignatelli et al [32] compared GCS values 1-year post-treatment to normal reference values [35] according to age (1–4, 5–9, 10–14, and 15–19 years of age). The reduction in GCS was greater with older age.

3.2.3 Radial Strain.—Ganame et al [27] and Mavinkurve-Groothius et al [31] compared baseline and post-treatment GRS, and GRS rate (GRSr) in patients; both studies showed a significant reduction in GRS (39% and 17% respectively), and GRSr (19% and 12% respectively) after anthracycline treatment. However, the post-treatment GRS was not significantly different when compared to healthy controls in one of the studies [31]. When compared to reference values [25], the patients in Ganame et al's [27] study had markedly elevated baseline GRS (74 ± 14%) which decreased after each of the 3 doses of anthracycline administration (56 ± 11% to 52 ± 12% to 45 ± 11%).

3.3 Evaluation of strain 1 to 10 years post-treatment

Ten papers [14,20,21,24,36–41], nine of which were cross-sectional studies [14,21,24,36–41], assessed changes in strain parameters 1 to 10 years after anthracycline treatment in patients aged 6.9 to 24 years (Table 2). All studies compared patients treated with anthracyclines to healthy controls except Ryerson et al [14]. Patients were treated with average or median doses of anthracyclines (normalized to doxorubicin) ranging from 220 to 401.1 mg/m^2. Strain was assessed in images captured by TDI [37,39], 2D-STE [14,24,36,38,41], 3D-STE [40] and VVI [20,21].

3.3.1 Longitudinal Strain.—Eight articles [14,20,21,24,37–39,41] assessed GLS following anthracycline administration and showed inconsistent findings. Four of the 8 studies [20,24,37,39] found that anthracycline administration was associated with a significant decrease in GLS. Moon et al [20] and Cheung et al [24] reported similar findings where the GLS was on average 7.4% lower in the patient group compared to controls. Yagci-Kupeli et al [39] did not provide numerical data. Ganame et al [37] graphically demonstrated that, while there is a similar pattern of regional variation in the strain values from base to apex in the septum and lateral LV wall, the absolute strain values are approximately 25% lower in patients compared to the control group. In contrast to the studies mentioned above, Park et al [21] showed that GLS was not significantly different in patients compared to

controls; however, patients did have significantly lower LS, diastolic Sr, and systolic Sr in the septum when compared to the lateral LV wall. Toro-Salazar et al [38] showed slightly increased GLS in patients versus controls; however, this trend was reversed with MRI-derived strain values. In contrast, Ryerson et al [14] showed a nonsignificant improvement in GLS in patients who received low-, moderate-, or high-dose anthracyclines compared to controls (35% increase, 22% increase, and 8.0% increase respectively), but GLS measurements were performed only in the apical 4-chamber view. The study by Ryerson et al [14] was unique because the control group consisted of 21 anthracycline-naïve cancer survivors, 15 of whom were overweight or obese which may account for the baseline lower strain values in the control group [42,43]. Lastly, Yu et al [41] found similar strain values between patients and controls, however no numerical values were provided.

Most of the studies also evaluated Sr and similarly found variable results [14,20,24,37,39]. Ganame et al [37] and Yagci-Kupeli et al [39] found that GLSr was significantly lower in patients compared to controls (data shown graphically in Ganame et al's article, and not provided by Yagci-Kupeli et al). In contrast, Cheung et al [24] and Ryerson et al [14] showed that changes in GLSr were similar between patients and controls. Moon et al [20] found diastolic LSr, but not systolic LSr, to be significantly lower in patients (12% lower than controls).

3.3.2 Circumferential Strain.—Of the four studies which examined CS, all showed consistently abnormal values in patients 1 to 10 years post chemotherapy [20,24,38,41]. Yu et al [41] examined transmural strain at the basal, papillary muscle, and apical levels. Patients displayed significantly lower transmural CS gradients at all three levels compared to controls (19%, 9.9%, and 13% lower at the basal, papillary muscle, and apical levels respectively). Interestingly, the difference in CS between groups was only observed in the endocardial portion, but not in the epicardial portion. This finding was attributed to worsened subendocardial function with preserved subepicardial function. Cheung et al [24] showed that patients had reduced segmental CS in the anteroseptal, inferoseptal, inferior, and anterior segments as well as 17% reduction in GCS. Similar reductions in the anteroseptal and inferior segments, as well as GCS were reported by Toro-Salazar et al [38]; however, no numerical values were provided. In regards to Sr, Cheung et al [24] found that patients' GCSr was significantly lower than controls' by 15%. Moon et al [20] similarly reported that, compared to controls, GCS was reduced in patients by 8.6% while CSr was decreased by 8.8% for systolic CSr and 14% for diastolic CSr. The severity of these abnormalities correlated with increasing anthracycline doses.

3.3.4 Radial Strain.—Radial strain was evaluated in three studies [24,37,41]. In Yu et al's [41] article, RS of the inner segment at the apex, and inner and outer segments of the papillary muscle level were significantly decreased in patients relative to control by 12%, 15%, 21% in the apical inner layer, mid-papillary inner level, mid-papillary outer level, respectively. There was no significant difference in the basal segments or the transmural radial strain in patients compared to controls. In contrast, Cheung et al [24] showed a decrease in GRS of 20% to just above reference values in patients compared to controls. The radial strain difference was present in all segments of myocardium. Statistically significant

differences between patients and controls in both peak radial systolic Sr and strain in the inferolateral wall were also reported (no numerical values provided) [37].

3.3.5 Torsion and Twist.—Three papers examined twist, torsion (twist/LV length), and twisting/untwisting rate [36,40,41]. Yu et al [40] examined twist and torsion using 3D-STE, and found that both were reduced significantly compared to the healthy cohort (33%, and 32% decrease, respectively). Cheung et al [36] examined peak apical and basal rotation, twisting, and untwisting rates, and LV torsion, systolic twisting velocity, and diastolic untwisting velocity. Peak apical rotation, and untwisting rate were significantly reduced (24%, and 26% reduction respectively), while basal parameters showed no significant change between patients and controls. All three LV parameters in patients were significantly reduced as compared to controls (peak torsion: 32% reduction, peak systolic twisting velocity: 25% reduction, peak diastolic untwisting velocity: 18% reduction). Yu et al [41] used 2D-STE to examine transmural rotation, twisting, and untwisting velocity at the base and apex. At the base, both the subendocardial and subepicardial rotation, twisting velocity, and untwisting velocity were significantly reduced in patients; hence, there was no significant difference in the transmural gradient between patients and controls. However, at the apex, only the subendocardial layer showed significant changes in rotation, twisting velocity, and untwisting velocity, which led to a significantly reduced transmural rotation gradient when compared to controls (41% reduction).

3.4 Evaluation of strain >10 years post-treatment

Six articles examined strain measurements greater than 10 years after treatment [44–49] (Table 3). Time of follow-up ranged from 13.2 to 23.4 years on average. Most studies compared strain measurements between patients treated with anthracyclines to normal controls [44–46]. One study [49] compared patients to anthracycline naïve cancer survivors. Yu et al [48] and Armstrong et al [47] divided patients based on whether they received treatment with anthracyclines only or anthracyclines and mediastinal radiotherapy (MSRT).

3.4.1 Longitudinal Strain.—Cheung et al [44], Mavinkurve-Groothuis et al [46], and Christiansen et al [49] all showed that GLS was significantly reduced in patients versus controls (between 6.4% to ~7.6% decrease). Changes in strain rate were variable: Cheung et al's [44] paper showed no significant change in systolic or diastolic Sr while Mavinkurve-Groothuis et al's [46] showed a significant 13% decrease in GLSr in patients. When comparing patients treated with anthracyclines-only to patients treated with anthracyclines and MSRT, Yu et al [48] showed that patients with dual-therapy had significantly lower GLS compared to those treated with mono-therapy; however GLSr showed no change between the two groups. Armstrong et al [47] presented that GLS was abnormal in 27% of anthracycline-only treated patients while LVEF was abnormal in only 4.3%. Abnormal GLS was associated with any dose of MSRT and anthracycline dose >300 mg/m^2.

3.4.2 Circumferential Strain.—Abnormal GCS was common in patients treated with anthracycline therapy alone (23%) [47]. Cheung et al [44] and Mavinkurve-Groothuis et al [46] both showed significant reductions of GCS in patients compared to controls (14%, and 30% decrease respectively). Both Cheung's and Mavinkurve-Groothius' papers reported

significant decreases in GCSr (11%, and 19% respectively). As with GLS, the mean value of GCS and GCSr in patients Cheung et al's [44] article was lower than in Mavinkurve-Groothuis et al's [46] article. Yu et al [48] showed that the GCS is abnormal in all patients treated with anthracyclines (average GCS 17.3 [15.2 – 19.7]); however unlike the change in GLS, there was no significant difference in the GCS with respect to radiation treatment.

3.4.3 Radial Strain.—Cheung et al [44] and Mavinkurve-Groothuis et al [46] both showed significant reductions in GRS (22%, and 14% respectively), and GRSr (11%, and 49% respectively) as compared to controls. However, despite the striking change, the GRS values in Mavinkurve-Groothuis's [46] article remained in the normal range likely illustrating lack of standardization in measurements among software vendors. Dietz et al [45] substituted radial displacement for radial strain due to variability in strain measurements ultimately finding a significant reduction (17%) between patients and controls. Yu et al [48] found minimal, nonsignificant changes in GRS when comparing anthracycline-treated patients with and without MSRT, however the majority of patients in both groups had GRS values below the reference range [26].

4. CONCLUSION

Despite a high degree of heterogeneity among studies using GLS and GCS to compare patients with normal controls, myocardial strain by echocardiography appears to be useful for intra-individual evaluation subclinical myocardial injury in childhood cancer patients treated with anthracycline therapy. Based on a review of the current body of literature, we found that during and immediately (<1 year) after treatment, the GLS, GCS, and strain rate all show significant changes. Radial strain is decreased compared to baseline; however, these changes are not necessarily different from controls or below the normal range. In the 1–10 years post-treatment, circumferential strain and strain rate are the most consistently abnormal measurements, followed by radial strain measurements. Longitudinal strain measurements appear to be less reliable in this group, with some papers even showing increased absolute strain in patients compared to controls. Patients >10 years post-treatment continue to display significant reductions of circumferential strain that are greater than longitudinal strain. Radial strain shows similar reductions in long-term follow-up.

Previous studies addressing anthracycline therapy and strain have focused on the effects of anthracyclines in all age groups [50], which includes many breast cancer survivors who are treated with other cardiotoxic medications (such as trastuzumab) and often receive mediastinal radiotherapy. In Thavendiranathan's review [50] for example, GLS was determined to be the most consistently affected measure during chemotherapy. In this article, where we focus on childhood cancer survivors only, we showed that GLS is most consistent for acute monitoring, but becomes less consistent >1 year after therapy. Our meta-analysis showed only moderate heterogeneity among studies when GLS is assessed in the same patient pre- and post-therapy and within 1 year of treatment.

Based of the available published data, it remains unclear which strain measurement is optimal for late follow-up in CAYA cancer survivors. As mentioned above, GCS was abnormal more often than GLS in patients who were >1 year post treatment, and hence may

be an important measurement for long-term follow up in childhood cancer survivors. This is different from the adult literature where GLS appears to be a more consistent marker across many pathologies including restrictive cardiomyopathy, coronary artery disease, and some valvular disease [16,51]. We evaluated the consistency of both GLS and GCS abnormalities across studies in patients post-therapy compared to controls. While there was a difference in the SMD when comparing GLS and GCS values in patients following treatment and a control cohort, there was high heterogeneity among studies. The heterogeneity was likely due to different strain tracking methods and software algorithms, as well as variable time-to-evaluation. Lack of standardization in the optimal views used for measuring strain may also explain some of the observed variability in strain measurements between studies. For example, strain data derived from two apical long-axis views that are foreshortened may not be as accurate as those derived from three apical long-axis views (2-chamber, 3-chamber, 4-chamber). In summary, while the findings from our meta-analysis are promising, they also suggest that additional studies with larger sample sizes and standardized image acquisition will be helpful for demonstrating value when relating myocardial strain changes to clinical outcomes.

There were limitations encountered in the included studies. Although strain showed good inter- and intra-observer reliability, certain measurements did show increased variability and may partly be due to inconsistent techniques, vendor-specific strain algorithms, or strain derivation (TDI vs speckle-tracking). The American Society of Echocardiography, the European Association of Cardiovascular Imaging, and industry partners have established a task force to identify sources of variability in strain measurements in order to improve standardization [52]. The sample size of the papers was modest and in some cases images were not analyzable due to poor image quality. Some papers did not include data or listed data as figures only. Ganame et al [27,37] and Yagci-Kupeli et al [39] papers used TDI, which led to generally increased strain values in comparison to other articles.

Strain is more sensitive to myocardial changes than traditional echocardiographic measures (LVEF, LV fractional shortening) in both early [27–31] and late-term [44–47,49] follow-up. Although clinical guidelines recommend obtaining strain measurements in patients who are undergoing treatment with anthracyclines in order to identify early myocardial dysfunction, it is unknown to what extent clinical labs are equipped with technical training and stringent image acquisition protocols to ensure accurate and reproducible strain assessment. Further, clinically significant myocardial strain thresholds are needed for CAYA survivors of childhood cancer, and how these thresholds relate to future development of cardiomyopathy require additional investigation. Understanding the natural history is imperative for testing of preventive strategies and treatments.

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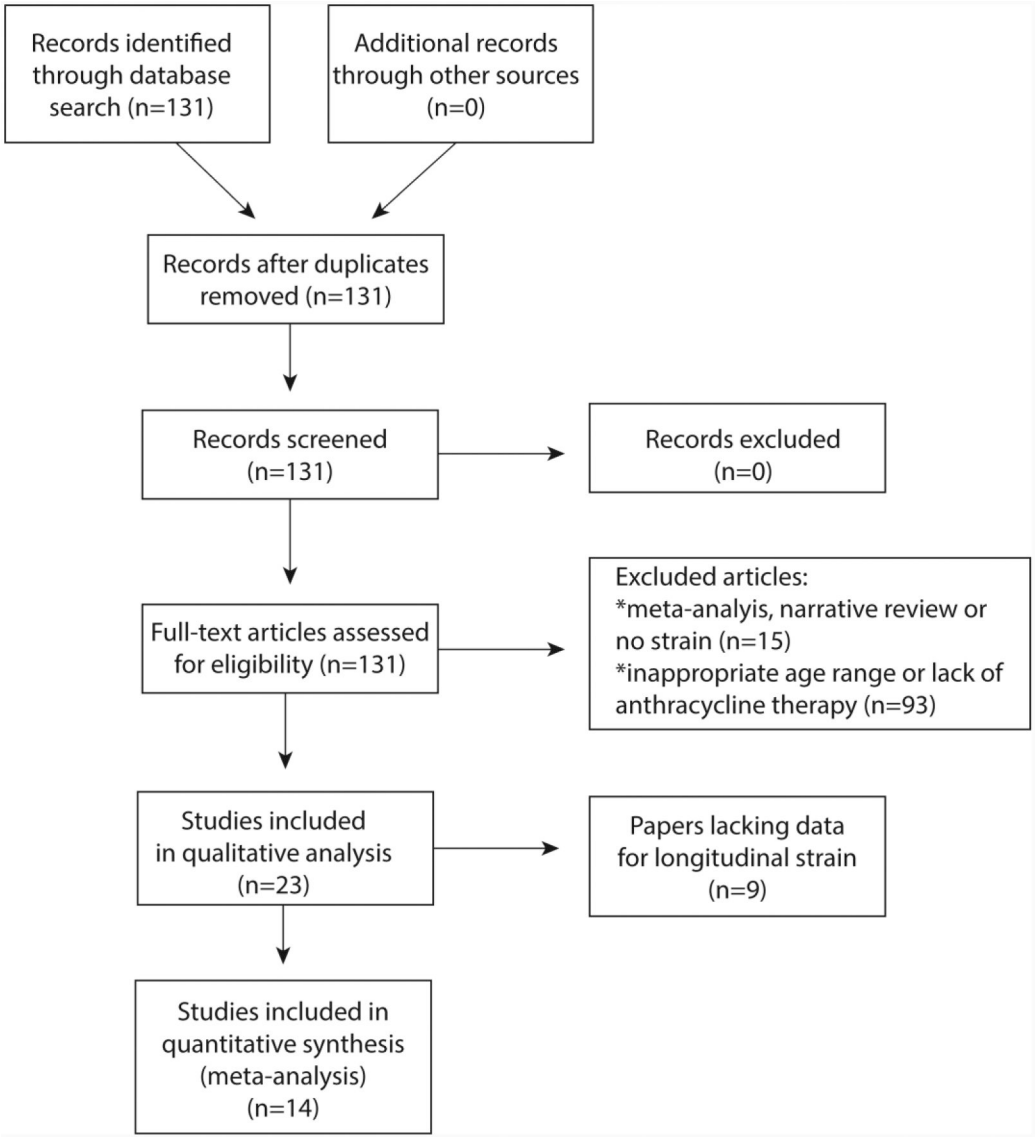

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram [53]

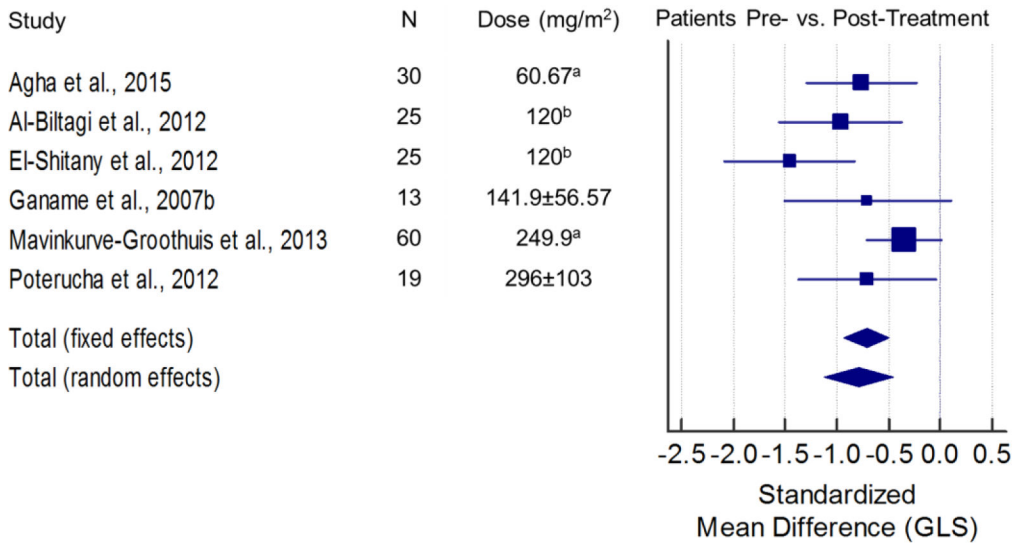

Figure 2. Standardized mean difference (SMD) and 95% confidence intervals of global longitudinal strain (GLS) between patients at baseline (prior to anthracyclines) and patients within one year of anthracycline treatment.

The size of the square marker is proportional to the weight assigned to each study in the pooled estimate (diamond) using a random effects model. The weighing is related to the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in calculating the pooled effect size. SMD Total (fixed effects) = −0.714; SMD Total (random effects) = −0.788 (both $p<0.001$). Level II evidence. There was no statistically significant difference among the findings of the included 6 articles [27–31,33] (X^2 (5)=10.32, p=0.067), and the inconsistency among included articles was quantified as I^2=51.56% [95% CI=0–80.7]. The reported decreases in GLS after treatment based on the 6 included papers [27–31,33] are moderately heterogeneous. Doses are reported as mean ± SD unless noted otherwise. [a]average; [b]median.

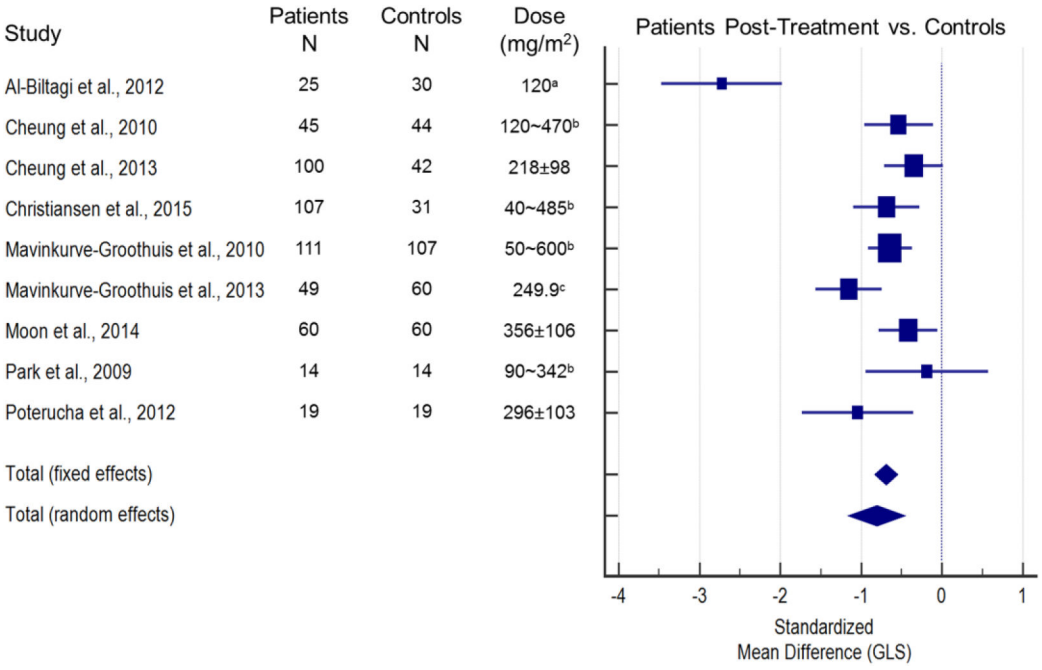

Figure 3. Standardized mean difference (SMD) and 95% confidence intervals of global longitudinal strain (GLS) between normal controls and patients treated with anthracyclines.

The size of the square marker is proportional to the weight assigned to the study in the pooled estimate (diamond) using a random effects model. The weighing is related with the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in calculating the pooled effect size. The results indicate that GLS is lower in anthracycline treated patients as compared to a normal, age-matched population (SMD Total (fixed effects) = −0.695; SMD Total (random effects) = −0.810 (both $p<0.001$); Level II evidence). There was a significant difference among the findings of the included 9 articles [20,21,24,29,31,33,44,46,49] (X^2 (8)=44.06, $p<0.001$), and the inconsistency among included articles was quantified as I^2=81.84% [95% CI=66.7–90.1]. Doses are reported as mean ± SD unless noted otherwise. [a]median; [b]range; [c]average.

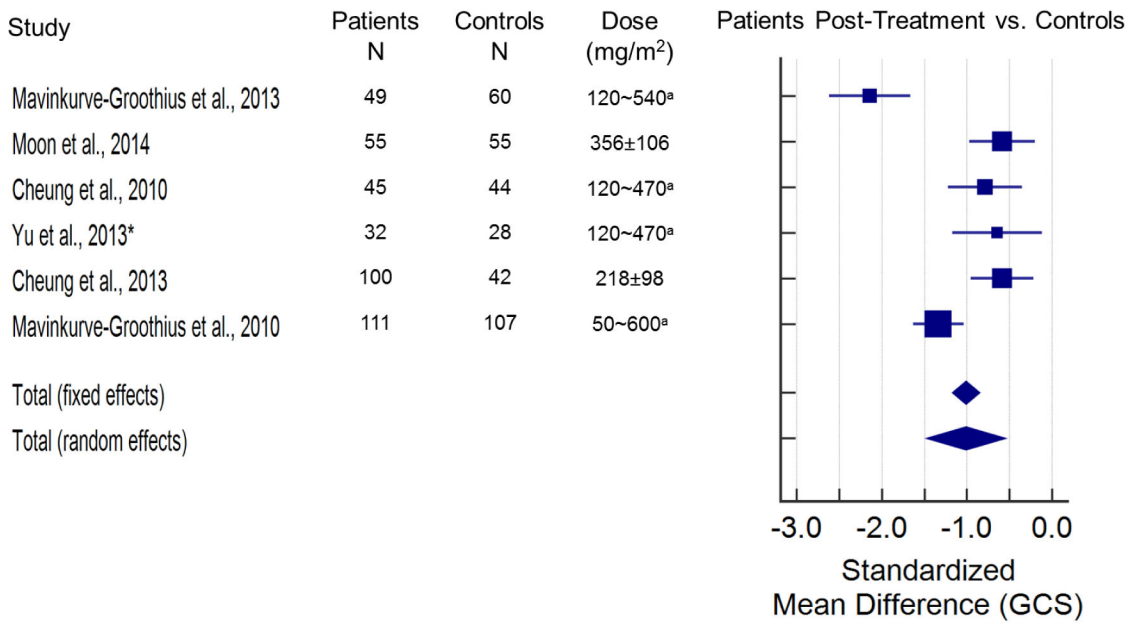

Figure 4. Standardized mean difference (SMD) and 95% confidence intervals of global circumference strain (GCS) between patients and controls following anthracycline-treatment.

The size of the square marker is proportional to the weight assigned to the study in the pooled estimate (diamond) using a random effects model. The weighing is related with the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in calculating the pooled effect size. The results indicate that GCS is lower in anthracycline treated patients as compared to a normal, age-matched population (SMD Total (fixed effects) = −1.013; SMD Total (random effects) = −1.010 (both $p<0.001$); Level II evidence). There was a significant difference among the findings of the included 6 articles [20,24,31,41,44,46] (X^2 (5)=40.01, $p<0.001$), and the inconsistency among included articles was quantified as I^2=87.50% [95% CI=75.2–93.7]. Doses are reported as mean ± SD unless noted otherwise. [a]range. *mid-papillary level GCS was used for analysis from the study by Yu et al[41].

TABLE 1

Summary of studies evaluating patients during and <1 year following anthracycline therapy.

Study	Patient Age (years)	Timing of Measurements (years)	Anthracycline Dose (mg/m^2)	Cancer Type	Software	Pre-chemotherapy[c]	Post-chemotherapy[c]	Controls[c]
Agha *et al* [28]	9.24 ± 4.14	Baseline and 1 week after last dose	60.67 ± 9.8	AML, ALL, HL, nHL	EchoPAC, GE	GLS: −21.58 ± 2.54	GLS: −19.18 ± 3.59	-
Al-Biltagi *et al* [29]	9.2 ± 2.9	Baseline and within 1 week after last dose	120 (median)	ALL	EchoPAC, GE	GLS: −18.65 ± 4.52	GLS: −15.10 ± 2.45	GLS: −21.5 ± 2.2
El-Shitany *et al* [30]	9.5 ± 2.6	Baseline and within 1 week after last dose	120	ALL	EchoPAC, GE	GLS: −18.65 ± 2.9	GLS: −15.1 ± 1.769	-
Ganame *et al* [27]	10.7 ± 3.8	Baseline and within 2 hours of the first 3 doses	141.9 ± 56.57	LY, ALL, OS, ES, AML	Proprietary software	GLS: −27 ± 5 GRS: 74 ± 14	GLS: −23 ± 6 GRS: 45 ± 11	-
Mavinkurve-Groothuis *et al* [31]	6 [2.2 – 15.4]	Baseline, after induction, and 1-year follow (>2 weeks after last dose)	120 mg/m^2 after induction; at 1-year follow-up; standard risk = 120, medium risk = 300, high risk = 540	ALL	EchoPAC 6.1, GE	GLS: −18.2 ± 3.1 GCS: −19.4 ± 4.3 GRS: 66.8 ± 12	GLS: −16.7 ± 5.2 GCS: −16.9 ± 3.1 GRS: 55.2 ± 16	GLS: −20.9 ± 1.3[a] GCS: −22.5 ± 2.1 GRS: 54.3 ± 6[a]
Poterucha *et al* [33]	15.3 ± 3	0, 4, and 8 months of treatment	296 ± 103	OS, ES, HL, BCL, RMS, MPNST, ALL	EchoPAC, GE	GLS: −19.9 ± 2.1	GLS: −18.1 ± 2.8	GLS: −20.5 ± 1.5
Pignatelli et al [32][b]	9.8 ± 5.8	1-year follow up (>3 weeks since last dose)	213.33 ± 124.4	ALL, AML, NB, OS, ES	EchoPAC, GE	-	**1– 4 years:** GLS: −19.31 ± 5.48 GCS: −15.88 ± 3.86 **5 to 9 years:** GLS: −18.33 ± 4.02 GCS: −15.74 ± 2.08 **10 to 14 years:** GLS: −19.43 ± 1.4 GCS: −15.81 ± 1.77 **15–19 years:** GLS: −18.79 ± 1.4	**1– 4 years:** GLS: −20.7 ± 1.30[a] GCS: erroneous value **5 to 9 years:** GLS: −21 ± 1.30[a] GCS: −20.90 ± 2.00 **10 to 14 years:** GLS: −21.8 ± 1.30 GCS: −21.5 ± 1.70 **15–19 years:** GLS: −22.5 ± 1.30

Study	Patient Age (years)	Timing of Measurements (years)	Anthracycline Dose (mg/m^2)	Cancer Type	Software	Pre-chemotherapy[c]	Post-chemotherapy[c]	Controls[c]
							GCS: −12.16 ± 2.09	GCS: −21.90 ± 2.10

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BCL=B-cell lymphoma; ES=Ewing sarcoma; HL=Hodgkin lymphoma; LY=lymphoma; MPNST=malignant peripheral nerve sheath tumor; NB=neuroblastoma;.nHL=non-Hodgkin lymphoma; OS=osteosarcoma; RMS=rhabdomyosarcoma;

[a] no significant difference between control group and patients.

[b] normal reference values were used as controls.

[c] units, strain (%).

TABLE 2

Summary of studies evaluating patients at 1 to 10 years following anthracycline therapy.

Study	Patient Age (yrs)	Timing (yrs)	Anthracycline Dose (mg/m2)	Cancer Type	Software	Pre-chemotherapy[e]	Post-chemotherapy[e]	Controls[e]
Park *et al* [21]	9.8 [6.1 – 17.5]	-	90 – 342	ALL, AML, NB, nHL, HL	Syngo US Workplace 3.0, Acuson	-	GLS: −22.89 ± 2.47	GLS: −23.55 ± 4.19[a]
Moon *et al* [20]	10.5 ± 4.7	3.9 ± 4.0	356 ± 106	AML, BL, ES, OS	Syngo Velocity Vector Imaging, Siemens	GLS: −19.26 ± 3.78 GCS: −26.84 ± 5.61	GLS: −18.27 ± 3.35 GCS: −24.21 ± 3.74	GLS: −19.74 ± 3.63 GCS: −26.48 ±4.0
Ryerson *et al* [14][b]	Low risk: 16 ± 2.89, Moderate risk: 14.5 ± 3.2, High risk: 16.2 ± 3.64	Low risk: 8.0 ± 2.73, Moderate risk: 9.6 ± 3.43, High risk: 8.3 ± 3.03	Low risk: 119.6 ± 43.29, Moderate risk: 171 ± 40.01, High risk: 344 ± 62.27	LE, LY, SA, WT, NB, Other	EchoPAC, GE	-	**Low risk:** GLS: −19.2 **Moderate risk:** GLS: −17.4 **High risk:** GLS: −15.4	**Low risk:** GLS: −14.26 **Moderate risk:** GLS: −14.26 **High risk:** GLS: −14.26
Cheung *et al* [36]	15.6 ± 5.5	7.0 [3.1 – 24.3]	240 [120 – 470]	ALL	EchoPAC, GE	-	Twist: 8.0 ± 4.1 Twist velocity: 68.1 ± 20.3 Untwisting velocity: −90.1 ± 34.3	Twist: 11.8 ± 4.5 Twist velocity: 91.0 ± 22.3 Untwisting velocity: −109.6 ± 33.4
Cheung *et al* [24]	15.3 ± 5.8	6.3 [2.7 – 19.8]	240 [120 – 470]	ALL	EchoPAC, GE	-	GLS: −17.6 ± 3.0 GCS: −14.5 ± 2.9 GRS: 40.1 ± 15.6	GLS: −19.0 ± 2.2 GCS: −17.4 ± 4.3 GRS: 50.0 ± 16.4
Ganame *et al* [37]	12.7 [4 – 28]	5.2 [2.0 – 15.2]	240 [90 – 300]	ALL, AML, LY, solid tumors	Proprietary software	-	GLS: shown graphically	GLS: shown graphically
Toro-Salazar *et al* [38]	22 [12 – 42]	9.6 [2.5 – 26.9]	328 [200 – 600]	AML, OS, HL, ES	-	-	GLS: −18.5 ± 2.4 GCS: shown graphically	GLS: data not provided GCS: shown graphically
Yagci-Kupeli *et al* [39]	14	5.8 ± 3.6	350 – 480	nHL, HL, HB, WT, LS, NB, OS, NEDT, NC	EchoPAC, GE	-	no numerical data	no numerical data
Yu *et al* [40][c]	18.6 ± 5.1	7.2 [2.4 – 16.4]	229 [40 – 644]	ALL, AML, OS, BL, HL, nHL, SS, NB, HB	Advanced Cardiology Package, Toshiba	-	Twist: 6.6 ± 2.5 Torsion: 1.3 ± 0.5	Twist: 9.9 ± 3.2 Torsion: 1.9 ± 0.7

Study	Patient Age (yrs)	Timing (yrs)	Anthracycline Dose (mg/m2)	Cancer Type	Software	Pre-chemotherapy[e]	Post-chemotherapy[e]	Controls[e]
Yu *et al* [41][d]	19.3 ± 5.4	6.9 [2.2 – 14.4]	220 [120 – 470]	ALL, AML, OS, HL, nHL	Advanced Cardiology Package, Toshiba	-	**Basal level:**	**Basal level:**
							GCS: 12.6 ± 5.0	GCS: 15.6 ± 3.2
							Mid-papillary level:	**Mid-papillary level:**
							GCS: 13.7 ± 1.9	GCS: 15.2 ± 2.7
							GRS (inner): 33.8 ± 4.2	GRS (inner): 39.7 ± 10.8
							GRS (outer): 23.0 ± 4.0	GRS (outer): 29.1 ± 6.3
							Apical level:	**Apical level:**
							GCS: 13.9 ± 2.9	GCS: 15.9 ± 3.1
							GRS (inner): 25.7 ± 4.5	GRS (inner): 29.1 ± 7.7

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; BL=Burkitt lymphoma; ES=Ewing sarcoma; HB=hepatoblastoma; HL=Hodgkin lymphoma; LE=leukemia; LS=liver sarcoma; LY=lymphoma; NB=neuroblastoma; NC=nasopharyngeal carcinoma; NEDT=neuroectodermal tumor; nHL=non-Hodgkin lymphoma; OS=osteosarcoma; RMS=rhabdomyosarcoma; SA=sarcoma; SS=synovial sarcoma WT=Wilms tumor.

[a] no significant difference between control group and patients.

[b] comparison group consists of anthracycline naïve cancer survivors.

[c] 3D measurements.

[d] absolute strain values provided.

[e] units, strain measurements (%), twist (°), torsion (°/cm), velocity (°/s).

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TABLE 3

Summary of studies evaluating patients at >10 years following anthracycline therapy.

Study	Patient Age (years)	Timing of Measurements (years)	Anthracycline Dose (mg/m^2)	Cancer Type	Software	Post-chemotherapy[c]	Controls[c]
Cheung et al[44]	24.1 ± 4.2	15.3 ± 5.8	218 ± 98	ALL, AML	EchoPAC, GE	GLS: −16.0 ± 3.1 GCS: −14.3 ± 3.5 GRS: 32.9 ± 10.9	GLS: −17.1 ± 3.2 GCS: −16.6 ± 4.7 GRS: 42.3 ± 12.5
Dietz et al[45]	27 [18 – 50]	17 [5 – 30]	440 [300 – 645]	OS, RMS, ES, SS, LY, WT	QLAB quantification, Phillips	**Radial displacement:** 5.61 ± 1.16	**Radial displacement:** 6.73 ± 1.52
Mavinkurve-Groothuis et al[46]	20 [5.6 – 37.4]	13.2 [5 – 29.2]	180 [50 – 600]	ALL, AML, EP, ES, HB, HL, NC, NB, nHL, OS, RMS, WT	EchoPAC, GE	GLS: −19.8 ± 2.6 GCS: −15.9 ± 6.7 GRS: 49 ± 12	GLS: −21.2 ± 1.6 GCS: −22.6 ± 2.1 GRS: 57 ± 5
Yu et al[48, *b*]	31 [18 – 62]	15 [2 – 39]	300 [27 – 660]	SA, HL, ALL, AML, nHL	EchoPAC 12.0, GE	**Anthracycline alone:** GLS: 19 [17 – 20] GCS: 17.6 [16 – 19.7] GRS: 42.0 [31.9 – 51.4] **Anthracycline and radiation:** GLS: 18 [16 – 19.5] GCS: 16.1 [14.5 – 19.7] GRS: 42.1 [26.5 – 55.2]	-
Armstrong et al[47]	31 [18 – 65]	22.6 [10.4 – 48.3]	Median not given [0 – 600]	LE, ALL, AML, LY, nHL, HL, CNS tumor, Bone tumor, ES, OS, Soft tissue SA, RMS, Nonrhabdo SA, GC, Melanoma, NB, RB, WT, Carcinoma, Other	EchoPAC, GE	**Anthracycline alone:** GLS: −19.3 ± 2.6 GCS: −20.2 ± 5.0 **Anthracyclines and radiation:** GLS: −18.5 ± 2.8 GCS: −20.1 ± 5.0	-

Study	Patient Age (years)	Timing of Measurements (years)	Anthracycline Dose (mg/m^2)	Cancer Type	Software	Post-chemotherapy[c]	Controls[c]
Christiansen et al[49, a]	28.6 [18.6 – 46.5]	23.4 [7.4 – 40]	Low dose: 120 [40 – 120], Mod-high dose: 240 [173 – 485]	ALL	EchoPAC 7, GE	**Low dose:** GLS: −18.1 ± 2.3 **Moderate dose:** GLS: −18.3 ±1.9	**Low dose:** GLS: −19.7 ± 2.4 **Moderate dose:** GLS: −19.7 ± 2.4

ALL=acute lymphoblastic leukemia; AML=acute myeloid leukemia; EP=ependymoma; ES=Ewing sarcoma; GC=germ cell tumor; HB=hepatoblastoma; HL=Hodgkin lymphoma; LE=leukemia; LY=lymphoma; NB=neuroblastoma; NC=nasopharyngeal carcinoma; nHL=non-Hodgkin lymphoma; OS=osteosarcoma; RB=retinoblastoma; RMS=rhabdomyosarcoma; SA=sarcoma; SS=synovial sarcoma; WT=Wilms tumor.

[a] comparison group consists of anthracycline naïve cancer survivors.

[b] absolute strain values provided.

[c] units, strain measurements (%), radial displacement (mm).