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Fitness, body composition and vascular health in adolescent and young adult survivors of paediatric brain cancer and cranial radiotherapy

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Abstract:
Background: Survivors of paediatric brain cancer and/or cranial radiotherapy (CRT) are at an increased risk of developing serious comorbidities. Established risk factors for chronic disease include central obesity, endothelial abnormalities and diminished fitness.
Objectives: Here we characterised anthropometry, body composition, bone mineral density (BMD), heart rate (HR), blood pressure (BP), endothelial function, muscular strength and endurance and aerobic fitness in adolescent and young adult (AYA) survivors.
Methods: Twenty survivors (10 male, 10 female; 20 ± 2 years) were compared with 19 matched controls. Muscular strength was assessed using three repetition maximum tests, while muscular endurance was determined as number of repetitions performed per minute. Peak oxygen uptake (VO_2 peak) was assessed on a treadmill using a modified chronotropic protocol. Anthropometric measurements, HR and BP were taken using standard clinical protocols, while body composition and BMD were determined using dual X-ray absorptiometry (DXA). Endothelial function was measured using the flow mediated dilation technique.
Results: Survivors demonstrated deficits in muscular strength (latissimus dorsi pull-down, $p = 0.020$; bicep curl, $p = 0.009$), muscular endurance (squats, $p = 0.012$; sit-ups, $p = 0.030$; push-ups, $p = 0.013$), minute ventilation at peak exericse ($p = 0.002$) and VO_{2peak} (L/min, $p = 0.002$; mL/kg/min, $p = 0.008$; mL/kg LBM/min, $p = 0.010$). Additionally, survivors had greater waist-to-hip ratios ($p = 0.032$), resting HR ($p = 0.048$) and higher percentage of total body ($p = 0.017$), central ($p = 0.009$) and peripheral ($p = 0.032$) fat. Lean body mass ($p = 0.004$) and BMD ($p = 0.005$) were lower in the survivor group.
Conclusion: AYA survivors of paediatric brain cancer and/or CRT exhibit altered body composition, increased resting HR and reduced BMD, muscular strength, muscular endurance and cardiorespiratory fitness compared to controls.

Keywords: brain cancer, long-term survival, radiation therapy
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Introduction

In recent years, overall survival rates for paediatric cancers have increased. Unfortunately, it is estimated that 62% of the paediatric cancer survivors develop at least one chronic health condition within 17 years of diagnosis [1]. Long-term survivors of paediatric brain cancer and/or cranial radiotherapy (CRT) who undergo invasive and intensive treatment have a higher incidence of adverse effects [2], [3], [4], [5]. Further, as a consequence of the cancer itself, survivors may develop a range of physical performance limitations that decrease quality of life and increase overall risk of developing comorbidities [2], [5]. Numerous studies have documented such predispositions in adolescent and young adult (AYA) survivors of paediatric brain cancer and/or CRT, indicating a

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considerable increase in disease risk and all-cause mortality within this population [2], [5], [6], [7], [8], [9], [10], [11]. However, many of these studies have relied upon self-report data and field-based estimations to characterise these deficits. As such, research containing accurate and reproducible measures of body composition, vascular health and functional fitness in this population are scarce [4], [6]. Here, we utilise standardised and well-recognised protocols to define cardiorespiratory fitness, muscular strength and endurance, anthropometry, heart rate (HR) and blood pressure (BP), endothelial function, body composition and bone mineral density (BMD) in a population of long-term paediatric brain cancer and/or CRT survivors once they have reached adolescence or early adulthood. This information could aid the development of future interventions to ameliorate these risk-factors and prevent chronic disease in this population.

Materials and methods

Participants

Twenty-one long-term (>5 years) AYA (15–23 years) survivors of paediatric brain cancer and/or CRT were recruited from the Princess Margaret Hospital (Western Australia) oncology database. One survivor dropped out of the study after initial recruitment due to personal reasons. Hence, 20 survivors (10 male, 10 female) participated in this study. Nineteen (9 male, 10 female) healthy control participants of similar age were recruited from the community. It was a requirement that all participants were ambulatory and capable of participating in exercise. Survivors with growth hormone deficiency (GHD) had ceased GH replacement 6 months prior to enrolling in the study as therapy was only available until skeletal maturity. Exclusion criteria included pregnancy, current inflammatory or malignant disease/s, and previous diagnoses of cardiovascular disease or dysfunction of clinical importance. Survivors with neurological and/or physical deficits were screened prior to recruitment by study doctors to determine exercise and participation capability. All participants were informed of the details and requirements of the study and provided written informed consent. Ethical approval was granted by the University of Western Australia (UWA) Human Research Ethics Committee and the Princess Margaret Hospital Ethics Committee (HREC approval number, 2013059). All procedures performed were in accordance with the 1964 Helsinki declaration and its later amendments.

Experimental design

Participants were invited to complete a single 2-h testing session at the UWA School of Sport Science, Exercise and Health. At this testing session anthropometry, body composition, BMD, HR, BP, endothelial function, muscular strength, muscular endurance and cardiorespiratory fitness were assessed.

Heart rate, blood pressure and endothelial function

Participants fasted for 4 h preceding their appointment and rested supine for 20 min upon arrival to the laboratory. During this time an electronic cuff (Dinamap Carescape V100, GE Healthcare, Chalfont St Giles, UK) was used to measure HR, BP and mean arterial pressure (MAP) at 5-min intervals.

Conduit artery function was then assessed using the flow mediated dilation (FMD) technique defined by Thijssen et al. [12]. A forearm cuff was placed distal to the olecranon process before the left brachial artery was imaged using non-invasive, high-resolution ultrasound (Terason, t3200, Burlington, MA, USA). After 1 min of recording brachial artery diameter, the cuff was inflated to 220 mm Hg for 5 min. Recordings of diameter and blood flow resumed 30 s before cuff deflation and continued for another 3 min following release.

Anthropometry, body composition and bone mineral density

Body mass, height, body mass index (BMI), waist circumference, hip circumference and waist-to-hip ratio were measured. Body mass was measured to the nearest 0.01 kg using an electronic scale (Sauter Model EB60, FSE Scientific, Sydney, Australia). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca 216 Measuring Pole, Birmingham, UK). BMI was calculated as body mass divided by height in metres squared (kg/m^2). The World Health Organisation (WHO)'s criteria for BMI were used for classification purposes [13]. Waist circumference was measured at the mid-level between the lateral T12 costal arch and the iliac

crest, while hip circumference was measured at the level of the greater trochanters according to guidelines from the American College of Sports Medicine (ACSM) [14]. Waist-to-hip ratio was calculated as waist circumference divided by hip circumference.

Total and regional body composition and BMD were assessed using dual X-ray absorptiometry (DXA; Lunar Prodigy, GE Medical Systems, Madison, WI, USA). Paediatric software and reference values were used for those participants aged 15–18 years. Total body fat, central and peripheral fat were presented in kg and as percentages of tissue mass. Central adiposity was defined as the area encompassing the trunk and android regions, while peripheral adiposity was defined as the sum of the arms, legs and gynoid region. Total lean body mass (LBM) was presented in kg and BMD was determined by dividing bone mineral content by bone area (g/cm^2).

Muscular strength and endurance

Protocols for muscular strength and endurance testing were in accordance with ACSM guidelines [14].

Before evaluation, participants were guided through a 5–10 min warm-up consisting of static stretching and familiarisation, consisting of several light intensity repetitions of the specific exercises being tested so that correct technique could be achieved and full range of motion (ROM) of each exercise successfully adhered to.

Muscular strength in the upper body was assessed using standardised three repetition maximum (RM) tests in which latissimus dorsi and biceps brachii strength was assessed using pull-down and unilateral curl exercises. In these tests, participants were required to move the greatest resistance they could manage three times through the full joint ROM in a controlled manner with good posture. To begin with, the average strength of each participant was gauged through questioning. Maximum strength was then assessed by increasing weight in 5–10 kg increments for latissimus dorsi pull-downs and 1–5 kg increments for bicep curls from an initial weight of ~50%–70% of predicted capacity. Repetition maximums were taken at the point before technique was compromised or when participants indicated a maximal effort.

Latissimus dorsi pull-downs were performed in a seated position on a standard, weighted pulley machine. A wide, over-hand grip was used to hold the bar, with one complete repetition performed when the bar could be lowered to the level of the chin and back above the head in a controlled motion. Participants performed bicep curls using dumbbell weights. Left and right arms were assessed individually, with one repetition taken as full elbow extension beside the body to full elbow flexion next to the chest. Results for left and right arms were combined and averaged for analysis.

Relative muscular endurance was assessed using standard 1-min maximum tests in which participants were required to complete as many repetitions of each exercise as possible in 1 min, with good form. Three of these tests were conducted in which strength of the trunk, legs and chest was assessed through the use of un-weighted abdominal crunches, squats and push-ups.

Cardiorespiratory fitness

Peak oxygen uptake ($\dot{V}O_2$ peak) was assessed on a treadmill using a modified chronotropic protocol designed for clinical populations. Prior to commencing the test, resting heart rate (HR; Polar Electro Oy, Kempele, Finland) and blood pressure (BP; Bronze Series DS54 DuraShock Hand Aneroid Sphygmomanometer, Welch Allyn, Skaneateles Fall, NY, USA) were recorded. Each stage was 3-min in duration with participants encouraged to continue until volitional exhaustion. At the end of each 3 min stage, HR, BP and ratings of perceived exertion (RPE), based upon the Borg scale (6-20) [15] were recorded. Recovery HR and BP were also measured and recorded 10 min after cessation of the exercise test.

During the assessment, participants breathed through a mouthpiece connected to a computerised gas analysis system. This system included a ventilometer (Universal ventilation meter, VacuMed, Ventura, CA, USA) to calculate minute ventilation ($\dot{V}_E$) and respiratory exchange ratio (RER) at 15-s intervals, in addition to oxygen and carbon dioxide analysers (Ametek Applied Electrochemistry S-3A/1 and CD-3A, AEI Technologies, Pittsburgh, PA) to measure the percentage of oxygen and carbon dioxide in the expired air. Calibration of the ventilometer was completed prior to each test and the analysers were calibrated prior to use and verified after each test using a standard reference gas of known concentration. Values were recorded in absolute (L/min) and relative (mL/kg/min) terms. Absolute $\dot{V}O_2$ peak was then converted into mL and divided by LBM for a true representation of aerobic capacity.

Statistical analyses

Data were analysed using SPSS (version 20.0, IBM, Armonk, NY, USA). All descriptive data was reported as mean ± standard deviation (SD). Unpaired (independent samples) two-tailed Student's t-tests were used to analyse the differences in outcome measures between the two groups. Statistical significance was set at $p \leq 0.05$ for all analyses.

Results

Participant characteristics

The mean age for both the survivors and control participants was 20 ± 2 years. The mean time since last treatment was 11.91 ± 4.60 years. At time of review, all participants had completed puberty based on menarchal timing in females and self-identified Tanner stages in males. Additional characteristics of the survivor group are presented in Table 1.

Table 1: Characteristics of the cancer survivor group.

	Survivor (n = 20)	
	No.	**%**
Age at first diagnosis		
<5 years	13	65
6–10 years	5	25
11–15 years	2	10
Age at first exposure		
N/A	6	30
<5 years	8	40
6–10 years	4	20
11–15 years	2	10
Age at last exposure		
N/A	6	30
<5 years	5	25
6–10 years	4	20
11–15 years	5	25
Underlying diagnosis		
Brain cancer	13	65
Tumour type		
Craniopharyngioma	1	5
Glioma	10	50
Medulloblastoma	1	5
Teratoma	1	5
Tumour location		
Brain stem	1	5
Cerebellum	1	5
Frontal lobe	2	10
Optic pathway	2	10
Posterior fossa	2	10
Subependymal zone	1	5
Supracellar cistern	1	5
Temporal lobe	2	10
Tempero-parietal region	1	5
Leukaemia	6	30
ALL	5	25
MML	1	5
Other		
Undifferentiated rhabdomyosarcoma of the right petrous temporal bone	1	5
Treatment		
Surgery	6	30

Surgery and chemotherapy	1	5
Surgery and XRT	2	10
Chemotherapy and XRT	2	10
Surgery, chemotherapy and XRT	5	25
Chemotherapy, XRT and HSCT	4	20
Treatment details		
XRT		
Dosage		
6–24 Gy	6	30
50–56 Gy	7	35
Location		
Cranial	9	45
Spinal	2	10
Total body	4	20
Chemotherapy		
Agents		
Alkylating agents	9	45
Anthracyclines	6	30
Vinca alkaloids	9	45
Other characteristics		
Growth hormone deficiency[a]	8	40

ALL, acute lymphoblastic leukaemia; HSCT, haematopoietic stem cell transplant; MML, myelo monocytic leukaemia; XRT, radiotherapy.
[a]Participants had not received hormonal supplements for the 6 months preceding the study.

Survivor data was further investigated for trends based on treatment (Appendix Table 5) and hormone status (Appendix Table 6). Survivors who received surgery and/or chemotherapy recorded higher maximal HR in the $\dot{V}O_2$ peak assessment than those who received radiotherapy. Survivors with GHD and thyroid stimulating hormone (TSH) deficiency were significantly shorter than their counterparts and had lower hip circumferences, LBM and absolute $\dot{V}O_2$ peak. There were no other significant differences observed between treatment or hormone groups.

Heart rate, blood pressure and endothelial function

All vascular data is presented in Table 2.

Table 2: Heart rate, blood pressure and endothelial function data for the cancer survivor group and the control group.

	Survivor (n = 20)		Control (n = 19)		
	Mean	**SD**	**Mean**	**SD**	**p-Value**
Heart rate and blood pressure					
Systolic blood pressure, mm Hg	117	17	120	12	0.637
Diastolic blood pressure, mm Hg	69	11	65	4	0.146
Mean arterial pressure, mm Hg	88	14	86	6	0.583
Heart rate, bpm	76	14	66	14	0.048[a]
Endothelial function					
Baseline diameter, cm	0.31	0.07	0.35	0.07	0.111
Peak diameter, cm	0.34	0.07	0.38	0.07	0.079
Delta diameter, cm	0.05	0.07	0.03	0.02	0.475
Delta percent, %	10.35	3.84	10.18	5.47	0.918
Time to peak, s	53.15	25.60	60.30	30.46	0.457

[a]Denotes statistical significance ($p \leq 0.05$).

Cancer survivors had significantly higher resting HR compared to control participants. There were no other significant differences between groups in BP or endothelial function data.

Anthropometry, body composition and bone mineral density

As a group, cancer survivors were shorter than the control participants and had higher waist-to-hip ratios (Table 3). According to the WHO criteria for BMI [13], 15.8% of individuals in the survivor group were un-

derweight (BMI < 18.5 kg/m^2), 36.8% were within the normal weight range (BMI 18.5–24.99 kg/m^2), 36.8% were overweight (BMI 25.0–29.99 kg/m^2) and 10.5% were obese (BMI > 30 kg/m^2). In comparison, no controls were underweight, 57.9% were normal weight, 36.8% were overweight and 5.3% were obese. There were no significant differences between groups in all other anthropometric measures (Table 3).

Table 3: Anthropometric, body composition and bone mineral density data for the cancer survivor group and the control group.

	Survivor (n = 20)		Control (n = 19)		
	Mean	SD	Mean	SD	p-Value
Anthropometry					
Height, cm	164.1	12.9	176.3	8.1	0.001[a]
Stature-for-age *z* score					
Females (15–18)	–3		–1		
Females (18+)	–0.5	1.1	1.2	1.2	0.009[a]
Males (15–18)	–1.1	1.8	0.6	0.9	0.121
Males (18+)	–0.7	1.6	0.3	0.8	0.243
Body mass, kg	66.55	22.50	74.69	14.83	0.193
Body mass index, kg/m^2	24.5	7.0	23.8	3.5	0.714
Waist circumference, cm	79.4	15.2	76.7	10.4	0.523
Hip circumference, cm	96.0	17.4	99.1	6.1	0.461
Waist:hip ratio	0.83	0.07	0.77	0.08	0.032[a]
Body composition					
Total fat mass, kg	23.62	13.41	19.69	9.90	0.307
Central fat mass, kg	14.20	9.33	10.60	6.36	0.171
Peripheral fat mass, kg	15.26	7.74	14.22	6.72	0.659
Total percent fat, %	36.08	9.82	27.53	11.52	0.017[a]
Central percent fat, %	37.50	9.79	27.98	11.81	0.009[a]
Peripheral percent fat, %	39.09	10.57	30.62	13.12	0.032[a]
Total lean body mass, kg	39.45	11.74	51.58	12.96	0.004[a]
Bone mineral density					
Total bone mineral density, g/cm	1.13	0.11	1.23	0.11	0.005[a]
z score					
Females (15–18)	–2.0		0.1		
Females (18+)	–0.6	1.7	0.5	0.8	0.121
Males (15–18)	–0.2	1.1	0.8	1.5	0.329
Males (18+)	0.2	1.1	1.4	0.8	0.070

[a]Denotes statistical significance ($p \leq 0.05$).

With regards to DXA measurements, total body, central and peripheral fat mass was not significantly different between groups; however, percentage values for each measure were comparatively higher in the survivor cohort. Further, reductions in total LBM and total BMD were observed in this group (Table 3).

Muscular strength and endurance

Cancer survivors had reduced measures of muscular strength and endurance when compared with controls (Table 4).

Table 4: Muscular strength, muscular endurance and aerobic capacity data for the cancer survivor group and the control group.

	Survivor (n = 20)		Control (n = 19)		
	Mean	SD	Mean	SD	p-Value
Muscular strength, kg					
Latissimus dorsi pull down	42	17	58	23	0.020[a]
Bicep curl	8	3	12	6	0.009[a]
Muscular endurance (60 s)					
Squats	32	15	43	11	0.012[a]
Sit-ups	26	9	34	11	0.030[a]

Push-ups	24	11	38	20	0.013[a]
Aerobic capacity					
Rating perceived exertion	17	3	18	2	0.102
Maximal heart rate, bpm	182	13	188	10	0.165
Minute ventilation, L/min	66.59	28.90	94.09	21.64	0.002[a]
Respiratory exchange ratio	1.05	0.28	1.06	0.07	0.930
$\dot{V}O_2$ peak, L/min	2.4	1.05	3.49	0.97	0.002[a]
$\dot{V}O_2$ peak, mL/kg/min	35.84	13.53	46.61	9.44	0.008[a]
$\dot{V}O_2$ peak, mL/kg LBM/min	57.42	13.18	67.29	6.29	0.010[a]

LBM, lean body mass.
[a]Denotes statistical significance ($p \leq 0.05$).

Peak oxygen uptake

All aerobic capacity data is presented in Table 4. Cancer survivors recorded lower absolute and relative $\dot{V}O_2$ peak values compared with control participants. Significant reductions were observed when $\dot{V}O_2$ peak was calculated based on LBM. Cancer survivors also recorded lower values for at peak exercise. There were no significant differences between cancer survivors and control participants in measures of maximal RPE, RER and maximal HR recorded during the assessment(s).

Discussion

This study utilised standardised and well-recognised protocols to characterise physical fitness and body composition in a cohort of adolescent and young adult survivors of paediatric brain cancer and/or CRT. When compared to healthy controls, survivors demonstrated poorer muscular performance and cardiorespiratory fitness, coupled with reduced LBM and BMD. Further, increased percentages of total body, central and peripheral fat were observed in the survivor cohort, as well as greater waist-to-hip ratios and resting HR. Finally, survivors were significantly shorter in stature than their counterparts.

Muscular strength, muscular endurance and aerobic capacity were assessed using optimal exercise physiology protocols, facilitating comparison with established reference values. Survivor ratings for these measurements were poor when compared to age-appropriate normative data. In fact, values for $\dot{V}O_2$ peak were equivalent to those expected for male and female cohorts aged 60–69 years and 50–59 years, respectively [14]. Similarly, abdominal endurance scores for the survivors corresponded to values typical for individuals between the third and fifth decades of life [16]. These results are consistent with those reported by Ness et al. [5] who found estimates of $\dot{V}O_2$ peak and muscular strength for adult survivors of paediatric brain cancer to be within the range expected for a cohort of individuals aged 60–69 years. Likewise, Wolfe et al. [11] reported significantly reduced estimates of treadmill maximal oxygen uptake for survivors of posterior fossa tumours when compared to similarly-aged, healthy control participants. This reinforces the notion that AYA survivors of paediatric brain cancer and/or CRT are at an enhanced risk of physical impairment and early-onset chronic disease typically associated with older-age [5], [17]. Moreover, aerobic insufficiency and muscular weakness are both causes and consequences of physical inactivity [18], [19]. This may create a deconditioning cycle that eventually restricts independence [20], [21] and further predisposes this cohort to inactivity-induced disease [18], [19], [22], [23], [24], [25], [26], [27].

Consistent with our muscular strength and endurance results, LBM was reduced in the survivor cohort – particularly in those with GHD and TSH deficiency. These findings are important as previously reported data on LBM in this population has failed to reach significance [28], although studies in other paediatric cancer survivor groups have corroborated our findings [10], [21], [28]. Our results may reflect the cancer-related fatigue, muscular catabolism and overall deconditioning that occurs in paediatric brain cancer and/or CRT survivors both during and after treatment [20], [21], [27].

Obesity is one of the most commonly reported side-effects of childhood cancer treatment [21], [24], [25], [27], [29], [30]. Survivors of paediatric brain cancer and/or CRT may develop obesity as a result of treatment consequences – such as GHD or hypothalamic damage – or imbalances between energy consumption and energy expenditure [3], [6], [7]. In this study, survivors had comparatively higher measurements of total body fat and demonstrated both peripheral and central adiposity. These findings parallel with those found by Heikens et al. [6] who reported increased waist-to-hip ratios in long-term survivors of paediatric brain cancer and Steinberger et al. [28] who observed abdominal adiposity in survivors of central nervous system tumours. This is of

particular concern given that accumulation of central adiposity is a major cardio-metabolic risk factor for other obesity-related diseases including insulin resistance, dyslipidaemia and hypertension [7], [9].

Another commonly reported side-effect of paediatric cancer treatment that was reflected in our results is short stature [31], [32]. As parental heights were not available, we were not able to determine if there was a familial contribution to the shorter stature of the survivor group. However, additional hormone deficiency is known to negatively correlate with final height [33] which was reflected in the stature differences between the GHD and TSH deficient group when compared to those with normal pituitary function. Further, treatment induced GHD and gonadal failure have been reported to negatively influence bone metabolism and mineral acquisition resulting in short stature and reduced BMD in this population [34], [35]. This is concomitant with our BMD results and highlights the risk of fracture and subsequent osteopenia and osteoporosis in these survivors [36], [37].

Limitations of our study include the small sample size and heterogeneous subject group. We were also unable to match the control participants for height and BMI. In order to account for these discrepancies, matches occurred based on age and gender and $\dot{V}O_2$ peak data was analysed in relative terms and by LBM. Secondly, while all of our participants were ambulatory, it is possible that potential treatment-induced balance and coordination disturbances may have influenced treadmill performance and prevented the survivors from attaining their true $\dot{V}O_2$ peak. It is important to note that cycle ergometry was considered for assessing $\dot{V}O_2$ peak in this study but was deemed inappropriate due to some participants suffering pathologies that induced pain upon seated movement and/or reduced limb range of motion. However, both of our cohorts recorded similar RPE, RER and maximal HR values using the treadmill protocol, suggesting that physiological intensity and aerobic effort were equal despite potential motor limitations in the survivor cohort. Whilst participants were asked to identify their tanner stage and timing of menstruation, pubertal examination was not performed as it was deemed too invasive for the purposes of this study. Historical details relating to timing of maximal growth velocity were not available. It is possible that pubertal timing in this cohort may affect interpretation of our BMD and strength data. Finally, while there were no stature differences in this study between those survivors who received irradiation and those who did not, we did not have measures of sitting height to confirm whether there was an impact on spinal growth.

In summary, AYA survivors of paediatric brain cancer and/or CRT have significantly decreased functional fitness, abnormal body composition and reduced BMD. These limitations not only have the potential to inhibit performance of everyday activities but considerably increase the risk of chronic disease and all-cause mortality within this population. Therefore, it is important to consider the inclusion of physical fitness, function and profile testing into the regular monitoring of survivors. As the testing protocols used in this study were time-efficient, well tolerated by participants and modifiable based on ability, they are highly appropriate for use in a clinical setting. The results of our study raise the question as to what extent implementation of exercise would ameliorate further decline in physical fitness in a population of paediatric brain cancer and/or CRT survivors. Specifically, determination of the most beneficial training modality (e.g. resistance training vs. aerobic training), training objective (e.g. decreased sedentary time or improved physical fitness) and initiation time should occur so future practice can involve the implementation of such programmes.

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Appendix

Table 5: Comparison data for cancer survivors who received surgery and/or chemotherapy and cancer survivors who received radiotherapy only.

	Surgery and/or chemotherapy (n = 7)		Radiotherapy (n = 13)		
	Mean	SD	Mean	SD	p-Value

Heart rate and blood pressure					
Systolic blood pressure, mm Hg	121	9	116	20	0.571
Diastolic blood pressure, mm Hg	69	6	69	13	0.911
Mean arterial pressure, mm Hg	89	5	87	17	0.836
Heart rate, bpm	76	10	75	16	0.905
Endothelial function					
Baseline diameter, cm	0.34	0.07	0.31	0.07	0.461
Peak diameter, cm	0.37	0.06	0.34	0.07	0.402
Delta diameter, cm	0.03	0.01	0.06	0.09	0.576
Delta percent, %	10.19	4.69	9.78	3.08	0.836
Time to peak, s	50.41	39.59	54.16	20.93	0.799
Anthropometry					
Height, cm	168.51	18.17	161.77	9.12	0.278
Body mass, kg	66.96	18.87	66.33	24.99	0.955
Body mass index, kg/m^2	23.1	3.5	25.2	8.3	0.542
Waist circumference, cm	75.6	10.0	81.6	17.6	0.421
Hip circumference, cm	95.0	8.6	96.5	21.4	0.863
Waist:hip ratio	0.79	0.07	0.85	0.07	0.133
Body composition					
Total fat mass, kg	20.91	8.06	25.08	15.68	0.521
Central fat mass, kg	12.02	5.10	15.37	10.98	0.459
Peripheral fat mass, kg	14.24	5.45	15.81	8.90	0.677
Total percent fat, %	33.56	10.13	37.43	9.78	0.415
Central percent fat, %	35.02	10.37	38.83	9.62	0.422
Peripheral percent fat, %	36.95	11.44	40.24	10.36	0.522
Total lean body mass, kg	42.96	15.54	37.57	9.30	0.341
Bone mineral density					
Total bone mineral density, g/cm	1.14	0.09	1.13	0.12	0.875
Muscular strength, kg					
Lateral pull downs	49	18	38	15	0.184
Bicep curl	8	3	7	4	0.805
Muscular endurance (60 s)					
Squats	34	12	30	17	0.612
Sit-ups	25	7	28	10	0.500
Push-ups	26	11	23	12	0.628
Graded exercise test					
Rating perceived exertion	17	1	16	3	0.345
Maximal heart rate, bpm	190	3	178	15	0.023[a]
Minute ventilation, L/min	80.63	39.55	58.41	17.75	0.200
Respiratory exchange ratio	1.01	0.06	1.08	0.35	0.634
$\dot{V}O_2$ peak, L/min	2.96	1.51	2.06	0.56	0.209
$\dot{V}O_2$ peak, mL/kg/min	43.99	13.66	31.40	11.75	0.064
$\dot{V}O_2$ peak, mL/kg LBM/min	65.68	11.29	52.92	12.28	0.053

LBM, lean body mass.
[a]Denotes statistical significance ($p \leq 0.05$).

Table 6: Comparison data for cancer survivors with and without hormone deficiency.

	GHD and TSH deficiency (n = 8)		Normal GH and TSH (n = 12)			FSH deficiency (n = 7)		Normal FSH (n = 13)		
	Mean	SD	Mean	SD	p-Value	Mean	SD	Mean	SD	p-Value
Heart rate and blood pressure										
Systolic blood pressure, mm Hg	112	15	121	18	0.247	119	24	116	14	0.784
Diastolic blood pressure, mm Hg	66	6	71	13	0.283	71	15	68	9	0.534
Mean arterial pressure, mm Hg	84	10	90	16	0.329	89	18	87	11	0.760
Heart rate, bpm	73	6	77	18	0.550	83	18	71	9	0.063
Endothelial function										
Baseline diameter, cm	0.28	0.07	0.34	0.06	0.060	0.29	0.06	0.33	0.07	0.229
Peak diameter, cm	0.30	0.07	0.37	0.06	0.053	0.31	0.07	0.36	0.07	0.235
Delta diameter, cm	0.07	0.11	0.03	0.01	0.267	0.08	0.12	0.03	0.01	0.182
Delta percent, %	11.77	3.53	9.36	3.91	0.213	11.93	1.89	9.49	4.41	0.222
Time to peak, s	50.03	14.80	55.66	32.43	0.657	55.21	27.09	51.85	25.86	0.795
Anthropometry										
Height, cm	155.53	12.21	169.87	10.24	0.011[a]	159.49	9.09	166.63	14.31	0.250
Body mass, kg	55.08	20.67	74.20	21.08	0.061	67.87	33.59	65.84	15.40	0.854
Body mass index, kg/m^2	22.19	5.73	25.99	7.53	0.242	26.03	11.16	23.63	3.53	0.478
Waist circumference, cm	73.57	13.80	82.78	15.49	0.212	82.50	25.70	77.95	8.01	0.559
Hip circumference, cm	85.86	10.35	101.88	18.34	0.050[a]	96.75	28.99	95.62	10.28	0.900
Waist: hip ratio	0.85	0.08	0.81	0.07	0.272	0.85	0.09	0.82	0.06	0.354
Body composition										
Total fat mass, kg	19.91	10.19	26.09	15.10	0.326	26.67	20.23	21.98	8.48	0.470
Central fat mass, kg	11.60	7.14	15.93	10.48	0.323	16.54	14.29	12.93	5.55	0.424
Peripheral fat mass, kg	12.96	5.63	16.79	8.77	0.290	16.65	11.40	14.51	5.30	0.569
Total percent fat, %	36.78	7.61	35.61	11.36	0.440	37.56	10.34	35.28	9.85	0.633
Central percent fat, %	37.63	9.03	37.41	10.66	0.953	38.31	11.46	37.06	9.25	0.793
Peripheral percent fat, %	40.29	7.21	38.30	12.58	0.099	41.10	9.90	38.01	11.15	0.547
Total lean body mass, kg	32.39	11.01	44.16	10.02	0.023[a]	37.48	12.22	40.2	11.84	0.594
Bone mineral density										
Total bone mineral density, g/cm	1.08	0.10	1.16	0.11	0.261	1.14	0.11	1.13	0.11	0.871
Muscular strength, kg										
Lateral pull downs	36	17	46	16	0.220	37	15	44	17	0.371
Bicep curl	7	2	8	3	0.215	7	2	8	3	0.444
Muscular endurance (60 s)										
Squats	27	13	35	16	0.255	30	11	33	17	0.696
Sit-ups	24	5	29	11	0.294	24	5	28	11	0.402
Push-ups	20	10	28	11	0.146	22	9	26	12	0.547
Graded exercise test										

Rating perceived exertion	17	3	17	3	0.791	16	3	17	2	0.606
Maximal heart rate, bpm	179	13	185	14	0.362	182	10	182	15	0.959
Minute ventilation, $L \cdot min^{-1}$	53.37	14.46	76.21	33.40	0.089	62.65	7.78	68.89	36.31	0.663
Respiratory exchange ratio	0.99	0.12	1.10	0.35	0.406	1.18	0.43	0.98	0.09	0.120
$\dot{V}O_2$ peak, L/min	1.75	0.41	2.82	1.15	0.033[a]	1.99	0.33	2.60	1.26	0.272
$\dot{V}O_2$ peak, mL/kg/mim	30.79	5.44	39.38	16.49	0.207	29.10	7.17	39.52	15.00	0.133
$\dot{V}O_2$ peak, mL/kg LBM/min	53.40	9.13	60.24	15.22	0.307	51.16	8.25	60.84	14.40	0.154

FSH, follicle stimulating hormone; GH, growth hormone; GHD, Growth hormone deficiency; LBM, Lean body mass; TSH, thyroid stimulating hormone.
[a]Denotes statistical significance ($p \leq 0.05$).

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