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Sarcopenia Predicts Cardiac Diastolic Dysfunction in Newly Diagnosed Oesophageal Cancer: Retrospective Cohort Study

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Abstract

Introduction: Sarcopenia is a high-impact condition in oesophageal cancer which can cause morbidity and mortality. It is well studied in striated muscle but impact on cardiac muscle is unknown. Cardiac dysfunction can majorly impact cancer symptoms, treatment tolerance, and survival.

Aim: The primary aim of this study was to explore the relationship between sarcopenia and cardiac structure and function in a consecutive prospective cohort of treatment-naïve patients with oesophageal adenocarcinoma treated with curative intent at the National Centre in Ireland.

Methods and Results: Treatment-naïve patients with oesophageal adenocarcinoma were recruited in an upper gastrointesti-

nal surgery referral centre. Sarcopenia was measured on positive emission tomography. Cardiac muscle mass and function were assessed on echocardiography.

Fifty-four participants were included. Ten were sarcopenic at baseline. Median skeletal muscle index (SMI) was 59 cm^2/m^2. Systolic function was normal; diastolic function was present (reduced E/A ratio; prolonged isovolumic relaxation time (IVRT)). Myocardial longitudinal strain was reduced. Myocardial performance index, IVRT, pulmonary artery pressure, left ventricular (LV) relaxation velocity, LV mass index and septal thickness differed in those with and without sarcopenia. Moderate correlation was seen between body composition measures and both IVRT and LV filling pressure. Lower SMI independently predicted prolonged IVRT. Baseline sarcopenia independently predicted increased left ventricular mass index on multivariable analysis. Sarcopenia and visceral obesity were independently associated with increased pulmonary artery pressure.

Conclusion: Cardiac function was assessed in treatment-naïve oesophageal adenocarcinoma with and without sarcopenia. Diastolic dysfunction was present on pre-treatment echocardiograms, predicted by sarcopenia. It is insufficient to assess systolic cardiac function alone in cancer. Assessment of sarcopenia and diastolic cardiac function could identify subclinical cardiac dysfunction and target reversible complications in potentially curable oesophageal cancer.

Keywords: Sarcopenia; Oesophageal Adenocarcinoma; Cardiac Dysfunction; Echocardiogram; Cardiac Atrophy; Deformation Imaging

Introduction

Sarcopenia, loss of skeletal muscle mass and function, is prevalent in cancer, particularly advanced gastrointestinal cancers such as oesophageal, gastric and pancreatic [1]. It may compromise muscle strength and related physical function, and contribute to the pathophysiology of cancer-related fatigue. It is also associated with increased all cause mortality [2-4]. Sarcopenia in cancer may be present independent of body-mass index (BMI) and body composition, with sarcopenic obesity increasingly recognized [5]. Ageing may also contribute to sarcopenia. In the modern scientific construct, sarcopenia should be viewed as part of the cancer-anorexia-cachexia continuum, with numerous endocrine, metabolic, immune and cytokine mediated inputs. Cancer cachexia is characterised by loss of skeletal muscle mass (with or without fat loss) that cannot be fully reversed by conventional nutritional support[6]. The consensus diagnostic criterion for cancer cachexia is weight loss >5% (>2% with low BMI or skeletal muscle mass) [6]. Survival is impaired with weight loss of ≥5%, but performance status declines with only 2.5kg loss over 6-8 weeks. Death usually occurs at >30% weight loss [7].

An intriguing question is whether sarcopenia, most usually studied with respect to striated muscle, is also evidenced in cardiac structure and function, with potential adverse clinical sequelae [8]. Symptoms common to both cachexia and heart failure include breathlessness, decreased mobility, exercise intolerance and fatigue, and therefore a putative association is of interest [1]. Cardiac muscle has minimal regenerative capacity [9]. Cancer patients have higher cardiac mortality, independent of pre-morbid heart disease [1,10]. Advanced cancer has been posited as a heart failure syndrome and the American College of Cardiology / American Heart Association suggest managing those with cancer as a stage A heart failure risk group [11,12]. Those with solid tumour malignancies have higher rates of cardiomyopathy, along with changes in resting heart rate, heart rate variability and cardiac biomarkers [13,14].

The impact of sarcopenia on cardiac muscle function is unknown. Cardiac atrophy has been seen in both clinical and cadaveric studies, and left ventricular mass atrophy has been seen in conjunction with loss of adipose tissue and skeletal muscle. Cardiac cachexia has been used to describe the cardiac atrophy, remodelling and dysfunction associated with cancer [1]. Cardiac atrophy in cancer may be due to overall weight loss reducing preload and left ventricle (LV) workload [15]. However, intentional weight loss is not associated with cardiac muscle changes, and in sarcopenia of ageing, LV mass is preserved [16]. The drivers of sarcopenia

and cachexia in cancer may be different, with all muscle types potentially susceptible to cytokine-mediated catabolism, with putative cardiac atrophy, remodelling and dysfunction associated with cancer[1]. Where cardiac muscle is affected in this context, damage may be subclinical and not identified until substantial damage has occurred. Myocardial dysfunction could play a major role in the fatigue and weakness of cancer cachexia [17]. This may impact on cancer treatment, increase treatment side effects and shorten survival [6].

Adenocarcinoma of the oesophagus has markedly increased in incidence in the western world over the last 40 years. Sarcopenia is reported in up to 75% at presentation, and increases markedly in patients undergoing chemotherapy or combination chemotherapy/radiation therapy prior to surgery[2]. As such it is an exemplar model for the study of sarcopenia. Systemic anticancer therapy plans for oesophageal cancer include cardiotoxic therapies, including chemotherapy, immunotherapy and thoracic radiotherapy. Thus, an increased pre-treatment cardiac risk is of significant importance.

The primary objective of this study was to explore the relationship between sarcopenia and cardiac structure and function in a consecutive prospective cohort of treatment-naïve patients with oesophageal adenocarcinoma treated with curative intent at the National Centre in Ireland. Although focused on oesophageal cancer, the implications of the study could apply more broadly across many different cancer types.

Methods

A clinicopathologic database of all patients with oesophageal cancer is maintained in our national surgical oncology centre. Records for all patients diagnosed with locally advanced (cT2-3, N0-3, M0) adenocarcinoma of the oesophagus treated with multimodal therapy in a 5-year period (January 2010 - March 2015) were reviewed for study inclusion. Patients were being treated with curative intent, although not all ultimately progressed to surgery. All patients had staging positron emission tomography with computed tomography (PET-CT) scans. Patients were eligible for inclusion if they had an echocardiogram (echo) within 90 days of their staging scan. Echoes were done as part of standard pre-operative work up. As these may have been done in a local or referring hospital, not all patients had an echo accessible for analysis, and were therefore excluded from the study. All study assessments were made at time of diagnosis and prior to any surgery or neoadjuvant therapy.

Prevalence of sarcopenia in this cohort, and relationship to operative and oncologic outcomes, has been reported [2]. Body composition was measured on PET-CT and sarcopenia calculated based on skeletal muscle index at the L3 vertebra via an automated algorithm with Hounsfield unit thresholds of -29 to 150 for skeletal muscle and -50 to -150 for adipose tissue [2]. Skeletal muscle index (SMI) is the ratio of lean tissue (cm^2) to height (m^2). The Prado definition of sarcopenia was used: SMI < $52.4cm^2/m^2$ for men and < $38.5cm^2/m^2$ for women [3].

Echoes were analysed retrospectively by a single blinded operator, an experienced research cardiac physiologist (GK). Echo measures were calculated according to British Society of Echocardiography specifications [18]. Ejection fraction was calculated using Simpson's biplane method. Transmitral flow (E/A) was computed as a ratio of peak velocity across the mitral valve during diastole in the early rapid (E wave) and late (A wave) filling phases. E/A and isovolumic relaxation time (IVRT) were recorded by Doppler ultrasound. The myocardial performance index was derived from mitral valve closure to opening time and LV ejection time. LV mass was determined from septal and posterior wall thickness and LV end diastolic diameter (EDD) using the Devereux formula [0.8(1.04[(LVEDD + IVSd + PWd)3 − LVEDD3])] + 0.6 where LVEDD, IVSd, and PWd represent LV, interventricular septal, and posterior wall thickness in diastole], and indexed to body surface area [19]. Tissue Doppler Imaging was used to measure Left Atrial (LA) volume, Pulmonary Artery systolic pressure and transmitral velocities. Myocardial strain – the change in myocardial fibre length over the cardiac cycle - was measured by tissue tracking analysis in the apical four chamber view and parasternal view centred on the left ventricle. All analysed segments were approved by both automated EchoPAC™ software (GE Healthcare, Norway) and the operator (GK).

Ethics was granted by the hospital research ethics committee, in accordance with the Declaration of Helsinki. Aspects of the study subsequent to May 2018 were executed in compliance with the General Data Protection regulation, Health Research Regulations and the Data Protection Act 2018. All participants in this study consented to the collection and use of their data.

Statistical analysis was performed with SPSS® (version 26.0) software (IBM SPSS Statistics for Windows, Chicago, IL, USA). Univariable and multivariable linear regression with a forward stepwise selection procedure was utilised to assess the independent impact of sarcopenia on cardiac physiology. A probability (p) level of 0.05 represented significance for all analyses; all p values reported are two-tailed. All results are median (interquartile range, IQR) unless otherwise specified.

Results

A database of oesophageal cancer patients planned for surgery identified 315 patients in the study period. Of these, 289 had sarcopenia data on baseline CT / PET available; 156 had echoes available, and 94 had these echoes within 3 months of the original CT / PET. For logistical reasons, not all echo discs were available for offline analysis. Of the 70 available, one study was removed from analysis due to infarction seen on echo, a second was removed due to the poor quality of the study, and 7 lacked baseline sarcopenia data. A further seven were excluded from this particular study as they had squamous cell carcinoma rather than adenocarcinoma.

Fifty-four participants fulfilled the inclusion criteria. The majority (87%) were male; median (range) age was 67 (46-83) years (Table 1). Prevalence of sarcopenia at diagnosis was 19%, 55% had visceral obesity, and 7% had both visceral obesity and sarcopenia. Median skeletal muscle index was $59cm^2/m^2$ (IQR 15). Of the ten participants sarcopenic at baseline, nine were male.

Table 1: Demographic data in the study cohort (N=54).

N=54		Frequency	Percent
Sex	Female	7	13
	Male	47	87
Diabetes	No	48	88.9
	Yes	6	11.1
Cardiovascular Disease	No	43	79.6
	Yes	1	20.4
Respiratory Disease	No	43	79.6
	Yes	11	20.4
ECOG	0	37	68.5
	1	16	29.6
	2	1	1.9
	3	0	0
BMI	<20	1	2
*Missing: 4	20-25	19	30
	25-30	20	36
	≥30	17	32
Sarcopenia	No	44	81.5

		Yes	10	18.5
Visceral Obesity		No	24	45.3
*Missing: 1		Yes	29	54.7
Overweight / Obese (per BMI)		No	16	32
*Missing: 4		Yes	34	63
	Median	Minimum	Maximum	IQR
Age (years)	67	46	83	14
BMI (kg/m^2)	27	19	37	7.3
SMI (cm^2/m^2)	59	38	87	15
L3 FFM (cm^2)	167	109	219	46
Whole Body FFM (kg)	58	39	79	13.6

BMI: body mass index; ECOG: Eastern Cooperative Oncology Group performance status; FFM: Fat free mass; IQR: Interquartile range; SMI: skeletal muscle index.

Table 2: Left ventricular (LV) function in treatment-naïve oesophageal adenocarcinoma

N=54 (except where noted)	Median	Minimum	Maximum	IQR
LVEF (%)	66	53	80	9.4
LV end diastolic diameter (mm)	51	37	59	7
E/A (ratio)	0.83	0.42	2	0.55
IVRT (ms)	99	50	158	21
Pulmonary artery pressure (mmHg) N=20	32	22	44	11.6
LA volume (cm^2)	18	11	26	6.3
Deceleration time (ms)	218	109	414	93
LV relaxation velocity (Ea, cm/sec) N=22	10	5	18	3
LV filling pressure (E/e) N=20	6.25	4	21	4
Myocardial performance index (ratio)	0.44	0.18	0.7	0.14
Septal thickness (mm)	9	6	11	1.3
Posterior wall diameter (mm)	9	7	12	1
LV mass (g)	164	82	242	46
LV mass index (g/m^2)	82	49	131	31.5
Longitudinal strain (%) N=14	17	12	21	3
Radial strain (%) N=8	41	14	90	23
Longitudinal strain rate (1/s)N=13	1	0.8	1.5	0.3

E/A: early (E) and late (A) diastolic transmitral peak flow; EF: Ejection fraction; IQR: Interquartile range; IVRT: Isovolumic relaxation time; LA: left atrium; LV: left ventricle.

Cardiac metrics are shown in Table 2. Due to echo quality, not all metrics could be measured in all participants. Notably, pulmonary artery pressure, LV relaxation velocity and LV filling pressure could only be measured in 20 (37%) and 22 (41%) participants while longitudinal strain was calculated in 14 participants (26%), radial strain in 8 (15%) and longitudinal strain rate in 13 (24%). Systolic function was normal by LVEF (66%, IQR 9.4, normal >55%). Pulmonary artery pressure was slightly raised (median 32mmHg, IQR 11.6, normal <30), deceleration time was normal (median 218ms, IQR 93, normal 160-260). Diastolic dysfunction was evident, with low E/A ratio (0.83, IQR 0.55, normal >1) and prolonged IVRT (99ms, IQR 21, normal 70-90). LV relaxation velocity was equivocal (Median 10cm/s, IQR 3; normal >12, abnormal ≤8) and estimated LV filling pressure (E/e) was 6.25 (IQR 4). Longitudinal strain was reduced (17%, IQR 3, normal 19-22%), radial strain was normal.

Table 3 shows the impact of sarcopenia on cardiac parameters. Myocardial performance index was significantly lower in those with sarcopenia (mean 0.37 v 0.45, p=0.038). Prolonged IVRT was more marked in sarcopenia (109.5ms v 98.6ms, p=0.087). There was a significant difference between those with and without sarcopenia in LV mass index (mean 100g/m^2 v 83g/m^2, p=0.018). Pulmonary artery pressure was higher (37.3mmHg v 30.9, p=0.08); left ventricular (LV) relaxation velocity was longer (12.9cm/s v 10.2, p=0.09) and LV filling pressure higher (10.5 v 6.5, p=0.36) in the subgroup with sarcopenia. Septal thickness, and LV mass were higher in the group with sarcopenia while deceleration time was shorter.

Table 3: Comparison between groups with and without sarcopenia. There was a significant difference in left ventricular (LV) mass and myocardial performance index in patients with adenocarcinoma. In those with sarcopenia: isovolumic relaxation time (IVRT) prolonged; pulmonary artery pressure higher; deceleration time shorter; left ventricular (LV) relaxation velocity longer; LV filling pressure higher; LV mass and septal thickness higher.

N=54	Without Sarcopenia	With Sarcopenia	Mean Difference	p
LVEF (%)	65.6	67.6	-2	0.36
LV end diastolic diameter (mm)	49.9	50.8	-0.9	0.58
E/A (ratio)	0.93	1	0.08	0.54
IVRT (ms)	98.6	109.5	-10.9	0.09
Pulmonary artery pressure (mmHg)	30.9	37.3	-6.4	0.08
Left atrial volume (cm^2)	18.5	18.1	0.4	0.8
Deceleration Time (ms)	219.7	209.2	10.5	0.67
LV relaxation velocity (Ea, cm/sec)	10.2	12.9	-2.7	0.09
LV filling pressure (E/e)	6.5	10.5	-4	0.36
Myocardial performance index (ratio)	0.45	0.37	0.07	0.04*
Septal thickness (mm)	9	9.6	-0.6	0.1
Posterior wall diameter (mm)	9.3	9.6	-0.3	0.5
LV mass (g)	162.3	181.1	-18.8	0.16
LV mass index (g/m^2)	83	100	-17	0.02*
Longitudinal strain (%)	16	17.8	-1.8	0.37
Longitudinal strain rate (1/s)	1.06	1.05	0.01	0.94

E/A: early (E) and late (A) diastolic transmitral peak flow; EF: Ejection fraction. *Statistical significance: p<0.05

Table 4: Cardiac dimensions correlated with skeletal muscle index (SMI) and body composition measures using Pearson Correlation in treatment-naïve patients with oesophageal adenocarcinoma. Isovolumic relaxation time (IVRT) was significantly correlated with all body composition measures. Left ventricular filling pressure was significantly correlated with both L3 fat free mass and Whole Body fat free mass

N=54		SMI (cm^2/m^2)	L3 Fat Free Mass (cm^2)	Whole Body FFM (kg)
LV EF (%)	ρ	-0.197	-0.087	-0.092
	Sig.	0.153	0.565	0.508
LV EDD (mm)	ρ	0.223	0.223	0.292*
	Sig.	0.105	0.136	0.032
E/A (ratio)	ρ	0.008	0.128	0.046
	Sig.	0.953	0.395	0.739
IVRT (ms)	ρ	-0.271*	-0.311*	-0.299*
	Sig.	0.049	0.035	0.029
Pulmonary artery pressure (mmHg)	ρ	0.181	0.214	0.214
	Sig.	0.446	0.365	0.365
Left atrial volume (cm^2)	ρ	0.031	-0.053	0.017
	Sig.	0.832	0.735	0.905
Deceleration Time (ms)	ρ	0.009	-0.041	0.027
	Sig.	0.949	0.788	0.847
LV relaxation velocity (Ea, cm/sec)	ρ	-0.185	0.041	-0.025
	Sig.	0.41	0.864	0.913
LV filling pressure (E/e)	ρ	-0.312	-0.568*	-0.476*
	Sig.	0.181	0.014	0.034
Myocardial performance index (ratio)	ρ	0.045	-0.107	-0.067
	Sig.	0.751	0.483	0.635
Septal thickness (mm)	ρ	-0.225	-0.121	-0.2
	Sig.	0.102	0.422	0.147
Posterior wall diameter (mm)	ρ	-0.031	-0.083	-0.038
	Sig.	0.822	0.584	0.783
LV mass (g)	ρ	0.019	0.038	0.08
	Sig.	0.892	0.805	0.571
LV mass index (g/m^2)	ρ	-0.208	-0.224	-0.212
	Sig.	0.135	0.14	0.127

E/A: early (E) and late (A) diastolic transmitral peak flow; EDD: end diastolic diameter; EF: ejection fraction; FFM: Fat free mass; LV: left ventricular. * Correlation is significant at the 0.05 level (2-tailed)

There was moderate positive correlation between LVEDD and whole-body fat free mass (ρ 0.29, p=0.029, Table 4). Moderate correlation was seen between all three body composition measures and IVRT (SMI ρ 0.27, p=0.049, L3 fat free mass ρ 0.31, p=0.035, whole-body fat free mass ρ 0.30, p=0.029). Left ventricular filling pressure

was significantly correlated with both L3 fat free mass and Whole Body fat free mass.

Univariable linear regression analysis (Table 5) confirmed these associations. Furthermore, lower SMI was independently predictive of prolonged IVRT (p=0.049), while baseline sarcopenia independently predicted increased LV mass index (p=0.017) on multivariable analysis. Sarcopenia and visceral obesity were independently associated with increased pulmonary artery pressure.

Table 5: Univariable and multivariable analysis of factors associated with cardiac physiology

	IVRT (ms)		Myocardial performance index (ratio)		LV mass index (g/m^2)		Pulmonary artery pressure (mmHg)		Deceleration time (ms)	
	P-value	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value	β (SE)	P-value	β (SE)
Age, years	0.184	-	0.027	-0.00 (0.00)	0.485	-	0.825	-	0.203	-
Sex, male vs female	0.387	-	0.286	-	0.664	-	0.5	-	0.619	-
Diabetes	0.809	-	0.358	-	0.137	-	0.794	-	0.587	-
Cardiovascular disease	0.372	-	0.903	-	0.949	-	0.692	-	0.218	-
Respiratory comorbidity	0.465	-	0.105	-	0.272	-	0.917	-	0.011	52.48 (19.69)
Ever smoking	0.285	-	0.577	-	0.332	-	0.312	-	0.319	-
Weight, kg	0.151	-	0.145	-	0.166	-	0.462	-	0.106	-
Body mass index, kg/m^2	0.127	-	0.704	-	0.171	-	0.384	-	0.105	-
Sarcopenia	0.62	-	0.531	-	0.017	18.98 (7.59)	0.014	5.23 (1.88)	0.667	-
Skeletal muscle index, cm^2/m^2	0.049	-0.71 (0.35)	0.388	-	0.413	-	0.687	-	0.172	-
Fat free mass, kg	0.847	-	0.058	-	0.447	-	0.71	-	0.22	-
Visceral obesity	0.124	-	0.88	-	0.801	-	<0.001	10.76 (2.09)	0.135	-
Fat mass, kg	0.156	-	0.803	-	0.237	-	0.75	-	0.11	-

IVRT, isovolumetric relaxation time; LV, left ventricular; SE, standard error *Statistical significance: p<0.05

Discussion

Sarcopenia, with an impact on symptoms, treatment tolerance, and operative and oncologic outcomes, has major importance in cancer research. However, there is a paucity of research on the link between structural somatic muscle loss associated with sarcopenia and cardiac structure and function. This study demonstrates, for the first time in oesophageal cancer, an association between sarcopenia and diastolic dysfunction, notably IVRT prolongation, and correlation with body composition. Myocardial performance index, IVRT, pulmonary artery pressure, left ventricular (LV) relaxation velocity, LV mass index and septal thickness differed in those with and without sarcopenia. The increased pulmonary artery pressure, reduced deceleration time, and increased LV filling pressure are all consistent with reduction in LV compliance. Moderate correlation was seen between body composition measures and

both IVRT and LV filling pressure. Lower SMI independently predicted prolonged IVRT. Baseline sarcopenia independently predicted increased left ventricular mass index on multivariable analysis. Sarcopenia and visceral obesity were independently associated with increased pulmonary artery pressure. This indicates the impact of body composition on cardiac function and cardiovascular health.

Contrary to our a priori hypothesis, LV mass index was higher in sarcopenia, a finding which may be more consistent with cardiac hypertrophy or cardiomyopathy than cardiac atrophy. Cancer-induced cachexia may cause cardiac remodeling [9]. Myocardial performance index and longitudinal strain were low, indicating abnormal myocardial function and contractile impairment. Left ventricular ejection fraction was preserved. Strain is a sensitive measure of subclinical deterioration in LV systolic function which provides additional information using conventional echocardiographic technique. Strain is an earlier marker of myocardial disease than ejection fraction, with a decrease in strain detectable prior to overt change in ejection fraction, and abnormal strain predictive of future decline in ejection fraction [20,21]. Early diastolic dysfunction predicts future systolic dysfunction [22]. These data highlight the importance of thoroughly assessing cardiac function in cancer, not exclusively systolic function and not just in those planned for potentially cardiotoxic treatments.

A scoping review of treatment-naïve cancer patients has identified a range of cardiac muscle changes including reduced myocardial strain, reduced ejection fraction, diastolic function, both left ventricular atrophy and reduced cardiac wall thickness, and hypertrophy or enlarged ventricles [14]. This study has established further hypotheses for prospective evaluation, as well as potential interventional studies.

The pathophysiology of diastolic changes associated with sarcopenia is unclear. We observed an increase in IVRT and LV mass index, and increase in pulmonary artery pressure and LV filling pressure, and a decrease in deceleration time. This may reflect fibrotic change, reduced LV compliance, or greater total peripheral resistance due to higher rates of atherosclerosis, hypertension or vascular calcification. Alternatively, it may reflect remodelling as an adaptive mechanism, as in hypertrophic cardiomyopathy, with cardiac atrophy a later event [16,23]. Relative LV hypertrophy has been seen in patients with early breast cancer and treatment-naïve colon cancer [24,25]. Subclinical myocardial dysfunction may trigger increased cardiac workload to maintain the same output.

The relevant literature is scant, particularly in treatment-naïve groups, and there are no studies of oesophageal cancer patients, although there are clinical, cadaveric studies & animal studies [1,26]. In the context of cachexia in patients with lung or gastrointestinal cancer, the actual heart weight of patients with cachexia is reported as significantly lower than non-cachectic subjects and controls, while the relative heart weight was higher in cachexia than controls [8]. Springer et al. have demonstrated that patients with lung, gastrointestinal and pancreatic cancer who died with cancer cachexia manifested cardiac cachexia with reductions of heart weight of 25.6%. There was reduced LV wall thickness compared with controls who died of non--cancer-related illness, while LV sections of those who died with cancer showed profound fibrosis, regardless of the presence of cachexia. Cardiomyocyte atrophy, myocardial fibrosis and oedema were the three key features in a second autopsy-based study in a mixed cancer group, in which heart rate did not show reduction compared to controls, but LV wall thickness was significantly reduced [27].

Pathology-based studies have described both hypertrophy and fibrosis in survivors of childhood cancer, suggesting restrictive cardiomyopathy [28]. In patients on chemotherapy, anthracyclines have been linked with increased LV mass, particularly at high doses (>400mg/m^2). Early hypertrophic remodelling, or induction of restrictive cardiomyopathy by anthracyclines differs from generally accepted theories of anthracycline-induced cardiotoxicity (loss of myocytes and dilated cardiomyopathy) [28]. Our study suggests remodelling may also be triggered by cancer itself, as all patients were treatment naive. In other hypercatabolic diseases, both atrophied and hypertrophied hearts can be significantly associated with severe skeletal muscle depletion. In liver cirrhosis, sarcopenia was more common in both increased and decreased LV mass index than those whose LV mass index was normal [29]. In a non-cancer older population, sarcopenic myocardium was evident by small-

er LV and atrial sizes, with gross preservation of LV function [30].

Atrophy of skeletal and cardiac muscle, both of which are striated, can be caused by both cancer and treatment through mitochondrial dysfunction [1]. Low cardiac mass may not produce clinical cardiac dysfunction immediately. Rodent studies show ≥20% LV mass loss is required before significant impairment in LV ejection fraction and diastolic diameters. The heart already has a high basal rate, with cardiac muscle having higher metabolic rate and protein turnover than skeletal muscle [31]. Baseline levels and activity of the ubiquitin-proteasome system in the heart may be sufficient to process the increased supply of substrates during cardiac atrophy. Myofibrillar proteins make up 40% of LV dry weight. A unique mechanism of cardiac muscle atrophy distinct from atrophy in skeletal muscle is decrease in myocyte size, with myocellular disarray and myofibrillar protein decrease, rather than increased cell death (apoptosis).

There is a clear need to further study the link between sarcopenia, cachexia, and cardiac structure and function [26]. Our study showed links between body composition measures and IVRT, LV filling pressure and pulmonary artery pressure. This indicates the impact of body composition on cardiac function and cardiovascular health. Prospective studies should examine any association between sarcopenia, cachexia and heart failure in humans [16]. Studies should be adequately powered, as interpretation may be confounded by existing cardiac disease, medication and comorbidities. Changes may be nuanced and subclinical as comorbid cardiovascular disease may be undiagnosed in a cancer population. One study noted heart failure identified on echo in up to 14% of non-small cell lung cancer patients referred for clinical trial, compared to 1.4% with an established diagnosis [32].

The importance of studying cardiac structure and function in prospective longitudinal studies in oesophageal and other cancer cohorts is not only to obtain an understanding of the impact on clinical outcome, but also to uncover potentially modifiable factors. Of particular interest are heart failure medications like aldosterone antagonists, β blockers and statins which reduce skeletal and heart muscle wasting, cardiac dysfunction and myocardial fibrosis [8,16]. ACE inhibitors slow progression of LV dysfunction in various cardiomyopathies, prevent cardiotoxicity and improve cardiac function during chemotherapy. Despite the well--known cardiovascular benefits of exercise, the implications of an exercise programme on cardiac function in the context of cancer sarcopenia or cachexia is unclear. The potential benefit of established cardiovascular drugs is that the translation from animal studies to clinical use could be rapid [1]. A multimodal approach, including nutritional support, pharmacological intervention and exercise training is likely required [1,8].

A major strength of this study is the treatment naïve cohort of patients. We can eliminate the role of cardiotoxic cancer treatments from the cardiac changes which were found. We used robust methodology. PET-CT is the standard for measuring sarcopenia as per Prado et al[3]. Metabolic information from 18F-FDG PET may complement that gained from CT for the characterization of muscle. Echo is widely available, versatile and provides a breadth of information on cardiac muscle and function [33]. The majority of our participants are male. This is in keeping with the demographics of the patients with this diagnosis in our centre, and oesophageal cancer as a global phenomenon [22].

We acknowledge limitations in the current study. Although prospectively evaluated, the cohort was identified from a retrospective database. As echoes were done for clinical, rather than research reasons, not all data required for analysis was available. Stored image quality and technical limitations in extraction limited strain analysis. Strain analysis was done by a single operator. This has the potential to introduce intra-operator bias [33]. Future developments in imaging analysis, including through the use of artificial intelligence, will reduce aspects of bias and increase speed of analysis. Due to the retrospective nature of the study, it is not possible to draw any conclusions on the role of cardiac hypertrophy in symptom development. More cardiovascular disease at baseline with sarcopenia was previously noted by the same research group [2]. However, this was not the case in this study cohort and would not explain our findings. Our sample size was small, with 54 participants overall, of whom 10 had sarcopenia. Study power was reduced,

most markedly in the parameters for which not all echoes were of sufficient quality for analysis. Small numbers in the sarcopenia subgroup limited statistical analysis due to increased risk of both type I and type II statistical errors.

In conclusion, although it is known that both sarcopenia and myocardial dysfunction can lead to reduced treatment tolerance, discontinuation of anti-cancer therapy, increased symptom burden and increased morbidity, the relationship between both is unclear. This study identifies a link between sarcopenia and specifically diastolic dysfunction in patients with locally advanced oesophageal cancer undergoing treatment with curative intent. This merits validation in prospective study design, including potentially the study of the added impact of pre-operative chemotherapy or radiation therapy on both somatic and cardiac muscle and function. Major side effects such as cancer-related fatigue attributed in part to sarcopenia should be evaluated with parallel study of cardiac function, as well as the mechanism of cancer-associated cardiac morbidity and mortality [1]. Interventional trials of targeted exercise interventions and prehabilitation to optimise outcomes should include study of cardiac structure and function.

Conclusions

We examined cardiac muscle morphology and function in treatment-naïve patients with oesophageal adenocarcinoma, who also had had body composition assessment. LV mass index differed with and without sarcopenia. LV mass index was higher in sarcopenia, which may suggest cardiomyopathy or hypertrophy rather than atrophy. This may be explained by subclinical myocardial dysfunction, with the cardiac muscle having to work harder to maintain the same output. Body composition measures (skeletal muscle index, fat free mass) were linked with cardiac parameters (IVRT, LV filling pressure, pulmonary artery pressure). This suggests that cardiac muscle may also be impacted by the systemic effects of sarcopenia. There was clinically significant evidence of diastolic dysfunction, across the entire study cohort, most marked in those with sarcopenia. However, ejection fraction was notably normal.

In potentially curable cancer, it is insufficient to assess only systolic cardiac function. Diastolic function should also be assessed using conventional echo measurements to include myocardial strain and strain rate. Assessment of sarcopenia and cardiac function could facilitate pre-treatment optimization towards the goal of improving treatment tolerance and reducing the quality-of-life impact of potentially curative oesophageal cancer treatment in long-term survivorship.

Author Contributions

Brady, B – Conceptualisation, Methodology, Validation, Formal analysis, Investigation, Writing, Visualisation, Project administration; King, G – Formal analysis, Investigation, Resources, Writing Elliott, J – Conceptualisation, Methodology, Formal analysis, Writing; Doyle, S – Methodology King, S – Data curation; Reynolds, JV – Resources, Writing, Supervision; Murphy, RT – Conceptualisation, Resources, Writing, Supervision; Walsh, D – Conceptualisation, Writing, Supervision, Funding acquisition

Ethics Approval

Ethics was granted by the Tallaght University Hospital/St. James's Hospital joint research ethics committee, and the study was performed in accordance with the Declaration of Helsinki. The study was executed in compliance with the General Data Protection regulation.

Data Availability

Data is available on request to the corresponding author.

Conflict of Interest Statement

The authors declare that there are no conflicts of interest to report.

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