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ORIGINAL ARTICLE

Sarcopenia during neoadjuvant therapy for oesophageal cancer: characterising the impact on muscle strength and physical performance

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Abstract

Purpose Preoperative chemo(radio)therapy for oesophageal cancer (OC) may have an attritional impact on body composition and functional status, impacting postoperative outcome. Physical decline with skeletal muscle loss has not been previously characterised in OC and may be amenable to physical rehabilitation. This study characterises skeletal muscle mass and physical performance from diagnosis to post-neoadjuvant therapy in patients undergoing preoperative chemo(radio)therapy for OC.

Methods Measures of body composition (axial computerised tomography), muscle strength (handgrip), functional capacity (walking distance), anthropometry (weight, height and waist circumference), physical activity, quality-of-life and nutritional status were captured prospectively. Sarcopenia status was defined as pre-sarcopenic (low muscle mass only), sarcopenic (low muscle mass and low muscle strength or function) or severely sarcopenic (low muscle mass and low muscle strength and low muscle function).

Results Twenty-eight participants were studied at both time points (mean age 62.86 ± 8.18 years, $n = 23$ male). Lean body mass reduced by 4.9 (95% confidence interval 3.2 to 6.7) kg and mean grip strength reduced by 4.3 (2.5 to 6.1) kg from pre- to post-neoadjuvant therapy. Quality-of-life scores capturing gastrointestinal symptoms improved. Measures of anthropometry, walking distance, physical activity and nutritional status did not change. There was an increase in sarcopenic status from diagnosis (pre-sarcopenic $n = 2$) to post-treatment (pre-sarcopenic $n = 5$, severely sarcopenic $n = 1$).

Conclusions Despite maintenance of body weight, functional capacity and activity habits, participants experience declines in muscle mass and strength. Interventions involving exercise and/or nutritional support to build muscle mass and strength during preoperative therapy, even in patients who are functioning normally, are warranted.

Keywords Sarcopenia · Physical fitness · Oesophageal cancer · Neoadjuvant therapy

Background

Surgery for oesophageal and gastric cancer represent exemplar models of complex operations that may be associated with significant weight loss, malnutrition and sarcopenia. In the modern era, surgery is preceded by either chemotherapy or combination chemoradiotherapy for the majority of patients who present with locally advanced disease [1]. Notwithstanding improved survival with such approaches compared with surgery alone in this cohort [2, 3]; both chemotherapy and radiation therapy can also impact on body composition, functional status and quality-of-life (QOL) [4, 5]. Accordingly, at a time when overall survival is improving, there is an increasing focus on nutritional and physical well-being over a period of several months in patients undergoing treatment for locally advanced disease [6].

The challenge of sarcopenia in cancer is well documented. Up to 75% of patients with oesophageal cancer (OC) are sarcopenic at diagnosis [7], with associated dose-limiting toxicity during preoperative chemotherapy [8], disease progression [9], and adverse postoperative outcomes [5].

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Neoadjuvant therapy can further reduce skeletal mass and strength, a process exacerbated by factors commonly reported in patients with OC, such as physical inactivity, systemic inflammation and malnutrition [10, 11]. From this Centre, we recently described a significant decline in lean body mass amongst 252 patients undergoing neoadjuvant therapy for OC, with an increase in prevalence of sarcopenia from 16% at diagnosis to 31% post-treatment and an associated worsening in physician-assigned performance status [9]. Importantly, preoperative sarcopenia independently predicted postoperative complication risk, postoperative pulmonary complications and hospital length of stay, and therefore interventions that preserve muscle mass and function have considerable clinical potential.

Sarcopenia is a multifactorial syndrome intrinsically linked with loss of functional performance, reduced engagement with activities of daily living and compromise to multiple domains of QOL [12]. To capture physical disability with sarcopenia, the European Working Group on Sarcopenia in Older People (EWGSOP) recommends that both primary (age-related) and secondary (non-age related) sarcopenia be characterised as loss of muscle mass accompanied by either low muscle strength or low muscle performance [11]. Subjectively reported QOL concerns, particularly in the domain of physical functioning, are well described among patients with OC and can remain impaired into survivorship [13, 14]. However, self-reported physical functioning correlates poorly with objective measures [15] and therefore inadequately quantifies functional decline and provides limited information to guide physical rehabilitation. While several observational studies have described loss of cardiopulmonary fitness during preoperative chemo(radio)therapy [16–18], the impact on other domains of physical function has not been systematically studied, with just one study of 27 patients with squamous cell carcinoma reporting no change in walking distance, lower leg strength or physical activity following preoperative chemotherapy [19]. The purpose of this study was to characterise the evolution of sarcopenia and associated muscle performance from pre- to post-neoadjuvant therapy for OC.

Methods

Study design

Patients scheduled for curative multimodal treatment for OC were identified from the upper gastrointestinal clinic at the Oesophageal and Gastric Centre at St James's Hospital (SJH), Dublin, Ireland, a high-volume national centre. Ethical approval was obtained from the SJH–Tallaght Hospital Joint Research Ethics Committee. Informed written consent was obtained prior to study commencement.

Using a prospective observational design, participants were recruited after diagnosis, prior to commencing treatment. Measurements were collected at diagnosis (pre-neoadjuvant therapy) and after neoadjuvant therapy (prior to surgery). Visits were conducted in the Wellcome Trust/HRB Clinical Research Facility at SJH.

Clinical treatment

All participants were treated using a multimodal treatment approach [1], involving pre- and/or postoperative chemotherapy as per the MAGIC regimen [Etoposide, Cisplatin, Fluorouracil or Capecitabine] [3] or neoadjuvant chemoradiation as per the CROSS protocol (Cisplatin/5-Fluorouracil, 40 Gy/15 Fr, or Carboplatin/Paclitaxel, 41.4 Gy/23 Fr) [2]. Tailored nutrition counselling was provided by a specialist dietitian in line with best practice guidelines [20]. Surgical resection was performed at least 6-weeks following neoadjuvant therapy, utilising either a transthoracic or transhiatal approach.

Measures of anthropometry

Weight (kg) was recorded using a calibrated seca scale. Height (cm) was measured barefoot using a seca stadiometer. BMI was calculated as weight (kg)/height (m^2). Waist circumference (cm) was measured at the mid-point between the iliac crest and the 12th rib following gentle expiration. Measures were taken in duplicate and averaged for data entry.

Body composition analysis by computed tomography

Axial computerised tomography (CT) scans were routinely obtained at diagnosis and post-neoadjuvant therapy using a Siemens Emotion single slice or a multi-slice Somatom Sensation scanner (Siemens Healthcare, Erlangen, Germany). Images were analysed by a single investigator [SLD] to determine the cross-sectional area (cm^2) of various tissue compartments using a standard Siemens Leonardo PACS Workstation (Siemens Healthcare, Erlangen, Germany). An automated algorithm was applied utilising CT Hounsfield unit thresholds of − 29 to 150 for skeletal muscle and − 50 to − 150 for adipose tissue [9]. The cross-sectional area of lean tissue and adipose tissue was determined at the level of L3 as previously described [21, 22].

Lean body mass (LBM) (kg) was derived using the following formula, which was developed and validated against DXA as gold standard [22]:

$$\mathrm{LBM\ (kg)} = 0.14 \times \left[Lean\ Tissue\ Area_{[L3]}\left(\mathrm{cm}^2\right)\right] + 0.72$$

Total fat mass (FM) was derived utilising a previously validated formula obtained from comparison with DXA [22]:

$$\mathrm{FM\ (kg)} = 0.042 \times \left[\mathit{Total\ Fat\ Area}_{[\mathrm{L3}]} \left(\mathrm{cm}^2\right)\right] + 11.2$$

Measurement and classification of sarcopenia

Skeletal muscle index (SMI) was derived as the ratio of lean tissue area to height:

$$\mathit{SMI}\ \left(\mathrm{cm}^2/\mathrm{m}^2\right) = \frac{\mathit{Lean\ Tissue\ Area}_{[\mathrm{L3}]}\left(\mathrm{cm}^2\right)}{\mathit{Height}\ \left(\mathrm{m}^2\right)}$$

Isometric hand grip strength (HGS) (kg) was measured using a handheld digital dynamometer (Jamar). Measures were taken in triplicate bilaterally and the highest measure recorded. Functional performance for activities of daily living was measured using the 6-min walk test (6MWT) [23]. Participants walked at their fastest pace for 6 min along a 30-m hospital corridor with the aim of achieving the furthest distance possible.

Sarcopenia was defined according to consensus criteria [11] encompassing low muscle mass (SMI < 52.4 cm^2/m^2 in men and < 38.5 cm^2/m^2 in women [22]) with either low muscle strength (HGS < 30 kg in men or < 20 kg in women [11]) or low physical performance (6MWT < 400 m) [12]. Pre-sarcopenic status was defined as low SMI without impact on muscle strength or physical performance; sarcopenic status as low SMI with either low muscle strength or low physical performance; and severe sarcopenia as low SMI, low muscle strength and low physical performance [11].

Physical activity

Physical activity was measured using the ActiGraph GT3X+ triaxial accelerometer (Actigraph Pensacola, FL). The accelerometer was worn on the hip, secured with an elastic belt, during waking hours for 7 days following both study visits. Data were analysed using the Actilife software using standardised algorithms to analyse time in physical activity domains and adherence to physical activity guidelines (150 min MVPA/week, accumulated in bouts ≥ 10 min [24]).

Measures of nutritional status

Malnutrition risk was screened using the Short Nutritional Assessment Questionnaire (SNAQ) [25]. Items on the 4-item tool are cumulatively scored with a maximum score of 20. Scores < 14 indicate risk of undernutrition [26].

Gastrointestinal symptoms were evaluated using the Gastrointestinal Symptoms Rating Scale (GSRS) [27]. Each item in the 15-item instrument is rated on a 7-point Likert scale and categorised into abdominal pain, reflux, diarrhoea, constipation or indigestion. Categorical scores are calculated as the mean of items within each category, with higher scores indicating more severe symptoms [28].

Habitual intake was assessed using the European Prospective Investigation of Cancer food frequency questionnaire (EPIC FFQ) [29]. Data from 131-item instrument were converted to nutrient intakes using the FETA FFQ EPIC Tool for Analysis (version 6.0) [30]. The adequacy of total energy, macronutrient and micronutrient intakes and the percentage contribution of each macronutrient to total energy intake were assessed.

Measures of QOL

QOL was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Core QOL Questionnaire, the QLQ-C30 (version 3.0) and the oesophageal-specific subscale (QLQ-OES18). This validated instrument assessed QOL in functional, symptom and global domains. Scores for each question were calculated according to the EORTC QLQ-C30 manual and linearly transformed into a 0–100 scale [31].

Statistical analyses

SPSS version 22.0 was used for analyses. Variables were tested for normality using the Shapiro-Wilks test. Normally, distributed variables were summarised as mean and standard deviation (SD). Non-normally distributed data were summarised as median and interquartile range (IQR). Categorical variables are presented as frequency (percentage).

Paired sample *t* tests and Wilcoxen signed-rank tests were used to examine differences in outcomes from diagnosis to post-neoadjuvant therapy. Differences between the groups were presented as *Cohen's d* effect sizes. The strength of the differences was interpreted as small ($d < 0.2$), medium ($d = 0.2–0.5$) or large ($d > 0.8$) [32]. Associations between sarcopenia and measures of functional performance were assessed using Pearson Product Moment Correlation Coefficients and Spearman's rho regression analyses. Independent sample *t* tests were used to compare differences between those treated according to the CROSS versus MAGIC regimen. Statistical significance was taken at $p < 0.05$.

Results

Between January 2014 and October 2016, 36 patients were recruited at diagnosis and 28 returned for repeat measures after neoadjuvant therapy. The mean time between

assessments was 92 days (range 61–118). Reasons for not completing follow-up measurements were: disease progression ($n = 5$); participant unavailable ($n = 2$) and participant drop-out ($n = 1$). Demographic characteristics did not differ between those who did and did not complete follow-up measures (Table 1).

Measures of anthropometry

Body weight (81.8 ± 14.1 kg vs. 80.9 ± 14.2 kg, $p = 0.12$) and BMI (28.1 ± 3.8 kg/m^2 vs. 27.8 ± 3.6 kg/m^2, $p = 0.21$) remained stable from diagnosis to post-neoadjuvant therapy. Percentage weight loss between these two time points (−1.1 ± 3.6%) was not clinically important. Whole body fat mass, as measured by CT scan, did not change (25.4 ± 5.9 kg vs. 25.1 ± 5.2 kg, $p = 0.49$). Mean waist circumference did not change for male (94.8 ± 9.3 cm vs. 95.1 ± 10.3 cm, $p = 0.85$) or female (90.3 ± 18.3 cm vs. 88.0 ± 12.7 cm, $p = 0.67$) participants.

Measures of sarcopenia

Body composition analysis revealed significant loss of SMI (mean (95% confidence interval [CI]) loss 5.6 (3.7 to 7.5) cm^2/m^2), LBM (4.9 (95%CI 3.2 to 6.7) kg) and lean tissue area at L3 (16.4 (10.7 to 22.2) kg) ($p < 0.001$, $d = 0.5$ for all, Table 2). There was no difference in SMI loss between those treated with chemoradiotherapy (mean loss 6.2 ± 4.7 cm^2/m^2) and those treated with chemotherapy only (3.2 ± 5.2 cm^2/m^2) (between group difference 2.9 (95%CI − 1.9 to 7.8, $p = 0.23$). Results did not change when patients with a diagnosis of squamous cell carcinoma ($n = 2$) were excluded from the analysis. Low muscle mass indicative of sarcopenia was evident in two participants (7%) at diagnosis, increasing to six participants (22%) post treatment.

HGS reduced significantly (4.3 (95%CI 2.5 to 6.1) kg, $p < 0.01$, $d = 0.5$), with an increase in the number of participants with sub-optimal HGS from zero at diagnosis to two post-neoadjuvant therapy (Table 3). There was no difference between those treated with chemoradiotherapy (4.5 ± 4.9 kg) compared chemotherapy only (3.7 ± 3.9 kg) (between group difference 0.7 (95%CI − 3.8 to 5.2, $p = 0.74$). At diagnosis, HGS correlated with lean tissue area at L3 ($r = 0.85$, $p = 0.000$), LBM ($r = 0.85$, $p = 0.000$), and SMI ($r = 0.72$, $p = 0.000$). Similarly, post neoadjuvant therapy HGS correlated with lean tissue area at L3 ($r = 0.78$, $p = 0.000$), LBM ($r = 0.78$, $p = 0.000$), and SMI ($r = 0.62$, $p = 0.001$).

Mean 6MWT distance did not change (529.4 ± 66.8 m vs. 515.5 ± 84.2 m, $p = 0.13$). At diagnosis one participant walked <400 m, increasing to two participants post-treatment. Walking distance did not correlate with LBM at either time point.

Using consensus diagnostic criteria [11], two participants were classed as pre-sarcopenic (low SMI only) at diagnosis. Post-neoadjuvant therapy, five participants were classed as pre-sarcopenic and one participant with low SMI, sub-optimal HGS and reduced 6MWT as severely sarcopenic (Fig. 1).

Table 1 Demographic characteristics

Characteristic	All participants ($n = 36$)		Pre- and post-neoadjuvant therapy data ($n = 28$)	
Age ± SD (years)	61.83 ± 9.08		62.86 ± 8.18	
	n	%	*n*	%
Gender				
Male	30	83	23	82
Female	6	17	5	18
Histological Subtype				
Adenocarcinoma	31	86	26	93
Squamous Cell Carcinoma	5	14	2	7
Neoadjuvant therapy protocol				
CROSS	25	70	22	89
MAGIC	10	28	6	21
Other	1	3	–	–
Tumour regression grade				
1	4	11	2	7
2	7	11	7	25
3	6	17	6	21
4	10	28	10	36
5	5	14	3	11
Surgery type				
Transthoracic	28	78	25	89
Transhiatal	1	3	1	4
Gastrectomy	2	6	2	7
Did not progress to surgery	5	16	–	–

Table 2 Change in body composition from diagnosis to post-neoadjuvant therapy

	Diagnosis ($n = 27$)	Post-neoadjuvant therapy ($n = 27$)	*p* value
BMI (kg/m^2)	28.1 ± 3.8	27.8 ± 3.6	0.21
Lean tissue area at L3 (cm^2)	176.8 ± 31.7	160.4 ± 30.0	< 0.01
Lean body mass (kg)	59.1 ± 9.5	54.2 ± 9.0	< 0.01
Skeletal muscle index (cm^2/m^2)	60.3 ± 8.1	54.7 ± 7.5	< 0.01
Wholebody fat mass (kg)	25.4 ± 5.9	25.1 ± 5.2	0.49
Sarcopenic status			
Pre-sarcopenic (*n* (%))	2 (7)	5 (18.5)	N/A
Sarcopenic (*n* (%))	0	0	
Severely sarcopenic (*n* (%))	0	1 (4)	

N/A = not applicable

Table 3 Change in isometric hand grip strength from diagnosis to post-neoadjuvant therapy

	Diagnosis ($n = 28$)	Post-neoadjuvant therapy ($n = 28$)	p value
Overall hand grip strength (kg)	41.6 ± 10.3	37.3 ± 8.8	< 0.01
Dominant hand (R) (kg)	41.1 ± 10.6	36.8 ± 9.3	< 0.01
Non-dominant hand (L) (kg)	38.9 ± 10.7	34.9 ± 8.8	< 0.01

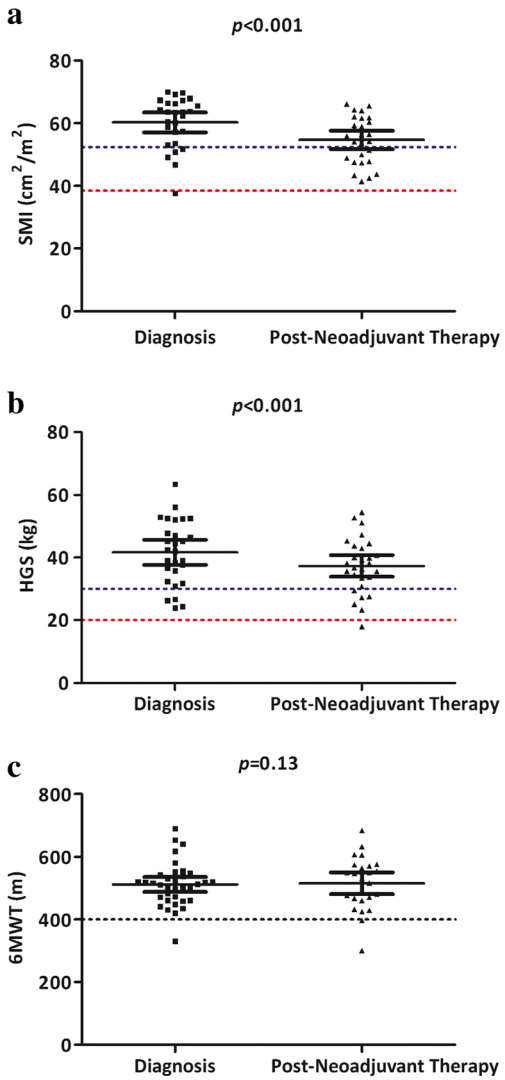

Fig. 1 Change in sarcopenic status from diagnosis to post-neoadjuvant therapy. Significant loss of skeletal muscle index (**a**) and muscle strength (**b**) during neoadjuvant therapy with associated increase in the number of participants with low skeletal muscle index (< 52.4 cm^2/m^2) males, < 38.5 cm^2/m^2 females) and low muscle strength (< 30 kg males, <20 kg females). Horizontal dotted lines represent sex-specific thresholds for male (blue) and female (red) participants. No reduction in walking distance was observed (**c**). Horizontal black dotted line represents threshold for low muscle performance (< 400 m). Abbreviations: SMI=skeletal muscle strength; HGS=hand grip strength; 6MWT= six minute walk test distance

Habitual physical activity

At diagnosis, participants spent 63.0 ± 11.1% of waking hours sedentary and 23.3 ± 29.5 min/day in moderate intensity activity. Five participants (18%) exercised to physical activity recommendations [24]. At diagnosis, MVPA correlated significantly with 6MWT distance (rho = 0.60, $p = 0.001$). Neither sedentary behaviour nor activity participation in any domain (light, moderate or vigorous) changed significantly following neoadjuvant therapy. Post-treatment, four participants exercised to recommended levels [24].

Measures of health-related QOL

Global QOL scores, including scores in the domains of physical and role functioning, remained unchanged from diagnosis to post-treatment. Participants experienced clinically important (> 10%) improvements across several gastrointestinal symptoms, including eating problems (37.7 ± 30.8 vs. 13.3 ± 24.1, $p = 0.002$); pain (20.4 ± 23.9 vs. 9.8 ± 17.4, $p = 0.013$); trouble with coughing (28.0 ± 31.5 vs. 5.3 ± 12.5, $p = 0.003$) and dysphagia (24.9 ± 25.3 vs. 12.9 ± 19.7, $p = 0.012$) ($d = 0.4$ for all). There was a small ($d = 0.28$), but clinically unimportant (< 10%), increase in fatigue (20.4 ± 20.2 vs. 23.3 ± 14.3, $p = 0.04$).

Measures of nutritional status

Mean SNAQ scores did not change (14.8 ± 3.3 vs. 15.3 ± 3.9, $p = 0.76$), and the number of participants with a score < 14 remained stable ($n = 3$ vs. $n = 2$). Similarly, GSRS scores remained constant with severity of discomfort ranging from 'none' to 'minor' (Table 4).

Nutritional intakes were recorded using the EPIC FFQ ($n = 10$). Total energy, protein, carbohydrate and fat intakes were adequate at both assessments. The percentage contributions of protein, fat and carbohydrate to total energy at diagnosis were 19.1 ± 2.9%, 39.9 ± 6.5% and 43.2 ± 8.5%, respectively, and were not significantly different when compared to percentage

Table 4 Change in self-reported gastrointestinal symptom scores from diagnosis to post-neoadjuvant therapy

	Diagnosis ($n = 21$)	Post-neoadjuvant therapy ($n = 21$)	p value
Abdominal pain	5.9 ± 2.3	5.0 ± 3.1	0.15
Reflux syndrome	3.1 ± 3.8	2.9 ± 1.9	0.67
Indigestion syndrome	7.7 ± 3.9	7.2 ± 3.8	0.66
Constipation syndrome	5.4 ± 3.3	5.2 ± 3.7	0.89
Diarrhoea syndrome	4.0 ± 2.5	4.6 ± 3.1	0.51

intakes post-neoadjuvant therapy, which were 17.1 ± 1.9%, 42.7 ± 7.7% and 44.2 ± 4.0%, respectively.

Fibre intakes did not differ, but were inadequate at both assessments (12.1 ± 6.8 g vs. 11.4 ± 6.4 g, $p = 0.79$). Similarly, both iron intakes (9.6 ± 3.5 mg vs. 8.8 ± 4.4 mg, $p = 0.67$) and vitamin D intakes (4.3 ± 2.9 μg vs. 3.1 ± 1.6 μg, $p = 0.18$) were inadequate at both time points. Intakes of calcium, vitamin A, vitamin C, vitamin E, and the B vitamins (except folate) were adequate at both time points (Table 4).

Discussion

This study provides novel characterisation of changes in skeletal muscle mass and associated muscle performance during preoperative therapy for OC, demonstrating that despite reductions in skeletal muscle mass and strength, other domains of physical functioning remained unchanged. This presentation is consistent with the pre-sarcopenia stage [11], characterised by loss of skeletal muscle below threshold values with limited impact on physical function. In line with best practice, body weight and nutritional status were maintained, and risk of undernutrition decreased. Results highlight the need for interventions to build muscle mass and strength during neoadjuvant treatments, even in patients who appear to be functioning normally.

Identifying patients who experience muscle wasting during anti-neoplastic therapy is challenging, particularly in obesity-attributed cancers, where the associated excess adiposity can mask skeletal muscle loss [21]. Use of direct methods, such as CT analysis of lean tissue area at L3 [22], has greatly enhanced the diagnosis of sarcopenia in cancer [4, 8]. Using this method, we observed reductions in SMI (5.6 (95%CI 3.7 to 7.5) cm^2/m^2) and LBM (4.9 (95%CI 3.2 to 6.7) kg), and an associated increase in sarcopenia defined by low SMI from 7% ($n = 2$) to 22% ($n = 6$), despite maintenance of body weight and BMI. These findings agree with other evaluations from our Centre (mean loss LBM 3.0 ± 5.4 kg) [9] and from a UK cohort treated with preoperative chemotherapy (mean loss fat free mass loss 2.9 ± 4.7 kg) [4]. The implications of this require further evaluation; however, recent reports describe a threefold increase in dose-limiting toxicity in patients who are sarcopenic at diagnosis (odds ratio, 2.95 (95%CI 1.23–7.09) $p = 0.015$) [8], and an independent association between post-treatment sarcopenic status and both disease progression [9] and overall survival [5]. Of interest, while in this cohort we observed no statistical difference in loss of SMI between those treated with the CROSS or MAGIC regimen, mean loss in SMI in those treated with chemoradiotherapy (6.2 kg) was almost double the reduction experienced with chemotherapy only (3.2 kg), suggesting that in a larger cohort, such as the ongoing Neo-AEGIS trial [1], important differences may be evident.

Physical disability is a direct consequence of skeletal muscle wasting [12], which preoperatively may adversely influence surgical risk [9]. In this study, we observed that HGS, a reliable indicator of whole-body muscle strength [11], reduced significantly by 4.3 (95% CI 2.5 to 6.1) kg over the course of neoadjuvant therapy, with values for two participants (7%) falling below sarcopenic thresholds for muscle strength [11]. Sub-optimal preoperative HGS (< 25 kg) correlates with postoperative hospital and critical care length of stay, and postoperative mortality [33]. In contrast, walking capacity and habitual physical activity levels remained unchanged. Comparably, a study from a Japanese cohort ($n = 27$) described no change in 6MWT distance (574.9 ± 77.8 m vs. 565.1 ± 75.3 m) or self-reported activity with preoperative chemotherapy [19]. Other reports using highly sensitive laboratory measures of cardiopulmonary fitness, an established predictor of postoperative outcome [6, 34], report significant declines in exercise capacity during therapy [16–18], which is associated with mortality at 1-year post resection; suggesting that considerable fitness is required to withstand multimodal treatments including surgery for OC [18]. While walking tests are more reflective of true physical function compared to self-reported questionnaires [13, 14] or physician-assigned functional performance scores [15], they may be insufficiently sensitive to change compared to laboratory measures of exercise tolerance [35] and may therefore have relatively limited clinical application in this setting.

There is a considerable role for adjunctive interventions involving diet and/or exercise to preserve muscle mass and strength during treatment. In line with best practice [20], participants in this study received early dietitian-led nutritional counselling throughout treatment, an approach associated with better postoperative outcomes [36] and higher radiotherapy completion rates [37] in OC. Progressive resistance exercise training has proven efficacy in catabolic conditions including sarcopenia [38] and is advocated as a non-pharmacological intervention in cancer-related skeletal muscle wasting [10]; however its role as a concomitant treatment to anti-cancer therapy is understudied. Of interest, resistance training during adjuvant breast cancer treatment has been reported to reverse sarcopenic status and lead to higher chemotherapy completion rates [39], and therefore the potential for such interventions to attenuate dose-limiting toxicity in OC [8] warrants investigation. Multimodal interventions incorporating nutritional support and exercise also have the potential to manage multiple components of sarcopenia syndrome and are currently under investigation in advanced cancer [40].

This work has some limitations. Firstly, while participants included in the final analysis were comparable to the overall cohort recruited at diagnosis, the disease trajectory was different between completers and non-completers due to disease

progression. However, the sample size analysed is adequate to address the primary question, is comparable to other published work in this field [4, 19], and represents a cohort most suited to physical rehabilitation. Secondly, while the prospective design is highly robust, the limitations of observational studies apply and causal inferences cannot be made. The use of CT to evaluate sarcopenia is a strength and highlights the value of high fidelity measures to evaluate sarcopenia.

Conclusion

These results highlight that despite preservation of body weight, functional capacity and habitual physical activity, patients undergoing neoadjuvant therapy experience a significant decline in muscle mass and muscle strength. Maintenance of muscle mass during anti-cancer therapy appears relevant to improving treatment tolerance and optimising surgical candidacy; consequently, there is a rationale to further explore the efficacy of prescribed exercise and/or dietary programmes as concomitant interventions with standard anti-cancer therapies.

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Compliance with ethical standards Ethical approval was obtained from the SJH–Tallaght Hospital Joint Research Ethics Committee. Informed written consent was obtained prior to study commencement.

Conflict of interest The authors declare that they have no conflict of interest.

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