Title: A longitudinal study of muscle strength and function in patients with cancer cachexia

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Conflict of interest
The authors have full control over primary data and allow the journal to review this if requested.

Ethical Statement
All procedures performed in this study were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

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Abstract (<250 words)

Purpose

Patients with cancer frequently experience an involuntary loss of weight (in particular loss of muscle mass), defined as cachexia, with profound implications for independence and quality of life. The rate at which such patients' physical performance declines has not been well established. The aim of this study was to determine the change in muscle strength and function over 8 weeks in patients with already established cancer cachexia, to help inform the design and duration of physical activity interventions applicable to this patient group.

Methods

Patients with thoracic and gastrointestinal cancer, with unintentional weight loss of >5% in 6 months or BMI < 20 plus 2% weight loss were included. Physical and functional assessments (baseline, 4 weeks, 8 weeks) included: isometric quadriceps and hamstring strength, handgrip, standing balance, 10m walk time and timed up and go.

Results

Fifty patients (32 male), mean ±SD age 65 ±10 years and BMI 24.9 ±4.3kg/m^2 were recruited. Thoracic cancer patients had lower muscle strength and function ($p<0.05$). Despite notable attrition, in patients who completed all assessments (8 thoracic and 12 gastrointestinal) there was little change in performance over 8 weeks ($p>0.05$). Baseline variables did not differentiate between completers and non-completers ($p>0.05$).

Conclusions

More than a third of patients with established cancer cachexia in our study were stable over 8 weeks, suggesting a subgroup who may benefit from targeted interventions of reasonable duration. Better understanding the physical performance parameters which characterize and differentiate these patients has important clinical implications for cancer multidisciplinary team practice.

Keywords:

Cancer, cachexia, strength, function

Background:

Patients with cancer frequently experience cachexia, defined as weight loss greater than 5%, or >2% in individuals with a low body-mass index (BMI <20kg/m^2) in the last 6 months [1]. This is associated with a decline in function, daily activities and quality of life (QoL) [2]. However, there is very little reproducible data available on the rate and size of decline in muscle strength in cancer site-specific patients with established cachexia [3]. Greater understanding of the progression of the disease will inform the targeted intervention to optimise function and wellbeing.

The mechanism of loss of muscle and physical function in cancer cachexia is multifactorial, including metabolic alterations, reduced nutritional stores and intake, and reduced activity [4]. Consequently there is a need for multimodal therapy to optimise patient outcomes [5]. As part of this approach, structured physical activity has potential to attenuate the process of muscle wasting in cachexia. In the advanced stages of chronic thoracic disease, exercise interventions are an effective means of improving muscle strength [6] and QoL [7], and there is evidence that programmed exercise is associated with improved outcomes in cancer patients undergoing active treatment [8].

Participants in studies of exercise interventions, even in advanced cancer, have been mainly drawn from non-cachectic populations [9]. Studies in those with advanced cancer have also been small in sample size and often in patients well enough to attend centres for group interventions [10]. For example Jensen et al's study of resistance and aerobic training (n=21) was deemed feasible and improved cancer-related symptoms in gastrointestinal (GI) cancer patients undergoing palliative chemotherapy, but the degree of cachexia was not defined [11]. Oldervoll et al's study of a group exercise intervention in palliative patients (n=34) showed potential for benefit, but highlighted issues of attrition, adherence and type of exercise [12].

This may have implications for multidisciplinary anticancer treatment planning and creates uncertainty in implementing structured physical activity interventions in clinical settings, with a lack of understanding for example of what duration of intervention might be feasible. From a clinical research perspective it also creates significant difficulty in estimating statistical power for pragmatic studies of physical activity interventions,, particularly in a heterogeneous population where standard deviation may be wide [13].

Identifying which patients with established cachexia are likely to tolerate targeted, longitudinal interventions to increase physical activity will increase compliance and reduce attrition, resulting in more patient-appropriate clinical treatment options [14].

The aim of this study, therefore, was to determine the size and rate of decline of muscle strength, balance and physical function, and the rate of attrition, in a patient population with established cancer cachexia. Muscle strength was assessed as maximal application of muscle force, physical function was assessed by 10m walk velocity and the timed up and go test (TUG). We also aimed to identify relationships between performance status, physical function and measures of strength and balance.

Methods

Participants

Participants were part of a larger study evaluating, self-confidence, perceived control as well as exercise preferences and motivations in patients with established cancer cachexia [14]. Of the 104 patients (45 thoracic and 59 GI) recruited at the two local sites, 50 patients were recruited from lung cancer, GI cancer or palliative care clinics in Cardiff between September 2011 and December 2013. Adults with unintentional, self-reported or recorded weight loss of >5%, or a BMI of <20 and any weight loss in the preceding 6 months were recruited from two outpatient clinics. Patients with a life expectancy of less than 8 weeks were excluded from the study as were those with musculoskeletal or neurological disorders which would compromise mobility or balance, e.g. Parkinson's disease, cerebrovascular accident or anatomical abnormality. The study was approved by the South East Wales Ethics committee, Cardiff and Vale University Health Board and Velindre R&D was obtained. All participants gave written informed consent.

Assessments

Assessments were completed by a trained researcher in a standardised manner in a home or clinical setting based on patient preference. At baseline, patients' cachexia status, demographic variables, disease stage and Karnosfsky performance score were recorded. The Karnosfsky Performance Scale is widely used to quantify the functional impairment in cancer patients with a score from 0 to 100, where 100 reflects normal functioning and health. The trained researcher explained the scale and asked patients to indicate which statement described their current ability [15]. The self assessed Karnofsky performance score was captured at baseline only in the context of a larger study where patients self-reported current and previous exercise levels. Motivational factors for physical activity were also examined [14]. The limitations of clinician reported performance status are well documented, with inter-observer variability between healthcare professionals [16] and also between clinicians and patients [17]. Clinicians tend to overestimate performance status, and where there is disagreement, patient reported performance status may more accurately correlate with survival [18]. We therefore felt it appropriate to use a patient reported measure in our study, whilst acknowledging the limitation of not having longitudinal data capture.

Longitudinal assessments, on initial visit, 4 and 8 weeks (+/- one week), were: BMI, muscle strength, balance and physical function including the 10m walk and the timed up and go (TUG). Maximal isometric knee extensor and flexor force (Newtons) was assessed in the dominant leg, in a seated position using an externally fixed force gauge (JTech Medical, Salt Lake City, UT). Knee flexor and extensor moment (turning effect produced by a force) was calculated by multiplying the perpendicular force by the distance from the knee joint and expressed as Newtons. Handgrip strength (Takei Dynamometer 5001) was measured twice in both hands with the mean used for analysis. Both were compared to normative data [19].

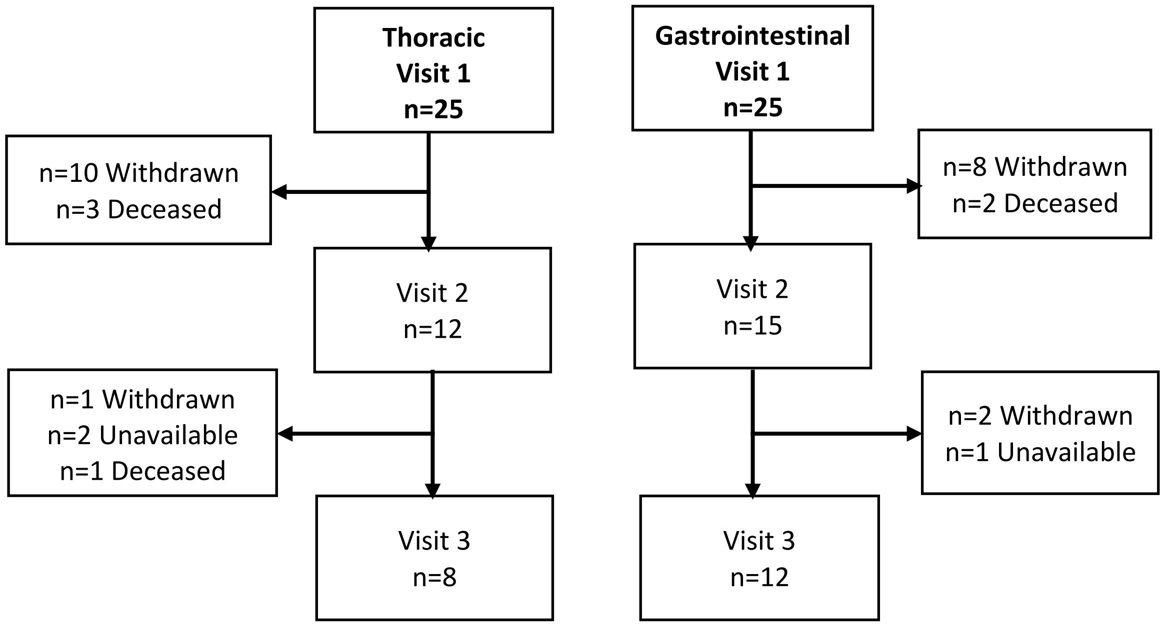
The Biodex Biosway (IRPS, Suffolk) was used to assess the ability to balance on firm surface situations with open eyes. A static sway index score was determined, with lower scores indicating greater stability. Dynamic stability was assessed by challenging patients to shift and control their center of gravity through an interactive timed balance game. Scores are expressed as a % with higher scores indicating greater stability. Acceptable reliability has been demonstrated with an intraclass correlation coefficient of 0.81 [20].

The time to walk 10m was also measured and used to calculate walking velocity [21] and the timed 'Up & Go' (TUG) test is a measure of task performance. Using standardised instructions the time taken for the participant to rise from a standardised armchair, walk 3 metres, turn and walk back to the seat was be recorded using a stopwatch [22].

Statistical Analysis

Descriptive results at each time point are presented as means ± standard deviation and median interquartile range (IQR) for nonparametric data. We aimed to recruit 50 participants taking part in a larger questionnaire study of motivation and preferences in relation to structured physical activity [23]. Baseline analysis included independent t tests, Mann Whitney U tests (nonparametric data) or the Chi Square test (ordinal data). Spearman's Rho (r_s) was used to evaluate the relationship of functional impairment (using Karnofsky scores), and demographic variables with muscle strength, task performance and balance. Repeated measures analysis of longitudinal data was undertaken using the Friedman test.

Figure 1: Flow diagram of assessments at baseline (Visit 1), four weeks (Visit 2) and eight weeks (Visit 3).



Results

Twenty-five patients (16 male) with GI and 25 patients (16 male) with thoracic cancer. Amongst the thoracic patients, 22 had non-small cell carcinoma, 2 had mesothelioma and 1 had small cell carcinoma. In the GI group 16 had upper GI malignancy and 9 had large bowel malignancy.

Baseline results

Self-reported Karnofsky scores did not differ between thoracic or GI patients, with most patients reporting themselves to be 70 or above (i.e. some limitations but mainly self-caring) (Table 1). Although groups were similar in mean BMI, unexpectedly the majority of thoracic and GI patients had BMI in or above the healthy (BMI >20 kg/m^2) range. Only 16% of thoracic patients and 12% of GI patients had low BMI (<19.9Kg/m^2) and there was a trend for more GI patients being in the overweight range (BMI>25 Kg/m^2) (Table 1).

The majority of patients (88% thoracic and 96% GI) were able to complete the assessments of strength and physical function at baseline, despite their disease status. With the exception of age, body mass and BMI, data are median interquartile range (IQR) due to the non-normal distribution.

Thoracic cancer patients, who were slightly older on average, had poorer quadriceps strength, and poorer task performance in the 10m walk and TUG compared to their GI counterparts (All $p<0.05$). When examining the group as a whole, the Karnofsky score correlated with walking velocity ($r_s= 0.406$) and dynamic balance ($r_s= 0.545$) (both $p<0.05$). There was a similar relationship between Karnofsky and dynamic balance when the group was divided into patients with thoracic and GI cancer (Table 2). There was no difference in the relationships between groups, and when assessed in each group alone and the relationship between Karnofsky and walking velocity did not reach significance ($p>0.05$), most likely due to reduced power. Although both walking velocity and TUG related to hamstring force, quadriceps force and handgrip strength, the relationship between TUG and self-reported Karnofsky score did not reach significance ($p=0.86$).

There was no difference in age, BMI, balance, walking velocity or TUG between males and females. As expected body mass, lower limb and handgrip strength were greater in males than females ($p<0.05$) (Supplementary data).

Longitudinal Results

Twenty-seven patients (54%) completed the 4-week assessment (12 thoracic and 15 GI) and 20 participants (40%) completed the 8-week assessment (8 thoracic and 12 GI). Of these one did not attend the 4-week assessment, thus 19 patients were included in the longitudinal analysis (Figure 1).

Six patients died within the eight-week period; three were lost to follow-up and 21 withdrew. Reasons for withdrawal included ‘feeling too unwell’, ‘too fatigued’ or ‘other time commitments’ while a number declined to give a reason.

Although it was expected that strength and performance measures would decline over time, there was no change compared to baseline in those who completed the 4 and 8 week assessments (n=19), except for a statistically significant difference in 10m walking velocity (Table 3). However, the clinical relevance may be limited and there were no other differences in any of the variables in whole group ($p>0.05$) or the thoracic and GI sub-groups separately ($p>0.05$) (data not displayed).

Differences between completers and non-completers were examined for a number of variables at baseline to identify potential predictors for future investigation. There were no differences in gender proportions, degree of weight loss at study presentation, time since diagnosis, BMI or muscle strength or performance measures between completers and non-completers of the physical assessments at eight weeks ($p<0.05$).

Discussion

In patients with loss of muscle mass, there appears to be a non-linear relationship between the degree of muscle loss and reduction in strength and function [24]. For patients with established cancer cachexia, the rate at which functional decline occurs in site-specific cancer patients is unclear. Better understanding of functional changes in this defined group would allow more targeted interventions in those most likely to tolerate a structured activity programme.

In the present study two patient groups were chosen, both of which have a high prevalence of cachexia [25], to allow exploratory comparison across cancer types over an 8 week period, particularly in relation to task performance, strength and study attrition. At baseline although self-reported performance based on Karnofsky scores were similar in both groups, there was significantly poorer task performance in the thoracic cancer patients. This may reflect an older population and different co-morbidity profile, and emphasises the need for caution in assuming a uniform effect of cachexia across site-specific cancer types and, by extension, the impact of specific interventions.

The physical assessment component of the study provided several important results. Although both cancer groups are traditionally associated with high rates of cachexia, BMI was higher than might be expected in both groups. Two thirds of thoracic cancer patients were in the normal BMI range despite weight loss and almost half of the GI patients were in the overweight or obese BMI category. Although the mean BMI was in the healthy range, baseline assessments revealed lower muscle force than normative values [26]. This highlights the limitations of BMI as a defining characteristic and raises concerns about the potential impact of a hidden loss of muscle mass and sarcopenic obesity [27].

Examination of the relationship between variables confirmed a positive correlation between the self-reported Karnofsky performance status scale and the objective measure of walking velocity. This demonstrates the potential utility of a simple, objective performance related measure rather than measures of muscle strength that did not relate to Karnofsky performance. The lack of relationship between the Karnofsky score, handgrip and TUG may be explained by small numbers. Alternatively, it may be that ambulatory activities are more sensitive to perceived performance in this patient group. This is supported by a relationship between walking capacity and performance status which has been shown [28].

The 10m walk test and TUG both related to lower limb force, handgrip strength and static balance and thus represent integrated measures of function. The finding that a simple and easily replicated assessment of physical performance - the ten-metre walk test and TUG - more closely correlated with perceived functional limitations than strength alone is promising and highlights both its potential utility as an outcome measure and the importance of assessing task performance rather than strength alone. Walking speed is a valid, and sensitive measure for assessing and monitoring functional status in a range of populations, and further exploration of specific walk speed cut off values is warranted in larger cancer cachexia populations [29].

In this study the Karnofsky score was self-reported by patients, rather than physician rated which is common in clinical practice. A previous study identified only a moderate correlation between self-reported and physician rated performance score [17], with some patients reporting a poorer performance using the Eastern Co-operative Oncology Group (ECOG) score than physicians, therefore this may have affected the results.

The 19 patients who completed all three assessments demonstrated a non-significant decline in knee extensor force but other physical and functional characteristics, including BMI, TUG, balance and handgrip were stable. The lack of deterioration over time was unexpected and is interpreted with caution given the degree of attrition. However, it aligns with findings by Prado et al [30] of residual anabolic potential even in advanced cancer.

It also reflects findings from a previous study in patients with advanced GI cancer, which included 16 patients with over 3% weight loss. This study found no significant changes in weight, BMI, upper limb skinfold thickness or Karnofsky performance status, over a six to eight week period of observation [31].

This suggests that there may be a subgroup of cachectic patients who are relatively stable over time, and who may tolerate a targeted intervention to increase physical activity and maintain function. Identifying this group would be key in administering patient-appropriate interventions in line with personalised patient care [32]. It also emphasises the importance of control groups in future intervention studies where maintaining performance or reducing the rate of decline is the outcome under examination.

The degree of attrition experienced over time in this study is similar to that reported in other palliative studies [33,34] and demonstrates the challenges of recruiting patients and retaining individuals within longitudinal research in this patient group. This was despite dedicated resource to follow patients up in their place of choice. The baseline and longitudinal measures, and their standard deviations, will also add to the knowledge base in defining future sample sizes.

It is disappointing that we were unable to identify a difference in characteristics between completers and non-completers. This is likely to relate to the small sample size. Given their association with other aspects of function the study does however identify simple performance measures (ten metre walk speed, TUG) which are worthy of further investigation, in addition to obvious targets such as degree of weight loss. The high rate of task completion at baseline and follow up is reassuring in terms of feasibility and acceptability of task performance measures in clinical settings.

Conclusion

Exercise, as a broad therapeutic strategy, has demonstrated efficacy in the earlier stages of cancer, reducing rates of functional decline and improving quality of life [35]. However, most exercise studies in cancer have recruited patients based on their disease stage rather than any defined impact of their cancer, with often no consideration of the degree of weight loss or other cachexia associated factors [9]. Where this has been reported, patients with established cachexia have been in the minority [36] contributing to the lack of evidence on benefit.

This study represents a step forward in using reliable criteria [37] for defining a population of increasing interest and exploring factors of relevance in this group to inform future feasibility testing and sample size. The study was exploratory in nature with a relatively small sample size, with resultant limitations in interpreting the data. However, strengths include the recruitment of participants with a clear definition of cancer cachexia, and the assessment of more than one cancer type with a high rate of cancer cachexia, which increases the generalisability of the study.

The findings highlight the potential utility of measures of task performance, easily undertaken in clinical settings, as outcomes reflective of perceived functional ability and the need to investigate – in a larger study population – baseline predictors of functional stability and rehabilitation potential in the setting of established cachexia. Combining such data with the attitudinal and motivational findings of our larger patient cohort reported elsewhere will benefit the development of interventions, which are acceptable and feasible in this patient group.

References

1. Fearon K, Strasser F, Anker SD *et al.*: Definition and classification of cancer cachexia: an international consensus. *The lancet oncology*, 12(5), 489-495 (2011).
2. Laviano A, Meguid MM, Inui A, Muscaritoli M, Rossi-Fanelli F: Therapy insight: cancer anorexia–cachexia syndrome—when all you can eat is yourself. *Nature Clinical Practice Oncology*, 2(3), 158-165 (2005).
3. Wallengren O, Iresjö B-M, Lundholm K, Bosaeus I: Loss of muscle mass in the end of life in patients with advanced cancer. *Supportive Care in Cancer*, 23(1), 79-86 (2015).
4. Donohoe CL, Ryan AM, Reynolds JV: Cancer cachexia: mechanisms and clinical implications. *Gastroenterology research and practice*, 2011 (2011).
5. Maddocks M, Hopkinson J, Conibear J, Reeves A, Shaw C, Fearon KC: Practical multimodal care for cancer cachexia. *Current opinion in supportive and palliative care*, 10(4), 298 (2016).
6. Vogiatzis I, Simoes DC, Stratakos G *et al.*: Effect of pulmonary rehabilitation on muscle remodelling in cachectic patients with COPD. *European Respiratory Journal*, 36(2), 301-310 (2010).
7. Klijn P, van Keimpema A, Legemaat M, Gosselink R, van Stel H: Nonlinear Exercise Training in Advanced Chronic Obstructive Pulmonary Disease Is Superior to Traditional Exercise Training. A Randomized Trial. *American Journal of Respiratory and Critical Care Medicine*, 188(2), 193-200 (2013).
8. Mock V, Pickett M, Ropka ME *et al.*: Fatigue and quality of life outcomes of exercise during cancer treatment. *Cancer Pract*, 9 (2001).
9. Grande AJ, Silva V, Riera R *et al.*: Exercise for cancer cachexia in adults. *The Cochrane Library*, (2014).
10. Lowe SS, Watanabe SM, Courneya KS: Physical activity as a supportive care intervention in palliative cancer patients: a systematic review. *J Support Oncol*, 7(1), 27-34 (2009).
11. Jensen W, Baumann F, Stein A *et al.*: Exercise training in patients with advanced gastrointestinal cancer undergoing palliative chemotherapy: a pilot study. Supportive Care in Cancer. *Supportive Care in Cancer*, 22(7), 1797-1806 (2014).
12. Oldervoll LM, Loge JH, Paltiel H *et al.*: The Effect of a Physical Exercise Program in Palliative Care: A Phase II Study. *Journal of Pain and Symptom Management*, 31(5), 421-430 (2006).
13. Hummler S, Thomas M, Hoffmann B *et al.*: Physical performance and psychosocial status in lung cancer patients: results from a pilot study. *Oncology research and treatment*, 37(1-2), 36-41 (2014).
14. Wasley D, Gale N, Roberts S *et al.*: Patients with established cancer cachexia lack the motivation and self-efficacy to undertake regular structured exercise. *Psycho-Oncology*, (2017).
15. Crooks V, Waller S, Smith T, Hahn TJ: The use of the Karnofsky Performance Scale in determining outcomes and risk in geriatric outpatients. *Journal of gerontology*, 46(4), M139-M144 (1991).
16. Zimmermann C, Burman D, Bandukwala S *et al.*: Nurse and physician inter-rater agreement of three performance status measures in palliative care outpatients. *Supportive care in cancer*, 18(5), 609-616 (2010).
17. Blagden S, Charman S, Sharples L, Magee L, Gilligan D: Performance status score: do patients and their oncologists agree? *British journal of cancer*, 89(6), 1022 (2003).
18. Schnadig ID, Fromme EK, Loprinzi CL *et al.*: Patient-physician disagreement regarding performance status is associated with worse survivorship in patients with advanced cancer. *Cancer*, 113(8), 2205-2214 (2008).
19. Bohannon RW: Reference values for extremity muscle strength obtained by hand-held dynamometry from adults aged 20 to 79 years. *Archives of physical medicine and rehabilitation*, 78(1), 26-32 (1997).

20. Biodex: Biodex, “Operation / Service Manual”, Biodex Medical Systems Inc., pp.123, 2014. [Online]. Available: http://www.biodex.com/sites/default/files/950440man_10205revc.pdf. [Accessed 11 Sept, 2015]. . (2010).
21. Watson MJ: Refining the ten-metre walking test for use with neurologically impaired people. *Physiotherapy*, 88(7), 386-397 (2002).
22. Podsiadlo D, Richardson S: The timed “Up & Go”: a test of basic functional mobility for frail elderly persons. *Journal of the American geriatrics Society*, 39(2), 142-148 (1991).
23. Wasley D, Gale NS, Robert SB *et al.*: Patients with established cancer cachexia lack the motivation and self-efficacy to undertake regular structured exercise. . *Pscholoncology*, (2017).
24. Goodpaster BH, Park SW, Harris TB *et al.*: The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 61(10), 1059-1064 (2006).
25. Bruera E: ABC of palliative care. Anorexia, cachexia, and nutrition. *BMJ: British Medical Journal*, 315(7117), 1219 (1997).
26. Bohannon R: Comfortable and maximum walking speed of adults aged 20—79 years: reference values and determinants. *Age and ageing*, 26(1), 15-19 (1997).
27. Prado CM, Lieffers JR, McCargar LJ *et al.*: Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *The lancet oncology*, 9(7), 629-635 (2008).
28. Jones LW, Cohen R-R, Mabe SK *et al.*: Assessment of physical functioning in recurrent glioma: preliminary comparison of performance status to functional capacity testing. *Journal of neuro-oncology*, 94(1), 79-85 (2009).
29. Middleton A, Fritz SL, Lusardi M: Walking speed: the functional vital sign. *Journal of aging and physical activity*, 23(2), 314-322 (2015).
30. Prado CM, Sawyer MB, Ghosh S *et al.*: Central tenet of cancer cachexia therapy: do patients with advanced cancer have exploitable anabolic potential? *The American journal of clinical nutrition*, 98(4), 1012-1019 (2013).
31. O'Gorman, P.McMillan DC, McArdle CS: Longitudinal study of weight, appetite, performance status, and inflammation in advanced gastrointestinal cancer. *Nutrition and Cancer* 35(2), 127-129 (1999).
32. Wales Cancer Network: Cancer Delivery Plan for Wales 2016-2020. Crown, (2016).
33. Oldervoll LM, Loge JH, Lydersen S *et al.*: *The oncologist*, 16(11), 1649-1657 (2011).
34. Oldervoll LM, Loge JH, Paltiel H *et al.*: Are palliative cancer patients willing and able to participate in a physical exercise program? *Palliative & supportive care*, 3(04), 281-287 (2005).
35. Lakoski SG, Eves ND, Douglas PS, Jones LW: Exercise rehabilitation in patients with cancer. *Nature reviews Clinical oncology*, 9(5), 288-296 (2012).
36. Maddocks M, Halliday V, Chauhan A *et al.*: Neuromuscular Electrical Stimulation of the Quadriceps in Patients with Non-Small Cell Lung Cancer Receiving Palliative Chemotherapy: A Randomized Phase II Study. *PloS one*, 8(12), e86059 (2013).
37. Blum D, Stene G, Solheim T *et al.*: Validation of the Consensus-Definition for Cancer Cachexia and evaluation of a classification model–A study based on data from an international multicentre project (EPCRC-CSA). *Annals of Oncology*, 25(8), 1635-1642. (2014).

Table 1 Baseline Characteristics in Patients with Thoracic and Gastrointestinal (GI) Cancer

	Thoracic n=25	GI n=25	p=
Age (years)	68.4 ± 8.4	62.4 ± 10.8	0.033
Karnofsky score	70.0 (60.0-75.0)	70.0 (70.0-80.0)	0.138
Body Mass (kg)	69.0 ± 19.0	74.5 ± 12	0.232
BMI (kg/m^2)	24.2 ±5.1	25.5 ±3.2	0.320
BMI <19.9 BMI 20-24.9 BMI 25-29 BMI>30	n=4 n=15 n=3 n=3	n=3 n=2 n=12 n=8	
Hamstrings (Newtons)	101.0 (65.4-130.4)[b]	118.8 (83.2-178.0)[b]	0.066
Quadriceps (Newtons)	169.1 (115.7-213.6)[b]	201.6 (163.3-275.9)[b]	0.046
Handgrip (kg)	23.5 (19.3-29.5)[a]	28.0 (16.5-34.8)[a]	0.337
Static balance (SI)	0.5 (0.4-0.7)[a]	0.4 (0.3-0.5)	0.062
Dynamic balance %	51.0 (40.3-57.3)[d]	57.0 (43.8-62.5)[c]	0.262
10M walk (secs)	9.9 (8.6-12.6)[c]	8.7 (7.4-10.2)	0.023
10M velocity(m/s)	1.0 (0.8-1.2)[c]	1.2 (1.0-1.4)	0.023
TUG (secs)	11.9 (9.9-13.7)[b]	9.4 (7.8-10.8)	0.001

Data are mean ± SD or median (IQR), missing data a=24, b=23, c=22 d=20
BMI = Body Mass Index; SI= stability index, TUG = Timed Up and Go;
p<0.05 significant difference between groups

Table 2 Relationship between Karnofsky Performance Status and Baseline Variables in Patients with Thoracic and Gastrointestinal (GI) Cancer individually and All Patients

	Thoracic	p	GI	p	all	p=
Age (years)	-0.006	0.978	-0.327[a]	0.119	-0.310	0.030
BMI (Kg/m^2)	-0.076	0.716	-0.080[a]	0.709	0.009	0.950
Hamstrings (Newtons)	0.216[b]	0.322	0.131[c]	0.562	0.198	0.193
Quadriceps (Newtons)	-0.050[b]	0.822	0.192[c]	0.393	0.137	0.370
Handgrip (kg)	0.312[a]	0.138	-0.058[b]	0.791	0.099	0.508
Static balance (SI)	-0.009[a]	0.966	0.272[a]	0.020	0.061	0.683
Dynamic balance %	0.500[e]	0.025	0.503[d]	0.198	0.545	<0.001
10M velocity(m/s)	-0.398[c]	0.066	-0.319[a]	0.128	-0.406	0.005
TUG (secs)	-0.264[b]	0.224	-0.080[a]	0.709	-0.253	0.086

Missing data a=24, b=23, c=22, d=21, e=20,

BMI = Body Mass Index; SI= stability index, TUG = Timed Up and Go;
p<0.05 significant relationship

Table 3 Longitudinal Assessments in Patients who completed all 3 Assessments

	Baseline n=19	Visit 2 n=19	Visit 3 n=19	p=
Gender male:female	12:7	-	-	-
Age (yrs)	63.4 ±10.1	-	-	-
BMI (Kg/m^2)	25.6 (22.7-27.3)	25.5 (22.7-28.3)	24.8 (22.9 -27.3)	0.510
Hamstrings (Newtons)	133.6 (86.1-181.1)	135.8 (86.9-172.6)	124.7 (66.2-162.5)	0.160
Quadriceps (Newtons)	249.4 (161.5-300.7)	247.6 (170.8-324.4)	204.9 (122.5-317.7)	0.577
Handgrip (kg)[a]	26.4 (17.1 -34.8)	28.6 (17.1-34.6)	26.8 (15.7-36.1)	0.270
Static balance (SI)	0.5 (0.3-0.7)	0.4 (0.3-0.7)	0.4 (0.3-0.6)	0.500
Dynamic balance (%)[b]	54.5 (49.0-64.8)	57.5 (49.8-62.3)	58.0 (43.8-67.0)	0.760
10M velocity (m/s)	1.1 (0.9-1.3)	1.2 (0.9-1.3)	1.2 (1.1-1.5)	0.031
TUG (secs)	9.9 (8.6-13.3)	10.3 (8.6-13.1)	9.7 (8.3-12.6)	0.230

Data are mean ± SD or median (IQR), missing data, a=17, b=16
BMI = Body Mass Index; SI= stability index, TUG = Timed Up and Go;
p<0.05 significant difference

Supplementary data

Baseline Characteristics in Males and Females

	Male n=32	Female n=18	p=
Age (years)	65.5 ±10.7	64.9 ±9.6	0.830
Karnofsky score	70 (60-80)	70 (60-80)	0.711
Body Mass (kg)	73.3 ±14.7	69.7 ±17.4	0.019
BMI (Kg/m^2)	24.4 ±4.1	25.9 ±4.7	0.266
Hamstrings (Newtons)	126.9 (98.0-171.4)[b]	89.1 (66.9-111.4)[e]	0.006
Quadriceps (Newtons)	207.1 (124.3-282.8)[b]	173.7 (106.9-209.4)[e]	0.092
Handgrip (kg)	29.0 (25.5-36.3)[b]	16.0 (12.9-20.6)	<0.001
Static balance (SI)	55.5 (47.5-60.3)[a]	48.0 (36.5-60.5)	0.186
Dynamic balance %	0.4 (0.3-0.5)[c]	0.5 (0.4-0.7)[d]	0.099
10M walk (secs)	8.8 (7.5-10.8)[b]	9.8 (8.5-12.2)[e]	0.226
10M velocity(m/s)	1.1 (0.9-1.3)[b]	1.0 (0.8-1.2)[e]	0.235
TUG (secs)	9.9 (8.8-12.2)[b]	10.4 (8.8-13.3)[d]	0.501

Data are mean ± SD or median (IQR) missing data a=30, b=31, c=30 c=25, d=17, e=16
BMI = Body Mass Index; SI= stability index, TUG = Timed Up and Go;
p<0.05 significant difference between males and females