BiCyCLE NMES - Neuromuscular electrical stimulation in the perioperative treatment of sarcopenia and myosteatosis in advanced rectal cancer patients: design and methodology of a phase II pilot study

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Background
Colorectal cancer is associated with secondary sarcopenia (muscle loss) and myosteatosis (fatty infiltration of muscle) and patients who exhibit these host characteristics have poorer outcomes following surgery. Furthermore, patients who undergo curative advanced rectal cancer surgery such as pelvic exenteration, are at risk of skeletal muscle loss due to immobility, malnutrition and a post-surgical catabolic state. Neuromuscular electrical stimulation (NMES) may be a feasible adjunctive treatment to help ameliorate these adverse side-effects. Hence, the purpose of this study is to investigate NMES as an adjunctive pre- and post-operative treatment for rectal cancer patients in the radical pelvic surgery setting and to provide early indicative evidence of efficacy in relation to key health outcomes.

Method
In a phase II, Double-blind, randomised controlled study, 58 patients will be recruited and randomised (1:1) to either a treatment (NMES plus standard care) or placebo (sham-NMES plus standard care) group. The intervention will begin two weeks pre-operatively and continue for eight weeks after exenterative surgery. The primary outcome will be change in mean skeletal muscle attenuation, a surrogate marker of myosteatosis. Sarcopenia, quality of life, inflammatory status and cancer specific outcomes will also be assessed.

Discussion
This pilot study will provide study important preliminary evidence of the potential for this adjunctive treatment. It will provide guidance on subsequent development of phase 3 studies on the clinical benefit of NMES for rectal cancer patients in the radical pelvic surgery setting.

Trial Registration
ClinicalTrials.gov Identifier: NCT04065984; Registered August 22, 2019; Recruiting.

Keywords: Advanced Rectal Cancer; Sarcopenia; Myosteatosis; Rehabilitation; Exenteration Surgery; NMES; Neuromuscular Electrical Stimulation
1.0 Background

Radical multi-visceral resection of pelvic tumours, known as pelvic exenteration, is being utilised to successfully treat a number of intra-abdominal malignancies\(^1\). Pelvic exenteration for locally recurrent (LRRC) or primary advanced rectal cancer has a high morbidity and mortality. The PelvEx Collaborative analysed data from 1184 patients who underwent surgery for LRRC, and found that 2% of patients died within 30 days of surgery and 32% of patients experienced a major complication\(^2\). Despite this high morbidity and mortality, these complex procedures are increasingly practiced in specialist centres. Following surgery, these patients enter a catabolic crisis where incapacitation and high protein and fat metabolism lead to a marked loss in skeletal muscle. Low skeletal muscle mass (sarcopenia) and fatty infiltration (myosteatosis) are independently associated with poorer post-operative outcomes following surgery for colorectal cancer\(^3,4\). The aetiology behind sarcopenia and myosteatosis is complex and multifactorial and includes inflammatory changes, hormonal changes, loss of function, fatigue and energy balance\(^5\). However, strategies to preserve skeletal muscle mass, quality and function may improve these outcomes.

A meta-analysis of resistance exercise training in patients with non-metastatic cancer showed significantly increased skeletal muscle mass \(^6\). Exercise can also impart an anti-inflammatory effect by attenuating the cellular response to inflammatory stimuli and pro-inflammatory cytokines such as IL-6, TNF\(\alpha\) and TGF\(\beta\)\(^7,8\). However, exercise programmes following a rectal cancer diagnosis and exenterative surgery are not always possible or practical due to patient anxieties and the need to expedite treatment, and the pain or disability associated with the extensiveness of the surgery itself. Furthermore, restriction upon rehabilitative resources, especially physiotherapy, often leaves patients immobile for long periods with resultant muscle atrophy. An alternative approach to traditional physiotherapy could be functional electrical stimulation (FES) via neuromuscular electrical stimulation (NMES). This is currently used in clinical practice for a number of diseases,
indeed, at the National Clinical FES Centre at Salisbury, UK over 2500 patients are currently undergoing FES. NMES of the lower-limb muscles requires less motivation than traditional exercise and can be undertaken whilst the patient is seated or lying down. NMES can be used to produce a muscle contraction equivalent to 20% to 40% of a maximum voluntary contraction thus meeting the criteria of the American College of Sports medicine definition of planned exercise.

A study of anterior cruciate ligament [of the knee] (ACL) reconstruction patients demonstrated NMES, implemented during the early rehabilitation stage, was effective in maintaining and increasing muscle thickness and strength in the operated limb. There is also evidence from meta-analyses that NMES increases muscle strength and shows potential benefit for joint range of motion, muscle atrophy, outcomes of ventilation and activity limitations in critically ill patients. A Cochrane review of NMES in a number of diseases that cause cachexia (muscle and fat loss secondary to disease) such as COPD (Chronic obstructive pulmonary disease), CCF (Congestive cardiac failure), HIV/AIDS and cancer, suggested that NMES may be an effective treatment for muscle weakness in adults with advanced progressive disease, and could be considered as a treatment within rehabilitation programs. Two studies, a phase 2 randomised trial and its pilot study, investigated NMES in cancer cachexia. Both studies were conducted in patients with non-small cell lung cancer receiving palliative chemotherapy. The pilot study demonstrated positive results; however, in the phase 2 study of 49 patients, in which 30 were randomised to NMES, there were no significant differences in quadriceps muscle strength, thigh lean mass or physical activity level between groups. The study team did however recommend further NMES studies in patients with cancer in other settings.
Previous studies have examined NMES in the palliative setting, with inconclusive conclusions regarding efficacy\textsuperscript{10,16}. No work has yet been done on clinical outcomes of NMES use in colorectal cancer nor any trial in the post-operative setting for cancer surgery. A phase II trial is required to determine whether there is evidence of a potential benefit prior to justifying a phase III study. The previous studies performed in cancer patients have not examined the relationship to the systemic inflammatory response, nor has there been an assessment of immediate post-operative outcomes. Our study aims to provide evidence of early indicative evidence of efficacy in relation to key health outcomes, including skeletal muscle mass and quality (myosteatosis), markers of systemic inflammation and post-operative recovery outcomes in rectal cancer patients undergoing radical pelvic surgery.

2.0 Study design, methods and analysis

Patients will be blinded as to which trial arm they enter and a sham protocol will be used by the control arm. Body composition analysis of the images will be done by automated software used by an assessor blinded to the intervention to remove operator or interpretation bias.

Our aim is to compare the effect on muscle of therapeutic NMES and current best practice against placebo NMES and current best practice alone in patients undergoing advanced radical surgery for complex rectal cancer.

2.1 Outcomes

2.1.1 Primary outcome

The difference in mean muscle attenuation (MA) measured in Hounsfield units and hence the degree of myosteatosis between the pre-operative and six-month post-operative CT scan in the NMES treatment group and the placebo NMES group.
2.1.2 Secondary outcomes

Our main secondary outcomes include change in muscle volume between treatment and no treatment groups as well as between time points for individuals. Difference in quality of life between groups using the validated questionnaires ED-5Q-5L & EORTC QLQ – CR29. Post-operative complications and length of hospital stay between both arms and comparison of the systemic inflammatory response between each group. A comprehensive list of secondary outcomes are shown in Box 1.

**Box 1. Secondary Outcomes**

2.1.3 Sample size estimation

We powered this pilot study based upon the primary outcome. Using data from the Alberta Cancer Registry Martin and colleagues described a standard deviation of MA at 8.6 Hounsfield units (HU) for males and 10.2 HU for females. We therefore assumed an overall mean SD of 9.4 HU for the both male and female patients. A difference in MA between groups of 8HU was considered to be of clinical importance, and the calculation was based on showing a difference of this size between groups.

The proposed analysis will adjust the differences at 6 months for the MA values at baseline. To allow for this approach, this adjusted is included in the sample size calculation. The size of the association between baseline and outcome MA values is relatively unknown. A fairly weak correlation of about 0.3 between the time points was assumed.

The calculations were performed using a 5% significance level and 90% power. Based on the information above, it was calculated that to show a difference in MA of 8 units between groups would require a sample size of 27 per group (54 patients in total).
To allow for an estimated dropout rate of 5%, 58 patients will be recruited into the study. The dropout rate of 5% is an estimate based on the fact that the treatment period is short and supervised for the most part in hospital. For the primary outcome to be measured we require the pre and post-operative CT scans and therefore are not taking into account the potential drop out from the trial outside this time period.

2.2 Trial protocol

2.2.1 Recruitment and eligibility screening

The inclusion and exclusion criteria are shown in Box 2. Following diagnosis of locally advanced rectal cancer patients are discussed in a multidisciplinary team (MDT) meeting. Some of these patients may be felt to be suitable for radical surgery – i.e. surgery performed with the intention of a cure. If patients are deemed fit for and consent to surgery then this is performed by one of three specialist surgeons in St Mark’s Hospital, London, UK.

**Box 2. Inclusion and Exclusion Criteria**

Patients who meet the inclusion criteria will be identified by the clinical team in the colorectal outpatient clinic or MDT and will then be approached by the study team with written information on the trial and given the option to enrol in the study. Consent to take part in the trial will be obtained at the next outpatient clinic appointment, which will occur in the weeks preceding surgery.

2.2.2 Randomisation
Randomisation, performed after the assessment of baseline outcomes, will take place by computer generated randomisation software (https://www.sealedenvelope.com) on a one to one basis. Recruitment will be performed by the study team; randomisation will be performed by the study principle investigator to ensure allocation concealment. Patients who are randomised to the either arm will be blinded as to intervention and will be taught by the research team to use the stimulator this will be at their clinic appointment following consent. The NMES intervention lasts a total of ten weeks with follow up over 5 years. The trial algorithm is shown in figure 1 and schedule of enrolment, interventions, and assessments in Figure 2.

Figure 1. Study Algorithm

Figure 2. Schedule of enrolment, interventions, and assessments

2.2.3 Blinding

Patients and the assessor of the primary outcome will be blinded. Patients will be blinded as to which arm they are in, the devices appear identical with the exception of a small coloured plastic tab indicating whether they are treatment or placebo devices. The assessor of the primary outcome, a consultant radiologist, will be blinded as to which trial arm the participant is in; assessment of the primary outcome is also automated and therefore will not allow bias. The clinical team caring for the participant will not be aware of which trial arm the patient is in. It is not possible for the individuals providing the NMES therapy to be blinded as they will need to be aware of which arm the patient is in in order to provide effective advice.

2.2.4 Data collection

Surveillance CT scans performed as part of sequential screening (i.e. not emergency or non-routine imaging) are performed as standard in this patient group and will undergo analysis.
measuring mean muscle attenuation (myosteatosis) and muscle area (sarcopenia) at the level of the third lumbar vertebrae. Routine bloods including CEA (Carcinoembryonic antigen) and inflammatory markers will be measured at each elective routine clinic visit and these data recorded. Quality of life will be assessed at 6 and 12 months using validated quality of life questionnaires (ED-5Q-5L & EORTC QLQ – CR29). The Berg Balance scale, 30 second sit-to-stand test and 6-minute walk test$^{18-21}$ will be used to assess functional outcome these tests will be performed at the patients three months post operatively clinic appointment. Pre and post-operatively we will measure bilateral thigh circumference at 15cm above the superior pole of the patella (which has been shown in earlier studies to correlate with muscle volume on MRI)$^{22}$. Bio-impedance analysis (BIA) will be undertaken at baseline, day two post operatively, day twenty-eight post operatively (if in hospital) day of discharge and first post-operative follow up appointment. We will record data from the device satisfaction questionnaires from both groups. Standard outcome data and covariates to be collected are shown in table 1.

Table 1. Outcomes and Covariates

2.2.5 Data Monitoring and Compliance

A sponsor approved independent data monitoring committee (IDMC) has been appointed to the trial as part of good trial governance to ensure safety, scientific validity and integrity of the trial. The data monitoring committee will have access to raw data and will review any significant adverse events or safety concerns within the trial. The IMDC will make recommendations and report directly to the sponsor representative and chief investigator.

2.3 Study Intervention
2.3.1 Stimulation of Muscle

We will endeavour to stimulate two major muscle groups during the study, the quadricep muscles and paraspinal muscles. The muscles of the quadriceps, particularly vastus lateralis and vastus medialis will be stimulated in both legs, this will be performed with a view to preserving muscle mass and encouraging earlier ambulation and better function.

We will also stimulate the erector spinae muscles and the muscles of the lower back. The reason for this is twofold, firstly, it is felt that some of the earliest muscles to atrophy following surgery or during bed rest are the core muscles of the back especially as these patients will not be sitting up or utilising these important supportive muscles in the first stages of their recovery. Patients are nursed on their side during the first 14 days following major pelvic surgery, which means they tend not to use their core muscles to flex or extend their back or support their weight leading to loss. This lateral position however would afford easy access to place the electrodes. Secondly, we are focussing on the muscle groups at the third lumbar vertebrae – the level this stimulation would take place, using the device in this location would give us the best chance of demonstrating the benefits of the device with regards muscle preservation. This site is well away from the operative site and tumour bed in these individuals and therefore there would be no risk of stimulating the tumour bed whilst using the device in this position.

Neuro-muscular stimulation will be delivered by a MicroStim Exercise Stimulator MS2v2 (Odstock Medical Limited (OML), Wiltshire, UK) using two self-adhesive electrodes placed on the anterior thigh over the body of the vastus medialis and lateralis and the muscles of the lower back. At their second clinic appointment at St Mark’s patients will be trained by the research fellow or other competent research team member (physiotherapist or specialist
nurse) to use the NMES. A study specific instruction leaflet will be given to this group along with the standard instruction manual by OML.

The program will commence pre-operatively and consist of daily stimulation to one thigh at a time followed by the lower back each for 15 minutes, increasing to 60 minutes within one week as tolerated. One treatment session for both thighs would last between 60 to 90 minutes in total per day – this can be taken in up to three discrete sessions. Treatment will last for two weeks pre-operatively and eight weeks postoperatively.

NMES would be used preoperatively to familiarise patients with and increase confidence in using the device prior to surgery and to aid prehabilitation.

2.3.2 Intervention training

Training in using the MicroStim 2v2 has been undertaken by the trial principle investigator at the device manufacturer, OML. Patient training will be conducted by the study PI or a trained member of their study team. Patients using the device will be observed and educated on correct usage by the study team. They will be asked to keep a usage diary and the device will record usage statistics via an inbuilt recorder. These data will feed into the analysis to provide a dose response model within the final analysis.

2.3.3 The Therapeutic NMES arm

Patients will be blinded as to which arm of the trial they are in. Therapeutic NMES will be delivered by a MicroStim Exercise Stimulator MS2v2 using two self-adhesive electrodes placed on the anterior thigh over the body of the vastus medialis and vastus lateralis muscles and the lower back.
Pulse waveform (symmetrical biphasic squared), frequency (40 Hz), and width (350 microseconds) would be used for the duration of treatment with the NMES. The amplitude (device output 0-120 mA, tested across 1000Ω) will be set to elicit a visible and comfortable muscle contraction; patients will be encouraged to subsequently increase the amplitude as tolerated. A “compliance diary” will be kept by the patients during their treatment period detailing their time spent using the device and the settings at which they are using it.

This program is adapted from one found to be of benefit in a pilot study of patients with non-small cell lung cancer which itself was based on an NMES exercise program developed for patients with COPD. The stimulation parameters were selected to favour gains in function and strength over endurance (frequency), minimise skin irritation (pulse width), and allow for sufficient recovery of the muscles between contractions (duty cycle).16,10

2.3.4 The placebo NMES arm

A modified model of MicroStim Stimulator MS2v2 (Odstock Medical Limited, Wiltshire, UK) will be provided to the placebo group who will apply two self-adhesive electrodes placed on the anterior thigh over the body of the vastus medialis and vastus lateralis muscles and the lower back as in the treatment group. This placebo device will be programmed to provide sub-therapeutic electrical stimulation. The device manufacturers have tailored a program to come on and off at specified timings with ramps of specified duration. The placebo devices output is restricted to around 18V and this gives little or no muscle recruitment. Patients will however perceive a sensation of electrical stimulation.

2.3.5 Both Groups
Patients in both arms will receive standard care including enhanced nutritional support (parenteral nutrition for a minimum of 5 days or until taking sufficient calories enterally) and physiotherapy in line with current guidelines and local hospital practices. Routine daily blood tests for inflammatory markers will be taken until discharge.

2.4 Assessment of outcomes

Patients from both the treatment and control arms will receive standard five year follow up. Histopathological data will be recorded following processing of the resected specimens by the pathologist. Quality of life data, patient satisfaction, bio-impedance analysis, CT Body composition and functional measurements will be taken as detailed below.

Early stage follow-up to identify changes within the pre and post-operative CT scans and analysis of NMES satisfaction and the initial inflammatory data will take place at three to six months following the recruitment of the final patient. We will then continue long term follow up for the standard 5 year follow up period or until patient death. Final analysis will take place at 5 years following recruitment of the final patient.

2.5 Body composition assessment

2.5.1 CT body composition parameters

CT image analysis using SliceOmatic version 5.0 software (TomoVision, Montreal, Quebec, Canada) will be performed. Total skeletal muscle and visceral adipose tissue surface area (cm$^2$) will be evaluated on a single image at the third lumbar vertebra (L3) using HU thresholds of −29 to 150 for skeletal muscle, −50 to 150 for VAT and −190 to −30 for subcutaneous adipose tissues. CT body composition analysis of all the included images will undergo automated segmentation using the ABACS L3 automated plug-in software$^{23}$ (Veronoi Health Analytics, BC, Canada), which complements SliceOmatic. The automated process will be
directed by a radiologist who will be blinded to the treatment group of individual patients. The automated segmentation process provided by the ABACS L3 plug-in also removes the possibility of operator bias in the analysis of the images. The sum of skeletal cross-sectional muscle areas will be normalised for stature (m²) and reported as lumbar skeletal muscle index (LSMI) (cm²/m²). Outcome variables will be continuous, categorical variables will be defined from these data using the cut-off values described earlier¹⁷,²⁴,²⁵.

2.5.2 Anthropometrics and Bio-impedance analysis
Bio-impedance analysis (BIA) will be undertaken using a SECA mBCA 525 analyser (SECA, Hamburg Germany). This will be performed at baseline, day two post-surgery, either hospital discharge or at 28 days post-surgery (whichever is first) and at 6 months. Patients will undergo analysis in a fasted state. Posterior upper arm skin fold thickness and waist circumference will be performed at baseline and 6 months. We will measure thigh circumference at 15cm above the superior pole of the patella (which has been shown in earlier studies to correlate with muscle volume on MRI)²². Phase angle from BIA and patient BMI will be utilised as categorical variables with other outcome variables being continuous.

2.5.3 Functional Assessment
It is important that we measure not only the anatomical effects of NMES i.e. increased muscle mass on CT and anthropometric changes but we identify whether these patients demonstrate both a functional and physiological improvement. To that end we will assess functionality preoperatively at diagnosis and post operatively at 3 months using the validated instruments of the 6-minute walk test²¹, 30 second sit-to-stand test²⁰ and Berg Balance scale (BBS).¹⁸,¹⁹ These data will be treated as continuous outcome variables with the exception of BBS which will be categorical.

2.5.4 Quality of Life
We will examine quality of life and patient experience of using the device. Quality of life will be measured using the validated questionnaires described above. On completing the intervention participants will complete a questionnaire on compliance, comfort and usability of the device in the postoperative setting. Qualitative data and free text comments from this will also be collected.

2.5.5 Systemic inflammatory response
To monitor the inflammatory response, we will use commonly utilised postoperative inflammatory markers, namely CRP and values derived from the full blood count and biochemistry including NLR and mGPS. These inflammatory markers are well-established metrics linked to both sarcopenia, myosteatosis and prognosis in colorectal cancer\textsuperscript{26–28}. We have chosen these markers for a number of reasons; they are routinely taken, cost effective and allow for comparison with substantial historical data. We may also require results from other trusts, due to the national spread of our patient population, and we cannot support them in obtaining non-routine tests as part of this study.

2.6 Planned statistical analyses
This study will be performed in line with the CONSORT criteria (http://www.consort-statement.org/consort-2010). Initially outliers, patterns of attrition and missing data will be identified using a combination of graphical displays and descriptive statistics allowing decisions on the assumption of normality.

Analyses of primary and secondary endpoints will be based on the full analysis set defined according to the intention to treat principle. Safety analysis will be performed for the on all enrolled individuals with disclosure of any significant adverse events. The full analysis set consists of all participants consented and randomised with valid baseline assessments.
Participants will be analysed according to the study arm they were assigned at randomisation.

The primary outcome is myosteatosis at 3-6 months post-surgery, derived from the mean muscle attenuation on CT body composition analysis. This will be analysed using analysis of covariance (ANCOVA), with muscle attenuation values at baseline used as a covariate in the analysis.

The secondary outcome measures measured on a continuous scale, and with a baseline measurement will be analysed using equivalent methods as the primary outcome. For continuous outcomes with no baseline measurement, group comparisons will be made using either the unpaired t-test or Mann-Whitney test, depending on data distribution. The Chi-square test, or Fisher’s exact test, will be used to compare categorical outcomes between the study groups.

Significance will be assumed when \( p < 0.05 \).

**3.0 Discussion**

Patients who undergo major pelvic surgery have limited mobility due to postoperative pain and disability. These patients are therefore at much greater risk of suffering from muscle wasting than patients undergoing more routine colorectal surgery. This is a result of greater loss of function, greater immobility and potentially a more profound immunogenic inflammatory response.

Currently these patients receive postoperative physiotherapy, due to limited time, postoperative pain, patient choice and resource availability it is unlikely that the patients are exercised to their full potential. A prescribed program with a NMES device would allow patients to choose when they undertake muscle stimulation exercise for example once they
had received adequate analgesia or at a time convenient to them. This would hopefully improve compliance and bring about a hypertrophic response in the muscle.

We know that in muscle disuse in healthy individuals NMES may provide an effective treatment to preserve muscle volume\textsuperscript{13}. Maddocks’ work in cancer patients\textsuperscript{10,16} however did not demonstrate a significant increase in muscle volume and therefore one may question the rationale behind use in this patient group (these differences are summarised in table 1). The cancer population in these studies is different from our own in a number of respects beyond the diagnosis alone and as such we may find NMES to be a more suitable intervention in our patient group. Maddocks’ work was performed in a palliative population with active cancer whilst postoperatively our patients will be theoretically cancer free with perhaps a few exceptions in patients who have solitary metastases (which, by the criteria of inclusion, are amenable to curative treatment). In view of their palliative status, Maddocks’ population would be expected to decline in health over time whilst our population would be expected to make a recovery up to or even beyond their preoperative state and therefore NMES may increase the rate of or facilitate this recovery. Our population is confined to bed rest for over a week’s duration following surgery and therefore activity provided by NMES may help arrest the muscle loss associated with disuse as in Hasegawa’s population. Finally, our patients will receive intensive inpatient support by the ward physiotherapists and the research team, they will receive positive reinforcement of their use of the device and will be asked to complete an exercise diary which the physiotherapy team, will review with them at each point they receive formal physiotherapy sessions. This level of direct input and positive reinforcement is notably more than in the previous NMES studies of Maddocks’ and therefore we would hope compliance and correct usage would be increased.

Table 2. Differences between BiCyCLE NMES and earlier studies by Maddocks’ et al
The inflammatory effects of exercise are known to be paradoxical in that exercise drives both a pro and anti-inflammatory response\textsuperscript{29,30}. We propose that the metabolic result of exercise in cancer patients will drive a beneficial anti-inflammatory response. This immunomodulation may in part help support the body’s immune system in the early stages of post-surgical recovery and as such may potentially support the cellular immune system in being able to identify and destroy malignant cells shed at the time of surgery.

In our patient group NMES will potentially allow a higher degree of exercise than the patients would otherwise be able to undertake due to their incapacity. Our hope is that this promotes muscle preservation, allowing earlier mobilisation and a more expedient return to “normal” exercise and function, further reinforcing the preservation of muscle mass. Increased muscle mass and quality are associated with improved long term outcome such as disease free survival\textsuperscript{3} we intend to follow our cohort for 5 years to see if NMES improves these oncological outcomes through muscle preservation.

4.0 Summary

Exercise in healthy individuals leads to increased muscle mass, exercise can bring about an anti-inflammatory effect due to muscle physiology thus obfuscating a key pathway driving secondary sarcopenia. Preservation of muscle mass through early post-operative intervention with NMES would allow a more rapid return to normal exercise and normal function leading to greater muscle preservation and subsequently improved outcomes.

4.1 Trial Status

BiCyCLE NMES is currently recruiting patients, recruitment began on the 31\textsuperscript{st} May 2019 and is expected to be completed by March 2021. Protocol version 6 dated 05/06/20 is currently approved by the research ethics committee and the HRA.
5.0 Declarations

5.1 Ethics approval and consent to participate

The BiCyCLE NMES Trial (ClinicalTrials.gov Identifier: NCT04065984) is a single centre double blind, randomised controlled trial. Ethics approval for the study has been obtained from the NHS England HRA and Health and Care Research Wales (19/LO/0259). Local approval has been obtained by the Research and Development department of London North West University Healthcare NHS Trust (RD18/115). Informed consent is obtained from patients as part of the BiCyCLE NMES Trial, the approved participant information sheet and consent form (version 3 11/03/19) are included in the supplementary material.

5.2 Consent for publication

The sponsor has designated the right to publication to the authors. Trial participants have consented to publication of their analysed data and qualitative responses. The study findings will be of interest to surgical oncologist performing exenterative procedures for locally advanced cancers. This study will inform a future multi centre RCT to determine whether NMES is an effective post-surgical rehabilitation option in the surgical oncology patient.

5.3 Availability of data and materials

Access to the final trial data set will be available to the trial team, the sponsor and for review by the independent data monitoring committee appointed by the sponsor.

5.4 Competing interests

The authors declare that they have no competing interests

5.6 Funding

Charitable funding received from the St Mark’s Hospital Foundation (Reg. 1140930)

5.7 Authors’ contributions
ETP devised the trial and trial protocol, is trial principle investigator and trial coordinator. JTJ is the chief investigator. LG, MB and MN advised on nutritional aspects of the trial design and method. PL provided advice and support on the radiological input into the trial. TF, DC and JS provided advice and input into trial design on the exercise physiology and assessment. PB is the trial statistician. GM and TA advised on trial design and aspects of the trial relation to body composition and trial method. CT advised on nursing and patient centred factors and acted as a patient advocate. NKF and TS acted as independent peer reviewers of the trial and provided advice and feedback on the trial method and design.

5.8 Acknowledgements

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The Independent Data Monitoring Committee: Mr Adam Stearns FRCS (Norfolk and Norwich NHS Foundation Trust, UK and University of East Anglia, UK) and Mr Christos Kontovounisios FACS, FRCS (Clinical Senior Lecturer Consultant Colorectal Surgeon, Imperial College London and The Royal Marsden NHS Foundation Trust). George and Arlene Davies for their support with the BiCyCLE research group.

1. Brown, K. G. M., Solomon, M. J. & Koh, C. E. Pelvic exenteration surgery: The evolution of radical surgical techniques for advanced and recurrent pelvic malignancy. *Dis. Colon Rectum* **60**, 745–754 (2017).

2. Kelly, M. E. *et al.* Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br. J. Surg.* **105**, 650–657 (2018).

3. Malietzis, G. *et al.* Influence of body composition profile on outcomes following colorectal cancer surgery. *Br. J. Surg.* **103**, 572–580 (2016).

4. Cespedes Feliciano, E. M. *et al.* Association of Systemic Inflammation and Sarcopenia With Survival in Nonmetastatic Colorectal Cancer. *JAMA Oncol.* **94612**, e172319 (2017).

5. Pring, E. T., Malietzis, G., Kennedy, R. H., Athanasiou, T. & Jenkins, J. T. Cancer cachexia and myopenia – Update on management strategies and the direction of future research for optimizing body composition in cancer – A narrative review. *Cancer Treat. Rev.* **70**, 245–254 (2018).

6. Strasser, B., Steindorf, K., Wiskemann, J. & Ulrich, C. M. Impact of resistance training in cancer survivors: A meta-analysis. *Med. Sci. Sports Exerc.* **45**, 2080–2090 (2013).
7. Keller, C., Keller, P., Giralt, M., Hidalgo, J. & Pedersen, B. K. Exercise normalises overexpression of TNF-α in knockout mice. *Biochem. Biophys. Res. Commun.* **321**, 179–182 (2004).

8. Starkie, R., Ostrowski, S. R., Jauffred, S., Febbraio, M. & Pedersen, B. K. Exercise and IL-6 infusion inhibit endotoxin-induced TNF-alpha productions in humans. *FASEB J* **17**, 884–6 (2003).

9. National Clinical FES Centre - Salisbury NHS Foundation Trust. Available at: http://www.salisbury.nhs.uk/INFORMATIONFORPATIENTS/DEPARTMENTS/CLINICALSCIENCEANDENGINEERING/Pages/NationalClinicalFESCentre.aspx. (Accessed: 9th January 2018)

10. Maddocks, M. *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**, 1–8 (2013).

11. Maffiuletti, N. A. Physiological and methodological considerations for the use of neuromuscular electrical stimulation. *Eur. J. Appl. Physiol.* **110**, 223–234 (2010).

12. Thompson, W., Gordon, N. & Pescatello, L. ACSM’s guidelines for exercise testing and prescription. *8th Ed. London Lippincott Williams Wilkins* (2010).

13. Hasegawa, S. *et al.* Effect of early implementation of electrical muscle stimulation to prevent muscle atrophy and weakness in patients after anterior cruciate ligament reconstruction. *J. Electromyogr. Kinesiol.* **21**, 622–630 (2011).

14. Burke, D., Gorman, E., Stokes, D. & Lennon, O. An evaluation of neuromuscular electrical stimulation in. *Clin. Respir. J.* 407–420 (2014). doi:10.1111/framework

15. Jones, S. *et al.* Neuromuscular electrical stimulation for muscle weakness in adults with advanced disease (Review). *Cochrane Database Syst. Rev.* (2016). doi:10.1002/14651858.CD009419.pub3.www.cochranelibrary.com

16. Maddocks, M., Lewis, M., Chauhan, A., Manderson, C. & Hocknell, J. Randomized Controlled Pilot Study of Neuromuscular Electrical Stimulation of the Quadriceps in Patients with Non-Small Cell Lung Cancer. *J. Pain Symptom Manage.* **38**, 950–956 (2009).

17. Martin, L. *et al.* Cancer cachexia in the age of obesity: Skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *Journal of Clinical Oncology* **31**, 1539–1547 (2013).

18. Berg, K. O., Wood-Dauphinee, S. L., Williams, J. I. & Maki, B. Measuring balance in the elderly: validation of an instrument. *Can. J. Public Health* **83 Suppl 2**, S7-11 (1992).

19. Berg, K., Wood-Dauphinee, S. & Williams, J. I. The Balance Scale: reliability assessment with elderly residents and patients with an acute stroke. *Scand. J. Rehabil. Med.* **27**, 27–36 (1995).

20. Jones, C. J., Rikli, R. E. & Beam, W. C. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res. Q. Exerc. Sport* **70**, 113–119 (1999).

21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am. J. Respir. Crit. Care Med.* **166**, 111–117 (2002).

22. Chen, B. B. *et al.* Thigh muscle volume predicted by anthropometric measurements and correlated with physical function in the older adults. *J. Nutr. Health Aging* **15**, 433–8 (2011).

23. Dabiri, S. *et al.* Muscle segmentation in axial computed tomography (CT) images at the lumbar (L3) and thoracic (T4) levels for body composition analysis. *Comput. Med. Imaging Graph.* **75**, 47–55 (2019).

24. Prado, C. M. *et al.* Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a
population-based study. *Lancet Oncol.* **9**, 629–635 (2008).

25. Doyle, S. L. *et al.* Establishing computed tomography-defined visceral fat area thresholds for use in obesity-related cancer research. *Nutr. Res.* **33**, 171–179 (2013).

26. Malietzis, G. *et al.* Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. *Ann. Surg.* **263**, 320–325 (2016).

27. Abbass, T., Dolan, R. D., Laird, B. J. & McMillan, D. C. The relationship between imaging-based body composition analysis and the systemic inflammatory response in patients with cancer: A systematic review. *Cancers (Basel).* **11**, 1–12 (2019).

28. Malietzis, G. *et al.* A Preoperative Neutrophil to Lymphocyte Ratio of 3 Predicts Disease-Free Survival After Curative Elective Colorectal Cancer Surgery. *Ann. Surg.* **260**, 287–292 (2014).

29. Petersen, A. M. W. & Pedersen, B. K. The anti-inflammatory effect of exercise. *J. Appl. Physiol.* **98**, 1154–1162 (2005).

30. Pedersen, B. K. & Hoffman-Goetz, L. Exercise and the immune system: regulation, integration, and adaptation. *Physiol. Rev.* **80**, 1055–1081 (2000).