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Predicting muscle loss during lung cancer treatment (PREDICT): protocol for a mixed methods prospective study

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ABSTRACT

Introduction Low muscle mass and low muscle attenuation (radiodensity), reflecting increased muscle adiposity, are prevalent muscle abnormalities in people with lung cancer receiving curative intent chemoradiation therapy (CRT) or radiation therapy (RT). Currently, there is a limited understanding of the magnitude, determinants and clinical significance of these muscle abnormalities in the lung cancer CRT/RT population. The primary objective of this study is to identify the predictors of muscle abnormalities (low muscle mass and muscle attenuation) and their depletion over time in people with lung cancer receiving CRT/RT. Secondary objectives are to assess the magnitude of change in these parameters and their association with health-related quality of life, treatment completion, toxicities and survival.

Methods and analysis Patients diagnosed with lung cancer and planned for treatment with CRT/RT are invited to participate in this prospective observational study, with a target of 120 participants. The impact and predictors of muscle abnormalities (assessed via CT at the third lumbar vertebra) prior to and 2 months post CRT/RT on the severity of treatment toxicities, treatment completion and survival will be assessed by examining the following variables: demographic and clinical factors, weight loss, malnutrition, muscle strength, physical performance, energy and protein intake, physical activity and sedentary time, risk of sarcopenia (Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls history (SARC-F) score alone and with calf-circumference) and systemic inflammation. A sample of purposively selected participants with muscle abnormalities will be invited to take part in semistructured interviews to understand their ability to cope with treatment and explore preference for treatment strategies focused on nutrition and exercise.

Ethics and dissemination The PREDICT study received ethics approval from the Human Research Ethics Committee at Peter MacCallum Cancer Centre (HREC/53147/PMCC-2019) and Deakin University (2019-320). Findings will be disseminated through peer review publications and conference presentations.

Strengths and limitations of this study

- This is a multisite study across three tertiary health services with specialist cancer services.
- Study outcomes are assessed using tools and techniques with established validity in the field.
- The use of tools and techniques that are widely used within clinical practice enhances the applicability of findings to future practice.
- Due to the observational study design, causality for muscle abnormalities cannot be established from the findings.
- Radiological data will be acquired from multiple scanners with consistent protocols and quality control in place.

INTRODUCTION

Over two million new cases of lung cancer were diagnosed globally in 2018, with lung cancer the leading cause of death from cancer worldwide accounting for almost 20% of cancer mortality.[1] The most common curative intent treatment for locally advanced non-small cell lung cancer (NSCLC) and limited stage small cell lung cancer (SCLC) is a lengthy and demanding course of chemoradiation therapy (CRT). CRT can be associated with severe acute toxicities and significant nutritional and functional decline related to muscle loss, a key feature of malnutrition and cancer cachexia.[2] Median survival following curative CRT is less than 2.5 years.[3] However, advances in immunotherapy are promising and demonstrate capacity to improve survival following definitive CRT.[4] Such advances highlight the increasing importance of ensuring that patients who complete CRT are in optimal physical condition to withstand the lengthy and demanding treatments.

The use of routine CT images has emerged as an opportunistic way to quantify muscle mass and assess muscle attenuation.[5 6] Low muscle attenuation (radiological density measured in Hounsfield Units (HU)) is reflective of increased intermuscular adiposity.[7] A number of studies have demonstrated the negative consequences associated

with muscle abnormalities in people with cancer.[5 8 9] Low muscle mass prior to treatment is highly prevalent (up to 47%) in patients with stage III and IV NSCLC treated with chemotherapy and is independently associated with up to a twofold increased risk of mortality.[10 11] In colorectal cancer, muscle loss of 9% or more during chemotherapy has been independently associated with an almost fivefold higher risk of shorter survival.[12] Several studies have also found low muscle mass to be predictive of chemotherapy-related toxicity in multiple cancer types.[8 13 14] Likewise, low muscle attenuation has been associated with reduced survival in patients with colorectal and renal cell cancers, increased inflammation and impaired muscle function in non-cancer populations.[12 15 16] To date, most research in patients with lung cancer treated with chemotherapy has focused on the prognostic impact of muscle abnormalities. Little is known about the magnitude of muscle loss and degree of muscle fat infiltration (attenuation) and their impact on treatment outcomes, function, quality of life or the experience of people with lung cancer treated with CRT or radiation therapy (RT). As the most common treatment modality for stage III NSCLC and limited stage SCLC, understanding the prevalence, magnitude and consequences of muscle abnormalities in patients treated with CRT/RT is of significant clinical importance. Furthermore, it can inform targeted nutrition and exercise interventions to improve outcomes given that there are currently no pharmaceutical agents available to counteract muscle abnormalities.

Complicating the identification of low muscle mass is the increasing prevalence of patients presenting with overweight or obesity, often masking the presence of low muscle mass. Although approximately 50% of patients with advanced lung cancer present with excess body weight, low muscle mass is present across all body mass index (BMI) categories.[5 17 18] Current nutrition assessment tools misclassify up to 60% of patients as well-nourished when they have low muscle mass defined on CT, meaning they may be overlooked for nutrition intervention.[19] Consequently, alternate methods are required to identify people presenting with adverse body composition changes such as low muscle mass at treatment commencement or experiencing muscle loss during treatment.

In a preliminary study in 41 patients with NSCLC, we found that 61% had low muscle mass before commencing CRT, despite 61% having overweight/obesity.[20] We also identified that 41% had low muscle attenuation, which has been linked to increased inflammation and impaired muscle function.[16] Further, loss of muscle mass occurred in over half the patients by 3 months following CRT.[20] Building on this work, the primary aim of this study is to identify the predictors of muscle abnormalities (low muscle mass and low muscle attenuation) and their loss relative to treatment commencement in people with lung cancer following curative intent CRT/RT. In addition, the magnitude of change in muscle mass and muscle attenuation, and associations of muscle abnormalities and changes in muscle mass or muscle attenuation with health-related quality of life (HR-QoL), treatment outcomes and survival, along with patient experience of living with muscle abnormalities, will be examined.

METHODS AND ANALYSIS

This mixed methods prospective study is recruiting at three tertiary hospitals in Victoria, Australia. The study is conducted by researchers and clinicians at Deakin University, Peter MacCallum Cancer Centre, University of Melbourne and University of Alberta.

Study population

Patients who are candidates for curative intent standard dose and fraction CRT/RT for a confirmed diagnosis of NSCLC or SCLC (any disease stage) are approached to participate in the study. Patients will receive volumetric modulated arc therapy with online cone-beam CT (CBCT) image guidance. Patients will be simulated and treated in free-breathing, without respiratory gating techniques. Simulation imaging involves acquisition of a four-dimensional CT, on which a gross tumour volume (GTV) will be segmented. The GTV on each phase of the respiratory cycle will be combined to form the internal GTV (iGTV). A 5 mm margin will be applied to the iGTV to obtain the clinical target volume, followed by an additional 1 cm margin to obtain the planning target volume. Adaptive radiotherapy is not routinely performed but may be considered in the case of significant anatomical change or tumour shrinkage as indicated on CBCTs acquired during treatment. Concurrent chemotherapy includes cisplatin/paclitaxel, cisplatin/etopiside, cisplatin/pemetrexed, carboplatin/paclitaxel, carboplatin/etopiside. Eligible patients are identified through screening clinic lists and discussion with the lung multidisciplinary team at each health service. Eligibility criteria are described in table 1. Non-English speaking patients are eligible to participate if they can provide informed consent and participate in the study with the aid of an interpreter or family member. Recruitment commenced in September 2019 was suspended from March to October 2020 due to the COVID-19 pandemic and recommenced in November 2020.

Table 1 Study eligibility criteria

Inclusion criteria	Exclusion criteria
Aged ≥18 years	Patients with a cognitive impairment or psychiatric illness reported in the medical history
Planned for standard dose and fraction radiotherapy regimens, that is, not stereotactic ablative body radiotherapy (SABR)	Conditions known to affect body composition including HIV, recent diagnosis of thyroid disease, muscular dystrophy or other neurodegenerative conditions
Have a CT image available within 30 days of the baseline study assessment	

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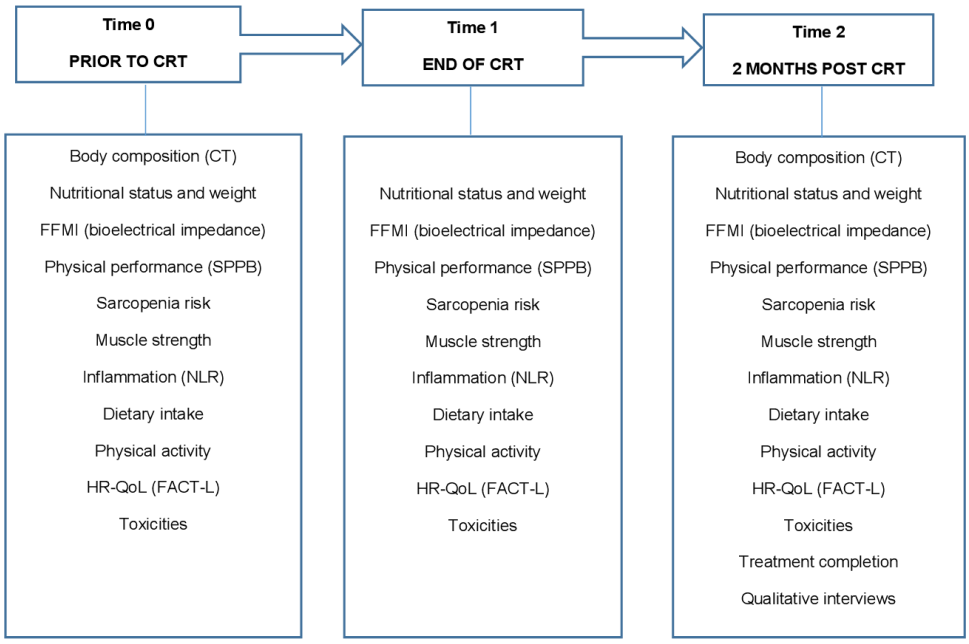

Figure 1 Study schema describing data collection time points and study assessments. CRT, chemoradiation therapy; FACT-L, functional assessment of cancer therapy—lung; FFMI, fat-free mass index; HR-QoL, health-related quality of life; NLR, neutrophil to lymphocyte ratio; SPPB, short physical performance battery.

Baseline data (T0) are collected prior to or within 1 week of commencing CRT/RT (figure 1). Follow-up data collection occurs at the end of CRT/RT (T1) and at 2 months following completion of CRT/RT (T2).

Participant and treatment characteristics

Demographic data on age, sex, living situation (alone or with others), level of education, smoking status, Charlson comorbidity score, medications, disease staging and treatment plan are collected at baseline from participants' medical records. Radiotherapy dose, volume (cc), location (left upper lobe, right upper lobe, right lower lobe, left lower lobe), and mean and maximum oesophageal dose are recorded from the radiotherapy treatment plan.

Measures

Data on CT derived muscle mass, muscle attenuation and visceral and subcutaneous adipose tissue, nutritional status, weight, bioimpedance spectroscopy fat-free mass and fat mass, physical performance, muscle strength, inflammation, dietary intake, physical activity and sedentary time, toxicities and HR-QoL are collected as described in the study schema (figure 1). Data on treatment completion are collected at the completion of CRT/RT and survival data will be censored at 12 months following recruitment of the final participant. Table 2 provides an overview of all study assessments.

Anthropometry, muscle mass and body composition

Weight is measured on a commercially available floor scale to the nearest 0.1 kg (Tanita Innerscan 50, Tanita, Australia). Height is obtained from the medical record. Calf-circumference is measured to the nearest 0.1 cm three times and the mean value recorded. Participants are asked to self-report their weight at 6 and 12 months prior to each assessment.

Muscle mass, muscle attenuation, visceral, subcutaneous and intramuscular adipose tissue at the third lumbar vertebra (L3) are assessed from routine CT images taken for diagnostic or staging purposes (T0) and treatment evaluation (T2) using the Alberta protocol and the date of the image recorded.[11 21] In brief, muscle attenuation measured in HU and skeletal muscle cross-sectional area (CSA, cm^2) are measured by a specifically trained observer from a single cross-sectional axial image L3 using SliceOmatic software (V.5.0, Tomovision, Quebec, Canada). L3 is the standard landmark that correlates best with whole body muscle mass,[6 21] and contains the psoas, paraspinal muscles (erector spinae, quadratus lumborum) and abdominal wall muscles (transversus abdominis, external and internal obliques, rectus abdominis). Total muscle CSAs, derived from the combined area of each of these individual muscles, are identified within an HU range of −29 to 150[22] and normalised for height (m^2) to determine skeletal muscle index (SMI, cm^2/m^2). Muscle attenuation is measured as the mean HUs within all the segmented muscles at L3. BMI and sex-specific cut-off points are used to identify low total muscle mass and low total muscle attenuation according to published definitions:

Low SMI (representing muscle mass) defined as $<43\,cm^2/m^2$ in men with a BMI $<24.9\,kg/m^2$, $<53\,cm^2/m^2$ in men with a BMI $\geq 25\,kg/m^2$, and $<41\,cm^2/m^2$ in women of any BMI.[5]

Low muscle attenuation defined as <41 HU in men and women with a BMI $<24.9\,kg/m^2$, and <33 HU in men and women with BMI $\geq 25\,kg/m^2$.[5]

Table 2 Study measures

Study measure	Instrument	T0	T1	T2
Potential predictors				
Malnutrition	PG-SGA	✓	✓	✓
Muscle strength	Handgrip dynamometer	✓	✓	✓
Bioimpedence spectroscopy	Total body and appendicular (arms+legs) fat-free mass, fat mass	✓	✓	✓
Physical activity and sedentary behaviour	Accelerometer, inclinometer, IPAQ-short form	✓	✓	✓
Physical performance	SPPB	✓	✓	✓
Sarcopenia risk	SARC-F, calf-circumference	✓	✓	✓
Protein and energy intake	3-day food record	✓	✓	✓
Systemic inflammation	Neutrophil to lymphocyte ratio	✓	✓	✓
Primary outcome				
Muscle mass	CT	✓	x	✓
Secondary outcomes				
Muscle attenuation	CT	✓	x	✓
Visceral, subcutaneous and intramuscular adipose tissue		✓	x	✓
Treatment completion	Medical record	x	x	✓
Toxicities	CTCAE V.5.0	✓	✓	✓
Survival	Medical record or death registry	12 months post final recruitment		

CTCAE, Common Terminology Criteria for Adverse Events; IPAQ, International Physical Activity Questionnaire-short form; PG-SGA, Patient-Generated Subjective Global Assessment; SARC-F, Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls history; SPPB, short physical performance battery.

Subcutaneous adipose tissue CSA (cm^2) is identified within a HU range of −190 to −30.[22] Visceral adipose tissue CSA (cm^2) is identified within a HU range of −150 to −50.[23] Intramuscular adipose tissue CSA (cm^2) is identified within a HU range of −190 to −30.[22] The CSAs of visceral and subcutaneous adipose tissue are combined to derive total abdominal adipose tissue and normalised for height to determine the total adipose tissue index (cm^2/m^2). Where possible, we will minimise variation between images used for CT assessments; this includes selection for analysis of the same intravenous contrast phase, reconstruction filter (soft tissue) and slice thickness. Finally, segmented structures are manually performed by an expert observer therefore will be subject to quality control during segmentation process.[24 25]

Tetrapolar bioimpedance spectroscopy (SOZO, Impedimed, USA) is used to estimate total body and appendicular (arms and legs) fat-free mass and fat mass (all in kg), total body water, extracellular and intracellular fluid and phase angle (ratio of resistance to reactance) using proprietary software provided by Impedimed (Brisbane, Australia). Participants are asked to stand on the SOZO scale, placing feet and hands on the corresponding foot and hand sensors.

Nutritional status

Nutritional status, that is, the presence or absence of malnutrition, is determined through the Patient- Generated Subjective Global Assessment (PG-SGA).[26] The PG-SGA is a common nutrition assessment tool used by oncology dietitians in clinical practice and categorises patients as: A—well-nourished, B—mild to moderate malnutrition, C—severe malnutrition. The PG-SGA has been evaluated as an outcome measure in clinical nutrition studies and validated for use in oncology patients undergoing radiotherapy.[27 28] Data collected will also allow determination of a diagnosis of malnutrition using the Global Leadership on Malnutrition criteria.[29]

Protein and energy intake

Protein and energy intake is assessed using 3-day food records which are suitable for capturing total dietary intake over the short term.[30] The 3-day period has been chosen in order to account for day-to-day variation in dietary intake including 2 weekdays and 1 weekend day.[31] Food records will be entered into the nutritional analysis tool, ASA-24-Australia. Individual participant energy and protein requirements will be estimated using standard equations recommended by the European Society for Clinical Nutrition and Metabolism guidelines on nutrition in cancer patients: 25–30 kilocalories/kg body weight, 1.0–1.5 g protein/kg body weight[32] to determine the proportion of energy and protein requirements met.

Physical performance, muscle strength, sarcopenia risk

Physical performance is assessed using the short physical performance battery (SPPB). The SPPB consists of three objective measures used to score each of static balance, gait speed (over 4 m) and lower body muscle strength (five times sit-to-stand test). The three objective measures are each scored from 0 to 4, and combined to derive a total SPPB score ranging from 0 to 12, with higher scores indicating better performance. The SPPB has been demonstrated to have predictive validity for survival among cancer survivors.[33] Upper limb muscle strength is assessed using the valid and reliable handgrip strength test which measures volitional grip force (kg) applied by the combined contraction of extrinsic and intrinsic hand muscles.[34] Handgrip strength is measured using a digital hand dynamometer (Jamar Digital Plus) following the standard protocol of the American Society of Hand Therapists.[35] In a seated position, 90° elbow flexion and forearm mid-prone, participants will be required to apply as much force as possible to the dynamometer for 3–5 s using the right and then left hand. Participants complete one practice test followed by three tests on each hand (with a 5 s rest interval between tests), with the maximum strength from either hand used in the analysis. Grip strength of <27 kg for men and <16 kg for women is considered impaired.[36] Sarcopenia risk is assessed using the SARC-F (Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls history) tool alone and in combination with calf-circumference. The SARC-F is a rapid screening tool for sarcopenia in older adults. Sarcopenia is defined as a decline in muscle mass, strength and/or function.[37] The SARC-F assesses five components including strength, assistance in walking, ability to rise from a chair, ability to climb stairs and occurrence of falls in the past year. The five components are scored from 0 to 2, and combined to derive a total SARC-F score ranging from 0 to 10, with a score ≥4 predictive of sarcopenia.[37] Calf-circumference <34 cm in men and <33 cm in women is considered low.[38] When used in combination with SARC-F, low calf-circumference is assigned an additional 10 points with a total score of ≥11 predictive of sarcopenia.[38]

The proposed cut-points that represent low muscle mass and low muscle strength will be reviewed prior to statistical analysis due to rapid, ongoing research in this field.

Physical activity

Daily sedentary time, light and moderate to vigorous physical activity are assessed over a 7-day period using an accelerometer attached by a belt at the hip level (ActiGraph wGT3X-BT, ActiGraph LLC, USA). The accelerometer measures accelerations at the hip (counts/min) in order to determine the time spent in sedentary, light, moderate or vigorous intensity activity based on sedentary (<100 counts/min), light (100–1951 counts/min), moderate (1952–5724 counts/min) and vigorous (≥5725 counts/min) intensity activity.[39 40] Participants are asked to keep a record of their sleep/awake times, periods of removal of the accelerometer (if any), naps taken (if any) and other relevant information. Step count and time spent sitting and standing are estimated using an inclinometer, which is attached to the participant's right thigh with a hypoallergenic patch (activPAL3, PAL Technologies, Glasgow, UK). The activPAL monitor has been demonstrated as valid and reliable in adults[41] and older adults.[42] Participants are instructed to wear the devices continuously (24 hours/day) for the 7-day period. Data for a minimum of any 4 valid days, with a valid day considered as 8 or more hours of wear time, will be required for analysis for both devices.[43] Devices are applied with education provided by the trial research staff at the end of each outcome assessment.

Patient-reported baseline physical activity is assessed using the International Physical Activity Questionnaire—Short Form (IPAQ) at T0. The IPAQ is also completed at T1 and T2 as a source of patient-reported physical activity during and post-treatment. The IPAQ allows participant activity levels to be categorised as low, moderate or high based on the IPAQ scoring protocol. The IPAQ has been validated in young, middle age and older adults and is used in lung cancer populations.[44 45]

Health-related quality of life

HR-QoL is measured using the Functional Assessment of Cancer Therapy—Lung (FACT-L) Scale, a self-report instrument designed and validated for use in patients with lung cancer.[46 47] FACT-L consists of 27 core items (FACT-General) to assess patient function in four domains: physical, social/family, emotional and functional well-being. These domains are supplemented by a 9-item subscale used to assess symptoms specific to lung cancers (LCS). Higher scores indicate a better HR-QoL. Scores for Global Quality of Life, Physical Well-being (PWB), Functional Well-being (FWB), LCS and the Trial Outcome Index (sum of PWB, FWB and symptom subscale) will be determined.

Inflammation

Systemic inflammation is assessed using the neutrophil to lymphocyte ratio (NLR) which is collected from pathology reports in the participant medical record from routine blood tests taken throughout CRT. NLR is an easily measured, reproducible and inexpensive marker of subclinical inflammation. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, participants with a ratio >3.53 will be considered to have the presence of inflammation.[48]

Treatment toxicity, treatment completion and survival

The presence and severity of treatment toxicities, including dysphagia/oesophagitis, nausea and vomiting, is assessed using the Common Terminology Criteria for Adverse Events V.5.0 (CTCAE, NCI, USA) by the trial research staff. Interruptions to radiotherapy and the prescribed and delivered dose of radiotherapy are recorded from participants' medical

Table 3 Common treatment regimens used for curative intent (chemo)radiotherapy treatment for non-small cell and small cell lung cancer

Diagnosis	Treatment
NSCLC	Radiotherapy 60 Gy in 30 fractions plus platinum-based chemotherapy* Radiotherapy 55 Gy in 20 fractions without chemotherapy
SCLC	Radiotherapy 45 Gy in 30 fractions plus platinum-based chemotherapy* Radiotherapy 40 Gy in 15 fractions plus platinum-based chemotherapy*

*Cisplatin/paclitaxel, cisplatin/etopiside, cisplatin/pemetrexed, carboplatin/paclitaxel, carboplatin/etopiside.
NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer.

records and confirmed with the treating team. Modifications to prescribed chemotherapy regimen, including dose reduction, early termination of chemotherapy or alteration to planned chemotherapy agents, are recorded from participants' medical records and confirmed with the treating team. Commencement of sequential immunotherapy within 3 months of completing CRT is recorded from participants' medical records and confirmed with the treating team. Table 3 describes the common treatment regimens. Overall survival time (months) will be calculated from the date of the baseline pre-CRT CT scan until death from any cause or the date of censoring at 12 months following recruitment of the final participant. Participant survival will be determined from the hospital medical record or death registry.

Patient interviews

A purposively selected sample of participants, who had low muscle mass at T0 or T2 and/or experienced any muscle loss at T2, are invited to participate in an interview following completion of T2 data collection. Interviews seek to understand their ability to cope with treatment and complete self-care, receptiveness to nutrition and exercise intervention, when and in what form (individualised, group, in-person, technology-supported) they would prefer to receive nutrition and exercise intervention (online supplemental file 1). Where possible, diversity in participant demographics (age, sex, BMI, impaired function and living situation) is sought. It is anticipated that approximately 15–20 interviews will be required to reach data saturation.[49]

Sample size

A recruitment target of 120 patients over 32 months is based on treatment of 90 patients with CRT annually and a participation rate of 50% indicated by previous studies at these sites.[50] Power calculations for the primary objective are based on the strength of associations between individual predictors and the outcomes in the population that could be detected with 80% power given the expected size of analysis samples. With an initial sample of 120, the expected analysis samples at end of CRT and 2 months post-CRT are 105 and 84, allowing for 12.5% and 30% dropout, respectively.[50] These sample sizes will provide 80% power to detect effect sizes of r^2=0.08 and 0.10 (ie, 8% and 10% of the outcome variance explained in a simple linear regression model), at T1 and T2, respectively, with α=0.05. In a multiple linear regression model including up to eight covariates, sample sizes of 105 and 84 will provide 80% power to detect squared partial correlations of 0.07 and 0.09, respectively, with α=0.05.

Based on our previous research,[20] we estimate (a) that the population HR is 1.87 for low muscle attenuation compared with normal muscle attenuation at baseline, (b) the proportion of the target population with low muscle attenuation will be 41% and (c) survival of 50% in the normal muscle attenuation group at the time of administrative censoring. Under these assumptions, a sample size of 120 at study commencement will provide 76% power to detect a difference in survivor functions between participants with low and normal muscle attenuation, with α=0.05. Similarly, assuming 61% target population prevalence of low muscle mass[20] and 50% survival in the normal muscle mass group, this sample size will provide 80% power to detect a minimum effect size of HR=2.06 for the difference in survivor functions between participants with low and normal muscle mass.

Statistical analysis

All data will be analysed using the Stata software programme (StataCorp). Prior to formal data analysis, descriptive statistics and graphical displays will be used to identify missing and out-of-range values, assess the plausibility of means and SDs for all variables, identify outliers and screen continuous variables for normality. Recruitment bias will be assessed by comparing demographic and clinical variables for consenters with those who decline participation using t-tests (or Mann-Whitney U tests) for continuous variables and χ^2 tests for categorical variables.

Modelling of study outcomes (eg, continuous scores, binary, counts) will be performed using generalised linear models with specification of appropriate distributions and link functions. For binary outcomes, the model that produces risk/rate ratios (RR), rather than ORs, (eg, binomial distribution with log link) will be used where possible due to the more intuitive interpretation of risk ratios when the outcome is common.[51] Log-transformation of continuous outcome variables may be undertaken as indicated by model diagnostics. All regression analyses will be adjusted for study site and baseline levels of outcome variables (where available).

Prediction/multiple-exposure models will be built as follows:[1] individual associations between exposure variables and the outcome will be tested in separate models;[2] exposure variables showing at least weak evidence of an association with the outcome (defined here as p value <0.20) in step 1 will be added to a multiple-exposure model;[3] exposure variables in the multiple-exposure model with p value >0.10 for their association with the outcome will be removed one at a time (in order of highest p value) and the model refitted until a final prediction model is determined. Given anticipated variability in time in treatment, models will be adjusted for treatment duration.

Statistical assumptions, including linearity and (lack of) multicollinearity, will be examined and handled as necessary during the model-building process. The potential inflation of type I errors due to multiple testing will be taken into consideration when interpreting the results. Sensitivity analyses will be conducted to assess robustness of prediction models to influential observations if this appears warranted.

Overall survival will be defined as the number of days from the date of the baseline CT scan prior to CRT to the date of death by any cause or the date of censoring at 12 months following recruitment of the final participant. For participants still alive, overall survival will be censored at the last study visit, the last contact date or the date they were last known to be alive, whichever is last. Overall survival curves will be estimated using Kaplan-Meier methodology. Survival analysis will be conducted with Cox proportional hazards regression models.

The semistructured interviews will be recorded and content transcribed verbatim. Interview transcripts will be subject to thematic analysis. This will consist of inductive coding of textual data, interpreting using a constant comparative manner where concepts are labelled as codes.[52] Codes will then be grouped into larger categories. An interrater process will be undertaken.

Patient and public involvement

A consumer representative was involved in this research from the time of the funding application where input was sought into the importance of the research question and expected outcomes from the study. During preparation of the study protocol, input was sought from our consumer representative regarding the wording and appropriateness of the qualitative interview questions, the participant information and consent form and the overall burden of participation. Consultation regarding dissemination of the study findings will occur with our consumer representative as well as a broader insight from a National Lung Cancer Patient Advisory Group.

ETHICS AND DISSEMINATION

The study received ethics approval from the Human Research Ethics Committee at Peter MacCallum Cancer Centre on 19 June 2019 (HREC/53147/PMCC-2019) and Deakin University (2019-320), and will be conducted in accordance with the principles of the Declaration of Helsinki.

The results of the study will be reported according to the Strengthening the Reporting of Observations Studies in Epidemiology guidelines. Dissemination of the findings will take the form of peer review publications and conference presentations.

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