STUDY TITLE: NutriCare Intervention on Optimizing Nutritional Status, Reducing Treatment-Related Toxicities, and Improving Quality of Life Among Vulnerable Patients with Lung Cancer

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Instructions: The written description of the clinical study, including objective(s), design, and methods. It may also include relevant scientific background and statistical considerations. The written description of the statistical considerations for analyzing the data collected in the study. Includes how data are analyzed, what specific statistical methods are used for each analysis, and how adjustments are made for testing multiple variables. If some analysis methods require critical assumptions, the written description should allow data users to understand how those assumptions were verified

1. Background and Rationale

Patients with lung cancer are among the most malnourished of all oncology patients, with depletion of body stores of fat and lean mass due to inadequate nutritional intake.(1) Up to 69% of the patients with lung cancer are malnourished,(2-4) and nearly 35% have clinically significant weight loss of more than 10%, indicating severe malnutrition.(5) Patients with lung cancer who are malnourished are significantly more likely to develop treatment-related toxicities, resulting in interruptions in treatment, and reduced treatment dose and/or completion.(6, 7) The prevalence of malnutrition could be even higher among cancer patients who are economically disadvantaged, uninsured, racial/ethnic minorities, the elderly, and rural residents, secondary to significant barriers to accessing healthcare and nutritious foods.(8, 9) Timely, effective, and tailored nutrition interventions are a critical component in countering lung cancer disparities among vulnerable populations in the US. Growing evidence also suggests that gut microbiota play a large role in how foods affect the body, including for cancer outcomes. Evaluating the response to a nutrition intervention benefits from taking into account differences in the microbiomes of participants.

We aim to assess the efficacy of an innovative intervention strategy to integrate nutrition into standard oncology care using the 5As model (Ask, Advise, Assess, Assist, and Arrange), an evidence-based behavioral counseling framework with proven application in other areas of clinical practice.(10, 11)To further address health inequities and limited access to nutritious foods among the most vulnerable patients with lung cancer, we will incorporate the provision of home-delivered medically tailored meals (MTM), an emerging promising strategy for improving the health outcomes of patients with several chronic diseases through achieving optimal nutritional status.(12, 13)

2. Objectives

We aim to evaluate the impact of an innovative nutrition intervention on improving the outcomes of patients with lung cancer. Specifically, we aim to:

Specific Aim 1. To assess the efficacy of the intervention for optimizing nutritional intake, reducing food insecurity, minimizing unintentional weight loss, improving treatment compliance, reducing treatment-related toxicities, reducing hospitalization, readmissions, and emergency department (ED) visits, and improving gut microbiome among vulnerable patients with lung cancer. We will examine: (a) change in diet quality and intake of key food groups and nutrients as assessed by the National Cancer Institute Diet History Questionnaire (DHQ III); (b) change in food insecurity measured by the U.S. Department

of Agriculture (USDA) Household Food Security Survey; (c) change in weight and percent weight loss as measured in the clinic; (d) treatment completion (dose reductions and treatment delays) assessed by the treating medical oncologist; (e) treatment-related toxicities assessed by the treating medical oncologist using the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE); (f) hospitalizations and ED visits assessed by medical record review and linkage with discharge data; and (g) change in gut microbiome via metagenomic whole shotgun sequencing (mWGS).

Specific Aim 2. To evaluate the efficacy of the intervention for improving patient-reported outcomes among vulnerable patients with lung cancer. We will assess: (a) change in patient-reported symptoms (fatigue, pain, nausea, vomiting, appetite loss, and sleep disturbance) as assessed by a Patient-Reported Outcomes version of the CTCAE (PRO-CTCAE); (b) change in quality of life as assessed by EORTC-QLQ-30 and EORTC-QLQ-LC13; (c) change in anxiety assessed by GAD-7; and (d) change in depressive symptoms assessed by PHQ-9.

3. Design and Methods

3.1 Study Design

Using a randomized controlled trial design, we aim to recruit 270 vulnerable patients with a newly diagnosed stage I-IV lung cancer from four sites (Fox Chase Cancer Center, Tufts Medical Center, M.D. Anderson Cancer Center, and Ohio State University) and randomize them equally into an intervention group (NutriCare) and an enhanced control group (NutriTool). There will be two cohorts for NutriCare with cohort 1 recruiting 150 patients completing an 8-month intervention and cohort 2 recruiting 120 patients completing a 6-month intervention.

The NutriTool (enhanced control) Group. Participants in the NutriTool group will receive a printed copy of a *Nutrition Toolkit* from providers and monthly emails with general nutrition information and healthy recipes.

The NutriCare (intervention) Group. For participants randomized to the NutriCare Group, participants will additionally receive the home delivery of *Medically Tailored Meals* and remote nutrition counseling provided by registered dietitian nutritionists.

- *Medically Tailored Meals (MTMs):* Medically tailored meals will be provided to participants in the intervention group for a total of 24 weeks for both cohorts. During the first 8 weeks of the intervention, 3 meals/day will be provided each week for a total of 168 meals per participant. It will be followed by less frequent meal provision during the subsequent 16 weeks following this schedule: 3 meals/day will be provided every other week for the next 8 weeks (a total of 84 meals per participant); and 3 meals/day will be provided every four weeks during the last 8 weeks (a total of 42 meals per participant). The number of meals provided to each participant may be adjusted according to participant's preference and needs.
- *Nutrition Counseling*: Medical oncology providers will refer participants to oncology RDs for remotely delivered medical nutrition therapy counseling. For cohort 1,

participants will receive nutrition counseling for 8 months. The counseling will be provided on a weekly basis during the first 6 months and every other week during the last 2 months (for cohort 1 only). For cohort 2, participants will receive nutrition counseling for 6 months. The ultimate frequency of nutrition counseling being provided to each participant will also be adjusted according to the participant's preference and needs.

3.2. Methods

Screening and Recruitment: The clinical team at each site will assess patient's eligibility based on inclusion and exclusion criteria. For patients who are determined eligible, the clinical team will consent the patient if there is interest. Consented patients will be randomized to either the NutriCare or the NutriTool group and asked to complete two pre-intervention forms: Contact Information Sheet that asks for their mailing address, phone number, and email address; Demographic and Health Survey that asks participants' socio-demographics (such as education and marital status) and health behaviors (such as cigarette smoking, alcohol intake, and physical activity).

Research Data Collection: Research data will be collected for all enrolled patients. Outcomes will be assessed at three time points (baseline, 3 months, and 6 months [for cohort 2] or 8 months [for cohort 1]) for most outcomes except weight, treatment completion, treatment-related toxicities, and hospitalization and ED visits will be assessed throughout the intervention.

At baseline, 3 months, and 6 months [for cohort 2] or 8 months [for cohort 1]), outcome data will be collected for: (a) dietary intake patterns and quality using the National Cancer Institute (NCI)'s Dietary History Questionnaire III (DHQ III); (b) malnutrition risk using the Patient-Generated Subjective Global Assessment (PG-SGA) short form; (c) food security using the Household Food Security Survey Module developed by the U.S. Department of Agriculture (USDA); (d) participant-reported outcomes, including the participant-reported outcomes version of the CTCAE (PRO-CTCAE), the EORTC QLQ-C30 and EORTC QLQ-LC13, Generalized Anxiety Disorder (GAD-7); the Patient Health Questionnaire (PHQ-9); and (e) Gut microbiome via metagenomic whole shotgun sequencing (mWGS) based on stool samples.

At each clinical visit, outcome data will be collected for (f) weight using calibrated electronic scales, (g) treatment-related toxicities using the NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0; and (h) hospitalization and emergency department (ED) visits through medical record review.

Other research data including cancer diagnosis, treatment plan, medical conditions, medication use, and lifestyle factors will be collected at baseline. New medical conditions and medication use will be collected during the course the study. Treatment history will be updated at 3 months and 6 months [for cohort 2] or 8 months [for cohort 1]) through chart review.

Laboratory tests: Gut microbiome sequencing: upon receipt samples will be aliquoted into two cryovials and stored at -80C in a locked freezer until batch processing. Cryovials

will be labeled with coded study ids. Upon study completion DNA will be purified (PowerFecal Pro, QIAGEN), sequencing libraries generated (QIAmp FX, QIAGEN) and sequencing performed (Illumina HiSeq 4000) on all samples ensuring data quality any remaining aliquots of stool samples will be destroyed.

4. Statistical Analysis

Descriptive statistics will first be compiled. Mean and standard deviation (and median and 25^{th} and 75^{th} quartiles, if appropriate) will be reported for continuous variables. Counts and percentiles will be reported for binary and categorial variables.

Intention-to-treat analysis will first be conducted. A series of unadjusted and adjusted models will be estimated. For the unadjusted models, the dependent variable will be each of the outcomes (see below). The main independent variables will be group assignment (binary), time (3-level categorical at baseline, 3-month, and 6 months [for cohort 2] or 8 months [for cohort 1]), and their interaction terms.

For inferential statistics, pairwise examinations between each time point will be conducted using paired sample t-test, Wilcoxon signed rank test, and chi-square test. Afterwards, we will apply generalized linear mixed-effects model since it can flexibly accommodate continuous, binary, as well as count dependent variables. Clustering at participant level within each site will be incorporated into the model as two-level nested random intercepts. If the site-level clustering deems negligible (indicated by intra-class correlation), we would simplify the model by only adjusting for participant-level clustering. Below we detail the analysis and modeling approach, followed by sample size justification.

For **Aim 1,** we will assess changes in outcomes from baseline (*T0*) to 3 months (*T3*) and from baseline (*T0*) to 6-months (*T6*) [for cohort 2] or 8 months (*T8*) [for cohort 1] within the two groups in most outcomes including diet, malnutrition risk, food security, weight, and participant-reported outcomes (3 time points: T0, T3, and T6/T8) using paired-sample *t*-test (continuous outcome) and McNemar's test (binary). Changes in weight and microbiome diversity (Simpson's index) will be assessed throughout the intervention using repeated measures mixed-effects linear regression. Treatment completion and the number of treatment-related toxicities, rehospitalization, and ER visits will be compared at 6-months (*T6*) [for cohort 2] or 8 months (*T8*) [for cohort 1] between the two groups. To evaluate the efficacy of the NutriCare intervention, we will apply the "difference-in-difference" approach in mixed-effects linear regression models. As an exploratory analysis, we will evaluate changes in weight and treatment-related toxicities are mediated by changes in gut microbiome. A subset of our outcomes such as knowledge will be collected in ordinal Likert's scale format. We will apply the overall analysis scheme but modify the regression into a mixed-effects ordered logistic regression to better capture the change in ranks.

For **Aim 2**, we will assess change in patient-reported outcomes in function and symptom domains from *T0* to *T3* and from *T0* to T6/*T8* within the two groups using paired sample *t*-test. Similar mixed-effects linear regression models will be used to evaluate the

effectiveness of the NutriCare intervention at the 3rd and 6th month [for cohort 2] or 8th month [for cohort 1].

We propose the follow per-protocol analyses. First, a complete-case analysis will be conducted using cases with data collected at all three time points. Second, a dose-response analysis will be conducted using the cases from the intervention group, adjusting for programmatic exposure such as total meals delivered and proportion of mean consumed. Third, a data missing pattern analysis will be performed to assess if we should employ imputation method to validate the findings from the intention-to-treat analysis.

Power analysis

Power calculations were performed for two of the outcomes: Healthy Eating Index and body weight. We chose these two based on the availability of reference literature with similar study setting as well as their immediate relevance to our study's aims. With budgetary and time constraints optimized, the study will be able to recruit 270 participants at most.

We estimated the power using the following procedures. First, we identified point and dispersion estimates from published literature and determine the monthly change in the outcomes. Second, we simulated the sample population (135 intervention, 135 control) at baseline, 3-month, and 6 months [for cohort 2] or 8 months [for cohort 1] with different degrees of monotonous loss-to-follow-up; the correlation between time points was set at 0.6. Third, for each loss-to-follow-up scenario, we simulated 1,000 data sets, examined the p-value of the difference-in-difference (time x group interaction), and tallied if the null hypothesis was rejected. Finally, the power was computed by estimating the prevalence of null hypothesis rejections. The results are tabulated as follows:

HEI: *Anderson et. al.* found 6.80 points increase in HEI for the intervention group, and 3.05 points increase in HEI for the control group over 6 months.(14) The cross-sectional standard deviation was found to be about 9.27.

Monotonous missing pattern (baseline → 3m → 6m/8m)	Simulated power to detect a difference as extreme as that in the cited literature:
0% → 15% → 20%	95.5%
0% → 20% → 35%	92.1%
0% → 25% → 40%	89.6%

Body weight: *Kiss et. al*. found a 1.0 kg increase in body for the intervention group, and 0.10 points increase in body weight for the control group over 5 months.(15) The cross-sectional standard deviation was found to be about 3.3 kg.

Monotonous missing pattern (baseline → 3m → 6m/8m)	Simulated power to detect a difference as extreme as that in the cited literature:
0% → 15% → 20%	90.3%
0% → 20% → 35%	82.9%
0% → 25% → 40%	80.2%

5. References

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