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# Frailty assessment predicts toxicity during first cycle chemotherapy for advanced lung cancer regardless of chronologic age

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## Abstract

**Background:** Improved assessment strategies are needed to individualize treatment for adults of all ages receiving palliative chemotherapy for non-small cell lung cancer (NSCLC). Our aim was to evaluate the utility of the Fried Frailty Index (FFI) and a cancer-specific geriatric assessment (GA) to predict chemotherapy toxicity and overall survival (OS).

**Methods:** We conducted a multi-site pilot study of 50 patients with newly diagnosed advanced NSCLC, age ≥ 18 years. All participants received carboplatin AUC 6, paclitaxel 200 mg/m$^2$ every 3 weeks. FFI and the GA were administered prior to chemotherapy. A GA toxicity risk score was calculated. Grade 3–5 toxicity was assessed during 1st two cycles of chemotherapy. OS was measured from chemotherapy initiation. Logistic regression and Cox proportional hazards models were fit to estimate the association between baseline characteristics and toxicity and OS respectively.

**Results:** Among 50 participants, 48 received chemotherapy and were evaluable. The mean age was 68.5 y (range 42–86), 79% male, 85% KPS ≥80. The median OS was 8 months. Many (27%) met FFI criteria for frailty with ≥3 impairments. Impairments detected by the GA were common.

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Disclosure and Conflicts of Interest

The authors have no conflicts of interest to disclose.

In multivariable analyses both FFI ≥ 3 and GA toxicity risk score > 7 were independently associated with higher odds of toxicity (Odds ratio [OR] 7.0; 95% confidence interval [CI] 1.1–44.6 and OR 4.3; 95% CI 1.0–17.7, respectively) in first cycle chemotherapy. Neither score was associated with OS.

**Conclusions:** Frailty predicts chemotherapy toxicity during first cycle. Frailty assessment may inform toxicity risk regardless of chronologic age.

### Keywords

Lung cancer; Frailty; Geriatric assessment; Metastatic; Elderly; Older

## 1. Introduction

Lung cancer is a common malignancy and a leading cause of death in the United States and worldwide. Most patients are diagnosed with advanced stage disease and as part of their treatment course will require palliative cytotoxic chemotherapy. There are multiple treatment options in non-small cell lung cancer (NSCLC) which include targeted therapies and immunotherapy as initial front-line options. However, the clear majority will develop progressive disease and require cytotoxic chemotherapy with evidence supporting the role of doublet chemotherapy even among older adults [1–3]. For these patients, optimal treatment decisions and supportive management remains a challenge. The ability to accurately predict risk of early treatment toxicity is of great importance and remains a challenge in clinical practice [4–8]. Patients with advanced lung cancer frequently present with high symptom burden and comorbidity regardless of chronologic age, which increases the risk of therapy-related toxicity. Assessment of age and performance status alone is inadequate to predict treatment tolerance particularly in the first cycle of chemotherapy. Improved assessment strategies are needed for lung cancer patients of all ages to identify patients who are frail in the context of a given therapy regardless of chronologic age. A proactive strategy to personalize anticipation of toxicity can potentially inform choice of treatment, dosing strategies, and supportive care interventions to avoid toxicity.

Assessment tools have been tested to a limited extent among older adults with lung cancer and in other settings to better predict treatment toxicity and benefit [9–16]. Approaches include geriatric assessment (GA), which uses standardized measures to assess multiple characteristics such as comorbidity, physical function, cognitive function, social and emotional health that may influence treatment tolerance [11, 17, 18]. Indices to measure and characterize the construct of frailty have also been developed and validated in older adult populations which identify people at higher risk for outcomes such as mortality and increased health care utilization; these have not yet been rigorously tested in advanced stage lung cancer patients [19]. A small number of studies have shown that use of GA can help predict treatment toxicity among older adults with lung cancer [13, 14, 20, 21]. Some have included heterogeneous populations receiving a wide range of treatment which may confound relationships between measured vulnerabilities and outcomes [13, 14]. While optimal assessment strategies are not yet clear, available data across tumor types have supported guideline recommendations to perform abbreviated geriatric assessment as part of the evaluation of older adults (typically ≥70 years) with lung cancer [22, 23]. No studies,

however, have addressed the utility of GA or frailty assessments to predict outcomes regardless of chronologic age, recognizing that measurable vulnerabilities which constitute a frailty phenotype may be detected in non-geriatric as well as geriatric patients. While geriatric assessment and frailty indices were developed and used to help characterize vulnerabilities and potential resilience among older adults, this concept is relevant for many patients younger than age 65 years. Tools that characterize physiologic age are needed to inform treatment decision-making and supportive care management for patients of any age.

Our aims in this pilot study were to evaluate the utility of the Fried Frailty Index (FFI) and a cancer-specific GA to predict toxicity in the first two cycles of chemotherapy and to explore their association with overall survival (OS) among patients with advanced lung cancer treated with doublet chemotherapy regardless of chronologic age. We hypothesized that the frailty phenotype measured by the Fried Frailty Index would be prevalent and that frailty would be associated with toxicity.

## 2. Methods

### 2.1. Study Design

We conducted a multi-site pilot study open at three outpatient oncology practices to enroll a convenience sample of 50 patients. The protocol was approved by each participating center's institutional review board. All patients provided written, informed consent to their participation in the study. We enrolled patients with newly diagnosed stage IV NSCLC, who had not received prior palliative chemotherapy. All participants received carboplatin area under the curve (AUC) 6 and paclitaxel 200 mg/m$^2$ every 3 weeks as initial therapy per study protocol. Granulocyte colony stimulation factor (GCSF) was not permitted in cycle 1 per protocol but allowed by physician discretion in subsequent cycles. Geriatric assessment and frailty measures were administered to all patients regardless of chronologic age by the study nurse prior to receipt of the first cycle of chemotherapy. Toxicity outcomes were recorded for the first 2 cycles of chemotherapy.

### 2.2. Study Population

Patients age ≥ 18 years with histologically or cytologically confirmed recurrent or stage IV NSCLC and adequate organ function were eligible. Key exclusion criteria included prior palliative chemotherapy and prior radiation therapy other than treated brain metastases. Additional exclusion criteria included pregnant or lactating women.

### 2.3. Assessment Measures

Frailty was assessed using the validated Fried Frailty Index (FFI) [19, 24]. This measure has been tested in older adult populations and is predictive of future disability [25]. Fried defined frailty as a clinical syndrome in which 3 or more of the following criteria are present: 1) self-reported unintentional weight loss >10 pounds in the past year;2) self-reported exhaustion (positive answer to one of two questions from the validated Center for Epidemiologic Studies Depression Scale (CES-D) [5]; 3) low self-reported physical activity <383 Kcals/week for men and <270 Kcals per week for women assessed using the Short Version of the Minnesota Leisure Time Activity Questionnaire; 4) slow usual gait speed over

eight feet using walk time of ≥7 s for the following height criteria-men ≤173 cm and women ≤159 cm and ≥6 s for the following height criteria- men >173 cm and women >159 cm; and 5) low grip strength measured using an adjustable, hydraulic grip strength dynamometer using published cutoffs which are dependent upon both gender and body mass index [24].

A cancer-specific geriatric assessment (GA) was performed using the Cancer and Aging Research Group assessment battery [10, 11, 17, 26]. The measures that comprise the tool are described in detail in a prior publication [17]. The assessment includes a healthcare provider and a patient self-reported questionnaire. The healthcare provider portion consists of three items: rating the patient's Karnofsky performance status (KPS) [27], the Timed Up and Go (a test of physical mobility which measures in seconds the time it takes for an individual to stand up from a standard arm-chair, walk a distance of 10 ft, turn, walk back to the chair, and sit down again) [28], and the Blessed Orientation-Memory-Concentration test [29] (a 6-item screening measure of cognitive function). The remaining measures are self-reported. Self-reported function is assessed with the following scales: 1) Activities of Daily Living (ADL) Subscale of the Medical Health Outcomes Physical Health Survey; 2) Instrumental Activities of Daily Living (Subscale of the Older Americans Resources and Services [OARS] Questionnaire); 3) Self-reported KPS; and 4) number of falls in the last 6 months. Comorbidity was assessed using the Physical Health Section of the OARS which assesses 14 specific conditions. The impact of cancer on patients' social functioning was assessed by the Social Activity Limitations scale from the MOS. Social support was assessed using the 20-item MOS Social Support Survey (Emotional/Information and Tangible Subscales). Nutrition was assessed by reporting the percent of unintentional weight loss in the last 6 months prior to study enrollment and by recording body mass index. For this study the (CES-D) was used to assess depressive symptoms. The full cancer-specific geriatric assessment will be referred to as geriatric assessment (GA) in this manuscript.

In addition to evaluating each component of the GA individually, a modified GA toxicity risk score was also calculated using published cut offs for the following variables: age (≥72 years), hemoglobin (<11 g/dL for men, b10 g/dL for women), creatinine clearance (<34 mL/min per Jeliffe caculation), hearing impairment (fair or worse), number of falls in last 6 months (1 or more), assistance with medications, limitation in walking one block, and decreased social activity because of physical/emotional health [10, 11, 14]. Additional risk factors of chemotherapy dose, number of chemotherapy drugs and cancer type did not differ between patients in this cohort. Weighted scores for each risk factor were applied based on original published scoring algorithm with maximal score possible in this cohort of 17. In this paper, we will refer to the GA toxicity risk score to denote the score described above which was derived from the GA.

### 2.4. Covariates

Demographic information (age, gender, race/ethnicity, education level, marital status) was collected with assessment questionnaires. Laboratory data (hemoglobin and creatinine), body surface area, smoking status and histology were abstracted from the medical record.

### 2.5. Outcomes

The primary outcome of interest in this study was treatment toxicity during the first 2 cycles of chemotherapy. Treatment-related toxicity was defined as grade 3 or 4 chemotherapy-related adverse events and any grade 5 toxicity. Toxicity was graded using National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. All adverse events were reviewed by the treating physician to confirm grading and provide attribution. A second review was performed by the study principal investigator using a similar process described by Hurria et al. [11] Secondary outcomes assessed were dose delay (defined as a delay of the second or third cycle of chemotherapy attributed to toxicity in the prior cycle), dose reduction (any reduction in protocol prescribed dose in cycles two or three attributed to toxicity to prior cycle of therapy) and unplanned hospitalization during the first two cycles of chemotherapy. Reasons for unplanned hospitalization were abstracted from the medical record. Use of growth factor support after first cycle was recorded. Overall survival was measured from the time of chemotherapy initiation.

### 2.6. Statistical Analyses

Descriptive statistics were used to characterize baseline characteristics, frailty and geriatric assessment measures and treatment-related adverse events. Frequencies of toxicities were summarized by number of events and number of participants. Chi-square tests or Fisher's exact tests were used to evaluate unadjusted differences in categorical variables by toxicity status. A Cochran-Armitage trend test was also performed for quartiles of continuous variables. Receiver operating characteristic curve analysis was used to evaluate the cut-point for the GA toxicity risk score. All variables with $p$-values ≤ .20 in the unadjusted analyses were considered as covariates in multivariable logistic regression models of attributable grade 3 or higher toxicities on either the frailty (FFI ≥ 3) or GA toxicity risk score (>7) [14] using a backward elimination approach with a $p$-value of 0.05 to stay in the model. Variables with a trend test $p$-value of 0.20 or lower were entered as continuous variables. We also fit a model using both frailty and the geriatric assessment score in the same model. Akaike information criterion (AIC) was used to compare the fit of these models. A lower AIC value indicates a better fit; AIC values within 2 indicate comparable models. Goodness of fit was also evaluated using the c-statistics and Hosmer-Lemeshow goodness of fit test. The relationship between frailty and geriatric assessment measures and toxicity was evaluated independently for cycle 1 and cycle 2 of chemotherapy. This approach was taken because changes are commonly made in cycle 2 based on toxicity observed intolerance learned from cycle 1. Fisher exact tests were used to compare dose reduction, dose delay, or hospitalization by frailty (FFI ≥ 3) or GA toxicity risk score (>7). Kaplan-Meier methods and Cox proportional hazards models were used to evaluate the association between frailty and geriatric assessment measures in the outcome of overall survival. All analyses were performed with a two-sided alpha level of 0.05 in SAS 9.4 (Cary, NC).

## 3. Results

Between October 2010 and April 2014, 50 patients enrolled in the study, 48 were evaluable for the primary outcome of toxicity. Two patients developed complications prior to initiation of chemotherapy which precluded treatment per protocol. No patients were lost to follow-up.

Baseline characteristics are presented in Table 1. The mean age of the study population was 69 years with a range from 42 to 86 years. Most patients were non-Hispanic white males with a high school or above education level. Most had adequate organ function, a good Karnofsky performance status score and were current or former smokers.

Over one quarter (27.1%) of the patient population screened positive for frailty based on the Fried Frailty Index (FFI) criteria (Table 2). Nearly half reported a >10-pound weight loss and low self-reported physical activity with the remaining criteria of self-reported exhaustion, slow gait speed and low grip strength each prevalent in 20 to 36% of patients. The majority (84%) of patients met at least one of the five frailty criteria.

Impairments detected by the GA were also common. More than one-third (38.3%) of patients screened positive for depression. Self-reported physical limitations were also common with approximately one-third (31.3%) of patients reporting a need for assistance in completing instrumental activities of daily living (IADLs). Nearly one-third of patients reported presence of three of more comorbid conditions. By contrast, only a minority screened positive for cognitive impairment. The average GA toxicity risk score calculated from items in the GA was 7.3 (range 4 to 12). The most common risk factors were decreased social activity, older age, a limitation in walking one block, and hearing impairment which were prevalent in 41.7%, 35.4%, 31.3% and 31.3% respectively.

Treatment related grade 3–5 toxicity occurred in 68.8% of evaluable patients during the first two cycles of chemotherapy. Hematologic toxicity was more common (52%) than non-hematologic toxicity (29%). The most common etiology for hematologic toxicity was neutropenia. Among non-hematologic toxicities, most common were fatigue and electrolyte abnormalities. Toxicity by cycle is described in Table 3. Six participants only had one cycle of chemotherapy. Among those with more than one cycle, dose reduction or dose delay attributed to the 1st 2 cycles of chemotherapy occurred in 28.6% and 11.9% respectively. Among all patients, 18.8% were hospitalized as a result of the 1st 2 cycles of chemotherapy. The primary reason for hospitalization was categorized as infection (33%), fatigue/dehydration (22.2%), pulmonary (pleural effusion, 11.1%), electrolyte abnormality (11.1%), cardiac (myocardial infarction, 11.1%) and arthralgia (11.1%). GCSF was added post cycle one among 14.6% of patients. Median overall survival was 8.0 months.

In univariate analyses the following variables were associated with incident grade 3–5 toxicity during the 1st cycle of chemotherapy: age ($p = .02$), presence of frailty (FFI ≥ 3, $p = .05$) and body surface area ($p = .05$). Among patients deemed frail at baseline (FFI ≥ 3), 77% experienced grade 3–5 toxicity during the 1st cycle of chemotherapy compared with only 43% of those with a score of 0 to 2. Among the component risk factors which compose the FFI both gait speed ($p = .08$) and grip strength ($p = .06$) appeared associated with toxicity in univariate analyses. Among patients with GA scores >7, 65% experienced grade 3 to 5 toxicity during the 1st cycle of chemotherapy compared with only 43% of those with a score of 4 to 7 ($p = .15$). In addition to age and body surface area, variables with unadjusted $p$-values < .20 that were considered in multivariable models included: gender, comorbidity score, and hemoglobin. Age was only considered in the FFI models due to its presence in the GA toxicity risk score.

In multivariate analyses (Table 4) frailty (FFI ≥ 3) [Odds ratio 7.0; 95% confidence interval 1.1–44.6] was independently associated with grade 3–5 toxicity in cycle 1 controlling for age, body surface area, and comorbidity score. Similarly, patients with a high GA toxicity risk score (>7) at baseline had a greater odds of grade 3–5 toxicity controlling for self-reported comorbidity score and body surface area [OR 4.3; 95% confidence interval 1.0–17.7]. AIC indicated that the frailty model provided the best fit to the data; the Hosmer-Lemeshow goodness of fit tests indicated the models fit well. Among all participants, frailty (FFI ≥ 3) was not associated with dose delay, dose reduction, or hospitalization; GA toxicity risk score (>7) was associated with having a dose delay (12.5% vs. 2.1%, $p = .02$), but not with dose reduction or hospitalization.

In all patients who completed cycle 2 ($N = 42$), there were no significant differences in the incidence of attributable grade 3 or higher toxicities in those classified as frail by FFI (≥3, $p = .16$) or by the GA toxicity risk score (>7, $p = .68$) in models adjusted for sex and current smoking at baseline. However, when we modeled those patients without dose reduction ($N = 37$), FFI became a significant predictor of attributable grade 3 or higher toxicities in the adjusted model (OR = 10.22, 95% CI1.24–84.27), although the GA toxicity risk score remained a non-significant predictor of toxicity in the adjusted model.

Neither frailty (FFI ≥ 3) nor the GA toxicity risk score (>7) were associated with overall survival in this cohort, in unadjusted (Table 5) and adjusted (baseline hemoglobin, Karnofsky Performance Status, BMI) models. Among component characteristics collected as part of the frailty index and GA, only lower self-reported physical activity (a component of the FFI, HR = 2.01, 95% CI 1.08–3.74) and lower creatinine clearance (HR = 4.94, 95% CI 1.11–22.03) were associated with survival in univariate analyses, although both became non-significant with adjustment for baseline hemoglobin, Karnofsky Performance Status, and BMI (data not shown). Age was not associated with survival in this cohort ($p = .49$).

## 4. Discussion

In this study of adults with advanced NSCLC we demonstrate that the frailty phenotype is prevalent and is predictive of toxicity during the first cycle of chemotherapy regardless of chronologic age. Similarly, a risk prediction score derived from a cancer-specific GA was also predictive of toxicity. These data highlight the potential utility of frailty assessment for patients with advanced stage lung cancer to inform treatment planning and support extending the study of these assessments to non-geriatric populations.

Our results are consistent with other studies in the literature. Specifically the prevalence of frailty, assessed by the FFI, in our cohort of advanced lung cancer patients was similar to that reported in studies of older adults cancer patients (12–35%) [30–32]. The prevalence of deficits detected by the cancer specific GA was also consistent with reports among older adults with varied cancer types with a substantial proportion demonstrating impairments in physical function, emotional health and high levels of comorbidity [9, 11, 12, 33, 34]. Importantly, increasing numbers of studies using a variety of approaches to assess frailty and geriatric assessment domains have consistently reported associations between vulnerabilities

detected and chemotherapy toxicity among older adults with varied cancer diagnoses [9–11, 35–39].

Among studies focused specifically on patients with lung cancer, several have demonstrated an association between vulnerabilities detected on baseline geriatric assessment and prediction of treatment outcomes [40]. A recent systematic review including 18 studies evaluating the role of GA among older adults (median age 76 years) with lung cancer confirmed the use of GA to detect a high prevalence of impairments despite good oncology performance status [40]. Among studies evaluating the following domains, the median percent impaired in instrumental activities of daily living, cognitive function, and mood were 70%, 29% and 31% respectively. Impaired objectively measured physical function and nutritional status were consistently associated with mortality [40]. The influence of GA vulnerabilities on toxicity was variable. Two of five studies identified IADL impairment and depression as factors associated with toxicity. Assessment strategies used were variable with most studies evaluating domains independently rather than assessing cumulative deficit burden, frailty index or a risk score approach. A randomized trial using GA for treatment allocation among older patients showed decreased toxicity in the GA-directed treatment arm without a difference in survival supporting the value of GA in decision-making in this context [15, 41, 42]. One study specifically evaluated the role of the Cancer and Aging Research Group GA toxicity risk score (also used in this analysis) to predict chemotherapy toxicity among adults ≥65 years with lung cancer of any stage treated with varied chemotherapy regimens [14]. Similar to our results, patients with a CARG score ≥ 7 experienced greater grade 3–5 toxicity (60%) versus those with score 3–6 (40%) or 0–2 (9%). Our study extends these observations by removing confounders of stage and varied treatment received and investigates the utility of phenotypic frailty assessment which is age agnostic.

A unique contribution of this study is the evaluation of frailty assessment among patients regardless of chronologic age. A key premise in the field of geriatric oncology is the need to identify strategies to characterize physiologic age rather than relying on chronologic age as a surrogate to optimally predict treatment tolerance. Many older adults may be resilient to the stress of therapies while a proportion of “younger” patients may be vulnerable due to competing comorbidities or functional impairments. To date, most studies evaluating frailty assessment among adult oncology patients have focused on adults of older chronologic age (typically >65 or 70 years) [30, 35]. However, it is clear from the pediatric oncology literature that measurement of the frailty phenotype has utility among young adult cancer survivors [43–45]. Similarly, here we demonstrate that the concept of frailty phenotype assessment can extend beyond age limits and may be a useful strategy to refine estimation of treatment tolerance among lung cancer patients.

In addition to providing evidence that supports risk prediction based on the Fried Frailty Index and the GA toxicity risk score our analysis also identifies specific vulnerabilities which are prevalent among NSCLC patients prior to initiation of chemotherapy. The most prevalent vulnerabilities included depressed mood and impaired physical function as seen in other studies [46, 47]. Each may provide an opportunity for design of interventions to

improve both QOL during and after treatment as well as potentially improving treatment tolerance during therapy [48–52].

In this study we did not see an association between the frailty phenotype, GA measures or the GA toxicity risk score and overall survival. One explanation for this finding is that our study was not powered for survival. Another explanation may be that factors which increase treatment toxicity risk may not necessarily influence survival in this patient population [53]. For example, hematologic toxicities are common but may not represent a primary mechanism which contributes to increased mortality risk for advanced lung cancer patients whose survival is driven primarily by their disease. In fact, some observations have shown a relationship between increased hematologic toxicity and improved mortality [54, 55]. Overall, research evaluating the predictive utility of impairments in geriatric domains show that the predictive utility of varied tools depends on outcomes studied; not all tools predict the same outcomes [56]. In particular, models used to develop toxicity risk scores may not be calibrated to optimize prediction of survival. For example, the GA toxicity risk score used in this analysis has not yet been shown to predict survival in older cancer patients, this work is ongoing. This hypothesis is relevant in consideration of trial design and for decision-making in practice as it is important to consider that the implications of specific vulnerabilities, and the assessment strategies used to capture them, may differ by outcome and may be disease and treatment specific.

This study has several limitations. The study sample size was small limiting power to detect modest relationships between assessed characteristics and toxicity and survival. The small sample size also creates a significant risk of overfitting given the number of variables to outcomes in multivariate models. The study was also limited in scope and assessed toxicity endpoints only during the first 2 cycles of therapy. As a result, longer term cumulative toxicity could not be assessed. Data specific to doublet chemotherapy regimens cannot necessarily be extrapolated to modern regimens that now include use of maintenance chemotherapy and early use of check point inhibitors with or without chemotherapy. However, many patients will continue to receive cytotoxic chemotherapy as part of their care paradigm. Additional larger studies will need to be conducted utilizing newer regimens, especially in subsets of patients that have targeted driver mutations or PDL-1 first line options. Despite this, our finding that frailty assessment may be useful among patients younger than age 65 years in the lung cancer setting remains relevant as an important concept to further evaluate regardless of specific cytotoxic regimen utilized. Finally, translation of the FFI into clinic warrants additional supportive research to validate its utility as well as testing of strategies to integrate the assessment components into the clinic flow. Future research may also help determine if components such as gait speed assessment may be useful as a screening tool for frailty; a similar approach has been promoted by the European Medicines Agency [57].

In conclusion, our data highlight the potential utility of frailty assessment for patients with advanced stage lung cancer to inform treatment planning and supportive care and provide proof of concept to support the study of these assessments in non-geriatric populations. Future studies are needed to validate these findings and evaluate the role of frailty assessment within the changing landscape of treatment options for NSCLC patients.

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**Table 1**

Baseline characteristics of study cohort ($N = 48$).

| | **Mean ± SD or %** |
|---|---|
| *Demographics* | |
| Age (yrs) | |
| Mean | 68.5 ± 9.5 |
| <65 years | 37.5 |
| 65–74 years | 35.4 |
| ≥75 years | 27.1 |
| Gender (male) | 79.2 |
| Race (non-Hispanic white) | 81.2 |
| Married | 64.6 |
| Education Level | |
| <High school | 43.7 |
| High school | 18.8 |
| >High school | 37.5 |
| Living alone | 16.7 |
| Employed | 12.5 |
| *Clinical* | |
| Histologic subtype | |
| Adenocarcinoma | 45.8 |
| Squamous | 33.3 |
| Mixed | 2.1 |
| Large cell | 2.1 |
| Poorly differentiated | 8.3 |
| Unspecified | 8.3 |
| Hemoglobin (g/dl) | 13.1 ± 1.6 |
| Creatinine clearance | 72.6 ± 22.7 |
| Body mass index ($kg/m^2$) | 26.0 ± 5.2 |
| Body Surface Area ($m^2$) | 1.9 ± 0.3 |
| Karnofsky Performance Status (KPS) ≥ 80 | 85.4 |
| Smoking status | |
| Current | 22.9 |
| Former | 75.0 |
| Never | 2.1 |

## Table 2

Frailty and geriatric assessment measures ($N = 48$[a]).

| | Mean ± SD | % impaired |
|---|---|---|
| Fried Frailty Index (FFI) | 1.8 ± 1.2 | 27.1 |
| Weight loss >10 pounds in past year | | 47.9 |
| Self-reported exhaustion | | 36.2 |
| Low self-reported physical activity | | 45.8 |
| Slow gait speed | | 21.7 |
| Low grip strength | | 31.3 |
| Frailty score | | |
| 0 | | 15.6 |
| 1 | | 24.4 |
| 2 | | 33.3 |
| 3 | | 17.8 |
| 4 | | 8.9 |
| Geriatric assessment (GA) | | |
| MOS physical (<75 indicates impairment) | 66.0 ± 25.7 | 54 |
| Impairment in IADL (<14 indicates impairment) | 13.2 ± 1.6 | 31.3 |
| KPS physician rated (<80 indicates impairment) | 82.1 ± 9.2 | 14.6 |
| KPS patient rated (<80 indicates impairment) | 83.8 ± 11.9 | 19.2 |
| Timed up and go | 11.4 ± 3.1 | 50 |
| Falls in past 6 months (≥1 fall indicates impairment) | 0.38 ± 1.3 | 14.6 |
| Comorbidity (Physical Health Subscale, >3 indicates impairment) | 2.4 ± 1.7 | 27.1 |
| Cognition (Blessed Orientation Memory Concentration Test, ≥11indicates impairment) | 3.6 ± 5.0 | 6.3 |
| CES-D≥16 | 15.1 ± 9.0 | 38.3 |
| MOS Social Activity Limitations | 52.8 ± 19.6 | N/A |
| MOS Social Support Survey | 88.9 ± 15.2 | N/A |
| Self-reported weight loss | 5.5 ± 6.9 | 54.2 |
| GA toxicity risk score | | |
| Age ≥ 72 | 7.3 ± 2.3 | 35.4 |
| Hemoglobin | | 8.3 |
| Creatinine clearance | | 4.2 |
| Hearing impairment | | 31.3 |
| Falls in past 6 months | | 14.6 |
| Assistance with medications | | 6.3 |
| Limitation in walking 1 block | | 31.3 |
| Decreased social activity | | 41.7 |

Legend: MOS = Medical Outcomes Survey; IADL = Instrumental Activities in Daily Living; KPS = Karnofsky Performance Score; CES-D = Center for Epidemiological Studies-Depression; CARG = Cancer and Aging Research Group; GA = geriatric assessment.

[a]All measures were obtained in 48 subjects except for the following due to missing data: FFI index = 45; self reported exhaustion $N = 47$; gait speed $N = 46$; Frailty Score $N = 45$; KPS patient rated $N = 47$, Time up and go $N = 46$; CES-D $N = 47$; MOS Social Activity $N = 47$; Self-reported weight loss $N = 47$.

## Table 3

Treatment-related adverse events in first two cycles of chemotherapy in patients with advanced non-small cell lung cancer.

| Adverse events | Incidence (%) | | | |
|---|---|---|---|---|
| | Grade 3–5 | Grade 3 | Grade 4 | Grade 5 |
| Cycle 1 (*N* = 48) | | | | |
| Any toxicity | 52 | 40 | 10 | 2 |
| *Any Hematologic* | 35 | 29 | 6 | 0 |
| Neutropenia | 27 | 21 | 6 | 0 |
| Infection with neutropenia | 4 | 4 | 0 | 0 |
| Anemia | 4 | 4 | 0 | 0 |
| Thrombocytopenia | 4 | 4 | 0 | 0 |
| *Any Non-Hematologic* | 21 | 15 | 4 | 2 |
| Fatigue | 4 | 4 | 0 | 0 |
| Arthralgia | 4 | 2 | 2 | 0 |
| Hyperglycemia | 4 | 4 | 0 | 0 |
| Infusion reaction | 2 | 2 | 0 | 0 |
| Neuropathy | 2 | 2 | 0 | 0 |
| Hyponatremia | 2 | 2 | 0 | 0 |
| Cardiac Ischemia | 2 | 0 | 2 | 0 |
| Death not otherwise specified | 2 | 0 | 0 | 2 |
| Cycle 2 (*N* = 42) | | | | |
| Any toxicity | 40 | 31 | 10 | 0 |
| *Any Hematologic* | 33 | 24 | 10 | 0 |
| Neutropenia | 31 | 21 | 10 | 0 |
| Infection with neutropenia | 2 | 2 | 0 | 0 |
| Thrombocytopenia | 5 | 5 | 0 | 0 |
| *Any Non-Hematologic* | 12 | 12 | 0 | 0 |
| Fatigue | 5 | 5 | 0 | 0 |
| Neuropathy | 5 | 5 | 0 | 0 |
| Hyponatremia | 5 | 5 | 0 | 0 |
| Hypophosphatemia | 5 | 5 | 0 | 0 |
| Rash | 2 | 2 | 0 | 0 |
| Hyperglycemia | 2 | 2 | 0 | 0 |
| Dyspnea | 2 | 2 | 0 | 0 |
| Hypotension | 2 | 2 | 0 | 0 |

## Table 4

Multivariate models evaluating the association between patient characteristics and treatment-related grade 3–5 toxicity during first cycle chemotherapy.

| Predictor variable | Odds ratio (OR) | 95% confidence interval (CI) |
|---|---|---|
| *Model 1(AIC = 55.1, c = 0.84)* | | |
| Frail (FFI ≥ 3) | 7.03 | 1.11–44.55 |
| Age (per year) | 1.14 | 1.03–1.27 |
| BSA (per SD) | 3.87 | 1.49–10.07 |
| Comorbidty score (per unit) | 1.48 | 0.93–2.36 |
| *Model 2 (AIC = 62.9, c = 0.77)* | | |
| GA toxicity risk score (>7) | 4.26 | 1.03–17.65 |
| Comorbidity Score (per unit) | 1.53 | 1.01–2.32 |
| BSA (per SD) | 2.25 | 1.13–4.47 |
| *Model 3 (AIC = 60.1, c = 0.81)* | | |
| Frail (FFI ≥ 3) | 5.82 | 1.06–31.81 |
| GA toxicity risk score > 7 | 3.75 | 0.85–16.53 |
| Comorbidity Score (per unit) | 1.57 | 1.01–2.45 |
| BSA (per SD) | 2.52 | 1.21–5.28 |

Legend: FFI=Fried Frailty Index; BSA = body surface area; SD = standard deviation; GA = geriatric assessment, c = c-statistic.

## Table 5

Univariate associations between baseline characteristics and mortality.

| Characteristic | Hazard ratio | Lower CI | Upper CI | *p*-Value |
|---|---|---|---|---|
| Age (per year) | 1.0 | 0.96 | 1.02 | 0.50 |
| Gender (male) | 2.1 | 0.92 | 4.73 | 0.08 |
| Race (non-hispanic white) | 0.95 | 0.44 | 2.06 | 0.89 |
| Married (yes) | 0.74 | 0.39 | 1.40 | 0.36 |
| Education level | | | | 0.09 |
| <High school | 0.43 | 0.18 | 1.0 | |
| High school | 1.00 | | | |
| >High school | 0.79 | 0.34 | 1.83 | |
| Living alone | 1.3 | 0.57 | 2.94 | 0.53 |
| Employed | 1.4 | 0.58 | 3.3 | 0.46 |
| *Clinical* | | | | |
| Histologic subtype | | | | 0.82 |
| Adenocarcinoma | 0.88 | 0.44 | 1.79 | |
| Squamous | 1.00 | | | |
| Other | 1.13 | 0.48 | 2.65 | |
| Hemoglobin (per unit increase) | 1.17 | 0.97 | 1.42 | 0.10 |
| Body mass index | | | | 0.09 |
| <25 $kg/m^2$ | 2.31 | 0.94 | 5.68 | |
| 25-<30 $kg/m^2$ | 2.73 | 1.11 | 6.72 | |
| ≥30 $kg/m^2$ | 1.00 | | | |
| Body surface area (per unit increase) | 0.88 | 0.24 | 3.16 | 0.85 |
| Smoking status | | | | 0.23 |
| Current | 0.32 | 0.04 | 2.66 | |
| Former | 0.22 | 0.03 | 1.73 | |
| Never | 1.0 | | | |
| Fried Frailty Index (FFI) ≥ 3 | 1.03 | 0.51 | 2.11 | 0.93 |
| Weight loss >10 pounds in past year | 1.27 | 0.68 | 2.36 | 0.45 |
| Self-reported exhaustion | 1.0 | 0.51 | 1.94 | 0.99 |
| Low self-reported physical activity | 2.01 | 1.08 | 3.74 | 0.03 |
| Slow gait speed | 0.86 | 0.41 | 1.83 | 0.70 |
| Low grip strength | 0.69 | 0.34 | 1.38 | 0.29 |
| Geriatric assessment (GA) | | | | |
| MOS physical (<75) | 1.19 | 0.64 | 2.19 | 0.60 |
| Impairment in IADL (<14) | 0.93 | 0.47 | 1.82 | 0.82 |
| KPS physician rated (<80) | 2.78 | 1.17 | 6.63 | 0.02 |
| KPS patient rated (<80) | 1.45 | 0.69 | 3.05 | 0.33 |
| Timed up and go (>11) | 0.69 | 0.36 | 1.30 | 0.25 |
| Comorbidity (Physical Health Subscale >3) | 1.04 | 0.52 | 2.08 | 0.91 |
| Blessed Orientation Memory | 1.18 | 0.36 | 3.84 | 0.79 |

| Characteristic | Hazard ratio | Lower CI | Upper CI | *p*-Value |
|---|---|---|---|---|
| Concentration Test ≥11 | | | | |
| CES-D ≥ 16 | 0.66 | 0.34 | 1.29 | 0.22 |
| MOS social activity limitations | 1.0 | 0.99 | 1.02 | 0.78 |
| MOS social support survey | 0.99 | 0.97 | 1.01 | 0.54 |
| Self-reported weight loss | 1.34 | 0.72 | 2.53 | 0.35 |
| GA toxicity risk score > 7 | 0.95 | 0.51 | 1.76 | 0.86 |
| Age ≥ 72 | 0.62 | 0.32 | 1.22 | 0.17 |
| Hemoglobin | 0.63 | 0.20 | 2.05 | 0.44 |
| Creatinine clearance (lower) | 4.94 | 1.11 | 22.03 | 0.04 |
| Hearing impairment | 0.84 | 0.43 | 1.66 | 0.062 |
| Falls in past 6 months | 1.93 | 0.83 | 4.49 | 0.13 |
| Assistance with medications | 1.32 | 0.40 | 4.35 | 0.65 |
| Limitation in walking 1 block | 0.91 | 0.46 | 1.78 | 0.77 |
| Decreased social activity | 0.83 | 0.44 | 1.55 | 0.55 |

Legend: MOS = Medical Outcomes Survey; IADL = Instrumental Activities in Daily Living; KPS = Karnofsky Performance Score; CES-D = Center for Epidemiological Studies-Depression; CARG = Cancer and Aging Research Group; GA = geriatric assessment.