

Lower Pectoralis Muscle Area Is Associated with a Worse Overall Survival in Non-Small Cell Lung Cancer

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Abstract

Background: Muscle wasting is a component of the diagnosis of cancer cachexia and has been associated with poor prognosis. However, recommended tools to measure sarcopenia are limited by poor sensitivity or the need to perform additional scans. We hypothesized that pectoralis muscle area (PMA) measured objectively on chest CT scan may be associated with overall survival (OS) in non-small cell lung cancer (NSCLC).

Methods: We evaluated 252 cases from a prospectively enrolling lung cancer cohort. Eligible cases had CT scans performed prior to the initiation of surgery, radiation, or chemotherapy. PMA was measured in a semi-automated fashion while blinded to characteristics of the tumor, lung, and patient outcomes.

Results: Men had a significantly greater PMA than women (37.59 vs. 26.19 cm², $P < 0.0001$). In univariate analysis, PMA was associated with age and body mass index (BMI). A Cox

proportional hazards model was constructed to account for confounders associated with survival. Lower pectoralis area (per cm²) at diagnosis was associated with an increased hazard of death of 2% (HR_{adj} 0.98; confidence interval, 0.96–0.99; $P = 0.044$) while adjusting for age, sex, smoking, chronic bronchitis, emphysema, histology, stage, chemotherapy, radiation, surgery, BMI, and ECOG performance status.

Conclusions: Lower PMA measured from chest CT scans obtained at the time of diagnosis of NSCLC is associated with a worse OS.

Impact: PMA may be a valuable CT biomarker for sarcopenia-associated lung cancer survival. *Cancer Epidemiol Biomarkers Prev*; 26(1); 38–43. ©2016 AACR.

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Introduction

Cancer cachexia has long been recognized as a consequence of malignancy and in lung cancer is associated with decreased physical performance, inability to tolerate therapy, and an overall poor prognosis (1–4). International consortia have thus identified early recognition of cancer cachexia as a critical goal, calling for interventions to be targeted early in the process rather than when end-stage wasting occurs (5).

Cachexia is defined by international consensus as weight loss greater than 5% or weight loss greater than 2% in individuals already showing depletion according to body mass index (BMI) or sarcopenia (6). Thus, accurately measuring muscle loss associated with sarcopenia may dramatically improve early detection of cachexia. Importantly, there is evidence that sarcopenia is asso-

ciated with a poorer overall prognosis for a number of cancers (7–9). Current recommendations for measurement of sarcopenia include anthropometric measurement of body dimensions (e.g., mid-upper arm), dual energy X-ray absorptance (DXA), bioimpedance studies, or abdominal CT scan (6, 10). However, these measurements all have limitations, particularly when applied to patients with lung cancers. Anthropometric measurements of skin fold thickness and body circumference overestimate muscularity by 15% to 25% compared with abdominal CT and are associated with high within-subject error (11). Bioimpedance is only considered valid in patients with "grossly altered body composition," limiting its utility for early detection of cachexia (6), whereas DXA and abdominal CT scanning are not routinely performed for evaluation and follow-up of patients with lung cancer.

Patients with chronic obstructive pulmonary disease (COPD), in the absence of cancer, are also plagued by cachexia (12). Pectoralis muscle area (PMA), measured from CT scans of the chest, has been demonstrated to correlate with bioimpedance measures of fat-free mass, as well as with lung function, symptoms, and exercise capacity (13). Importantly, PMA is a better predictor of these outcomes than BMI, implying that PMA may be an independent measure of muscularity. We hypothesized that PMA, a novel marker of sarcopenia, may be associated with overall survival (OS) for patients with non-small cell lung cancer (NSCLC).

Materials and Methods

Patients

This study was approved by the Partners Human Research Committee (1999-P-004935/118). Details of enrollment and

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follow-up of this cohort have been described previously (14–16). Briefly, patients (>18 years old) with pathologically confirmed, newly diagnosed NSCLC were consecutively recruited and followed at Massachusetts General Hospital (Boston, MA) between 2002 and 2006. This time period was selected to have adequate follow-up time for analysis of OS. More than 85% of eligible patients were enrolled. Detailed demographic, past medical history, and exposure history were collected via a dedicated questionnaire, as described previously (17–19). This questionnaire included questions that asked the subject whether they had ever been diagnosed, by a physician, with either chronic bronchitis or emphysema (the two components of COPD).

CT scans

Included cases had to have a chest CT scan with intravenous contrast performed prior to initiation of surgery, radiation, or chemotherapy, and within three months of enrollment in the study. All CT scans were acquired with GE scanners (GE Healthcare) at either a 2.5- or 5-mm slice thickness and constructed using the "Standard Body" kernel. All CT scans were performed with the arms in the adducted position. Measurement of pectoralis area was performed using 3D Slicer (www.slicer.org; refs. 14, 20–23). Quantitative assessment of pectoralis muscle was performed on a single axial slice of the CT scan above the aortic arch by a single reader (C.M. Kinsey). This reader was trained by the senior author (G.R. Washko), who has extensive experience with this methodology (13, 24). The reader demonstrated an intrareader variability of 0.97 (concordance correlation coefficient) in this cohort. The slice used for evaluation was selected by scrolling toward the apex of the lungs and identifying the first axial image above the arch. The ability of a reader to select this slice across large cohorts, and among different cohorts, has previously been demonstrated, and the subsequent measurement of PMA using this slice was shown to have low interreader variability (13, 24). The borders of the pectoralis muscles were then identified objectively using the predefined attenuation thresholds of –50 to 90 Hounsfield units (Fig. 1). Using these predefined thresholds limited potential bias when identifying the borders of the muscles. These measures were

performed for each subject and pectoralis muscle area (cm^2) presented as the aggregate of right and left pectoralis major and minor muscles.

Statistical analysis

All statistical analyses were performed using STATA (version 12). $P \leq 0.05$ was considered significant, and all statistical tests were two sided. Student *t* test was used to compare normally distributed data between categories. ANOVA was used to evaluate differences in continuous variable among more than two categories. Simple linear regression was used to evaluate the relationship between two continuous variables. OS time was computed as the number of days from study entry until death from any cause. Patients still alive were censored at the most recent follow-up date.

Initial survival analysis was performed by dichotomizing PMA at the 50th percentile and creating Kaplan–Meier survival curves. Given the known dramatic differences in PMA between men and women, these curves were stratified by gender (24). For time-to-event analyses, the results of the Wilcoxon (Breslow) test for equality of the survivor function were performed to minimize the effect of the small risk sets in the tails of the survival distributions. The stratified version of this test was used to evaluate for statistical significance among the strata of gender and histology (adenocarcinoma vs. other).

Two different Cox proportional hazards models were created to account for confounders associated with survival. We included PMA as a continuous predictor in each model. For categorical predictors, we used Wald tests to evaluate the overall association between the predictor and survival. The "full" model included all predictors listed in Table 1. The "reduced" model included only those predictors having $P \leq 0.1$. The proportional hazards assumption was tested via the nonzero slope method of Grambsch and Therneau (25).

Results

During the time period noted, 304 cases were enrolled in the study. A total of 260 had CT scans available for evaluation. In eight

Figure 1.

Axial CT images demonstrating measurement of PMA. The areas shaded in yellow are the pectoralis major, whereas the areas in brown are the pectoralis minor. PMA is the sum of the yellow and brown areas. The inset demonstrates the utility of using *a priori* Hounsfield unit thresholds to define the borders of the pectoralis muscles. This approach allows the border of the muscles to be determined in an unbiased and accurate manner.

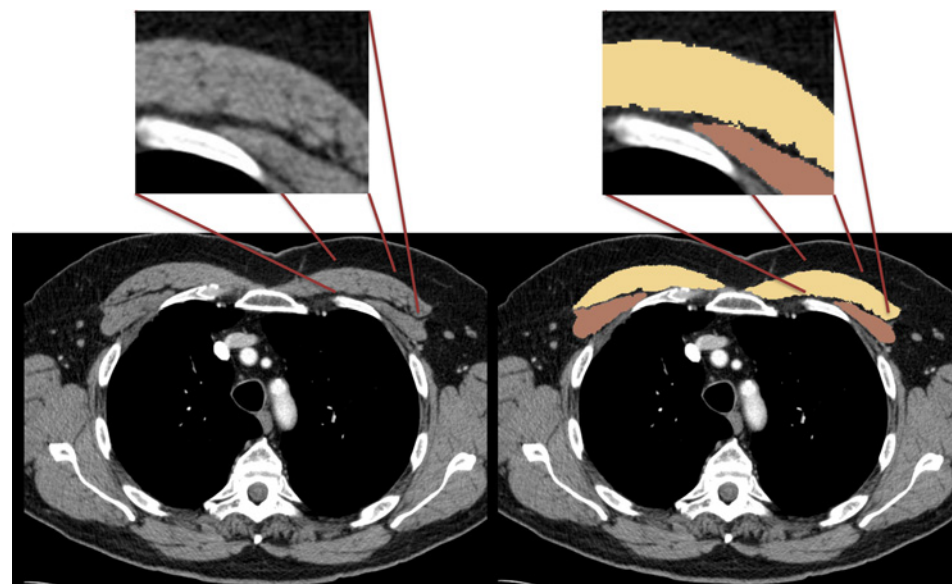


Table 1. Characteristics of the cohort

| | | |
|----------------------------------|--------------|-----|
| Age (y) ^a : | 66.2 (±10.9) | 252 |
| Sex: <i>n</i> (%) | | |
| Female | 135 (53.6) | |
| Male | 117 (46.4) | 252 |
| Smoking: <i>n</i> (%) | | |
| Never | 29 (11.5) | |
| Former | 139 (55.2) | |
| Current | 84 (33.3) | 252 |
| Chronic bronchitis: <i>n</i> (%) | 31 (12.6) | 245 |
| Emphysema: <i>n</i> (%) | 41 (16.7) | 245 |
| BMI ^a : | 26.4 (±4.9) | 237 |
| ECOG performance: <i>n</i> (%) | | |
| Status 0-2 | 240 (96.5) | |
| Status 3-4 | 9 (3.5) | 249 |
| Histology: <i>n</i> (%) | | |
| Adenocarcinoma | 136 (53.9) | |
| Squamous cell | 33 (13.1) | |
| Large cell | 17 (6.8) | |
| NSCLC (NOS/mixed) | 66 (26.2) | 252 |
| Stage: <i>n</i> (%) | | |
| I | 48 (19.1) | |
| II | 10 (4.0) | |
| III | 69 (27.4) | |
| IV | 124 (49.5) | 252 |
| Therapy: | | |
| Surgery: <i>n</i> (%) | 105 (41.7) | 252 |
| Chemotherapy: <i>n</i> (%) | 191 (75.8) | 252 |
| Radiation: <i>n</i> (%) | 76 (30.2) | 252 |

Abbreviation: NOS, not otherwise specified.

^aMean ± SD presented.

cases, the CT scan was unreadable for PMA. A total of 252 cases were included in the main analysis. The demographics and characteristics of the cohort are shown in Table 1. Data on BMI

were available for 237 (94%) cases and on Eastern Cooperative Oncology (ECOG) performance score for 249 (99%) cases. There were no significant differences in demographic data between those with CT scans that were available versus those without CT data. A total of 191 individuals (75%) received chemotherapy and 105 (41%) underwent surgery. Of the 76 (30%) patients who received radiotherapy, only one was stage I.

PMA was significantly larger for men than for women (37.6 vs. 26.2 cm², *P* < 0.0001). Notably, the SD of PMA for men was much larger than for women (10.9 vs. 7.2). Associations of PMA with demographic variables are listed in Table 2. Lower PMA was associated with increased age and lower BMI.

The median follow-up time for the cohort was 2,412 days (range: 63 to 3,373 days). Figure 2 shows the Kaplan–Meier analysis of OS according to gender. As demonstrated in the survival curves in Fig. 2, PMA < 50th percentile was associated with a possible trend toward worse OS for both men and women, although this was not statistically significant (Fig. 2A and B). When limited to the most common histology of adenocarcinoma, the association of PMA < 50th percentile with a worse OS was stronger in each analysis (Fig. 2C and D), reaching statistical significance independently for the strata of women (*P* = 0.039).

To account for possible confounders of the relationship between PMA and NSCLC survival, we performed a regression analysis using the Cox proportional hazards model. The "full" model included PMA and all variables included in Table 1. Lower PMA (per cm²) at diagnosis was associated with a 2% increase in the HR for death while adjusting for age, sex, smoking, chronic bronchitis, emphysema, histology, stage, radiation, chemotherapy, surgery, BMI, and ECOG performance score [HR_{adj}, 0.98; confidence interval (CI), 0.96–0.99; *P* = 0.044;

Table 2. Relationship of PMA and demographic variables

| | Women | | Men | |
|------------------------|------------------------|----------|------------------------|----------|
| | PMA (cm ²) | <i>P</i> | PMA (cm ²) | <i>P</i> |
| Total: | 26.2 (±7.9) | | 37 (±10.2) | |
| Age: (change per year) | −0.235 | 0.047 | −0.321 | 0.001 |
| Smoking | | | | |
| Never | 27.3 (±7.3) | | 39.1 (±13.1) | |
| Former | 26.3 (±7.8) | | 36.9 (±9.4) | |
| Current | 25.5 (±8.3) | 0.707 | 38.5 (±10.8) | 0.651 |
| Chronic bronchitis | | | | |
| No | 25.9 (±8.1) | | 31.5 (±10.9) | |
| Yes | 27.8 (±8.0) | 0.334 | 31.9 (±9.8) | 0.731 |
| Emphysema | | | | |
| No | 26.7 (±8.2) | | 31.8 (±10.9) | |
| Yes | 22.7 (±5.8) | 0.050 | 30.4 (10.1) | 0.416 |
| Histology: | | | | |
| Adenocarcinoma | 26.3 (±7.3) | | 39.1 (±11.3) | |
| Squamous cell | 24.9 (±6.1) | | 36.2 (±7.6) | |
| Large cell | 26.6 (±12.7) | | 32.1 (±10.2) | |
| NSCLC (NOS/mixed) | 26.1 (±8.0) | 0.955 | 36.1 (±8.6) | 0.243 |
| Stage | | | | |
| I | 26.0 (±6.6) | | 34.2 (±8.4) | |
| II | 26.7 (±8.0) | | 39.9 (±10.5) | |
| III | 27.3 (±7.2) | | 39.3 (±7.0) | |
| IV | 25.6 (±8.9) | 0.788 | 37.7 (±11.8) | 0.341 |
| ECOG performance | | | | |
| Status 0-2 | 26.2 (±7.9) | | 37.7 (±10.0) | |
| Status 3-4 | 27.0 (±9.2) | 0.811 | 38.1 (±15.2) | 0.927 |
| BMI (change per unit) | 0.603 | <0.000 | 0.874 | <0.001 |

NOTE: All data presented as mean ± SD with the exception of age and BMI.

Abbreviation: NOS, not otherwise specified.

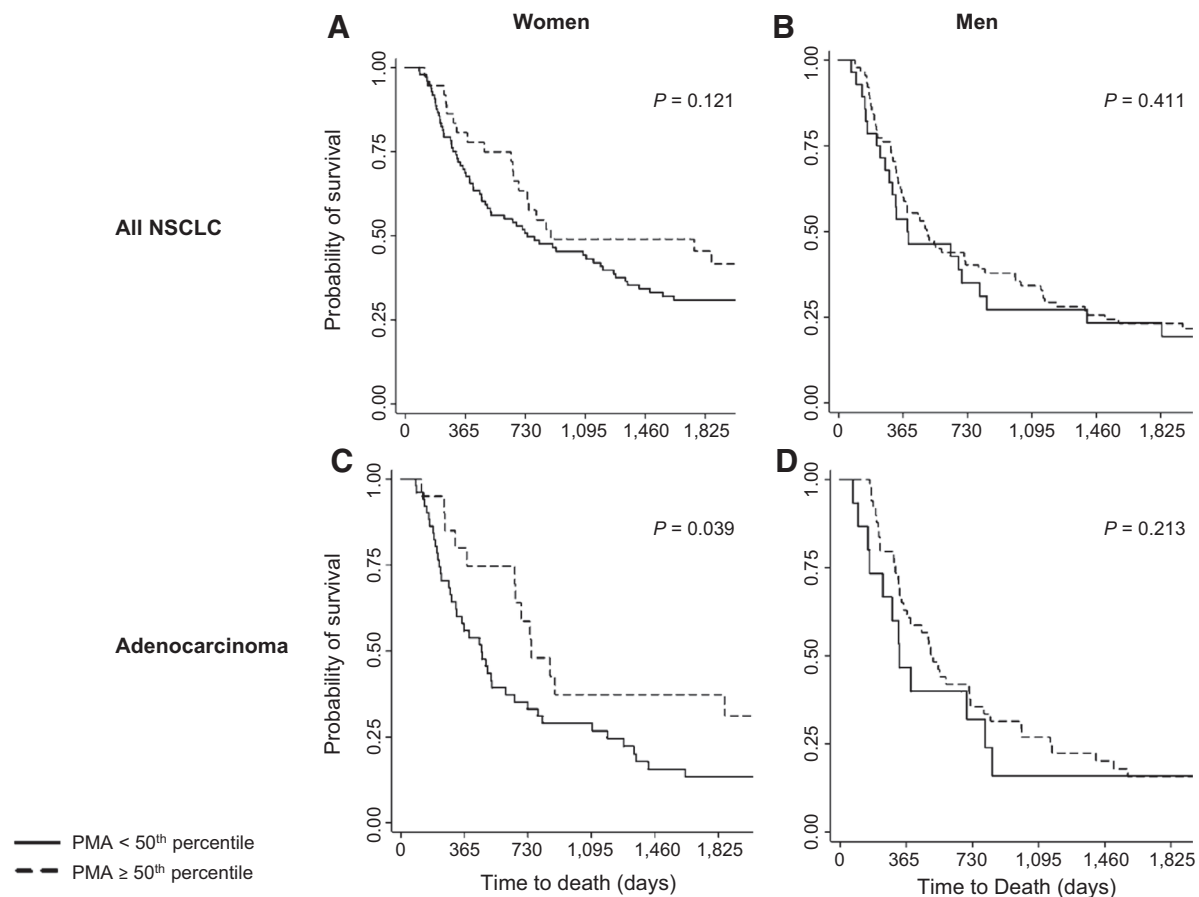


Figure 2.

Kaplan-Meier estimates of OS by dichotomized PMA among different strata within the cohort. Curves were generated for all NSCLC cases among women (A) and men (B). Panels C (women) and D (men) demonstrate survival curves in patients with adenocarcinoma histology (representing more than half of all cases).

Table 3]. A test of the proportional hazards assumption found no evidence that the assumption was violated.

We also performed a backward selection to build a second "reduced" model. This was achieved via inclusion of predictors that met a significance level of less than or equal to 0.10. This reduced model did not result in a significantly different result with regard to PMA (HR_{adj} , 0.97; CI, 0.96–0.99; $P = 0.002$; Table 3). PMA remained a statistically significant predictor of OS while adjusting for sex, histology, stage, surgery, emphysema, and performance status.

Discussion

In this report, lower pectoralis muscle area at diagnosis was associated with a worse OS for patients with NSCLC, despite adjustment for BMI and performance status. Measurement of PMA for determining sarcopenia has several advantages. First, the measurement is straightforward to perform using open-source software (3D Slicer) and reliable. Prior investigations have demonstrated that the slice used to make the measurement is easily identified on CT scans across multiple cohorts (13, 24). The technique for measurement of pectoralis muscle area has also been shown to be highly reproducible (concordance correlation

coefficient: 0.985) between different readers (21, 24). Here, we also used density threshold limits to remove any potential bias when selecting the borders of the muscles.

PMA is readily available from clinically acquired CT scans and does not require specific research protocols. It may be performed from diagnostic or screening studies and potentially could be followed over time given that chest CT scans are commonly obtained to assess treatment response. In contrast, the standard cross-sectional imaging measurement of sarcopenia, lumbar spinal muscle index measured at L3, requires performance of an abdominal CT scan. One of the largest studies that applied this measure to cancers of the respiratory and gastrointestinal tract reported that approximately 25% of patients in the study did not have CT scans that could be used for lumbar skeletal muscle index analysis (7). In contrast, only 3% of CT scans in this cohort were not evaluable for PMA. This is strikingly similar to the number of CT scans not evaluable for PMA reported from the ECLIPSE and COPD gene cohorts (13). In addition, abdominal CT scans are not necessarily performed for evaluation or follow-up of cancers of the respiratory tract, limiting their utility in evaluating all patients with lung cancer for changes in muscularity over time. One limitation of the current study is the inability to compare the chest CT measure

Table 3. Proportional hazards models for risk of death

| | Adjusted estimates | | | |
|--------------------|------------------------|--------|------------------------|--------|
| | Full model | | Reduced model | |
| | HR _{Adj} (CI) | P | HR _{Adj} (CI) | P |
| PMA ^a | 0.98 (0.96–0.99) | 0.044 | 0.97 (0.96–0.99) | 0.002 |
| Age: | 1.01 (0.99–1.03) | 0.297 | | |
| Sex: | | | | |
| Male | 1.65 (1.11–2.46) | 0.014 | 1.80 (1.24–2.63) | 0.002 |
| Female | Ref | | Ref | |
| Smoking | | | | |
| Never | Ref | | | |
| Former | 0.85 (0.49–1.43) | | | |
| Current | 0.84 (0.48–1.44) | 0.797 | | |
| Chronic bronchitis | 1.09 (0.66–1.80) | 0.745 | | |
| Emphysema | 1.51 (0.98–2.33) | 0.064 | 1.51 (0.98–2.19) | 0.070 |
| Histology: | | | | |
| Adenocarcinoma | Ref | | Ref | |
| Squamous cell | 0.82 (0.50–1.36) | | 0.83 (0.50–1.36) | 0.451 |
| Large cell | 0.66 (0.36–1.21) | | 0.64 (0.35–1.17) | 0.147 |
| NSCLC (NOS/mixed) | 0.62 (0.41–0.94) | 0.121 | 0.61 (0.41–0.94) | 0.113 |
| Stage | | | | |
| I | Ref | | Ref | |
| II | 1.72 (0.52–5.65) | | 1.46 (0.45–4.73) | |
| III | 4.05 (1.56–10.5) | | 3.46 (1.36–8.81) | |
| IV | 7.32 (3.07–17.4) | <0.001 | 6.28 (2.69–14.7) | <0.001 |
| Radiation | 1.03 (0.59–1.79) | 0.915 | | |
| Chemotherapy | 0.73 (0.37–1.41) | 0.344 | | |
| Surgery | 0.57 (0.37–0.87) | 0.010 | 0.59 (0.39–0.90) | 0.015 |
| ECOG performance | | | | |
| Status 0–2 | Ref | | Ref | |
| Status 3–4 | 2.01 (0.95–4.25) | 0.070 | 2.15 (1.03–4.446) | 0.101 |
| BMI | 0.98 (0.94–1.02) | 0.262 | | |

NOTE: For chronic bronchitis and emphysema, references are "no chronic bronchitis" and "no emphysema," respectively. For radiation, chemotherapy, and surgery, references are "no radiation," "no chemotherapy," and "no surgery," respectively.

Abbreviation: NOS, not otherwise specified.

^aPer 1 cm² increase in PMA.

of PMA to the lumbar spinal muscle index, due to the rarity with which abdominal CT scans are performed.

PMA may be a sensitive measure of cancer-associated sarcopenia. In COPD, fat-free mass as measured by bioimpedance is highly correlated with PMA (13). Interestingly, bioimpedance is only considered useful in the setting of "grossly altered body composition" in cancer cachexia (6). Measurement of PMA may be more sensitive. In this cohort, we were able to identify differences in survival above and below the 50th percentile of pectoralis muscle area. This is striking as these data were not adjusted for stage, a predictor associated with a very large magnitude of effect on lung cancer survival, and imply consistency of the effect across stages. In contrast, sarcopenia associated with cancer cachexia has traditionally been defined as muscularity less than the 5th percentile (6).

To ensure that PMA was not a measure specifically tied to COPD, we also adjusted for physician-diagnosed chronic bronchitis and emphysema in the proportional hazards model. Adjusting for these covariates was particularly important in this case as COPD (using the identical measures as reported here) has previously been reported to be associated with a worse OS (26). In addition, PMA appeared to have a stronger relationship to survival (in unadjusted analysis) in the strata of those with adenocarcinoma, potentially implying a cancer-specific effect. A known limitation of stratified analysis is the decrease in sample size that limits power to detect differences in the groups. We did not have the statistical power to further assess potential differences by histology in stratified analysis.

Although there was a clear effect among those with adenocarcinoma, adjustment for histology in the proportional hazards model demonstrated that the effect was present across categories of histology and not limited to adenocarcinoma.

This study has several important limitations. Although BMI and performance status correlate with loss of muscle mass, we do not have other direct measures of sarcopenia available from this cohort. Thus, we cannot report frequency of sarcopenia in this cohort. Prospective studies in cancer patients simultaneously using PMA and other established metrics for muscularity will be needed to better define the operating characteristics and establish cutoffs for PMA-determined sarcopenia. We also do not have longitudinal data on BMI and PMA and cannot comment further on how PMA at diagnosis (or over time) may be associated with changes in BMI over time. These data would prove valuable to determine whether change in PMA may be more important than a single measurement at diagnosis and to assess the effect of differing therapies, which may have differential effects on muscle loss. PMA as a predictor of survival may be stronger in women. Men have a larger variance of measured PMA, implying that larger samples sizes may be needed to demonstrate significance within these strata. Regardless, the proportional hazards model suggests that the effect of PMA on survival is present across the strata of both men and women.

Here, we report the first data to demonstrate that lower pectoralis muscle area at diagnosis is associated with a worse OS for NSCLC. This association remains after adjustment for predictors

associated with NSCLC, COPD, ECOG performance status, and BMI.

Disclosure of Potential Conflicts of Interest

G.R Washko is a consultant/advisory board member for GlaxoSmithKline. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C.M. Kinsey, R. San José Estépar, D.C. Christiani, G.R. Washko

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): C.M. Kinsey, B.F. Cole, D.C. Christiani, G.R. Washko
Writing, review, and/or revision of the manuscript: C.M. Kinsey, R. San José Estépar, J. van der Velden, B.F. Cole, D.C. Christiani, G.R. Washko

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.M. Kinsey, D.C. Christiani

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Other (PI of the parent study and population): D.C. Christiani

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BLOOD CANCER DISCOVERY

Lower Pectoralis Muscle Area Is Associated with a Worse Overall Survival in Non–Small Cell Lung Cancer

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