



Role that anorexia and weight loss play in patients with stage IV lung cancer

Juliana Pereira Franceschini¹ , Sergio Jamnik¹ , Ilka Lopes Santoro¹ 

1. Disciplina de Pneumologia, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

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ABSTRACT

Objective: To evaluate the prevalence of anorexia and weight loss at diagnosis (pre-treatment), to identify the factors associated with pre-treatment weight loss, and to determine the prognostic role of anorexia and weight loss in the overall survival of patients with stage IV lung cancer. **Methods:** This was a retrospective observational cohort study. The patients were stratified by the presence/absence of anorexia and of pre-treatment weight loss, which generated a measure composed of four categories, which were the independent variables. **Results:** Among the 552 patients included in the study, anorexia and pre-treatment weight loss were present in 39.1% and 70.1%, respectively. After adjusting for age, male gender, and Karnofsky performance status, we found that anorexia and tumor size were significantly associated with pre-treatment weight loss. In a Cox multivariate analysis, adjusted for age, male gender and low Karnofsky performance status were found to be independent predictors of worse survival, as was concomitance of anorexia and weight loss. **Conclusions:** Anorexia and pre-treatment weight loss appear to be relevant problems in the follow-up of patients with advanced (stage IV) lung cancer. Specific interventions are of crucial importance in individualized treatment plans, even within the context of palliative care.

Keywords: Lung neoplasms; Anorexia; Weight loss; Neoplasms/mortality.

INTRODUCTION

Anorexia, defined as a loss of appetite, is a common symptom in patients with lung cancer, especially in those with advanced disease. Caused by the adverse effects of treatment or by comorbidities related to the evolution of the disease, anorexia is seen in 30-40% of cancer patients, leading to reduced food intake or reduced nutrient absorption and, consequently, to a worsening of quality of life, as well as to increased morbidity and mortality.⁽¹⁻³⁾

Unintentional pre-treatment weight loss, which can be a consequence of anorexia,⁽⁴⁻⁷⁾ is also associated with a worsening of functional capacity and tolerance to treatment.⁽⁸⁻¹⁰⁾ Previous studies have reported that 60% of patients with advanced lung cancer present this sign,⁽¹¹⁾ which makes them more prone to fatigue and pain, as well as worsening their overall quality of life.^(12,13)

The combination of anorexia and weight loss can be present in more than two-thirds of patients with advanced lung cancer. This combination has been linked to decreased effectiveness of treatment modalities, especially chemotherapy, and to an increase in the frequency of side effects of such treatment, including fatigue.⁽¹⁴⁾

Despite the growing number of studies showing the impacts of anorexia and weight loss on the quality of life and survival of patients with lung cancer, these conditions are underdiagnosed and undertreated in

clinical practice because of the scarcity of protocols for diagnosis and effective treatment.^(6,15) In addition, predictive factors for unintentional weight loss in the period preceding the diagnosis of lung cancer are not well described in the literature, nor is the importance of the role that anorexia and weight loss play in the prognosis of lung cancer in Brazil. Therefore, the objectives of the present study were to determine the prevalence of anorexia and pre-treatment weight loss, to identify the factors associated with unintentional pre-treatment weight loss, and to define the role that anorexia and pre-treatment weight loss play in the overall survival of patients with stage IV lung cancer.

METHODS

This was a retrospective, observational nested cohort study involving patients diagnosed with stage IV lung cancer, selected from a structured database of patients with lung cancer within the electronic records of a tertiary referral outpatient clinic in the city of São Paulo, Brazil. The study was approved by the local research ethics committee, and all patients had previously given written informed consent.

The starting date for inclusion of patients in this study was 2 January 2000, and the ending date was 1 October 2017. For the purposes of data analysis, patients were followed until 30 December 2017. Included in the study were patients diagnosed with stage IV lung cancer,

Correspondence to:

Ilka Lopes Santoro. Disciplina de Pneumologia, Universidade Federal de São Paulo, Rua Botucatu, 740, CEP 04023-062, São Paulo, SP, Brasil.
Tel./Fax: 55 11 97143-4396. E-mail: ilkasantoro@gmail.com
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confirmed by histological or cytological analysis or by complete clinical evaluation.

At diagnosis, we assessed the following demographic and clinical variables: age; gender; functional performance, expressed as the Karnofsky performance status; smoking status (never smoker vs. current or former smoker); current weight (measured in kg); pre-cancer weight; and presence of anorexia. We also assessed variables related to the tumor, including the histological type (e.g., adenocarcinoma, squamous cell carcinoma, and small cell carcinoma) and the presence of metastases, based on the 7th edition of the tumor-node-metastasis staging of lung cancer, categorized as intrathoracic metastases (stage M1A) or extrathoracic metastasis (stage M1B).

The instrument used in order to evaluate anorexia and weight loss consisted of the following questions: "Are you eating less because of decreased appetite?"; "What is your usual weight?"; "Have you lost weight recently without trying to do so?"; and, if so, "How much weight have you lost?"

Anorexia was defined above as a loss of appetite or a state of reduced calorie intake, whereas pre-treatment weight loss was defined as the involuntary loss of more than 2.4 kg⁽¹¹⁾ and estimated by the formula *pre-cancer weight minus weight at diagnosis*.

The patients were stratified by the presence/absence of anorexia and of pre-treatment weight loss. The stratification resulted in a four-category variable: no anorexia and no weight loss (the reference category); weight loss and no anorexia; anorexia and no weight loss; and anorexia plus weight loss.

Survival was defined as the time from the histological diagnosis to the final event. The final event was defined as all-cause mortality (date of death) or was censored if the patient was alive at the end of the study (30 December 2017) or at the date of the last contact, for patients who were lost to follow-up.

The *post hoc* calculation was performed to assess the power of the study by means of one-way ANOVA, with the program G*Power, version 3.1 (Heinrich Heine University, Düsseldorf, Germany). Considering the four categories of anorexia and weight loss as independent variables, an effect size of 0.29, and an alpha error of 5%, we obtained a power of 99% (with an estimated variation of 7.043 and an error of variance of 84.098) for identifying differences in survival among the categories with a sample of 552 patients.

Categorical variables are expressed as absolute and relative frequencies, evaluated by either the chi-square test or Fisher's exact test. Continuous variables are expressed as means \pm standard deviations or as medians (interquartile ranges) and were analyzed by one-way ANOVA or the Kruskal-Wallis test and the Jonckheere-Terpstra test (for trend analysis). We performed univariate and multivariate analyses, using logistic regression to explore the associations between pre-treatment weight loss and the following

(continuous, dichotomous, and categorical) variables: age; male gender (reference, female); current or former smoker (reference, never smoker); Karnofsky performance status (as a continuous variable); tumor size (as a continuous variable); the presence of anorexia (reference, no anorexia); stage M1B (reference, stage M1A), and histological type (adenocarcinoma, squamous cell, or small cell—reference, all other types). The univariate and multivariate analyses of independent risk factors for survival were assessed by Cox proportional hazards regression with stepwise selection. The final model was derived from the variables with $p < 0.10$ in the univariate analysis or of clinical relevance for the analysis of survival (age). Survival was analyzed with Kaplan-Meier curves, and the curves were compared by using the log-rank test. The statistical analysis was performed with the IBM SPSS Statistics program, version 19.0 (IBM Corporation, Armonk, NY, USA). For all statistical tests, the level of significance was set at 5%.

Table 1. Characteristics of patients with stage IV lung cancer (N = 552).^a

| Characteristics | Results |
|-------------------------------|----------------|
| Age, years | 65 [56-71.5] |
| Karnofsky performance status | 80 [70-90] |
| Size of tumor, cm | 5 [3.5-7.0] |
| Anorexia | 216 (39.1) |
| Pre-treatment weight loss, kg | 6.7 [0.0-13.1] |
| Gender | |
| Male | 324 (58.7) |
| Female | 228 (41.3) |
| Smoking history | |
| Never smoker | 115 (20.8) |
| Current smoker | 116 (21.0) |
| Former smoker | 321 (58.2) |
| Histological type | |
| Adenocarcinoma | 277 (50.2) |
| Squamous cell | 168 (30.4) |
| Small cell | 44 (8.0) |
| Other | 63 (11.4) |
| Metastatic stage | |
| M1A | 263 (47.6) |
| Lungs | 143 (25.9) |
| Pleura | 118 (21.4) |
| Pericardium | 2 (0.4) |
| M1B | 289 (52.4) |
| Adrenal | 50 (9.1) |
| Brain | 80 (14.5) |
| Liver | 53 (9.6) |
| Bones | 89 (16.1) |
| Other | 17 (3.5) |
| Death | 304 (55.1) |
| Overall survival, months | 6.8 [2.8-13.1] |

M1A: intrathoracic metastases; and M1B: extrathoracic metastases. ^aValues expressed as n (%) or median [interquartile range].

RESULTS

The prevalence of anorexia and unintentional pre-treatment weight loss in 552 patients with stage IV lung cancer was 39.1% and 70.1%, respectively. The median pre-treatment weight loss was 6.7 kg (interquartile range, 0.0-13.1 kg). Although we identified an association between anorexia and pre-treatment weight loss, the correlation coefficient can be considered low (0.305). Table 1 describes this and other variables related to the patients and tumors.

The variables related to the patients, the tumors, and overall survival were compared among the four categories (Table 2). It is of note that the proportion of patients with squamous cell carcinoma was more pronounced in the categories including the presence of pre-treatment weight loss. In addition, survival was shorter in patients with presence of anorexia and pre-treatment weight loss.

The logistic regression analysis of factors associated with pre-treatment weight loss is presented in Table 3. In the univariate analysis, age, male gender, Karnofsky performance status, tumor size, anorexia, and histological type were significant predictors of pre-treatment weight loss. After adjustments for age, male gender, Karnofsky performance status, and histological type, the presence of anorexia and the size of the tumor were significantly associated with pre-treatment weight loss.

Figure 1 shows the Kaplan-Meier survival curves as functions of the concomitant presence of anorexia and pre-treatment weight loss; the presence or absence of anorexia; and the presence or absence of pre-treatment weight loss.

In the univariate analysis of survival, the significant predictors of survival were male gender ($p = 0.034$), Karnofsky performance status ($p < 0.001$), and the concomitant presence of anorexia and weight loss ($p <$

Table 2. Characteristics of patients with stage IV lung cancer according to the combinations (categories) of anorexia and pre-treatment weight loss (N = 552).

| Characteristics | Category | | | | p |
|------------------------------|-----------------------------|-----------------------------|---------------------------|-----------------------------|-----------------------|
| | AN – /WL – n = 138 (25%) | AN – /WL + n = 198 (36%) | AN + /WL – n = 27 (5%) | AN + /WL + n = 189 (34%) | |
| Age, years | 62 [51-72] | 65 [58-72] | 65 [60-70] | 64 [55-72] | ns* |
| Karnofsky performance status | 80 [70-90] | 80 [70-90] | 70 [70-90] | 70 [60-80] | < 0.001 ¹⁵ |
| Size of tumor, cm | 4.5 [2.9-6.4] | 5.2 [4.1-7.0] | 4.0 [3.0-8.2] | 4.2 [3.0-7.0] | ns ¹ |
| Gender | | | | | |
| Male | 73 (53) | 118 (60) | 14 (52) | 119 (63) | ns ¹ |
| Female | 65 (47) | 80 (40) | 13 (48) | 70 (37) | |
| Smoking history | | | | | |
| Never smoker | 30 (22) | 38 (19) | 7 (26) | 40 (21) | ns ¹ |
| Current smoker | 24 (21) | 47 (41) | 8 (30) | 37 (20) | |
| Former smoker | 84 (57) | 113 (40) | 12 (44) | 112 (59) | |
| Histological type | | | | | |
| Adenocarcinoma | 79 (57) | 91 (46) | 7 (26) | 65 (34) | 0,044 [‡] ?? |
| Squamous | 26 (19) | 70 (35) | 17 (56) | 92 (49) | |
| Small cells | 18 (13) | 13 (7) | 2 (7) | 11 (6) | |
| Other | 15 (11) | 24 (12) | 3 (11) | 21 (11) | |
| Metastases | | | | | |
| M1A | | | | | ns ¹ |
| Lungs | 40 (62) | 45 (52) | 8 (62) | 50 (51) | |
| Pleura | 25 (38) | 42 (48) | 5 (38) | 46 (47) | |
| Pericardium | - | - | - | 2 (2) | |
| M1B | | | | | ns ¹ |
| Adrenal | 9 (12) | 17 (15) | 5 (36) | 19 (21) | |
| Brain | 26 (36) | 33 (30) | - | 21 (23) | |
| Liver | 12 (16) | 21 (19) | 3 (21) | 17 (19) | |
| Bones | 19 (26) | 35 (32) | 6 (43) | 29 (32) | |
| Other | 7 (10) | 5 (4) | - | 5 (5) | |
| Mortality | 80 (58) | 96 (48) | 13 (48) | 115 (61) | ns ¹ |
| Overall survival, months | 14.4 [12.4-16.4] | 9.4 [7.1-11.7] | 12.4 [5.5-19.4] | 7.6 [5.9-9.2] | < 0.001 ¹⁵ |

AN–: no anorexia; WL–: no weight loss; WL+: weight loss; AN+: anorexia; ns: not significant; M1A: intrathoracic metastases; and M1B: extrathoracic metastases. ^aValues expressed as n (%) or median [interquartile range]. ^{*}Univariate ANOVA. ¹Kruskal-Wallis test. [‡]Chi-square test. [§]Jonckheere-Terpstra Test.

0.001). In the multivariate analysis, after adjustments for age, male gender, the concomitant presence of anorexia and pre-treatment weight loss, and low Karnofsky performance status were independent predictors of shorter survival (Table 4).

DISCUSSION

The present study investigated the prevalence of anorexia and pre-treatment weight loss, as well as

their impact on prognosis, in patients with advanced lung cancer. We found that anorexia and weight loss at diagnosis were both highly prevalent among patients with stage IV lung cancer. The presence of anorexia and the size of the tumor were considered factors associated with pre-treatment weight loss, whereas being male, presenting concomitant anorexia and weight loss, and presenting a low Karnofsky performance status were independent predictors of mortality. In addition, the

Table 3. Unadjusted and adjusted logistic regression analysis of factors associated with pre-treatment weight loss in patients with stage IV lung cancer.*

| Variables | Univariate analysis | | Multivariate analysis | |
|------------------------------|---------------------|---------|-----------------------|-------|
| | Unadjusted OR | p | Adjusted OR | p |
| Age, years | 1.02 | 0.046 | 1.02 | 0.357 |
| Male gender | 1.42 | 0.063 | 0.95 | 0.873 |
| Current or former smoker | 1.15 | 0.548 | - | - |
| Karnofsky performance status | 0.97 | < 0.001 | 0.98 | 0.167 |
| Size of tumor, cm | 1.12 | 0.077 | 1.14 | 0.049 |
| Anorexia | 4.88 | < 0.001 | 6.09 | 0.001 |
| M1B | 0.91 | 0.980 | - | - |
| Histological type | | < 0.001 | | |
| Other | Ref. | | Ref. | |
| Adenocarcinoma | 0.78 | 0.414 | 0.51 | 0.285 |
| Squamous cell | 1.64 | 0.147 | 0.63 | 0.494 |
| Small cell | 0.48 | 0.075 | 0.36 | 0.222 |

Ref.: reference variable; and M1B: extrathoracic metastases. * $-2 \log$ likelihood of 197,380; overall accuracy of the model = 71.2%.

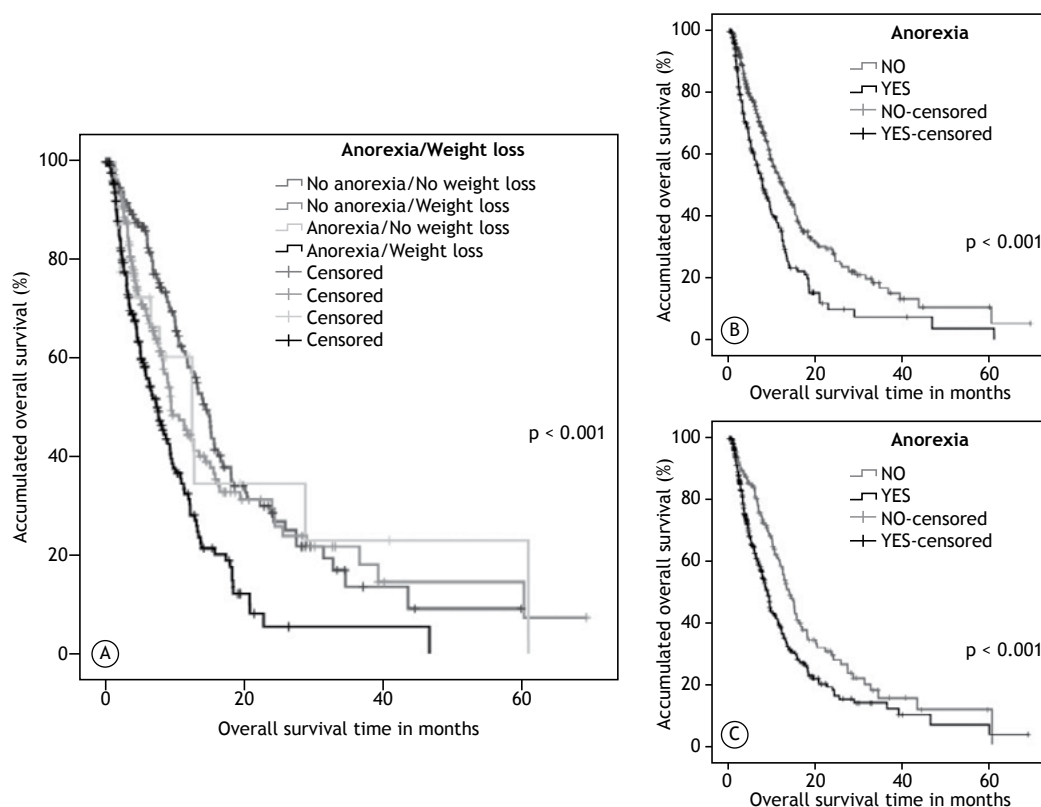


Figure 1. Overall survival in patients with stage IV lung cancer by category of anorexia and weight loss in concomitance (in A), presence or absence of pre-treatment anorexia (in B), and presence/absence of pre-treatment weight loss (in C).

Table 4. Unadjusted and adjusted Cox proportional hazards regression analysis of overall mortality in patients with stage IV lung cancer.*

| Variables | Univariate analysis | | Multivariate analysis | |
|------------------------------|---------------------|---------|-----------------------|---------|
| | Unadjusted HR | p | Adjusted HR | p |
| Age, years | 1.00 | 0.990 | 0.99 | 0.288 |
| Male | 1.28 | 0.034 | 1.31 | 0.021 |
| Karnofsky performance status | 0.97 | < 0.001 | 0.97 | < 0.001 |
| Size of tumor, cm | 0.99 | 0.743 | - | - |
| Anorexia/weight loss | | < 0.001 | | |
| AN-/WL- | Ref. | | Ref. | |
| AN-/WL+ | 1.22 | 0.185 | 1.11 | 0.510 |
| AN+/WL- | 1.09 | 0.767 | 1.12 | 0.700 |
| AN+/WL+ | 2.08 | < 0.001 | 1.90 | < 0.001 |
| M1B | 1.09 | 0.460 | - | - |
| Histological type | | 0.380 | | |
| Other | Ref. | | - | - |
| Adenocarcinoma | 0.20 | 0.250 | - | - |
| Squamous cell | 0.00 | 0.980 | - | - |
| Small cell | 1.18 | 0.905 | - | - |

HR: hazard ratio; AN-: no anorexia; WL-: no weight loss; WL+: weight loss; AN+: anorexia; Ref.: reference variable; and M1B: extrathoracic metastases. * $-2 \log$ likelihood of 3148.004.

presence of anorexia and pre-treatment weight loss were both strongly associated with shorter survival.

In our sample, the prevalence of anorexia at diagnosis was approximately 40%. Other studies have shown that anorexia is a common symptom in the scenario of advanced disease and is often accompanied by weight loss.^(5,16) However, in our study, pre-treatment weight loss was present in nearly two times as many patients than was anorexia.

Two different factors contribute to explaining the weight loss and decreased appetite in patients with advanced lung cancer. First, the shock of receiving the diagnosis of lung cancer, especially if the cancer has metastasized, can reduce the desire for food. Second, the inflammatory response caused by the tumor can lead to changes in hypothalamic function, with an impact on appetite.⁽¹⁷⁻¹⁹⁾ Even though the correlation between anorexia and weight loss in our study was low, anorexia and the size of the tumor were found to be major determinants of the intensity of pre-treatment weight loss.

The presence of anorexia or weight loss in patients with advanced lung cancer is not a new finding.^(12,20-22) However, we have demonstrated that the concomitance of these conditions is an important predictor of shorter survival. Other studies have shown that the presence of these symptoms may result in complications, including reduced tolerance to chemotherapy, as well as decreased mobility and functionality, leading to a worse quality of life and a consequent reduction of

survival.^(23,24) Therefore, the appropriate management of this clinical condition is probably the key to holistic care in this context.

It is noteworthy that the size of the tumor did not influence mortality in our sample of patients. Therefore, we can speculate that death can be associated not only with the size of the tumor but also, more particularly, with the interactions between the primary tumor and the adjacent vital structures, as well as with distant metastases.⁽²⁵⁾

Our study has some limitations. Because of the retrospective and observational nature of the analysis, some data to supplement or explain the results were not available, such as those related to the measurement of inflammatory markers, immunological markers, metabolic markers, and muscle mass. It is recognized that the measurement of weight does not differentiate between lean and fat mass; therefore, patients with sarcopenic obesity might have been overlooked.^(2,10,12,13) Finally, we recognize that the pre-cancer weight was self-reported, which could have introduced a memory bias.

In conclusion, the present study demonstrated that anorexia and pre-treatment weight loss are relevant factors in the follow-up of patients with advanced (stage IV) lung cancer, and that this combination was associated with higher mortality. Specific interventions are of crucial importance in individualized treatment plans, even within the context of palliative care.

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