Supportive Care in Cancer (2019) 27:3439–3447
https://doi.org/10.1007/s00520-018-4632-0

ORIGINAL ARTICLE

Assessment of baseline symptom burden in treatment-naïve patients with lung cancer: an observational study

Tito R. Mendoza[1] · Kenneth L. Kehl[2,3] · Oluwatosin Bamidele[1] · Loretta A. Williams[1] · Qiuling Shi[1] · Charles S. Cleeland[1] · George Simon[4]

Received: 7 May 2018 / Accepted: 27 December 2018 / Published online: 19 January 2019

Abstract

Background Patients with newly diagnosed lung cancer who have not yet begun treatment may already be experiencing major symptoms produced by their disease. Understanding the symptomatic effects of cancer treatment requires knowledge of pretreatment symptoms (both severity and interference with daily activities). We assessed pretreatment symptom severity, interference, and quality of life (QOL) in treatment-naïve patients with lung cancer and report factors that correlated with symptom severity.

Methods This was a retrospective analysis of data collected at initial intake. Symptoms/interference were rated on the MD Anderson Symptom Inventory (MDASI) between 30 days prediagnosis and 45 days postdiagnosis. We examined symptom severity by disease stage and differences in severity by histology. Linear regression analyses identified significant predictors of severe pain and dyspnea.

Results Of 460 eligible patients, 256 (62%) had adenocarcinoma, 30 (7%) had small cell carcinoma, and 100 (24%) had squamous cell carcinoma; > 30% reported moderate-to-severe (rated ≥ 5, 0–10 scale) pretreatment symptoms. The most-severe were fatigue, disturbed sleep, distress, pain, dyspnea, sadness, and drowsiness. Symptoms affected work, enjoyment of life, and general activity (interference) and physical well-being (QOL) the most. Patients with advanced disease ($n = 289$, 63%) had more-severe symptoms. Cancer stage was associated with pain severity; both histology and cancer stage were associated with severe dyspnea.

Conclusion One third of lung cancer patients were symptomatic at initial presentation. Quantification of pretreatment symptom burden can inform patient-specific palliative therapy and differentiate disease-related symptoms from treatment-related toxicities. Poorly controlled symptoms could negatively affect treatment adherence and therapeutic outcomes.

Keywords Lung cancer · Symptoms · Interference · Patient-reported outcomes · Quality of life

✉ Tito R. Mendoza
tmendoza@mdanderson.org

Kenneth L. Kehl
kenneth_kehl@dfci.harvard.edu

Oluwatosin Bamidele
obamidele@mdanderson.org

Loretta A. Williams
loriwilliams@mdanderson.org

Qiuling Shi
qshi@mdanderson.org

Charles S. Cleeland
ccleeland@mdanderson.org

George Simon
gsimon@mdanderson.org

[1] Department of Symptom Research, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1450, Houston, TX 77030, USA

[2] Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 112, Houston, TX 77030, USA

[3] Present address: Division of Population Sciences, Dana-Farber Cancer Institute, 450 Brookline Ave, Boston, MA 02215, USA

[4] Department of Thoracic/Head & Neck Medical Oncology, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 432, Houston, TX 77030, USA

Introduction

Along with curative intent, a major goal of cancer treatment is to reduce cancer-related symptoms and improve quality of life. Assessing how well this goal is achieved must begin with an understanding of the patients' symptom burden before treatment is initiated, as these "baseline" symptoms will largely be related to the disease itself and will therefore provide a standard by which to judge treatment effects on disease-related symptoms and to identify other symptoms that are likely produced by the treatment [1]. In 2000, symptom researchers at the University of Texas MD Anderson Cancer Center in Houston, Texas, developed and psychometrically validated the MD Anderson Symptom Inventory (MDASI), a patient-reported outcomes questionnaire that includes a set of common cancer-related symptoms (pain, fatigue, nausea, disturbed sleep, distress, shortness of breath, difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness, vomiting, and numbness/tingling) frequently rated by patients in a national multicenter study as moderate to severe [2]. Subsequently, the National Cancer Institute's Symptom Management and Health-Related Quality of Life Steering Committee recommended a set of core symptoms to be assessed in oncology trials [3]. This set of core symptoms overlapped considerably with the MDASI's symptom items, suggesting that the MDASI is an adequate representation of cancer-related symptom burden—a conclusion that is supported by the validation studies of the MDASI and its several disease-specific modules, which were shown to be valid and reliable measures of disease and treatment-related symptoms in patients with cancer [2, 4–7].

At our institution, the MDASI is often used to evaluate patients' symptoms at their initial visit. We have utilized such MDASI data and collected information on patients' prior treatments in order to identify cohorts of treatment-naïve patients. Our objectives in identifying these cohorts are to (1) assess baseline symptom severity and interference ("symptom burden") in treatment-naïve patients and (2) report demographic, disease-related, and treatment-related factors that correlate with symptom burden in these patients. The symptoms of treatment-naïve patients with head and neck cancer were reported by Hanna et al. [1]; here, we present results from patients with lung cancer. Major symptoms reported in the literature as being present at the time of a lung cancer diagnosis included pain, coughing, shortness of breath/dyspnea, and fatigue [8–11].

Methods

Patients

The retrospective study was an analysis of routinely collected symptom data from treatment-naïve patients with lung cancer who first presented at our institution between February 2008 and February 2015. A "treatment-naïve patient" was defined as one who had not previously been treated for cancer. To be included in the analysis, the patient must have completed a MDASI assessment between 30 days prediagnosis and 45 days postdiagnosis.

The study was approved by our Institutional Review Board. As this was a retrospective review of deidentified data, the requirement for informed consent was waived.

Measures

Demographic variables (e.g., age, sex, race) and clinical characteristics (e.g., cancer stage, disease site) were extracted from patient medical records.

Symptom assessment

Patient-reported symptom data were obtained via the MDASI, which was administered at the time of intake. The MDASI is a concise, easily understood measure for assessing symptom burden in patients with cancer [2, 12]. Patients rate the severity of the 13 commonly experienced cancer-related symptoms listed above on a 0–10 numeric scale that ranges from "not present" to "as bad as you can imagine."

Patients also rate six items related to how much symptoms are interfering with various activities of daily living, including walking, general activity, work (including work around the house), relations with others, enjoyment of life, and mood, on 0–10 numeric scales ranging from "did not interfere" to "interfered completely."

Quality of life and functional well-being

Four single-item scales measuring different domains of overall quality of life (QOL) were used to assess QOL and functional well-being. For all four questions (overall QOL, social support, emotional well-being, and physical well-being), patients rated the item on a 0–10 scale ranging from "as bad as it can be" to "as good as it can be," with a lower score corresponding to a poorer outcome. These scales have a long history of use in National Cancer Institute-sponsored cancer-control studies [13]. Simple one-item questions have been shown to be valid and appropriate for use in cancer studies [14].

Statistical analysis

Symptoms, interference, and quality of life

To promote clinical interpretability, we used cutpoints to report the proportions of patients with moderate-to-severe

symptoms and severe symptoms. We defined a symptom as moderate to severe if it was rated ≥ 5 on the MDASI's 0–10 scale. This was based from various studies that showed "pain at its worst" is related to greater interference with function when rated ≥ 5 by cancer patients [15–17] and by community-dwelling samples representing the general population [18], selecting a cutpoint of 5 seemed reasonable and provided analytical consistency across all symptoms. We based our choice of a cutpoint of 7 to delineate a severe symptom on results from studies of pain and fatigue [15, 19, 20]. In addition, the utility of a rating of ≥ 7 to define a severe symptom is supported by symptom-prevalence results from a large multicenter cooperative study [21] and by the routine use of this cutpoint to assess pain and fatigue in clinical practice [22], where pain rated ≥ 7 is considered a clinically significant problem that requires immediate intervention [21, 22].

Because "nausea" and "vomiting" are combined into 1 item in our institution's electronic medical record, our symptom analysis for this study included only 12 items.

Patient demographic and clinical characteristics were summarized with descriptive statistics (means, standard deviations, and 95% confidence intervals (CI)). We dichotomized patients by cancer stage (early vs advanced) according to American Joint Committee on Cancer rules, whereby stage 0–IIB tumors are considered early stage and stage III–IVA tumors are considered advanced stage [23]. Disease site/histology was collapsed into four groups: adenocarcinoma, small cell carcinoma, squamous cell carcinoma, and others. Mean symptom severities were compared by disease stage using independent *t* tests. Differences in symptom severity by histology were performed using an omnibus analysis of variance *F* test for each symptom with Bonferroni correction as a post-hoc comparison method. Although the different symptoms are closely related, we consider each one to be conceptually distinct in their effect. For example, pain is distinguishable from fatigue. All *P* values are two-tailed and were considered significant if < 0.05. Analyses were performed using SPSS Statistical Software for the Social Sciences version 22 (IBM Corporation, Armonk, NY, USA) and SAS Statistical Analysis Software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Predictors of high symptom severity

We expected that pain and shortness of breath would be among the most incapacitating symptoms for patients with lung cancer. We performed multiple linear regression analyses with the variables age, sex, tumor stage, and histology to determine significant predictors of high symptom severity for pain and shortness of breath.

Results

During the study period, 1503 patients with lung cancer were seen at their first visit to our institution; of those, 941 had not received prior treatment and, of those, 460 had completed the MDASI within the stated timeframe. See Table 1 for demographic and disease characteristics. Patients were categorized into two groups based on tumor stage: those with early-stage cancer ($n = 171$, 37%) and those with advanced cancer ($n = 289$, 63%). Patients were categorized into four groups by disease site/histology: those with adenocarcinoma ($n = 256$, 62%), those with small cell carcinoma ($n = 30$, 7%), those with squamous cell carcinoma ($n = 100$, 24%), and others (n = 30, 7%).

Symptoms, interference, and quality of life

Table 2 presents symptoms in order of decreasing mean severity. The seven most-severe MDASI symptoms in decreasing magnitude were fatigue, disturbed sleep, distress, pain, shortness of breath, sadness, and drowsiness. More than 30% of the patients reported moderate-to-severe fatigue, disturbed sleep, distress, or pain (rated ≥ 5 on the 0–10 scale). All symptoms with the exception of nausea/vomiting were reported to be moderate-to-severe by at least 8% of the patients. Severe fatigue and disturbed sleep (rated ≥ 7) each were reported by 21% of patients. Distress, pain, shortness of breath, and sadness each were reported to be severe by at least 16% of the patients.

Among the MDASI symptom interference items, work, enjoyment of life, and general activity were the functional

Table 1 Patient demographic and disease characteristics ($N = 460$)

Variable	Number	Percent
Mean age (SD)	64.9 (10.4)	
Sex		
Women	237	52
Men	223	48
Race		
White non-Hispanic	408	89
Others	52	11
Disease stage		
Early	171	37
Advanced	289	63
Disease site		
Adenocarcinoma	256	62
Small cell carcinoma	30	7
Squamous cell carcinoma	100	24
Others	30	7

SD standard deviation

Table 2 Descriptive statistics for symptoms, interference, and quality of life ($N = 460$)

			Percentage of patients reporting	
	Mean severity	SD	Moderate to severe symptoms (rated ≥ 5)	Severe symptoms (rated ≥ 7)
Symptom[1]				
Fatigue	3.5	3.0	37	21
Disturbed sleep	3.1	3.2	33	21
Distress	3.1	3.2	33	20
Pain	2.9	3.4	32	19
Shortness of breath	2.8	3.1	28	17
Sadness	2.5	3.0	26	16
Drowsiness	2.2	2.9	21	12
Lack of appetite	1.8	2.7	17	10
Dry mouth	1.7	2.7	16	10
Difficulty remembering	1.4	2.1	11	6
Numbness or tingling	1.1	2.2	11	5
Nausea or vomiting	0.9	2.1	8	4
Symptom interference[2]				
Work	3.6	3.5		
Enjoyment of life	3.3	3.4		
General activity	3.2	3.3		
Mood	3.0	3.1		
Walking	2.8	3.2		
Relations with others	1.8	2.7		
Quality of life[3]				
Social support	8.0	3.1		
Emotional well-being	6.7	2.9		
Overall quality of life	6.6	2.8		
Physical well-being	6.0	2.9		

SD standard deviation

[1] Higher scores indicate greater symptom severity (0: symptom not present; 10: symptom as bad as you can imagine)

[2] Higher scores indicate greater symptom interference (0: does not interfere; 10: completely interferes)

[3] Lower scores indicate poorer quality of life (0: as bad as it can be; 10: as good as it can be)

domains most affected by symptoms, whereas relations with others were the least affected (Table 2). Physical well-being was reported to be the poorest QOL domain, followed by overall QOL and emotional well-being.

Differences in symptoms, interference, and quality of life by tumor stage

Most patients ($n = 289$, 63%) had advanced disease and, as expected, these patients had significantly more severe symptoms (Table 3). Only nausea, difficulty remembering, and numbness or tingling did not differ significantly by tumor stage.

On the symptom interference scale, all six items representing different functional domains demonstrated a significantly higher level of interference among advanced stage patients (Table 3). For the different domains of quality of life, patients with advanced cancer reported poorer overall quality of life, poorer emotional well-being, and poorer physical well-being. Only social support did not differ significantly by tumor stage.

Differences in symptoms, interference, and quality of life by disease site/histology

Patients with small cell carcinoma reported the most-severe pain and shortness of breath (Table 4). Despite the relatively small numbers of patients with small cell carcinoma ($n = 30$), these reported significantly more-severe pain compared with patients with squamous cell carcinoma ($N = 100$) (4.1 vs 2.3; $P < 0.05$). Patients with small cell carcinoma or squamous cell carcinoma reported significantly more-severe shortness of

Table 3 Mean (SD) severity by tumor stage

	Early-stage, $n = 171$ (37%)	Advanced, $n = 289$ (63%)	P
Symptom[1]			
Pain	2.1 (3.1)	3.5 (3.4)	0.001
Fatigue	2.2 (2.9)	3.9 (2.9)	0.001
Nausea	0.6 (1.9)	1.0 (2.2)	0.080
Disturbed sleep	2.5 (2.9)	3.5 (3.2)	0.001
Distress	2.4 (2.8)	3.5 (3.2)	0.002
Shortness of breath	2.2 (2.7)	3.2 (3.2)	0.001
Difficulty remembering	1.2 (2.0)	1.1 (2.2)	0.134
Lack of appetite	1.3 (2.3)	2.1 (2.9)	0.001
Drowsiness	1.6 (2.6)	2.6 (2.9)	0.001
Dry mouth	1.2 (2.4)	1.9 (2.8)	0.008
Sadness	1.9 (2.7)	2.9 (3.1)	0.002
Numbness or tingling	1.1 (2.2)	1.1 (2.2)	0.560
Symptom interference[2]			
General activity	2.0 (2.8)	3.9 (3.3)	< 0.001
Mood	2.3 (2.8)	3.4 (3.1)	< 0.001
Work	2.3 (3.0)	4.4 (3.5)	< 0.001
Relations	1.2 (2.2)	2.2 (2.9)	< 0.001
Walking	1.8 (2.7)	3.4 (3.4)	< 0.001
Enjoyment of life	2.3 (3.0)	3.8 (3.4)	< 0.001
Quality of life[3]			
Overall quality of life	7.2 (2.8)	6.3 (2.8)	0.001
Social support	8.0 (3.1)	7.9 (3.1)	0.690
Emotional well-being	7.1 (2.9)	6.5 (2.9)	0.030
Physical well-being	6.6 (2.6)	5.7 (2.9)	0.002

SD standard deviation

[1] Higher scores indicate greater symptom severity (0: symptom not present; 10: symptom as bad as you can imagine)

[2] Higher scores indicate greater symptom interference (0: does not interfere; 10: completely interferes)

[3] Lower scores indicate poorer quality of life (0: as bad as it can be; 10: as good as it can be)

breath compared with patients with adenocarcinoma (4.2 and 3.5 vs 2.5, respectively; $P < 0.05$). Patients with squamous cell carcinoma reported worse lack of appetite compared with the other-cancers group (2.3 vs 0.8; $P < 0.05$). Although the overall omnibus test (F test comparing all four groups simultaneously) indicated a significant association between nausea and histology, no significant pairwise comparisons were found. For interference, only walking was found to be more impaired for small cell carcinoma than other groups (4.2 vs 1.8; $P < 0.05$). No other group differences were found for the rest of the interference items or any of the quality of life domains.

Predictors of high symptom burden

Multiple linear regression analysis showed that cancer stage was a significant predictor of pain severity after controlling for histology, age, and sex. No differences according to histology were found (Table 5). Patients with advanced disease had a pain level that was 1.2 points higher than patients with early-stage disease (95% CI = 0.5–1.8; $P < 0.001$). The change in R^2 between the model with three covariates (histology, age, and sex) and the full model was significant ($R^2 = 0.044$, $P < 0.001$).

Both histology and cancer stage were significant predictors of severe levels of shortness of breath after controlling for age and sex. Shortness of breath levels were 0.9 points higher among patients with advanced-stage disease than among patients with early-stage disease (95% CI = 0.4–1.6; $P < 0.001$). Shortness of breath levels were 1.5 points higher among patients with small cell carcinoma than among those with adenocarcinoma (95% CI = 0.35–2.6; $P = 0.01$). Shortness of breath levels were 1.2 points higher among patients with squamous cell carcinoma than among those with adenocarcinoma (95% CI = 0.56–1.9; $P < 0.001$). See Table 5. The change in R^2 between the model with two covariates (age and sex) and the full model was significant ($R^2 = 0.067$; $P < 0.001$).

Table 4 Mean (SD) severity by disease site/histology

	Adenocarcinoma ($n = 256$)	Small cell carcinoma ($n = 30$)	Squamous cell carcinoma ($n = 100$)	Others ($n = 30$)
Symptom[1]				
Pain[2]	3.1 (3.4)	4.1 (3.0)A	2.3 (3.2) B	2.3 (3.1)
Fatigue	3.3 (2.8)	4.5 (3.1)	3.8 (3.1)	3.5 (3.1)
Nausea	0.7 (1.9)	1.4 (2.6)	1.3 (2.6)	0.4 (1.4)
Disturbed sleep	2.9 (3.0)	4.1 (3.1)	2.9 (3.3)	2.9 (3.5)
Distress	3.1 (3.1)	3.6 (3.5)	2.9 (3.1)	3.2 (3.2)
Shortness of breath[2]	2.5 (2.9) A	4.2 (3.4)B	3.5 (3.1) B	2.0 (2.6)
Difficulty remembering	1.4 (2.1)	1.4 (2.3)	1.5 (2.3)	0.9 (1.7)
Lack of appetite[2]	1.7 (2.6)	2.3 (3.0)	2.3 (2.9) A	0.8 (1.5) B
Drowsiness	2.1 (2.8)	2.3 (2.8)	2.3 (3.0)	1.3 (1.9)
Dry mouth	1.5 (2.5)	2.3 (3.1)	1.6 (2.7)	1.1 (2.1)
Sadness	2.5 (2.9)	2.8 (3.1)	2.2 (2.9)	2.4 (3.1)
Numbness or tingling	1.1 (2.3)	1.4 (2.4)	1.1 (2.1)	0.4 (0.9)
Symptom interference[3]				
General activity	3.1 (3.3)	4.6 (2.6)	3.2 (3.3)	3.0 (3.4)
Mood	3.0 (3.0)	3.9 (3.0)	2.6 (2.8)	2.9 (3.3)
Work	3.5 (3.4)	4.5 (3.3)	3.7 (3.7)	3.2 (3.6)
Relations	1.7 (2.5)	2.0 (2.6)	2.0 (3.0)	2.4 (3.1)
Walking[2]	2.7 (3.2)	4.2 (3.3) A	3.1 (3.4)	1.8 (2.4) B
Enjoyment of life	3.2 (3.3)	4.1 (3.3)	3.2 (3.4)	2.7 (3.4)
Quality of life[4]				
Quality of life	6.5 (2.9)	5.8 (2.4)	6.5 (2.9)	7.1 (2.8)
Social support	7.9 (3.0)	7.5 (3.4)	7.7 (3.4)	8.3 (2.9)
Emotional well-being	6.6 (2.9)	6.2 (2.8)	6.7 (3.0)	7.1 (3.0)
Physical well-being	5.9 (3.0)	5.7 (2.5)	5.7 (2.8)	6.6 (2.8)

The same letters indicate no statistically significant difference, whereas different letters indicate a statistically significant difference. For example, for shortness of breath, adenocarcinoma differs significantly from small cell carcinoma and squamous cell carcinoma, while small cell cancer and squamous cell cancer do not differ

SD standard deviation

[1] Higher scores indicate greater symptom severity (0: symptom not present; 10: symptom as bad as you can imagine)

[2] Significant at $P < 0.05$

[3] Higher scores indicate greater symptom interference (0: does not interfere; 10: completely interferes)

[4] Lower scores indicate poorer quality of life (0: as bad as it can be; 10: as good as it can be)

Discussion

The onset of symptoms often motivates patients to seek medical attention, which may lead to a diagnosis of an underlying condition, such as lung cancer in the present study. In this sample of treatment-naïve patients with lung cancer, more than 30% reported having moderate-to-severe symptoms attributable to their disease. Severe fatigue and disturbed sleep were reported by 21% of patients, followed closely by distress and pain. These data suggest that these patients require significant symptom management, even prior to treatment initiation, and that early referral to supportive care is therefore warranted. With subsequent therapy, any improvement in these initial

Table 5 Multiple regression models predicting the severity of pain and shortness of breath with histology and stage, adjusted for the effects of age and sex

Variable		Estimate	95% LCL	95% UCL	*P*
Pain					
Histology	Adenocarcinoma vs small cell	0.85	− 0.38	2.10	0.180
	Adenocarcinoma vs squamous cell	− 0.51	− 1.20	0.25	0.190
	Adenocarcinoma vs other	− 0.92	− 2.20	0.34	0.150
Stage	Early vs advanced	1.20	0.50	1.80	< 0.001
Age		− 0.04	− 0.07	− 0.01	0.005
Sex	Male vs female	0.09	− 0.53	0.71	0.767
Shortness of breath					
Histology	Adenocarcinoma vs small cell	1.50	0.35	2.60	0.010
	Adenocarcinoma vs squamous cell	1.20	0.56	1.90	< 0.001
	Adenocarcinoma vs other	− 0.65	− 1.80	0.50	0.270
Stage	Early vs advanced	0.90	0.40	1.60	0.001
Age		− 0.04	− 0.07	− 0.01	0.002
Sex	Male vs female	0.46	− 0.11	1.00	0.110

LCL lower confidence limit, *UCL* upper confidence limit

symptoms may be curtailed by toxicities from the treatments, indicating that close and continuous symptom monitoring is required as an integral part of patient management.

We stratified our patient population by extent of disease (early vs advanced), expecting significant differences in symptom burden between the two groups. Patients with more-advanced cancer had more directly attributable symptoms, including pain and shortness of breath. However, symptoms that are more likely to emerge with treatment, such as nausea, difficulty remembering, and numbness, did not differ according to stage in this pretreatment population. Coughing, a major symptom of lung cancer, was not on the list of symptoms screened in the core MDASI version used for pretreatment assessment. A lung cancer module of the MDASI, the MDASI-LC, does include coughing and is currently being used in the clinic both as a component of standard of care and in clinical trials.

Our data suggest that a significant proportion of patients with lung cancer are symptomatic at presentation. An accurate understanding of the baseline symptom burden is critical, not only to inform patient-specific palliative treatments but also to separate disease-related symptoms from future potential treatment-related toxicities. The presence of disabling or poorly controlled symptoms prior to the initiation of therapy may limit the patient's ability to tolerate further treatment, which in turn could affect treatment adherence and treatment outcomes [24]. The results of this study establish a baseline for symptom burden among patients with lung cancer and underline the need for multisymptom assessment as part of the initial evaluation.

Conclusion

In this report, we assessed baseline symptom burden (i.e., symptom severity and interference with functioning and QOL) in treatment-naïve patients with newly diagnosed lung cancer and examined demographic, disease-related, and treatment-related factors that correlate with symptom burden in these patients. We found that approximately one third of the patients were experiencing moderate-to-severe symptoms before they began their cancer treatment. Although other factors such as co-morbid conditions might affect the severity of these "baseline" symptoms, they are more likely related to the disease itself and, as such, provide a standard by which to judge the symptomatic benefits or harms of treatment and to identify other symptoms that the treatment may be producing. Given that poorly controlled symptoms could negatively affect treatment adherence and therapeutic outcomes, these results underscore the need for baseline symptom assessment in all patients with newly diagnosed lung cancer. Information about baseline symptoms can be used to screen patients for symptom management and for the early institution of supportive care to palliate these symptoms, if needed.

Acknowledgments The authors acknowledge Jeanie F. Woodruff, BS, ELS, for editorial assistance. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Cancer Institute or the National Institutes of Health.

Author contributions Tito Mendoza: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing—original draft, and writing—review and editing

Kenneth Kehl: conceptualization, investigation, and writing—review and editing

Oluwatosin Bamidele: conceptualization, investigation, writing—original draft, and writing—review and editing

Loretta Williams: conceptualization, investigation, and writing—review and editing

Qiuling Shi: data curation, methodology, and writing—review and editing

Charles Cleeland: conceptualization, investigation, resources, supervision, writing—original draft, and writing—review and editing

George Simon: conceptualization, investigation, writing—original draft, and writing—review and editing

Funding information All research at The University of Texas MD Anderson Cancer Center is supported in part by the institution's Cancer Center Support Grant, NCI P30 CA016672. The sponsors played no role in study design, in the collection, analysis, or interpretation of data, in the writing of the report, or in the decision to submit the article for publication.

Compliance with ethical standards

The study was approved by our Institutional Review Board. As this was a retrospective review of deidentified data, the requirement for informed consent was waived.

Conflict of interest The MD Anderson Symptom Inventory is copyrighted and licensed by The University of Texas MD Anderson Cancer Center and Charles S. Cleeland. The authors report no other conflicts of interest in this work.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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