




Patient-centered outcomes in non-small-cell lung cancer: a real-world perspective

Luiz H Araujo^{*,1,2,3} , Clarissa S Baldotto^{1,2} , Mariana R Monteiro^{1,2}, Pedro N Aguiar^{1,2} , Maria Clara Andrade^{1,2}, Cecília L Longo^{1,2}, Mayara Batista¹, Raphaela Lima¹, Débora Azevedo¹, Natalia Carvalho¹, Perla Andrade¹, Mauro Zukin^{1,2} & Nelson Teich^{1,2}

¹Instituto COI de Educação e Pesquisa, Avenida das Américas, 6205 Loja F Barra da Tijuca, Rio de Janeiro, 22793-080, Brazil

²Americas Centro de Oncologia Integrado, Av. Jorge Curi, 550 Barra da Tijuca, Rio de Janeiro, 22775-001, Brazil

³Instituto Nacional de Câncer (INCA), Rua André Cavalcanti, 37, Quinto Andar Prédio Anexo, Centro, Rio de Janeiro, 20.230-050, Brazil

*Author for correspondence: Tel.: +55 213 385 2088; luizaraujo@institutocoi.org

Aims: To assess non-small-cell lung cancer (NSCLC) patient-centered outcomes in the real world. **Methods:** This is a prospective study of NSCLC patients treated at a private cancer care institution in Brazil between 2014 and 2019. **Results:** The report comprises 337 patients. Advanced stage was associated with higher symptom burden – fatigue ($p = 0.03$), pain ($p < 0.001$) and arm pain ($p = 0.022$) – and worse global, social and physical functioning (all $p < 0.001$). In the first 2 years, most factors evolved to either improvement or stability: cough ($p = 0.02$), pain ($p = 0.002$), global functioning ($p < 0.001$) and emotional functioning ($p < 0.001$). Staging ($p < 0.001$), fatigue ($p = 0.001$) and gender ($p = 0.004$) were independently associated with overall survival. **Conclusions:** Our results demonstrate the feasibility of conducting real-world prospective analysis of patient-centered outcomes.

Lay abstract: This study looked at patient-centered outcomes in lung cancer in a real-world setting. Standardized quality-of-life questionnaires were used to actively measure patients' perception of their functional well-being and health in a clinical setting. Three hundred thirty-seven patients were enrolled in a private cancer center in Brazil between 2014 and 2019. We demonstrated that patients diagnosed at advanced stages presented with more symptoms and lower capacity to perform daily activities. However, symptoms and functioning tended to improve during treatment. Our results show that it is possible to put patients at the heart of cancer care and use their experience to guide clinical approach.

First draft submitted: 27 September 2020; Accepted for publication: 8 January 2021; Published online: 25 February 2021

Keywords: health care • lung neoplasms • outcome assessment • patient-reported outcomes • quality of life • survival analysis

Many advances have been achieved in the approach to lung cancer patients in recent decades. These include improvements in screening [1–3], diagnostics [4] and treatment [5–7]. However, lung cancer remains the most common malignancy worldwide, contributing 2.1 million new cases in 2018 (11.6% of all new cancer cases) [8]. It is also the leading cause of cancer death, with more than 1.7 million deaths a year [8]. Despite a decrease in lung cancer incidence and mortality in some regions, [9] it remains a major burden especially in low- and middle-income countries [8]. Unfortunately, most cases present at advanced stages where curative intent is not an option, and efforts are directed to improve survival and quality of life (QoL) [9].

Most policy-relevant decisions on lung cancer care still rely exclusively on results from randomized clinical trials, where only a restricted group of patients are represented [10–12]. To better understand the impact of the disease on patient routine and how baseline factors could influence the ultimate treatment results, well-annotated, real-world registries are essential. Moreover, evaluating patient-centered outcomes has become highly relevant, especially nowadays because currently available treatment options have expanded the survival of lung cancer patients [13,14]. Patient-centered outcome measures focus on the physical, mental and social health, directly reported by patients rather than indirect report by health care providers [13].

A variety of tools are available to assess patient-centered outcomes in oncology [13], including the European Organization for Research and Treatment of Cancer (EORTC) QoL questionnaires, the QLQ-C30 and QLQ-LC13 [15,16]. QLQ-C30 is the core questionnaire for cancer patients, composed of multi- and single-item scales [15]. These include five functional scales (physical, role, cognitive, emotional and social), a global health status/QoL scale, symptom scales (fatigue, pain, nausea and vomiting, dyspnea, appetite loss, insomnia, constipation and diarrhea) and perceived financial impact of the disease [15]. The QLQ-LC13 is a supplementary questionnaire module of lung cancer-specific scales, including dyspnea, pain, cough, sore mouth, dysphagia, peripheral neuropathy, alopecia and hemoptysis [16]. Originally designed to assess health-related QoL in clinical trials, the EORTC questionnaires have been widely applied to various research settings including real-world data [17].

To harmonize efforts around the globe, the International Consortium for Health Outcomes Measurement (ICHOM) has defined standard sets of outcomes to serve as a guide for aligning outcome measurement initiatives internationally [14]. In line with the ICHOM group [14], COI Institute launched the infrastructure to conduct prospective registries with focus on collecting patient-centered outcomes in patients with newly diagnosed cancer – including a lung cancer registry that is presented in this article. The current study provides a unique dataset of non-small-cell lung cancer (NSCLC) patient-centered outcomes in the private health care system in Brazil [18]. The primary aim was to describe patient-centered outcomes, including survival and patient-reported domains of health-related QoL as determined by the ICHOM Lung Cancer Standard Set. Herein, we present the preliminary results of this study, assessing the impact of lung cancer on patient outcome and QoL.

Methods

Study design

This is a prospective, observational study of NSCLC patients treated at Americas Oncologia, a private cancer care institution in Brazil. Approximately 500 new lung cancer patients are seen each year, mostly covered by one of the 63 health plans that are affiliated (information from 2020). Eligible patients were at least 18 years old, had a histology-proven diagnosis of lung cancer between July 2014 and December 2019 and formally consented to participate. For this analysis, NSCLC patients with an invasive histological component were included. Patients with prior malignancies in the 5 years before lung cancer diagnosis (except for nonmelanoma skin cancer and cervical cancer) and patients who received first therapy (except for surgery) in other institutions were excluded. These criteria minimize the risk of selection biases that could have an impact on prognosis.

For data collection, an electronic clinical research form was created, including characteristics such as age, gender, ethnicity, educational level, weight loss and smoking status. Former smoker status was defined as patients who had quit smoking at least 1 year before diagnosis. Comorbidities were assessed using a modified self-administered comorbidity questionnaire [19]. Baseline tumor factors included histological subtype and the presence of *EGFR* mutation or *ALK* translocation. Staging was defined according to the eighth edition of the UICC/IASLC/AJCC (Union for International Cancer Control/International Association for the Study of Lung Cancer/American Joint Committee on Cancer) [20]. Treatment intent was defined as either curative or palliative, with the latter including best supportive care, according to the ICHOM standard sets.

To measure the degree of health at diagnosis, the Eastern Cooperative Oncology Group Performance Status (PS) scale was annotated [21], together with the EORTC QoL questionnaires, QLQ-C30 [15] and QLQ-LC13 [16]. QoL questionnaires were applied at baseline; at 3, 6 and 12 months after treatment initiation; and then annually. When patients did not present to regular follow-up, an electronic version of the QoL questionnaires was used to respond remotely. Alternatively, responses were also collected by telephone calls to ensure that all information was annotated. Data quality was certified by regular monitoring. This study was approved by the local Research Ethics Committee.

Statistical methods

Questionnaire scales/items were scored according to EORTC published algorithms [22]. For each scale or item, a linear transformation was applied to standardize the raw score to a range of 0 to 100. The resulting score was reported as means and standard error when applicable. Prespecified patient-reported symptoms of interest were cough (assessed by QLQ-LC13 question 1), dyspnea (composite of QLQ-LC13 questions 3–5), pain (QLQ-LC13 questions 10–12 and QLQ-C30 questions 9 and 19) and fatigue (QLQ-C30 questions 10, 12 and 18). Chest pain, arm and shoulder pain and other pain refer to data collected with the QLQ-LC13 questionnaire, and pain alone was collected with QLQ-C30. Throughout this article, arm and shoulder pain are referred to as arm pain.

Functioning scores were also assessed using the QLQ-C30 questionnaire. Global (questions 29 and 30), social (26 and 27), physical (1–5), emotional (21–24) and cognitive (20 and 25) functioning scores were selected based on the ICHOM standards.

Patients completing at least a baseline QoL questionnaire were included in a comparison between baseline self-reported symptoms, functioning scores and other clinical-demographic characteristics. Chi-square test was used to compare the proportion of baseline characteristics between categorical variables, whereas one-way analysis of variance was applied to compare continuous variables (including all QoL scores) to categorical factors. The comparison between two continuous variables, including the QoL scores, was performed using the Spearman's rank correlation.

For repeated assessments within individual subjects, the determinants of QoL were investigated using a linear mixed model. The score for each domain was used as the dependent variables and compared with time and treatment intent (radical vs palliative). Data from patients with at least three consecutive questionnaires completed were included. QoL mean scores were normalized and plotted in linear graphics.

Overall survival (OS) was estimated using the Kaplan–Meier method and defined as the interval between date of diagnosis and death. For patients still alive or lost to follow-up, data were censored at the date of last contact. Variable analysis for survival was performed using the log-rank method for categorical variables and Cox proportional hazard models for continuous variables (including all QoL scores). All positive factors associated with survival in the univariate analysis were included in a multivariate analysis. Survival curves are presented for factors that remained positive in the multivariate analysis. To better illustrate the prognostic value of fatigue, a categorical variable defined by low (below the median baseline value) or high (equal or above the median) was created to generate a survival plot. For all comparisons, p -values ≤ 0.05 were considered statistically significant. Statistical analyses were performed using the statistical software IBM SPSS version 26.0 (IBM Corp, NY, USA).

Results

Baseline characteristics

Three hundred ninety-nine patients were enrolled (Figure 1). Sixty-two were excluded in this analysis, 57 due to neuroendocrine origin, two without a component of invasive carcinoma and three for unspecified histology. The final report comprises 337 patients; baseline characteristics are described in Table 1. Most patients were males (57.0%), White (64.7%), smokers (81.3%) and presented with favorable PS (0–1 in 91.7%). Educational level was diverse; 52.5% had only secondary degree or less. Adenocarcinoma was the most prevalent histological subtype (70.9%), and driver alterations were present in 14.3%. Most patients presented with advanced disease (stages III/IV in 80.7%).

One hundred eighty-three patients (54.3%) were primarily treated with palliative intent. Seventy-two patients received a surgical intervention, including 61 thoracic surgeries with curative intent (18.1%). Chemotherapy was recommended in 276 patient cases (81.9%), including adjuvant treatment in 29 (8.6%) and neoadjuvant in 12 (3.6%). Targeted therapy was used in 49 patients (14.6%) and immunotherapy in 113 (33.5%). Two hundred nine patients (62.0%) received radiation therapy at some point of disease treatment.

Degree of health at baseline

EORTC QLQ-LC13 questionnaire was responded by 333 patients at baseline, and then 262, 225, 180 and 128 at subsequent time points. EORTC QLQ-C30 was responded by 290, 227, 192, 153 and 104 patients at the first five time points. The main reasons for not responding the questionnaires were disease progression and death, especially at subsequent time points.

Symptoms at baseline according to EORTC-QLQ C30 & LC13

At baseline, cough, other pain and fatigue were the symptoms with highest scores (means of 42.4, 34.3 and 31.9, respectively), suggesting a higher prevalence and depth of these symptoms. Cough was more frequent among males ($p = 0.017$) and squamous cell histology ($p = 0.007$), whereas dyspnea was associated with weight loss ($p = 0.037$) and higher comorbidity score ($p = 0.006$). Arm pain was associated with the presence of weight loss ($p = 0.04$), advanced stage ($p = 0.022$), older age ($p = 0.015$) and palliative intent ($p = 0.005$). Chest pain was more frequent in patients with driver alterations ($p = 0.046$) and older age ($p < 0.001$). Fatigue was more prevalent at advanced stages ($p = 0.03$) and was associated with weight loss ($p = 0.001$) and palliative intent ($p < 0.001$). Pain was associated with weight loss, advanced stages and palliative intent (all $p < 0.001$).

Table 1. Baseline characteristics (N = 337).	
Characteristic	n (%)
Demographic factors	
Mean age, years (SE)	67.4 (0.61)
Gender	
– Male	192 (57.0)
– Female	145 (43.0)
Ethnicity	
– White	218 (64.7)
– Black	29 (8.6)
– Brown	59 (17.5)
– Asian	2 (0.6)
– Unknown	29 (8.6)
Educational level	
– Pre-primary education	3 (0.9)
– Primary education	43 (12.7)
– Secondary education	131 (38.9)
– Tertiary education	159 (47.2)
– Unknown	1 (0.3)
Clinical factors	
Weight loss	
– Yes	106 (31.5)
– No	138 (40.9)
– Unknown	93 (27.6)
Modified SCQ	
– Mean (SE)	2.0 (0.068)
Smoking status	
– Current smoker	94 (27.9)
– Former smoker	180 (53.4)
– Never smoker	63 (18.7)
Performance status	
– 0	137 (40.7)
– 1	172 (51.0)
– 2	9 (2.7)
– 3	2 (0.6)
– Unknown	17 (5.0)
Tumor and treatment factors	
Histology	
– Adenocarcinoma	139 (70.9)
– Squamous cell carcinoma	91 (27.0)
– Adenosquamous	3 (0.9)
– NSCLC NOS	4 (1.2)
Driver alteration	
– <i>EGFR</i> mutation	41 (12.2)
– <i>ALK</i> translocation	7 (2.1)
Clinical stage	
– I	35 (10.4)
– II	30 (8.9)
– III	117 (34.7)
– IV	155 (46.0)
Treatment intent	
– Radical/curative	154 (45.7)
– Palliative	183 (54.3)

NSCLC NOS: Non-small-cell lung cancer not otherwise specified; SCQ: Self-administered comorbidity questionnaire; SE: Standard error.

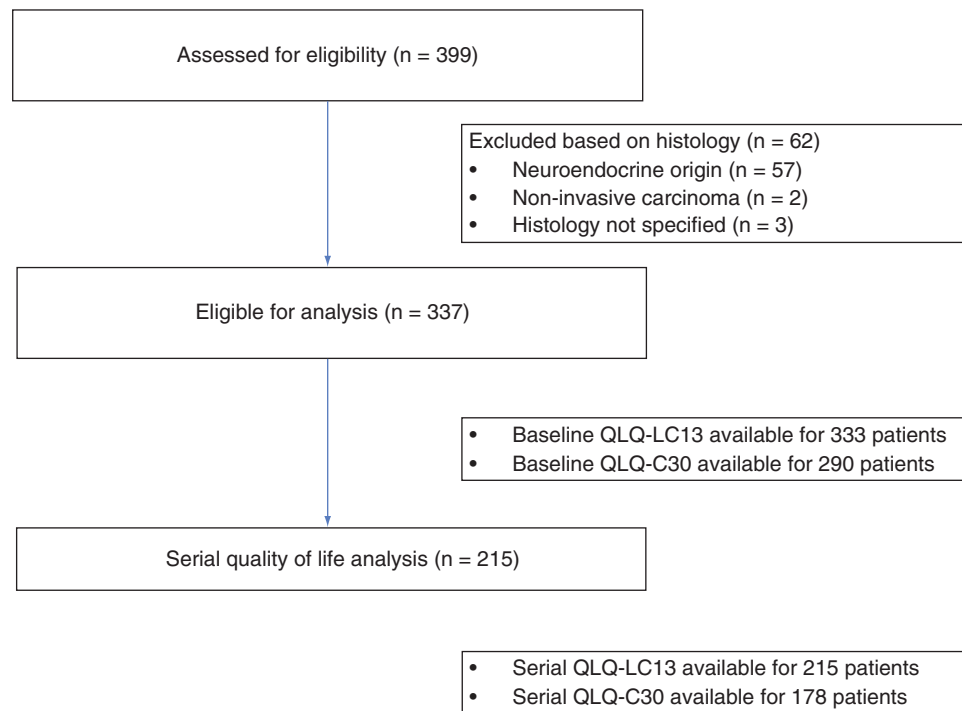


Figure 1. Flow diagram of patient enrollment and analysis.
QLQ: Quality of life questionnaire.

PS was worse in patients presenting weight loss ($p < 0.001$) and treated with palliative intent ($p = 0.004$). Worse PS was also associated with more symptoms such as pain ($p = 0.005$), other pain ($p = 0.001$) and fatigue ($p = 0.001$). The relation between symptoms and other discrete variables are illustrated in [Figure 2](#).

Functioning at baseline according to EORTC QLQ-C30

Functioning scores were highly associated with other baseline factors and symptoms. Patients with weight loss ($p = 0.017$) and advanced stages ($p < 0.001$) had lower global functioning scores. Early stages ($p < 0.001$), older age ($p = 0.011$) and curative intent ($p = 0.001$) were associated with higher social scores. Patients with advanced stages ($p < 0.001$), weight loss ($p = 0.004$), more comorbidities ($p = 0.013$) and treated with palliative intent ($p = 0.016$) had worse physical scores. Males ($p < 0.001$) of older age ($p < 0.001$) and with more comorbidities ($p < 0.001$) had higher emotional scores. Global ($p < 0.001$), physical ($p < 0.001$) and social ($p = 0.001$) functioning scores were lower in patients with poor PS. The relation between functioning and other discrete variables are illustrated in [Figure 3](#).

Serial comparisons of QoL parameters

Upon serial comparisons of QoL parameters during the first 2 years, most factors evolved to either improvement or stability. Cough ($p = 0.02$) and pain ($p = 0.002$) were symptoms that presented significant improvement over time, more pronouncedly in patients receiving palliative therapy. Other symptoms such as dyspnea ($p = 0.322$), chest pain ($p = 0.445$), arm pain ($p = 0.086$), other pain ($p = 0.505$) and fatigue ($p = 0.863$) were stable during the first 24 months. Global and emotional functioning showed significant improvement over time ($p < 0.001$ in both), whereas social ($p = 0.282$), physical ($p = 0.60$) and cognitive ($p = 0.561$) functioning were stable.

Patients receiving palliative therapy demonstrated significantly lower social ($p = 0.003$) and physical ($p = 0.018$) functioning scores over time and lower cough score ($p < 0.001$). Other symptoms and functioning scores were not distinct. [Figure 4](#) depicts the evolution of QoL parameters with significant change over time, according to treatment intent.

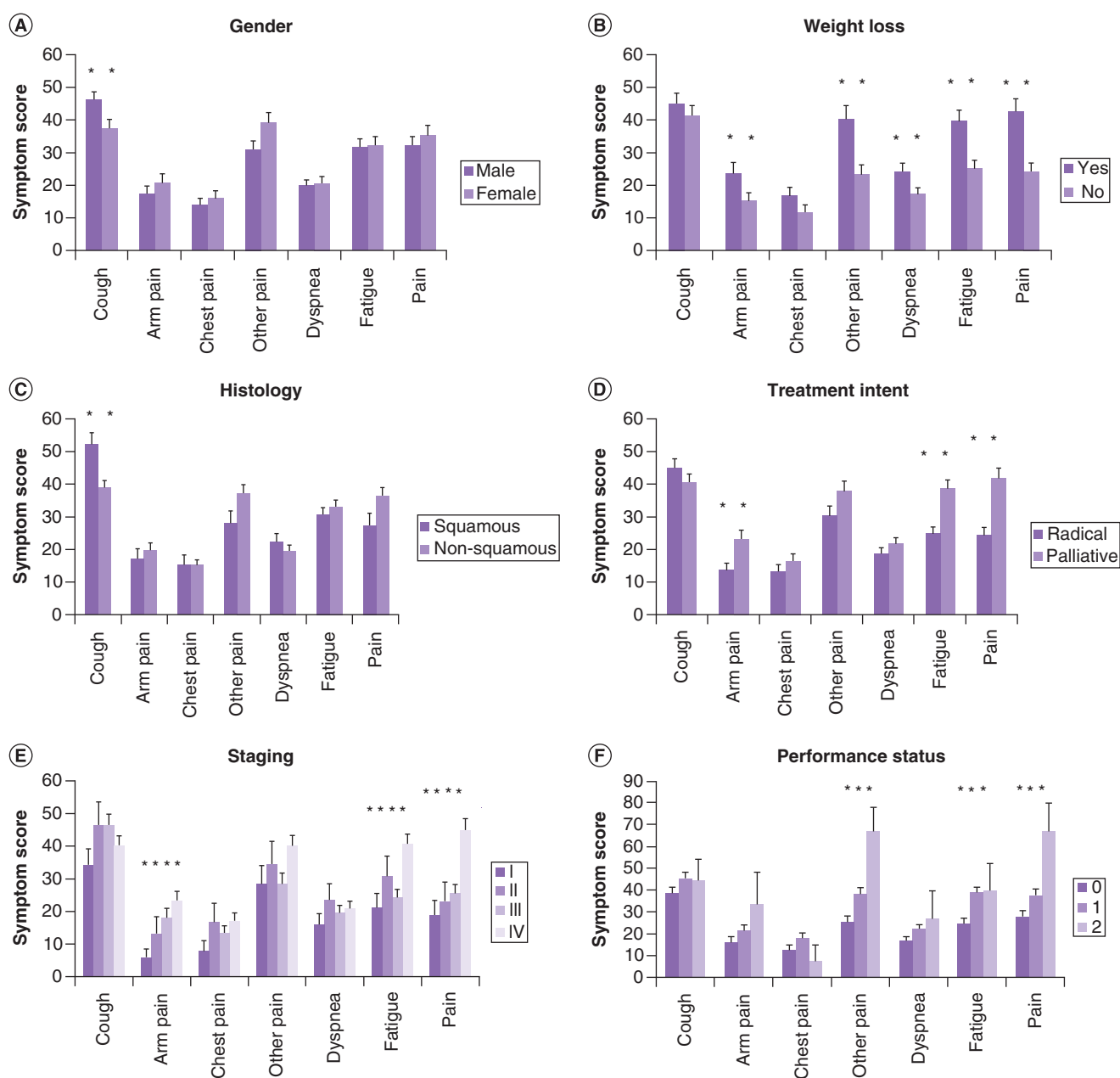


Figure 2. Bar chart depicting the association between baseline symptom score and baseline characteristics. Each symptom score is presented according to (A) gender, (B) weight loss, (C) histology, (D) treatment intent, (E) staging and (F) performance status. *Cases in which p-value was ≤ 0.05 . Symptoms were predefined based on EORTC QLQ-LC13 (cough, arm pain, chest pain, other pain and dyspnea) and EORTC QLQ-C30 (fatigue and pain). EORTC QLQ: European Organization for Research and Treatment of Cancer quality of life questionnaire.

OS & risk factors

After a median follow-up of 24.7 months (95% CI 20.0–29.4), 161 (47.8%) deaths were reported. The estimated 2-year OS was 48.9%, and median OS was 22.2 months (95% CI 15.8–28.8). OS was significantly longer among patients at stages I–II (2-year OS 97.0% and 90.6%, respectively) than at stages III and IV (53.4% and 28.0%, respectively; $p < 0.001$). Median OS was 26.5 months (95% CI 18.8–34.3) and 12.1 months (95% CI 8.2–16.0) at stages III and IV, respectively.

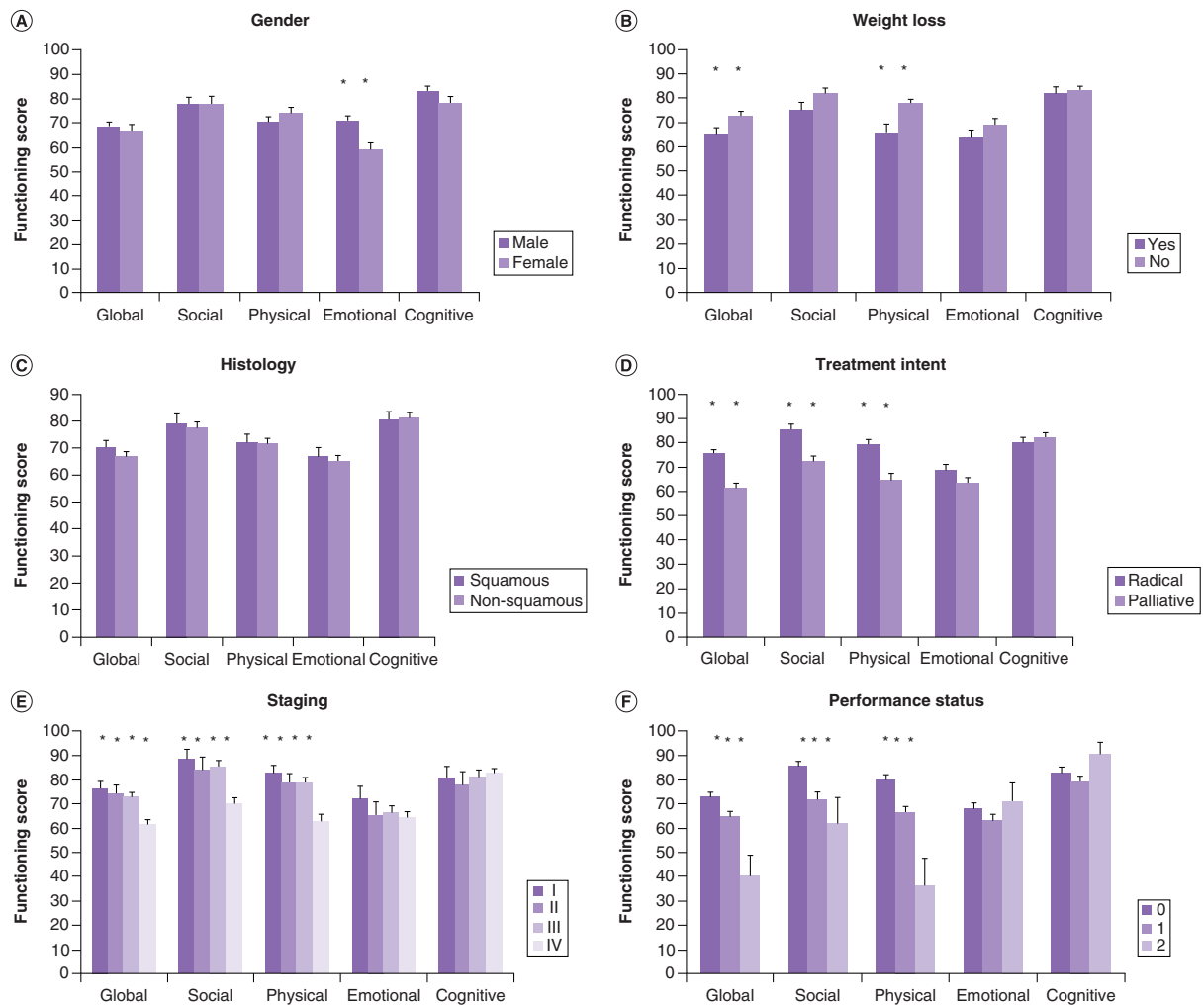


Figure 3. Bar chart depicting the association between European Organization for Research and Treatment of Cancer quality of life questionnaire-C30 baseline functioning scores and baseline clinical characteristics. Each functioning score is presented according to (A) gender, (B) weight loss, (C) histology, (D) treatment intent, (E) staging and (F) performance status. * $p \leq 0.05$.

OS was associated with the presence of patient-reported symptoms such as fatigue ($p < 0.001$), dyspnea ($p = 0.007$), pain (C30) ($p < 0.001$), arm pain ($p = 0.001$) and other pain ($p < 0.001$). Global ($p < 0.001$), physical ($p < 0.001$) and social ($p = 0.001$) functioning scores were significantly associated with OS. Other factors significantly associated were gender ($p = 0.001$), smoking status ($p = 0.047$), PS ($p < 0.001$), weight loss ($p = 0.003$) and treatment intent ($p < 0.001$). The presence of a driver alteration was marginally associated with better OS ($p = 0.056$).

In the multivariate analysis, staging ($p < 0.001$), fatigue ($p = 0.001$) and gender ($p = 0.004$) were independently associated with OS. Pain ($p = 0.056$) and driver alterations ($p = 0.087$) were not independent prognostic factors. Survival curves are illustrated in Figure 5, and prognostic impact of patient-reported outcomes are summarized in Supplementary Table 1.

Discussion

Value-based healthcare is a moving concept that takes into account health outcomes and costs incurred [10,14]. To fully implement measures that support a value-based approach in oncology, cancer care institutions must comply with well-annotated registries that include real-world data to support informed decisions [10,14]. Whereas hard

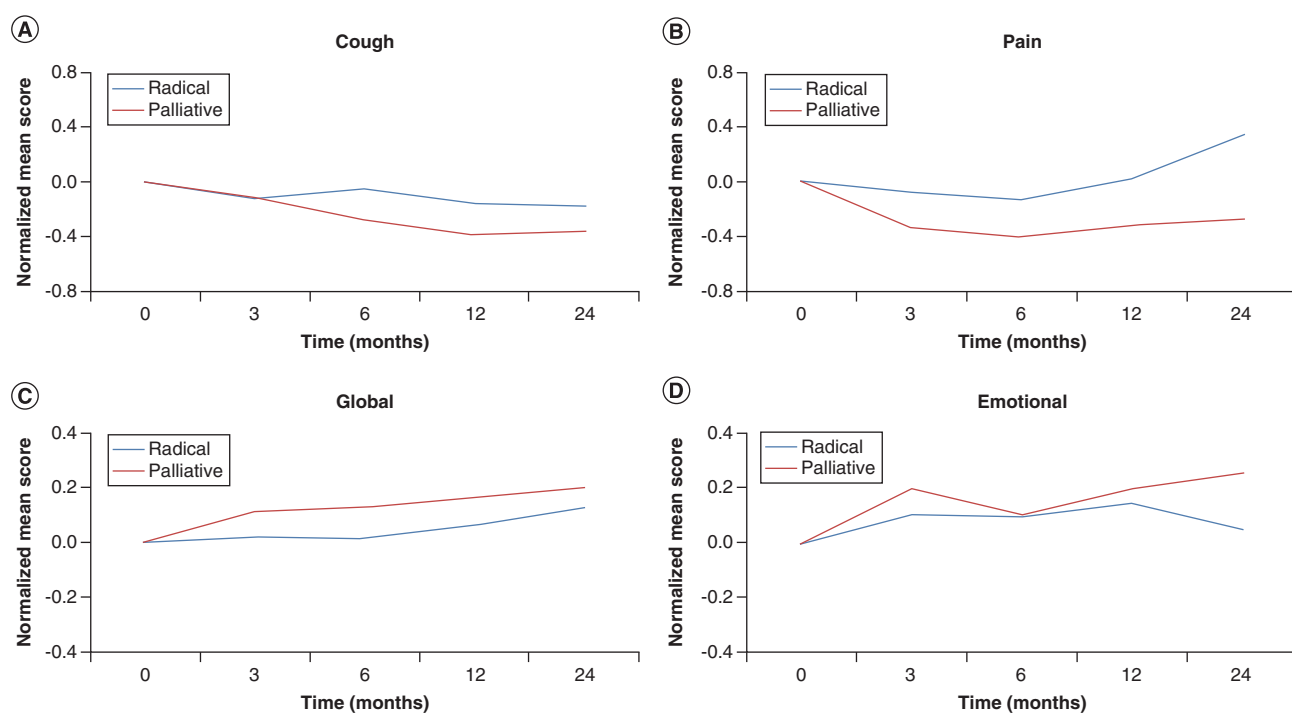


Figure 4. Linear plots depicting the serial evolution of symptom and functioning scores according to treatment intent. Normalized mean scores are presented at baseline, 3, 6, 12 and 24 months. (A) Cough ($p = 0.02$), (B) pain ($p = 0.002$), (C) global ($p < 0.001$) and (D) emotional ($p < 0.001$) functioning scores showed significant improvement over time.

outcomes such as OS are easily accessible in retrospective datasets, a comprehensive analysis that includes QoL questionnaires requires research infrastructure that supports prospective data collection, analysis and interpretation, in a similar fashion to what is exercised in classic clinical trials [23]. Additionally, quality assurance and data monitoring are highly recommended throughout the study [24].

In our dataset, most patients were males, with an average age of 67 years, and were diagnosed at advanced stages, which is in line with most data generated from global NSCLC registries [9]. On the other hand, our dataset presents greater heterogeneity in terms of ethnicity and educational levels [25]. For instance, 17.5% of patients were reported as browns, a denomination rarely seen in high-income countries, representing the admixture of White and Black ethnic backgrounds. Other 8.6% of patients were defined as Blacks. Moreover, our dataset was representative of different educational levels. 13% of patients had only primary education or less, and 38.9% had only secondary education. These numbers illustrate the diversity of patients who have access to private health insurance, which may also determine different levels of access to proper and timely diagnosis and treatment [26].

Approximately 80% of patients presented with stages III/IV at diagnosis. These figures are in line with other real-world data in the literature [27] and also with past reports from the same institution as the current article [28]. Because low-dose computed tomography screening for lung cancer was not standard during the period of enrollment, it is possible that a shift toward early diagnosis will be observed in the upcoming years. The current study is ongoing and should be able to evaluate the impact of screening on patient presentation and mortality in the future. As expected, patients presenting with stages I or II had better survival, lower symptom burden and greater functioning and were more likely to receive curative-intent therapy [27,29].

At baseline, 91.7% of patients presented with a PS of 0 or 1, which indicates a favorable clinical scenario and reasonable degree of health. Indeed, poor PS was associated with greater level of signs and symptoms such as weight loss, pain and fatigue. These patients also had lower global, social and physical functioning scores. However, it became clear that PS alone was not able to fully capture how the disease manifested in each patient and how such discrepancy could affect patients' life and outcome [30]. For instance, fatigue was an independent prognostic factor in our dataset, in detriment to PS. This finding opens a discussion on how proper symptom annotation

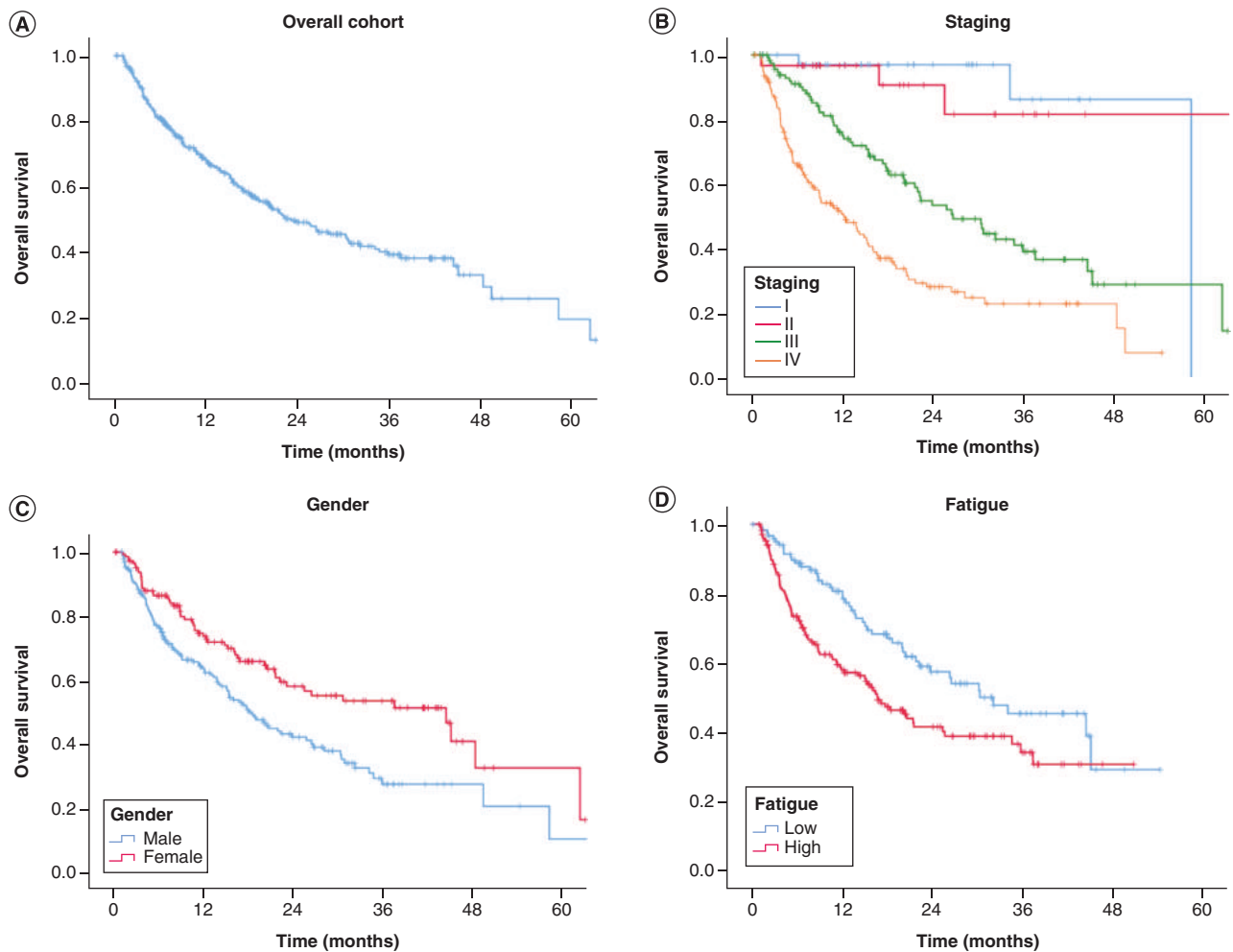


Figure 5. Survival curves depicting overall survival according to independent prognostic factors. Overall survival is presented in the total cohort (A) and according to disease stage (B), gender (C) and fatigue (D) in patients diagnosed with non-small-cell lung cancer.

should be handled. First, fatigue was self-reported, assessed through the QLQ-C30 questionnaire, whereas PS was routinely assessed by the assistant physician. This illustrates how patients should be listened to carefully and how health complaints should be valorized. Furthermore, fatigue was compared with survival as a continuous variable, whereas PS was analyzed as discrete. Transforming symptom burden into defined categories may be troublesome and may not ideally represent the full spectrum of its impact. Other studies have demonstrated how QoL measures can predict survival in NSCLC and in other cancer types, mostly in clinical trial settings [31,32].

Baseline factors were often associated with symptom and functioning scores; some of these associations merit debate. Cough was the symptom with highest baseline score and was associated with male gender and squamous cell histology. Indeed, cough is a predominant symptom in lung cancer patients, mostly attributable to bulky intrathoracic disease but may also relate to comorbidities such as chronic obstructive pulmonary disease [33]. It generally anticipates many other constitutional symptoms that may relate to more advanced stages such as weakness, anorexia and weight loss. Because squamous cell carcinoma tends to present with central primary tumors, invading large airways, it is reasonable to assume that cough was predominant in such cases [34]. In addition, patients presenting with squamous cell carcinoma are more often smokers, who may present with chronic cough, although a relation between cough and smoking status was not observed in our study.

Worse global, social and physical functioning often mirrored the presence of advanced disease, greater symptom score and poor PS. On the other hand, emotional and cognitive functioning scores were highly independent. In

fact, cognitive functioning was not associated with any other factor in the current analysis, whereas emotional functioning was higher in males, at older age and with greater comorbidity score. This association suggests that emotional functioning was not linked to cancer presentation *per se* but that a subset of patients may be more emotionally prepared to cope with the disease and its stigma. It is possible that these patients may have learned to manage the presence of chronic disease and may be more prepared to face the process of diagnosis and treatment. Indeed, it has been noted that younger people may experience cancer differently from older patients because of a lack of prior experience with severe illness [35,36]. It is important to note that emotional and cognitive aspects are not systematically assessed in clinical practice. Our study shows the feasibility of collecting this information through the QLQ-C30 questionnaire. The best approach to managing such information remains unclear, and dedicated trials should be encouraged.

It is noteworthy that QoL parameters presented either improvement or stability during the first 2 years of follow-up. Improvement was more pronounced in patients receiving palliative therapy, which is in line with greater baseline disease burden in this instance and reassures the benefits of proper patient care even at advanced stages [37]. In fact, symptoms such as cough and pain, which may impact patients' daily lives, were significantly improved over time, as well as global and emotional functioning scores. Future analysis should focus on the impact of each individual intervention on patients' QoL, especially at advanced stages.

In the current study, staging, fatigue and gender were independent prognostic factors. Interestingly, smoking status and the presence of driver mutations were not statistically significant. It is reasonable to speculate that the relatively small sample size of driver-positive patient cases may have caused a numeric difference that was not sufficient to reach statistical significance. However, the fact that smoking status was not related to OS is surprising and contrasts with most of the literature on advanced NSCLC [38]. A possible explanation for this is the growing access to immunotherapy, which has sharply changed expectations for many NSCLC patients [39]. The impact of such novel therapies may cause a relevant bias on OS. In the current study, one-third of patients were able to receive immunotherapy as second line or beyond and, more recently, as first-line treatment. It is possible that smoking status may lose its classic prognostic relevance in other contemporary, real-world studies like the current one [38]. The authors plan to explore this field in a future analysis focusing specifically on the impact of immune checkpoint inhibitors in the present cohort. This analysis will require a specific design and a larger sample size and is beyond the focus of the current article.

Among the potential limitations is the selection bias. Only patients that presented with newly diagnosed NSCLC and agreed to participate before treatment began were included. The prospective study design and the use of baseline QoL questionnaires require that patients consent before any procedures are applied, which limit the number of patients that fulfill all the criteria. These factors also limited the sample size and final analysis. Despite this, our sample size is larger than efforts from other single institutions worldwide [40]. There is a need to deepen the analysis on the impact of specific diagnostic and therapeutic interventions on patients' QoL and outcomes. This study is ongoing; future analysis will provide larger sample size with power to perform such comparisons.

Patient-centered outcome measures are mainly used in clinical trials with focus on systemic therapy [41]. However, several groups have created institutional registries to understand the impact of novel technology on patient outcomes in the real world. One such example is the Advanced Non-Small-Cell Lung Holistic Registry (ANCHoR), assessing the impact of immunotherapy on metastatic NSCLC patient outcomes [40]. Nonetheless, these efforts are largely limited to institutions from high-income countries such as the UK, Sweden, Australia and the USA [41]. There are limited data from low- and middle-income countries or from other institutions in Latin America.

There is increasing interest in integrating the collection of patient-centered outcomes in routine practice to improve patient care [42]. Potential benefits include better management of symptoms and side effects, which will likely result in higher QoL and greater satisfaction with care providers [13,43,44]. The current study provides a deeper analysis of NSCLC patient-centered measures in the real world. Our results shed light onto relevant symptoms and functioning that affect patients' lives and could be clinically relevant. From a practical perspective, future efforts should include the local implementation of multidisciplinary interventions that will respond to patient alerts and specifically address patients' self-reported needs [42,45].

Conclusion

Our results demonstrate the feasibility of conducting prospective analysis of patient-centered outcomes in the real world and highlight the impact of NSCLC on patients' symptoms and functioning outside of controlled clinical trials. Fatigue, a score based on self-reported evaluation, was an independent prognostic factor in the current dataset,

reinforcing the need to closely examine patients' symptoms and functioning. Our results may reflect the reality in other low- and middle-income countries and may serve as a basis for encouraging the collection of patient-centered outcomes in clinical practice. The implementation of the ICHOM initiative in cancer centers may help validate the quality of care and will likely support healthcare improvement in the years to come.

Future perspective

Cancer care is an exciting and evolving field, where novel diagnostic and therapeutic opportunities are under continuous development. Given the growing number of interventions, many times oncologists – and other healthcare providers – are challenged to focus on selecting the best approach, and patients' perception and expectations may be left behind. Moving the focus to patients will of key importance in the near future, and patient-centered outcome measures will be instrumental. Cancer centers worldwide will enhance their capacity to offer such measures in clinical practice and improve workflows to respond in a timely manner. Technology will be essential to enable this process, using modern, portable and user-friendly devices or apps that will deliver real-time information to care providers. As a growing amount of data is generated, real-world data storage and analysis will be required. Large international consortiums will be able to explore these data to improve cancer care around the globe.

Summary points

- Patient-centered outcome measures focus on the physical, mental and social health, directly reported by patients.
- The current study provides a unique dataset of non-small-cell lung cancer (NSCLC) patient-centered outcomes in the private healthcare system in Brazil.
- Baseline factors were often associated with symptom and functioning scores.
- Advanced stage was associated with higher symptom burden and worse functioning.
- Quality-of-life parameters presented either improvement or stability during treatment.
- Staging, fatigue and gender were independent predictors of overall survival.
- Our results demonstrate the feasibility of conducting prospective analysis of patient-centered outcomes in the real world.
- Future efforts should include the implementation of multidisciplinary interventions that will respond to patient alerts and specifically address patients' self-reported needs.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2020-0991

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1. National Lung Screening Trial Research Team/National Lung Screening Trial Research Team, Aberle DR, Adams AM *et al.* Reduced lung-cancer mortality with low-dose computed tomographic screening. *N. Engl. J. Med.* 365(5), 395–409 (2011).

2. De Koning HJ, van der Aalst CM, De Jong PA *et al.* Reduced lung-cancer mortality with volume CT screening in a randomized trial. *N. Engl. J. Med.* 382(6), 503–513 (2020).
3. Arbour KC, Riely GJ. Systemic Therapy for locally advanced and metastatic non-small cell lung cancer: a review. *JAMA.* 322(8), 764–774 (2019).
4. Rami-Porta R, Asamura H, Travis WD, Rusch VW. Lung cancer – major changes in the American Joint Committee on Cancer eighth edition cancer staging manual. *CA Cancer J. Clin.* 67(2), 138–155 (2017).
5. Khaitan PG, D’Amico TA. Milestones in thoracic surgery. *J. Thorac. Cardiovasc. Surg.* 155(6), 2779–2789 (2018).
6. Ball D, Mai GT, Vinod S *et al.* Stereotactic ablative radiotherapy versus standard radiotherapy in stage I non-small-cell lung cancer (TROG 09.02 CHISEL): a Phase 3, open-label, randomised controlled trial. *Lancet Oncol.* 20(4), 494–503 (2019).
7. Herbst RS, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature* 553(7689), 446–454 (2018).
8. Bray F, Ferlay J, Soerjomataram I, *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* 68(6), 394–424 (2018).
9. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J. Clin.* 70(1), 7–30 (2020).
10. Booth CM, Karim S, Mackillop WJ. Real-world data: towards achieving the achievable in cancer care. *Nat. Rev. Clin. Oncol.* 16(5), 312–325 (2019).
11. Glatzer M, Panje CM, Siren C *et al.* Decision making criteria in oncology. *Oncol.* 98(6), 370–378 (2020).
12. Zikos E, Ghislain I, Coens C *et al.* Health-related quality of life in small-cell lung cancer: a systematic review on reporting of methods and clinical issues in randomised controlled trials. *Lancet Oncol.* 15(2), e78–89 (2014).
13. Strong LE. The past, present, and future of patient-reported outcomes in oncology. *Am.Soc. Clin. Oncol. Educ. Book* doi:10.14694/EdBook_AM.2015.35.e616 e616–620 (2015) (Epub ahead of print).
- **Excellent review of patient-reported outcomes in oncology.**
14. Mak KS, van Bommel AC, Stowell C *et al.* Defining a standard set of patient-centred outcomes for lung cancer. *Eur. Respir. J.* 48(3), 852–860 (2016).
- **This is a highly relevant publication from the ICHOM group defining standard sets to measure patient-centered outcomes in lung cancer.**
15. Aaronson NK, Ahmedzai S, Bergman B *et al.* The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J. Natl. Cancer Inst.* 85(5), 365–376 (1993).
16. Bergman B, Aaronson NK, Ahmedzai S *et al.* The EORTC QLQ-LC13: a modular supplement to the EORTC Core Quality of Life Questionnaire (QLQ-C30) for use in lung cancer clinical trials. EORTC Study Group on Quality of Life. *Eur. J. Cancer* 30A(5), 635–642 (1994).
17. Husson O, De Rooij BH, Kieffer J *et al.* The EORTC QLQ-C30 summary score as prognostic factor for survival of patients with cancer in the “real-world”: results from the population-based PROFILES Registry. *Oncologist* 25(4), e722–e732 (2020).
18. Mathias C, Prado GF, Mascarenhas E *et al.* Lung cancer in Brazil. *J. Thorac. Oncol.* 15(2), 170–175 (2020).
19. Sangha O, Stucki G, Liang MH *et al.* The Self-Administered Comorbidity Questionnaire: a new method to assess comorbidity for clinical and health services research. *Arthritis Rheum.* 49(2), 156–163 (2003).
20. Goldstraw P, Chansky K, Crowley J *et al.* The IASLC Lung Cancer Staging Project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J. Thorac. Oncol.* 11(1), 39–51 (2016).
21. Oken MM, Creech RH, Tormey DC *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am. J. Clin. Oncol.* 5(6), 649–655 (1982).
22. Fayers P, Aaronson NK, Groenwold M *et al.* *EORTC QLQ-C30 Scoring Manual.* European Organisation for Research and Treatment of Cancer, Brussels, Belgium (2001).
23. Ashley L, Jones H, Thomas J *et al.* Integrating patient reported outcomes with clinical cancer registry data: a feasibility study of the electronic Patient-Reported Outcomes From Cancer Survivors (ePOCS) system. *J. Med. Internet Res.* 15(10), e230 (2013).
24. Cook JA, Collins GS. The rise of big clinical databases. *Br. J. Surg.* 102(2), e93–e101 (2015).
25. Willen L, Berglund A, Bergstrom S *et al.* Educational level and management and outcomes in non-small cell lung cancer. A nationwide population-based study. *Lung Cancer* 131, 40–46 (2019).
26. Dickman SL, Himmelstein DU, Woolhandler S. Inequality and the health-care system in the USA. *Lancet* 389(10077), 1431–1441 (2017).
27. Chansky K, Detterbeck FC, Nicholson AG *et al.* The IASLC Lung Cancer Staging Project: external validation of the revision of the TNM stage groupings in the eighth edition of the TNM Classification of Lung Cancer. *J. Thorac. Oncol.* 12(7), 1109–1121 (2017).
28. Araujo LH, Baldotto CS, Zukin M *et al.* Survival and prognostic factors in patients with non-small cell lung cancer treated in private health care. *Rev. Bras. Epidemiol.* 17(4), 1001–1014 (2014).

29. Koo MM, Swann R, Mcphail S *et al.* Presenting symptoms of cancer and stage at diagnosis: evidence from a cross-sectional, population-based study. *Lancet Oncol.* 21(1), 73–79 (2020).
30. Broderick JE, May M, Schwartz JE *et al.* Patient reported outcomes can improve performance status assessment: a pilot study. *J. Patient Rep. Outcomes* 3(1), 41 (2019).
31. Mierzynska J, Piccinin C, Pe M *et al.* Prognostic value of patient-reported outcomes from international randomised clinical trials on cancer: a systematic review. *Lancet Oncol.* 20(12), e685–e698 (2019).
- **Systematic review of patient-reported outcomes in clinical trials.**
32. Braun DP, Gupta D, Staren ED. Quality of life assessment as a predictor of survival in non-small cell lung cancer. *BMC Cancer* 11, 353 (2011).
33. Beckles MA, Spiro SG, Colice GL, Rudd RM. Initial evaluation of the patient with lung cancer: symptoms, signs, laboratory tests, and paraneoplastic syndromes. *Chest* 123(Suppl. 1), 97S–104S (2003).
34. Travis WD, Brambilla E, Nicholson AG *et al.* The 2015 World Health Organization Classification of Lung Tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J. Thorac. Oncol.* 10(9), 1243–1260 (2015).
35. Piazza JR, Charles ST, Almeida DM. Living with chronic health conditions: age differences in affective well-being. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 62(6), P313–321 (2007).
36. Ubel PA, Jankovic A, Smith D *et al.* What is perfect health to an 85-year-old? Evidence for scale recalibration in subjective health ratings. *Med. Care* 43(10), 1054–1057 (2005).
37. Wintner LM, Giesinger JM, Zubernigg A *et al.* Quality of life during chemotherapy in lung cancer patients: results across different treatment lines. *Br. J. Cancer* 109(9), 2301–2308 (2013).
38. Debieuvre D, Oster JP, Riou R *et al.* The new face of non-small-cell lung cancer in men: results of two French prospective epidemiological studies conducted 10 years apart. *Lung cancer* 91, 1–6 (2016).
39. Topalian SL, Hodi FS, Brahmer JR *et al.* Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non-small cell lung cancer treated with nivolumab. *JAMA Oncol.* 5(10), 1411–1420 (2019).
40. Williams L, Dibaj S, Chandwani S *et al.* Real-world patient-reported outcome assessment of patients with metastatic non-small cell lung cancer. *J. Thorac. Oncol.* 13(10), S907–S908 (2018).
41. Bouazza YB, Chiairi I, El Kharbouchi O *et al.* Patient-reported outcome measures (PROMs) in the management of lung cancer: a systematic review. *Lung cancer* 113, 140–151 (2017).
42. Basch E, Barbera L, Kerrigan CL, Velikova G. Implementation of patient-reported outcomes in routine medical care. *Am. Soc. Clin. Oncol. Educ. Book* 38, 122–134 (2018).
43. Snyder CF, Aaronson NK. Use of patient-reported outcomes in clinical practice. *Lancet* 374(9687), 369–370 (2009).
44. Howell D, Molloy S, Wilkinson K *et al.* Patient-reported outcomes in routine cancer clinical practice: a scoping review of use, impact on health outcomes, and implementation factors. *Ann. Oncol.* 26(9), 1846–1858 (2015).
45. Brandt J, Scotte F, Jordan K. Patient-reported outcomes (PROs) as a routine measure for cancer inpatients: the final missing piece of the puzzle? *Ann. Oncol.* 30(2), 167–169 (2019).