

# Feasibility and Utility of Incorporating Patient-Reported Outcomes into Surveillance Strategies for Advanced Lung Cancer

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**Purpose:** To identify and to describe patient-reported outcomes (PROs) in lung cancer patients and to evaluate the feasibility and utility of PROs into surveillance strategies, a review was carried out.

**Patients and Methods:** A systematic search in bibliographic databases evaluating the instruments used in PROs of non-small-Cell lung cancer (NSCLC) patients was done.

**Results:** From August 2014 to August 2019, 33 studies were included in this review and 16,491 patients were evaluated. PROs were divided into 6 different categories: 1) PROs as a guide in therapeutic choice, 2) PROs as indicator of disease progression, 3) agreement between PROs and the evaluated parameters, 4) PROs to evaluate the effects of immunotherapy, 5) need to deepen the knowledge of PROs, and 6) use of new electronic PROs.

**Conclusion:** The most frequently used instruments are EORTC QLQ-30 (16, 50%) and EORTC LC-13 (14, 43.75%) and in some studies (37.5%) they are used together. For different reasons (disease progression, adverse event, death, incomplete participation, etc.), the completion of these instruments decreased over time from baseline to subsequent measurements. This review demonstrates that PROs can play an important role as part of health care, and that routine use implementation could improve patient management in addition to the traditionally collected outcome.

**Keywords:** quality of life, lung cancer, patient-reported outcomes, PROs

## Introduction

Lung cancer still has a particularly poor prognosis: 60-month survival ranges are between 68% in patients with stage I disease, to 0–10% in stage IV patients. It is the leading cause of cancer deaths in Western countries.<sup>1,2</sup> Due to its symptom-free course, lung cancer is often diagnosed in an advanced stage and the most frequent and clinically relevant disease-related symptoms experienced by patients in an advanced stage are pain, fatigue, dyspnea, and cough, with a significant impact on the health-related quality of life (HR QoL).<sup>3,4</sup> It must be emphasized that patients with advanced/metastatic lung cancer during the course of the disease develop devastating physical and psychosocial symptoms, though new target therapies and immunotherapies are changing the situation of advanced/metastatic lung-cancer patients, improving disease-free survival (DFS) and overall survival (OS).<sup>5</sup> However, old and new therapies for metastatic lung cancer show adverse effects that can worsen the quality of life and worsen the prognosis if not promptly diagnosed and treated. Some studies reported that incorporating patient-reported

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outcomes (PROs) into surveillance strategies for advanced lung cancers appears to improve both quality of life and outcome in patients with advanced/metastatic lung cancer.<sup>6</sup> Therefore, to analyze the role of PROs in the management of patients with advanced/metastatic lung cancer, we performed a review regarding feasibility and utility of incorporating patient-reported outcomes into surveillance strategies for advanced lung cancer.

## Materials and Methods

A systematic search in the bibliographic databases, PubMed, Cochrane Library and EMBASE to identify all relevant publications was performed. In accordance with the guideline Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA),<sup>7</sup> the latest database search was conducted on 19 Aug 2019 using the following search terms: “reported outcomes” AND “advanced lung cancer” with the restricted publication date “last 5 years”. For each study, data about authors, year of publication, type of study, number of patients included, treatment, instruments were used to assess QoL and timing for data collection were extracted. Only prospective observational studies, randomized-controlled trials and a post-hoc analysis are reported in this review. Two authors (LC and CC) independently evaluated the paper for the potential eligibility in this systematic review based on the inclusion criteria, with disagreements resolved by consensus with the third author. We cannot evaluate utility and feasibility of PROs directly, using a parameter common to all PROs, so we reported them evaluating clinical applicability but also the limits.

## Instruments Utilized in the Reviewed Studies

In the articles analyzed, a total of 21 different PROs were described focused on different dimensions of the QoL (ie functional, physical, emotional and social function). The quality-of-life instruments evaluated can be categorized in general (ESAS), cancer-specific (EORTC QLQ-C30, RALS, PMC, FACT - G, SF-36, PRO-CTCAE, MDASI), lung-cancer-specific (EORTC LC-13, LCSS, FACT - L, LCS, NSCLC-SAQ, MDASI-LC), specific symptoms (FACT - F and SCFS for fatigue, FAAct and PG-SGA for Anorexia/Cachexia/nutrition and EAT-10 and SWAL-QoL for dysphagia), specific for Work Productivity and Activity Impairment (WPAIGH) and instruments to evaluate the caregivers' burdens (ZBI).

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)<sup>8</sup> is a standardized cancer-specific instrument for measuring HRQL and symptom and functional domains consisting of 30 items, with subscales related to physical, role, emotional, cognitive and social functioning, global health status/quality of life, symptoms and financial issues. Scores are reported on a scale of 0–100.

The EORTC Lung Cancer-13 (EORTC LC-13)<sup>9</sup> is a standardized instrument that measures lung-cancer-specific symptoms (dyspnea, cough, hemoptysis and site-specific pain), chemotherapy/radiotherapy-related side effects and medication use for pain. Scores are reported on a scale of 0–100.

The Lung Cancer Symptom Scale (LCSS)<sup>10,11</sup> is a standardized instrument for measuring lung cancer symptoms and HRQL; it evaluates different symptoms (pain, loss of appetite, fatigue, cough, dyspnea and hemoptysis) and general effects related to QoL. Each item is measured using a visual analogue scale, with scores reported on a scale of 0–100.

The MD Anderson Symptom Inventory (MDASI) and lung cancer module of the MDASI (MDASI-LC)<sup>12,13</sup> is a multi-symptom patient-reported outcome measurement for clinical and research use. It includes symptoms found to have the highest frequency and/or severity in patients with various cancers and treatment types. The MDASI-LC is specific for lung cancer. It includes coughing.

The Rotterdam Activity Level Scale (RALS) of the Rotterdam Symptom Checklist (RSCL)<sup>14</sup> was developed to measure the symptoms reported by cancer patients participating in clinical trials but it is also applicable to monitoring the levels of the patient's anxiety and depression, and reflects the presence of psychological illness.

The Patients' symptoms via the Patient Care Monitor (PCM) v2.0<sup>15–17</sup> is a review of system surveys with different lengths depending on gender. Each question is scored on a scale ranging from 0 to 10. This instrument has been validated and demonstrates a significant correlation with other validated instruments.

The FACT measurement system includes FACT - G Functional Assessment of Cancer Therapy – General, FACT - L Functional Assessment of Cancer Therapy – Lung Cancer, FACT - F Functional Assessment of Cancer Therapy – Fatigue, FAAct Functional Assessment of Anorexia/Cachexia Treatment.<sup>18–20</sup> Since 1987 the FACT measurement system has been developed; FACT - G was developed to measure QoL in cancer patients receiving

therapy. Now it is also a well-established instrument in cancer-related treatment evaluations and clinical interventions. To this questionnaire, problems that are specific to a particular type of cancer can be added. The FACT - L questionnaire asks about symptoms reported by lung cancer patients which may affect their quality of life. The FACT - F questionnaire assessing fatigue and anemia-related concerns in people with cancer; the FAACT uses an anorexia-cachexia subscale as a marker of QoL in patients with advanced lung cancer and cancer anorexia-cachexia syndrome.

The 36-item Short-Form Health Survey (SF-36)<sup>21,22</sup> is a generic questionnaire that generates eight subscale scores with values from 0 to 100. It can be used to evaluate the physical and mental condition of the patient.

The Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy – Lung (FACT - L)<sup>23,24</sup> is an independently validated tool to assess symptoms of lung cancer. The maximum score is 28; lower scores represent more severe symptoms.

The Schwartz Cancer Fatigue Scale (SCFS)<sup>25</sup> is a reliable and valid patient-reported measure of fatigue severity with a 5-point scale to generate a score ranging from 6 to 30.

The Patient-Generated Subjective Global Assessment (PG-SGA)<sup>26</sup> is a highly sensitive and specific screening tool to identify the need for nutritional intervention in patients with cancer; data produce 3 categories: well-nourished, moderately malnourished and severely malnourished.

The Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events (PRO-CTCAE)<sup>27</sup> is a validated PRO measurement system developed by the US NCI to assess symptoms possibly related to cancer treatments. PRO-CTCAE items are listed in publicly available libraries and cover 78 symptoms, each item reflects specific symptom attributes included in the corresponding CTCAE.

The Eating Assessment Tool (EAT-10)<sup>28</sup> is used to obtain a self-reported prevalence estimate for both oropharyngeal and esophageal dysphagia in the samples.

The Swallowing Quality of Life instrument SWAL-QoL is used to measure the impact of dysphagia on QoL.<sup>29</sup>

The Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ)<sup>30</sup> is a 7-item PRO measurement for use in advanced NSCLC. It uses a 7-day recall period and verbal rating scale.

The Work Productivity and Activity Impairment: General Health (WPAI: GH)<sup>31</sup> is a validated, non-disease-specific tool and consists of items about work (employment status,

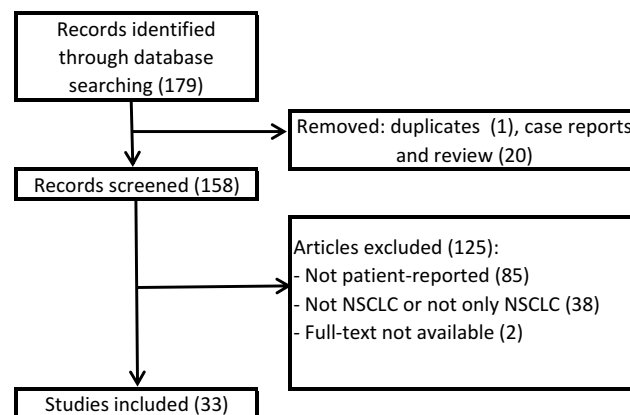
hours missed from work, etc.) used to give four data: work time missed; impairment while working; overall work impairment; and activity impairment.

The Zarit Burden Interview (ZBI)<sup>32</sup> is a validated scale that measures feelings of the burdens of caregivers for patients with a range of medical and psychological conditions.

The Edmonton Symptom Assessment Scale (ESAS)<sup>33</sup> consists of 9 common symptoms that patients rate on an 11-point scale, from 0 to 10: pain, fatigue, nausea, depression, anxiety, drowsiness, inappetence, malaise and dyspnea.

## Results

The search yielded a total of 179 articles (Figure 1). After removing duplicates and case reports, 21 were excluded. We screened 158 articles and 126 were excluded since they did not meet the inclusion criteria: 84 used instruments not patient-reported, 39 included patients suffering from different types of cancer, not lung cancer or not only lung cancer, 2 reports were available only in abstract form. Finally, 33 studies were included (Table 1). Four articles were published in 2015, 5 in 2016, 10 in 2017, 8 in 2018 and 6 in 2019. Seventeen studies are randomized clinical trials, 15 observational studies and 1 is a post-hoc analysis. The number of patients included in the studies ranges from a minimum of 32 to a maximum of 1466 for a total of 16,491 included patients. In most studies, the PROs reported data on standard chemotherapy (first or second line), or target therapy, such as tyrosine kinase inhibitors (TKIs), or immunotherapy. Other studies also use chemoradiotherapy, second-line and maintenance therapies. Fifteen (45.45%) compare the QoL of patients treated with two different therapeutic regimens; 1 (3.03%) was a validation study, 2 (6.06%) evaluated PROs ability to detect symptom, 4 (12.12%) evaluated symptom



**Figure 1** Flowchart of study selection.

Table 1 Identified Literature Overview

	Author	Year	Study Type	Patient Number	Treatment	Methods	PROs Outcomes	Results	Category
1	King-Kallimanis et al <sup>56</sup>	2018	Randomized controlled trials	695	Anti-PD-1/PD-L1	EORTC QLQ-C30, EORTC LC-13, LCSS baseline and after 3 months	Examine age-related differences in patient-reported symptoms and functional domains	No large differences at baseline or in the distributions of change from baseline in PROs between younger and older patients	C4
2	Wu et al <sup>68</sup>	2018	Randomized controlled trials	301	Afatinib vs chemotherapy	EORTC QLQ-C30 every 21 days until progression	EGFR Mutation Type Influence patient-reported outcomes	First-line afatinib improved lung cancer-related symptoms and GHS/QoL compared with chemotherapy	C1
3	Bordonni et al <sup>57</sup>	2018	Randomized controlled trials	850	Atezolizumab or docetaxel	EORTC QLQ-30, EORTC LC-13 day 1 of every cycle and at treatment discontinuation	Evaluate the QoL of patient treated with atezolizumab or docetaxel	PROs data support the clinical benefit of atezolizumab in patients with previously treated advanced or metastatic NSCLC	C4
4	Lee et al <sup>59</sup>	2018	Randomized controlled trials	419	Osimertinib Versus Chemotherapy	EORTC QLQ-30, EORTC LC-13 baseline, 3 months, 1 year	Evaluate the QoL of patient treated with Osimertinib or Chemotherapy	A higher proportion of patients treated with osimertinib had improvement in global health status/quality of life	C4
5	Walker et al <sup>40</sup>	2017	Prospective observational	145	Platinum-based doublets including combinations with bevacizumab or pemetrexed	EORTC QLQ-30, EORTC LC-13, MDASI, RALS baseline, 1 year	Effect of Brain Metastasis on patient reported outcomes	PROs measures show disease progression is associated with worsening HR QoL. Delaying disease progression can sustain better HRQL and reduce symptom burden	C2
6	McCarrier et al <sup>62</sup>	2017	Prospective observational	51	Routine cancer care	NSCLC-SAQ	Development of a patient reported outcome Instrument	NSCLC-SAQ is currently undergoing quantitative testing to confirm its measurement properties and support FDA qualification	C6
7	Blackhall et al <sup>52</sup>	2015	Post hoc analysis	343	Crizotinib vs chemotherapy	EORTC QLQ-30, EORTC LC-13, EQ-5D baseline, day 1 of each cycle and end of treatment	Evaluate the QoL of patient treated with crizotinib or Chemotherapy	The benefits of crizotinib in improving symptoms and QoL are demonstrated regardless of whether the comparator is pemetrexed or docetaxel	C3

8	LeBlanc et al <sup>53</sup>	2016	Prospective observational	97	Chemotherapy or palliative	Electronic patient-reported outcomes: Patient Care Monitor Patient Care Monitor (PCM) v2.0 four assessments in 6 months	Characterized patients' symptoms	Patients with aNSCLC face a significant symptom burden, which increases with proximity to death	C3
9	LeBlanc et al <sup>41</sup>	2015	Prospective observational	99	Routine cancer care	FACT - G, FACT - L, FACT - F; FAFACT four assessments in 6 months	Correlation between CACS and PROs	The weight-based definition is useful in identifying patients with advanced NSCLC who are likely to have significantly inferior survival and who will develop more precipitous declines in physical function and QoL	C2
10	Von Verschuer et al <sup>51</sup>	2017	Prospective observational	1239	Carboplatin or cisplatin based doublet chemotherapy	EORTC QLQ-30, EORTC LC-13 each visit, any change in treatment or every 6 months	Evaluate the QoL of patient treated with carbo or cisplatin	HR QoL data comparing treatments show no difference between carboplatin and cisplatin	C3
11	Shallwani et al <sup>50</sup>	2016	Observational	47	First line chemotherapy	SF-36, LCS, SCFS, PG-SGA pre and post chemotherapy	Identify predictors of change in HR QoL in patients undergoing chemotherapy	Pre-chemotherapy 6MWT distance and fatigue severity predicted change in the mental component of HR QoL in patients with advanced NSCLC undergoing chemotherapy, while physical performance declined during treatment	C3
12	Sebastian et al <sup>34</sup>	2018	Randomized controlled trials	161	Chemotherapy vs osimertinib	PRO-CTCAE first weekly for 18 weeks and then every 3 weeks for up to 57 weeks	Evaluate the QoL of patient treated with chemo or osimertinib	Symptoms were generally mild and not frequent, with some differences in symptom patterns between the two treatment groups	C1
13	Brady et al <sup>65</sup>	2017	Prospective observational	72	Surgery, radiotherapy, chemotherapy	EAT-10, SWAL- QOL	Impact of dysphagia on QOL	Dysphagia is a potential symptom in advanced lung cancer which may impact QOL	C3

(Continued)

Table 1 (Continued).

	Author	Year	Study Type	Patient Number	Treatment	Methods	PROs Outcomes	Results	Category
14	Walker et al <sup>49</sup>	2017	Prospective observational	147	First line (±bevacizumab)	EORTC QLQ-C30, EORTC QLQ-LC13, MDASI-LC, RALS every cycle during active treatment and monthly in fu for up to 1 year	Impact of disease progression on effectiveness outcomes and QoL	Newly diagnosed advanced NSCLC patients with baseline BM experienced a significantly faster and clinically meaningful deterioration in PRO-based HR QoL compared with those without baseline BM	C3
15	Felip et al <sup>48</sup>	2017	Randomized controlled trials	795	1' Platinum-Based Chemotherapy, 2' Afatinib Versus Erlotinib	EORTC QLQ-C30, EORTC QLQ-LC13 first visit of each treatment at the end of treatment, and 28 days after treatment	Evaluate the QoL of patient treated with afatinib or erlotinib	Significantly more patients who received afatinib versus erlotinib experienced improved scores for GHS/QoL	C3
16	Brahmer et al <sup>58</sup>	2017	Randomized controlled trials	299	Pembrolizumab vs chemotherapy	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D baseline and w15	Evaluate the QoL of patient treated with pembrolizumab or chemotherapy	Pembrolizumab improves or maintains health-related QOL compared with that for chemotherapy	C4
17	Reck et al <sup>66</sup>	2018	Randomized controlled trials	582	Nivolumab or docetaxel	LCSS, EQ-5D at baseline, on day 1 of every other cycle for 6 months, two follow-up visits after treatment discontinuation; EQ-5D assessments continued every 3 months for 12 months and then every 6 months thereafter	Evaluate the QoL of patient treated with nivolumab or docetaxel	Nivolumab improved disease-related symptoms and overall health status versus docetaxel for second-line treatment of advanced non-squamous NSCLC	C3
18	Denis et al <sup>43</sup>	2017	Randomized controlled trials	60	Chemotherapy or tyrosine kinase inhibitor	E-FAP every three months	Web-mediated follow-up (SR) improved OS due to early relapse detection and better PS at relapse	A web-mediated follow-up algorithm based on self-reported symptoms improved OS due to early relapse detection and better performance status at relapse	C2



19	Sztankay et al <sup>36</sup>	2017	Prospective observational	83	First-line palliative chemotherapy	EORTC QLQ-C30, EORTC QLQ-LC13 each chemotherapy cycle to the start of second-line palliative chemotherapy or at study completion	Symptom severity during MT compared with first-line therapy	HR QOL and symptom burden improve between first-line treatment to MT, the integration of patient-reported outcomes is required to enable shared decision-making and personalised healthcare	C1
20	Sloan et al <sup>42</sup>	2016	Prospective observational	1466	Surgery, chemotherapy, radiotherapy	NCCTG, EORTC QLQ-LC13, FACT - L, LCSS follow-up	Correlation between being physically active and QOL	Being physically active was related to profound advantages in QOL and survival in a large sample of lung cancer survivors	C2
21	Wang et al <sup>61</sup>	2016	Prospective observational	92	IMRT, BPT, 3DCRT, chemoradiotherapy	MDASI baseline, weekly during and after therapy for up to 12 weeks	Validate MDASI ability to detect symptom	Patients receiving PBT reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT	C5
22	Spigel et al <sup>67</sup>	2019	Randomized controlled trials	1426	Nivolumab	EQ-5D, LCSS every 3 months for the first 12 months, then every 6 months	Evaluate the QoL of patient treated with nivolumab	The median overall survival for patients with an ECOG PS of 2 was lower than for the overall population but comparable with historical data	C1
23	Nguyen et al <sup>46</sup>	2018	Prospective observational	32	Concurrent chemoradiation	EORTC QLQ-C30 baseline, during therapy, at therapy stop and till 1 year after therapy end every 3 months	Evaluate the QoL of patient treated with concurrent chemoradiation	Measuring PROs can help to identify issues for improvement of the value of care delivered	C3
24	Mendoza et al <sup>60</sup>	2019	Prospective observational	460	Treatment-naive	MDASI between 30 days prediagnosis and 45 days postdiagnosis	Assessment of baseline QoL for palliative therapy evaluation, disease-related symptoms differentiation and control	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	C5

(Continued)

Table 1 (Continued).

	Author	Year	Study Type	Patient Number	Treatment	Methods	PROs Outcomes	Results	Category
25	Novello et al <sup>47</sup>	2015	RANDOMIZED controlled trials	1314	Nintedanib plus docetaxel vs placebo plus docetaxel	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D, EQ-5D screening, day 1 of each cycle, at the end of active treatment, first FU	Evaluate the QoL of patient treated with second-line nintedanib	The significant OS benefit observed with the addition of nintedanib to docetaxel therapy was achieved with no detrimental effect on patient self-reported QoL	C3
26	Pérol et al <sup>44</sup>	2016	Randomized controlled trials	1253	Ramucirumab plus docetaxel vs placebo plus docetaxel	LCSS baseline, every 3-week cycle, the summary visit, and at the 30-day FU	Evaluate the QoL of patient treated with ramucirumab plus docetaxel vs placebo plus docetaxel	Adding ramucirumab to docetaxel did not impair patient QoL, symptoms, or functioning	C3
27	Boye et al <sup>45</sup>	2016	Randomized controlled trials	218	Pemetrexed plus cisplatin followed by gefitinib maintenance therapy or gef monotherapy	LCSS baseline, at each study visit, after discontinuation	Evaluate the QoL of patient treated with pemetrexed plus cisplatin followed by gef maintenance therapy or gef monotherapy	LCSS scores were more favorable in the G group than in the PC/G group	C3
28	Wood et al <sup>54</sup>	2019	Prospective observational	1030	First line	EQ-5D, WPAI-GH, EORTC QLQ-C30 (+ZBI for caregivers)	Linking patient clinical factors to patient and caregiver burden	As patients' functionality deteriorates as measured by the ECOG-PS, so do their outcomes related to health utility, work productivity, activity impairment and HR QoL. This deterioration is also reflected in increased caregiver burden and activity impairment	C3
29	Barlesi et al <sup>55</sup>	2019	Randomized controlled trials	1034 +427 caregivers	Pembrolizumab vs Docetaxel	EORTC QLQ-C30, EORTC QLQ-LC13, EQ-5D cycles 1, 2, 3, 5, and every 4 cycles until discontinuation and 30-day safety assessment	Evaluate the QoL of patient treated with pembrolizumab vs docetaxel	HR QoL and symptoms are maintained or improved to a greater degree with pembrolizumab than with docetaxel	C4



30	Geater et al <sup>35</sup>	2015	Randomized controlled trials	364	Afatinib or gemcitabine followed by cisplatin d1 and gem d8	EORTC QLQ-C30, EORTC QLQ-LC13 randomization and every 3 weeks until PD or start of new treatment	Evaluate the QoL of patient treated with Afatinib Versus Cisplatin/ Gemcitabine	Afatinib improved PFS and PROs versus chemotherapy in EGFR mutation-positive NSCLC patients. Progression was associated with statistically significant worsening in QoL	C1
31	Reck et al <sup>39</sup>	2019	Randomized controlled trials	583	Nivolumab plus ipilimumab versus chemotherapy	LCSS, EQ-5D baseline, w6, w12, w18, w24, w30, w36	Evaluate the QoL of patient treated with nivolumab plus ipilimumab versus chemotherapy	First-line nivolumab plus ipilimumab demonstrated early, sustained improvements in PROs versus chemotherapy	C2
32	Kawata et al <sup>38</sup>	2019	Randomized controlled trials	208	Two dosing regimens of brigatinib	EORTC QLQ-C30 every cycle	Evaluate the impact of brigatinib treatment on health utilities using two published algorithms	Converting QLQ-C30 scores into utilities in trials using established mapping algorithms can improve evaluation of medicines from the patient perspective. Both algorithms suggested that brigatinib improved health utility in crizotinib-refractory ALK + NSCLC patients	C1
33	McGee et al <sup>37</sup>	2018	Retrospective observational	528	Surgery, chemotherapy, radiotherapy	ESAS prior to each outpatient consultation	ESAS scale to identify patient-reported factors that may predict for treatment decisions in advanced NSCLC	Novel role for the ESAS as a prognostic tool that could complement existing patient assessment models	C1

**Abbreviations:** CACS, Cancer Anorexia-Cachexia Syndrome; 6MWT, 6-min Walk Test; BM, brain Metastasis; GHS, global Health Status; MT, maintenance Therapy; PC/G, maintenance Gefitinib; G, gefitinib Monotherapy; IMRT, Intensity-Modulated Radiation Therapy; 3DCRT, three-Dimensional Conformal Radiation Therapy; PBT, Proton-Beam Therapy; C1, PROs as Guide in Therapeutic Choice; C2, PROs as Indicator of Disease Progression; C3, Agreement Between PROs and the Evaluated Parameter; C4, PROs to Evaluate the Effects of Immunotherapy; C5, Need to Deepen the Knowledge of PRO; C6, Use of a New Electronic PRO.

severity, 2 (6.06%) evaluated QoL of patients treated with a specific regimen (nivolumab and brigatinib), 1 (3.03%) evaluated the QoL of patients treated with concurrent chemoradiation, 8 (24.24%) analyzed the correlation between QoL and different factors: age, EGFR mutation, brain metastasis, Cancer Anorexia-Cachexia Syndrome, dysphagia, disease progression, physical activity and patients' and caregivers' burdens.

We can classify the results of these articles into six categories (Table 2); the first includes all those studies where results indicate the use of PROs as a guide in therapeutic choice: the PRO-CTCAE has the potential to bring the patient's voice to clinical trials, and to provide insights into the patient's experiences of treatment,<sup>34</sup> the use of PROs measures in addition to PFS in the development of new treatments and as a consideration when choosing available treatment options for patients in the out-patient clinics were provided,<sup>35</sup> the integration of PROs generated in clinical trials as well as at an individual patient level is required to enable shared decision-making and personalized health care based on a mutual understanding of treatment objectives and expectations.<sup>36</sup> The ESAS questionnaire has a key role for the data it provides not only as a guide to symptom management for improved quality of life, but also in the development of optimal treatment plans and estimation of OS.<sup>37</sup> In addition, it was reported that converting QLQ-C30 scores into utilities in trials using established mapping algorithms can improve the evaluation of medicines from a patient's perspective.<sup>38</sup>

The second part of the article concerns the use of PROs as an indicator of disease progression, patient's QoL and survival. The differences of HR QoL evaluated with different PROs for patients treated with the two treatments under evaluation and their concordance about the outcome evaluated in the study were reported.<sup>39</sup> Disease progression had a significant adverse impact on many PROs'

**Table 2** Results Classification in Categories About the Topic of the Article

Topic	Number of Studies
PROs as guide in therapeutic choice	7
PROs as indicator of disease progression	5
Agreement between PROs and the evaluated parameter	13
PROs to evaluate the effects of immunotherapy	5
Need to deepen the knowledge of PRO	2
Use of a new electronic PRO	1

**Abbreviation:** PROs, Patient-Reported Outcomes.

endpoints;<sup>40</sup> PROs showed that they were useful in identifying patients with advanced NSCLC who are likely to have significantly lower survival.<sup>41</sup> The prognostic power of overall QoL on the survival of lung cancer patients and the advantages for lung cancer survivors reporting to be physically active was demonstrated versus those who were not physically active;<sup>42</sup> the early detection of symptomatic relapse and management of symptoms through a web-mediated individualized follow-up strategy provided an improvement in quality of life and overall survival.<sup>43</sup>

The third group included the studies that evaluated the agreement between the PROs and the evaluated parameters: concordance between LCSS and ECOG PS measurements and tumor-related symptoms is reported.<sup>44,45</sup> The use of PROs for the accurate assessment of health-related QoL in patients with lung cancer and to identify instruments to improve the value of care delivered was reported.<sup>46,47</sup> The utility of PROs to evaluate improvements in HR QoL and symptoms burden of the subgroups of patients treated with nivolumab and to analyze the AEs between the two treatment groups was reflected in PRO outcomes.<sup>48</sup> The correlation between PRO scores and deterioration of HR QoL in patient with brain metastases at the diagnosis of lung cancer was evaluated.<sup>49</sup> Using the EAT-10 and SWAL-QoL questionnaires, dysphagia was demonstrated a potential symptom in advanced lung cancer which may impact QoL, and some studies reported change in the mental component of HR QoL related to PROs outcomes<sup>50</sup> or showed the symptoms that need to be addressed in routine care of advanced NSCLC;<sup>51</sup> different studies reported that PROs are arguably more representative of the patient perspective than physician-reported outcomes.<sup>52–54</sup>

The fourth group concerned the evaluation of the role of PROs in assessing the effects of immunotherapy: the EORTC QLQ-LC13 instrument may not adequately reflect the experiences of patients who receive new therapies.<sup>55</sup> They concluded that commonly occurring symptoms attributed to immunotherapy can be found by using the EORTC QLQ-C30 and EORTC QLQ-LC13 questionnaires. PROs disease questionnaire find some, but not all relevant symptoms in a disease area and are unlikely to discover several common toxicities related to immunotherapy drugs.<sup>56</sup> PROs assessments should be considered standard tools in the future of cancer immunotherapy research because their use will lead to a better understanding of the effect of immunotherapy on patients' outcomes. Beyond the traditional parameters of OS and radiographic endpoints,<sup>57</sup> some

authors reported the need to develop instruments capable of evaluating the treatment-related symptoms hand-in-hand with the introduction of new therapies with specific related symptoms,<sup>58</sup> the prospective evaluation of PROs with the appropriate hypothesis and instruments, is vital particularly in clinical trials that evaluate new therapeutics in incurable cancers.<sup>59</sup>

Another group of studies expresses the need to deepen the knowledge of PROs: the MDASI scale was used to evaluate patient-reported symptoms. This scale does not evaluate coughing, a common symptom in lung cancer; as a standard of care and in clinical trials, the MDASI-LC test, which includes coughing, must be used to a complete evaluation of the patient's symptoms.<sup>60</sup> Widely used PRO-based symptom assessment tools are needed to facilitate a comparison of results with those of other published studies.<sup>61</sup> Only one study<sup>62</sup> reported the use of a new electronic PRO: the NSCLC-SAQ, after Food and Drug Administration (FDA) qualification, will be publicly available to capture patient-reported NSCLC-related symptoms via electronic data entry platforms. The use of PROs in the studies evaluated, it is not always a primary outcome. In some cases, especially for studies that evaluate PROs as a guide in therapeutic choice, PROs as indicators of disease progression and agreement between PROs and the evaluated parameters, the data obtained from the use of PROs is a secondary outcome of the study.

## Discussion

The purpose of this systematic review was to identify and describe peer-reviewed PROs used to evaluate QoL in lung cancer patients and to evaluate the feasibility and utility of PROs in surveillance strategies. Worldwide, lung cancer remains a disease with severe morbidity and mortality. Therefore, in addition to survival, the QoL of the patient is of great importance. There is a growing interest in measuring the QoL with the aid of PROs.<sup>63</sup> The subjective data about how therapies and diseases can modify patients' lives can be useful for the physicians and can compensate for the lack of time the physicians have for outpatients to understand the patients' point of view. In the studies reviewed, PRO-based endpoints are indicative of clinical benefit in terms of patient symptoms and overall quality of life. The addition of PROs to traditionally collected outcome measures (OS, PFS, DFS) can offer a comprehensive overview of patient status. In an optimal setting, the PROs should allow for an overall assessment of QoL, along with specific questionnaires to assess

specific effects associated with the disease and treatment. The most frequently used instruments are EORTC QLQ-30 (16, 50%) and EORTC LC-13 (14, 43.75%) and in some studies (37.5%) EORTC QLQ-C30 was supplemented with the EORTC QLQ-LC13, result in agreement with the European literature.<sup>64</sup>

There was great dispersion in data collection timing: the baseline is often collected, and subsequent checks ranging from a few weeks to some years or until PD or the start of a new treatment.

It must be emphasized that there is much evidence in the literature about the benefits of collecting and using PROs in lung cancer populations, for treatment monitoring,<sup>35,38-40,44-48,51,55,57-59,65-67</sup> detection of symptoms,<sup>36,37,41,50,53,54,60,65</sup> the role of patient or pathology characteristics on QoL,<sup>40,42,56,68</sup> to improve patient-clinician communication and patient satisfaction.<sup>43,61,62</sup> Only one study about the effect of disease progression on QoL was identified<sup>49</sup> assessing the use of PROs related to efficacy outcomes (PFS, OS). Data on PRO completion rates are available for 20 studies (60.61%) (Table 3), only in 3 studies (15%) was it lower than 80%,<sup>44,47,59</sup> for the others 17 (85%) it was higher than 80%.<sup>35,36,39,40,45,48,49,51,52,55-58,61,66-68</sup> Only in one study (5%) did the authors report a completion rate of 100%.<sup>52</sup> In most cases, frequencies decreased over time from baseline to subsequent measurements. The reasons given in the different studies were the increasing number of patients who discontinued the study due to disease progression, physician decision, adverse events, or death and the incomplete patient participation at each time point.

PROs are primarily collected in the context of scientific research. Moreover, the majority of the clinical trials do not use generic instruments but give preference to disease-specific instruments as they are more sensitive to subtle changes. Assessment of HRQL can help to better understand the physical, mental, and emotional implications of cancer and the effects of treatment on patients. PRO use was developed in scientific research to understand the efficacy of a treatment and to evaluate symptom type and impact on QoL and to act in a timely manner to control the symptom and its consequences on QoL. They become important also to evaluate new therapies taking into consideration, in addition to clinical results, also the quality of life of the patient. Since the association of QoL with survival PROs use appears to be a strong and independent factor in the prediction of survival in lung cancer.<sup>64,69</sup>

**Table 3** Literature Data

Author	Number of Patients Complied PROs (%)	Compliance	Results
King-Kallimanis et al <sup>56</sup>	695 (100)	90–80% >95%	No large differences at baseline or in the distributions of change from baseline in PROs between younger and older patients
Wu et al <sup>68</sup>	301(100)	90%	First-line afatinib improved lung cancer-related symptoms and GHS/QoL compared with chemotherapy
Bordoni et al <sup>57</sup>	850(100)	>95%, >80%	PROs data support the clinical benefit of atezolizumab in patients with previously treated advanced or metastatic NSCLC
Lee et al <sup>59</sup>	419(100)	88–72% 60%	A higher proportion of patients treated with osimertinib had improvement in global health status/quality of life
Walker et al <sup>40</sup>	145(100)	98%	PROs measures show disease progression is associated with worsening HR QOL. Delaying disease progression can sustain better HRQL and reduce symptom burden
McCarrier et al <sup>62</sup>	10(19.6)	nr	NSCLC-SAQ is currently undergoing quantitative testing to confirm its measurement properties and support FDA qualification
Blackhall et al <sup>52</sup>	343(100)	83–100%	The benefits of crizotinib in improving symptoms and QOL are demonstrated regardless of whether the comparator is pemetrexed or docetaxel
LeBlanc et al <sup>53</sup>	97(100)	nr	Patients with a NSCLC face a significant symptom burden, which increases with proximity to death
LeBlanc et al <sup>41</sup>	99(100)	nr	The weight-based definition is useful in identifying patients with advanced NSCLC who are likely to have significantly inferior survival and who will develop more precipitous declines in physical function and QOL
von Verschuer et al <sup>51</sup>	495(39.96)	87–68%	HR QOL data comparing treatments show no difference between carboplatin and cisplatin
Shallwani et al <sup>50</sup>	47(100)	nr	Pre-chemotherapy 6MWT distance and fatigue severity predicted change in the mental component of HR QOL in patients with advanced NSCLC undergoing chemotherapy, while physical performance declined during treatment
Sebastian et al <sup>34</sup>	161(100)	nr	Symptoms were generally mild and not frequent, with some differences in symptom patterns between the two treatment groups
Brady et al <sup>65</sup>	72(100)	nr	Dysphagia is a potential symptom in advanced lung cancer which may impact QOL
Walker <sup>49</sup>	147(100)	98%	Newly diagnosed advanced NSCLC patients with baseline BM experienced a significantly faster and clinically meaningful deterioration in PRO-based HR QOL compared with those without baseline BM
Felip et al <sup>48</sup>	795(100)	95%	Significantly more patients who received afatinib versus erlotinib experienced improved scores for (GHS)/QoL.
Brahmer et al <sup>58</sup>	299(100)	90–80%	Pembrolizumab improves or maintains health-related QOL compared with that for chemotherapy
Reck et al <sup>66</sup>	582(100)	98%	Nivolumab improved disease-related symptoms and overall health status versus docetaxel for second-line treatment of advanced non-squamous NSCLC
Denis et al <sup>43</sup>	60(100)	nr	A web-mediated follow-up algorithm based on self-reported symptoms improved OS due to early relapse detection and better performance status at relapse

(Continued)

**Table 3** (Continued).

Author	Number of Patients Complied PROs (%)	Compliance	Results
Sztankay et al <sup>36</sup>	83(100)	84%	HR QOL and symptom burden improve between first-line treatment to MT, the integration of patient-reported outcomes is required to enable shared decision-making and personalized healthcare
Sloan et al <sup>42</sup>	1466(100)	nr	Being physically active was related to profound advantages in QOL and survival in a large sample of lung cancer survivors
Wang et al <sup>61</sup>	92(100)	96%	Patients receiving PBT reported significantly less severe symptoms than did patients receiving IMRT or 3DCRT
Spigel et al <sup>67</sup>	1426(100)	80%	The median overall survival for patients with an ECOG PS of 2 was lower than for the overall population but comparable with historical data
Nguyen et al <sup>46</sup>	32(100)	nr	Measuring PROs can help to identify issues for improvement of the value of care delivered
Mendoza et al <sup>60</sup>	460(100)	nr	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
Novello et al <sup>47</sup>	1051(79.98)	70%	The significant OS benefit observed with the addition of nintedanib to docetaxel therapy was achieved with no detrimental effect on patient self-reported QoL
Pèrol et al <sup>44</sup>	1253(100)	75%	Adding ramucirumab to docetaxel did not impair patient QoL, symptoms, or functioning
Boye et al <sup>45</sup>	236(100)	92%	LCSS scores were more favorable in the G group than in the PCnrg group
Wood et al <sup>54</sup>	1030(100)	nr	As patients' functionality deteriorates as measured by the ECOG-PS, so do their outcomes related to health utility, work productivity, activity impairment and HR QoL. This deterioration is also reflected in increased caregiver burden and activity impairment
Barlesi et al <sup>55</sup>	1034+427 (100)	95–85%	HR QoL and symptoms are maintained or improved to a greater degree with pembrolizumab than with docetaxel
Geater et al <sup>35</sup>	364(100)	96–88%	Afatinib improved PFS and PROs versus chemotherapy in EGFR mutation-positive NSCLC patients. Progression was associated with statistically significant worsening in QoL
Reck et al <sup>39</sup>	583(100)	90–80%	First-line nivolumab vs ipilimumab demonstrated early, sustained improvements in PROs versus chemotherapy
Kawata et al <sup>38</sup>	208(100)	nr	Converting QLQ-C30 scores into utilities in trials using established mapping algorithms can improve evaluation of medicines from the patient perspective. Both algorithms suggested that brigatinib improved health utility in crizotinib-refractory ALK + NSCLC patients
McGee et al <sup>37</sup>	528(100)	nr	Novel role for the ESAS as a prognostic tool that could complement existing patient assessment models

**Abbreviations:** CACS, Cancer Anorexia-Cachexia Syndrome; 6MWT, 6-minWalk Test; BM, brain metastasis; GHS, global Health Status; MT, maintenance Therapy; PCnrg, maintenance Gefitinib; G, gefitinib Monotherapy; IMRT, Intensity-Modulated Radiation Therapy; 3DCRT, three-Dimensional Conformal Radiation Therapy; PBT, Proton-Beam Therapy; Nr, not reported.

The literature demonstrates that the use of PROs continues to increase, the collected data support the hypothesis that PROs can play an important role as part of the health care and that routine use implementation could improve patient management: early identification of symptoms and adverse events due to treatment, monitor the patient's response to therapy and improve communication between patient, health care professional and caregivers<sup>70</sup> with a consequent reduction of costs for exams, therapies and hospitalizations avoidable with a timely intervention. Steps for routine implementation of PROs were previously reported<sup>71</sup> but cost-effectiveness of the use of PROs is still under evaluation. Despite the good psychometric properties and all the possible advantages of instruments already mentioned, the feasibility of the routine implementation of PROs finds some practical difficulties: the availability of personnel, programming of training for the correct administration and interpretation of PROs, costs, time required and the need for people able to analyze the data collected.<sup>72</sup> Without proper preparation and organization, their use is disruptive to normal work routines. One of the things that made the PROs easier to administer, but mostly simplified the data collection and analysis phase, was the transition from paper versions to electronic platforms, with a significant reduction of time.<sup>73</sup>

Considering the fact that there are almost 200 tumor types, PROs are not cancer-specific because they do not consider that different cancers involved different symptoms, as well as they do not specify selected treatment benefits or toxicity. There is no objective consideration and no comparison between the questionnaires that can be formulated. Further studies would be useful to assess the symptoms associated with different therapies such as immunotherapy.

However, there are many considerations that need attention to enable long-term, quality collection and use of PRO data within routine clinical settings.<sup>71</sup> These include identifying the goals of PROs collection; patient selection; setting and timing of assessments; choice of questionnaire; scale of interpretation and the way to facilitate it, developing strategies for responding to issues detected by the questionnaires and evaluating the impact of the PROs in the practice. To our knowledge, there are no comparison parameters between the various PROs and therefore it is difficult to find a method of evaluation of utility and feasibility applicable in the comparison between the different used tools. Utility and feasibility are described by the assessment of costs, times, staff required, limits of applicability and interpretation issues.

The limitations of this revision are the reduced time period of publication, the choice of PROs also not specific for lung cancer and the exclusion of studies in which PROs were not the primary objective. PROs results, obtained in a routine collection could provide the basis on which adapt therapy and interventions to the needs of the patient, to improve both QoL and the probability of survival. A study carried out in 2011<sup>74</sup> shows the improvement of the communication between the patient and the health care professional, and the monitoring of the response to treatment and the satisfaction of the patient when routinely collecting PROs. More recently, a randomized clinical trial investigated the influence of routinely collecting PROs in cancer patients.<sup>75</sup> It evaluated the use of e-mail alerts to severe symptoms or to usual care; the e-mail system allowed an immediate action such as medications or access to the emergency room. The results were a better control of symptoms in the e-mail group, resulted in a better HR QoL, fewer visits to the emergency room, fewer hospitalizations, longer duration of palliative chemotherapy and both improved one-year survival and quality-adjusted survival.<sup>76</sup> PROs are also applied in the field of palliative care, where different studies have tried to evaluate the impact on the OS and patients QoL but the factors to be evaluated, including those related to the families and the patient's caregivers are complex. The number of studies is still reduced and the results are difficult to compare.<sup>77,78</sup>

The inclusion of PROs as endpoints in clinical trials is encouraged by the FDA, the European Medicines Agency (EMA)<sup>79</sup> and scientific societies as the European Society of Medical Oncology.<sup>80</sup> US Food and Drug Administration has recently published guidelines on the review and evaluation of PROs to encourage their appropriate use in regulatory studies and decisions.

## Conclusion

A great variety of PROs are used with lung cancer patients in order to improve quality of care. A general questionnaire to assess overall QoL, which can be supplemented with disease-specific questionnaires allowing for the assessment of QoL of different treatment methods seems to be most effective. PROs can be used for different purposes and can be focused on the specific disease or symptoms or related to the progression of the disease. The standard routine use of PROs is still not widely recognized, despite the



positive aspects reported. This can be related to organization, timing and personnel difficulties. A step towards solving these problems is the introduction of electronic PROs. We emphasized the unmet need for focused research to justify and to guide the analytic method of PROs to facilitate the interpretation of patient experience. Future research should assess the applicability of PROs in routine clinical practice.

## Abbreviations

SF-36, 36-item Short-Form Health Survey; MDASI, MD Anderson Symptom Inventory; DFS, disease-free survival; EAT-10, Eating Assessment Tool; ESAS, Edmonton Symptom Assessment Scale; EMA, European Medicines Agency; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FDA, Food and Drug Administration; FAACT, Functional Assessment of Anorexia/Cachexia Treatment; FACT - F, Functional Assessment of Cancer Therapy - Fatigue; FACT - G, Functional Assessment of Cancer Therapy - General; FACT - L, Functional Assessment of Cancer Therapy - Lung Cancer; HR QoL, health-related quality of life; LCSS, Lung Cancer Symptom Scale; NSCLC-SAQ, Non-Small Cell Lung Cancer Symptom Assessment Questionnaire; OS, overall survival; PROs, Patient Reported Outcomes; PG-SGA, Patient-Generated Subjective Global Assessment; PRO-CTCAE, Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events; PCM, Patients' symptoms via the Patient Care Monitor; RALS, Rotterdam Activity Level Scale; SWAL-QoL, Swallowing Quality of Life instrument; LCS, The Lung Cancer Subscale; SCFS, The Schwartz Cancer Fatigue Scale; TKIs, tyrosine kinase inhibitors; WPAIGH, Work Productivity and Activity Impairment: General Health; ZBI, Zarit Burden Interview.

## Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Luigi Cavanna reports consulting and advisory roles for AstraZeneca and Merck; travel and accommodation expenses from Celgene, Pfizer, and Ipsen. The other authors have no financial support or relationships that may pose a conflict of interest with this work.

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