



Characteristics and patient-reported outcomes of long-term lung cancer survivors

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Background: Due to advances in screening and treatment of lung cancer, there has been increased interest in long-term lung cancer survivors (LTLCS). The aim of this study was to evaluate the prevalence of LTLCS, their characteristics and patient-reported outcomes (PROs) of LTLCS.

Methods: Cross-sectional study that included patients diagnosed with primary lung cancer between Jan 2012 and Dec 2016 whose overall survival (OS) was greater than 5 years. A self-administered questionnaire was applied, including European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), Patient Health Questionnaire-4 (PHQ-4) and two open questions regarding quality of life (QoL) and suggestions for improvements. Factors potentially related to QoL were analysed.

Results: Of 767 lung cancer patients, 158 (20.6%) were LTLCS and LTLCS' proportion increased yearly. Most patients were male (70.9%) with median age of 65 [interquartile range (IQR), 56–71] years. Fifty-seven percent had adenocarcinoma, 66.2% were diagnosed at early stages but 8.9% were at stage IV. During follow-up, 77.1% quit smoking, 31.8% had disease progression/relapse and 15.2% developed other tumours. Of all living LTLCS, 100 (85%) patients answered the PROs questionnaire. The median Global Health score was 66.67 (IQR, 50–83), social functioning had the best score and emotional functioning the worst. Pain and fatigue were the symptoms with the worst impact on QoL. PHQ-4 identified mental distress in 36% and patients with a lower QoL were more likely to present anxiety (35.3% *vs.* 9.4%, $P=0.007$) or depression (27.9% *vs.* 3%, $P=0.006$). In the open questions, patients reported pain (17%), lack of familiar/financial support (16%), dyspnoea (14%), depression (8%), concern for the future (8%) and limitations performing daily activities (8%) as the aspects with most impact in QoL. The most suggested measures were improvement of care provided by health institutions (25%) and better social support (16%).

Conclusions: Prevalence of LTLCS is increasing and survivors may experience a high prevalence of anxiety and depression as well as a high disease burden affecting QoL. Therefore, it's important to provide multidisciplinary continuous patient-centred care and a careful follow-up for all lung cancer patients, including LTLCS.

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Introduction

Lung Cancer is the second most common cancer worldwide and the main cause of death by cancer (1). According to the 8th tumour, node, metastasis (TNM) edition for lung cancer, the five-year lung cancer survival rate varies between 92% (stage IA1) and <1% (stage IVB) (2) with only 23% diagnosed early (3).

Recent progress in lung cancer molecular characterization and immune system interactions (4) led to the development of new targeted therapies and immunotherapy, improving clinical outcomes, including overall survival (OS) (5-9). Furthermore, the worldwide spread of lung cancer screening will shift the staging of new lung cancer diagnoses to earlier stages (10) increasing long-term survival and long-term lung cancer survivors (LTLCS) prevalence in coming years.

The definition of LTLCS has also evolved over time. The first publications defined it as the population with lung cancer with a survival longer than 2 years after diagnosis (11-15) but recent publications extend it to 5 years (8,16-20),

aligning with recent therapeutic and diagnostic advances.

Identifying clinical, demographic and tumour characteristics of LTLCS may help to identify these patients earlier (21). Furthermore, the evaluation of patient-reported outcomes (PROs) of LTLCS is of particular interest as it may have an impact on their follow-up (22). Nevertheless, LTLCS have been underrepresented in research (19).

This study aims to assess the LTLCS prevalence, describe their demographic and clinical characteristics, understand what happened throughout their follow-up and evaluate PROs. We present this article in accordance with the STROBE reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1494/rc>).

Methods

Study design and data collection

We conducted a cross-sectional study at a Portuguese tertiary hospital's Multidisciplinary Thoracic Tumours Unit (MTTU). This unit is responsible for the treatment and follow up of all referred lung cancer patients, regardless of their stage at diagnosis or prior treatments. Inclusion criteria were primary lung cancer diagnosed between Jan 2012 and Dec 2016; age >18 years at diagnosis; and OS >5 years. Patients who abandoned follow-up or refused to participate were excluded.

OS was defined as the duration from the date of diagnosis to death or last follow-up, with no restriction on the cause of death (23). The patient's vital status was verified via the national health registry.

Patients' demographics, clinical characteristics, treatments, the number of emergency visits, hospitalizations, the occurrence of other tumours, and the evolution of their smoking habits were collected from medical records. Living LTLCS in 2022 filled a self-administered PROs questionnaire, on paper support, when they went to MTTU for their scheduled consultation. Cause of death was collected for all LTLCS who had already died in 2022. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved

Highlight box

Key findings

- The prevalence of long-term lung cancer survivors (LTLCS) is increasing and these patients may present significant physical and psychological challenges. Implementing multidisciplinary, patient-centered care with careful follow-up is imperative.

What is known and what is new?

- Advancements in lung cancer molecular characterization, immune system interactions, and lung cancer screening may contribute to the growing prevalence of LTLCS. Despite this, this population remains understudied.
- Our study revealed a high incidence of anxiety, depression, and a substantial disease burden among LTLCS, impacting their quality of life.

What is the implication, and what should change now?

- Prioritizing long-term, comprehensive healthcare alongside social, financial, and family support is essential for LTLCS.
- The establishment of follow-up guidelines is crucial to streamline efficient and timely procedures for these patients.

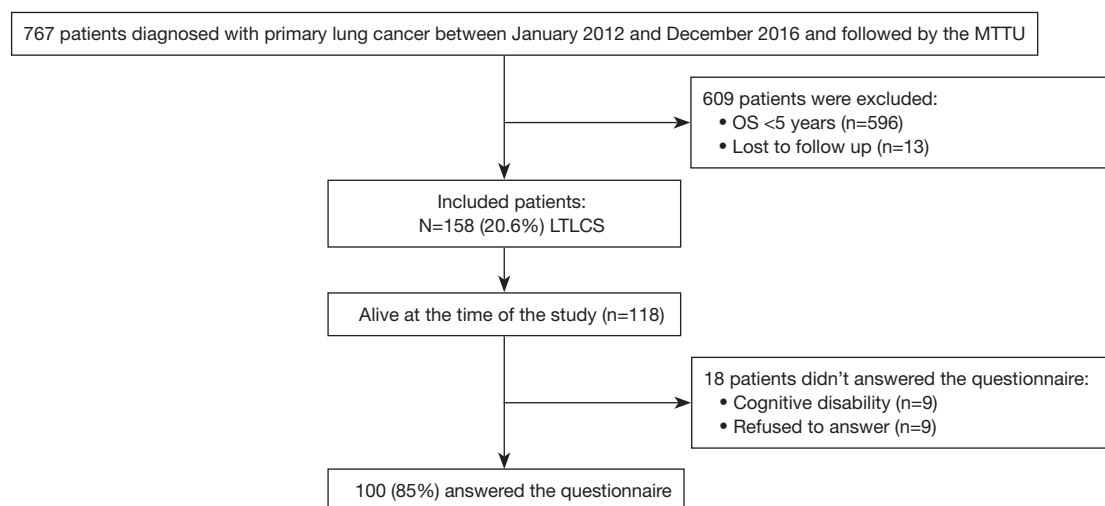


Figure 1 Study flow diagram. MTTU, multidisciplinary thoracic tumours unit; OS, overall survival; LTLCs, long-term lung cancer survivors.

by the institutional review board of Centro Hospitalar Vila Nova de Gaia e Espinho (No. 236-2022-1). All participants provided written informed consent.

Assessment of PROs

Quality of life (QoL) was assessed as part of the patient self-administered questionnaire using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) (17,24,25). Anxiety and depression were measured using the four-item self-reported Patient Health Questionnaire-4 (PHQ-4) (25).

We added two open questions to the self-administered questionnaire: (I) “What most affects your current quality of life?” and (II) “Which measures would you suggest for supporting lung cancer patients diagnosed more than 5 years ago?”.

EORTC QLQ-C30

The EORTC QLQ-C30, a validated 30-item questionnaire (25), has five functioning scales (physical, role, emotional, cognitive, social functioning) and assesses nine symptoms (fatigue, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties) (26). Score ranges from 0 to 100 and higher scores indicate better QoL on global QoL and functioning scales, while on symptom scales, higher scores indicate poorer QoL (26).

After scoring, patients were grouped in two categories:

(I) worse QoL (global QoL score $\leq 50^{\text{th}}$ percentile) and (II) better QoL (global QoL score $> 50^{\text{th}}$ percentile).

PHQ-4

PHQ-4 combines a two-item depression measure—Patient Health Questionnaire-2 (PHQ-2) and a two-item anxiety measure—Generalized Anxiety Disorder-2 (GAD-2). Scores range from 0 to 6, with 3 or more indicating probable mental distress on either PHQ-2 or GAD-2 (25).

Statistical analysis

Descriptive statistics of the variables of interest were expressed as absolute and relative frequencies or median and interquartile range (IQR). Group comparisons (worse versus better QoL) were made using chi-square test for categorical variables, and Mann Whitney *U*-test for nonparametric variables, with *P* value < 0.05 considered statistically significant. Kaplan-Meier curves were used for survival analysis. Statistical analysis was performed using SPSS version 27. Regarding the answers to the two open questions, we conducted a qualitative analysis, following Colaizzi’s seven-step method (27).

Results

Out of 767 patients diagnosed with primary lung cancer during the selected period, 158 (20.6%) were LTLCs patients. *Figure 1* illustrates the study flow. The proportion

Table 1 Baseline characteristics of long-term lung cancer survivors and their evolution during follow-up

Characteristics	LTLCS (n=158)
Gender, n (%)	
Female	46 (29.1)
Male	112 (70.9)
Age at diagnosis, years, median [IQR]	65 [56–71]
Smoking habits at diagnosis, n (%)	
Never smoker	45 (28.5)
Smoker	48 (30.4)
Former smoker	65 (41.1)
ECOG, n (%)	
0	99 (62.7)
1	58 (36.7)
2	1 (0.6)
Histology, n (%)	
Adenocarcinoma	90 (57.0)
Squamous cell carcinoma	30 (19.0)
Typical carcinoid	19 (12.0)
SCLC	7 (4.4)
Atypical carcinoid	6 (3.8)
Other	6 (3.8)
7 th TNM stage, n (%)	
Stage I–II	104 (65.8)
Stage III	39 (24.7)
Stage IV	14 (8.9)
Missing data (patient not staged)	1 (0.6)
Number of treatments, n (%)	
0	1 (0.6)
1	111 (70.3)
2	23 (14.6)
3	15 (9.5)
4	4 (2.5)
6	4 (2.5)
First treatment, n (%)	
Surgery	61 (38.6)
Surgery + ACh	36 (22.8)
CRT	27 (17.1)
SBRT	18 (11.4)
Ch	10 (6.3)
TKI	4 (2.5)
Clinical trial	1 (0.6)
None	1 (0.6)

Table 1 (continued)**Table 1** (continued)

Characteristics	LTLCS (n=158)
Tumour follow up during 5 years	
Progression/relapse, n (%)	50 (31.6)
Number of emergency visits, median [IQR]	3 [1–8]
Number of hospitalizations, median [IQR]	1 [0–2]
Presence of other tumours, n (%)	
No	124 (78.5)
Yes	34 (21.5)
Metachronous*	24 (15.2)
Synchronous [‡]	6 (3.8)
Previous to lung cancer [§]	4 (2.5)

*, second primary lung cancer (n=12), head and neck cancer (n=4), bladder cancer (n=4), kidney cancer (n=2), rectal cancer (n=2), colon cancer (n=1), abdominal liposarcoma (n=1) and breast cancer (n=1). [‡], second primary lung cancer (n=3), head and neck (n=2) and colon cancer (n=1). [§], head and neck (n=2), kidney cancer (n=1), prostate cancer (n=1) and cervix cancer (n=1). LTLCS, long-term lung cancer survivors; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; SCLC, small cell lung cancer; TNM, tumour, node, metastasis; ACh, adjuvant chemotherapy; CRT, chemoradiotherapy; SBRT, stereotactic body radiation therapy; Ch, chemotherapy; TKI, tyrosine kinase inhibitor.

of LTLCS increased annually: in 2012 it was 22/149 (14.8%), in 2013: 31/170 (18.2%), in 2014: 27/141 (19.1%), in 2015: 39/155 (25.2%) and in 2016: 39/152 (25.7%).

Characteristics of the population

Baseline characteristics of the LTLCS are described in *Table 1*. Most were male, with a median age at diagnosis of 65 (IQR, 56–71) years and predominantly had lung adenocarcinoma (57%). Although most patients (65.8%) were diagnosed at early stages (stage I–II), 8.9% were stage IV at diagnosis. Among stage IV patients, 78.6% were male, with a median age of 70 (IQR, 55–73) years old, 42.9% had oligometastatic disease, 35.7% received at some point tyrosine kinase inhibitors (TKIs) and 28.6% received immunotherapy.

Evolution during follow up

After 5 years of follow up, 77.1% of the 48 active smokers at diagnosis quitted smoking. Of all active smokers at diagnosis, 31.3% (n=15) had a smoking cessation

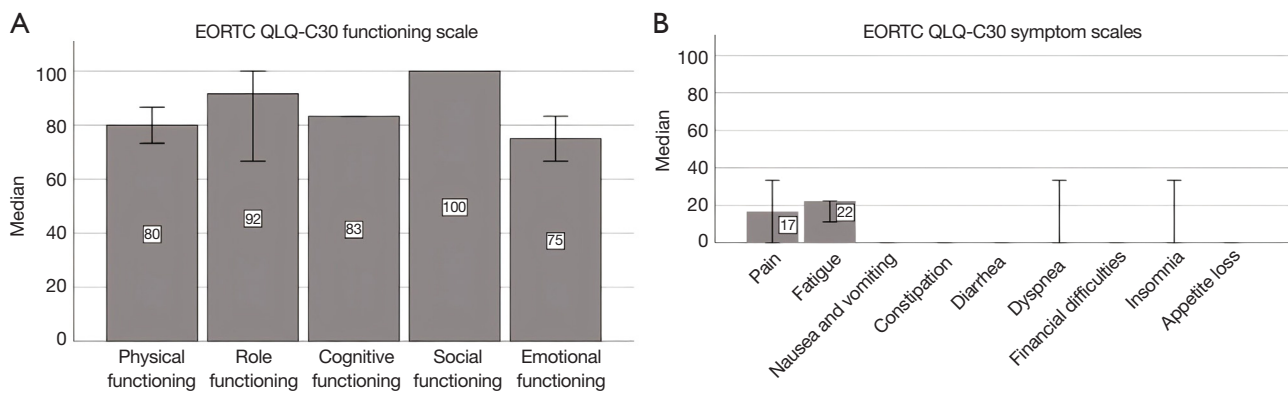


Figure 2 Evaluation of EORTC QLQ-C30. (A) EORTC QLQ-C30 functioning scales results. (B) EORTC QLQ-C30 symptom scales results. Bars represent median values and error bars represent interquartile range. EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30.

consultation. There was no significant difference in success rates between patients who had and who didn't have a smoking cessation appointment (60% *vs.* 84.8%, $P=0.074$).

Over a median follow up of 90 (IQR, 78–106) months, 31.6% patients had disease progression or relapse (48% were stage I–II at diagnosis, 24% stage III and 28% stage IV). Of all patients who were treated with curative intent, 7 (24%) progressed after 5 years of follow up. Additionally, 24 (15.2%) developed metachronous tumours, mainly a second primary lung cancer ($n=12$), head and neck cancer ($n=4$) and bladder cancer ($n=4$). Of these, 75% had a history of smoking.

Among LTLCS, 40 (25.3%) were dead at the time of the study and from the living patients in 2022, 83 patients (70.3%) were disease-free: 54 with stage I at diagnosis, 8 with stage II and 21 with stage III. The median OS of LTLCS was not reached at 7.5 years of follow up and the median OS of patients who had perished was 76 (IQR, 70–82) months. Fourteen patients died from lung cancer disease progression and 3 from treatment related adverse events caused by everolimus ($n=1$), pembrolizumab ($n=1$) and chemotherapy ($n=1$). From the remaining, 11 died due to infectious intercurrents, 4 due to other tumours, 2 due to cardiac disease, 2 due to kidney disease, 1 due to seizures and 3 due to unknown causes.

PROs

Out of 118 living patients at the time of the study, 100 (85%) answered the questionnaire.

Figure 2 describes the EORTC QLQ-C30 results. The

median global QoL score of our population was 66.67 (IQR, 50–83) and 68% had a worse QoL (global QoL $\leq 50^{\text{th}}$ percentile). Patients with worse QoL visited the emergency department more frequently [4 (IQR, 1–9) *vs.* 2 (IQR, 0–3) visits; $P=0.012$]. The worse scores were in emotional and physical function and in fatigue and pain symptoms (Figure 2).

PHQ-4 identified mental distress in 36% of patients, with 27% having anxiety and 20% having depression. Of those, 41.7% had a psychology or psychiatry appointment within the first year after diagnosis and 19.4% of them were still in follow-up. Patients with a lower QoL were more likely to experience anxiety (35.3% *vs.* 9.4%, $P=0.007$) or depression (27.9% *vs.* 3%, $P=0.006$).

Tables 2,3 presents the results for the content analysis of the open questions. Patients mentioned emotional/psychological issues, physical symptoms, physical limitations and lack of support. The most prevalent issues included depression (“I feel this is the end”), and concern for the future (“I feel that life is unpredictable”). Pain and dyspnoea were the symptoms that most often affected QoL. Other aspects with impact on their QoL included limitations in performing their daily activities (“I can't do my job”) and insufficient financial or family support (“I don't have enough money to buy medication”; “I lack support from my family”). Twelve percent answered that there was nothing affecting their QoL at that moment. The answers were meaningless in 5% of patients and 6% did not respond.

Regarding the question “Which measures would you suggest for supporting lung cancer patients diagnosed more than 5 years ago?”, 37% of patients gave suggestions.

Table 2 Content analysis of the question 1 “What most affects your current quality of life?”

Category	%	Examples
Emotional/psychological issues		
Depression	8	“I feel this is the end”
Concern for the future	8	“I feel that life is unpredictable” “I’m worried about the future”
Anxiety	4	“I feel a lot of anxiety”
Physical symptoms		
Pain	17	“Headache”, “Back pain”, “Pain”
Dyspnea	14	“Shortness of breath”
Fatigue	6	“I feel tired”
Skin symptoms	2	“Photosensitivity in the skin”, “Skin problems”
Urinary symptoms	2	“Prostatic symptoms” “Urinary issues”
Other symptoms	5	“I cough a lot”, “I sweat a lot”, “Impaired sex life”, “Problems with my vision”, “Gastrointestinal problems”
Physical limitations		
In daily activities	8	“I can’t do my daily activities”, “I can’t do my job”
In exercise	7	“I can’t pick up heavy things”, “I have difficulty in exercising”
In mobility	7	“I walk with limitations”
Lack of support		
Family	10	“I lack support from my family”, “I am a widower”
Financial	6	“I don’t have enough money to buy medication”, “I spend a lot of money on medication”

Table 3 Content analysis of the question 2 “Which measures would you suggest for supporting lung cancer patients diagnosed more than 5 years ago?”

Category	%	Examples
Provision of health care	25	“Better conditions at the hospital” “The interval between consultations should be shorter” “Screening lung cancer programs to prevent late diagnosis”
Social support	10	“I would like more human support from society” “I need more social support”
Psychological support	7	“A multidisciplinary team responsible for the follow up, including a psychologist” “I would like to have psychology consultations”
Financial support	6	“Smoking cessation medication to be reimbursed by the state” “More financial support to buy the medication”

Twenty-five patients recommended enhancing healthcare conditions, such as “Better conditions at the hospital” or “Screening lung cancer programs to detect lung cancer earlier”. Seven emphasized the need for increased psychological support, and 16 proposed better social and/or financial assistance, including aid for smoking cessation medication. The answers were meaningless in 5% of patients and 14% did not answer this question.

Discussion

Our study showed that almost one-quarter of lung cancer patients are LTLCS, with this proportion increasing annually. LTLCS displayed varying QoL scores and those with worse QoL were more likely to present anxiety and/or depression and went more often to the emergency room.

The prevalence of LTLCS reported in our study is higher than in previous studies (16,28), likely due to be a more recent study. This increasing prevalence of LTLCS highlights the need to know more about these patients.

As expected, most LTLCS had an early stage at diagnosis (16), reinforcing the need of making the diagnosis as early as possible, to which lung cancer screening can contribute (10). Interestingly, in our study 1 in 11 LTLCS (8.9%) had metastases at diagnosis, which is slightly higher than previous studies (3,16). This is probably related to the fact that almost half of these patients had oligometastatic disease and more than two third were treated with TKI or immunotherapy, which are factors associated with better outcomes (5-9). Therefore, it is important to reinforce among the medical community that the presence of metastases at diagnosis is not always associated with a poor short-term prognosis, as this may affect clinical decisions.

Most patients were smokers or former smokers at diagnosis, as previously described (29), emphasizing that smoking is one of the most important risk factors for lung cancer. Smoking cessation is the most effective way to reduce the risk of developing lung cancer and has an impact on the success of lung cancer treatment (10,29,30). Of active smokers at diagnosis, 77.1% quit within 5 years, but only one-third had specialized cessation appointments. This highlights that the diagnosis of lung cancer can be a moment when patients are more receptive to smoking cessation, even without specialized cessation appointments (31). However, it was not possible to evaluate if patients received smoking cessation interventions during lung cancer appointments, if they refused smoking cessation consultations or if they were not offered to them. Nevertheless, one of the measures

suggested by our LTLCS was more financial support for smoking cessation medication, suggesting that financial support to buy these medications may improve the success rate.

Moreover, another important aspect in the follow-up of these survivors is the possibility of the appearance of other tumours. In our study, around 15% of patients developed metachronous tumours, often linked to current or past smoking habits. This emphasizes the importance of smoking cessation and the need for adequate follow-up to diagnose new primary tumours and recurrences earlier. In fact, one third of patients had disease progression or relapse and 14.5% required at least three different lines of treatment which indicates that LTLCS is not always synonymous with cure.

Like in other studies, primary lung cancer was a significant cause of death among LTLCS (16,18,32). Still, over half of the patients died from infections or comorbidities. This highlights the importance of monitoring and optimizing comorbidities, as they may greatly affect the survival and QoL of LTLCS (16,17,19).

Besides survival analysis, assessing PROs is crucial. Our study evaluated not only scales of QoL and mental distress but also open questions that allowed patients to share impactful aspects on their QoL and proposed measures to be implemented.

The median EORTC QLQ-C30 Global Health score was 66.67 (IQR, 50–83) better than reference values for all stages of lung cancer (33). As far as we know, no prior studies provided EORTC QLQ-C30 median scores in the general Portuguese population, limiting comparisons. However, compared to the general European population (34), LTLCS had a poorer median Global Health score. While interpretation requires caution, it suggests LTLCS patients have better QoL than other lung cancer patients (19,20,24,25,35) but still lower than the general population.

Pain and fatigue had the worst symptom scores, as confirmed in the open QoL question where patients mentioned them along with dyspnoea, cough and erectile dysfunction. These findings highlight the significant impact of symptom burden on patients' QoL (20,25,36,37). Regarding functioning, physical and emotional functioning had the lowest QoL scores, consistent with prior studies (17,20). To enhance QoL, early integration of primary healthcare, palliative care and emotional support is essential for these patients.

Anxiety and depression also contribute to a lower QoL

(19,37,38). In our study, PQH-4 revealed over a third of patients had probable mental distress and those patients had more frequently a worse QoL. In fact, 41.7% had a psychology or psychiatry appointments within the first year after diagnosis, and 7% suggested greater psychological support. Identifying and consistently addressing these patients is crucial to prevent, detect and treat mental distress. Moreover, patients with worse QoL also visited emergency care units more often, an association that may be bidirectional. No other clinical or demographic characteristics, including stage IV at diagnosis, were statistically significant associated with worse QoL, though a lowest score was found in stage IV LTLCS (61.52 in stage I–II; 63.43 in stage III and 52.78 in stage IV).

Our study had several limitations. First, it is a cross-sectional study, making it impossible to identify predictive factors for being LTLCS and to analyse the evolution of PROs over time. Secondly, being a single institution study may introduce selection bias. Nevertheless, this unit treats and follows up on all referred lung cancer patients, regardless of their geographic address, making it comparable to other institutions. Thirdly, the self-administered questionnaire had an 85% response rate, which may represent a selection bias. Half of the non-responders had cognitive disability and the others refused to answer without known reasons. Furthermore, the lack of validation for the two open questions might have led to misinterpretations. Lastly, qualitative content analysis can be subject to interpretation errors and observer bias, though final agreement among all authors aimed to minimize these issues.

Nevertheless, this study provides real world data and new insights from an understudied population. It addressed PROs of LTLCS, including not only validated numeric scales but also patients' input on improving their QoL.

Conclusions

In conclusion, LTLCS prevalence is increasing and survivors may experience a significant physical and psychological burden. These patients should receive continuous healthcare along with social, financial and family support. Multidisciplinary patient-centered care may enhance LTLCS outcomes. Establishing follow-up guidelines is vital for efficient and timely procedures.

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This manuscript has not been published in another journal;

however, this study was the theme of the master's thesis of a medical student, Mariana Antunes, and for this reason, it is included in the University of Porto's repository.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1494/rc>

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-23-1494/coif>). M.D. reports to have received fees/honoraria from AstraZeneca and MSD in the context of presentations and meetings related to lung cancer, but no specific lung cancer medication related to these companies is mentioned in this manuscript. J.F.M. reports that he has provided consultancy services in clinical research training to MSD and given lectures to train health professionals in the field of clinical research for both MSD and Pfizer, but not related to the topic or the current manuscript. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the institutional review board of Centro Hospitalar Vila Nova de Gaia e Espinho (No. 236-2022-1). All participants provided written informed consent.

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