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Quality of life analysis in lung cancer: A systematic review of phase III trials published between 2012 and 2018

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ABSTRACT

Objectives: We previously reported that quality of life (QoL) is not included among trial endpoints and QoL results are underreported in a significant proportion of phase III oncology trials. Here we describe QoL adoption, reporting and methodology of QoL analysis in lung cancer trials.

Materials and methods: We selected all primary publications of lung cancer phase III trials assessing anticancer drugs published between 2012 and 2018 by 11 major journals.

Results: 122 publications were included. In 39 (32.0%) publications, QoL was not listed among endpoints: in 10/17 (58.8%) early stage/locally advanced NSCLC, in 15/54 (27.8%) first-line of advanced NSCLC; in 10/41 (24.4%) second and further lines of advanced NSCLC, in 4/10 (40.0%) SCLC. Proportion of trials not including QoL was similar over time: 32.9% publications in 2012–2015 vs. 30.6% in 2016–2018. Out of 83 trials including QoL among endpoints, QoL results were absent in 36 primary publications (43.4%). Proportion of trials without QoL results in primary publication increased over time (30.6% 2012–2015 vs. 61.8% 2016–2018, p = 0.005). Overall, QoL data were not available in 75/122 (61.5%) primary publications, due to the absent endpoint or unpublished results. QoL data were lacking in 48/68 (70.6%) publications of trials with overall survival as primary endpoint, 27/54 (50.0%) with other primary endpoints and 28/54 (51.9%) publications with a positive result. For trials including QoL among endpoints but lacking QoL results in primary publication, probability of secondary publication was 6.3%, 30.1% and 49.8% after 1, 2 and 3 years respectively, without evidence of improvement comparing 2012–2015 vs. 2016–2018.

Conclusion: QoL is not assessed or published in many phase III lung cancer trials, a setting where QoL value should be highly considered, due to high symptom burden and generally limited life expectancy. Timely inclusion of results in primary publications is worsening in recent years.

1. Introduction

The treatment landscape of lung cancer is rapidly evolving, with an increasing number of therapeutic options and personalized approaches as never before. In the context of the precision medicine approach, lung cancer management takes into consideration, beyond staging and patients' clinical characteristics, also histology and molecular pathology with the identification of oncogenic driver alterations and other predictive factors. Cytotoxic chemotherapy, usually platinum-based, the cornerstone of treatment for unselected patients for almost three

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decades, is now challenged in many patients by targeted therapies and immune checkpoint inhibitors, and, in the near future, by chemo-immunotherapy [1]. Despite significant improvements in terms of treatment efficacy and tolerability, lung cancer, often diagnosed as advanced or metastatic disease, has a disappointing long term survival rate, remaining one of the first causes of cancer-related deaths among both men and women [2]. Progression free survival (PFS) often remains unsatisfying and, moreover, patients are generally symptomatic and clinically vulnerable.

In this context, the awareness of the real, overall treatment value is of crucial importance and is linked to patients' subjective experience. Patient reported outcomes (PROs) are the self-measurement of the personal status of the patient, without any external interpretation, and represent a valid tool to assess subjective perception of disease burden and treatment impact, both in clinical trials and in daily clinical practice [3]. Health-related quality of life (QoL) is a specific and multidimensional type of PRO related to the physical, psychological and social impact of the disease and its treatment perceived by patients [4]. It is universally considered a measure of clinical benefit and a tool of achieving a global patient-centered treatment approach. Furthermore, QoL allows, together with data of efficacy and safety, allows a more complete assessment of risks and benefits of each treatment in clinical research and a more accurate patient-physician communication in daily practice.

In recent years, the most important scientific societies as the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) have generated some framework schemes in order to define the value of anticancer treatments, incorporating QoL among the variables contemplated [5–8].

In addition, regulatory agencies, both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have underlined the importance of QoL inclusion among the endpoints of clinical trials, highlighting the relevance of patient's perspective as a standard outcome measure [9–11].

However, regardless the widely recognized importance of QoL evaluation, the attention to QoL results is still suboptimal. In a recent systematic review of randomized phase III trials testing anticancer drugs in all solid tumours, published by major journals between 2012 and 2016, we showed an alarming deficiency of QoL among endpoints. In particular, among the 446 publications identified, QoL was apparently not included as trial endpoint in 210 (47.1%). Even when QoL was present, data were significantly underreported, were not available in the majority of primary publications and were published with important delay compared to primary results [12].

Aim of this systematic review is to describe QoL adoption and reporting in randomized phase III trials testing anticancer drugs in lung cancer patients, published between 2012 and 2018 by 11 major journals. We analyzed QoL inclusion among endpoints, presence of QoL results, methodology of analysis and presentation of results.

2. Materials and methods

As reported before [12], we selected eleven major journals where most of cancer randomized phase III trials are generally published: three general medical journals (JAMA, Lancet and New England Journal of Medicine) and eight oncology journals (Annals of Oncology, British Journal of Cancer, Cancer, JAMA Oncology, European Journal of Cancer, Journal of Clinical Oncology, Journal of the National Cancer Institute and Lancet Oncology). We hand-searched all the issues of the journals listed above and identified all the primary publications of randomized phase III trials testing anticancer drugs in patients with lung cancer. The eligible papers published between 2012 and 2016 had already been included in a previous publication, that included all solid tumors [12]. For the present analysis, we expanded the research to the two-year period 2017–2018, with the same methods of analysis. We did not include trials evaluating supportive care drugs, unless the objective was anticancer efficacy (e.g. zoledronic acid tested to delay disease progression or recurrence in patients with controlled stage IIIA/B non-small cell lung cancer [NSCLC]). Trials testing non-pharmacologic interventions or prevention strategies were excluded. We selected both trials conducted in early stage, locally advanced, or metastatic NSCLC and in limited and extended stage small cell lung cancer (SCLC).

The same dedicated case report form (CRF) adopted in the previous database was used to gather information from every single paper. The electronic database, with one record for each selected publication, was updated.

For each study we recorded data about the publication: journal, year, first author, date of definitive and ahead-of-print publication, availability of supplementary material and/or study protocol. On the basis of the impact factor (IF) corresponding to the year of publication and obtained from the Journal of Citation Reports, papers were classified into three groups: low IF (< 15), intermediate IF (15–30) and high IF (> 30).

We classified the papers according to different characteristics: open label (trials in which patients and physicians were aware of the treatment received) versus blinded (trials in which participants and physicians were kept unaware of the assigned treatment arm), superiority versus non-inferiority design. In addition, we divided the studies into two groups: for-profit versus no-profit, defining for-profit a trial sponsored by a drug company and no-profit a trial supported by an academic institution or a cooperative group, even if receiving drug supply and/or financial support from a pharmaceutical company (if not reported in the publication, information about the study sponsor were searched on ClinicalTrials.gov). We collected data about the disease setting (early stages / locally advanced / metastatic NSCLC and limited / extended stage SCLC) and the details of treatment of both experimental and control arms. In particular, experimental treatments were classified into three main groups (not mutually exclusive): chemotherapy +/- other drugs; targeted agents +/- other drugs; immunotherapy +/- other drugs.

Studies were defined 'positive' or 'negative' according to the results of the primary endpoint.

Data about the study endpoints (primary / secondary / exploratory) were acquired from the methods section of the paper and from the study protocol, when present as supplementary material. When QoL was not included among endpoints and the study protocol was unavailable, it was classified as apparently absent. When instead, despite an apparent absence, QoL data were reported in the results section or published in a secondary publication, QoL was listed *de facto* among endpoints.

Chi square test was applied to determine the presence of a statistically significant association between inclusion of QoL among study endpoints, presence of QoL results in primary publications and characteristics of publication: source of funding (for-profit; non-profit), year (2012–2015; 2016–2018) and journal Impact Factor (low; intermediate; high). A p value < 0.05 was considered statistically significant.

For every paper, secondary QoL publications were researched in PubMed, using as search terms: the name of the drug(s) and/or tumor type and/or the name of authors of the primary publication and/or the study acronym/code, when present. Time to secondary QoL publication was calculated according to Kaplan-Meier method, from the date of primary definitive publication to the date of secondary QoL definitive publication, if any, or to the date of last PubMed check (March 18th, 2019).

Furthermore, we gathered information about QoL methodology: QoL tools adopted, type of statistical analysis and modality of presentation of results (e.g. mean scores at different time points, mean changes from baseline, proportion of responding / worsening patients, time to deterioration).

All analyses were performed with SPSS for Windows, version 25.0.

Table 1
Characteristics of the 122 primary publications included in the analysis.

	N. publications	(%)
Year of primary manuscript		
2012	22	18.0%
2013	15	12.3%
2014	15	12.3%
2015	21	17.2%
2016	9	7.4%
2017	28	23.0%
2018	12	9.8%
Primary manuscript journal		
Journal of Clinical Oncology	38	31.1%
Lancet Oncology	31	25.4%
Annals of Oncology	18	14.8%
New England Journal of Medicine	16	13.1%
Lancet	5	4.1%
European Journal of Cancer	5	4.1%
Cancer	3	2.5%
British Journal of Cancer	2	1.6%
JAMA Oncology	2	1.6%
J Natl Cancer Inst	1	0.8%
JAMA	1	0.8%
Sources of funding		
Profit	80	65.6%
Non-profit	42	34.4%
Setting of disease		
NSCLC early stages – locally advanced	17	13.9%
NSCLC advanced / metastatic first line (incl. maintenance)	54	44.3%
NSCLC advanced / metastatic second / further lines	41	33.6%
SCLC (all stages and lines)	10	8.2%
Study design		
Superiority	115	94.3%
Non-inferiority	7	5.7%
Masking		
Open label	78	63.9%
Blinded	44	36.1%
Type of experimental therapy[a]		
Chemotherapy +/- other	63	51.6%
Targeted therapy +/- other	73	59.8%
Immunotherapy +/- other	22	18.0%
Other	4	3.3%
Primary endpoint		
Overall survival (alone or as co-primary)	68	55.7%
Other	54	44.3%
Study results (primary endpoint)		
Positive	54	44.3%
Negative	68	55.7%

[a] Categories are not mutually exclusive.

Table 2
Inclusion of health-related quality of life among study endpoints according to characteristics of study and publication.

	Number of publications	QoL included among endpoints	QoL not included among endpoints
Whole series	122	83 (68.0%)	39 (32.0%)
Year of primary manuscript			
2012	22	15 (68.2%)	7 (31.8%)
2013	15	9 (60.0%)	6 (40.0%)
2014	15	13 (86.7%)	2 (13.3%)
2015	21	12 (57.1%)	9 (42.9%)
2016	9	7 (77.8%)	2 (22.2%)
2017	28	17 (60.7%)	11 (39.3%)
2018	12	10 (83.3%)	2 (16.7%)
Sources of funding			
Profit	80	64 (80.0%)	16 (20.0%)
Non-profit	42	19 (45.2%)	23 (54.8%)
Setting of disease			
NSCLC early stages – locally advanced	17	7 (41.2%)	10 (58.8%)
NSCLC advanced / metastatic first line (incl. maintenance)	54	39 (72.2%)	15 (27.8%)
NSCLC advanced / metastatic second / further lines	41	31 (75.6%)	10 (24.4%)
SCLC (all stages and lines)	10	6 (60.0%)	4 (40.0%)
Study design			
Superiority	115	77 (67.0%)	38 (33.0%)
Non-inferiority	7	6 (85.7%)	1 (14.3%)
Masking			
Open label	78	51 (65.4%)	27 (34.6%)
Blinded	44	32 (72.7%)	12 (27.3%)
Type of experimental therapy[a]			
Chemotherapy +/- other	63	42 (66.7%)	21 (33.3%)
Targeted therapy +/- other	73	52 (71.2%)	21 (28.8%)
Immunotherapy +/- other	22	17 (77.3%)	5 (22.7%)
Other	4	2 (50.0%)	2 (50.0%)
Primary endpoint			
Overall survival	68	46 (67.6%)	22 (32.4%)
Other	54	37 (68.5%)	17 (31.5%)
Study result			
Positive	54	42 (77.8%)	12 (22.2%)
Negative	68	41 (60.3%)	27 (39.7%)

[a] Categories are not mutually exclusive.

3. Results

3.1. Study characteristics

Overall, 122 primary publications were included in the analysis (**Supplementary** Tables 1–4). Their main characteristics are detailed in Table 1. Seventy-three studies (59.8%) were published between 2012 and 2015 and forty-nine (40.2%) between 2016 and 2018. The three most represented journals were: Journal of Clinical Oncology (38 papers, 31.1%), Lancet Oncology (31 papers, 25.4%) and Annals of Oncology (14 papers, 18.8%).

Eighty studies (65.6%) were classified as profit trials and 42 (34.4%) as non-profit trials.

Most of the trials (54, 44.3%) were conducted in patients affected by advanced or metastatic NSCLC in first line treatment or maintenance therapy (Supplementary Table 2), followed by studies in advanced/metastatic NSCLC in second or further line of treatment (41, 33.6%) (Supplementary Table 3), in early stages or locally advanced (17, 13.9%) (Supplementary Table 1) and, finally, by studies in all lines of treatment for patients affected by all-stages SCLC (10, 8.2%) (Supplementary Table 4). The majority of the study had a superiority (115, 94.3%) and open label (78, 63.9%) design.

Targeted therapy +/- other drugs (73, 59.8%) was the most represented category of experimental arm, followed by chemotherapy (63, 51.6%) and immunotherapy (22, 18%), as single agents or in combination.

3.2. Inclusion of QoL among study endpoints

As shown in Table 2, in 39 (32.0%) publications, QoL was not included as an endpoint. In particular, the proportion of trials lacking QoL

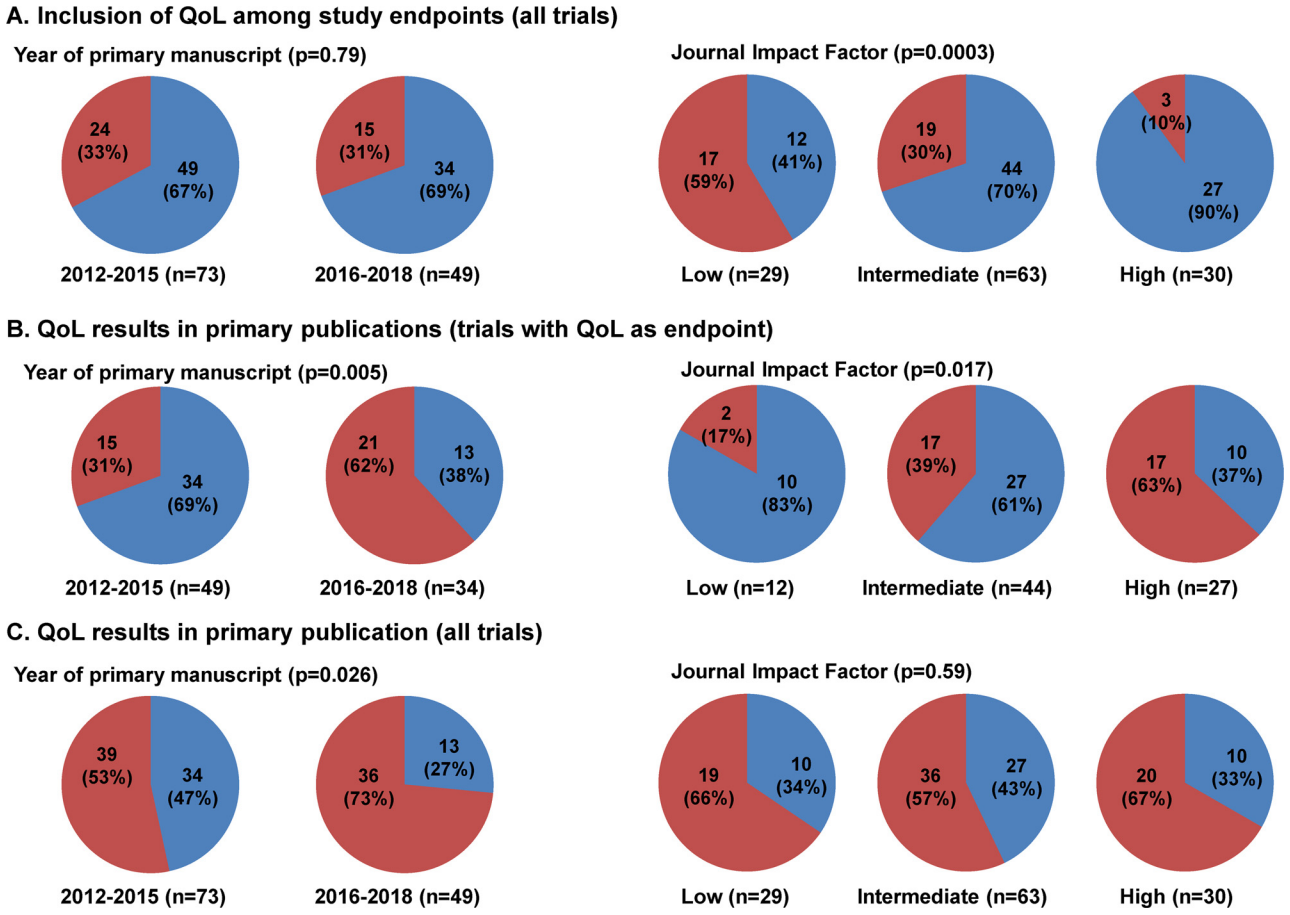

Fig. 1. A. Inclusion of QoL among study endpoints (all trials). B. QoL results in primary publications (trials with QoL as endpoint). C. QoL results in primary publication (all trials).

was higher in the early stage/locally advanced NSCLC setting (10/17; 58.8%), followed by all stages and lines of treatment of SCLC (4/10; 40.0%), second and further lines of advanced NSCLC (10/41; 24.4%) and first-line of advanced NSCLC (15/54; 27.8%).

Proportion of trials not including QoL was similar over time: 32.9% publications in years 2012–2015 vs. 30.6% in years 2016–2018. The proportion of trials without QoL as an endpoint was 58.6%, 30.2% and 10% among papers published respectively in low, intermediate and high IF journals. (Fig. 1, **A**)

QoL was not listed as an endpoint in an important percentage of for-profit trials (20%) and in more than half of non-profit trials (54.8%) ($p < 0.0001$).

3.3. Presence of QoL results in the primary publication

As shown in Table 3, out of 83 trials including QoL among endpoints, QoL results were not reported in 36 primary publications (43.4%). Namely, the proportion of publications not reporting QoL results was relevant in all settings: 66.7% in SCLC, 48.7% in first line of advanced/metastatic NSCLC, 42.9% in early stages/locally advanced and 32.3% in second or further lines of metastatic NSCLC.

Proportion of trials without QoL results in primary publication significantly increased over time (30.6% in the years 2012–2015 vs. 61.8% in the years 2016–2018, $p = 0.005$). QoL results were not reported in the 16.7%, 38.6% and 63% of papers published, respectively, in low, intermediate and high IF journals. (Fig. 1, **B**) The proportion of trials without QoL results was 50% in for-profit trials and 21.1% in non-profit trials ($p = 0.025$).

Overall, as reported in Table 4, QoL data were not available in 75/122 (61.5%) primary publications, due to the absence as endpoint or to unpublished results. Namely, the proportion of publications lacking QoL results was relevant in all settings: 80% in SCLC, 76.5% in early stages/locally advanced NSCLC, 63.0% in first line of advanced/metastatic NSCLC, and 48.8% in second or further lines of metastatic NSCLC.

Proportion of trials without QoL results in primary publication significantly increased over time (53.5% in the years 2012–2015 vs. 73.4% in the years 2016–2018, $p = 0.026$). QoL results were not reported in the 65.5%, 57.1% and 66.7% of papers published, respectively, in low, intermediate and high IF journals (Fig. 1, **C**). The proportion of trials without QoL results was 60% in profit and 64.3% in non-profit trails ($p = 0.64$).

3.4. QoL secondary publications

Overall, 20 secondary publications were identified (Supplementary Tables 1–4). For trials including QoL among endpoints but lacking QoL results in primary publication, probability of secondary publication was 6.3%, 30.1% and 49.8% after 1, 2 and 3 years respectively, without evidence of improvement comparing trials published in the years 2012–2015 vs. 2016–2018. (Supplementary Fig. 1)

3.5. QoL reporting according to study primary endpoint and study results

Sixty-eight trials reported overall survival (OS) as primary endpoint: among them QoL was not included among endpoints in 22 (32.4%) (Table 2) and, as reported in Table 3, out of the remaining 46, 26 (56.5%) did not report QoL results. Overall, as shown in Table 4, QoL data were lacking in 48 publications with OS as primary endpoint

Table 3
Details about health-related quality of life in the primary publications of trials with QoL as endpoint.

	Number of publications	QoL results available in primary publication	QoL results absent in primary publication
Whole series	83	47 (56.6%)	36 (43.4%)
Year of primary manuscript			
2012	15	11 (73.3%)	4 (26.7%)
2013	9	7 (77.8%)	2 (22.2%)
2014	13	8 (61.5%)	5 (38.5%)
2015	12	8 (66.7%)	4 (33.3%)
2016	7	3 (42.9%)	4 (57.1%)
2017	17	9 (52.9%)	8 (47.1%)
2018	10	1 (10.0%)	9 (90.0%)
Sources of funding			
Profit	64	32 (50.0%)	32 (50.0%)
Non-profit	19	15 (78.9%)	4 (21.1%)
Setting of disease			
NSCLC early stages – locally advanced	7	4 (57.1%)	3 (42.9%)
NSCLC advanced / metastatic first line (incl. maintenance)	39	20 (51.3%)	19 (48.7%)
NSCLC advanced / metastatic second / further lines	31	21 (67.7%)	10 (32.3%)
SCLC (all stages and lines)	6	2 (33.3%)	4 (66.7%)
Study design			
Superiority	77	42 (54.5%)	35 (45.5%)
Non-inferiority	6	5 (83.3%)	1 (16.7%)
Masking			
Open label	51	29 (56.9%)	22 (43.1%)
Blinded	32	18 (56.3%)	14 (43.8%)
Type of experimental therapy[a]			
Chemotherapy +/- other	42	22 (52.4%)	20 (47.6%)
Targeted therapy +/- other	52	34 (65.4%)	18 (34.6%)
Immunotherapy +/- other	17	2 (11.8%)	15 (88.2%)
Other	2	2 (100%)	0
Primary endpoint			
Overall survival	46	20 (43.5%)	26 (56.5%)
Other	37	27 (73.0%)	10 (27.0%)
Study result			
Positive	42	26 (61.9%)	16 (38.1%)
Negative	41	21 (51.2%)	20 (48.8%)

[a] Categories are not mutually exclusive.

(70.6%). Considering the other 54 trials, with primary endpoints different from OS, as shown in Table 2, 17 (31.5%) did not include QoL among endpoints and, out of the remaining 37, only 27 (73%) reported QoL results in the primary publication (Table 3). Overall, due to the absence of QoL as an endpoint or lacking of results, QoL data were absent in 27 (50%) of 54 trials with a primary endpoint other than OS (Table 4).

As shown in Table 1, studies were classified as negative or positive according to the primary endpoint results: 68 (55.7%) vs 54 (44.3%). Among the latter, forty-two (77.8%) included QoL among the endpoints (Table 2), but only in 26 papers (61.9%) QoL results were actually available in the primary publication (Table 3). Overall, as reported in Table 4, QoL results were absent in primary publications in 28/54 (51.9%) positive trials and in 47/68 negative ones (69.1%).

Table 4
Details about health-related quality of life in the primary publications of all trials.

	Number of publications	QoL results available in primary publication	QoL results absent in primary publication
Whole series	122	47 (38.5%)	75 (61.5%)
Year of primary manuscript			
2012	22	11 (50.0%)	11 (50.0%)
2013	15	7 (46.7%)	8 (53.3%)
2014	15	8 (53.3%)	7 (46.7%)
2015	21	8 (38.1%)	13 (61.9%)
2016	9	3 (33.3%)	6 (66.7%)
2017	28	9 (32.1%)	19 (67.9%)
2018	12	1 (8.3%)	11 (91.7%)
Sources of funding			
Profit	80	32 (40.0%)	48 (60.0%)
Non-profit	42	15 (35.7%)	27 (64.3%)
Setting of disease			
NSCLC early stages – locally advanced	17	4 (23.5%)	13 (76.5%)
NSCLC advanced / metastatic first line (incl. maintenance)	54	20 (37.0%)	34 (63.0%)
NSCLC advanced / metastatic second / further lines	41	21 (51.2%)	20 (48.8%)
SCLC (all stages and lines)	10	2 (20.0%)	8 (80.0%)
Study design			
Superiority	115	42 (36.5%)	73 (63.5%)
Non-inferiority	7	5 (71.4%)	2 (28.6%)
Masking			
Open label	78	29 (37.2%)	49 (62.8%)
Blinded	44	18 (40.9%)	26 (59.1%)
Type of experimental therapy[a]			
Chemotherapy +/- other	63	22 (34.9%)	41 (65.1%)
Targeted therapy +/- other	73	34 (46.6%)	39 (53.4%)
Immunotherapy +/- other	22	2 (9.1%)	20 (90.9%)
Other	4	2 (50.0%)	2 (50.0%)
Primary endpoint			
Overall survival	68	20 (29.4%)	48 (70.6%)
Other	54	27 (50.0%)	27 (50.0%)
Study result			
Positive	54	26 (48.1%)	28 (51.9%)
Negative	68	21 (30.9%)	47 (69.1%)

[a] Categories are not mutually exclusive.

3.6. QoL methodology

Details of QoL methodology in terms of instruments adopted, type of analysis and presentation of results are reported in Table 5.

Most common QoL tools used were European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (42, 50.6%); EORTC-lung cancer 13 (EORTC LC13) (39, 47.0%); EuroQoL five dimensions questionnaire (EQ-5D) (37, 44.6%); Lung Cancer Symptom Scale (LCSS) (19, 22.9%); Functional Assessment of Cancer Therapy-Lung (FACT-L) (15, 18.1%).

Methods of analysis most commonly used were mean scores or changes (45, 77.6%), time to deterioration (31, 53.4%) and proportion of responders (19, 32.8%).

The number of different methods of analysis and modalities of presentation (mean scores or changes, time to deterioration, proportion of responders) is significantly higher for studies with a secondary

Table 5
Details of methodology of quality of life analysis and presentation of results (n = 83 trials including quality of life among endpoints).

QoL questionnaire (not mutually exclusive)	N (%)
EORTC QLQ C30	42 (50.6%)
EORTC QLQ LC 13	39 (47.0%)
EQ5D	37 (44.6%)
FACT-L	15 (18.1%)
LCSS	19 (22.9%)
Other tools	9 (10.8%)

Modality of QoL analysis (not mutually exclusive) (not available in 25 trials without QoL results)	N (%)
Mean changes / mean scores	45 (77.6%)
Proportion of responders	19 (32.8%)
Time to deterioration	31 (53.4%)
Other	2 (3.4%)

Number of modalities of QoL presentation (modalities: mean changes/scores; proportion of responders; time to deterioration; other)	Second publication not available (N = 64)	Second publication available (N = 19)
0	25 (39.1%)	0
1	26 (40.6%)	4 (21.1%)
2	13 (20.3%)	4 (21.1%)
3	0	11 (57.9%)

QLQ-C30: European Organisation for the Research and Treatment of Cancer (EORTC) quality-of-life questionnaire; QLQ-LC13: EORTC quality-of-life lung cancer module; LCSS: Lung Cancer Symptom Scale; EQ-5D: EuroQol Group 5-Dimension; FACT-L: Functional Assessment of Cancer Therapy (FACT)-Lung; QoL: quality of life.

publication available: namely, 0, 1, 2 and 3 methods of analysis were found in 25 (39.1%), 26 (40.6%), 13 (20.3%) and 0 of the 64 trials without a secondary publication, compared to 0, 4 (21.1%), 4 (21.1%) and 11 (57.9%) of the 19 trials with a secondary publication available (p = 0.001).

4. Discussion

This systematic review demonstrates that QoL is not assessed in a relevant proportion of phase III trials evaluating lung cancer patients. Furthermore, QoL results are significantly under-reported, with a disappointing worsening in the timely inclusion of results in primary publications in the last years.

Lung cancer patients could consider symptom control and quality of life even more important than life prolongation [13]. However, our analysis shows a significant proportion of studies not reporting QoL as a trial endpoint in all settings of disease, results in line with those already reported in other solid tumors and in prostate and colorectal cancer [12,14,15]. If in the early stages, where systemic therapy is administered as adjuvant/neoadjuvant option, a potential detrimental effect on QoL can be considered transient and tolerable, compared to the possibility of a definitive cure, whereas in the advanced setting, representing the majority of trials included in the analysis and the majority of patients in clinical practice, life expectancy is definitely different. Efficacy of systemic therapies, in terms of OS and PFS, is still limited, while symptoms' burden can be relevant and the balance between disease control and treatment side effects is far from being obviously positive. In this scenario, it is quite discouraging that in the first line setting for advanced/metastatic NSCLC and in further lines of treatment, 27.8% and 24.8% of papers analyzed, respectively, did not include QoL among endpoints. This proportion grows to 40% in SCLC, setting in which, as well known, options of treatment and outcomes are still suboptimal.

QoL evaluation is even more relevant when the main endpoint of trial is a surrogate endpoint, other than overall survival (44.3% of selected trials), e.g. PFS, in which the radiological definition of treatment efficacy should be necessarily completed by the patient's perspective.

A not negligible proportion (22.2%) of trials with positive results did not include QoL among endpoints. Generally, if the absence of QoL data in an otherwise negative trial could be considered trivial, a positive trial is the first step for a drug to gain the subsequent regulatory approval and to be introduced in clinical guidelines and daily clinical practice. In this scenario, our data are quite disappointing and seem to confirm the previous analysis reported by Davis C. et al [16]. Their systematic evaluation of oncology approvals by the EMA in 2009-13 showed, indeed, that just over half (37/68, 54%) of all drug indications had a supporting pivotal trial evaluating quality of life and that, at the time of market approval, there was an improvement in QoL in seven of 68 indications (10%) [16].

As described above, we divided trials into for-profit (when sponsored by a drug company) and no-profit (when sponsored by an academic institution or a cooperative group), and we found a high proportion of trials not including QoL among endpoints in both categories: 20% among for-profit trials and 54.8% among non-profit trials, with a statistically significant difference between the two groups. On the other hand, among the studies with QoL as endpoint, we found a significant better reporting of QoL results among non-profit trials (trials without QoL results were 50% in profit and 21.1% in non-profit group). These results confirm, in lung cancer, the suboptimal results in terms of QoL assessment and reporting observed in our previous analysis in all solid tumors, where QoL was not included among endpoints in the 39.7% of trials promoted by drug companies and in the 53.6% of the academic trials, and QoL results were not reported in the 37% and 39% of, respectively, for-profit and non-profit trials [12]. One possible explanation of the lower inclusion of QoL in non-profit trials could derive from the greater awareness of QoL value from pharma companies in the process of drug approval and reimbursement. Academic research, instead, has to face with intrinsic limits in terms of poor resources, limited financial support, fewer dedicated personnel, with the consequent sacrifice *ab initio* of important aspects of the clinical research, such as QoL inclusion among endpoints. When included, QoL data are reported with an higher rate than in for-profit trials, but, this issue remains, however, particularly disappointing: academic research, designed with the aim of improving patients' care, should not disregard QoL evaluation to optimize treatment choices in the daily clinical practice.

In addition we found that trials published in journals with low or intermediate IF included less often QoL among endpoints rather than high IF journals (QoL is not included respectively in the 58.6%, 30.2% and 10%). This is reasonable, considering that QoL inclusion could be

considered a surrogate of trial quality, and high-quality trials are expected to be published, on average, by journals with higher IF. However, disappointingly, the proportion of trials without QoL results in primary publication, despite the inclusion among endpoints, is higher in the subgroup of trials published on high IF journals (63% vs 38.6 and 167% in intermediate and low IF ones). In particular, analyzing the time range from 2012 to 2018, we divided trials in two temporal subgroups: 2012–2015 and 2016–2018. Although the proportion of trials that included QoL among endpoints seems to have a slightly positive trend (from 67.1% to 69.4%), we found a significant worsening of the timely inclusion of QoL results in primary publications (from 69.4% to 38.2%). This is quite disappointing, particularly if we consider that QoL results are gathered during the treatment and are, generally, accessible simultaneously with other data of efficacy presented in the primary publications. Many reasons can underlie these results and explain the delayed reporting of QoL data in secondary publications, after the primary outcome analysis: poor compliance, high rate of missing data, word-count limitations imposed by most scientific journals [17].

Secondary publications, identified in 20 studies, allow, surely, a more complete description of QoL results. Not surprisingly, we found that the completeness of QoL results presentation (measured as number of different modalities of analysis) is significantly higher when a secondary publication is available. However, this strategy that we found to be particularly common (and increasing) for trials published in high IF journals, may decrease the interest for QoL results, with the concrete possibility of not publishing, publishing with important delay or publishing in low impact journals. Moreover, it implies a delay in QoL data availability with the consequent incomplete understanding of the value of the treatment [17]. For instance, in March 2019, FDA approved atezolizumab in combination with carboplatin and etoposide, for the first-line treatment of patients with extensive stage SCLC. Approval was based on IMpower133 that showed a statistically significant improvement of PFS by 0.9 months and OS by 2 months in patients receiving atezolizumab with chemotherapy compared with placebo with chemotherapy. SCLC is a very aggressive disease, whose prognosis is still poor, so any improvement is certainly important, but, even if differences are statistically significant, the survival gain showed by the trial is quite modest. Therefore, it is quite disappointing that, in this setting and considering these results, drug approval has preceded QoL data, reported as secondary endpoint in the study protocol [18].

Obviously, the presence of QoL among endpoints implicates different methodological questions referring to, e.g., the choice of the more suitable type of questionnaire and the best timing of administration [19]. Most of the studies analyzed used generic QoL questionnaires such as EORTC-QLQ-C30, which incorporates different physical, social, functional, emotional domains [20]. The 47% of trials used the lung cancer module EORTC QLQ LC 13 with specific disease symptoms evaluation. In addition, the type of analysis and description of data are not homogeneous. Mean changes or mean scores compared to baseline emerged as the most used modality of analysis and presentation. These results, however, do not indicate how many patients actually felt a significant improvement or worsening. From this point of view, the proportion of responders is useful for a better evaluation of this aspect, but we found it reported only in 32.8% of papers. Time to deterioration of specific symptoms or general QoL, instead, was present in the 53.4% of trials analyzed. This evaluation is of crucial importance above all in studies where the primary endpoint is different from OS (44.3% of trials included in this analysis) because it allows to determine if a surrogate parameter, such as the radiological response in case of PFS, is associated to subjective clinical improvements too. Actually, we don't have a single method complete and exhaustive for the evaluation of QoL. The integration of different tools could allow a better comprehension of QoL changes, but this scenario is far from reality taking into consideration the confined space dedicated to QoL analysis in primary publications by the major scientific journals [12].

The importance of QoL evaluation, when assessing the real value of each treatment, derived also by the poor concordance between toxicities and symptoms reported by patients with PROs and by clinicians with the traditional Common Terminology Criteria of Adverse Events (CTCAE) system, because of the well-known physicians' propensity of downgrading and underreporting [21]. Basch et al. compared the results of questionnaire with 11 common CTCAE symptoms completed by patients with lung (non-small-cell or small-cell) and genitourinary cancer and by their clinicians. For most symptoms, concordance among patients and clinicians was high, above all for symptoms that were directly detectable and measurable, such as vomiting and diarrhea. Agreement was lower for more subjective symptoms, such as fatigue and dyspnea (respectively 41% and 52%) in lung cancer patients. These data highlight, therefore, how much PROs could help in symptoms recognition and monitoring both in cancer treatment trials and anticancer drug development [22].

Moreover, PRO measures seem to have an independent prognostic value for lung cancer patients that can't be ignored [23]. They allow, also, an improvement in communication among patients and clinicians about treatments when they become accessible in clinical practice paving the way for a real patient-centralized therapy choice.

5. Conclusions

In conclusion, this analysis found that QoL is not assessed in a relevant proportion of phase III trials evaluating lung cancer patients, with significant under-reporting of QoL results in primary publications. Furthermore, timely inclusion of QoL results in primary publications is significantly worsening in last years, and this is particularly frequent in papers published in high impact factor journals. In the era of the precision medicine, however, PROs and QoL analyses could play a crucial role for a shared decision-making process, representing a tool to guide physicians in the selection of the most tailored therapy for every single patient. Although the well known methodological difficulties, every member of the scientific community, aware of the value of QoL data, should encourage the completeness of study endpoints and timely punctual data reporting for a full understanding of treatment value. Indeed, even if the potential role of QoL evaluation and reporting in clinical research is almost universally recognized, much remains to do for its wide implementation, and all of us are called to work together in this direction.

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Declaration of Competing Interest

Massimo Aglietta had roles as consultant or advisor for Roche, Bristol Myers Squibb, Merck and Co.; Silvia Novello declared a role as Speaker Bureau for Roche, Boeringer Ingelheim, Eli Lilly, Astra Zeneca, MSD; Giorgio Vittorio Scagliotti received honoraria, research funding and had roles as consultant or advisor for Roche, Pfizer, AstraZeneca, Lilly Pharma and MSD; Francesco Perrone received honoraria from Bayer, Daiichi Sankyo, Ipsen, AstraZeneca and Bristol Myers Squibb and received research funding from Roche and Bayer; Massimo Di Maio received honoraria and had roles as consultant or advisor for AstraZeneca, Lilly Pharma, Bristol Myers Squibb, MSD and Janssen. All remaining authors declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.lungcan.2019.10.022.

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