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Health-related quality of life is underestimated and underreported in phase III clinical trials in NSCLC

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ABSTRACT

Major associations of medical oncologists remark that novel anticancer treatments should guarantee improvement of survival outcomes as well as of patients' quality of life (QoL). Herein, we investigated QoL assessment and reporting in phase III randomized controlled trials (RCTs) testing new drugs in metastatic non-small cell lung cancer (NSCLC), published between 2010 and 2021. We selected 172 RCTs for further analysis. Only 2/172 (1.2%) trial included QoL among primary study endpoints. Of note, 40/172 (23.3%) trials did not include QoL assessment among endpoints. The majority of RCTs (102/172, 59.3%) did not report QoL results in primary publications. Particularly, RCTs testing immunotherapy, target therapy and chemotherapy did not disclose QoL data in primary publications in 97.0%, 51.5% and 46.5% of cases, respectively. Next, we found that only 43/95 (45.3%) positive studies reported QoL results in primary articles. Of the 102 trials missing QoL data in primary manuscripts, only 21 (20.6%) disclosed QoL results in a secondary publication. Finally, we found a common fail in adherence to CONSORT-PROs items in publications reporting QoL results. In summary, our study reveals a relevant inadequate assessment and under-reporting of QoL in RCTs of novel systemic treatments for patients with metastatic NSCLC.

1. Introduction

In randomized controlled trials (RCTs), the choice of endpoints is essential to define the safety and efficacy of new drugs or other novel therapeutic strategies, compared to standard available treatments [1]. Overall survival (OS) is considered the gold standard outcome to evaluate the efficacy of experimental therapies [2]. Surrogate endpoints, like progression-free survival (PFS) or overall response rate (ORR), are generally listed as primary endpoints in phase III RCTs and are used to obtain fast approval of oncology drugs [3]. In this context, interest in evaluation of quality of life (QoL) and in control of cancer-related symptoms has increased [4]. In oncology, the evaluation of health-related quality of life (HRQoL) includes the assessment of objective and subjective impact of cancers related aspects, such as symptoms or side effects of treatments, on daily life domains (social, emotional, physical and cognitive functions).

European society of medical oncology (ESMO) remarks that the benefits of a new treatment must be both "living longer", as measured by OS, and "living better", determined by QoL, patient-reported outcome measures (PROMs) and safety [5]. For these reasons, the ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) was developed to evaluate relative benefits of new therapeutic approaches through the measurement of different outcomes, among which QoL assessment has a prominent position [6,7]. In recent years, the number of tools and tests to evaluate QoL in RCTs raised [8]. Furthermore, several systematic reviews and *meta*-analysis investigating the performance of distinct measurement instruments have been published [9,10]. Despite a growing awareness about the relevance of QoL assessment among clinicians and researchers, previous studies showed that a large fraction of RCTs did not report QoL results in primary publications, revealing an attitude to underestimate the importance of QoL data in clinical oncology research [11–13]. The CONsolidated Standards of Reporting Trials (CONSORT) statement was developed to reduce inadequate and incomplete data reporting in clinical trials. It provided a checklist of

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items and instruction to build the flow diagram of participants through different steps of the trial. In 2013, due to the a general lack of methods about the assessment of PROs in RCTs, 5 more items were developed and added to the CONSORT statement (CONSORT PRO extension) [14,15].

Patients diagnosed with metastatic non-small cell lung cancer (NSCLC) experience a wide spectrum of symptoms negatively influencing their life domains such as fatigue, shortness of breath, lack of appetite, pain, cough and respiratory distress syndrome. In addition, these manifestations influence psychological dimension of patients ultimately leading to irritation, depression, malnutrition, cachexia and sarcopenia [16]. Therefore, while RCTs testing novel therapies for patients with NSCLC certainly aim to improve survival, they should address the need to relief cancer related symptoms [17]. Of note, more than 50 different types of questionnaires have been developed to investigate general health conditions and specific life domains of patients with diagnosis of NSCLC [18].

Herein, we report results from our investigation about the assessment of QoL in publications of phase III RCTs testing novel drugs in patients with metastatic NSCLC published between 2010 and December 2021. We collected data concerning the evaluation of QoL as primary, secondary or exploratory endpoint and reporting of related results in primary or secondary publications. Furthermore, we explored whether the recommended CONSORT PRO checklist items were followed.

2. Methods

Data collection. We collected publications of phase III clinical trials investigating novel agents for the treatment of metastatic NSCLC published between January 2010 and December 31, 2021, in 18 different major journals that commonly publish results from RCTs and/or typically publishing lung cancer studies (*Annals of Oncology, British Journal of Cancer, Cancer Discovery, Cancers, Clinical Cancer Research, Clinical Lung Cancer, European Journal of Cancer, JAMA, JAMA Oncology, Journal of Clinical Oncology, Journal for Immunotherapy of Cancer, Journal of National Cancer Institute, Journal of Thoracic Oncology, Lancet, Lancet Oncology, Lancet Respiratory Medicine, Lung Cancer* and *New England Journal of Medicine*). The following terms were searched in Pubmed: "Lung cancer" OR "NSCLC" OR "lung adenocarcinoma" OR "squamous cell carcinoma". We selected the additional Pubmed filters "Clinical Trial" and "English Language". The exact research string can be found in Supplementary Table 1.

Titles and abstracts were examined separately. Reasons for exclusion were: 1) Trials testing non-pharmacological therapies, such as surgery and radiotherapy; 2) Trials testing different schedules of the same drug; 3) Trials of supportive care or behavioural interventions; 4) Not phase III RCTs; 5) Trials in adjuvant or locally advanced settings; 6) Study protocol or design; 7) Subgroup, post-hoc or subset analysis of previously published trials; 8) Brief reports; 9) Studies of screening methodologies. The remaining full texts were next downloaded for further analysis.

All information regarding clinical trials were collected from the article or through the https://www.clinicaltrials.gov/ website and reported in an electronic database. These included first author, digital object identifier (DOI), name of the study, journal, date of definitive publication, impact factor of the journal (IF) at time of publication, class of therapy investigated (chemotherapy, immunotherapy or target therapy). Data were collected by one junior investigator and double-checked by a senior researcher. Discrepancies were resolved by consensus.

Trials were also classified based on: Histological subtype (squamous cell carcinoma "SCC", non-squamous cell carcinoma "NSCC", "non specified histology"); Mutational status of recruited patients ("*EGFR* mutations", "*ALK* translocations" or "*KRAS* mutations"); Funding sources ("profit", when the trial was supported by a pharma company, or "no profit", when the trial was designed and conducted by academic institution/s); Results ("positive", when statistically significant advantage in primary endpoint was reached in experimental group over control group, or "negative", when the trial did not meet its primary endpoint);

Table 1
Characteristics of the phase III RCTs included in the analysis.

	n	%
Total	172	100
Year of primary publication		
2010	9	5.2
2011	15	8.7
2012	18	10.5
2013	13	7.6
2014	11	6.4
2015	22	12.8
2016	8	4.7
2017	19	11
2018	12	7
2019	15	8.7
2020	16	9.3
2021	14	8.1
Journal of primary publication		
Annals of Oncology	21	12.2
British Journal of Cancer	3	1.7
Clinical Cancer Research	4	2.3
Clinical Lung Cancer	4	2.3
European Journal of Cancer	9	5.2
JAMA	1	0.6
JAMA Oncology	7	4.1
Journal of Clinical Oncology	40	23.3
Journal of Thoracic Oncology	17	9.9
Lancet	9	5.2
Lancet Oncology	30	17.5
Lancet Respiratory Medicine	2	1.2
Lung Cancer	9	5.2
New England Journal of Medicine	16	9.3
Class of Therapy Investigated†		
Immunotherapy	33	19.2
Target Therapy	99	.5
• **EGFR inhibitors**	41	23.8
• **ALK inhibitors**	12	7
• **Other***	46	26.7
Chemotherapy	43	25
Control arm: placebo		
Yes	56	32.6
No	116	67.4
Primary tumor‡		
Non specified histology	85	49.4
NSCC	38	22.1
SCC	15	8.7
***EGFR* Mutations**	21	12.2
***ALK* Rearrangements**	12	7
***KRAS* Mutations**	1	0.6
Funding		
Profit	130	75.6
Non-profit	42	24.4
Study design		
Superiority	159	92.4
Non-inferiority	13	7.6
Results of the trial		
Positive	95	55.2
Negative	77	44.8
Masking		
Blinded	59	34.3
Open label	113	65.7
Countries involved in the trial		
Two or more	109	63.4
Single country	63	36.6
Primary endpoint†^		
OS	87	50.6
PFS	92	53.5
ORR	4	2.3
Safety	2	1.2
QOL	2	1.2
Time to Progression	1	0.6

† Categories are not mutually exclusive.
* "Other" included: 3 trials investigating COX-2 inhibitors; 1 Dendritic Cell inhibitor; 1 HSP90 inhibitor; 2 IGF1R inhibitors; 1 MAPK inhibitor; 3 MET inhibitors; 15 multi-kinase inhibitors; 1 PARP inhibitor; 1 phosphatidylserine directed Ab; 1 RANKL ligand; 2 TLR9 agonist; 15 VEGF pathway inhibitors.
‡ The presence of *EGFR* mutations, *ALK* rearrangements or *KRAS* mutations was

mandatory to enroll patients in the trials reported in the table.
ˆ In 15 trials co-primary endpoints were OS and PFS; In 1 OS and safety.

Study design ("superiority" when the aim of trial was to detect an advantage in investigational drug over standard available treatment or "non-inferiority" when the aim was to show a same efficacy between the drug investigated and the control arm); Masking ("blinded", when neither the researcher nor the recruited patients were aware about the assigned treatment, or "open label"); Involved countries ("multi", when hospitals or institutions of two or more different countries were involved in the trial or "single" when they belonged to a single country); Primary endpoints (OS, PFS, Safety, QoL and ORR).

We evaluated the assessment of QoL in RCTs by examining the methods section of the manuscripts or study protocols. When protocols were not available as supplementary material of corresponding publications, they were searched on the https://www.clinicaltrials.gov/ website. Particularly, we interrogated study protocols to find out whether QoL was assessed among endpoints (primary, secondary, exploratory endpoint or non-analysed). We also collected data about the type of test utilized in the trial to assess QoL and these data will be subject of a different publication.

For RCTs non-reporting QoL results in primary publication, we assessed their disclosure in secondary publications. Secondary manuscripts were searched among the list of articles obtained with our research strategy reported above and indicated in Supplementary Table 1. For RCTs whose secondary QoL-focused manuscripts were not present in this list, potential secondary publications were searched in PubMed using the name of the drug and the study's acronym. When PubMed research did not give results, possible secondary publications and abstract presented at international conferences were also searched on Google indicating the name of drug and the study's acronym. We only included in our analysis secondary manuscripts published earlier than April 30, 2022. These articles were also classified according to the journal and the date of publication, DOI, IF and the time span between primary and secondary publication (months).

Finally, CONSORT PRO checklist items were assessed in articles published after 2013.

Statistical analysis. Statistically significant differences between analysed groups, when relevant, were calculated using Fisher's exact test in Prism – GraphPad software. The same software was also used to obtain Kaplan-Meier curves describing the probability of publication of QoL results. Finally, Student's *t*-test was employed to evaluate the statistically significant difference between IFs of journals at time of primary and secondary publications including QoL results.

3. Results

3.1. Study characteristics.

We found 172 phase III RCTs testing novel systemic treatments in patients with metastatic NSCLC whose primary manuscript was published between January 2010 and December 2021 (Fig. 1). The list of these RCTs is reported in supplementary table 1. Characteristics of these studies are summarized in Table 1. The 172 articles were published in 14 journals (*Annals of Oncology, British Journal of Cancer, Clinical Cancer Research, Clinical Lung Cancer, European Journal of Cancer, JAMA, JAMA Oncology, Journal of Clinical Oncology, Journal of Thoracic Oncology, Lancet, Lancet Oncology, Lancet Respiratory Medicine, Lung Cancer and New England Journal of Medicine*). None of the studies was published in *Cancer Discovery, Cancers (Basel), Journal of the National Cancer Institute or Journal for immunotherapy of cancer*. The highest percentage of trials were found in *Journal of Clinical Oncology* (23.3 %, n = 40) and *Lancet Oncology* (17.5 %, n = 30). Immunotherapy and chemotherapy were investigated in 33 (19.2 %) and 43 (25.0 %) trials, respectively. Target therapies were investigated in 99 trials (57.5 %), of which 41 (23.8 %) were agents directed against EGFR, 12 (7.0 %) ALK inhibitors and 46

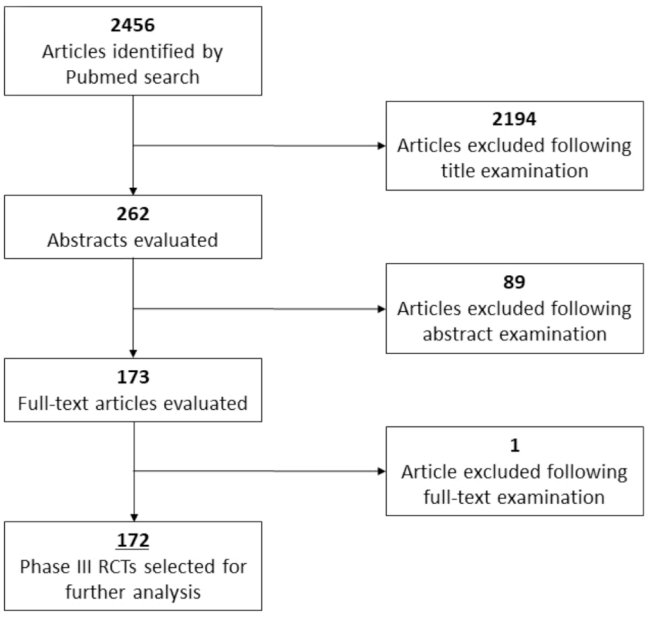


Fig. 1. PRISMA diagram for selection of the studies included in the analysis.

(26.7 %) other drugs. Patients were recruited in 85 (49.4 %) studies regardless of NSCLC histology. Patients with non-squamous cell carcinoma (NCSS) or squamous cell carcinoma (SCC) were exclusively enrolled in 38 (22.1 %) and 15 (8.7 %) trials, respectively. The presence of *EGFR* mutations, *ALK* rearrangements or *KRAS* mutations was mandatory in 21 (12.2 %), 12 (7.0 %) and one (0.6 %) trials, respectively. Pharmaceutical companies funded 130 (75.6 %) RCTs, while non-profit studies were only 42 (24.4 %). Placebo treatment was present in the control arm of 56 (32.6 %) RCTs. One hundred thirteen (n = 113, 65.7 %) and 59 (34.3 %) RCTs had open or blinded masking, respectively. One hundred fifty-nine (n = 159, 92.4 %) and 13 (7.6 %) trials had a superiority or non-inferiority design, respectively. Results of the trial were positive in 95 (55.2 %) cases and negative in the remaining 77 (44.8 %). Finally, 63 (36.6 %) trials were conducted only in one country.

4. Primary endpoints and assessment of QoL.

OS was the primary endpoint in 87 (50.6 %) RCTs. PFS, ORR and safety were assessed among primary endpoints in 92 (53.5 %), 4 (2.3 %) and 2 (1.2 %) trials, respectively (Table 1). Only two (n = 2, 1.2 %) trials included QoL assessment among primary endpoints (Table 2). Assessment of QoL was declared among secondary or exploratory endpoints in 100 (58.1 %) and 17 (9.9 %) trials, respectively. In 13 (7.5 %) RCTs, QoL assessment was included among both secondary and exploratory endpoints (Table 2). Of note, 40 (23.3 %) RCTs did not include at all QoL assessment among study endpoints (Table 2). Interestingly, a consistent fraction of positive trials (n = 16/95, 16.8 %) did not include QoL evaluation among study endpoints. Instead, 24/77 (31.2 %) negative RCTs did not include QoL among study endpoints. Furthermore, the rates of RCTs non-assessing QoL among study endpoints were 12.1 %, 22.2 % and 32.5 % of trials testing immunotherapy, target therapies and chemotherapy, respectively. More in detail, 9/41 (22.0 %) trials investigating agents targeting EGFR did not evaluate QoL among endpoints. In addition, QoL was not assessed in 23/130 (17.7 %) and 17/42 (40.5 %) profit and non-profit RCTs, respectively. Complete analysis of endpoints according to study characteristics can be found in Table 2.

5. QoL results in primary publications

We found that only 70/172 (40.7 %) RCTs reported QoL results in primary publication (Table 3). As a result, the 59.3 % (n = 102/172,

Table 2
Inclusion of QoL among endpoints, based on study characteristics.

	Number of articles	QoL primary end point n (%)	QoL secondary end point n (%)	QoL secondary AND exploratory end point n (%)	QoL exploratory end point n (%)	QoL not evaluated as end point n (%)
Whole series	172	2(1.2)	100(58.1)	13(7.5)	17(9.9)	40(23.3)
Year of primary publication						
2010	9	–	6(66.7)	–	–	3(33.3)
2011	15	1(6.7)	8(53.3)	–	–	6(40)
2012	18	–	16(88.8)	–	1(5.6)	1(5.6)
2013	13	–	10(76.92)	–	–	3(23.1)
2014	11	–	9(81.8)	–	–	2(18.2)
2015	22	1(4.6)	11(50.0)	2(9.1)	3(13.6)	5(22.7)
2016	8	–	4(50.0)	1(12.5)	1(12.5)	2(25.0)
2017	19	–	9(47.3)	1(5.3)	3(15.8)	6(31.6)
2018	12	–	6(50.0)	1(8.3)	4(33.4)	1(8.3)
2019	15	–	7(46.7)	3(20.0)	–	5(33.3)
2020	16	–	6(37.5)	4(25.0)	2(12.5)	4(25.0)
2021	14	–	8(57.2)	1(7.1)	3(21.4)	2(14.3)
Journal of primary publication						
Annals of Oncology	21	1(4.8)	11(52.4)	–	–	9(42.8)
British Journal of Cancer	3	–	1(33.3)	–	–	2(66.7)
Clinical Cancer Research	4	–	2(50.0)	–	–	2(50.0)
Clinical Lung Cancer	4	1(25.0)	–	–	1(25.0)	2(50.0)
European Journal of Cancer	9	–	8(88.9)	–	–	1(11.1)
JAMA	1	–	–	–	1(100)	–
JAMA Oncology	7	–	4(57.1)	1(14.3)	2(28.6)	–
Journal of Clinical Oncology	40	–	25(62.5)	1(2.5)	4(10.0)	10(25.0)
Journal of Thoracic Oncology	17	–	9(52.9)	2(11.8)	2(11.8)	4(23.5)
Lancet	9	–	6(66.7)	–	1(11.1)	2(22.2)
Lancet Oncology	30	–	24(80.0)	2(6.6)	2(6.6)	2(6.6)
Lancet Respiratory Medicine	2	–	1(50.0)	–	–	1(50.0)
Lung Cancer	9	–	4(44.4)	–	1(11.2)	4(44.4)
New England Journal of Medicine	16	–	5(31.2)	7(43.8)	3(18.8)	1(6.2)
Class of Therapy Investigated†						
Immunotherapy	33	–	10(30.3)	10(30.3)	9(27.3)	4(12.1)
Target Therapy	99	1(1.0)	66(66.7)	3(3.0)	7(7.1)	22(22.2)
• EGFR inhibitors	41	–	29(70.7)	1(2.4)	2(4.9)	9(22.0)
• ALK inhibitors	12	–	11(91.7)	1(8.3)	–	–
• Others*	46	1(2.2)	26(56.5)	1(2.2)	5(10.9)	13(28.2)
Chemotherapy	43	2(4.7)	26(60.5)	–	1(2.3)	14(32.5)
Control arm: placebo						
Yes	56	–	33(58.9)	2(3.6)	10(17.9)	11(19.6)
No	116	2(1.7)	67(57.8)	11(9.5)	7(6.0)	29(25.0)
Primary tumor‡						
Non specified histology	85	1(1.2)	54(63.5)	4(4.7)	5(5.9)	21(24.7)
NSCC	38	1(2.6)	15(39.5)	4(10.5)	5(13.2)	13(34.2)
SCC	15	–	6(40.0)	2(13.3)	4(26.7)	3(20.0)
***EGFR* Mutations**	21	–	14(66.7)	2(9.5)	2(9.5)	3(14.3)
***ALK* Rearrangements**	12	–	11(91.7)	1(8.3)	–	–
***KRAS* Mutations**	1	–	–	–	1(100)	–
Primary endpoint†^						
OS	87	–	49(56.3)	10(11.5)	9(10.3)	19(21.8)
PFS	92	–	54(58.7)	10(10.9)	11(12.0)	17(18.5)
ORR	4	–	1(25.0)	–	–	3(75.0)
Safety	2	–	–	–	–	2(40.0)
QOL	2	2(100)	–	–	–	–
Time to Progression	1	–	–	–	–	1(100)
Funding						
Profit	130	1(0.8)	78(60.0)	13(10.0)	15(11.5)	23(17.7)
Non-profit	42	1(2.3)	22(52.4)	–	2(4.8)	17(40.5)
Study design						
Superiority	159	2(1.3)	91(57.2)	13(8.2)	17(10.7)	36(22.6)
Non-inferiority	13	–	9(69.2)	–	–	4(30.8)
Results of the trial						
Positive	95	1(1.1)	60(63.2)	10(10.5)	8(8.4)	16(16.8)
Negative	77	1(1.3)	40(51.9)	3(3.9)	9(11.7)	24(31.2)
Masking						

(*continued on next page*)

Table 2 (*continued*)

	Number of articles	QoL primary end point n (%)	QoL secondary end point n (%)	QoL secondary AND exploratory end point n (%)	QoL exploratory end point n (%)	QoL not evaluated as end point n (%)
Blinded	59	–	34(57.6)	2(3.4)	10(17.0)	13(22.0)
Open label	113	2(1.8)	66(58.4)	11(9.7)	7(6.2)	27(23.9)
Countries involved in the trial						
Two or more	109	1(0.9)	64(58.7)	13(11.9)	14(12.9)	17(15.6)
Single country	63	1(1.6)	36(57.1)	–	3(4.8)	23(36.5)

† Categories were not mutually exclusive.
* ‡ ˆ See Table 1 for description.

Table 3) RCTs testing novel systemic treatments in patients with metastatic NSCLC did not report QoL data. Characteristics of studies reporting or not QoL results in primary publications are summarized in Table 3. Further analysis revealed that RTCs testing immunotherapy, target therapies and chemotherapy did not report QoL results in primary publications in 32/33 (97.0 %), 51/99 (51.5 %) and 20/43 (46.5 %) cases, respectively. We did not find a relevant difference in reporting QoL data between profit and non-profit studies (60.0 % and 57.1 % of RCTs non-reporting QoL results in primary publications, respectively). Trials with non-inferiority design reported QoL data in primary manuscripts in 69.2 % (n = 9/13) of cases, in contrast to 38.4 % (n = 61/159) of RCTs with a superiority design. Remarkably, only 43/95 (45.3 %) positive trials disclosed QoL data in primary publications. Instead, the rate of negative RTCs reporting QoL results in primary articles was 35.1 % (n = 27/77).

6. QoL in secondary publications

For the 172 RCTs selected in our analysis, the aggregated probability of publication of QoL results within 12, 24 and 36 months was 44.8 %, 49.4 % and 52.3 %, respectively (Supplementary Fig. 1A). Furthermore, we found a discrepancy in publication of QoL results between positive and negative RCTs. Indeed, the probability of publication of QoL results within 12, 24 and 36 months for positive RCTs, was 49.5 %, 56.8 % and 62.1 %, respectively (Supplementary Fig. 1B). Instead, the probability of publication of QoL results within 12, 24 and 36 months for negative RCTs, was 39.0 %, 40.3 % and 40.3 %, respectively (Supplementary Fig. 1B).

Of the 102 RCTs without QoL results in primary publications from 2010 to December 2021, only 21 (20.6 %) disclosed QoL data later in a secondary article (Table 4). Of note, out of 52 positive trials, only 17 (32.7 %) disclosed QoL data in a secondary publication (Table 4). On the other hand, only 4/50 (8.0 %) trials with negative results published a secondary article with QoL results (Table 4). More in detail, for the 102 RCTs non-reporting QoL results in primary publication, the probability of secondary publications disclosing QoL results within 12, 24 and 36 months was, respectively, 6.9 %, 14.7 % and 19.6 % (Fig. 2A). In addition, we observed that the probability of secondary publications with QoL results within 12, 24 and 36 months was, respectively, 7.7 %, 21.2 % and 30.8 % for positive RCTs (Fig. 2B). Instead, the probability of secondary publications with QoL results within 36 months was 8.0 % for negative RCTs (Fig. 2B).

Next, we analyzed the probability of publication of QoL results in secondary articles for the 62 RCTs non-reporting QoL data in primary publication but declaring assessment of QoL among study endpoints. Of these 62 RCTs, positive and negative trials were 36 and 26, respectively. The probability of secondary publications with QoL results within 12, 24 and 36 months was, respectively 11.3 %, 24.2 % and 32.3 % (Fig. 3A). Furthermore, for the 36 positive trials, the probability of secondary publications with QoL results within 12, 24 and 36 months was, respectively 11.1 %, 30.6 % and 44.4 % (Fig. 3B). Instead, for the 26 negative RCTs, the probability of secondary publication with QoL results within 36 months was 15.4 % (Fig. 3B).

For RCTs non-reporting QoL results in primary publications, the impact factors (IFs) of the journals in which QoL-focused secondary manuscripts were published were lower than primary publications (Fig. 4). Indeed, the median IFs of primary (non-reporting QoL data) and secondary publications were 47.83 and 6.83, respectively (Fig. 4, $p = 8.64e^{-04}$). Finally, for the 21 RCTs exclusively reporting QoL results in secondary manuscripts, the median time between primary and secondary publication was 15.8 months (Fig. 4).

7. Assessment of CONSORT PRO items in publications

We evaluated the presence of CONSORT PRO items in manuscripts published starting from 2013, after development of CONSORT PRO extension [15] (Table 5). Sixty-four RCTs, in which assessment of QoL was disclosed, were selected for further analysis (Table 5). Of these, 11/64 (17.2 %) RCTs reported QoL results in primary and secondary publications, 35/64 (54.7 %) only in primary publications and 18/64 (28.1 %) only in secondary publications. In 42/64 (65.6 %) trials, PROs could be identified in abstract. In 34 RCTs (53.1 %) PRO hypothesis was present in the introduction section of the manuscript. In 46 (71.8 %) and 28 (43.7 %) RCTs, PRO questionnaires validity and statistical approaches of missing data were listed in "materials and methods", respectively. Finally, in 38 (59.3 %) RCTs critical reviews of QoL data was identifiable in the discussion section.

8. Discussion

This work revealed that a substantial fraction of phase III RCTs conducted in the recent years and investigating novel therapeutic strategies in patients with advanced NSCLC did not give adequate relevance to assessment of QoL in the management of these patients. Particularly, the rate of primary publications non-reporting QoL results was higher than manuscripts disclaiming QoL data (59.3 % vs 40.7 %, Table 3). In addition, when QoL results were reported in secondary manuscripts, we observed a remarkable delay between primary and corresponding secondary publication (Figs. 2-4). As a result, these findings reveal that a comprehensive understanding of the efficacy of experimental therapies in advanced NSCLC is generally affected by under-reporting of QoL results.

In patients with NSCLC control of symptoms such as dyspnoea, dysphagia, shortness of breath, pain, has a relevant impact on quality of life, sometimes even more than prolongation of life [19]. Despite this awareness, our analysis showed that 40/172 (23.3 %) RTCs testing novel systemic treatments in patients with advanced NSCLC did not include at all QoL assessment among study endpoints (Table 2). A previous study, evaluating publications between 2012 and 2018, found that 32.0 % of RCTs testing novel drugs in lung cancer did not include QoL evaluation among endpoints [20]. However, the study from Reale and colleagues also included RCTs enrolling patients with early stages/locally advanced NSCLC and small cell lung cancer (SCLC) histology. Furthermore, the rate of RCTs non-reporting QoL assessment among endpoints in NSCLC (23.3 %, Table 2) is lower than the value of 40.1 % previously observed for all solid malignancies in the metastatic setting [11].

Immune checkpoint inhibitors (ICIs), as monotherapy or in combination with chemotherapy, currently represent the mainstay of

Table 3
Disclosure of QoL results in primary publications, based on study characteristics.

	Number of articles	QoL results reported in primary publication n (%)	QoL results non-reported in primary publication n (%)
Whole series	172	70(40.7)	102(59.3)
Year of primary publication			
2010	9	6(66.7)	3(33.3)
2011	15	9(60.0)	6(40.0)
2012	18	11(61.1)	7(38.9)
2013	13	7(53.8)	6(46.2)
2014	11	5(45.5)	6(54.5)
2015	22	9(40.9)	13(59.1)
2016	8	2(25.0)	6(75.0)
2017	19	8(42.1)	11(57.9)
2018	12	3(25.0)	9(75.0)
2019	15	1(6.7)	14(93.3)
2020	16	5(31.3)	11(68.7)
2021	14	4(28.6)	10(71.4)
Journal of primary publication			
Annals of Oncology	21	6(28.6)	15(71.4)
British Journal of Cancer	3	1(33.3)	2(66.7)
Clinical Cancer Research	4	1(25.0)	3(75.0)
Clinical Lung Cancer	4	2(50.0)	2(50.0)
European Journal of Cancer	9	3(33.3)	6(66.7)
JAMA	1	1(100)	–
JAMA Oncology	7	2(28.6)	5(71.4)
Journal of Clinical Oncology	40	17(42.5)	23(57.5)
Journal of Thoracic Oncology	17	5(29.4)	12(70.6)
Lancet	9	4(44.4)	5(55.6)
Lancet Oncology	30	19(63.3)	11(36.7)
Lancet Respiratory Medicine	2	–	2(100)
Lung Cancer	9	5(55.6)	4(44.4)
New England Journal of Medicine	16	4(25.0)	12(75.0)
Class of Therapy Investigated†			
Immunotherapy	33	1(3.0)	32(97.0)
Target Therapy	99	48(48.5)	51(51.5)
• **EGFR inhibitors**	41	24(58.5)	17(41.5)
• **ALK inhibitors**	12	6(50.0)	6(50.0)
• **Others***	46	18(39.1)	28(60.9)
Chemotherapy	43	23(53.5)	20(46.5)
Primary tumor‡			
Non specified histology	85	39(45.9)	46(54.1)
NSCC	38	9(23.7)	29(76.3)
SCC	15	4(26.7)	11(73.3)
***EGFR* Mutations**	21	11(52.4)	10(47.6)
***ALK* Mutations**	12	6(50.0)	6(50.0)
***KRAS* Mutations**	1	1(100)	–
Primary endpoint†ˆ			
OS	87	30(34.5)	57(65.5)
PFS	92	39(42.4)	53(57.6)
ORR	4	1(25.0)	3(75.0)
Safety	2	–	2(100.0)
QOL	2	2(100)	–
Time to Progression	1	–	1(100)
Control arm: placebo			
Yes	56	25(44.6)	31(55.4)
No	116	45(38.8)	71(61.2)
Funding			
Profit	130	52(40.0)	78(60.0)
Non-profit	42	18(42.9)	24(57.1)

Table 3 (*continued*)

	Number of articles	QoL results reported in primary publication n (%)	QoL results non-reported in primary publication n (%)
Study design			
Superiority	159	61(38.4)	98(61.6)
Non-inferiority	13	9(69.2)	4(30.8)
Results of the trial			
Positive	95	43(45.3)	52(54.7)
Negative	77	27(35.1)	50(64.9)
Masking			
Blinded	59	26(44.1)	33(55.9)
Open label	113	44(38.9)	69(61.1)
Countries involved in the trial			
Two or more	109	43(39.4)	66(60.6)
Single country	63	27(42.9)	36(57.1)

† Categories are not mutually exclusive.
* ‡ ˆ See Table 1 for description.

Table 4
Rate of secondary publications reporting QoL results.

	Number of articles	QoL results reported in secondary publication n (%)	QoL results non-reported in secondary publication n (%)
Articles from 2010 to 2021 non-reporting QoL results in primary publication	102	21 (20.6)	81 (79.4)
Results of the trial			
Positive	52	17 (32.7)	35 (67.3) *
Negative	50	4 (8.0)	46 (92.0) ˆ

We only included articles published between 2010 and December 2021 non-reporting QoL results in primary publications. * In 4 cases QoL results were only presented at international conferences. ˆ In 1 case QoL results were presented at an international conference.

treatment for most patients with diagnosis of advanced NSCLC. We found that 29/33 (87.9 %, table 2) RCTs testing ICIs in advanced NSCLC included QoL assessment among endpoints, as declared in study protocols. However, in agreement with our previous findings [12], only 1/33 (3.0 %) RCTs reported QoL results in primary publication (Table 3), preventing an accurate and comprehensive evaluation of the efficacy of immunotherapy in patients with metastatic NSCLC.

Instead, a substantial fraction of phase III trials testing target therapies (n = 22/99, 22.2 %) did not assess QoL (Table 2). Recent evidences reported that, despite a common perception among clinicians, some trials of experimental target therapies in solid cancers failed to demonstrate an improvement in quality of life compared to standard treatments, with results that are even worse than the ones observed with chemotherapy [21]. We acknowledge that in patients with oncogene-addicted NSCLC, selective inhibitors have certainly prolonged life expectancy. However, since chemotherapy-free regimens do not always imply an improvement in quality of life, a rigorous comparison between target therapies and cytotoxic agents should include analysis of QoL data.

Previous studies clarified that PFS cannot be considered as a surrogate of patients' quality of life in RCTs [22,23]. In addition, recent evidences reported that in 15 % of trials in solid cancers, experimental treatments determined PFS improvement but also inferior QoL outcomes, compared to control arms [21]. Hence, in RCTs using PFS as primary study endpoint, in absence of OS improvement, evaluation of QoL is even more relevant because the radiological assessment of disease

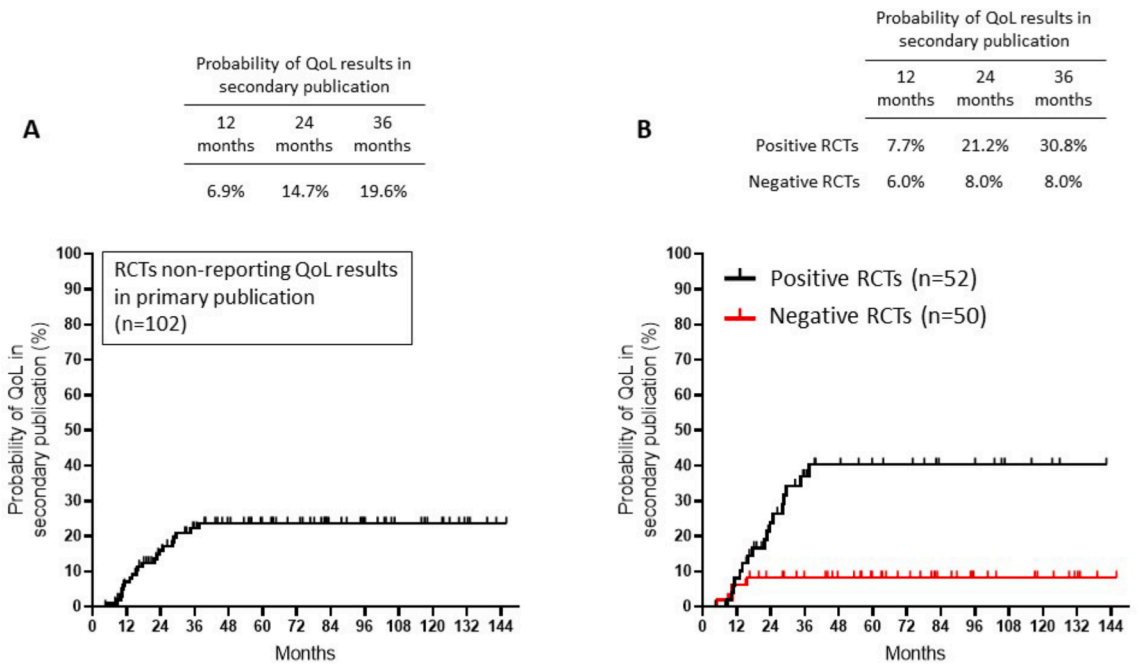


Fig. 2. Kaplan-Meier curves of time to secondary publication of QoL results, for trials non-reporting QoL results in primary manuscript (n = 102). (B) Kaplan-Meier curve of differential time to secondary publication with QoL results between positive and negative RCTs, for trials non-reporting QoL data in primary manuscripts (Positive trials, n = 52; Negative trials, n = 50).

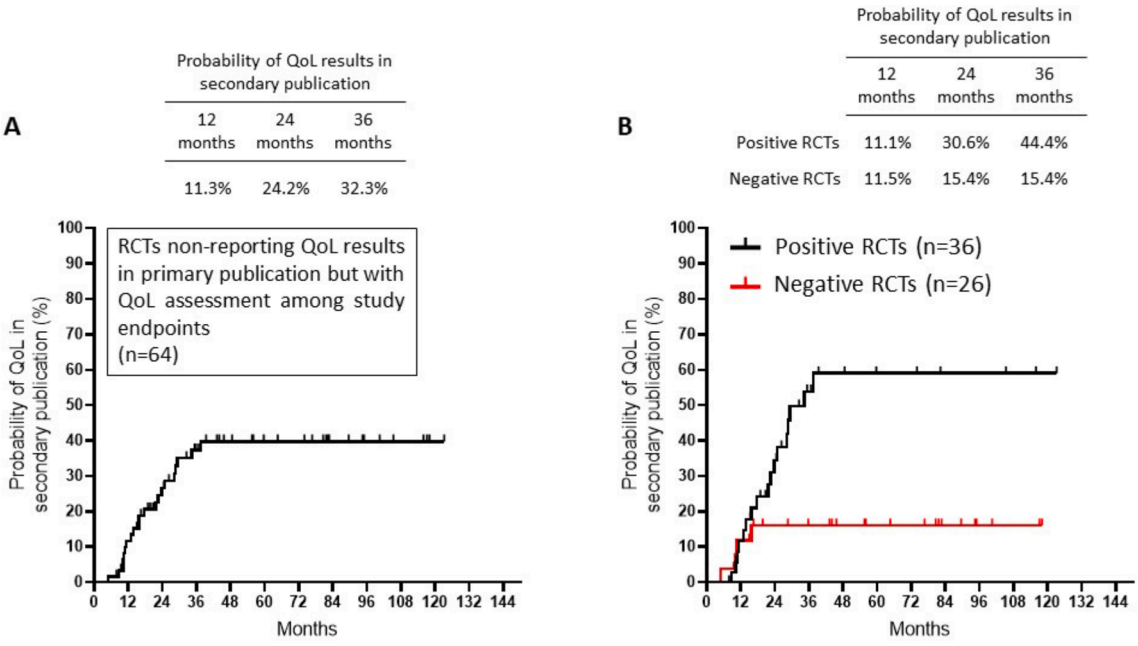
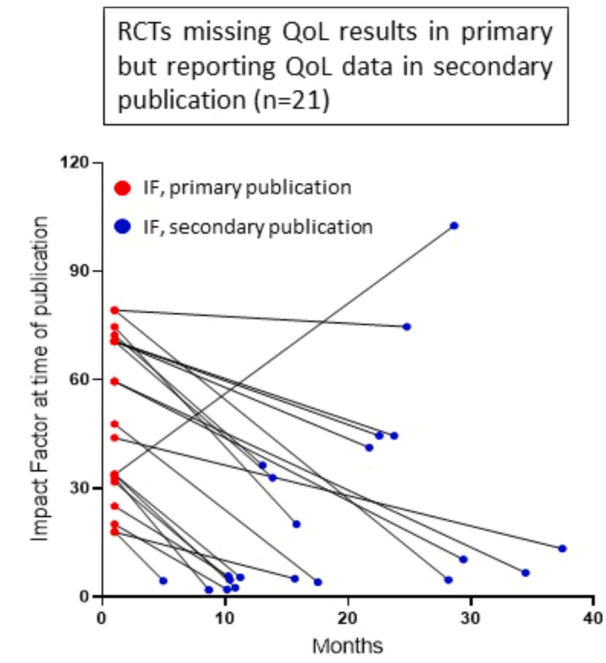


Fig. 3. Kaplan-Meier curves of time to secondary publication of QoL results, for trials non-reporting QoL results in primary manuscript, but with QoL assessment among study endpoints. (B) Kaplan-Meier curve of differential time to secondary publication with QoL results between positive and negative RCTs shown in A (Positive trials, n = 36; Negative trials, n = 26).

extension cannot appraise and explain the patients' perspective of the disease. Based on these considerations, it was disappointing to find that out of 92 RCTs using PFS as primary endpoint, a substantial fraction (n = 17, 18.5 %) did not include QoL among study endpoints (Table 2) and only 39 (42.4 %) reported QoL results in primary publications (Table 3).

We believe that one of the most dramatic findings of our study was that more than half of positive trials (n = 52/95, 54.7 %, Table 3) did not report QoL results in primary publications. In many cases, regulatory agencies grant approval of new drugs for treatment of solid cancers based on primary publications showing advantages in OS and/or PFS. However, it means that for some of newly approved treatments, QoL results are not publicly available at time of approval, interfering with a complete assessment of efficacy of new drugs by clinicians. These data are concordant with previous findings revealing a lack of evaluation of QoL outcomes for the majority of drugs approved by European Medicines Agency (EMA) between 2015 and 2020 [24]. Furthermore, previous evidences reported high rates of positive RCTs non-reporting QoL data in primary publications in multiple solid cancers and with various



Publication	Median IF	Range	*p* value
Primary	47.83	17.96 – 79.26	8.64^{e-04}
Secondary	6.68	1.98 – 102.64	

Fig. 4. Graph showing values of IFs of journals at time of primary (red dots) and secondary (blue dots) publications and time to secondary publications including QoL results. Statistics: two-sided *t*-test. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 5
CONSORT PRO checklist items in clinical trial presenting QoL data in primary and/or secondary publications from 2013.

	n	%
RCTs reporting QoL in primary, secondary publication or both from 2013	64*	100
P1b: the PRO should be identified in the abstract as a primary or secondary outcome	42	65.6
P2b: the PRO hypothesis should be stated, and relevant domains identified, if applicable	34	53.1
P6a: evidence of PRO instrument validity and reliability should be provided or cited	46	71.8
P12a: statistical approaches for dealing with missing data are explicitly stated	28	43.7
P20/21: PRO-specific limitations and implications for generalizability and clinical practice	38	59.3

*35 trials reported QoL results in primary publication, 11 reported QoL results in both primary and secondary publication. 18 RCTs reported PRO analysis in secondary publication.

classes of drugs [11,12,20,22]. We acknowledge that, in contrast with ORR and PFS data, analysis of mature QoL results, as well as OS, might need long time. Therefore, QoL outcomes are generally disclosed in secondary QoL-focused manuscripts. However, our analysis also revealed that out of 52 positive trials non-reporting QoL data in primary publications, only 17 (32.7 %) presented QoL results in a secondary manuscript (Table 4). Moreover, the median time to secondary QoL-focused secondary publication was 15.8 months (Fig. 4), causing a delay in clinicians' complete understanding of the effect of novel experimental treatments.

We observed that the rates of profit and non-profit RCTs non-including QoL among study endpoints were 17.7 % and 40.5 %, respectively (Table 2). This difference was statistically significant (Fisher's exact test, p = 0.0055). These results are concordant with previous publications, revealing a tendency of non-including QoL assessment among study endpoints higher for non-profit than profit RCTs [20]. This difference may be explained by various reasons. Despite academic institutions, companies have better knowledge and understanding of the requirements to expedite the process of drug approval by regulatory agencies. Furthermore, pharma companies have greater economic resources to guarantee adequate assessment of QoL outcomes. However, it has to be noted that, although in many cases companies declare in the protocol of the study that QoL assessment will be performed, in a large fraction of publications QoL results are not disclaimed [12]. In addition, our analysis revealed that there is no difference between profit and non-profit studies in reporting QoL results in primary publications (Table 3). In summary, it is conceivable that overall academic research devotes more effort and funding in assessment of QoL outcomes in patients with solid cancers, aiming at a comprehensive amelioration of patients' care.

Non-inferiority trials are expected to be conducted more frequently in academic institutions. However, among the trials selected for our analysis, we found that 8/13 (61.5 %) and 5/13 (38.5 %) non-inferiority studies were profit and non-profit RCTs, respectively. Of the 8 profit studies, 6 (75.0 %) reported QoL data in primary publications. The remaining 2 RCTs did not report QoL data in secondary articles. Of the 5 non-profit studies, 3 (60.0 %) disclosed QoL data in primary publications, while the remaining 2 RCTs did not publish QoL results in secondary manuscripts. Nevertheless, we acknowledge that this analysis might be biased by the low number (n = 13) of non-inferiority studies.

The development of CONSORT-PRO extension aimed to provide specific guidance to improve the quality of PRO reporting in publications of RCTs. These advices were formulated to assist researchers in improving clinical trial design and increase the transparency of results, as well as to help clinicians in understanding the benefits of experimental treatments. Recent evidences highlighted a common inadequate reporting of CONSORT-PRO items in publications [25]. In addition, studies reviewing PRO reporting in publications of RCTs often did not assess whether CONSORT-PRO items were followed in manuscripts [25]. Our study uncovers a common unreporting of CONSORT-PRO items in publications of RCTs in NSCLC (Table 5). More, in detail, in agreement with previous findings [26], our analysis revealed that providing statistical approaches for dealing with missing PROs data was the CONSORT-PRO item less represented in publications of RCTs in NSCLC. Indeed, this item was present only in 43.7 % of publication reporting QoL data (Table 5). Further dissemination and knowledge of CONSORT-PRO items is critical to improve QoL assessment and reporting in clinical trials.

We acknowledge that this work has some limitations. First, we only selected articles from a limited list of journals and in a specific timeline, from 2010 to 2021. However, the journals that we have included in our analysis are the ones that publish results of the most important phase III RCTs in oncology, as well as in the field of NSCLC. These publications generally may affect decisions made by regulatory agencies. Moreover, we have selected the timeline of 2010–2021, encompassing clinical trials of chemotherapy, target therapies and immunotherapy that have influenced the current routine management of patients with NSCLC. We also acknowledge that our study is limited to description of researchers' habits in assessment of QoL in clinical trials of NSCLC. However, future publications may further clarify some unanswered questions in this field. First, in our analysis we did not evaluate whether the experimental treatment in RCTs was associated with improvement of QoL outcomes, when assessed. Of note, an accurate evaluation of treatment benefits, in terms of QoL outcomes, has several confounding factors. Indeed, as also discussed elsewhere, the QoL effects of new treatments should be evaluated not only by "before and after comparisons", but overall against the

standard of care treatment [21,27]. Furthermore, a large number of different tools assessing QoL outcomes is used in clinical trials. As a result, a standardization of the methodology, that we believe would help to better interpret the QoL effects of novel treatments, is hindered by the use of several different tools. Finally, future analysis of the published RCTs in NSCLC are needed to clarify whether QoL benefits are also associated with survival (OS and PFS) benefits, as recently reported in a retrospective analysis of RCTs of cancer drugs published in 2019 [21].

9. Conclusions

Our analysis revealed an inadequate rate of assessment and reporting of QoL data in RCTs of systemic treatments in advanced NSCLC. We recommend that future phase III clinical trials led by either academic institutions or pharma companies recognize the importance of examining QoL of patients receiving experimental anticancer treatments. These efforts are needed to guarantee that clinicians can comprehensively assess the safety and efficacy of novel treatments for patients with NSCLC.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2022.10.003.

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