VOLUME 29 · NUMBER 15 · MAY 20 2011

JOURNAL OF CLINICAL ONCOLOGY

REVIEW ARTICLE

Health-Related Quality of Life in Non–Small-Cell Lung Cancer: An Update of a Systematic Review on Methodologic Issues in Randomized Controlled Trials

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Submitted September 1, 2010; accepted January 19, 2011; published online ahead of print at www.jco.org on April 4, 2011.

Supported by Grants No. 5U10 CA011488-39 through 5U10 CA011488-40 from the National Cancer Institute (Bethesda, MD) and by a contribution in part by the Kankerbestrijding/KWF from the Netherlands through the European Organisation for Research and Treatment of Cancer (EORTC) Charitable Trust. The Pfizer Global Partnerships Foundation also partially funded this work through EORTC PROBE.

The content of this article is solely the responsibility of the authors and does not necessarily reflect the official views of the National Cancer Institute.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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0732-183X/11/2915-2104/$20.00

DOI: 10.1200/JCO.2010.32.3683

ABSTRACT

Purpose
This study is an update of a systematic review of health-related quality-of-life (HRQOL) methodology reporting in non–small-cell lung cancer (NSCLC) randomized controlled trials (RCTs). The objective was to evaluate HRQOL methodology reporting over the last decade and its benefit for clinical decision making.

Methods
A MEDLINE systematic literature review was performed. Eligible RCTs implemented patient-reported HRQOL assessments and regular oncology treatments for newly diagnosed adult patients with NSCLC. Included studies were published in English from August 2002 to July 2010. Two independent reviewers evaluated all included RCTs.

Results
Fifty-three RCTs were assessed. Of the 53 RCTs, 81% reported that there was no significant difference in overall survival (OS). However, 50% of RCTs that were unable to find OS differences reported a significant difference in HRQOL scores. The quality of HRQOL reporting has improved; both reporting of clinically significant differences and statistical testing of HRQOL have improved. A European Organisation for Research and Treatment of Cancer HRQOL questionnaire was used in 57% of the studies. However, reporting of HRQOL hypotheses and rationales for choosing HRQOL instruments were significantly less than before 2002 ($P < .05$).

Conclusion
The number of NSCLC RCTs incorporating HRQOL assessments has considerably increased. HRQOL continues to demonstrate its importance in RCTs, especially in those studies in which no OS difference is found. Despite the improved quality of HRQOL methodology reporting, certain aspects remain underrepresented. Our findings suggest need for an international standardization of HRQOL reporting similar to the CONSORT guidelines for clinical findings.

J Clin Oncol 29:2104-2120. © 2011 by American Society of Clinical Oncology

INTRODUCTION

Lung cancer is the most common cancer worldwide in both incidence and mortality for men and women. In 2008, there were 1,608,823 new cases of lung cancer diagnosed and 1,378,415 lung cancer–related deaths, accounting for 18.2% of cancer deaths in the world.[1] Incidence rates for men and women are on the increase worldwide. Survival estimates for patients with lung cancer remain poor; the 1-year survival rate of lung cancer is 42%, and the 5-year rate is 16%.[2]

Non–small-cell lung cancer (NSCLC) accounts for 85% of all lung cancer diagnoses.[3] For the 60% of patients who present with advanced NSCLC, palliative chemotherapy is the preferred treatment, which results in a significant, albeit small, median survival benefit of 8 to 10 weeks.[4] Further improvements can be obtained by adding biologic agents that target specific molecular pathways of lung carcinogenesis and by segmenting the population of patients with lung cancer into subgroups according to their presumed predominant molecular pathway.[5] However, progress is expected to be incremental at the cost of adverse effects and new toxicities.[6] Therefore, it is important to assess treatment effectiveness both in terms of objective outcomes (eg, progression-free or overall survival [OS]) and subjective, patient-reported outcomes (PROs). This detailed information can help both clinicians and patients to make informed and comprehensive decisions regarding the best available treatments.

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PROs are any information self-reported by the patient regarding their functioning or symptoms in relation to their health condition or therapy. Patient-reported health-related quality of life (HRQOL) falls under the umbrella of PROs and covers physical symptoms and functioning domains and usually provides an overall patient evaluation of their health and quality of life. HRQOL measurement in clinical trials provides additional, patient-based information and can be particularly helpful in randomized controlled trials (RCTs), comparing treatments with similar effectiveness (eg, survival) but with different adverse effect profiles.[7]

Several publications[8-11] have raised issues regarding the various aspects of HRQOL reporting in RCTs, such as the concept, measurement, methodology, and interpretation of HRQOL data. These publications have highlighted that although there have been improvements in the past decade, there are still limitations in some areas of reporting of HRQOL results. This paucity of HRQOL information, particularly for new drugs, may have interfered with their implementation in clinical practice (eg, bevacizumab and cetuximab for NSCLC).[12] When the new drug treatment results in only a small benefit in traditional objective outcomes or in equipoise, good HRQOL data that show differences in subjective patient outcomes may influence the process of clinical implementation.

It is critical that HRQOL results in RCTs are reported in a robust and rigorous manner in order to ensure that both clinicians and patients feel confident in using the information when making critical treatment decisions. This systematic literature review was undertaken with the aim of evaluating the reporting standards of HRQOL methodology incorporated in NSCLC RCTs published between April 2002 and July 2010. This review was conducted as a continuation of the systematic review by Bottomley et al[13] published in 2003. Because the previous review found an increase in the quality of HRQOL reporting from 1980 to March 2002, and more guidelines[8] have come out regarding the reporting of HRQOL results, our hypothesis is that there will be a trend showing a continued improvement of both HRQOL methodology and reporting in RCTs for patients with NSCLC. This systematic review evaluates data collected from RCTs on NSCLC published in the past 8 years and compares the findings with those from the previous report.

METHODS

In this systematic literature review, a methodology identical to the one used in the previous review was implemented. Inclusion criteria for the studies evaluated in this review were predefined as RCTs including adult patients (18 years or older) with newly diagnosed NSCLC, regardless of the grade of the tumor, undergoing any anticancer treatment (surgery, chemotherapy, radiotherapy, or a combination). Exclusion criteria were evaluation of psychological interventions or any supplementary treatment other than surgery, chemotherapy or radiotherapy; assessments that were not patient-reported (eg, HRQOL reported by the clinician or other proxies); and studies with fewer than 100 patients at baseline. Substudies focusing only on HRQOL were included, but were reviewed in conjunction with the original publication of the main trial describing the clinical outcomes and the trial design.

Publications that met the inclusion criteria were identified through PubMed using the following search strategy: (quality of life [MeSH Terms] OR quality of life [Text Word]) AND (non[All Fields]) AND (carcinoma, small cell [MeSH Terms] OR small-cell lung cancer [Text Word]) AND (randomized controlled trial) AND (lung neoplasm [MeSH Terms]). The publication type was restricted to the subheading of clinical trial, taking into account all clinical trials regardless of their type and phase. No restriction in the search field description was performed. The search was limited to RCTs published between April 2002 and July 2010. Only articles published in English language journals were used. All identified studies were evaluated by two reviewers, and a third was available as a mediator in case of disagreement. The main evaluation criteria were identical to the ones used previously and comprised four categories: (1) key characteristics of the RCTs, such as time of publication, study location, treatment outline, and main outcomes; (2) trial design aspects relevant to HRQOL end points; (3) the quality of the HRQOL measurements; and (4) statistical analysis and presentation of HRQOL results. The full set of criteria can be seen in Table 1.

RESULTS

Identified RCTs

A total of 53 NSCLC RCTs published between 2002 and 2010 met the inclusion criteria for this review. The 53 RCTs included a total of 19,956 patients, with study sample sizes ranging from 103 patients to 1,218 patients. This review retrieved a significantly larger number of studies published that involved NSCLC with an HRQOL end point (53 studies over an 8-year span, compared with 29 studies over a 22-year span), as well as more than double the number of patients assessed in the studies reviewed by Bottomley et al[13] (nearly 20,000 compared with 8,500 patients).

We only present direct comparisons with data from the previous review if the evaluation criteria show relevant changes over time. The key comparisons of all key criteria between the two reviews are summarized in Table 1.

Clinical and Main HRQOL Results

All but one of the RCTs that were found in the current review incorporated outcomes in terms of survival (Table 2, Socinski et al[45]). Of the 52 studies that did address OS differences, 42 (81%) reported that there were no significant OS differences between treatment arms. However, HRQOL was found to be significantly different between treatment arms in 50% of the studies in which no OS difference was found. Significant differences in HRQOL among patients with NSCLC were observed on symptom and functional levels, with the most prominent ones being hair loss, nausea/vomiting, appetite loss, physical and role functioning, and global health status/HRQOL. With regard to the 10 RCTs that did detect significant survival differences, we found that seven of these (70%) demonstrated significant HRQOL differences between treatment arms, covering HRQOL issues that are similar to the ones described above. In five of these studies, better survival was associated with better HRQOL, whereas in two studies better survival was seen, but HRQOL was worse.

Key Characteristics of the RCTs

Table 2 summarizes the key characteristics of the 53 RCTs included in this review. Of the 53 evaluated studies, 72% were published in high-impact peer-reviewed clinical journals such as the *Journal of Clinical Oncology*, *Annals of Oncology*, or *Lung Cancer*. This is an increase when compared with the previous review, in which 66% of the reviewed articles were published in high-impact journals. For seven (13%) of the RCTs, additional HRQOL publications were released (providing an HRQOL sub-article) that included further analysis and detailed description of the HRQOL design and outcomes. The largest percentage of the RCTs were conducted in the United States or

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Table 1. Comparison of Current (2002 to 2010) Results With Those From the Systematic Review by Bottomley et al[13] (1980 to 2002)

Review Criteria	Bottomley et al,[13] 1980-2002 (n = 29)		Present Study, 2002-2010 (n = 53)	
	No.	%	No.	%
Clinical and main HRQOL results				
OS: Difference demonstrated in the RCT	**12 of 27**	**44**	**10 of 52**	**19**
HRQOL: Reported difference when no difference in OS was reported	**9 of 15**	**60**	**21 of 42**	**50**
Key characteristics of the RCTs				
Published in high-quality cancer journals	19	66	38	72
Majority of studies: location	**Italy 7**	**24**	**US/Canada 11**	**21**
Industry-funded	**16**	**55**	**39**	**74**
Treatment focus				
Chemotherapy alone	24	83	48	90
Radiotherapy alone	3	10	4	2
Chemotherapy plus radiotherapy	2	7	3	6
Trial design aspects relevant to HRQOL end points				
Method of randomization not stated	**5**	**17**	**15**	**28**
Reporting of informed consent	**25**	**86**	**53**	**100**
Reporting of inclusion and exclusion criteria	29	100	53	100
No. of patients				
Range of patients in each study	**109-599**		**103-1,218**	
Total patients	**8,445**		**19,956**	
HRQOL as a primary end point	6	21	9	17
Baseline HRQOL assessment mandatory	4	14	7	13
A priori HRQOL hypothesis stated	**9**	**31**	**8**	**15**
Quality of the HRQOL measurements				
Rationale for instruments	**10**	**34**	**4**	**8**
Instrument administration reported	**0**	**0**	**10**	**19**
"Help will be provided" administration statement	**10**	**34**	**2**	**4**
Timing of assessments	29	100	50	94
Most used HRQOL assessment tool				
EORTC QLQ-C30	**9**	**31**	**30**	**57**
HRQOL domains covered	25	88	39	74
Statistical analysis and presentation of HRQOL results				
Test of significance between arms applied	**22**	**76**	**48**	**91**
Difference between treatment arms reported (if statistical test was reported)	**15 of 22**	**68**	**27 of 48**	**56**
Clinical significance assessed	6	21	16	30
Presentation of results				
Yes	17	59	33	62
Limited	10	34	17	32
No	2	7	3	6
Missing data reported				
Yes	18	62	33	62
Limited	5	17	6	11
No	6	21	14	26

NOTE. Results for which the difference between the two reviews is ≥ 10 are highlighted in bold, with the exception of study location, which is highlighted to mark the change in location of the majority of studies conducted.

Abbreviations: HRQOL, health-related quality of life; OS, overall survival; RCT, randomized controlled trial; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30.

Canada (21%), internationally (15%), by Norway and Sweden (11%), and by Italy (9%). RCTs focusing on NSCLC have become much more international in recruitment since 2002. Whereas the largest percentage of RCTs since 2002 (21%) were conducted in the United States and/or Canada, the largest percentage of RCTs in the former study (24%) took place in Italy.

Thirty-nine RCTs (74%) appeared to be industry-funded or affiliated with the pharmaceutical industry through one or more of the authors/investigators, whereas in the previous review, only 55% of the studies were industry-funded. Similar to the previous report, the majority of RCTs focused on chemotherapy (90%). Only two studies investigated the effectiveness of radiotherapy, and three studies used a combination of radiotherapy and chemotherapy.

Finally, Table 3 demonstrates demographic characteristics of the patients participating in all 53 RCTs, including age, sex, and—if provided—race. Although the median age varied from 57 to 76 years, the majority of trials included patients from a wide range of ages. As far as we could gather, only three RCTs have exclusively studied elderly patients (age > 60 years). In most RCTs (96%), the study sample involved more male than female patients.

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Table 2. Summary of Selected RCTs Key Characteristics, Experimental Treatments, Main Survival Outcomes, and HRQOL Outcomes

Firsts Author	Journal	Year of Publication	Study Location*	Industry Funded†	Treatment Outline	Survival Difference‡	Main HRQOL Outcomes‡
Vansteenkiste[14] Vansteenkiste[15]	Ann Oncol Lung Cancer	2001 (Sept) 2003 (May)	Belgium	Yes	Single-agent gemcitabine (GEM) *v* cisplatin-vindesine	No significant survival differences	Significantly larger number of GEM patients had better scores for anorexia, ability to carry on daily activities, and overall QOL
Falk[16]	BMJ	2002 (Aug)	International	No	Supportive treatment together with immediate, palliative, thoracic radiotherapy *v* supportive treatment and radiotherapy given when indicated	No significant survival differences	No significant difference between arms
Souquet[17]	Ann Oncol	2002 (Dec)	International	Yes	Vinorelbine-cisplatin *v* vinorelbine-ifosfamide-cisplatin	No significant survival differences	No significant difference between arms
Gridelli[18]	J Natl Cancer Inst	2003 (Mar)	Italy	Yes	Vinorelbine plus gemcitabine compared with vinorelbine or gemcitabine individually	No significant survival differences	Significantly worse hair loss for those who received vinorelbine plus gemcitabine than for those receiving gemcitabine only
Gridelli[19]	J Clin Oncol	2003 (Aug)	International	Yes	Gemcitabine plus vinorelbine compared with cisplatin plus vinorelbine or cisplatin plus gemcitabine	No significant survival differences	No significant difference in general QOL and health status. Significantly higher scores for appetite, vomiting, and hair loss in the cisplatin-based arm
Fossella[20] Belani[21]	J Clin Oncol Lung Cancer	2003 (Aug) 2006 (Aug)	International	Yes	Docetaxel plus cisplatin (DC) and docetaxel plus carboplatin (DCb) *v* vinorelbine plus cisplatin (VC)	No significant survival differences	Significantly better general QOL/health status in DCb arms than in the VC arm. Significantly more pain relief in DC than in VC (see Belani)
Wachters[22]	Br J Cancer	2003 (Oct)	Netherlands	Yes	Gemcitabine with cisplatin (CG) or epirubicin (EG)	No significant survival differences	No significant difference in global QOL or in the functional scales. However, symptoms of nausea and vomiting were significantly more common in the CG arm. Sore mouth and dysphagia were significantly more common in the EG arm
Smit[23]	J Clin Oncol	2003 (Nov)	International	Yes	Two cisplatin-based regimens (with paclitaxel, arm A, or gemcitabine, arm B) *v* paclitaxel plus gemcitabine (arm C)	No significant survival differences	No significant difference in global QOL between arms. Increase of nausea and vomiting in arm C was significantly less compared with the cisplatin arms. In arm B there was statistically significant stronger improvement than in arm A on peripheral neuropathy and alopecia
Paccagnella[24]	Lung Cancer	2004 (Jan)	Italy	No	Cisplatin (MVP) *v* carboplatin (MVC) in combination with mitomycin and vinblastine	No significant survival differences	Statistically significant improvement in global QOL in the MVC arm. Significantly less nausea/vomiting, appetite loss, and constipation in the MVC arm, as well as less peripheral neuropathy and minor hair loss
Kubota[25]	J Clin Oncol	2004 (Jan)	Japan	Yes	Docetaxel plus cisplatin (DC) *v* vindesine plus cisplatin (VdsC)	Median survival time was significantly greater for the DC arm than for the VdsC arm	Significantly stronger improvement for the functional (nonphysical) domain in the DC arm
Groen[26]	Ann Oncol	2004 (Mar)	The Netherlands	No	Carboplatin administered continuously with radiotherapy *v* radiotherapy alone	No significant survival differences	No significant difference between arms
O'Brien[27]	Ann Oncol	2004 (June)	European (Germany, Austria, UK, Poland)	Yes	Chemotherapy plus SRL172 *v* chemotherapy alone	No significant survival differences	Significantly greater deterioration in global health status in the chemotherapy alone group

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Table 2. Summary of Selected RCTs Key Characteristics, Experimental Treatments, Main Survival Outcomes, and HRQOL Outcomes (continued)

Firsts Author	Journal	Year of Publication	Study Location*	IndustryFunded†	Treatment Outline	Survival Difference‡	Main HRQOL Outcomes‡
Laack[28]	J Clin Oncol	2004 (June)	Germany	Yes	Gemcitabine, vinorelbine, and cisplatin (GVP) *v* gemcitabine and vinorelbine (GV)	No significant survival differences	No significant difference between arms
Stathopoulos[29]	Ann Oncol	2004 (July)	Greece	No	Front-line paclitaxel-vinorelbine *v* paclitaxel-carboplatin	No significant survival differences	No significant difference between arms
Spiro[30] Brown[31]	Thorax Clin Oncol	2004 (Oct) 2007 (June)	International	Yes	Supportive care plus chemotherapy (cisplatin-based) *v* supportive care alone	Patients allocated chemotherapy had a significantly better survival	No significant difference between arms
Lilenbaum[32] (phase II study)	Ann Oncol	2005 (Jan)	US	Yes	Vinorelbine plus gemcitabine (VG) *v* paclitaxel plus carboplatin (CP)	No significant survival differences	No significant difference between arms
Rudd[33]	J Clin Oncol	2005 (Jan)	UK	Yes	Gemcitabine plus carboplatin (GCa) *v* mitomycin, ifosfamide and cisplatin (MIC)	Overall survival is significantly higher in GCa than in MIC	Persistent significant advantage (baseline to 12 weeks) for GCa over MIC on nausea, vomiting, and hair loss
Baka[34] (Phase II study)	J Clin Oncol	2005 (Apr)	UK	Yes	Gemcitabine (3w4) plus best supportive care (BSC) *v* gemcitabine (2w3) plus BSC for up to six cycles	No significant survival differences	Significantly stronger deterioration for weakness in 2w3 arm
Movsas[35] Sarna[36] Movsas[37]	J Clin Oncol Int J Radiat Oncol Biol Phys J Clin Oncol	2005 (Apr) 2008 (Dec) 2009 (Dec)	US and Canada	Yes	Chemoradiotherapy (paclitaxel plus carboplatin plus radiation) with or without amifostine (AM)	No significant survival differences	Overall QOL was not significantly different between treatment arms. Reporting of pain improvement was more clinically significant (at 6 weeks) in the AM arm
Leighl[38]	J Clin Oncol	2005 (Apr)	International	Yes	Paclitaxel plus carboplatin with either BMS-275291 or a placebo	No significant survival differences	Not reported
Pujol[39]	Ann Oncol	2005 (Apr)	France	Yes	Gemcitabine-docetaxel *v* cisplatin-vinorelbine	No significant survival differences	No significant difference between arms
Sundstrøm[40] Sundstrøm[41]	Radiother Oncol J Clin Oncol	2005 (May) 2004 (Mar)	Norway	No	Immediate *v* delayed thoracic radiotherapy between symptomatic and nonsymptomatic patients	No significant survival differences	No significant difference between arms
Georgoulias[42]	J Clin Oncol	2005 (May)	Greece	No	Vinorelbine plus cisplatin (VC) *v* docetaxel plus gemcitabine (DG)	No significant survival differences	No significant difference between arms. Significant improvement between baseline and end CT assessment for hemoptysis and pain for the DG regimen only (thus within, not between)
Belani[43]	Ann Oncol	2005 (July)	US	Yes	Carboplatin plus paclitaxel *v* cisplatin plus etoposide	No significant survival differences	The difference in the FACT-L total score between baseline and cycle 3 was significantly better in the carboplatin plus paclitaxel arm
Sederholm[44]	J Clin Oncol	2005 (Nov)	Sweden	Yes	Gemcitabine plus carboplatin (GC) *v* gemcitabine alone (G)	Overall survival and the 2-year survival rate was significantly higher in the GC arm	No significant difference between arms
Socinski[45] (phase II study)	Ann Oncol	2006 (Jan)	US	No	Carboplatin with either paclitaxel 225 mg/m^2 every 3 weeks × 4 (arm A) or paclitaxel 75 mg/m^2/wk × 12 (arm B)	NA (no formal survival comparison planned)	Patients in arm A had significantly more taxane therapy side effects than those in arm B on the TAX subscale and significantly poorer QOL on the FACT-G than those in arm B
Booton[46]	Ann Oncol	2006 (Jul)	UK	Yes	Docetaxel plus carboplatin (DCb) *v* mitomycin/ifosfamide/cisplatin (MIC) or mitomycin/vinblastine/cisplatin (MVP)	No significant survival differences	The overall EORTC score reduced to a significantly less extent and mean global health status developed significantly more favorable in the DCb arm

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Table 2. Summary of Selected RCTs Key Characteristics, Experimental Treatments, Main Survival Outcomes, and HRQOL Outcomes (continued)

Firsts Author	Journal	Year of Publication	Study Location*	Industry Funded†	Treatment Outline	Survival Difference‡	Main HRQOL Outcomes‡
Kudoh[47]	J Clin Oncol	2006 (Aug)	Japan	No	Docetaxel *v* vinorelbine (in elderly patients)	Median progression-free survival time with docetaxel was significantly longer than with vinorelbine	Significantly better improvement in overall symptom score with docetaxel than with vinorelbine
Von Plessen[48]	Br J Cancer	2006 (Oct)	Norway and Sweden	Yes	Carboplatin and vinorelbine with either three (C3) or six (C6) courses	No significant survival differences	Significantly lower dyspnea scores at 18 and 26 weeks for C6 patients than for C3 patients (with LC13)
Manegold[49]	Clin Lung Cancer	2007 (Jan)	Germany	Yes	Gemcitabine (first-line) followed by docetaxel (second-line; GD) *v* docetaxel (first-line) followed by gemcitabine (second-line; DG)	Median TTP and median overall survival were significantly longer in the DG arm than in the GD arm, according to rank-sum test	Small significant differences in EORTC QLQ-C30/LC13 and SS14 mean total scores after cycle 2 in favor of GD arm
Ohe[50]	Ann Oncol	2007 (Feb)	Japan	Yes	Carboplatin plus paclitaxel (TC), cisplatin plus gemcitabine (GP), cisplatin plus vinorelbine (NP) *v* cisplatin plus irinotecan (IP) as reference arm	No significant survival differences	Only the physical domain (by QOL-ACD) was significantly better in TC, GP, NP than in IP
Gauthier[51] Bezjak[52] Winton[53]	Lung Cancer J Clin Oncol N Engl J Med	2007 (Mar) 2008 (Nov) 2005 (Jun)	Canada	Yes	Vinorelbine plus cisplatin *v* observation	Overall survival was substantially improved with chemotherapy	A significantly higher proportion of patients in the observation arm reported improved global QOL (plus physical, cognitive, social functioning, and less worse fatigue, appetite, hair loss, nausea, and vomiting)
Crawford[54]	J Thorac Oncol	2007 (Mar)	US	Yes	Epoetin initiated at the start of chem-otherapy (immediate epoetin alfa group) *v* no epoetin (delayed group)	No significant survival differences	No significant difference between arms
Leong[55] (phase II study)	J Thorac Oncol	2007 (Mar)	Singapore	No	Gemcitabine *v* vinorelbine *v* docetaxel	No significant survival differences	No significant difference between arms
Lilenbaum[56] (phase II study)	J Thorac Oncol	2007 (Apr)	US	Yes	Docetaxel weekly versus every 3 weeks	No significant survival differences	No significant difference between arms
Gatzemeier[57]	J Clin Oncol	2007 (Apr)	International	Yes	Cisplatin and gemcitabine with or without erlotinib	No significant survival differences	No significant difference between arms
Gridelli[58]	Lancet Oncol	2007 (June)	Italy	Yes	Gemcitabine constant and cisplatin (group A) and with rofecoxib (group C) or gemcitabine 30-min and cisplatin (group B) and with rofecoxib (group C)	No significant survival differences	Small but significant differences for global QOL, physical, emotional, role functioning, sleeping, fatigue, in favor of the rofecoxib groups
Gilligan[59]	Lancet	2007 (June)	European	Yes	Surgery alone (S) *v* 3 cycles of platinum-based chemotherapy followed by surgery (CT-S)	No significant survival differences	Significantly higher scores on the role physical domain for the S group at 6 months, and change over time from baseline to 6 months was significantly different between the treatment arms
Helbekkmo[60]	Br J Cancer	2007 (Aug)	Norway	No	Vinorelbine/carboplatin *v* gemcitabine/carboplatin	No significant survival differences	No significant difference between arms
Park[61]	J Clin Oncol	2007 (Nov)	Korea	No	Two (arm B) *v* four (arm A) additional cycles after two cycles of platinum-based chem-otherapy	No significant survival differences	Significant improvement in role-functioning and less nausea/vomiting, sore mouth, dyspnea in arm B
Georgoulias[62]	Lung Cancer	2008 (Jan)	Greece	No	Docetaxel (D) *v* docetaxel plus gemcitabine (DG)	The median overall survival was significantly longer in the DG arm than in the D arm	Appetite, fatigue, cough, dyspnea, total symptomatic distress, and overall QOL were significantly improved in the DG arm

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Table 2. Summary of Selected RCTs Key Characteristics, Experimental Treatments, Main Survival Outcomes, and HRQOL Outcomes (continued)

Firsts Author	Journal	Year of Publication	Study Location*	Industry Funded†	Treatment Outline	Survival Difference‡	Main HRQOL Outcomes‡
Lilenbaum[63] (phase II study)	J Clin Oncol	2008 (Feb)	US	Yes	Erlotinib *v* standard chemotherapy	Median survival time was significantly longer in the standard chemotherapy arm	No significant difference between arms
Johnson[64] Yang[65]	Lung Cancer J Thorac Oncol	2008 (May) 2009 (Apr)	US	Yes	CAI at a dose of 250 mg daily *v* placebo, after completion of at least 3 and no more than 6 months of chemotherapy	No significant survival differences	A significantly higher proportion of patients in the CAI group had a decline on the functional domain of the FACT-L and UNISCALE
Crinò[66] (phase II study)	J Clin Oncol	2008 (Sep)	Italy	Yes	Gefitinib *v* vinorelbine	No significant survival differences	Overall QOL improvement rates were higher with gefitinib than with vinorelbine
Gebbia[67]	Lung Cancer	2008 (Sep)	Italy	No	Cisplatin plus weekly vinorelbine *v* cisplatin plus vinorelbine on days 1 and 8	No significant survival differences	No significant difference between arms
Fidias[68]	J Clin Oncol	2009 (Feb)	US	Yes	Immediate *v* delayed docetaxel after front-line therapy with gemcitabine plus carboplatin	No significant survival differences	No significant difference between arms
Nyman[69]	Lung Cancer	2009 (July)	Sweden	Yes	A B C: two cycles of induction chemotherapy followed by A, third cycle of chemo plus RT; B, daily concomitant paclitaxel plus fractionated RT; C, weekly concomitant paclitaxel plus identical RT	No significant survival differences	No significant difference between arms
Grønberg[70]	J Clin Oncol	2009 (July)	Norway	Yes	Pemetrexed plus carboplatin *v* gemcitabine plus carboplatin	No significant survival differences	No significant difference between arms
Zwitter[71] (phase II study)	J Thorac Oncol	2009 (Sept)	Slovenia	No	1,250 mg/m^2 gemcitabine in 20 to 30 min *v* 250 mg/m^2 in 6-hour infusion. All received gemcitabine on days 1 and 8 and cisplatin at 75 mg/m^2 on day two of 3-week cycle for four cycles, followed by two cycles gemcitabine as monotherapy	No significant survival differences	No significant difference between arms
Lee[72]	J Clin Oncol	2009 (Nov)	UK	Yes	Placebo *v* thalidomide for 2 years. All patients received gemcitabine and carboplatin	No significant survival differences	No significant difference in global QOL. Significantly higher scores for constipation and peripheral neuropathy in treatment arm
Takeda[73]	J Clin Oncol	2010 (Feb)	Japan	Yes	A, platinum-doublet chemotherapy followed by gefitinib, *v* B, continued platinum-doublet chemotherapy	No significant survival differences	No significant difference between arms
Lynch[74]	J Clin Oncol	2010 (Feb)	US	Yes	TC (either paclitaxel or docetaxel) plus cetuximab *v* TC alone	No significant survival differences	No significant difference between arms
Zwitter[75] (phase II study)	Anticancer Drugs	2010 (July)	Slovenia	No	200 mg/m^2 gemcitabine in 6- hour infusion plus 60 mg/m^2 cisplatin *v* gemcitabine alone	Significantly higher overall survival in arm B (gemcitabine + cisplatin)	Significantly better HRQOL reported in arm B (gemcitabine + cisplatin)

Abbreviations: RCTs, randomized controlled trials; HRQOL, health-related quality of life; QOL, quality of life; FACT-L, Functional Assessment of Cancer Therapy–Lung; NA, not applicable; TAX, Taxane Subscale; FACT-G, Functional Assessment of Cancer Therapy–Gastrointestinal; CAI, carboxyaminoimidazole; RT, radiotherapy; TC, taxane/carboplatin.

*A trial involving nations from different continents was defined as international.

†Assessed if explicitly stated or if authors were related to a pharmaceutical company. This evaluation is based solely on information extracted from the article referenced in this table.

‡Only statistically significant results discussed ($P < .05$).

Trial Design Aspects Relevant to HRQOL End Points

The RCTs design aspects related to the HRQOL end points such as the method of randomization, HRQOL hypotheses and patient selection criteria are presented in Table 4. Although all included trials were randomized (this was a key eligibility criterion), 15 studies (28%) did not define the exact randomization procedure. All studies included a statement on the requirement of patient informed consent and specifications of the patient inclusion and exclusion criteria. Almost all trials focused on patients with NSCLC having stage III and/or IV disease, with the exception

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Table 3. Demographic Characteristics of the Patients Participating in the 53 RCTs

First Author	Age (years)*		Male		Female		Race (%)
	Median	Range	No.	%	No.	%	
Vansteenkiste[14]	63 (mean)	8 (SD)	140	83	29	17	—
Vansteenkiste,[15] 2003							—
Falk[16]	71	47-87	160	70	70	30	—
Souquet[17]	60	34-76	191	74	68	26	—
Gridelli[18]	74	63-86	581	83	117	17	—
Gridelli[19]	62	35-74	402	80	101	20	—
Fossella[20]	60	23-87	888	73	330	27	—
Belani,[21] 2006 August							—
Wachters[22]	60	29-80	179	75	61	25	—
Smit[23]	57	27-75	318	66	162	34	—
Paccagnella[24]	60 (mean)	—	76	50	77	50	—
Kubota[25]	64	30-74	200	76	102	34	—
Groen[26]	60 (mean)	—	141	88	19	12	—
O'Brien[27]	61	30-78	300	72	119	28	White (99) Asian (0.5) Black (0.25) Other (0.25)
Laack[28]	61	40-75	215	75	72	25	—
Stathopoulos[29]	65	30-84	312	87	48	13	—
Spiro[30]	63 (mean)	8 (SD)	197	72	76	28	—
Brown[31]							
Lilenbaum[32]	64	38-86	93	56	72	44	—
Rudd[33]	62	34-81	296	70	126	30	—
Baka[34]	69	42-84	104	60	70	40	—
Movsas[35]	60% ≥ 60		150	62	92	38	—
Sarna[36]							
Movsas,[37] 2009							
Leighl[38]	61	—	565	73	209	27	—
Pujol[39]	58	37-75	248	80	63	20	—
Sundstrom[40]	68	41-88	306	75	101	25	—
Sundstrøm,[41] 2004							
Georgoulias[42]	63	36-75	365	88	48	12	—
Belani[43]	61 (mean)	28-80	226	61	143	39	—
Sederholm[44]	66	42-82	178	56	147	44	—
Socinski[45]	61	38-85	105	65	56	35	White (68) African American (24) Other (8)
Booton[46]	63	35-83	295	68	138	32	—
Kudoh[47]	76	70-86	137	76	43	24	—
Von Plessen[48]	64	34-84	188	63	109	37	—
Manegold[49]	64	28-84	232	72	89	28	—
Ohe[50]	62	28-74	398	69	183	31	—
Gauthier[51]	61	34-82	313	65	169	35	—
Bezjak[52]							
Winton[53]							
Crawford[54]	62 (mean)	11 (SD)	124	59	87	41	White (75) Black (19) Asian (3) Other (3)
Leong[55]	72	42-94	90	67	44	33	—
Lilenbaum[56]	75	46-86	64	58	47	42	—
Gatzemeier[57]	61	26-84	892	77	267	23	White (92) Black (< 1) Asian (4) Other (4)
Gridelli[58]	60	29-71	322	81	78	19	—
Gilligan[59]	63	25-79	374	72	143	28	—
Helbekkmo[60]	67	37-86	264	61	168	39	—
Park[61]	58	26-81	312	69	140	31	—

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Table 3. Demographic Characteristics of the Patients Participating in the 53 RCTs (continued)

First Author	Age (years)*		Male		Female		Race (%)
	Median	Range	No.	%	No.	%	
Georgoulias[62]	63	33-78	265	85	47	15	—
Lilenbaum[63]	< 70 (53%) ≥ 70 (47%)		51	50	52	50	White (66) African American (21) Other (13)
Johnson[64] Yang[65]	66	—	107	58	79	42	White (97) Black/African American (< 1) American Indian/Alaska (1) Not reported (2)
Crinò[66]	74	70-89	148	76	48	24	White (83) Asian (16) Other (1)
Gebbia[67]	62	36-73	214	77	64	23	—
Fidias[68]	65	35-87	352	62	214	38	White (87) African American (8) East/Southeast Asian (2) Hispanic (3)
Nyman[69]	62	43-78	78	52	73	48	—
Grønberg[70]	65	25-90	251	58	185	42	—
Zwitter[71]	58	40-79	188	76	61	24	—
Lee[72]	63	33-84	465	64	257	36	—
Takeda[73]	62	25-74	383	64	215	36	—
Lynch[74]	64	34-87	396	59	280	41	White (88) Black (7) Asian (3) Other (2)
Zwitter[75]	66	40-81	83	74	29	26	—

Abbreviations: RCTs, randomized controlled trials; SD, standard deviation.
*Median and range unless otherwise noted.

of four RCTs that included stage I and/or II disease (92%). Only one of these studies included exclusively patients with stage I and II disease.

In 44 (83%) of the included trials, survival outcomes were predefined as main end points. Only nine studies (17%) reported HRQOL to be a primary end point. An HRQOL hypothesis was rarely mentioned in the publications included in this review, with only eight (15%) of the 53 studies formulating an a priori hypothesis stated in the introduction or statistical analysis sections. These hypotheses described the anticipated differences in general HRQOL between treatment arms. Only seven studies (13%) specifically stated that baseline HRQOL assessment was mandatory for study participation.

When compared with the earlier review, methods of randomization and HRQOL hypotheses were substantially less frequently reported in the RCTs of the current review (a decrease of 11% and 16%, respectively). However, the reporting on informed consent was seen more frequently (an increase of 14% since 2002).

Quality of the HRQOL Measurements

Table 5 summarizes the quality of the measurement aspects of HRQOL in the RCTs. In general, HRQOL concepts were measured by using well-known instruments with adequate psychometric properties. The EORTC core questionnaire Quality of Life Questionnaire C30 (QLQ-C30)[76] was the most frequently used instrument. It was used in 57% of the evaluated studies since 2002, compared with 31% in the previous review. In all but two studies, the QLQ-C30 was supplemented with a lung cancer–specific questionnaire: EORTC QLQ-LC13,[77] or an EORTC tool with minor adaptations such as the reported QLQ-LC14 or QLQ-LC17. In one study, the QLQ-LC13 was used without the core questionnaire. The Lung Cancer Symptom Scale[78,79] and the questionnaires from the Functional Assessment for Chronic Illness Therapy[80] were used in 13% and 23% of the studies, respectively. Other HRQOL instruments included the Visual Analog Scale, the Rotterdam Symptom Checklist,[81] a Symptom Scale covering 14 commonly reported lung cancer symptoms (SS14), the Brief Fatigue Inventory,[82] EuroQol,[83] and the Linear Analog Self Assessment scale.[84] Baseline compliance was reported by the majority of studies (75%). Validity and reliability issues of the instruments were addressed by means of referencing the appropriate validation studies (66% of RCTs). In the remaining 34% of the RCTs, no statement or reference was provided with regard to validity or reliability, although most of the chosen instruments did have sufficient psychometric properties. Six studies (11%) incorporated ad hoc instruments in addition to a validated existing questionnaire. In contrast to the frequent reporting of instrument validity and reliability, the overall number of studies that addressed cultural validity was low. Of the 35 studies that used a translated version of an HRQOL tool in a population that the tool was not originally developed for, 60% failed to report on the cultural validation process or study, regardless of whether or not the instrument was culturally validated.

The domains covered by the questionnaires were considered adequate in 74% of the RCTs in which both symptoms and functional status results were reported. Many of these studies did not formulate a specific research question and thus complicated the evaluation of the

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Table 4. Trial Design Aspects Relevant to HRQOL End Points

First Author	Method of Randomization Stated*	Informed Consent Reported	Inclusion and Exclusion Criteria Reported	No. of Patients†	Disease Stage	HRQOL End Point	Hypothesis Stated‡	Baseline HRQOL Compliance Mandatory
Vansteenkiste[14] Vansteenkiste,[15] 2003	Yes	Yes	Yes	169	Stage IIIB (not amendable to surgery or radical radiotherapy)	Primary	No	No
Falk[16]	Yes	Yes	Yes	230	Locally too advanced for surgical resection or radical radiotherapy with curative intent	Secondary	No	No
Souquet[17]	Yes	Yes	Yes	259	Stage IV or relapse after local treatment	Secondary	No	No
Gridelli[18]	Yes	Yes	Yes	707	Stage IIIB (with pleural effusion or metastatic supraclavicular lymph nodes) or stage IV	Secondary	No	No
Gridelli[19]	Yes	Yes	Yes	503	Stage IV or stage IIIB with malignant pleural effusion or supraclavicular nodes	Primary	Yes	Yes
Fossella[20] Belani,[21] 2006 August	Yes	Yes	Yes	1,218	Stage IIIB (locally advanced or recurrent) or stage IV (metastatic)	Secondary	Yes	No
Wachters[22]	Yes	Yes	Yes	240	Unresectable stage III or stage IV	Secondary	No	No
Smit[23]	Yes	Yes	Yes	480	Stage IIIB (malignant pleural effusion or supraclavicular lymph nodes only) and stage IV	Secondary	No	No
Paccagnella[24]	No	Yes	Yes	153	Stage IIIB (with pleura effusion or supraclavicular lymph nodes) or stage IV (metastatic)	Primary	Yes	No
Kubota[25]	No	Yes	Yes	311	Stage IV	Secondary	No	No
Groen[26]	Yes	Yes	Yes	160	Locally advanced and unresectable NSCLC	Secondary	No	No
O'Brien[27]	No	Yes	Yes	419	Stage IIIA, IIIB, or IV	Secondary	Yes	No
Laack[28]	Yes	Yes	Yes	300	Stage IIIB with malignant pleural effusion or stage IV	Secondary	No	No
Stathopoulos[29]	Yes	Yes	Yes	360	Stage IIIB (pleural effusion or N3 nodal disease) or stage IV (extrapulmonary metastases including asymptomatic brain metastases) and stage IIIA N2 inoperable disease	Secondary	No	No
Spiro[30] Brown[31]	Yes	Yes	Yes	273	Stage I-IV	Secondary	Yes	Yes
Lilenbaum[32]	No	Yes	Yes	165	Stage IIIB or IV	Primary	No	No
Rudd[33]	Yes	Yes	Yes	422	Stage IIIB or IV	Secondary	No	No
Baka[34]	No	Yes	Yes	174	Stage III or IV	Secondary	No	No
Movsas[35] Sarna[36] Movsas,[37] 2009	No	Yes	Yes	243	Locoregionally advanced with stages II, IIIa, or IIIB	Secondary	Yes	Yes
Leighl[38]	Yes	Yes	Yes	774	Stage IIIB or IV	Secondary	No	No
Pujol[39]	Yes	Yes	Yes	311	Stage IIIB or IV	Secondary	No	Yes
Sundstrom[40] Sundstrøm,[41] 2004	Yes	Yes	Yes	421	Stage III or IV	Primary	No	No
Georgoulias[42]	No	Yes	Yes	413	Inoperable stage IIIB (with pleural effusion) or stage IV	Secondary	No	No
Belani[43]	Yes	Yes	Yes	369	Inoperable stage IIIB or IV	Secondary	No	No
Sederholm[44]	Yes	Yes	Yes	334	Stage IIIB or IV (not amenable to surgery or radiation of curative intent)	Secondary	No	No
Socinski[45]	Yes	Yes	Yes	161	Stage IIIB or IV	Secondary	No	No
Booton[46]	Yes	Yes	Yes	433	Stage III or IV	Secondary	No	No
Kudoh[47]	Yes	Yes	Yes	182	Stage IIIB or IV	Secondary	No	No
Von Plessen[48]	Yes	Yes	Yes	297	Stage IIIB or IV	Primary	No	Yes
Manegold[49]	Yes	Yes	Yes	330	Stage "wet IIIB" with malignant pleural effusion or stage IV	Secondary	No	No
Ohe[50]	Yes	Yes	Yes	602	Stage IV or IIIb (without indication for curative radiotherapy)	Secondary	No	No

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Table 4. Trial Design Aspects Relevant to HRQOL End Points (continued)

First Author	Method of Randomization Stated*	Informed Consent Reported	Inclusion and Exclusion Criteria Reported	No. of Patients†	Disease Stage	HRQOL End Point	Hypothesis Stated‡	Baseline HRQOL Compliance Mandatory
Gauthier[51] Bezjak[52] Winton[53]	Yes	Yes	Yes	482	Stage IB or II	Secondary	Yes	No
Crawford[54]	Yes	Yes	Yes	216	Stage IIIB or IV	Primary	No	No
Leong[55]	Yes	Yes	Yes	135	Stage IV or III (not amenable to curative treatment)	Primary	No	No
Lilenbaum[56]	Yes	Yes	Yes	111	Stage IIIB (malignant effusion) and IV	Secondary	No	No
Gatzemeier[57]	No	Yes	Yes	1,172	Stage IIIB or IV	Secondary	No	No
Gridelli[58]	Yes	Yes	Yes	400	Stage IV or IIIB with malignant pleural effusion or supraclavicular	Secondary	No	No
Gilligan[59]	Yes	Yes	Yes	519	Stages IA to IIIB	Secondary	No	No
Helbekkmo[60]	Yes	Yes	Yes	444	Stage IIIB or IV	Secondary	No	No
Park[61]	Yes	Yes	Yes	452	Stage IIIB (with malignant effusion) or stage IV	Secondary	No	No
Georgoulias[62]	Yes	Yes	Yes	322	Stage IIIB (with carcinomatous pleural effusion) or IV	Secondary	No	No
Lilenbaum[63]	No	Yes	Yes	103	Stage IIIB (malignant effusion) and IV	Secondary	No	Yes
Johnson[64] Yang[65]	Yes	Yes	Yes	186	Stage III or IV	Secondary	No	No
Crinò[66]	No	Yes	Yes	196	Stage IIIB or IV	Secondary	No	No
Gebbia[67]	No	Yes	Yes	278	IIIB with cytology-positive pleural effusion and/or metastatic supraclavicular nodes or metastatic stage IV	Secondary	No	No
Fidias[68]	Yes	Yes	Yes	566	IIIB plus pleural effusion or stage IV	Secondary	No	No
Nyman[69]	No	Yes	Yes	152	Inoperable stage III A/B	Secondary	No	No
Grønberg[70]	Yes	Yes	Yes	446	Stage IIIB or IV	Primary	Yes	Yes
Zwitter[71]	No	Yes	Yes	249	Stage IIIB or IV	Secondary	No	No
Lee[72]	Yes	Yes	Yes	722	Stage IIIB or IV disease	Secondary	No	No
Takeda[73]	Yes	Yes	Yes	604	Advanced stage IIIB/IV	Secondary	No	No
Lynch[74]	No	Yes	Yes	676	Stage IIIB (pleural effusion) or IV	Secondary	No	No
Zwitter[75]	No	Yes	Yes	112	Stage IIIB (wet) or IV	Secondary	No	No

Abbreviations: HRQOL, health-related quality of life; NSCLC, non–small-cell lung cancer.
*Assessed if indicated that patients were randomly assigned centrally or if the randomization method was explicitly stated.
†Overall number of patients enrolled onto the trial. When the number of patients registered was not available, the number of patients randomly assigned was listed.
‡Assessed if authors had a pretrial hypothesis on possible HRQOL changes (eg, related to specific domains).

reporting adequacy of the domains. Whenever HRQOL, as a general term, was the subject of research, we expected that at least global HRQOL would be addressed. However, 17% percent of the studies addressed physical functioning, but excluded social and/or emotional functioning or merely included symptoms and no domains of functioning at all. Given the multidimensional character of global HRQOL, we rated these latter instruments as limited in their capacity for overall HRQOL assessment.

Rationales for selecting the chosen HRQOL instruments were provided in only 8% of the analyzed trials. This is considerably fewer in comparison with the RCTs found between 1980 and 2002, in which 34% reported a rationale for the selected HRQOL instrument. A rationale was defined as present if the authors clearly referred to characteristics of the instrument as a basis for its intended use or if a reason was specified for choosing the particular instrument rather than any other HRQOL instrument.

Details on instrument administration were often left undefined. Ten studies (19%) noted only a few details, such as the place or time of questionnaire completion or the procedure of sending reminders. This is a considerably higher percentage when compared with the RCTs from the previous review, which found no studies that reported any information on this topic at all. However, a second glance showed that only two studies (4%), compared with 10 studies (34%) reported in Bottomley et al,[13] explained that help would be provided by relatives or a research assistant for patients unable to complete the assessment independently. All but three studies (94%) reported the timing of HRQOL assessments.

Statistical Analysis and Presentation of HRQOL Results

Table 6 summarizes details regarding the reporting of HRQOL analysis and results in the NSCLC clinical trials. Overall, the studies specified the statistical tests used to investigate the significance of between-treatment HRQOL difference (91%), which shows an increase of 15% when compared with the RCTs studied in the previous review (76%). Out of the 49 RCTs in which a test of statistical significance was reported, 56% demonstrated significant differences in HRQOL scores, which is notably less than was seen in the previous review (68%). Only 30% of all evaluated

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Table 5. Quality of the HRQOL Measurements

First Author	Instrument Used*	Compliance Baseline Reported†	Validity Data Presented	Reliability Data Presented	Cultural Validity Verified‡	Rationale for Instruments§	Adequacy of Domains Covered‖	Instrument Administration Reported¶	Timing of Assessment
Vansteenkiste[14] Vansteenkiste[15] 2003	VAS	No	Referenced	Referenced	No	No	Limited	Yes	Yes
Falk[16]	RSCL (and ad hoc 4 items) and the Hospital Anxiety and Depression Scale	Yes	Referenced	Referenced	No	No	Limited	No	Yes
Souquet[17]	VAS for lung cancer symptoms	No	No	No	NA	No	Yes	No	Yes
Gridelli[18]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Gridelli[19]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Fossella[20] Belani[21] 2006 Aug	LCSS and EuroQol	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Wachters[22]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	Yes	Yes
Smit[23]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Yes	No	Yes
Paccagnella[24]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	Yes	Yes	Yes	Yes
Kubota[25]	QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (developed in Japan)	Yes	Referenced	Referenced	NA	No	Yes	No	Yes
Groen[26]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Yes	No	Yes
O'Brien[27]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Yes	No	No
Laack[28]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Yes	No	Yes
Stathopoulos[29]	EORTC QLQ-C30 Adjusted	No	Referenced	Referenced	Yes	No	Yes	No	No
Spiro[30] Brown[31]	EORTC QLQ-C30/LC17 and daily diary card	Yes	Referenced	Referenced	NA	No	Yes	Yes	Yes
Lilenbaum[32]	LCSS	Yes	Referenced	Referenced	NA	No	Limited	No	Yes
Rudd[33]	EORTC QLQ-C30/LC17 and the London Lung Cancer Group daily diary card	Yes	Referenced	Referenced	NA	No	Yes	Yes	Yes
Baka[34]	SS14 lung cancer-specific questions (derived from EORTC QLQ-C30/LC13 plus 3 additional questions)	No	No	No	NA	No	Yes	No	Yes
Movsas[35] Sarna[36] Movsas[37] 2009	EORTC QLQ-C30/LC13 and the daily swallowing diary	Yes	Referenced	Referenced	NA	Yes	Yes	No	Yes
Leighl[38]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Limited	No	Yes
Pujol[39]	EORTC QLQ-C30/LC13	Yes	Referenced (only C30)	Referenced (only C30)	Yes	No	Yes	No	Yes
Sundstrom[40] Sundstrøm[41] 2004	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Georgoulias[42]	LCSS	Yes	Referenced	Referenced	No	No	Limited	No	Yes
Belani[43]	FACT-L	No	Referenced	Referenced	NA	No	Yes	No	Yes
Sederholm[44]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	Yes	No	Yes
Socinski[45]	FACT-G, LCSS, TAX, and FACIT-Fatigue	Yes	Referenced	Referenced	NA	Yes	Yes	No	Yes
Booton[46]	EORTC QLQ-C30/LC13 and the HAD	Yes	No	No	NA	No	Yes	No	Yes
Kudoh[47]	Visual face scale for global QOL and ad hoc eight separate measures for disease-related symptom	Yes	Referenced	Referenced	NA	No	Limited	No	Yes
Von Plessen[48]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	Yes	Yes
Manegold[49]	EORTC QLQ-C30/LC13 and ad hoc SS14	No	Referenced.	Referenced	No	No	Yes	No	Yes
Ohe[50]	FACT-L and QOL-ACD	No	Referenced	Referenced	Yes	No	Yes	No	Yes
Gauthier[51] Bezjak[52] Winton[53]	EORTC QLQ-C30/ad hoc 15-item symptom checklist (selected from NCIC CTG item bank)	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Crawford[54]	LASA and FACT-G and FACT-An, and FACT-L and BFI	No	Referenced	Referenced	NA	No	Yes	No	Yes
Leong[55]	EORTC QLQ-C30/LC13	Yes	No	No	Yes	No	Yes	Limited	Yes
Lilenbaum[56]	FACT-L (TOI)	Yes	Referenced	Referenced	NA	No	Yes	No	Yes
Gatzemeier[57]	LCSS	No	No	No	No	No	Yes	No	No
Gridelli[58]	EORTC QLQ-C30/LC13 and a visual analog scale for pain	Yes	No	No	No	No	Yes	No	Yes
Gilligan[59]	SF-36	Yes	No	No	No	Yes	Yes	No	Yes

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Table 5. Quality of the HRQOL Measurements (continued)

First Author	Instrument Used*	Compliance Baseline Reported†	Validity Data Presented	Reliability Data Presented	Cultural Validity Verified‡	Rationale for Instruments§	Adequacy of Domains Covered‖	Instrument Administration Reported¶	Timing of Assessment
Helbekkmo[60]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	Yes	Yes
Park[61]	EORTC QLQ-C30/LC13	No	Referenced (only C30)	Referenced (only C30)	No	No	Yes	No	Yes
Georgoulias[62]	LCSS	Yes	Referenced	Referenced	No	No	Limited	No	Yes
Lilenbaum[63]	EORTC QLQ-LC13	Yes	No	No	NA	No	Limited	No	Yes
Johnson[64] Yang[65]	FACT-L and UNISCALE	No	Referenced	Referenced	NA	No	Yes	No	Yes
Crinò[66]	FACT-L (+ LCS)	No	Referenced	Referenced	No	No	Yes	Yes	Yes
Gebbia[67]	EORTC QLQ-C30/LC13	Yes	No	No	No	No	No	Yes	Yes
Fidias[68]	LCSS	Yes	Referenced	Referenced	NA	No	Yes	No	Yes
Nyman[69]	EORTC QLQ-C30/LC14	Yes	No	No	No	No	Limited	Yes	Yes
Grønberg[70]	EORTC QLQ-C30/LC13	Yes	Referenced	Referenced	Yes	No	Yes	No	Yes
Zwitter[71]	LCSS + ad hoc scale	No	No	No	No	No	No	No	Yes
Lee[72]	EORTC QLQ-C30/LC14	Yes	Referenced	Referenced	NA	No	Yes	No	Yes
Takeda[73]	FACT-L (LCS)	Yes	Referenced	Referenced	No	No	No	No	Yes
Lynch[74]	FACT-L (LCS + 5)	No	Referenced	Referenced	NA	No	No	No	Yes
Zwitter[75]	Ad hoc scale	Yes	No	No	No	No	No	No	Yes

Abbreviations: HRQOL, health-related quality of life; VAS, visual analog scale; RSCL, Rotterdam Symptom Checklist; NA, not applicable; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30; LCSS, Lung Cancer Symptom Scale; FACT-L, Functional Assessment of Cancer Therapy–Lung; FACT-G, Functional Assessment of Cancer Therapy–Gastrointestinal; TAX, Taxane Subscale; FACIT, Functional Assessment of Chronic Illness Therapy; HAD, Hospital Anxiety and Depression; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; LASA, Linear Analog Self-Assessment; FACT-An, Functional Assessment of Cancer Therapy-Anemia; BFI, Brief Fatigue Inventory; TOI, trial outcome index.

*A measure was defined ad hoc if no psychometric evaluation was reported or referenced.

†Assessed if authors reported the number of patients providing an HRQOL assessment before the start of treatment.

‡Refers to the international validation of the measure. We assessed as "NA" if the HRQOL instrument was validated in the same population (language) as the one of the trial.

§Rationale for instrument selection was assessed if authors justified or explained the choice processes in selecting the measure(s).

‖Assessed as "yes" if the questionnaire that was used covered the general HRQOL issues (according to the research question), as "limited" if covering selected areas, and as "no" if unlikely to detect few HRQOL issues.

¶Assessed if authors specified who administered the HRQOL instrument and/or in which clinical setting the HRQOL instrument was administered.

studies reported and discussed the clinical significance of the observed HRQOL differences. These studies included prespecifications regarding the minimum amount of change that is required to define a response in HRQOL that is meaningful to the patient. The evaluation of clinical meaningfulness provides an added value to studies involving HRQOL.[85]

The presentation of the results was considered adequate if the authors provided detailed descriptions of the outcome scores, supported by graphs or tables; if the results were compared with outcomes from related research, or conclusions were drawn based on the currently investigated therapies and HRQOL; and if these were followed by implications for clinical practice. Results of the review found that, of the 53 studies, 62% met the criteria for adequate reporting of HRQOL, and 32% reported only brief HRQOL details without interpretation and were labeled as having limited information presented on HRQOL. In addition, two studies explained that further reporting of HRQOL would be presented in future reports.

Of the 53 RCTs evaluated in this review, 62% reported adequate information with regard to compliance or "missingness." These studies had mentioned the issue of missing data or had listed compliance percentages or numbers according to treatment arm. Due to the lack of missing data reported specific to each treatment arm, 11% of the 53 studies were classified as having limited presentation of missing data, and 26% presented no data at all. Noncompliance, when reported, was due to death, deterioration of health, or institution error.

DISCUSSION

The aim of this review was to examine the developments in HRQOL assessments and reporting of results in RCTs in NSCLC since 2002, as well as to determine whether the findings may support physicians and patients in clinical decision making. Results from this updated systematic review are best interpreted in comparison with those of the previous systematic review covering RCTs between 1980 and 2002.

Overall, we observed an increase in the number of NSCLC RCTs that involved HRQOL measurement and that were published in high-impact journals, thus reaching the clinical community. The studies were geographically more widespread and multinational and more frequently supported by commercial sponsors over recent times.

The increase in industry-funded trials could be explained by the significant increase in the cost of conducting clinical trials,[86] making it difficult for academic groups and individual centers to conduct large-scale RCTs. Another reason may be related to the rapid development and evaluation in the past decade of promising new targeted therapies, some of which have been tested in NSCLC, such as erlotinib. Our results show that recently, almost all studies focused on the effects of systemic treatments alone rather than on radiotherapy alone or radiotherapy plus systemic treatments. This again may reflect the increased clinical evaluation of new targeted therapies.

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Table 6. Statistical Analysis and Presentation of HRQOL Results

First Author	Test of Statistical Significance Between Arms Applied	Difference Between Treatment Arms*	Clinical Significance Assessed†	Presentation of Results‡	Missing Data Documented According to Bottomley et al[13]
Vansteenkiste[14]	Yes	Yes	No	Yes	No
Vansteenkiste,[15] 2003					
Falk[16]	Yes	No	No	Yes	No
Souquet[17]	Not reported	No	Yes	No	No
Gridelli[18]	Yes	Yes	No	Limited	Yes
Gridelli[19]	Yes	Yes	Yes	Yes	Yes
Fossella[20]	Yes	Yes	No	Yes	Yes
Belani,[21] 2006 August					
Wachters[22]	Yes	Yes	No	Yes	Limited
Smit[23]	Yes	Yes	Yes	Yes	No
Paccagnella[24]	Yes	Yes	No	Yes	Yes
Kubota[25]	Yes	Yes	No	Yes	Yes
Groen[26]	Yes	No	No	Limited	Limited
O'Brien[27]	Yes	Yes	No	Yes	Yes
Laack[28]	Yes	No	No	Yes	Yes
Stathopoulos[29]	Yes	No	No	Limited	No
Spiro[30]	Yes	No	Yes	Yes	Yes
Brown[31]					
Lilenbaum[32]	Yes	No	Yes	Yes	Yes
Rudd[33]	Yes	Yes	No	Yes	Yes
Baka[34]	Yes	Yes	Yes	Yes	Yes
Movsas[35]	Yes	Yes	Yes	Yes	Yes
Sarna[36]					
Movsas,[37] 2009					
Leighl[38]	Yes	Not reported	No	No	No
Pujol[39]	Yes	No	No	Limited	No
Sundstrom[40]	Yes	No	Yes	Yes	Yes
Sundstrøm,[41] 2004					
Georgoulias[42]	Yes	No	No	Limited	Yes
Belani[43]	Yes	Yes	No	Limited	Yes
Sederholm[44]	Yes	Yes	No	Limited	Yes
Socinski[45]	Yes	Yes	No	Yes	Yes
Booton[46]	Yes	Yes	Yes	Yes	Yes
Kudoh[47]	Yes	Yes	No	Yes	Yes
Von Plessen[48]	Yes	Yes	Yes	Yes	Yes
Manegold[49]	Yes	Yes	No	Yes	Yes
Ohe[50]	Not reported	Yes	No	No	No
Gauthier[51]	Yes	Yes	Yes	Yes	Yes
Bezjak[52]					
Winton[53]					
Crawford[54]	Yes	No	No	Yes	Yes
Leong[55]	No	No	No	Limited	Yes
Lilenbaum[56]	Yes	No	No	Yes	Limited
Gatzemeier[57]	Not reported	No	Yes	Limited	No
Gridelli[58]	Yes	Yes	No	Yes	Limited
Gilligan[59]	Yes	Yes	No	Yes	Yes
Helbekkmo[60]	Yes	No	Yes	Yes	Yes
Park[61]	Yes	Yes	No	Yes	Yes
Georgoulias[62]	Yes	Yes	No	Limited	Yes
Lilenbaum[63]	Yes	Yes	No	Limited	No
Johnson[64]	Yes	Yes	Yes	Yes	Limited
Yang[65]					
Crinò[66]	Yes	Yes	Yes	Limited	No
Gebbia[67]	Yes	No	No	Yes	No
Fidias[68]	Yes	No	No	Yes	No
Nyman[69]	Yes	No	No	Limited	Limited
Grønberg[70]	Yes	No	Yes	Yes	Yes
Zwitter[71]	Not reported	No	No	Limited	No
Lee[72]	Yes	No	No	Yes	Yes
Takeda[73]	Yes	No	No	Limited	Yes
Lynch[74]	Yes	No	No	Limited	No
Zwitter[75]	Yes	Yes	No	Limited	No

Abbreviation: HRQOL, health-related quality of life.

*We applied "yes" if a trial showed at least a significant difference in one HRQOL domain at any time point assessment.

†This refers to the analysis of HRQOL data according to clinical significance, not statistical significance. If the authors fail to report this, we classified as "no."

‡Assessed independently by three reviewers examining whether the authors discussed the HRQOL outcomes in detail (eg, reporting of scores, meaning of scores, interpretation of data, and implications of HRQOL results).

§Assessed if authors gave specific details on HRQOL missing data during the trial.

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Encouragingly, some aspects of the HRQOL methodology reporting in RCTs for NSCLC have improved. This review has found an increase in the reporting of formal statistical tests in HRQOL analyses and of the clinical significance and meaning of the results. The increased frequency of use of the EORTC QLQ-C30 suggests that it is becoming the tool of choice for use in NSCLC RCTs. It includes many of the characteristics defined by the current *Guidance for Industry*, which should be part of an effective HRQOL PRO assessment tool (eg, adequacy of both validity and reliability).[87]

Unfortunately, other aspects of reporting HRQOL methodology did not improve over time, and some even showed deterioration. For example, the limited reporting of missing HRQOL data was addressed in the previous systematic review and continued to be a problem in the present review. Although most of the studies were considered to have addressed the issue of missing data appropriately, the standards for critical evaluation were difficult to determine as a result of huge variability between the RCTs in the way that the missing data were reported or the level of detail included. Not adjusting for missing data often limits the robustness of the results and reduces confidence in the HRQOL conclusions. The reporting of missing data by treatment arm and over time needs to be standardized to aid in the interpretation of the final HRQOL results. It should be acknowledged that journal space is often limited, and authors may not have been able to report missing data in full detail.

Reporting of a priori hypotheses of HRQOL and reporting on the rationale for instruments used has decreased by almost a half from the previous review. This trend is a huge concern, because defining an a priori hypothesis is an essential requirement of a good study design and helps to reduce multiple testing of HRQOL variables and chance findings. The infrequent reporting on rationale for the use of a particular HRQOL instrument is probably related to availability of well-validated standard HRQOL tools, which are becoming the instruments of choice (such as the EORTC or Functional Assessment of Cancer Therapy questionnaires). Ideally authors should still outline the reasons for using a specific instrument on the basis of their a priori hypothesis. However, we recognize that this is mainly relevant in cases in which the selected HRQOL tools are not considered standard or widely accepted.

Our study has several limitations. A weakness of our systematic review procedure was the need for subjective judgments on several of the evaluation criteria. For example, evaluating whether a study adequately reported missing data and HRQOL domains or whether a study had appropriately reported the cultural validity of the HRQOL instrument is difficult because of the differences in interpretations of the preset definitions of adequate versus limited reporting. Nevertheless, using two reviewers helped to standardize our assessments, and only rarely was there a significant disagreement between the reviewers. We did not approach the authors of the RCTs, who may have had additional information on the HRQOL data, as the objective of this study was to review the quality of reporting of HRQOL in the published RCTs, rather than the actual RCT itself. This literature review focused on RCTs published in English only, so five studies published in Chinese were excluded. Finally, RCTs evaluating surgical interventions were absent in this review. This was due to the fact that such trials were published in a language different from English, were not randomized, or had small patient samples (< 100).

In conclusion, results from the comparison of this review to the earlier one of Bottomley et al[13] provide evidence that overall the quality and frequency of HRQOL reporting in NSCLC RCTs has increased since 2002. The clinical effectiveness of systemic treatments in NSCLC is unfortunately still limited, and therefore it is crucial to consider the impact on patient HRQOL when making difficult treatment decisions. This is evident in our review, which shows that HRQOL has become a major secondary end point included in numerous NSCLC RCTs. We encourage continued improvement in the methodology and reporting of HRQOL studies, specifically the need for defining a priori hypothesis and detailed reporting of missing data and its potential impact on interpretation of HRQOL results. Although the inclusion and presentation of HRQOL results has improved over the past decade, it still requires further development. We reiterate our recommendation for the development of a CONSORT-style checklist to ensure that all necessary HRQOL data are reported in a standardized manner. We believe that HRQOL data are being used to alter clinical practice and that future reporting standards will improve the added value of HRQOL data in NSCLC RCTs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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