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REVIEW

Deficiencies in health-related quality-of-life assessment and reporting: a systematic review of oncology randomized phase III trials published between 2012 and 2016

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Quality of life (QoL) is a relevant end point and a topic of growing interest by both scientific community and regulatory authorities. Our aim was to review QoL prevalence as an end point in cancer phase III trials published in major journals and to evaluate QoL reporting deficiencies in terms of under-reporting and delay of publication. All issues published between 2012 and 2016 by 11 major journals were hand-searched for primary publications of phase III trials in adult patients with solid tumors. Information about end points was derived from paper and study protocol, when available. Secondary QoL publications were searched in PubMed. In total, 446 publications were eligible. In 210 (47.1%), QoL was not included among end points. QoL was not an end point in 40.1% of trials in the advanced/metastatic setting, 39.7% of profit trials and 53.6% of non-profit trials. Out of 231 primary publications of trials with QoL as secondary or exploratory end point, QoL results were available in 143 (61.9%). QoL results were absent in 37.6% of publications in the advanced/metastatic setting, in 37.1% of profit trials and 39.3% of non-profit trials. Proportion of trials not including QoL as end point or with missing QoL results was relevant in all tumor types and for all treatment types. Overall, 70 secondary QoL publications were found: for trials without QoL results in the primary publication, probability of secondary publication was 12.5%, 30.9% and 40.3% at 1, 2 and 3 years, respectively. Proportion of trials not reporting QoL results was similar in trials with positive results (36.5%) and with negative results (39.4%), but the probability of secondary publication was higher in positive trials. QoL is not included among end points in a relevant proportion of recently published phase III trials in solid tumors. In addition, QoL results are subject to significant under-reporting and delay in publication.

Key words: health-related quality of life, cancer, end points, patient-reported outcomes, randomized controlled trials

Introduction

From both a regulatory and a clinical point of view, the main goal of any anticancer treatment is to allow patients to live longer and/or to live better [1]. Although appropriate end points in randomized controlled trials (RCTs) depend on the clinical setting, experimental treatments should ideally demonstrate a tangible clinical benefit for patients [2]. In principle, a statistically significant and clinically meaningful improvement in overall survival (OS) and/or health-related quality of life (QoL) should be required to judge the efficacy of new anticancer treatments. Among survival end points, OS should be considered the most

robust demonstration of benefit in the field of medical oncology. However, in recent years, progression-free survival (PFS) has been often adopted as primary end point in many RCTs [2]. When the experimental treatment demonstrates a benefit in PFS, patient-reported outcomes (PROs) and QoL are particularly important to better define the real clinical impact of a treatment. Furthermore, even when the experimental treatment demonstrates a clinically relevant improvement in OS, PROs and QoL results are still of interest, allowing a more complete definition of benefits and harms associated with the treatment. Finally, when therapies compared within randomized trials show similar efficacy results, for instance within non-inferiority trials, PROs and QoL can be crucial to tip the balance [3].

Both the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO) formally include QoL results among the parameters considered for the evaluation of clinical value of anticancer treatments [4–7]. Namely, in the ASCO framework, a 'palliation bonus' (10 points) is awarded by the experimental treatment if a statistically significant improvement in cancer-related symptoms is shown, and a 'QoL bonus' (10 points) is awarded if a statistically significant improvement in QoL is demonstrated [5]. Similarly, in the ESMO scale, preliminary scores based on treatment efficacy can be upgraded when the experimental arm demonstrates improved QoL or delayed deterioration in QoL (or substantial reduction in severe toxicity) [7]. Notably, the maximum score can be achieved only if optimal survival outcomes are further enhanced by data indicating reduced toxicity or improved QoL.

Furthermore, adoption of PROs in clinical trials can be very helpful to avoid underestimation of subjective side effects [8]. In fact, even when data are prospectively collected within randomized trials, the agreement between patients and physicians can be low, with high risk of under-reporting of toxicities by physicians [9].

As the nature of QoL is by definition subjective, QoL assessment and interpretation are challenging and need the same rigorous methodology as does the evaluation of survival end points [2, 10]. However, the use of PROs and QoL as end points in clinical trials is widely variable [11, 12], and QoL reporting is still suboptimal [10, 13]. For instance, a review evaluating PROs reporting in phase III medical oncology RCTs, published between 2007 and 2011, showed that methods and results related to PROs were often poorly reported according to the 2013 PROs CONSORT recommendations, and the space devoted to PROs in the main text was frequently small [13]. More detailed description of QoL results was found, as expected, when PROs were reported in a separate PROs-specific secondary publication. However, even in those cases when a secondary publication exists, a delay between the publication of primary end point and QOL results is common for many trials. This delay interferes with a complete and timely evaluation of treatment value, which can be properly made only if scientific community could evaluate QoL results at the same time of the other end points of a trial [14].

Aim of this systematic review was to evaluate the adoption of QoL as an end point in cancer RCTs published in major journals in recent years. In addition, we investigated QoL reporting deficiencies (in terms of underreporting and delay of publication), considering both primary publications and subsequent QoL-focused secondary publications, when available.

Methods

Eleven major journals—where oncology RCTs are usually published—were selected for this analysis: namely, eight oncology journals (*Lancet Oncology, Journal of Clinical Oncology, JAMA Oncology, Journal of the National Cancer Institute, Annals of Oncology, European Journal of Cancer, British Journal of Cancer* and *Cancer*) and three general medical journals (*New England Journal of Medicine, Lancet* and *JAMA*). All issues of these journals published between 2012 and 2016 were hand-searched for primary publications of randomized phase III trials testing anticancer drugs in adult patients with solid tumors. Trials testing supportive care drugs were excluded from the analysis, unless their outcome was anticancer efficacy (e.g. zoledronic acid tested to improve disease-free survival as adjuvant treatment of breast cancer patients). Trials testing non-pharmacologic interventions were not included, as well as trials conducted in pediatric patients and in hematologic malignancies. Both trials conducted in early stages of disease (adjuvant/neoadjuvant) and trials conducted in advanced/metastatic setting were included, while trials testing prevention were excluded.

A dedicated case report form (CRF) was used to collect data for each selected paper, and an electronic database was generated with one record for each paper. For all the relevant data, each selected paper was reviewed by two young investigators. Inconsistencies between the two investigators were discussed and settled with one senior investigator.

For each study, information about publication (journal, year, first author, date of definitive and ahead-of-print publication, availability of supplementary material and/or study protocol) was collected. Impact factor (IF) corresponding to the year of publication was considered, according to the *Journal of Citation Reports*. Papers were divided into three categories according to IF: low (<15), intermediate (15–30) and high (>30). Information recorded about the clinical trial included: single institution versus multicenter trial, study conducted in a single country versus two or more countries, profit versus no-profit, open label versus blinded, superiority versus non-inferiority design, disease setting (adjuvant versus neoadjuvant versus advanced/metastatic), type of primary tumor, details of treatment in both experimental and control arms. Experimental treatments were classified into four main groups (not mutually exclusive): chemotherapy ± other drugs; targeted agents ± other drugs; hormonal treatment ± other drugs; immunotherapy ± other drugs. Trials were considered as profit when sponsored by the drug company and as no-profit when sponsored by an academic institution or a cooperative group, even if receiving drug supply and/or economic support from one or more drug companies. Studies were classified according to results into 'positive' (superiority trials when the experimental treatment was declared superior to control, or non-inferiority trials when the experimental treatment was declared non-inferior to control) or 'negative' (superiority trials when the experimental treatment was not superior to control, or non-inferiority trials when the experimental treatment did not respect the predefined threshold to declare non-inferiority).

Information about end points (primary/secondary/exploratory) was derived from the paper and from the study protocol when available as supplementary material, available at *Annals of Oncology* online. When QoL was not listed among end points in

Table 1. Characteristics of the 446 primary publications included in the analysis

	n	%
Year of primary manuscript		
2012	94	21.1
2013	96	21.5
2014	87	19.5
2015	95	21.3
2016	74	16.6
Primary manuscript journal		
Annals of Oncology	61	13.7
British Journal of Cancer	8	1.8
Cancer	7	1.6
European Journal of Cancer	22	4.9
JAMA	7	1.6
JAMA Oncology	1	0.2
Journal of Clinical Oncology	139	31.2
Journal of the National Cancer Institute	3	0.7
Lancet	30	6.7
Lancet Oncology	123	27.6
New England Journal of Medicine	45	10.1
Sources of funding		
Profit	209	46.9
Non-profit	237	53.1
Type of malignancy		
Breast	84	18.8
Lung	83	18.6
Colorectal	52	11.7
Prostate	34	7.6
Gynecological	29	6.5
Esophago-gastric	29	6.5
Melanoma	20	4.5
Pancreas	16	3.6
Head and neck	14	3.1
Brain	14	3.1
Kidney	12	2.7
Liver	12	2.7
Urothelial	9	2.0
Other	38	8.5
Study design		
Superiority	410	91.9
Non-inferiority	36	8.1
Masking		
Open label	308	69.1
Blinded	138	30.9
Countries involved		
Single country	152	34.1
Two or more countries	294	65.9
Type of experimental therapy[a]		
Chemotherapy ± other	273	61.2
Targeted therapy ± other	210	47.1
Hormonal therapy ± other	43	9.6
Immunotherapy ± other	33	7.4
Other	8	1.8
Disease stage		
Localized	124	27.8
Advanced/metastatic	322	72.2

[a]Categories are not mutually exclusive.

the paper and study protocol was not available, QoL was considered as absent, except when QoL results were actually presented in the Results section: in the latter case, QoL was included *de facto* among exploratory end points.

Space allocated to QoL details was measured as number and percentage of rows in the 'Methods' and in the 'Results' sections [13]. In addition, the presence of QoL details in tables and/or figures, in the main text and/or in the supplementary appendix was recorded. For all records, secondary QoL publications were searched in PubMed, by using the name of the drug(s) and/or tumor type and/or the name of authors of the primary publication and/or the study acronym/code, when available. Time to secondary QoL publication was calculated according to Kaplan–Meier method, from the date of primary definitive publication to the date of secondary QoL definitive publication, if any, or to the date of last PubMed check. When the secondary QoL publication was synchronous, and in the few cases when it preceded primary publication, time to secondary QoL publication was made equal to 0.

Details of QoL analysis (type and timing of QoL questionnaires, QoL compliance, type of statistical analysis) were also collected and will be object of a separate publication.

Results

Study characteristics

Overall, 446 eligible publications were identified in the 11 journals (the complete list is reported in the supplementary Appendix, available at *Annals of Oncology* online). The main characteristics of the eligible publications are reported in Table 1. The three most represented journals were *Journal of Clinical Oncology* (139 papers, 31.2%), *Lancet Oncology* (123 papers, 27.6%) and *Annals of Oncology* (61 papers, 13.7%). Median IF of the eligible publications was 20.982 (interquartile range 17.960—26.509, range 4.817—72.406). The majority of trials (322, 72.2%) were conducted in patients with advanced/metastatic disease. The three most represented settings were breast cancer (84, 18.8%), lung cancer (83, 18.6%) and colorectal cancer (52, 11.7%). Chemotherapy ± other drugs (273, 61.2%) and targeted therapy ± other drugs (210, 47.1%) were the most common experimental treatments. Nearly half of the trials (209, 46.9%) were sponsored by the drug company, while the remaining (237, 53.1%) were promoted by academic institution or cooperative group.

Inclusion of QoL among study end points

The inclusion of QoL among end points according to study characteristics is detailed in Table 2. In the whole series, QoL was a primary end point in five trials (1.1%), a secondary end point in 195 trials (43.7%), an exploratory end point in 36 trials (8.1%), while in the remaining 210 (47.1%) QoL was not listed at all among study end points. The proportion of trials without QoL as an end point was 60.4%, 49.0% and 27.7% among papers published in journals with low, intermediate and high IF, respectively. QoL was not included among end points in a relevant proportion both in profit trials (39.7%) and even more in non-profit trials (53.6%). The proportion of trials not including QoL as an end point was relevant in all the

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

	Number of publications *n*	QoL primary end point *n* (%)	QoL secondary end point *n* (%)	QoL exploratory end point[a] *n* (%)	QoL not included among end points *n* (%)
Whole series	446	5 (1.1)	195 (43.7)	36 (8.1)	210 (47.1)
Year of primary manuscript					
2012	94	1 (1.1)	44 (46.8)	4 (4.3)	45 (47.9)
2013	96	1 (1.0)	34 (35.4)	8 (8.3)	53 (55.2)
2014	87	1 (1.1)	41 (47.1)	9 (10.3)	36 (41.4)
2015	95	-	37 (38.9)	7 (7.4)	51 (53.7)
2016	74	2 (2.7)	39 (52.7)	8 (10.8)	25 (33.8)
Journal impact factor					
Low (<15)	101	-	35 (34.7)	5 (5.0)	61 (60.4)
Intermediate (15–30)	251	3 (1.2)	110 (43.8)	15 (6.0)	123 (49.0)
High (>30)	94	2 (2.1)	50 (53.2)	16 (17.0)	26 (27.7)
Sources of funding					
Profit	209	2 (1.0)	99 (47.4)	25 (12.0)	83 (39.7)
Non-profit	237	3 (1.3)	96 (40.5)	11 (4.6)	127 (53.6)
Type of malignancy					
Breast	84	-	32 (38.1)	4 (4.8)	48 (57.1)
Lung	83	-	47 (56.6)	6 (7.2)	30 (36.1)
Gastrointestinal	112	2 (1.8)	43 (38.4)	8 (7.1)	59 (52.7)
Genitourinary	57	2 (3.5)	24 (42.1)	9 (15.8)	22 (38.6)
Other	110	1 (0.9)	49 (44.5)	9 (8.2)	51 (46.4)
Study design					
Superiority	410	4 (1.0)	179 (43.7)	33 (8.0)	194 (47.3)
Non-inferiority	36	1 (2.8)	16 (44.4)	3 (8.3)	16 (44.4)
Masking					
Open label	308	4 (1.3)	127 (41.2)	20 (6.5)	157 (51.0)
Blinded	138	1 (0.7)	68 (49.3)	16 (11.6)	53 (38.4)
Type of experimental therapy[b]					
Chemotherapy ± other	273	2 (0.7)	122 (44.7)	13 (4.8)	136 (49.8)
Targeted therapy ± other	210	1 (0.5)	98 (46.7)	20 (9.5)	91 (43.3)
Hormonal therapy ± other	43	1 (2.3)	19 (44.2)	3 (7.0)	20 (46.5)
Immunotherapy ± other	33	1 (3.0)	14 (42.4)	7 (21.2)	11 (33.3)
Disease stage					
Localized	124	1 (0.8)	37 (29.8)	5 (4.0)	81 (65.3)
Advanced/metastatic	322	4 (1.2)	158 (49.1)	31 (9.6)	129 (40.1)

[a]One study with quality of life (QoL) as tertiary end point and three studies where QoL was not explicitly listed among end points.
[b]Categories are not mutually exclusive.

types of tumors, ranging from 36.1% for lung cancer to 57.1% for breast cancer, and for all types of treatment, ranging from 33.3% with immunotherapy to 49.8% with chemotherapy. In the subgroup of trials conducted in patients with advanced/metastatic disease, QoL was a primary end point in 4 trials (1.2%), a secondary end point in 158 trials (49.1%) and an exploratory end point in 31 trials (9.6%), while in the remaining 129 (40.1%) QoL was not listed at all among study end points. The proportion of trials not including QoL as an end point was higher in the adjuvant/neoadjuvant setting (65.3%).

Presence of QoL results in the primary publication

The presence of QoL results according to study characteristics is detailed in Table 3. Out of 231 primary publications of trials with QoL as a secondary or exploratory end point, QoL results were available in 143 publications (61.9%), while QoL results were absent in the remaining 88 (38.1%). In the 143 publications with available QoL results, the median space dedicated to QoL details in the 'Results' section was 12 rows (interquartile range 6–18, range 0–84), corresponding to the 9.2% of the section (interquartile range 5.4%–14.2%, range 0%–44.6%). In 79 cases (55.2%), QoL results included figures and/or tables in the main paper and/or in the supplementary appendix.

The proportion of publications without QoL results was 30.0%, 39.2% and 40.9% among papers published in journals with low, intermediate and high IF, respectively. QoL results were not reported in a relevant proportion both in publications of profit trials (37.1%) and non-profit trials (39.3%). The proportion of publications not reporting QoL results was relevant in all

Table 3. Details about health-related quality of life (QoL) in the publications of trials with QoL as secondary/exploratory end point

	Number of publications *n*	QoL results available in primary publication *n* (%)	QoL results absent in primary publication *n* (%)
Whole series	231	143 (61.9)	88 (38.1)
Year of primary manuscript			
2012	48	32 (66.7)	16 (33.3)
2013	42	25 (59.5)	17 (40.5)
2014	50	32 (64.0)	18 (36.0)
2015	44	27 (61.4)	17 (38.6)
2016	47	27 (57.4)	20 (42.6)
Journal impact factor			
Low (<15)	40	28 (70.0)	12 (30.0)
Intermediate (15–30)	125	76 (60.8)	49 (39.2)
High (>30)	66	39 (59.1)	27 (40.9)
Sources of funding			
Profit	124	78 (62.9)	46 (37.1)
Non-profit	107	65 (60.7)	42 (39.3)
Type of malignancy			
Breast	36	16 (44.4)	20 (55.6)
Lung	53	38 (71.7)	15 (28.3)
Gastrointestinal	51	33 (64.7)	18 (35.3)
Genitourinary	33	21 (63.6)	12 (36.4)
Other	58	35 (60.3)	23 (39.7)
Study design			
Superiority	212	131 (61.8)	81 (38.2)
Non-inferiority	19	12 (63.2)	7 (36.8)
Masking			
Open label	147	88 (59.9)	59 (40.1)
Blinded	84	55 (65.5)	29 (34.5)
Type of experimental therapy[a]			
Chemotherapy ± other	135	78 (57.8)	57 (42.2)
Targeted therapy ± other	118	77 (65.3)	41 (34.7)
Hormonal therapy ± other	22	15 (68.2)	7 (31.8)
Immunotherapy ± other	21	9 (42.9)	12 (57.1)
Disease stage			
Localized	42	25 (59.5)	17 (40.5)
Advanced/metastatic	189	118 (62.4)	71 (37.6)

[a]Categories are not mutually exclusive.

types of tumors, ranging from 28.3% for lung cancer to 55.6% for breast cancer, and for all types of treatment, ranging from 31.8% with hormonal treatment to 57.1% with chemotherapy. In the subgroup of trials conducted in patients with advanced/metastatic disease and including QoL among end points, QoL results were not reported in 37.6% of publications versus 40.5% of trials conducted in adjuvant/neoadjuvant setting.

QoL secondary publications

Overall, with a median follow-up of 43 months, 70 secondary QoL publications were found (the complete list of secondary publications is available in the supplementary Appendix, available at *Annals of Oncology* online). Median IF of the secondary QoL publications was 6.029 (interquartile range 4.646–17.96, range 0–47.831), compared with 26.509 (interquartile range 18.443–47.831, range 5.417–72.406) of the respective primary publication. For the 88 trials including QoL as an end point, but without any QoL result in the primary publication, probability of secondary publication was 12.5%, 30.9% and 40.3% after 12, 24 and 36 months, respectively (Figure 1). Similarly, considering the subgroup of 71 trials conducted in advanced/metastatic patients, probability of secondary publication was 11.3%, 29.1% and 40.6% after 12, 24 and 36 months, respectively.

QoL reporting according to study results

According to authors' conclusions, studies were divided into positive (173, 38.8%) and negative (273, 61.2%). Among 173 trials with positive results, 65 (37.6%) did not include QoL as an end point. The proportion of publications including QoL as an end point without reporting QoL results was quite similar in

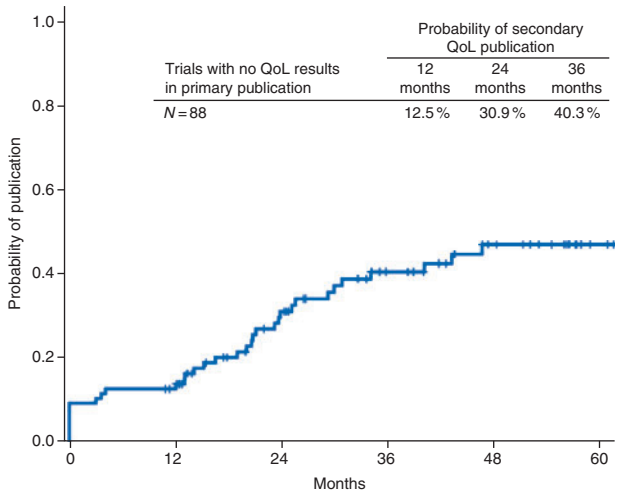

Figure 1. Kaplan–Meier curve of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary/exploratory end point, but without any QoL result in the primary publication.

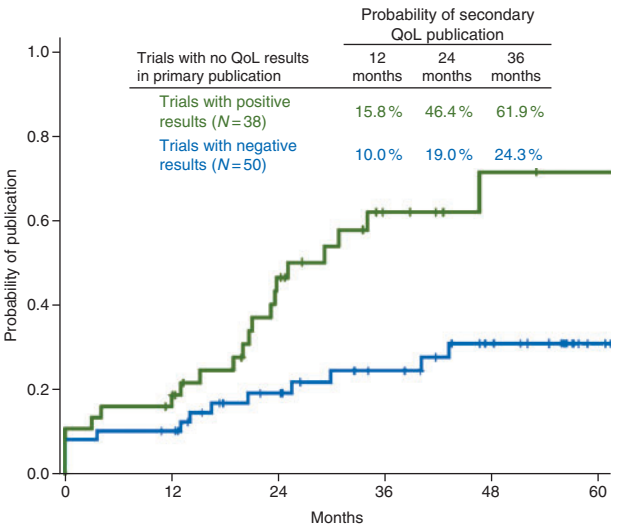

Figure 2. Kaplan–Meier curves of time to secondary publication with quality of life (QoL) results, for trials including QoL as a secondary/exploratory end point, but without any QoL result in the primary publication. Studies with negative results (blue line) and studies with positive results (green line).

trials with positive results (38/104, 36.5%) and in trials with negative results (50/127, 39.4%). For trials including QoL as an end point, but without any QoL result in the primary publication, probability of secondary publication was 15.8%, 46.4% and 61.9% after 12, 24 and 36 months, respectively, in the 38 trials with positive results, and 10.0%, 19.0% and 24.3% after 12, 24 and 36 months, respectively, in the 50 trials with negative results (Figure 2).

Discussion

In this systematic review, we showed that QoL is not included as an end point in a relevant proportion of recently published phase III trials in oncology, even those conducted in patients with advanced/metastatic disease. In addition, QoL results are subject to significant under-reporting and delay in publication.

QoL is recognized as a relevant end point and matter of growing interest by both scientific community and regulatory authorities. More than 20 years ago, when defining the outcomes to be used for technology assessment and development of cancer treatment guidelines, ASCO listed QoL among relevant outcomes, especially in the metastatic setting [15]. Even though the inclusion of QoL as an end point is not considered mandatory by regulatory authorities, in its recent guidance on the use of PROs in oncology studies, European Medicines Agency underlined that 'the experience of patients of how a treatment impacts on their well-being and everyday life is an important aspect of the evaluation of the clinical benefits of new medicines' [16]. Nevertheless, our review did not show an improvement of QoL assessment and reporting over time. At least in the interval of time considered in our analysis (2012–2016), we found a suboptimal proportion of trials including QoL as an end point in all the years considered. Actually, a slight improvement in QoL inclusion as an end point was shown for trials published in 2016: QoL was not included among end points in 33.8% of the trials published in 2016, versus a range from 41.4% to 55.2% in the previous years. However, this signal of improvement did not correspond at all to an advancement in the presence of QoL results in the primary publication. We acknowledge that the limited period of time included in the analysis (5 years) makes it unlikely to observe a relevant trend of changing. Furthermore, the year of publication is not a perfect surrogate of the year of study design (when decisions about study end points are actually made). The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement has been extended to include PRO-specific guidelines, with the aim of improving the PRO content of clinical trial protocols, only in 2018 [11]. However, besides the improvement in study protocols, a growing attention to QoL should induce a more frequent inclusion of QoL results when the study is published.

Moreover, we found that, even when QoL results were available in the primary publications, the space allocated to QoL details was rather small, with a median space of 12 rows, corresponding to 9.2% of the section of results. This result is similar to that shown by a previous review evaluating PROs reporting, which found that, in phase III medical oncology RCTs published between 2007 and 2011, the median percentage of the space allocated to the PROs in the results section was only the 10% [13]. Therefore, with all the limitations of this 'rough' measure, there was no substantial improvement in QoL reporting over time.

We found that trials published in journals with high (>30) IF evaluated QoL as an end point more often than studies presented in journals with lower IF. Presumably, well-designed and high-quality clinical trials (that are published in journals with higher IF) more frequently include QoL among outcome measures, in accordance with the best scientific recommendations. However, the studies published in journals with higher IF did not perform better in terms of presentation of QoL results: rather, QoL results were absent in 40.9% of the primary publications in high IF journals versus 39.2% and 30% in intermediate and low IF journals. Probably, a word-count limitation imposed by most scientific journals could discourage a single publication including QoL

results together with the other end points of the trial [3]. Of course, this is not the only potential reason for QoL under-reporting: for instance, authors could be discouraged to publish QoL results because of poor compliance and high amount of missing data, difficulties in statistical analyses or in case of negative results, leading to the risk of a reporting bias. In many cases, QoL results are object of a secondary publication, but we showed that this is regularly associated with a relevant delay in publication, and QoL results are usually published in journals with substantially lower IF.

The proportion of trials not evaluating QoL as a study end point was relevant both in the subgroup of trials conducted in the adjuvant/neoadjuvant setting and in the subgroup of trials enrolling patients with advanced/metastatic disease. In the former setting, it is reasonably anticipated that treatment can produce a significant negative impact—hopefully temporary—on QoL, and in most clinical situations this could be considered a 'justified' risk to be taken from both patients' and clinicians' point of view, in exchange for the auspicated improvement in the chance of a definitive cure. This could justify, at least in part, the lower attention to QoL evaluation in this setting and the fact that almost two-thirds of the trials analyzed did not include QoL among the end points. On the other hand, we believe that, in most patients with advanced or metastatic disease, QoL should be a relevant end point, considering the delicate balance between symptoms, disease control and side effects associated with treatment. In the latter setting, the efficacy of treatments in terms of OS and PFS is often modest, and QoL should be carefully considered for a proper evaluation of the benefit/risk ratio. From this point of view, we judge disappointing that almost 40% of trials published in recent years, conducted in patients with advanced or metastatic tumors, did not include QoL among the study end points. Furthermore, even in trials in which QoL was an end point, the delay in publication of QoL results is a common phenomenon, which may limit a comprehensive evaluation of treatment value. Of course, when the results, in terms of efficacy and toxicity, are both markedly in favor of the experimental treatment, this could make the results of QoL comparison less interesting. Nevertheless, in many cases, the difference in efficacy is not outstanding and the toxicity is not negligible, making useful the presentation of QoL results for the global interpretation of the trial.

Disappointingly, the absence of QoL among the study end points and the under-reporting of QoL results are both a common issue across all types of tumors and all types of treatment. In our analysis, QoL appears to be particularly neglected in breast cancer trials (57.1% of them did not include QoL among end points). This could be reasonably explained, at least in part, by the high proportion of breast cancer trials conducted in the adjuvant or neoadjuvant setting (46 out of 84 trials, compared, for instance, with only 6 out of 83 lung cancer trials). However, even when limiting the analysis to trials that did actually include QoL among end points, breast cancer is also characterized by suboptimal QoL reporting, with complete absence of QoL results in 55.6% of primary publications. When looking at the category of experimental drug, trials with new therapeutic approaches (like targeted agents and immunotherapy) did not perform better than 'traditional' chemotherapy trials: the proportion of trials without QoL as an end point was only slightly better with these drugs (43.3% with targeted agents and 33.3% with immunotherapy) compared with chemotherapy (49.8%), but the absence of QoL results in the primary publication remains a common issue (34.7% with targeted agents and even 57.1 with immunotherapy).

The absence of QoL among end points is common both in trials promoted by drug companies and in trials promoted by academic researchers and cooperative groups, being even higher among the latter (53.6% compared with 39.7% in profit trials). Furthermore, under-reporting of QoL results in the primary publication is a common issue in both categories. At least in principle, one could argue that interest in PROs and QoL should be potentially higher in academic research, often conducted with the aim of optimizing treatment choices in clinical practice, but our results demonstrate that there is still great room for improvement.

Interestingly, we found that 37.6% of trials with positive conclusions did not include QoL among the study end points. This implies that QoL information is not available for many treatments that, based on a positive result, are subsequently considered for clinical practice guidelines and/or regulatory approval and/or introduction in clinical practice. In accordance to this finding, a recent study showed that none of the pivotal studies supporting oncology drug approvals from 2009 to 2013 by EMA included QoL as a primary end point, and only 54% of the indications (37/68) were supported by a pivotal trial in which QoL was a secondary end point [17]. As for the frequent absence of QoL results in primary publications, one could argue that, in the case of trials with globally negative results, the specific interest in QoL results could be 'physiologically' lower, given that many of these treatments will never be adopted in clinical practice, due to the lack of superiority in the primary end point. However, when considering trials that included QoL evaluation among end points, the probability of absence of QoL results in the primary publication in positive trials is practically as much high as in negative trials (36.5% and 39.4%, respectively). Even if the probability of a subsequent secondary publication with QoL results appears to be much higher in case of positive studies than in case of negative studies, the under-reporting in primary publication and the delay in the publication of QoL results remain a crucial issue for a complete evaluation of treatment value, that is particularly relevant for trials with positive results [3, 14].

In conclusion, our analysis demonstrated that the adoption of QoL as an end point in oncology clinical trials and the attention in timely and complete reporting of QoL results is still suboptimal. A serious reflection should be made by the scientific community, including clinical researchers and methodologists, regulatory agencies and scientific journals, in order to allow both the optimal choice of study end points and the completeness of reporting of clinical trials in scientific publications. Clinical trial protocols and publications should include all the outcomes that are relevant for an exhaustive evaluation of the value of new treatments.

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References

1. Booth CM, Tannock I. Reflections on medical oncology: 25 years of clinical trials—where have we come and where are we going? J Clin Oncol 2008; 26(1): 6–8.
2. Wilson MK, Karakasis K, Oza AM. Outcomes and endpoints in trials of cancer treatment: the past, present, and future. Lancet Oncol 2015; 16(1): e32–e42.
3. Di Maio M, Perrone F. Lessons from clinical trials on quality-of-life assessment in ovarian cancer trials. Ann Oncol 2016; 27(6): 961–962.
4. Schnipper LE, Davidson NE, Wollins DS et al. American Society of Clinical Oncology statement: a conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015; 33(23): 2563–2577.
5. Schnipper LE, Davidson NE, Wollins DS et al. Updating the American Society of Clinical Oncology value framework: revisions and reflections in response to comments received. J Clin Oncol 2016; 34(24): 2925–2934.
6. Cherny NI, Sullivan R, Dafni U et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015; 26(8): 1547–1573.
7. Cherny NI, Dafni U, Bogaerts J et al. ESMO-Magnitude of Clinical Benefit Scale version 1.1. Ann Oncol 2017; 28(10): 2340–2366.
8. Di Maio M, Basch E, Bryce J, Perrone F. Patient-reported outcomes in the evaluation of toxicity of anticancer treatments. Nat Rev Clin Oncol 2016; 13(5): 319–325.
9. Di Maio M, Gallo C, Leighl NB et al. Symptomatic toxicities experienced during anticancer treatment: agreement between patient and physician reporting in three randomized trials. J Clin Oncol 2015; 33(8): 910–915.
10. Joly F, Vardy J, Pintilie M, Tannock IF. Quality of life and/or symptom control in randomized clinical trials for patients with advanced cancer. Ann Oncol 2007; 18(12): 1935–1942.
11. Calvert M, Kyte D, Mercieca-Bebber R et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. JAMA 2018; 319(5): 483–494.
12. Mehran R, Baber U, Dangas G. Guidelines for patient-reported outcomes in clinical trial protocols. JAMA 2018; 319(5): 450–451.
13. Bylicki O, Gan HK, Joly F et al. Poor patient-reported outcomes reporting according to CONSORT guidelines in randomized clinical trials evaluating systemic cancer therapy. Ann Oncol 2015; 26(1): 231–237.
14. Di Maio M. Quality of life: an important element of treatment value. Lancet Oncol 2017; 18(12): 1557–1558.
15. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines. American Society of Clinical Oncology. J Clin Oncol 1996; 14: 671–679.
16. European Medicines Agency. EMA/CHMP/292464/2014 Committee for Medicinal Products for Human Use (CHMP). Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man. The use of patient-reported outcome (PRO) measures in oncology studies. 1 April 2016; http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/04/WC500205159.pdf (23 October 2018, date last accessed).
17. Davis C, Naci H, Gurpinar E et al. Availability of evidence of benefits on overall survival and quality of life of cancer drugs approved by European Medicines Agency: retrospective cohort study of drug approvals 2009-13. BMJ 2017; 359: j4530.