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Evaluating Progression-Free Survival as a Surrogate Outcome for Health-Related Quality of Life in Oncology
A Systematic Review and Quantitative Analysis

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IMPORTANCE Progression-free survival (PFS) has become a commonly used outcome to assess the efficacy of new cancer drugs. However, it is not clear if delay in progression leads to improved quality of life with or without overall survival benefit.

OBJECTIVE To evaluate the association between PFS and health-related quality of life (HRQoL) in oncology through a systematic review and quantitative analysis of published randomized clinical trials. Eligible trials addressed oral, intravenous, intraperitoneal, or intrapleural chemotherapy or biological treatments, and reported PFS or health-related quality of life.

DATA SOURCES For this systematic review and quantitative analysis of randomized clinical trials of patients with cancer, we searched Medline, Embase, and the Cochrane Central Register of Controlled Trials from January 1, 2000, through May 4, 2016.

STUDY SELECTION Paired reviewers independently screened citations, extracted data, and assessed risk of bias of included studies.

DATA EXTRACTION AND SYNTHESIS We examined the association of difference in median PFS duration (in months) between treatment groups with difference in global, physical, and emotional HRQoL scores between groups (standardized to a range of 0-100, with higher scores representing better HRQoL) using weighted simple regressions.

MAIN OUTCOME AND MEASURE The association between PFS duration and HRQoL.

RESULTS Of 35 960 records screened, 52 articles reporting on 38 randomized clinical trials involving 13 979 patients across 12 cancer types using 6 different HRQoL instruments were included. The mean (SD) difference in median PFS between the intervention and the control arms was 1.91 (3.35) months. The mean (SD) differences in change of HRQoL adjusted to per-month values were −0.39 (3.59) for the global domain, 0.26 (5.56) for the physical domain, and 1.08 (3.49) for the emotional domain. The slope of the association between the difference in median PFS and the difference in change for global HRQoL (n = 30 trials) was 0.12 (95% CI, −0.27 to 0.52); for physical HRQoL (n = 20 trials) it was −0.20 (95% CI, −0.62 to 0.23); and for emotional HRQoL (n = 13 trials) it was 0.78 (95% CI, −0.05 to 1.60).

CONCLUSIONS AND RELEVANCE We failed to find a significant association between PFS and HRQoL in cancer clinical trials. These findings raise questions regarding the assumption that interventions prolonging PFS also improve HRQoL in patients with cancer. Therefore, to ensure that patients are truly obtaining important benefit from cancer therapies, clinical trial investigators should measure HRQoL directly and accurately, ensuring adequate duration and follow-up.

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The goal of patient-centered cancer care is to extend survival or improve health-related quality of life (HRQoL).[1-3] Patients, clinicians, and investigators value overall survival (OS), an objective end point representing survival duration, as the most important cancer trial outcome.[3,4] However, HRQoL, which reflects patients' subjective feelings about their health,[1,3] is also important, and represents a research priority for the American Society of Clinical Oncology.[1] Although important benefit should ultimately be established by improved OS and HRQoL, regulatory authorities have also approved cancer treatments on the basis of surrogates such as progression-free survival (PFS)[3] or time to progression (TTP).[5]

Originally developed as a measurement tool to identify signals of activity in early drug development,[2] PFS has become a widely used surrogate outcome in cancer. The appeal of PFS use in randomized clinical trials (RCTs)[2] reflects limitations associated with OS,[2,3,5] including higher cost, longer follow-up, larger sample sizes, and confounding effects arising from crossover designs and subsequent postprogression therapies. The increasing use of PFS is also reflected in drug regulatory approvals,[2] with at least a dozen drugs approved by the US Food and Drug Administration (FDA) between 2005 and 2010 using PFS as primary end point.[6]

There are only 2 reasons to use PFS as a valid end point in oncology. The first reason is the belief that PFS is a valid surrogate marker for OS. The second reason is the assumption that patients who live longer without disease progression will have better HRQoL, even without longer survival. However, valid surrogate end points should reliably and precisely predict treatment effect on the corresponding patient-important outcome, either survival or how a patient feels or functions.[6] This definition is currently implemented by regulatory agencies that grant oncology drugs either accelerated or traditional marketing approvals (eg, the FDA).[7] Currently, evidence suggests that PFS serves as a valid surrogate for OS only in limited scenarios, being both variable and unpredictable.[2,6,8] Additionally, because HRQoL is likely to be impaired by adverse events (AEs) resulting from the treatments responsible for prolonged PFS, its association with improved HRQoL is far from self-evident.[5] These uncertainties have led oncological experts to raise concerns regarding the appropriateness of using PFS as a primary outcome for evaluating new treatments,[1,2,5] suggesting that the convenience of shorter and smaller trials made possible by measuring PFS is driving its use, rather than compelling evidence of its adequate surrogacy for either OS or HRQoL.[2]

Because few studies measure the value or benefits of PFS for patients, and few trials collect and report HRQoL data,[5,9] resolving the question of PFS as a satisfactory surrogate for HRQoL is challenging. To our knowledge, there exists only 1 systematic analysis of the PFS-HRQoL association, and that study yielded inconclusive results.[6]

Given the increased use of PFS as the primary outcome in new oncology drug trials, and uncertain surrogacy of PFS for either OS or HRQoL, it remains possible that patients are receiving toxic and/or expensive treatments without experiencing important benefit, and an examination of evidence regarding whether delay in progression leads to better HRQoL is critical. We have therefore examined the PFS-HRQoL association through a systematic review and quantitative analysis of published studies of oral, intravenous, intraperitoneal, or intrapleural chemotherapy or biological therapy designed to improve disease-related outcomes among patients with cancer in RCT settings.

Key Points

Question How strongly is progression-free survival (PFS) associated with health-related quality of life (HRQoL) in studies of cancer treatments?

Findings This systematic review and quantitative analysis of 52 articles reporting on 38 randomized clinical cancer trials did not find a significant association between PFS and HRQoL.

Meaning These findings raise questions about the assumption that interventions prolonging PFS also improve HRQoL in patients with cancer and suggest that HRQoL should be measured directly and accurately, with adequate follow-up time, in future studies.

Methods

Our study protocol detailing design and analysis was previously published[10] and registered on the International Prospective Register of Ongoing Systematic Reviews (CRD42016047162).[11,12] We conducted a review of human cancer RCTs published from January 1, 2000, to May 4, 2016, using standard methodology described by the Cochrane Collaboration.[13] Our systematic review adheres to PRISMA Statement[14,15] guidelines ensuring transparent and complete reporting. We included trials reporting on PFS outcome estimates and HRQoL measures with chemotherapy and/or biological type cancer therapies as the primary investigational anticancer treatment. Randomized clinical trials with OS benefit were excluded from the original protocol but were included in the final analysis. We used the global HRQoL domain score in the final base-case analysis as opposed to the physical domain score in the original protocol. Changes to the original protocol were made as a response to comments received during the peer-review process.

Literature Search

We used comprehensive search strategies developed with help from an experienced research librarian (eAppendix in the Supplement).[10] We used the OVID platform to search in MEDLINE, Embase, and the Wiley Cochrane databases, and used MeSH terms and free text to capture RCTs published in *Abridged Index Medicus*.[16] Our search strategies were built by combining terms from disease key areas (cancer categories), HRQoL, cancer therapies, and an RCT filter. To increase comprehensiveness, we included a list of drugs approved by the FDA based on PFS benefit,[6] and set no language limitations. We used a previous report[6] to preidentify key articles eligible for review, and performed search strategy validation check through verification of inclusion of key articles in search results. All references were managed using EndNoteX version 7.0.2 (Thomson Reuters).

Study Screening and Data Abstraction

Ten pairs of reviewers working independently conducted eligibility screening and data abstraction. The international team allowed for article screening and abstraction in multiple languages, reducing language limitations. Reviewers resolved disagreement by either discussion or adjudication by an arbitrator (B.K.).

Screening was performed using pilot-tested electronic forms in DistillerSR (Evidence Partners), constructed per eligibility criteria.[10] Reviewers received training and detailed written instructions to perform title and abstract and full-text screening, including meetings with calibration and sample data review exercises. We measured reviewer agreement on full-text screening using Kappa (κ), per guidelines proposed by Landis and Koch,[17] by using the VassarStats Kappa online calculator.[18]

Oncology trials often report PFS results first and subsequently separately publish HRQoL results. Therefore, we classified trial publications into 3 categories of outcome reporting: (1) only PFS outcome data (ie, typical oncology trial publication), (2) only HRQoL data, or (3) publications reporting PFS and HRQoL. Because all categories of publications are potentially relevant, we performed trial-level publication matching and searching prior to data abstraction for publications reporting only PFS or HRQoL. We first cross-referenced categorized publication types against each other (ie, trial-level matching) for eligible full-text articles to identify and capture trials reporting required data across multiple publications. Furthermore, we performed additional supplemental searches through OVID for additional unmatched publications using author, intervention, and cancer type keywords in the MEDLINE and Embase databases.

For data abstraction, reviewers underwent similar training and calibration as for screening, and undertook abstraction using pilot-tested electronic forms in Microsoft Excel software. Data abstraction included PFS and HRQoL information for median PFS time and/or PFS hazard ratios (HRs) for intervention and control groups, HRQoL scores and corresponding error estimates for global domain, time of each successive HRQoL measurement in each group, and sample size at each HRQoL measurement point. We also abstracted physical and emotional HRQoL domain scores to conduct sensitivity analyses. Additional data originally intended for further sensitivity and subgroup analyses (ie, risk of bias, cancer types and stages, industry funding) within each HRQoL domain were abstracted[10]; however, an insufficient number of trials within each HRQoL domain precluded these analyses.

Data Analyses

All included trials reported median progression times for intervention and control groups, and we calculated incremental PFS for each study by taking difference in median PFS duration between arms. Although PFS includes death, while TTP does not, approximately 25% of trials (10 of 38) used TTP, so we assumed TTP to be equal to PFS, since most trials reported PFS.

Although per-trial instrument selection had no effect on calculation of HRQoL scores owing to score standardization, we established a hierarchy of measures, using the highest in the hierarchy for our analyses as follows: FACT-G,[19] then the EORTC-QLQ-C30,[20,21] and finally any other instrument available. All HRQoL scores across instruments were standardized to the scale from 0 to 100, with higher scores representing better HRQoL. In each arm, HRQoL for the duration of provided measures was calculated by using an area under the curve (AUC) approach, adjusting for different durations in measuring and/or reporting HRQoL between arms. Then incremental HRQoL was calculated as the difference in the AUC between 2 arms, adjusted to per-month values. This served to reduce overall heterogeneity of the y-axis by reducing variability due to differences in HRQoL time durations across trials, and it allowed for facilitated visual comparison of relative HRQoL benefits across trials in constructed PFS-HRQoL scatterplots (eAppendix in the Supplement).

Global HRQoL domain scores were used for the base case analysis, since global scores were reported most often. The physical and emotional HRQoL domain scores from each trial were used in sensitivity analyses to maximize comparability across cancer types by using these commonly measured specific domains of perceived importance.

We constructed a scatterplot of incremental HRQoL (y-axis) vs incremental PFS (x-axis), with each study point representing an individual trial. To estimate the PFS-HRQoL association, we used weighted simple regression to calculate the slope (regression coefficient) between PFS and HRQoL domains. To account for different sample sizes across studies, each study point in the regression was weighted by the inverse of total variance.

All analyses were conducted using Microsoft Excel and SPSS software (version 22). The eAppendix in the Supplement of the present report and the eAppendix in the Supplement of our protocol provide a detailed description of the methods for our analyses.[10]

Results

We initially identified 35 960 citations in the MEDLINE, Embase, and Cochrane databases, with a total of 30 294 articles after duplicate removal. We removed 27 943 articles after title and abstract screening, leaving 2351 full-text articles assessed for eligibility, with 2307 being excluded. In addition to the 44 articles finally identified in the primary search, we included 8 more articles identified through a supplemental search on the trials that reported OS benefits. Finally, our review included a total of 38 trials reported in 52 articles.[22-73] **Figure 1** presents the article selection process.[74] We calculated that κ = 0.75 (95% CI, 0.73-0.78) indicated substantial agreement[17] between reviewers in assessments of study inclusion during full-text screening.

Of the 52 articles representing 38 trials, 24 reported both PFS and HRQoL data in a single article. Trial-level matching and searching identified another 28 articles representing 14 eligible RCTs. In relation to the low number of finally eligible articles, it is worth noting that although cancer trials might measure HRQoL, many of these trials fail to publish or report their HRQoL data to allow for the quantitative analyses, resulting in these being excluded from our analysis according to our eligibility criteria.

The 30 294 potentially eligible articles included 1607 non-English language publications (in Chinese, French, German,

Japanese, Korean, Polish, and Spanish). Three Chinese articles,[35,60,66] the largest non-English language group, were finally included in our quantitative synthesis.

Table 1 details the trial characteristics organized alphabetically by cancer type, with Trial ID format corresponding to the specific cancer type (abbreviated by a single or double letter) and trial number for each type. A plus sign set at the end of the Trial ID indicates that the trial found statistically significant OS benefits.

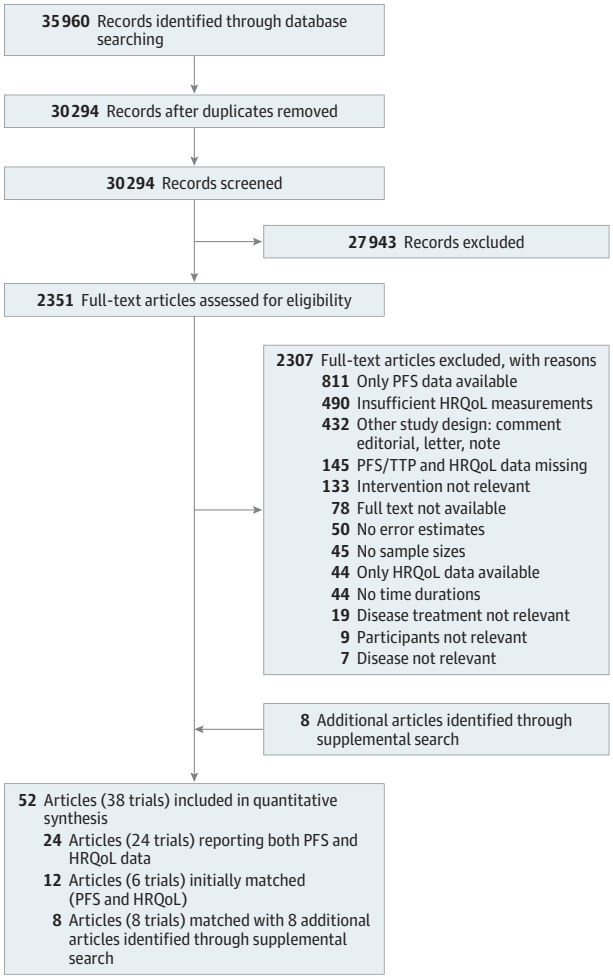
The 38 eligible trials, published between 2000 and 2016, involved 13 979 patients across 12 cancer types. Nine cancer types were studied in multiple trials. Trials enrolled from 40 to 1253 adult patients aged 18 to 93 years. Intervention treatments varied widely, both across and within cancer types. The variability of comparators was lower, with some repetition within cancer type. Reported median follow-up ranged from 10.5 to 66.0 months across trials. Median PFS of trial interventions ranged from 1.8 to 33.7 months, and the duration of reported or measured HRQoL ranged from 1 to 34 months. Of the 38 trials, 24 had shorter HRQoL follow-up than median PFS for the intervention. The HRQoL instrument completion rates from baseline to last measurement for global, physical, or emotional (reported in this order—depending on availability) ranged across trials from 13% to 100% completion. The 38 studies included in our analysis used 6 different HRQoL instruments: 19 trials used the EORTC-QLQ-C30[20,21]; 13 used the FACT-G[19]; 3 used the Lung Cancer Symptom Scale[75]; and 1 each used the EQ-5D,[76] the 8-item linear analog self-assessment (LASA) questionnaire,[77] and clinician-reported Karnofsky score.[78] Of the 38 trials, 32 (84%) had high risk of bias in at least 1 of 4 domains (ie, loss to follow-up, failure to follow up with patients after progression, absence of blinding in participants or study personnel, or outcome assessment),[10] with 16 of 38 trials failing to follow up with patients after progression.

Table 2 details the study data results used in our regression analyses. Of the 38 trials, 28 (74%) reported improved PFS for intervention vs comparator. The mean (SD) difference in median PFS between the intervention and the control arms was 1.91 months (3.35). Global HRQoL was the most common domain, reported in 30 of 38 trials (79%), followed by physical HRQoL reported in 20 of 38 trials (53%), while emotional HRQoL was reported in 13 of 38 RCTs (34%). Of the RCTs reporting HRQoL across the different domains, 16 of 30 (53%), 11 of 20 (55%), and 8 of 13 (62%) trials demonstrated improved global, physical, and emotional HRQoL, respectively, for the intervention vs the comparator. The mean (SD) incremental HRQoL adjusted to per-month values were −0.39 (3.59) for the global domain, 0.26 (5.56) for the physical domain, and 1.08 (3.49) for the emotional domain.

Figure 2 presents scatterplots of the relationship between PFS and each of the HRQoL domains. The slope of the association between the difference in median PFS and the difference in change for global HRQoL (n = 30 trials) was 0.12 (95% CI, −0.27 to 0.52); for physical HRQoL (n = 20 trials), −0.20 (95% CI, −0.62 to 0.23); and for emotional HRQoL (n = 13 trials), 0.78 (95% CI, −0.05 to 1.60).

It became clear after graphing Figure 2A and B (global and physical HRQoL, respectively) that trial MM1 was an outlier, so we used deletion diagnostics to assess the magnitude of influence on the regression coefficients. After MM1 was removed from analysis, the new global HRQoL slope was 0.28 (95% CI, −0.50 to 1.05), and the new physical HRQoL slope was −0.30 (95% CI, −1.30 to 0.70). The level of outlier influence on the main analyses, therefore, seemed to be low, since the deletion of this data point did not change the overall conclusions found.

Figure 1. Study Inclusion Flow Diagram



HRQoL indicates health-related quality of life; PFS, progression-free survival; TTP, time to progression.

Discussion

We performed a systematic review and quantitative analysis of published RCTs, and estimated the PFS-HRQoL association using simple regression to calculate the slope between PFS and HRQoL. Our review and analysis failed to find a significant association between any of the 3 HRQoL domains and PFS. We noted that there was no consistent PFS-HRQoL directional association with similar regression coefficient confidence interval results across the 3 HRQoL domains.

To our knowledge, the question of PFS-HRQoL association in oncology has been examined in only 1 previous study,

Table 1. Summary of Included Studies

Trial ID[a]	Source	Age Range, y	No. of Patients	Cancer Type	Intervention (No. of Patients)	Comparator (No. of Patients)	Follow-up, mo		HRQoL Instrument Completion, No.[b]	
							Median PFS[c]	HRQoL	Baseline	Last Follow-up
B1	Biganzoli et al,[22] 2002 Bottomley et al,[23] 2004	28-70	273	Breast cancer	Doxorubicin + paclitaxel (138)	Doxorubicin + cyclophosphamide (135)	6	4.5	219	105
B2	Bottomley et al,[24] 2005	26.1-79.8	448	Breast cancer	Cyclophosphamide + epirubicin + filgrastim (224)	Cyclophosphamide + epirubicin + fluorouracil (224)	33.7	34	384	100
B3	Cameron et al,[25] 2008 Zhou X et al,[26] 2009	26-83	528	Breast cancer	Lapatinib + capecitabine (264)	Capecitabine (264)	6.2	6	335	74
B4	Di Leo et al,[27] 2008 Sherrill et al,[28] 2010	23-87	579	Breast cancer	Lapatinib + paclitaxel (291)	Placebo + paclitaxel (288)	7.25	11.25	559	73
B5	Nuzzo et al,[29] 2011	30-69	139	Breast cancer	Docetaxel (weekly) (70)	Docetaxel (3× weekly) (69)	15.2	1.5	89	89
B6+	Fountzilas et al,[64] 2009	27-84	272	Breast cancer	Paclitaxel + carboplatin (136)	Paclitaxel (136)	11.5	6	202	146
B7+	Jones et al,[65] 2005	22-93	449	Breast cancer	Docetaxel (225)	Paclitaxel (224)	5.7	3	212	120
C1	Comella et al,[30] 2008	37-84	322	Colorectal cancer	Oxaliplatin + capecitabine (158)	Oxaliplatin + xuorouracil or leucovorin (164)	6.6	6	312	72
C2+	Chen et al,[66] 2014	26-78	40	Colorectal cancer	Double-channel chemotherapy (20)	Intravenous chemotherapy (20)	6	1.5	40	40
L1	Wachters et al,[31] 2003	29-80	240	Non-small cell lung cancer	Epirubicin + gemcitabine (121)	Cisplatin + gemcitabine (119)	5.75	5.25	168	108
L2	Lilenbaum et al,[32] 2005	42-86	165	Non-small cell lung cancer	Vinorelbine + gemcitabine (82)	Carboplatin + paclitaxel (83)	3.9	3	139	65
L3	Maruyama et al,[33] 2008 Sekine et al,[34] 2009	≥20	489	Non-small cell lung cancer	Gefitinib (245)	Docetaxel (244)	11.5	3	358	357
L4	Han et al,[35] 2011	NA	126	Non-small cell lung cancer	Paclitaxel + carboplatin + recombinant human endostatin (63)	Paclitaxel + carboplatin (63)	7.1	2.25	119	88
L5	Sun et al,[36] 2012	30-78	135	Non-small cell lung cancer	Gefitinib (68)	Pemetrexed (67)	9	1.5	132	120
L6+	Pérol,[67] 2016	≥18	1253	Non-small cell lung cancer	Ramucirumab + docetaxel (628)	Placebo + docetaxel (625)	4.5	1	1016	629
M1	Middleton et al,[37] 2000 Kiebert et al,[38] 2003	21-88	305	Melanoma	Temozolomide (156)	Dacarbazine (149)	1.9	6	220	30
M2	Avril et al,[39] 2004	18-79	229	Melanoma	Fotemustine (112)	Dacarbazine (117)	1.8	2	156	156
M3	Grob et al,[40] 2014	≥18	250	Melanoma	Dabrafenib (187)	Dacarbazine (63)	6.9	3	241	151
MM1	Palumbo et al,[41] 2012 Dimopoulos et al,[42] 2013	65-91	306	Multiple myeloma	Lenalidomide + melphalan + prednisone + maintenance lenalidomide (152)	Melphalan + prednisone + maintenance placebo (154)	31	16	284	129
NE1	Arnold et al,[43] 2005	18-77	109	Neuroendocrine foregut and midgut tumors	Octreotide + interferon alfa (54)	Octreotide (55)	6	3	45	45
O1	du Bois et al,[44] 2003	20.8-83.6	783	Ovarian cancer	Paclitaxel + carboplatin (397)	Paclitaxel + cisplatin (386)	17.2	2.25	679	525
O2	Pujade-Lauraine et al,[45] 2010 Brundage et al,[46] 2012	24-82	976	Ovarian cancer	Carboplatin + pegylated liposomal doxorubicin (467)	Carboplatin + paclitaxel (509)	11.3	6	855	465

(continued)

Table 1. Summary of Included Studies (continued)

Trial ID[a]	Source	Age Range, y	No. of Patients	Cancer Type	Intervention (No. of Patients)	Comparator (No. of Patients)	Follow-up, mo		HRQoL Instrument Completion, No.[b]	
							Median PFS[c]	HRQoL	Baseline	Last Follow-up
O3	Monk et al,[47] 2010 Krasner et al,[48] 2012	≥18	672	Epithelial ovarian, fallopian tube, or primary peritoneal carcinoma	Trabectedin + pegylated liposomal doxorubicin (337)	Pegylated liposomal doxorubicin (335)	7.3	5	615	430
O4	Pokrzywinski et al,[49] 2011	≥18	148	Ovarian cancer	Docetaxel + carboplatin (74)	Docetaxel followed by carboplatin (74)	13.7	5.25	131	74
O5	Burger et al,[50] 2011 Monk et al,[51] 2013	22-89	1248	Epithelial ovarian, primary peritoneal, or fallopian-tube cancer	Chemotherapy + bevacizumab (623)	Chemotherapy + placebo (625)	14.1	23	1120	737
O6+	Armstrong et al,[68] 2006	NA	415	Ovarian or primary peritoneal cancer	Intravenous paclitaxel plus intraperitoneal cisplatin (205)	Intravenous paclitaxel plus cisplatin (210)	23.8	16.5	399	279
P1	Philip et al,[52] 2010 Moinpour et al,[53] 2010	30-87	743	Pancreas adenocarcinoma	Gemcitabine + cetuximab (372)	Gemcitabine (371)	3.4	4.25	715	288
P2+	Mukherjee et al,[69] 2013	57-70	74	Pancreatic cancer	Capecitabine (36)	Gemcitabine (38)	12	13	68	31
PR1	Small et al,[54] 2002 Ahles et al,[55] 2004	40-85	256	Prostate cancer	Suramin (high dose) (127)	Suramin (low dose) (129)	3	5.5	229	162
PR2	Dawson et al,[56] 2010	49-91	214	Prostate cancer	Zibotentan, 10 mg (107)	Placebo (107)	4	6	110	28
RC1	Cella et al,[57] 2012	≥18	435	Renal cell carcinoma	Pazopanib (290)	Placebo (145)	9.2	12	427	121
S1	Al-Batran et al,[58] 2013	≥65	143	Stomach or esophagogastric junction adenocarcinoma	Fluorouracil + leucovorin + oxaliplatin + docetaxel (72)	Fluorouracil + leucovorin + oxaliplatin (71)	9	6	123	21
S2	Bonnetain et al,[59] 2005	37-76	90	Gastric adenocarcinoma	Fluorouracil + leucovorin + irinotecan (45)	Fluorouracil + leucovorin(45)	6.9	6	75	23
S3	Jiang et al,[60] 2009	35-69	42	Stomach carcinoma	Recombinant human endostatin + capecitabine + oxaliplatin (20)	Capecitabine + oxaliplatin) (22)	6.9	1.5	42	42
UC1	Long et al,[61] 2006	NA	123	Uterine cervix carcinoma	Methotrexate + vinblastine + doxorubicin + cisplatin (63)	Cisplatin (60)	4.4	9	122	28
UC2	Monk et al,[62] 2009 Cella et al,[63] 2010	20-81	215	Cervical cancer	Cisplatin + gemcitabine (112)	Cisplatin + paclitaxel (103)	4.7	9.75	178	58
UC3+	Tewari et al,[70] 2014 Penson et al,[71] 2015	20-85	452	Cervical carcinoma	Bevacizumab + chemotherapy (227)	Chemotherapy (cisplatin/topotecan + paclitaxel) (225)	8.2	9.75	426	193
UC4+	Long et al,[72] 2005 Monk et al,[73] 2005	22-84	293	Cervical carcinoma	Cisplatin + topotecan (147)	Cisplatin (146)	4.6	9	284	73

Abbreviations: B, breast; C, colorectal; HRQoL, health-related quality of life; L, lung; M, melanoma; MM, multiple myeloma; NA, not available; NE, neuroendocrine; O, ovarian; P, pancreas; PR, prostate; RC, renal cell; S, stomach; UC, uterine cervical; +, trial with statistically significant OS benefit; PFS, progression-free survival.

[a] Trial identifiers (trial IDs) detail the trial characteristics by specific cancer type (letter abbreviations) followed by the trial number for each type. Trial IDs followed by a plus sign represent trials that found statistically significant overall survival benefits.

[b] HRQoL instrument completion for intervention + control groups.

[c] Median PFS times provided for trial intervention arms used in quantitative analyses.

Table 2. Regression Analyses Study Data

Trial ID[a]	Incremental Median PFS Time, mo	Incremental Monthly HRQoL AUC Units (Monthly Variance)		
		Global Domain (n = 30)	Physical Domain (n = 20)	Emotional Domain (n = 13)
B1	0.000	0.150 (0.046)	NA	NA
B2	−0.300	−2.599 (0.023)	NA	NA
B3	1.900	NA	−1.071 (1.395)	−0.260 (1.141)
B4	1.525	−0.074 (0.560)	0.627 (0.732)	NA
B5	2.100	−3.350 (13.339)	−4.350 (10.827)	−2.750 (17.052)
B6+	0.100	−2.5000 (10.826)	NA	NA
B7+	2.100	−0.972 (3.455)	NA	NA
C1	0.100	NA	5.000 (2.803)	0.500 (3.188)
C2+	2.000	NA	3.000 (6.888)	NA
L1	−0.750	1.036 (6.212)	−3.621 (10.091)	−0.943 (6.833)
L2	−0.900	−5.700 (3.131)	NA	NA
L3	−2.500	2.397 (1.206)	2.804 (1.989)	NA
L4	0.800	0.297 (1.689)	NA	NA
L5	6.000	3.050 (12.022)	1.950 (10.168)	3.600 (11.190)
L6+	1.500	1.05 (2.636)	NA	NA
M1	0.400	8.175 (11.386)	11.275 (12.044)	2.875 (8.929)
M2	−0.100	−0.950 (11.174)	6.160 (12.144)	NA
M3	4.200	0.320 (4.061)	0.370 (3.375)	6.638 (4.513)
MM1	18.000	−0.075 (1.164)	−3.375 (1.394)	NA
NE1	0.000	−3.950 (29.415)	NA	NA
O1	−1.900	2.787 (1.198)	NA	NA
O2	1.900	1.000 (1.493)	1.725 (0.902)	1.475 (1.367)
O3	1.500	1.720 (3.341)	NA	NA
O4	5.300	−4.276 (1.499)	−7.755 (2.579)	0.714 (2.218)
O5	3.800	NA	−0.718 (0.265)	NA
O6+	5.500	−4.420 (1.049)	NA	NA
P1	0.400	NA	NA	−0.588 (1.012)
P2+	1.600	5.847 (0.376)	NA	NA
PR1	0.000	−9.083 (1.358)	−14.026 (2.498)	−5.682 (2.314)
PR2	0.400	NA	5.357 (4.442)	1.354 (4.902)
RC1	5.000	−1.513 (3.135)	NA	NA
S1	1.900	0.517 (7.951)	NA	NA
S2	3.700	1.200 (47.245)	6.000 (18.220)	7.100 (37.884)
S3	3.000	3.190 (2.612)	NA	NA
UC1	1.500	−6.155 (6.979)	NA	NA
UC2	−1.120	NA	−2.289 (2.115)	NA
UC3+	2.300	NA	−1.877 (0.436)	NA
UC4+	1.700	1.188 (3.378)	NA	NA

Abbreviations: AUC, area under the curve; B, breast; C, colorectal; HRQoL, health-related quality of life; L, lung; M, melanoma; MM, multiple myeloma; NA, not available; NE, neuroendocrine; O, ovarian; P, pancreas; PR, prostate; RC, renal cell; S, stomach; UC, uterine cervical.

[a] Trial identifiers (trial IDs) detail the trial characteristics by specific cancer type (letter abbreviations) followed by the trial number for each type. Trial IDs followed by a plus sign represent trials that found statistically significant overall survival benefits.

by the Agency for Healthcare Research and Quality.[6] Since this study chose to include only studies with a direct quantitative statistical comparison of PFS with HRQoL, there was limited comprehensiveness, resulting in the inclusion of only 4 studies, and inconclusive findings.

The increasing use of PFS as an end point in oncology RCTs and as a criterion for drug regulatory approvals over recent years has been based 2 practical advantages of using PFS over OS to evaluate drugs: (1) lower requirements for both sample size and extended follow-up, and thus greater speed of trial completion; and (2) a reduction in confounding by crossover designs and subsequent postprogression therapies. In addition to these practical advantages, PFS advocates believe that PFS indicates disease control and stabilization, leading to reduction in disease symptoms, thus implying clinical benefit through improvement in HRQoL.[6,9] Our results cast doubts on such assumptions.

These results have important implications for the design and conduct of oncology RCTs. One possible conclusion is that trials with a primary PFS end point also need to be designed to provide high-quality findings regarding whether the interventions affect HRQoL, including adequate power and data quality (duration of follow-up and high patient compliance). This approach will avoid assumptions[79] and would make the relationship between PFS outcomes and HRQoL outcomes clear, allowing clinical judgment to assess benefits vs risks should the HRQoL outcomes be compromised by treatments that increase PFS. In contrast to the so-

lution for the apparent inadequacy of PFS as a surrogate by ensuring trials are powered to definitively establish effect on OS, ensuring that results demonstrate the effect on HRQoL may not require larger studies. Oncology-specific instruments are responsive to small but important changes in HRQoL[80,81] and may require sample sizes of the same order as those powered to establish PFS. Our finding of approximately the same proportion of trials showing HRQoL benefit as those showing PFS benefit supports this observation.

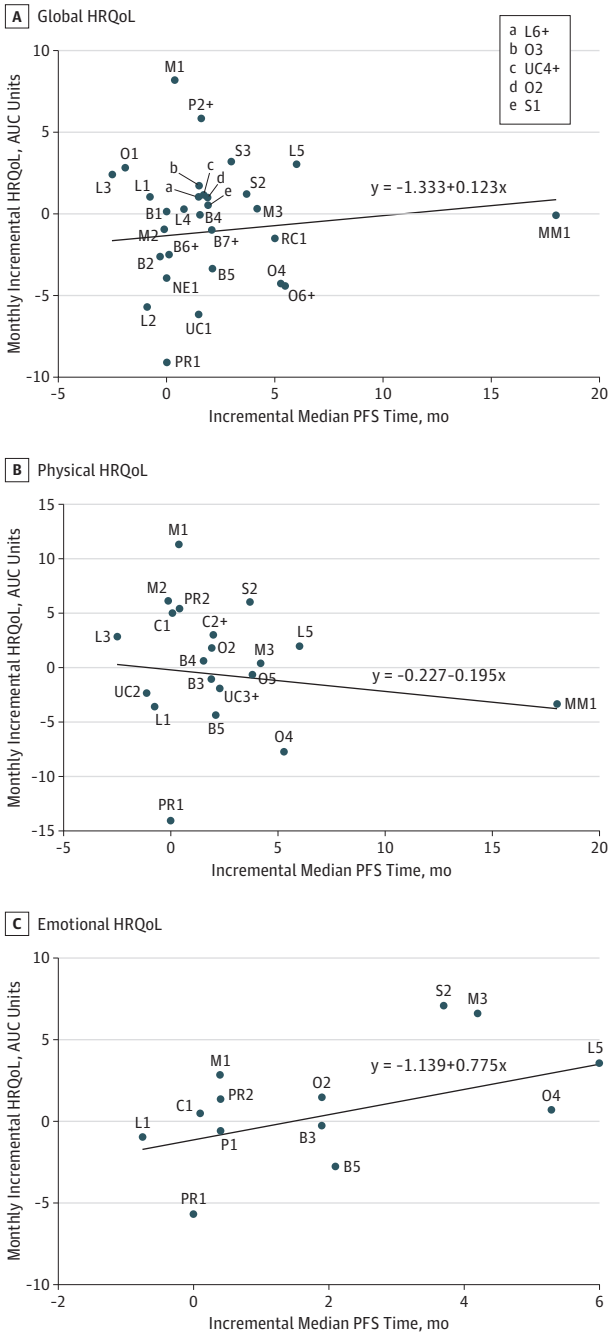
The necessary measurement of HRQoL in RCTs will come with logistical challenges. Investigators will have to implement strategies to minimize the missing HRQoL data, a frequent problem in current RCTs that address HRQoL. Such strategies would include requiring baseline measurement of HRQoL prior to randomization into trials,[82,83] careful monitoring to ensure that measurement takes place at each patient visit, obtaining contact information for a number of individuals with whom patients are not living but who are likely to be aware of their whereabouts, ensuring that resources are available for tracking patients who prove hard to follow, and using electronic administration of HRQoL instruments completed by patients themselves. Furthermore, investigators will have to ensure adequate logistical planning and institutional staff training that will further minimize missing data and ensure optimal administration of HRQoL instruments.[6,83-85]

Strengths and Limitations

The present study, which quantitatively evaluates the PFS-HRQoL association in oncology, has several strengths. First, we conducted an exhaustive search with no language limitations. Second, we developed explicit eligibility criteria and conducted duplicate assessment of eligibility and data abstraction that included use of standardized and pilot-tested screening and data abstraction forms, review team meetings, and communications to ensure resolution of reviewer concerns. As a result, excellent agreement between raters was achieved. Third, we developed a quantitative analysis methodology that allowed inclusion of the widest possible range of relevant publications. Finally, our trial data set had widely distributed patient and trial characteristics, ensuring optimally generalizable results.

The study also has limitations. First, since more than 60% of the trials had shorter HRQoL follow-up than median PFS for the interventions, and 16 of the 38 trials failed to follow up with patients after progression, we may not have captured some HRQoL benefit attributable to PFS that could have occurred later, and thus our findings may underestimate the association between PFS and HRQoL. Second, a large proportion of the included studies (24 of 38) involved traditional cytotoxic chemotherapeutic agents, and since different correlations may exist based on therapy class, our results are potentially more applicable to cytotoxic agents. Third, our failure to show an association could be a result of a lack of statistical power arising from the limited number of trials included in the analysis. For example, the magnitude of the association for the emotional domain was relatively large, but its statistical nonsignificance might be due to the small number of trials reported this domain score. Fourth, with only 38 eligible RCTs, we could not perform some planned sensitivity and subgroup analyses, and there may therefore be subgroups in which the association is stronger than the overall evidence suggests.

Figure 2. Incremental Health-Related Quality-of-Life Measures Plotted Against Incremental Median Progression-free Survival Time, Weighted Least Squares–Treatment vs Control



Trial identifiers (trial IDs) detail the trial characteristics by specific cancer type (letter abbreviations) followed by the trial number for each type. Trial IDs followed by a plus sign represent trials that found statistically significant overall survival benefits. AUC indicates area under the curve; B, breast; C, colorectal; L, lung; M, melanoma; MM, multiple myeloma; NE, neuroendocrine; O, ovarian; P, pancreas; PR, prostate; RC, renal cell; S, stomach; UC, uterine cervical.

Conclusions

The present systematic review and quantitative analysis failed to find a significant association between PFS and HRQoL in oncology RCTs. This finding challenges the use of PFS as the primary efficacy end point in oncology trials. The results suggest that optimally meeting the needs of cancer patients requires trials that are adequately powered for OS, and/or designed to ensure rigorous and trustworthy measurement of HRQoL.

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