Inclusion of older patients with cancer in randomised controlled trials with patient-reported outcomes: a systematic review

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ABSTRACT

Objectives Inclusion of patient-reported outcomes (PROs) in cancer randomised controlled trials (RCTs) may be particularly important for older patients. The objectives of this systematic review were to quantify the frequency with which older patients are included in RCTs with PROs and to evaluate the quality of PRO reporting in those trials.

Methods All RCTs with PRO endpoints, published between January 2004 and February 2019, which included a patient sample with a mean/median age ≥70 years, were considered for this systematic review. The following cancer malignancies were considered: breast, colorectal, lung, prostate, gynaecological and bladder cancer.

Quality of PRO reporting was evaluated using the International Society for Quality of Life Research–PRO standards. Studies meeting at least two-thirds of these criteria were considered to have high-quality PRO reporting.

Results Of 649 RCTs identified with a PRO endpoint, only 72 (11.1%) included older patients. Of these, 35 trials (48.6%) were conducted in patients with metastatic/advanced disease. PROs were primary endpoints in 20 RCTs (27.8%). Overall survival was the most frequently reported clinical outcome in studies of patients with metastatic/advanced cancer (n=28, 80%). One-third of the RCTs (n=24, 33.3%) were considered to have high-quality PRO reporting. Overall, the largest prevalence of RCTs with high-quality PRO reporting was observed in prostate and colorectal cancers.

Conclusions Our review indicates not only that PRO–RCT-based studies in oncology rarely include older patients but also that completeness of PRO reporting of many of them is often suboptimal.

INTRODUCTION

Due to the ageing of the society, the number of older persons is projected to more than double worldwide, rising from 962 million in 2017 to 2.1 billion in 2050.[1] As cancer incidence increases with age, the number of older patients diagnosed with cancer is expected to increase over the next decades.[2 3] Currently, 53.4% of new cancer cases in the USA are diagnosed in people aged 65 years or over, and the median age at cancer diagnosis is 66 years.[4] However, despite the high incidence of cancer in older people, these patients are frequently under-represented in clinical trials evaluating new cancer treatments.[5–8]

Low recruitment of older patients in cancer clinical trials often reflects age-related exclusion criteria, such as comorbidity, reduced life expectancy, polypharmacy and its interaction with chemotherapy.[9–11] Additionally, there is concern that disease symptoms and treatment toxicities may have a greater impact on the health-related quality of life (HRQOL) of older patients, limiting their functional independence and ability to carry out daily activities.[12 13] Thus, when older patients are included in clinical trials, it becomes particularly important to assess outcomes such as physical, role and social functioning, and HRQOL,[14] alongside the more traditional survival outcomes.[2 12]

Compared with younger patients, older people tend to weigh HRQOL as being more important than duration of life when making treatment decisions.[15] However, some earlier research has

suggested that HRQOL and other patient-reported outcomes (PROs) are rarely included in the design of randomised controlled trials (RCTs) that involve older patients with cancer.[16] Also, previous reviews have shown that, regardless of the specific cancer populations enrolled, RCTs with a PRO endpoint are frequently poorly reported, thereby limiting availability of high-quality data that can robustly inform patient care.[17–19]

The main objectives of this review were to quantify the frequency with which older patients are included in cancer RCTs with PROs as primary or secondary endpoints and to evaluate the quality of the PRO results generated in those studies. The secondary objective was to summarise outcomes from the higher quality PRO studies.

MATERIALS AND METHODS

Criteria for trial inclusion

The analysis reported here was based on data collected in the Patient-Reported Outcomes Measurements Over Time In ONcology Registry (http://promotion.gimema.it).[20] This registry includes a wide range of information mainly covering PRO assessment methodology, statistical analysis and outcomes from published cancer RCTs reports. Also, to maximise data quality, detailed information from each RCT is extracted by two independent reviewers and, in case of disagreement, a third senior reviewer is consulted for the final decision. If an RCT generates multiple publications (eg, a primary paper on clinical outcomes and a secondary paper on PROs), information from all related papers are considered. Data are collected and stored into a password-protected online platform: REDCap system.[21] The studies included in this registry are identified using systematic literature searches with PubMed/MEDLINE, the Cochrane Library, PsycINFO and PsycARTICLES. Additional studies are identified through hand searching of the literature, and references of publications are checked to find relevant studies for inclusion. Details on search strategies used for each cancer site considered in this review are reported in online supplementary appendix A. RCTs published since January 2004 that enrolled at least 50 patients (combined arms) and employed at least one PRO measure are included in this registry. Studies published since 2004 are included as the quality of PRO reporting in RCTs was broadly known for the main cancer disease sites before that date.[22] Studies comparing conventional medical treatments (eg, surgery, chemotherapy, radiotherapy or targeted therapies) are included. Studies on prevention and screening programmes, psychological interventions or complementary medicine are excluded. Only English articles are considered, while case reports and conference abstracts are excluded.

Data collection

For the purpose of this review, we first selected from the registry all RCTs published up to February 2019 in breast, colorectal, lung, prostate, gynaecological and bladder cancers. These are the cancer sites with the highest incidence in the European Union in 2018.[23] We then included only those RCTs whose patients had a mean or a median age of at least 70 years. When the mean/median age was not available for the overall sample but reported for individual treatment arms, we included those RCTs with mean/median age per study arm of at least 70 years. We chose this age threshold as it is commonly used as a chronological landmark in oncology clinical trials.[13 24] Two reviewers were involved in screening the RCTs included for current analysis.

Type of information considered

Data considered from each RCT, for the purpose of this analysis, were basic trial characteristics; information about clinical and PRO endpoints; information about difference in overall survival (OS); and the quality of the PRO reporting, based on the International Society for Quality of Life Research (ISOQOL)-PRO checklist[25] and the Consolidated Standards of Reporting Trials (CONSORT)–PRO extension[26] (see further for more detail). Clinical endpoint classification was based on the categories used by Hamaker and colleagues[16]: OS, progression-free survival (PFS), toxicity, efficacy, healthcare utilisation, biological parameters and completion of treatment (online supplementary appendix B). Disease stage was classified according to the following four categories: only patients with metastatic/advanced cancer, only patients with non-metastatic/local cancer, both and unclear. If trials included patients with both metastatic/advanced and non-metastatic/local cancer, when possible, this was reclassified in either categories according to the most represented patient population.

Assessment of the quality of PRO reporting

We evaluated the quality of the PRO reporting using previously defined criteria[27 28] based on the ISOQOL consensus-based recommendations for reporting PRO in publications of RCTs.[25] This represents one of the most widely endorsed set of guidelines that formed the basis for the CONSORT–PRO extension.[26] Briefly, the ISOQOL checklist consists of a set up to 28 issues that should be reported (in case PRO is a primary endpoint).

We defined an RCT as being of high quality, regarding the PRO assessment, if at least two-thirds of the ISOQOL checklist criteria were met. Further details on criteria definition have been previously reported.[27 28] All analyses were performed with SAS V.9.4.

Table 1 General characteristics of cancer randomised controlled trials including elderly patients

Variable	Category	Total (n=72)
International (if more than one country)	No	48 (66.7)
	Yes	24 (33.3)
Industry supported (fully or in part)	No	35 (48.6)
	Yes	37 (51.4)
Disease stage	Only metastatic/advanced	35 (48.6)
	Only non-metastatic/local	27 (37.5)
	Both	8 (11.1)
	Unclear	2 (2.8)
Overall study sample size	≤200	33 (45.8)
	>200	39 (54.2)
Secondary paper on PRO	No	51 (70.8)
	Yes	21 (29.2)
Year of publication	2004–2010	37 (51.4)
	2011–2019	35 (48.6)
Type of treatment used*	Radiotherapy	11 (15.3)
	Surgery	8 (11.1)
	Chemotherapy	26 (36.1)
	Targeted therapy	9 (12.5)
	Hormonal therapy	26 (36.1)
	Other	14 (19.4)
PRO endpoint	Primary	20 (27.8)
	Secondary	52 (72.2)

*More than one option could be chosen.
PRO, patient-reported outcome.

RESULTS

A total of 950 papers were identified, which referred to 649 unique RCTs published in breast, colorectal, lung, prostate, gynaecological and bladder cancers. Of these, 577 did not meet our age cut-off criteria and the remaining 72 RCTs (11.1%) were included in our analysis.

Overview of study characteristics

Of the 72 RCTs identified, 39 (54.1%) were conducted in prostate cancer, 13 (18.1%) in lung cancer, 10 (13.9%) in colorectal cancer, 5 (6.9%) in breast cancer, 4 (5.6%) in bladder cancer and 1 (1.4%) in gynaecological cancer. In total, 35 trials (48.6%) were conducted in patients with metastatic/advanced disease. The majority of lung (n=10, 76.9%), colorectal (n=5, 50%) and prostate (n=19, 48.7%) studies enrolled patients with metastatic/advanced cancer, while the majority of breast (n=4, 80%) and all the bladder (n=4, 100%) studies enrolled patients with non-metastatic/local cancer.

Twenty-one RCTs (29.2%) published a secondary paper reporting additional PRO data. In 19 of these RCTs, PROs were included as secondary endpoints, and the average time between publication of the PRO paper and the primary trial publication was 23.4 months (range 0–50 months). PROs were a primary endpoint in 20 RCTs (27.8%) and a secondary endpoint in 52 RCTs (72.2%) (table 1).

Type of endpoints in RCTs in non-metastatic/local disease

Among the RCTs in patients with non-metastatic/local disease (n=27), PROs were a primary endpoint in 9 RCTs (33.3%) and a secondary endpoint in 18 RCTs (66.7%). Toxicity was evaluated in more than half of the trials (n=15, 55.6%), while survival endpoints were less frequently used: OS was an endpoint in 14 RCTs (51.9%) and PFS was an endpoint in 13 RCTs (48.2%) (table 2).

Type of endpoints in RCTs in metastatic/advanced disease

Among the studies conducted in patients with metastatic/advanced disease (n=35), PROs were a primary endpoint in 8 RCTs (22.9%) and a secondary endpoint in 27 RCTs (77.1%). In these 35 RCTs, OS was the most frequently reported (n=28, 80%), followed by PFS (n=26, 74.3%), toxicity (n=24, 68.6%) and efficacy (n=21, 60%) (table 2).

Overview of the methodological quality of PRO reporting

Twenty-four of the 72 studies (33.3%) were evaluated to have high-quality PRO reporting (see full list of references in online supplementary appendix C). Of these, 13 (54.2%) were conducted in patients with metastatic/advanced disease cancer. Overall, the largest prevalence of RCTs with high-quality PRO

Table 2 Study outcomes of randomised controlled trials in patients with metastatic/advanced and non-metastatic/local cancer

Variable	Category*	Metastatic/advanced (n=35)	Non-metastatic/local (n=27)
Clinical endpoint/s of the study†	Overall survival	28 (80%)	14 (51.9%)
	Progression-free survival	26 (74.3%)	13 (48.2%)
	Toxicity	24 (68.6%)	15 (55.6%)
	Efficacy	21 (60%)	8 (29.6%)
	Biological parameters	1 (2.9%)	2 (7.4%)
	Completion of treatment	2 (5.7%)	1 (3.7%)
	Healthcare utilisation	0 (0%)	4 (14.8%)

*Study outcome categories were based on classification by Hamaker *et al*.[16]
†More than one option could be chosen.

reporting was observed in prostate (n=18/39, 46.2%) and colorectal (n=4/10, 40%) cancers.

Summary of outcomes from higher quality PRO studies in non-metastatic/local disease

Of the non-metastatic/local disease RCTs with higher quality PRO reporting (n=11), four (36.4%) had a PRO as primary endpoint and seven (63.6%) had a PRO as secondary endpoint. The number of patients enrolled in these trials ranged from 98 to 1532. In four trials (36.4%), PROs favoured the experimental arm, and in five trials (45.5%), PROs did not differ between arms. OS was an endpoint in five trials (45.5%). In three of these trials, OS did not differ between study arms, and in one trial, OS was better in the experimental arm. In three trials, there were no significant differences observed between treatment arms in either OS or PROs. In one trial, OS did not differ, while PROs (role and social functioning) favoured the experimental arm. Another study reported improvement in OS in the experimental group (immediate androgen-deprivation therapy), but PROs (sexual activity, hormone treatment-related symptoms, hot flushes and breast symptoms) favoured the control group (delayed therapy). More details are reported in table 3.

Summary of outcomes from higher quality PRO studies in metastatic/advanced disease

Of the metastatic/advanced disease RCTs with higher quality PRO reporting (n=13), 2 (15.4%) had a PRO as a primary endpoint and 11 (84.6%) had a PRO as a secondary endpoint. The trial sample sizes ranged from 82 to 3040. In eight trials (61.5%), PROs were better for the experimental arm, and in four trials (30.8%), they did not differ between arms. OS was an endpoint in nine trials (69.2%), in seven (77.8%) of which survival was not different between arms and in only two (22.2%) of which survival improved in the experimental arm. In three of nine studies with OS as an endpoint (33.3%), both OS and PROs did not differ between arms, and in one study (11.1%), both favoured the experimental arm. In one study (11.1%), OS improved in the experimental group, but PROs did not differ between treatment arms, and in four RCTs (44.4%), PRO data favoured the experimental arm, while no differences in OS were detected between arms. Further details are reported in table 4.

DISCUSSION

This comprehensive literature review examined publications extending over the past 15 years and found that, of 649 RCTs that included a PRO assessment, only 72 (11.1%) of the trials had a sample whose mean/median age was 70 years or greater. In only one-third of these 72 studies was the reporting of PROs considered as being of high quality. In view of the ageing population and predominance of cancer in older age groups that are often not studied or precluded from trials, this study shows that more research aimed at patients aged 70 years and older meeting higher PRO methodological standards is needed.

Among the majority of higher quality PRO studies, PRO data provided novel information that complemented traditional clinical endpoints. Of the 14 higher quality PRO studies evaluating OS, the majority (n=11, 78.6%) found no significant differences between arms in survival. Of these, in almost half of the cases, the PRO results favoured the experimental arm (n=5, 45.5%). For example, in a study conducted in patients with metastatic colorectal cancer, the addition of bevacizumab to fluorouracil and leucovorin was not found to provide OS benefits as compared with a placebo added to fluorouracil and leucovorin.[29] However, time to deterioration in HRQOL outcomes was significantly longer in the bevacizumab arm compared with placebo.[30]

A recent US Food and Drug Administration analysis of trials supporting registration of new cancer therapies and conducted from 2005 to 2015 found that older people, in particular, those aged >75 years, were under-represented.[31] Earlier, Lewis and colleagues[5] found that only 32% of phase II and III cancer trials enrolled older patients, despite the fact that 61% of patients with incident cancers were older. Our results further extend these data by documenting that, even among RCTs that included PROs in their trial protocol, only few focused on older patient populations with cancer.

In a recent review, Marandino and colleagues[32] found that, of 446 RCTs conducted between 2012 and 2016, only 236 included a PRO endpoint. In our review, we found that, in the same period, 21 RCTs with a PRO endpoint included older patients. Although it is difficult to make a direct comparison between our results and those of Marandino and colleagues[32] due to differences in the methodology used to identify the studies, our data suggest that fewer RCTs that include an evaluation of PROs are conducted in older patient populations.

In 2011, the European Organisation for Research and Treatment of Cancer (EORTC) Elderly Task Force indicated that the inclusion of HRQOL, as composite endpoint (ie, in combination with efficacy endpoint) or primary endpoint, in clinical trials involving older people was one of its priorities.[33] Our results suggest that this recommendation has not been followed unfortunately, as the proportion of RCTs with a PRO as primary endpoint included in our review actually also declined after 2011 (36.6% in RCTs published up to 2011 vs 16.1% in RCTs published after 2011). A recent analysis of the endpoints used in ongoing trials conducted in haematological malignancies found that,

Table 3 Summary of outcomes from higher quality PRO studies in non-metastatic/local disease

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Prescott *et al* 2007 Williams *et al* 2011	Breast	Mean: 72.6	255	The standard treatment of postoperative breast irradiation versus the omission of radiotherapy	PRO	The acute morbidity recorded by clinicians showed that breast erythema was significantly more common in the radiotherapy arm, at 2 weeks from completion of treatment (p<0.0001). At 8 and 12 months after surgery, breast oedema and telangiectasia were observed significantly more in women who had radiotherapy. At 12 months, breast retraction scores were significantly higher in the radiotherapy group (p=0.003).	Not applicable	Breast radiotherapy is tolerated well by most older patients with breast cancer without impairing their overall HRQoL.
Van Hooft *et al* 2011	Colorectal	Mean (SD): 71 (10.8)	98	Colonic stenting versus emergency surgery	PRO	No difference was recorded between treatment groups in mortality, morbidity and stoma rates.	Not applicable	No differences between arms were found.
Janson *et al* 2004 Kuhry *et al* 2005 Janson *et al* 2007 Janson *et al* 2009 Buunen *et al* 2009	Colorectal	Median (range): 71 (54–83)	1248	Laparoscopic versus open surgery	Disease-free survival	The combined 3year disease-free survival for all stages was 74.2% (95% CI 70.4% to 78.0%) in the laparoscopic group and 76.2% (95% CI 72.6% to 79.8%) in the open surgery group (p=0.70).	No difference between treatment arms	The HRQOL, as measured by the EORTC QLQ-C30, demonstrated no difference at baseline. In social function, there was a statistically significant benefit of laparoscopic at the assessments at 2 and 4 weeks (p=0.046 and 0.031, respectively). At the 12-week assessment, a borderline significance was found (p=0.050). In role function, there was a significant benefit of laparoscopic at the 2-week assessment (p=0.006).
Fernando *et al* 2014 Fernando *et al* 2015	Lung	Median (range): 71 (49–87)	222	Sublobar resection plus adjuvant intraoperative brachytherapy versus sublobar resection alone	Time to local recurrence	There was no difference in time to local recurrence (HR 1.01, 95% CI 0.51 to 1.98; log-rank p=0.98) or in the types of local recurrence.	No difference between treatment arms	There were no significant differences between the study arms in baseline QOL scores and in percentage change of QOL scores from baseline to 3, 12 or 24 months.

Continued

Table 3 Continued

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Irani *et al* 2010	Prostate	Mean (SD): group A 71.3 (8.1), group B 73.0 (6.7), group C 73.6 (7.3)	311	Venlafaxine versus medroxyprogesterone acetate versus cyproterone acetate	PRO	Serious side effects occurred in four, seven and five patients in the venlafaxine, cyproterone and medroxyprogesterone groups, respectively, of which none, one (dyspnoea) and one (urticaria) were considered related to the drug, respectively (p not reported).	Not applicable	The change in median daily hot-flush score between randomisation and 1 month was −47.2% (IQR −74.3 to −2.5) in the venlafaxine group, −94.5% (−100.0 to −74.5) in the cyproterone group and −83.7% (−98.9 to −64.3) in the medroxyprogesterone group. The decrease from baseline was significant for all three groups (p<0.0001). Pairwise comparison of treatment groups adjusted by the Bonferroni method confirmed that the decreases in hot-flush score were significantly larger in the cyproterone and medroxyprogesterone groups than in the venlafaxine group, regardless of the interval considered (p<0.0001 in all cases).
Fradet *et al* 2007	Prostate	Mean (range): 75 (47–94)	282	Oral tamoxifen (1.0, 2.5, 5.0, 10.0 or 20.0 mg/day) versus placebo	PRO§ PSA inhibition (ie, baseline level minus PSA level at protocol visit expressed as a percentage of the baseline value)	There was no evidence of a negative effect on PSA inhibition at any assessment.	Not applicable	At 6 and 12 months, tamoxifen decreased the incidence of breast events in a dose-dependent manner, with breast events observed in 86.2%, 60.0%, 55.3%, 23.5% and 8.8% of patients receiving tamoxifen 1.0, 2.5, 5.0, 10.0 and 20.0 mg, respectively, compared with 96.7% of patients receiving placebo at 6 months (p≤0.0002 for doses of >1 mg, p=0.0891 for tamoxifen 1 mg)
Michalski *et al* 2018 Bruner *et al* 2015 Michalski *et al* 2013	Prostate	Median (range): group A 71 (50–88), group B 71 (54–83), group C 71 (51–88), group D 72 (54–82)	1532	Conventional-dose (70.2 Gy) radiation therapy versus dose-escalated (79.2 Gy) conformal radiation therapy	OS	There was no difference in OS between the 751 men in the 79.2 Gy arm and the 748 men in the 70.2 Gy arm. The 8-year rates of OS were 76% with 79.2 Gy and 75% with 70.2 Gy (HR 1.00, 95% CI 0.83 to 1.20; p= 0.98).	No difference between treatment arms	There were no significant differences between treatment modalities for any of the FACE or IIEF subscale scores or total scores at any time point.

Continued

Table 3 Continued

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Mason *et al* 2013	Prostate	Median: 71	305	Degarelix versus goserelin plus bicalutamide	Total prostate volume reduction	Total prostate volume decreased significantly from baseline to week 12 in both treatment groups (adjusted difference: −0.3%; 95% CI −4.74% to 4.14%; non-inferiority established).	Not applicable	At the end of the therapy, more degarelix-treated than goserelin-treated patients reported IPSS decreases of >3 points (37% vs 27%, p=0.21). In addition, in patients with a baseline IPSS of >13, the magnitude of the decrease was larger in degarelix-treated (n=53) than in goserelin-treated patients (n=17) (6.04 vs 3.41, p=0.06).
Axcrona *et al* 2012	Prostate	Mean: 72.5	201	Monthly degarelix (240/80 mg) or goserelin (3.6 mg) for 12 weeks	Total prostate volume reduction	At week 12, changes in total prostate volume for degarelix and goserelin were similar (−37.2% vs − 39.0%) and met the predefined non-inferiority criterion.	Not applicable	Decreases in IPSS were greater in degarelix-treated than in goserelin-treated patients, with differences being statistically significant in patients with baseline IPSS of >13 (−6.7±1.8 vs −4.0±1.0, p=0.02). The number of patients with an IPSS change of ≥3 over baseline was also significantly higher in patients treated with degarelix (61.0 vs 44.3%, p=0.02).
Duchesne *et al* 2017 Duchesne *et al* 2016	Prostate	Median (IQR): group A 70.0 (50.7–85.0), group B 71.1 (54.0–88.0), group C 80.0 (76.4–84.9), group D 78.8 (59.4–88.9)	293	Immediate androgen-deprivation therapy versus delayed therapy	OS	5-year OS was 86.4% (95% CI 78.5% to 91.5%) in the delayed therapy arm vs 91.2% (95% CI 84.2% to 95.2%) in the immediate therapy arm (log-rank p=0.047).	Improved in the experimental arm	Sexual activity was lower in the immediate therapy group than in the delayed group at 6 and 12 months (p<0.0001), with the differences exceeding the clinically significant threshold of 10 points until beyond 2 years. The immediate therapy group also had more hormone treatment-related symptoms at 6 and 12 months (p<0.0001), but with differences below the threshold of clinical significance. For the individual symptoms, hot flushes were clinically significantly higher in the immediate group over the 5-year period (p<0.0001), as were nipple or breast symptoms (p=0.00013).

Continued

Table 3 Continued

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Smith *et al* 2018 Saad *et al* 2018	Prostate	Median (range): 74 (48–97)	1207	Apalutamide plus androgen-deprivation therapy versus placebo plus androgen-deprivation therapy	Metastasis-free survival	Median metastasis-free survival was 40.5 months in the apalutamide group as compared with 16.2 months in the placebo group (HR for metastasis or death 0.28, 95% CI 0.23 to 0.35; p<0.001).	No difference between treatment arms	Group mean PRO scores over time show that HRQOL was maintained from baseline after initiation of apalutamide treatment and was similar over time among patients receiving apalutamide versus placebo. Least-squares mean change from baseline shows that HRQOL deterioration was more apparent in the placebo group.

*The full list of references are reported in the online supplementary appendix C .

†Overall number of patients recruited in the study regardless of those with a baseline PRO assessment.

‡When an RCT had no primary clinical endpoint, we reported the results of the main secondary clinical endpoint.

§In this study, PRO and PSA inhibition were co-primary endpoints.

EORTC, European Organisation for Research and Treatment of Cancer; FACE, functional alterations due to changes in elimination; HRQOL, health-related quality of life; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; OS, overall survival; PRO, patient-reported outcome; PSA, prostate-specific antigen; QOL, quality of life;RCT, randomised controlled trial.

even in trials developed for older patients, less than one-fifth included a PRO measure.[16]

Although there is no consensus on how to best evaluate HRQOL in older patients with cancer, a specific questionnaire developed by the EORTC (ie, the EORTC Quality of Life Questionnaire - Elderly Cancer Patients Module QLQ-ELD14)[34] has been available since 2013 and could facilitate implementation of HRQOL in this setting. However, inspection of the US National Institutes of Health clinical trial registry (www.clinicaltrials.gov) indicates that, among the 5192 cancer trials recruiting older patients registered from 2014 onward and currently ongoing, only 1045 (20.1%) included a PRO measure and only 8 used a measure specifically designed for older patients, such as the EORTC QLQ-ELD14.[34]

In our systematic review, we found that, not only PRO–RCT-based studies do rarely include older patients with cancer but also methodological rigorousness of many of them is often suboptimal. Indeed, in two-thirds of the studies, the minimum level of adherence to the well-established international quality standards[25] was not reached. One of the reasons for the poor methodological quality of PRO reporting might be the limited space dedicated to PROs in the primary publication, which may result in the under-reporting of PRO information. Marandino and colleagues found that, even when PRO results are presented in the primary paper, space dedicated in the Results section is less than 10%, and that secondary PRO papers are likely to be published 2 or 3 years after the primary publication.[32] Among the studies included in our review with a PRO as secondary endpoint, only 36.7% dedicated a secondary paper on PRO outcomes, and the average time to secondary publication was 2 years.

Our study has several limitations that should be noted. First, we included only trials investigating pharmacological, surgical or medical interventions, and excluded studies on prevention, psychological interventions or complementary medicine. This may have excluded some trials conducted specifically on older patients with cancer. Second, we did not perform a meta-analysis on the quantitative data obtained. However, given the heterogeneity of PRO measures used across all studies and large variability in data reporting across studies, we did not make any attempt to perform such analysis. Also, although we used a comprehensive searching strategy, it is possible that some RCTs with a PRO endpoint might have been missed. Lastly, we selected RCTs where the median or mean age was at least 70 years. This selection criterion permitted inclusion of studies that recruited patients with a wide age range, also those younger than 70 years.

Our work also has key strengths. To the best of our knowledge, we have provided the first evidence-based data, from a large sample of RCTs conducted across a wide range of solid tumours, on the frequency of

Table 4 Summary of outcomes from higher quality PRO studies in metastatic/advanced disease

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Price *et al* 2004 Kabbinavar *et al* 2005 Kabbinavar *et al* 2008	Colorectal	Mean: placebo 70.7, experimental 71.3. Median (range): placebo 73.0 (41–90), experimental 71.3 (35–89)	209	Bevacizumab plus FU/LV versus placebo plus FU/LV	OS	Median OS was 16.6 months for the FU/LV/bevacizumab group and 12.9 months for the FU/LV/placebo group (HR 0.79, p=0.16)	No difference between treatment arms	Time to deterioration in HRQOL was similar between groups as measured by the CCS and TOI-C scores, but was significantly longer in the experimental arm than in the control arm for the FACT-C total score (FACT-C total, δ≥9; HR 0.69; 95% CI 0.49 to 0.98; p=0.0396)
Aparicio *et al* 2017 Aparicio *et al* 2016 Aparicio *et al* 2013	Colorectal	Median (range): 80 (75-91)	282	FU versus FU plus irinotecan	PFS	No significant difference was observed for the median PFS: FU 5.2 months vs irinotecan 7.3 months, HR=0.84 (0.66–1.07), p=0.15.	No difference between treatment arms	The median time before deterioration in QoL (measured with VAS) was 11.9 months (95% CI: 3.6-not reached) in FU vs 17.7 months (95% CI: 10.8 to 22.0) in irinotecan (p=0.46). Baseline QoL evaluations were not associated with toxicity, reductions in dose-intensity, or unexpected hospitalisation in multivariate analyses.
Berry *et al* 2006 Petrylak *et al* 2004	Prostate	Median (range): 70 (43-88)	770	Docetaxel plus estramustine versus mitoxantrone plus prednisone	OS	Median OS was longer in docetaxel plus estramustine than in mitoxantrone plus prednisone (17.5 months vs 15.6 months, p=0.02)	Improved in the experimental arm	There were no statistically significant differences in pain palliation between the treatment arms. The sensitivity analyses showed a consistent lack of statistically significant global QoL differences for the two arms.
Small *et al* 2002 Ahles *et al* 2004	Prostate	Median (range): group A 70 (64-75), group B 71 (63-75), group C 70 (65-75)	390	Suramin at a low dose (total, 3.192 g/m2), intermediate dose (total, 5.320 g/m2), or high dose (total, 7.661 g/m2)	Response rate	The objective response rate was 9%, 7%, and 15%, respectively (p=0.10). PSA response rates were 24%, 28%, and 34%, respectively (p=0.082).	No difference between treatment arms	Patients who received low-dose suramin reported improvement in QOL (FACT-General: p<0.01; FACT-Treatment outcome index: p<0.01) and decreased levels of depression (CES-D: p<0.0006) during treatment compared with patients in the intermediate- and high-dose arms. After treatment, all groups experienced equal decreases in FACT and CES-D scores.
Saad *et al* 2002 Saad *et al* 2004 Saad *et al* 2005 Saad *et al* 2007 *Saad et al* 2010 Weinfurt *et al* 2005	Prostate	Mean±SD: group A 71.8±7.9, group B 71.2±8.0, group C 72.2±7.9. Median: group A 72, group B 72, group C 73	643	Zoledronic acid at 4 mg, zoledronic acid at 8 mg or placebo	Proportion of patients having at least one skeletal-related event	A greater proportion of patients who received placebo had skeletal-related events than those who received zoledronic acid at 4 mg (44.2% vs 33.2%; difference=−11.0%, 95% (CI)=-20.3% to -1.8%; p=0.021) or those who received zoledronic acid at 8/4 mg (38.5%; difference vs placebo=−5.8%, 95% CI=-15.1% to 3.6%; p=0.222).	No difference between treatment arms	Pain scores increased more in patients who received placebo than in patients who received zoledronic acid, but there were no differences in QoL scores among the groups.

Continued

Table 4 Continued

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Salonen *et al* 2013 Salonen *et al* 2012 Salonen *et al* 2008	Prostate	Mean: 72. median (range): 72 (46-95)	554	Intermittent versus continuous androgen-deprivation therapy	Time to progression	Median time from randomisation to progression in the IAD and CAD arms was 34.5 and 30.2 months (not statistically significant)	No difference between treatment arms	Significant differences in QoL, favouring IAD emerged in activity limitation, physical capacity, and sexual functioning. IAD showed benefits in the treatment of advanced prostate cancer with respect to QoL (P not reported).
Schroder *et al* 2004 Schroder *et al* 2000 Collette *et al* 2003	Prostate	Median (range): 71 (48.9–85.7)	310	Flutamide versus cyproterone acetate	OS	There was no significant difference between arms with respect to OS (p=0.1252)	No difference between treatment arms	No differences between groups in sexual function were found.
Green *et al* 2002 Green *et al* 2002 Green *et al* 2004	Prostate	Mean, SD (range): 73.3, 6.4 (56–86)	82	Leuprorelin, goserelin, cyproterone acetate or close clinical monitoring	PRO	Compared with baseline, men receiving androgen suppression monotherapy performed worse in two of 12 tests of attention (decreased performance at T2 for men assigned to goserelin, p=0.029) and memory (leuprorelin significantly slower at T2 than at baseline, p=0.012)	Not applicable	Sexual dysfunction increased for patients assigned to goserelin (p<0.001), leuprorelin (p=0.033) and cyproterone acetate (p=0.067), and emotional distress increased in those assigned to cyproterone acetate (p=0.041) or close clinical monitoring (p=0.002).
Beer *et al* 2014 Loriot *et al* 2015 Devlin *et al* 2017	Prostate	Median (range): group A 72 (43–93), group B 71 (42–93)	1717	Enzalutamide versus placebo	OS, PFS	Treatment with enzalutamide, as compared with placebo, resulted in an 81% reduction in the risk of radiographical progression or death (p<0.001) and in a 29% decrease in the risk of death (p<0.001)	Improved in the experimental arm	Median time to deterioration in FACT-P total score was 11.3 months (95% CI 11.1–13.9) in the enzalutamide group and 5.6 months (5.5–5.6) in the placebo groups (p<0·0001). A significantly greater proportion of patients in the enzalutamide group than in the placebo group reported clinically meaningful improvements in FACT-P total score, in EQ-5D utility index and in the VAS scale.
Hussain *et al* 2013	Prostate	Median (range): 70 (39-97)	3040	Intermittent versus continuous androgen-deprivation therapy	OS, PRO	Median survival was 5.8 years in the continuous therapy group and 5.1 in the intermittent therapy group (HR for death with intermittent therapy, 1.10; 90% CI, 0.99 to 1.23).	Non-inferiority of experimental arm not demonstrated	Intermittent therapy was associated with better erectile function and mental health (p<0.001 and p=0.003, respectively) at month three but not thereafter.
Langley *et al* 2013 Langley *et al* 2016 Gilbert *et al* 2017	Prostate	Median (range, IQR): group A 75 (56–92, 69–80), group B 73 (49–90, 69–78)	875	tE2 or LHRHa	OS, PFS	Data on disease progression and survival are not yet available.	Not applicable	At 6 months, patients on tE2 reported higher global QOL than those on LHRHa (mean difference +4.2, 95% CI 1.2 to 7.1; p=0.006), less fatigue (mean difference −4.3, 95% CI −8.1 to −0.6; p=0.02) and improved physical function (mean difference +5.8, 95% CI 2.8 to 8.8; p<0.001).

Continued

Table 4 Continued

References*	Disease	Age of patients (years)	Patients enrolled (n)†	Treatments being compared	Primary endpoint	Results of the primary clinical endpoint‡	OS difference	Main PRO findings
Shore *et al* 2016 Heidenreich *et al* 2017	Prostate	Median (range): 71 (48–96)	559	Enzalutamide versus bicalutamide	PFS	Patients in the enzalutamide group had significantly improved median PFS (15.7 months, 95% CI 11.5 to 19.4) compared with patients in the bicalutamide group (5.8 months, 95% CI 4.8 to 8.1; HR 0.44, 95% CI 0.34 to 0.57; p<0·0001).	Not applicable	Risk of first deterioration was lower with enzalutamide for FACT-P total (HR 0.64, 95% CI 0.46 to 0.89; p=0.007), FACT-G total (HR 0.70, 95% CI 0.50 to 0.98; p=0.04), Prostate cancer subscale pain (HR 0.74, 95% CI 0.54 to 1.00; p=0.048) and EQ-5D index (HR 0.66, 95% CI 0.47 to 0.93; p=0.02) scores versus bicalutamide.
Annala *et al* 2018 Khalaf *et al* 2018	Prostate	Median (IQR): arm A 72.9 (67.4–79.05); arm B 77.6 (69.1–83.4)	202	Abitarone plus prednisone versus enzalutamide	PSA response rate	Enzalutamide achieved greater PSA responses than abiraterone, including a higher proportion of patients with PSA decline ≥50% from baseline within 12 weeks (75% vs 54%, p=0.004, Fisher exact test), and a lower proportion of patients with rising PSA as best response within the first 12 weeks of therapy (9% vs 20%, p=0.046, Fisher exact test.	Not applicable	FACT-P change from baseline over time was better for abiraterone than for enzalutamide in the 75-year model (p=0.003), with no difference in the <75-year model (p>0.9). A higher proportion of patients experienced clinically meaningful worsening with enzalutamide for the physical and functional well-being domains (37% vs 21%, p=0.013; 39% vs 23%, p=0.015).

*The full list of references are reported in the online supplementary appendix C.

†Overall number of patients recruited in the study regardless of those with a baseline PRO assessment.

‡When an RCT had no primary clinical endpoint, we reported the results of the main secondary clinical endpoint.

CCS, Colorectal Cancer Subscale; EQ-5D, EuroQoL-5D; FACT, Functional Assessment of Cancer Therapy; FU/LV, fluorouracil and leucovorin; HRQOL, health-related quality of life; LHRHa, luteinising hormone-releasing hormone agonists; OS, overall survival;PFS, progression-free survival; PRO, patient-reported outcome; PSA, prostate-specific antigen; QOL, quality of life; TOI-C, Trial Outcome Index.

inclusion of older patients with cancer in trials with a PRO endpoint. Also, evaluation of the PRO methodological quality was based on the highest quality standards endorsed by major scientific societies.[25 26] Finally, our review covered a large time window, which extends over the last 15 years, and reported very up to date studies being published until early 2019.

In conclusion, our analysis indicates that, among cancer RCTs including PROs, the proportion of those conducted in older patients is low. Investigators should minimise barriers that may exclude older people from participating in trials, incorporate PRO outcomes that may be particularly relevant to this population and ensure that the methodology used to collect and analyse PROs meets high-quality standards.

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