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Commentary

Listening to the Patient Voice Adds Value to Cancer Clinical Trials

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COMMENTARY

Abstract

Randomized clinical trials are critical for evaluating the safety and efficacy of interventions in oncology and informing regulatory decisions, practice guidelines, and health policy. Patient-reported outcomes (PROs) are increasingly used in randomized trials to reflect the impact of receiving cancer therapies from the patient perspective and can inform evaluations of interventions by providing evidence that cannot be obtained or deduced from clinicians' reports or from other biomedical measures. This commentary focuses on how PROs add value to clinical trials by representing the patient voice. We employed 2 previously published descriptive frameworks (addressing how PROs are used in clinical trials and how PROs have an impact, respectively) and selected 9 clinical trial publications that illustrate the value of PROs according to the framework categories. These include 3 trials where PROs were a primary trial endpoint, 3 trials where PROs as secondary endpoints supported the primary endpoint, and 3 trials where PROs as secondary endpoints contrast the primary endpoint findings in clinically important ways. The 9 examples illustrate that PROs add valuable data to the care and treatment context by informing future patients about how they may feel and function on different treatments and by providing clinicians with evidence to support changes to clinical practice and shared decision making. Beyond the patient and clinician, PROs can enable administrators to consider the cost-effectiveness of implementing new interventions and contribute vital information to policy makers, health technology assessors, and regulators. These examples provide a strong case for the wider implementation of PROs in cancer trials.

Randomized clinical trials (RCTs) are critical for evaluating the safety and efficacy of interventions in oncology and thus for informing regulatory decisions, clinical practice guidelines, and health policy. Typically, RCTs evaluate a new intervention against a standard of care for a specific patient population, based on a hypothesis that the new intervention is either superior, equivalent, or not worse (noninferior) than the standard arm by a prespecified clinically relevant margin on the primary study outcome. Patient-reported outcomes (PROs) are commonly included in these RCTs to reflect the impact of receiving cancer therapies from the patient perspective. PROs vary in their content, including symptoms (eg, fatigue, appetite loss, anxiety), psychological well-being, and functional status (eg, physical functioning, sexual functioning, ability to work). PROs are scored based on questionnaires referred to as PRO measures (PROMs), completed directly by the patient, without modification or interpretation by another observer (1,2). A PRO may be the primary outcome, or more frequently, secondary outcomes that, for example, assess physical function or tolerability. Importantly, PROs have the potential to inform evaluations of

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oncological interventions by providing evidence that cannot be obtained or deduced from clinicians' reports or from other biomedical measures (eg, to assess pain, nausea, neuropathy) (3,4).

PROs are increasingly being included in cancer clinical trials (2,5), complementing other clinical assessments including clinician-reported outcomes, observer-reported outcomes, or performance-based outcomes (2). Over several decades, the field has benefited from the development of several established PROMs with strong evidence of reliability and validity in a broad range of cancer patient populations. Recent US Food and Drug Administration guidance provides recommendations for the collection and analysis of a core set of PROs for use in cancer clinical trials, including measures of disease-related symptoms, symptomatic adverse events, measures of physical function and role function, and an overall measure of the impact of side effects (2,6). Further, the guidance recognizes the need to use specific measures in relevant clinical trials that are fit for purpose for patient populations with specific symptoms and functional domains of interest (for example, xerostomia and swallowing function in patients with head and neck cancers). A fit for purpose measure's properties include the following: it validly and reliably measures concepts important to patients and clinicians and can be communicated in a way that is accurate, interpretable, and not misleading (2). There now exist many PROMs of health status, health-related quality of life (HRQOL), and symptom burden that have been rigorously developed and tested to ensure that they address issues relevant to clinicians and patients and that also meet standards for reliability and validity (5,7), some of which are available in multiple languages and cultural adaptations. PROs addressing adverse events [such as the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) system (8)] are now available. Beyond measures of symptoms and HRQOL, health utility measures, such as the EQ-5D (9), may also be of value for cost-effectiveness analyses and health technology assessments.

But do these PROs add value to the interpretation of RCTs by providing information that can inform clinical and regulatory decision making? This commentary addresses this question with illustrative examples of how PROs have added value beyond that provided by conventional clinical outcome measures such as survival, disease response, and clinician-reported toxicity rates. We undertook this commentary as a key strategic initiative of the Patient-Reported Outcomes Tools: Engaging Users & Stakeholders (PROTEUS) Trials Consortium—a collaboration of 27 international stakeholder organizations that aims to optimize the use of PROs in research studies (10). This summary was designed to demonstrate ways in which PROs were key components (as either primary or secondary outcomes) of well-conducted cancer clinical trials.

Methods

We purposively selected published peer-reviewed articles from high-impact journals that could, collectively, provide a spectrum of added-value exemplars of PROs in oncology RCTs. To conduct the review, we assembled a working group (represented in the author list) from the PROTEUS stakeholder organizations. Based on their combined breadth of expertise across medical and scientific disciplines, working group members recommended a preliminary set of published RCT papers and sought additional recommendations from the broader group of PROTEUS members. The selection and description of illustrative RCTs were guided by 2 conceptual frameworks. First, the classification framework proposed by Au et al. (3) was used to describe the spectrum of ways in which PROs add value to RCTs, focusing on 3 main categories (primary endpoint, secondary endpoint supporting the primary, and secondary endpoint contrasting the primary). Second, a framework for evaluating the impact of PROs in clinical trials proposed by Cruz-Rivera et al. (11) was used to describe key impact dimensions (informing clinical decision making, clinical guidelines, drug labeling claims, cost-effectiveness, or health policy, among others). Illustrative RCTs were selected to represent 3 oncology contexts (curative, adjuvant, or palliative settings) and multiple disciplines (surgery, radiotherapy, systemic therapy, and palliative care). Given our intent to illustrate trials with impact in a variety of dimensions, we focused on phase III studies.

Illustrative Clinical Trials

In keeping with the Au et al. classification (3), we selected 3 RCTs in which PROs were a primary endpoint, 3 RCTs where the PROs supported the primary endpoint (ie, 1 trial arm was superior on both the primary endpoint and secondary PRO endpoints), and 3 RCTs in which the PROs were valuable in contrasting the benefits of the primary endpoint. Tables 1-3 summarize the settings and the study characteristics of the included RCTs. With regard to the quality of reporting the trial-specific PROs, 5 publications met all of the Consolidated Standards of Reporting Trials (CONSORT) PRO extensions and elaborations (12); 2 of the 9 trials did not report the mode of PRO administration, 2 did not report baseline PRO scores, and 2 did not report statistical methods for dealing with missing PRO data. Tables 1-3 also briefly summarize the primary outcome and PRO findings, describe the added value of the PROs, and provide examples of trial impact using the citation count (using Google Scholar since year of publication) and the domains of the Cruz-Rivera framework (11).

PROs as the Primary Study Endpoint

Three trials illustrate the use of PROs as primary RCT outcomes and were selected because of their impact on both clinical practice and policy. Given that PROs were the primary outcome in each study, the findings added directly to the respective evidence bases for each clinical context, as summarized in Table 1.

In the Axillary Lymphatic Mapping Against Nodal Axillary Clearance trial (13), PROs were used to evaluate 2 different surgical approaches to the management of the regional nodes in women with early stage breast cancer, with a primary outcome of patient-reported shoulder morbidity (joint function and lymphedema). The finding that patients randomly assigned to sentinel node staging reported statistically and clinically significantly less shoulder and arm dysfunction with sentinel node staging informed practice guidelines [eg, the National Comprehensive Cancer Network guidelines (14)], influenced patterns of care (uptake in practice) (15), and informed related cost-effectiveness evaluations (16,17) and health technology assessments (18).

In the Radiation Therapy Oncology Group 9714 trial (19), 2 radiation fractionation strategies were evaluated in patients with breast or prostate cancer and bone metastases, with a primary outcome of patient-reported pain relief 3 months following treatment. This trial showed that 15% and 50% of patients in the shorter fractionation arm reported complete and partial pain

Table 1. Summary of illustrative trials: trials with PRO(s) as primary study outcome[a]

Trial name	Setting	Study arms	Sample size primary	Sample size PRO endpoint	PRO measures used	Primary outcome findings	Key PRO findings	Value of PROs	Examples of impact		
									Citations	Clinical decision-making or practice guideline inclusion	Policy, regulatory, or other
ALMANAC Mansel et al. (13)	Clinically node-negative breast cancer	Sentinel lymph node biopsy vs standard management of the axillary nodes	1035	816	FACT-B + 4 STAI	Patients reported less shoulder and arm morbidity (eg, lymphedema) with sentinel node approach compared with standard axillary node surgery.	No increase in patient-reported anxiety scores and shorter times to resume normal activities with sentinel node approach.	PROs as primary outcome illustrated the benefits of sentinel node approach beyond objective clinical measures such as wound complications and toxicities. As secondary outcomes, PROs showed no negative impact on patient anxiety rates.	1641	Practice guidelines (14) Patterns of care (15)	Cost-effectiveness (16) Health technology assessment (17,18)
RTOG 9714 Hartsell et al. (19)	Breast or prostate cancer patients with 1-3 sites painful bone metastases	Single fraction of radiotherapy vs 10 fractions over 2 weeks	898	845	FACT BPI	Both single-fraction and 10-fraction regimens were equivalent for pain and narcotic relief at 3 months.	Complete and partial pain and analgesia response rates were not statistically different between arms.	PROs as primary outcome confirmed equivalent rates of symptom relief. As secondary outcomes, PROs illustrated successful reductions in narcotic use and fewer adverse events with a single fraction.	780	Decision making (20) Practice guidelines (21)	Choosing wisely (22) Cost-effectiveness (23)
Temel et al. (24)	Metastatic non-small cell lung cancer	Early palliative care integrated with standard oncologic care or standard oncologic care alone	151	151	FACT-L (including LCS and TOI subscores), HADS, PHQ-9	Overall QOL favored early palliative care integration over standard oncologic care.	Early palliative care patients had less depression.	PROs as primary outcome showed the benefits of early palliative care on overall QOL, as well as secondary benefits in domains such as mental health.	6031	Practice guidelines (25,26)	Cost-effectiveness (27)

[a]ALMANAC= Axillary Lymphatic Mapping Against Nodal Axillary Clearance; BPI = Brief Pain Inventory; FACT = Functional Assessment of Cancer Therapy (-B = breast; -L = lung; +4 = four additional arm specific items); HADS = Hospital Anxiety and Depression Scale; LCS = Lung Cancer Subscale; PHQ = Patient Health Questionnaire; PRO = Patient-reported outcome; QOL = quality of life; RTOG = Radiation Therapy Oncology Group; STAI = State-Trait Anxiety Inventory; TOI = Trial Outcome Index;.

response, respectively, compared with 18% and 48% in the longer fractionation arm. As such, PROs confirmed equivalent rates of symptom relief. As secondary outcomes, PROs further illustrated successful reductions in narcotic use and fewer adverse events with a single fraction of treatment. These trial findings influenced clinical recommendations for shorter treatment schedules (20), American College of Radiology practice guidelines (21), Choosing Wisely recommendations (22), and cost-effectiveness assessments (23).

In a novel trial evaluating early integration of palliative care vs standard of care in a population of advanced non-small cell lung cancer patients, Temel et al. (24) reported that the primary outcome of overall quality-of-life assessments favored early palliative integration: the mean score on the Functional Assessment of Cancer Therapy–Lung (FACT-L) scale (higher scores indicating better quality of life) was 98.0 vs 91.5. The secondary PRO of depression also showed that fewer patients in the palliative care group had depressive symptoms (16% vs 38%). Although not a primary outcome, median survival also favored early palliative care (11.6 vs 8.9 months). These findings impacted on American Society of Clinical Oncology (25) and European Society of Medical Oncology (26) practice guidelines and on cost-effectiveness (27).

Further, in each of these 3 trials, PROs not only were used as the primary outcome but also served as secondary outcomes that in some instances demonstrated additional treatment benefits (eg, mental health benefits of early introduction of palliative care) and sometimes reflected tolerability (eg, potential anxiety in breast cancer patients receiving conservative surgical management). These examples illustrate how a multidimensional PROM(s) can test several trial-specific hypotheses. That said, clear hypothesis testing of a primary PROM and statistical correction for multiple testing are critical in avoiding type I errors when analyzing data sets with multiple PRO domains. In sum, each of these studies has been cited frequently and included in reviews of clinical decision making, in formally developed clinical practice guidelines and in support of health policies based on cost-effectiveness analyses.

PROs Support the Primary Endpoint

Three trials illustrate how PROs added value across the spectrum of systemic, surgical, and radiotherapy interventions (Table 2).

The Controlled Myelofibrosis Study with Oral Janus-activated kinase (JAK) Inhibitor Treatment (COMFORT-II) trial (28,29) compared ruxolitinib with the best available therapy in patients with myelofibrosis (primary and variants). Ruxolitinib is a small-molecule inhibitor of the Janus kinases (JAK1 and JAK2) and was, at the time, a novel targeted agent. Patients with splenomegaly and symptoms of myelofibrosis were randomly assigned to ruxolitinib or best available therapy (a contemporaneous randomized trial [COMFORT-1] used a placebo control). The primary endpoint of reduction in spleen size was statically significant between arms in both trials, but the PROs were critical in illustrating that ruxolitinib also improved patients' symptoms. Accordingly, the PRO data informed clinical decision making, clinical practice guidelines, and economic analyses (Table 1). Further, because ruxolitinib treatment did not confer a survival advantage, the evidence of symptom control was critical to the US Food and Drug Administration and National Institute for Health and Care Excellence approvals of ruxolitinib for this indication (30). The trial is often cited as a paradigm for PROs influencing drug labeling claims (31).

Four RCTs in the setting of early stage breast cancer have reported long-term outcomes of shorter (moderately hypofractionated) radiation treatment schedules compared with the then standard of care of 5-week (25 fraction) schedules (32). These trials tested the hypotheses that shorter schedules were equally effective and resulted in comparable breast cosmetic outcomes. Two such trials, the standardization of breast radiotherapy trials (START) A and B included PROs in the assessment of these shorter schedules (33,34). Collectively, the randomized trials showed the shorter fractionation schedules to be equally efficacious to longer regimens for local and distant disease control but superior in terms of skin cosmesis and no worse for other breast symptoms. Although clinician-rated cosmetic outcomes were also statistically significantly superior with shorter fractionation schedules, patient self-ratings of breast symptoms provided independent confirmation of superior cosmesis, with no associated negative impact on body self-image. PROs also demonstrated statistically significant rates of arm and shoulder symptoms associated with axillary surgery that persisted over time and that were independent of radiotherapy dose scheduling, further demonstrating the value of PROs in these trials. These outcomes were critical in establishing shorter fractionation schedules as a cost-effective standard of care (32,35) and have become particularly relevant to best practice during the COVID pandemic (36).

The Prostate Testing for Cancer and Treatment (ProtecT) trial randomly assigned 1643 men with low-risk prostate cancer to initial active surveillance, radical prostatectomy, or radiotherapy and demonstrated no difference in cancer-specific outcomes between the active intervention arms (37). The PRO profiles of the 3 treatment strategies differed considerably (38): prostatectomy had the greatest negative effect on sexual function and urinary continence with sustained worse scores over time compared with other treatments, whereas bowel function and urinary frequency were worse with radiotherapy at 6 months (both domains showing some recovery at later time periods). No statistically significant differences were observed among treatments for anxiety, depression, or HRQOL scores. The trial was pivotal as a large, randomized study addressing treatment efficacy (in contrast to previous reported nonrandomized comparative effectiveness studies). The differential impact on patient-reported sexual, urinary, and bowel domains was critical for informing patients about potential side effects. A joint clinical practice guideline from urological and radiotherapy associations stated: "Counseling of patients to select a management strategy for localized prostate cancer should incorporate shared decision making and explicitly consider cancer severity, patient values, preferences … and expected post-treatment functional status" (39). Although the ProtecT trial reported 6- and 10-year outcomes and was thus based on older surgical and radiotherapy technologies, more recent prospective cohort studies of robotic surgery and intensity-modulated radiotherapy confirmed the observed PRO differences between strategies (40). PROs also informed cost-effective analyses by clarifying differences in the proportions of men with substantial functional impact at 6 years posttreatment (41).

PROs Contrast the Primary Endpoint

Three trials illustrate cases in which the PROs contrasted with the primary study outcome (Table 3).

Table 2. Summary of illustrative trials: trials where PRO findings support the primary outcome(s)[a]

Trial name	Setting	Study arms	Sample size primary	Sample size PRO endpoint	PRO measures used	Primary outcome findings	Key PRO findings	Value of PROs	Examples of impact		
									Citations	Clinical decision making or practice guideline inclusion	Policy, regulatory, or other
COMFORT-II Harrison et al. (28, 29)	Myelofibrosis patients with splenic enlargement	Ruxolitinib vs best available therapy	219	219	EORTC QLQ-C30; FACT-Lym	Higher proportion of patients met splenic volume reduction endpoints with ruxolitinib vs best available therapy.	Patients receiving ruxolitinib had fewer myelofibrosis-associated symptoms (eg, appetite loss, dyspnea, fatigue, insomnia, and pain).	PROs confirmed that beyond spleen size reduction, the intervention had symptom-domain benefits and functional-domain benefits (eg, superior physical functioning).	1460	Decision making (73,74) Practice guidelines (75)	Cost-effectiveness (76) Drug approval (30,31)
START Trials Haviland et al. (34) Hopwood et al. (33)	Early stage breast cancer	Longer vs shorter radiation schedule post lumpectomy	4451	2208	EORTC QLQ-C30 and protocol-specific radiotherapy items	Local recurrence rates not statistically different between longer vs shorter radiation schedule post lumpectomy.	Patient-rated cosmesis and QOL findings supported shorter fractionation schedule.	PROs confirmed that shorter treatment did not compromise breast-specific outcomes and was superior for skin cosmesis. Late shoulder and arm PROs were independent of radiotherapy schedule.	1126	Decision making (32) Practice guidelines (14,36)	Cost-effectiveness (35)
ProtecT Hamdy et al. (37) Donovan et al. (38)	Clinically localized low-risk prostate cancer	Active surveillance vs radical prostatectomy vs radiotherapy	1643	1643	EPIC-26; EORTC QLQ-C30; others (bowel, bladder, sexual, general QOL domains)	Prostate cancer-specific mortality not statistically significantly different between management options (metastatic progression higher in active monitoring group).	Patterns of severity, recovery, and decline in urinary, bowel, and sexual function domains and associated QOL, differed among the 3 groups.	Active management options were demonstrated to be equivalent for disease-specific outcomes. The differences in PROs for bladder, bowel, and sexual functioning domains were informative for patient-centered decision making.	1618	Clinical guidelines: joint AUA, SUO, ASTRO (39); ASCO (77)	Health technology assessment (78) Cost-effectiveness (41)

[a]ASCO = American Society of Clinical Oncology; ASTRO = American Society for Radiation Oncology; AUA = American Urological Association; COMFORT = Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment; EORTC QLQ-C30 = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core-30; EPIC-26 = Expanded Prostate Inventory Cancer Short Form; FACT-Lym = Functional Assessment of Cancer Therapy, lymphoma; PRO = Patient-reported outcome; ProtecT = Prostate Testing for Cancer and Treatment; QOL = quality of life; START = Standardisation of Breast Radiotherapy; SUO = Society of Urologic Oncology.

Table 3. Summary of illustrative trials: trials where PRO findings contrast the primary study outcome(s)[a]

Trial name	Setting	Study arms	Sample size primary	Sample size PRO endpoint	PRO measures used	Primary outcome findings	Key PRO findings	Value of PROs	Examples of Impact		
									Citations	Clinical decision making or practice guideline inclusion	Policy, regulatory, or other
ICON7 Oza et al. (42) Stark et al. (43)	Advanced ovarian cancer	Carboplatin paclitaxel vs carboplatin paclitaxel plus bevacizumab	1528	890	EORTC QLQ-OV28 EORTC QLQ-C30 EQ5D utility scores	Prolonged progression-free survival with addition of bevacizumab to carboplatin/paclitaxel; no difference in overall survival.	Global QOL inferior if bevacizumab added.	Quantified the negative impact of the intervention on QOL and informed recommendations against its routine use in some patients.	1949	Decision making (79) Clinical guidelines (46)	Cost-effectiveness (44,45) Health technology assessment (47)
COMPARZ Motzer, McCann, Deen (48)	Metastatic renal-cell carcinoma	Pazopanib vs sunitinib	1110	927	FACIT-F FACT, Kidney Symptom Index, CTSQ, SQLQ	Pazopanib was noninferior for progression-free survival compared with sunitinib.	Pazopanib resulted in better PROs for 11 of 14 domains tested (eg, fatigue, mouth soreness).	PROs illustrated that the intervention resulted in better QOL on most domains despite equivalence in progression-free survival rates.	1553	Decision making (51,80) Clinical guidelines (49,50,52)	Cost-effectiveness (52)
CCTG SR.1 O'Sullivan et al. (54)	Operable soft-tissue sarcoma of the limbs	Pre-operative vs postoperative radiotherapy	190	186	Musculoskeletal Tumor Society rating scale; Toronto extremity salvage score; SF-36	Wound complications favored postoperative radiotherapy.	Shoulder mobility and function favored pre-operative radiotherapy.	PROs demonstrate that postoperative radiotherapy may inhibit functional outcomes despite having benefit for wound complications.	1250	Decision making (55,58) Clinical guidelines (56,57)	Cost-effectiveness (81)

[a]COMPARZ = Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma; CTSQ = Cancer Therapy Satisfaction Questionnaire; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (-C30 = core 30; -OV28 = ovarian 28); EQ5D = EuroQol 5 dimension; FACIT-F = Functional Assessment Chronic Illness Therapy, fatigue; FACT = Functional Assessment of Cancer Therapy; ICON7 = International Collaboration on Ovarian Neoplasms 7; SF-36 = 36 item Short Form Survey; SQLQ = Supplementary Quality of Life Questionnaire; PRO = Patient-reported outcome; QOL = quality of life.

The Gynecologic Cancer Intergroup International Collaboration on Ovarian Neoplasms 7 (ICON7) trial randomly assigned 1528 women with high-risk ovarian cancer to standard first-line chemotherapy (carboplatin and paclitaxel for 6 cycles) vs the same chemotherapy plus bevacizumab (continued as a single drug for up to 18 cycles) (42). The addition of bevacizumab marginally improved the trial primary endpoint of progression-free survival (PFS), however, no difference in overall survival was seen for the entire intent-to-treat population. Participants completed PRO assessments at week 54, testing the key secondary PRO endpoint hypothesis that the treatment arms would have differential impact on patients' global quality of life (43). The mean global quality-of-life score at 54 weeks was clinically and statistically significantly better in the standard chemotherapy group than in the bevacizumab group, indicating that bevacizumab continuation treatment was associated with a clinically relevant negative impact on global quality of life compared with standard treatment. The authors recommended that the trade-off between prolongation of PFS and the quality of time on treatment be considered in clinical practice when making treatment decisions (43). As such, the ICON7 trial represents a common paradigm wherein PRO key secondary endpoints reflect tolerability of a new intervention compared with standard of care. Clinical decision making must then weigh PRO and safety findings against improvements in cancer control. Formal considerations of these trade-offs are reflected in the many cost-benefit analyses in the literature informed by the ICON7 PRO findings (44). These analyses estimated incremental cost-effectiveness ratios that exceeded accepted thresholds, even when the analysis was limited to use of a low-dose regimen in a predefined high-risk subgroup of participants (45). Given the small gains in PFS, which were not sustained with longer follow-up, and the small differences between arms in safety and PRO findings, the use of bevacizumab for this indication has mixed support, being recommended by National Comprehensive Cancer Network guidelines (46) but not by National Institute for Health and Care Excellence guidelines (47).

The COMPARZ (Pazopanib Versus Sunitinib in the Treatment of Locally Advanced and/or Metastatic Renal Cell Carcinoma) trial randomly assigned 1110 patients with clear-cell, metastatic renal-cell carcinoma to either pazopanib or sunitinib, powered as a noninferiority study on the primary endpoint of PFS (48). Previous trials had shown each drug to be superior to either placebo or interferon for this indication. The COMPARZ study showed pazopanib to be noninferior to sunitinib for PFS (hazard ratio of 1.05 with confidence limits meeting the predefined noninferiority margin), and overall survival was also not statistically significantly different between agents. However, patients allocated to pazopanib had less clinician-rated grade 1-4 fatigue (55% vs 63%) and mouth-hand-foot syndrome (29% vs 50%) and lower rates of thrombocytopenia but higher rates of alanine aminotransferase elevation. The PRO data further elucidated differences in tolerability between the 2 agents: mean change from baseline for 11 of 14 PROs statistically significantly favored pazopanib (including fatigue and soreness in the mouth, hands, or feet), and between arm differences increased (or were sustained) with further treatment cycles. Moreover, functional domains revealed medium effect-size differences in patients' limitations because of symptoms and in their satisfaction with treatment. The COMPARZ study thus had considerable impact: the PRO data provided a more nuanced picture of treatment effects on fatigue and mouth-hand-foot symptoms than did the summative toxicity data and shed light on the differential functional impacts of these treatment effects on trial participants. The findings informed clinical practice guidelines (49,50), clinical reviews (51), and cost-effectiveness analyses (52). The study is also seen as an exemplar of an RCT addressing tolerability and safety using robust clinical and patient-reported data (53).

Finally, the SR.1 study was a randomized comparison of preoperative vs postoperative radiotherapy for resectable soft-tissue sarcomas of the limb (54). Although both strategies were used in practice, preoperative treatment had the advantage of employing lower dose and smaller treatment fields (thus with potentially less functional impact) but with a higher risk of wound healing complications. SR.1 randomly allocated 190 patients to preoperative or postoperative radiotherapy with a primary endpoint of wound complication rate and showed that wound complications were recorded in 35% of preoperative vs 17% of postoperative cases, respectively (superiority of postoperative treatment for the primary trial endpoint). However, assessment of patients 2 years after random assignment showed that patient-reported limb functioning was statistically significantly superior with the preoperative approach. In sum, the management strategy favored by the primary trial endpoint was ultimately less preferred owing to the secondary endpoint findings, including PROs. Although the selection of treatment strategy considers multiple factors (such as tumor size and location) (55), the PRO findings have been used to support a preoperative approach in the majority of cases, as reflected in a number of clinical practice guidelines (56,57), clinical reviews of evidence-based clinical decision making (55,58), and changes in patterns of clinical practice in favor of preoperative treatment (58).

Discussion

The clinical trials selected for this commentary demonstrate the value of trial-specific data provided directly by patients. Collectively, these trials used PROs to test a spectrum of primary and secondary hypotheses that augmented the evaluation of the study interventions in ways that could not have been achieved with clinician-reported data alone.

For the 3 trials that used PROs as primary study endpoints, it is evident that the PROs were critical to the study design and interpretation. Nonetheless, the validity of these primary outcomes required that the PRO elements of the studies were designed, conducted, analyzed, and interpreted with scientific rigor. As described earlier, these 3 publications met all of the CONSORT-PRO extension reporting recommendations thereby promoting sufficient transparency for the quality of the PRO aspects of the trials to be adjudicated—a necessary condition for the trial findings to be judged as valid and thus to have potential impact.

PROs also added value as key secondary outcomes in each of the 6 illustrative RCTs, both in terms of supporting the primary outcome and/or providing contrasting information that was clinically informative. As secondary measures, PROs illustrated both additional benefits and risks beyond the primary trial outcome and toxicity data. PROs also served in providing valuable evidence on which to base clinical decision making when no statistically significant difference in primary outcome was observed (eg, ProtecT) or when the trial was explicitly designed as a noninferiority study (eg, COMPARZ). PROs further informed important additional domains such as satisfaction with treatment and utility estimates that had impact on additional evaluation of the study interventions.

In the absence of systematic reviews, and given the evidence of underreporting of PROs, it is unclear how frequently PRO data provide clinically meaningful added value to other trial outcomes. However, these illustrative trials demonstrate that PROs can provide value when they are thoughtfully and systematically incorporated in clinical trials. The value of PROs as either primary or key secondary outcomes is conditional on the scientific rigor of the PRO components of the clinical trial, including that PRO hypotheses be explicitly stated and tested with appropriate statistical analyses using high-quality data. However, in a systematic review of clinical trials with PRO endpoints from the UK National Institute for Health Research Portfolio, Kyte et al. (59) found that protocols, on average, included only 10 of 33 recommended items and that 38% of completed trials (including 49 568 participants) failed to report their PRO findings. In a review of US National Cancer Institute trials with funding supporting PROs, St. Germain et al. (60) found that 62% of trials with published findings also published the trial PRO findings. These reviews suggest that there is considerable room for improvement in achieving high-quality PROs in cancer clinical trials.

The PROTEUS Consortium promotes existing methodologic tools for guiding high-quality design, analysis, and reporting of clinical trials. These include the Standard Protocol Items: Recommendations for Interventional Trials–PRO extension (61) that provides items guiding the PRO components of clinical trial protocols, the Setting International Standards for Analysis of quality of life recommendations (62) for statistical analyses of PRO data, and the CONSORT-PRO extension (63) that provides items guiding the reporting of trial PROs. Greater adherence of trial protocols and publications to these and other recommendations will continue to improve the scientific rigor of trial PRO endpoints. We did not systematically review the protocols for the illustrative trials but found that they were generally well reported with respect to the CONSORT-PRO recommendations as described earlier.

We purposefully selected mature trials to demonstrate their impact over time and, consequently, were typically designed with established PRO instruments. More recently, 2 additional measurement systems have emerged that allow more flexibility in assessing PROs. The US National Institutes of Health's Patient-Reported Outcomes Measurement Information System includes measures of a broad range of HRQOL domains for use in clinical trials (64). The PRO-CTCAE enables the assessment of a broad range of symptomatic adverse events associated with cancer treatments (8). Along with the European Organization for Research and Treatment of Cancer and the Functional Assessment of Chronic Illness Therapy item libraries, Patient-Reported Outcomes Measurement Information System and PRO-CTCAE can be used to capture key PROs and treatment-related tolerability, respectively, allowing investigators to tailor the measures for their target study population. Many of these measures are also available in pediatric versions that allow children with cancer as young as 8 years to self-report their symptoms and functioning (65,66). Availability of these comprehensive assessment tools will facilitate broader capture of patients' voices in oncology trials. For both established and newer PROMs, the science of PROs in cancer trials is now well established. Guidance for the design (7,67,68), analysis (62), reporting (12,69), and clinical interpretation (70) of PROs in RCTs is available to ensure the scientific rigor of PROs in RCTs and other comparative effectiveness research applications (10).

We conclude that collecting data directly from patients, as opposed to relying solely on the observations of clinicians and others, is often critical in the evaluation of clinical trial interventions. Without the data provided by clearly defined and rigorously assessed PRO endpoints, the trial findings may not be complete, as would have been the case had our 9 RCT examples not included PROs. New systems and libraries of PROMs now enable the gathering of PRO data in a more targeted manner appropriate to the condition, disease, or treatment being tested. These examples further illustrate that PROs add valuable data to the care and treatment context, providing future patients with vital information on how they may feel and function on different treatments, providing clinicians with evidence to support changes to clinical practice and shared decision making, and enabling managers to consider the cost-effectiveness of implementing new interventions. These examples provide a strong case for wider implementation of PROs in cancer clinical research using thoughtful approaches and clear hypotheses, rigorous methods, and transparent reporting, as supported by the PROTEUS methodological resources, including the Standard Protocol Items: Recommendations for Interventional Trials–PRO, Setting International Standards for Analysis of Quality of Life, and CONSORT-PRO. It is acknowledged that results such as those in our chosen examples may be infrequent, but they will occur more often as PROs are increasingly used as primary endpoints and may sometimes occur unexpectedly when key secondary endpoints become crucial to the study interpretation. Further, patients are also calling for the wider use of PROs in cancer research (71,72), and the growth of patient involvement and engagement in clinical research and regulatory practice will increase the pressure for PROs to be used in the appraisal of all new cancer treatments and innovations.

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Data Availability

Given the descriptive nature of this work, no new data were generated or analyzed in support of this research.

References

1. Acquadro C, Berzon R, Dubois D, et al.; for the PRO Harmonization Group. Incorporating the patient's perspective into drug development and communication: an ad hoc task force report of the Patient-Reported Outcomes (PRO) Harmonization Group meeting at the Food and Drug Administration, February 16, 2001. *Value Health*. 2003;6(5):522-531.
2. US Food and Drug Administration. Core patient-reported outcomes in cancer clinical trials - draft guidance for industry. *FDA-2020-D-2303*. Rockville MD: US Food and Drug Administration; 2021.
3. Au H-J, Ringash J, Brundage M, et al.; for the NCIC CTG Quality of Life Committee. Added value of health-related quality of life measurement in cancer clinical trials: the experience of the NCIC CTG. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10(2):119-128.
4. Lipscomb J, Gotay CC, Snyder CF. Patient-reported outcomes in cancer: a review of recent research and policy initiatives. *CA Cancer J Clin*. 2007;57(5): 278-300.
5. Giesinger JM, Efficace F, Aaronson N, et al. Past and current practice of patient-reported outcome measurement in randomized cancer clinical trials: a systematic review value in. *Value Health*. 2021;24(4):585-591.
6. US Food and Drug Administration. *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics, Guidance for Industry*; 2018. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics.
7. Reeve BB, Wyrwich KW, Wu AW, et al. ISOQOL recommends minimum standards for patient-reported outcome measures used in patient-centered outcomes and comparative effectiveness research. *Qual Life Res*. 2013;22(8): 1889-1905.
8. Basch E, Reeve BB, Mitchell SA, et al. Feasibility of implementing the patient-reported outcomes version of the common terminology criteria for adverse events in a multicenter trial: NCCTG N1048. *J Clin Oncol*. 2018;36(31): 3120-3125.
9. EuroQol Group EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
10. PROTEUS Consortium. http://www.TheProteusConsortium.org. Accessed January 10, 2022.
11. Rivera SC, Kyte DG, Aiyegbusi OL, et al. The impact of patient-reported outcome (PRO) data from clinical trials: a systematic review and critical analysis. *Health Qual Life Outcomes*. 2019;17(1):156.
12. Calvert M, Blazeby J, Altman DG, et al.; for the CONSORT PRO Group. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. *JAMA*. 2013;309(8):814-822.
13. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J National Cancer Inst*. 2006;98(9):599-609.
14. Gradishar WJ, Anderson BO, Balassanian R, et al. NCCN guidelines insights: breast cancer, version 1.2017. *J Natl Compr Canc Netw*. 2017;15(4):433-451.
15. Schrodi S, Niedostatek A, Werner C, et al. Is primary surgery of breast cancer patients consistent with German guidelines? Twelve-year trend of population-based clinical cancer registry data. *Eur J Cancer Care (Engl)*. 2015; 24(2):242-252.
16. Verry H, Lord SJ, Martin A, et al. Effectiveness and cost-effectiveness of sentinel lymph node biopsy compared with axillary node dissection in patients with early-stage breast cancer: a decision model analysis. *Br J Cancer*. 2012; 106(6):1045-1052.
17. Research Excellence Framework. Impact Case Studies. Cardiff research yields evidence for benefits of sentinel node biopsy and spearheads training in the technique as a standard of care in breast cancer surgery. Published 2014. https://impact.ref.ac.uk/casestudies/CaseStudy.aspx?Id=3417. Accessed February 5, 2022.
18. National Institute for Health and Care Excellence (NICE). Breast cancer (early and locally advanced): diagnosis and treatment; NG101. Published 2009. https://www.nice.org.uk/guidance/ng101. Accessed April 20, 2022.
19. Hartsell WF, Scott CB, Bruner DW, et al. Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases. *J Natl Cancer Inst*. 2005;97(11):798-804.
20. Ashworth A, Kong W, Chow E, et al. Fractionation of palliative radiation therapy for bone metastases in Ontario: do practice guidelines guide practice? *Int J Radiat Oncol Biol Phys*. 2016;94(1):31-39.
21. Janjan N, Lutz ST, Bedwinek JM, et al.; for the American College of Radiology. Therapeutic guidelines for the treatment of bone metastasis: a report from the American College of Radiology Appropriateness Criteria Expert Panel on Radiation Oncology. *J Palliat Med*. 2009;12(5):417-426.
22. Wallace AS, Fiveash JB, Williams CP, et al. Choosing wisely at the end of life: use of shorter courses of palliative radiation therapy for bone metastasis. *Int J Radiat Oncol Biol Phys*. 2018;102(2):320-324.
23. Sher DJ. Cost-effectiveness studies in radiation therapy. *Expert Rev Pharmacoecon Outcomes Res*. 2010;10(5):567-582.
24. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363(8):733-742.
25. Ferrell BR, Temel JS, Temin S, et al. Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol*. 2017;35(1):96-112.
26. Novello S, Barlesi F, Califano R, et al.; for the ESMO Guidelines Committee. Metastatic non-small-cell lung cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2016;27(suppl 5):v1-v27.
27. Lowery WJ, Lowery AW, Barnett JC, et al. Cost-effectiveness of early palliative care intervention in recurrent platinum-resistant ovarian cancer. *Gynecol Oncol*. 2013;130(3):426-430.
28. Harrison CN, Mesa RA, Kiladjian JJ, et al. Health-related quality of life and symptoms in patients with myelofibrosis treated with ruxolitinib versus best available therapy. *Br J Haematol*. 2013;162(2):229-239.
29. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366(9):787-798.
30. National Institute for Health and Care Excellence (NICE). Ruxolitinib for treating disease-related splenomegaly or symptoms in adults with myelofibrosis TA386. Published 2016. https://www.nice.org.uk/guidance/ta386. Accessed April 20, 2022.
31. Deisseroth A, Kaminskas E, Grillo J, et al. U.S. Food and Drug Administration approval: ruxolitinib for the treatment of patients with intermediate and high-risk myelofibrosis. *Clin Cancer Res*. 2012;18(12):3212-3217.
32. Holloway CL, Panet-Raymond V, Olivotto I. Hypofractionation should be the new "standard" for radiation therapy after breast conserving surgery. *Breast*. 2010;19(3):163-167.
33. Hopwood P, Haviland JS, Sumo G, et al.; for the START Trial Management Group. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol*. 2010;11(3):231-240.
34. Haviland JS, Owen JR, Dewar JA, et al.; for the START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol*. 2013;14(11):1086-1094.
35. Deshmukh AA, Shirvani SM, Lal L, et al. Cost-effectiveness analysis comparing conventional, hypofractionated, and intraoperative radiotherapy for early-stage breast cancer. *J Natl Cancer Inst*. 2017;109(11):01.
36. Coles CE, Aristei C, Bliss J, et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. *Clin Oncol (R Coll Radiol)*. 2020;32(5):279-281.
37. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016; 375(15):1415-1424.
38. Donovan JL, Hamdy FC, Lane JA, et al.; for the ProtecT Study Group. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2016;375(15):1425-1437.
39. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *J Urol*. 2018;199(3):683-690.
40. Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA*. 2017;317(11):1141-1150.
41. Sharma V, Wymer KM, Borah BJ, et al. Cost-effectiveness of active surveillance, radical prostatectomy and external beam radiotherapy for localized prostate cancer: an analysis of the ProtecT trial. *J Urol*. 2019;202(5):964-972.
42. Oza AM, Cook AD, Pfisterer J, et al.; for the ICON7 trial investigators. Standard chemotherapy with or without bevacizumab for women with newly

diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. *Lancet Oncol*. 2015;16(8):928-936.
43. Stark D, Nankivell M, Pujade-Lauraine E, et al. Standard chemotherapy with or without bevacizumab in advanced ovarian cancer: quality-of-life outcomes from the International Collaboration on Ovarian Neoplasms (ICON7) phase 3 randomised trial. *Lancet Oncol*. 2013;14(3):236-243.
44. Mehta DA, Hay JW. Cost-effectiveness of adding bevacizumab to first line therapy for patients with advanced ovarian cancer. *Gynecol Oncol*. 2014;132(3): 677-683.
45. Hinde S, Epstein D, Cook A, et al. The cost-effectiveness of bevacizumab in advanced ovarian cancer using evidence from the ICON7 Trial. *Value Health*. 2016;19(4):431-439.
46. Armstrong DK, Alvarez RD, Bakkum-Gamez JN, et al. Ovarian cancer, version 2.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2021;19(2):191-226.
47. National Institute for Health and Care Excellence (NICE). Bevacizumab in combination with paclitaxel and carboplatin for first-line treatment of advanced ovarian cancer; TA284. Published 2013. https://www.nice.org.uk/guidance/ta284. Accessed April 20, 2022.
48. Motzer RJ, McCann L, Deen K. Pazopanib versus sunitinib in renal cancer. *N Engl J Med*. 2013;369(20):1970.
49. North SA, Basappa N, Basiuk J, et al.; for the Canadian Kidney Cancer Forum 2015. Management of advanced kidney cancer: Canadian Kidney Cancer Forum consensus update. *Can Urol Assoc J*. 2015;9(5-6):164-170.
50. Ljungberg B, Bensalah K, Canfield S, et al. EAU guidelines on renal cell carcinoma: 2014 update. *Eur Urol*. 2015;67(5):913-924.
51. Mendez-Vidal MJ, Molina A, Anido U, et al. Pazopanib: evidence review and clinical practice in the management of advanced renal cell carcinoma. *BMC Pharmacol Toxicol*. 2018;19(1):77.
52. Liviu Preda A, Galieta Minca D. Cost-effectiveness analysis of treatment for metastatic renal carcinoma in Romania. *J Med Life*. 2018;11(4):306-311.
53. Kluetz PG, O'Connor DJ, Soltys K. Incorporating the patient experience into regulatory decision making in the USA, Europe, and Canada. *Lancet Oncol*. 2018;19(5):e267-e274.
54. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. *Lancet*. 2002;359(9325):2235-2241.
55. Shah C, Verma V, Takiar R, et al. Radiation therapy in the management of soft tissue sarcoma: a clinician's guide to timing, techniques, and targets. *Am J Clin Oncol*. 2016;39(6):630-635.
56. Dangoor A, Seddon B, Gerrand C, et al. Guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res*. 2016;6:20.
57. Casali PG, Abecassis N, Aro HT, et al.; for the ESMO Guidelines Committee and EURACAN Soft tissue and visceral sarcomas: ESMO-EURACAN Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018; 29(suppl 4):iv51-iv67.
58. Panwar U, Sankaye P. Preoperative versus postoperative radiotherapy in extremity soft tissue sarcoma: a changing trend towards preoperative radiotherapy in the UK. *Clin Oncol (R Coll Radiol)*. 2015;27(6):369-370.
59. Kyte D, Retzer A, Ahmed K, et al. Systematic evaluation of patient-reported outcome protocol content and reporting in cancer trials. *J Natl Cancer Inst*. 2019;111(11):1170-1178.
60. St Germain D, Denicoff A, Torres A, et al. Reporting of health-related quality of life endpoints in National Cancer Institute-supported cancer treatment trials. *Cancer*. 2020;126(11):2687-2693.
61. Calvert M, King M, Mercieca-Bebber R, et al. SPIRIT-PRO extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials. *BMJ Open*. 2021;11(6):e045105.
62. Coens C, Pe M, Dueck AC, et al.; for the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data Consortium. International standards for the analysis of quality-of-life and patient-reported outcome endpoints in cancer randomised controlled trials: recommendations of the SISAQOL Consortium. *Lancet Oncol*. 2020;21(2): e83-e96.
63. Calvert M, Blazeby J, Revicki D, et al. Reporting quality of life in clinical trials: a CONSORT extension. *Lancet*. 2011;378(9804):1684-1685.
64. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): progress of an NIH roadmap cooperative group during its first two years. *Med Care*. 2007;45(5 suppl 1):S3-S11.
65. Reeve BB, McFatrich M, Mack JW, et al. Validity and reliability of the pediatric patient-reported outcomes version of the Common Terminology Criteria for Adverse Events. *J Natl Cancer Inst*. 2020;112(11):1143-1152.
66. Hinds PS, Wang J, Cheng YI, et al. PROMIS pediatric measures validated in a longitudinal study design in pediatric oncology. *Pediatr Blood Cancer*. 2019; 66(5):e27606.
67. Calvert M, Kyte D, Mercieca-Bebber R, et al.; for the SPIRIT-PRO Group. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. *JAMA*. 2018;319(5):483-494.
68. Crossnohere NL, Brundage M, Calvert MJ, et al. International guidance on the selection of patient-reported outcome measures in clinical trials: a review. *Qual Life Res*. 2021;30(1):21–40.
69. Snyder C, Smith K, Holzner B, et al.; for the PRO Data Presentation Delphi Panel. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. *Qual Life Res*. 2019; 28(2):345-356.
70. Wu AW, Bradford AN, Velanovich V, et al. Clinician's checklist for reading and using an article about patient-reported outcomes. *Mayo Clin Proc*. 2014; 89(5):653-661.
71. Wilson R. Patient led PROMs must take centre stage in cancer research. *Res Involv Engagem*. 2018;4(1):1-8.
72. Addario B, Geissler J, Horn MK, et al. Including the patient voice in the development and implementation of patient-reported outcomes in cancer clinical trials. *Health Expect*. 2020;23(1):41-51.
73. Ellis MH, Lavi N, Mishchenko E, et al. Ruxolitinib treatment for myelofibrosis: efficacy and tolerability in routine practice. *Leukemia Research*. 2015;39(11): 1154-1112.
74. Padrnos L, Mesa RA. Myeloproliferative neoplasms: translating new discoveries into better outcomes, better quality of life. *Oncology (Williston Park)*. 2017; 31(7):521-529.
75. Mesa RA. NCCN debuts new guidelines for myeloproliferative neoplasms. *J Natl Compr Canc Netw*. 2017;15(5S):720-722.
76. Wade R, Rose M, Neilson AR, et al. Ruxolitinib for the treatment of myelofibrosis: a NICE single technology appraisal. *Pharmacoeconomics*. 2013;31(10): 841-852.
77. Bekelman JE, Rumble RB, Chen RC, et al. Clinically localized prostate cancer: ASCO clinical practice guideline endorsement of an American Urological Association/American Society for Radiation Oncology/Society of Urologic Oncology Guideline. *J Clin Oncol*. 2018;36(32):3251-3258.
78. Hamdy FC, Donovan JL, Lane JA, et al. Active monitoring, radical prostatectomy and radical radiotherapy in PSA-detected clinically localised prostate cancer: The ProtecT three-arm RCT. *Health Technol Assess*. 2020;24(37):1-176.
79. Cherny NI, Dafni U, Bogaerts J, et al. ESMO-magnitude of clinical benefit scale version 1.1. *Ann Oncol*. 2017;28(10):2340-2366.
80. Bergmann L, Beck J, Bothe K, et al. Treatment algorithm for metastatic renal cell carcinoma—recommendations based on evidence and clinical practice. *Oncol Res Treat*. 2014;37(3):136-141.
81. Qu XM, Louie AV, Ashman J, et al. Cost-effectiveness analysis of preoperative versus postoperative radiation therapy in extremity soft tissue sarcoma. *Int J Radiat Oncol Biol Phys*. 2017;97(2):339-346.