Editorial Commentary

The value of patient reported outcomes in palliative radiotherapy: A discussion in light of current findings

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Why patient reported outcomes (PROs) should be routinely captured in trials and the clinic

Radiation therapy is commonly delivered with palliative intent (1,2). The aim is to either alleviate or prevent symptoms, such as pain and breathlessness, or to prolong life expectancy (3). Especially under palliative conditions, radiation oncologists aim to avoid serious short-term side effects.

Often, the alleviation or prevention of symptoms, the prolongation of life, and the avoidance of treatment morbidity are intended at the same time. Even when extending survival is the primary aim for select patients with incurable and progressive diseases, ensuring the best possible quality of life (QoL) and symptom management are still important goals of care when treating and following these patients. This is part of the *general* (or *primary*) palliative care assignment of radiation oncologists and their teams who provide care for such patients (4). A considerable number of clinical scores exist to select the adequate aggressiveness of radiotherapy and the best fractionation regimen to fulfil all goals of palliation using the best achievable balance (5). Unfortunately, none of these scores integrate individual patient preference, nor the severity of perceived symptoms. Under such circumstances, patient-reported outcome measures may help to optimize the palliative treatment decision and to assess treatment efficacy (6).

According to the WHO definition, palliative care focuses on the alleviation of suffering, which according to the wording of the definition demands "early identification" and monitoring of symptoms and QoL. Symptom severity (i.e., pain, anxiety, breathlessness, nausea) and QoL, in general, are completely subjective experiences and can only be judged by the patients themselves (7). They should be captured routinely during patient visits via PROs as single item questions (i.e., symptoms) or questionnaires (i.e., complex domains such as QoL). Also, they should be used as mandatory secondary or primary endpoints in clinical trials involving palliative radiotherapy (7). This is important because traditional endpoints in interventional cancer trials, such as progression-free survival (PFS) or overall survival, do not correlate well with QoL (8). Surrogate endpoints have created uncertainties in translating surrogate measures into patient-centric clinically and economically meaningful outcomes (9). Nevertheless, in the last decade, such surrogate markers like PFS and tumour response have been increasingly used in clinical trials to reduce trial cost by

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decreasing the needed number of patients or shortening the duration of trials. This has led to a trend towards smaller and earlier phase trials and, therefore, less generalizable data with the potential for bias and disproportionately positive results (10).

Surrogate endpoint data were also sufficient to achieve adoption and reimbursement (11,12), but more clinically relevant and patient-related QoL endpoints have been used much more sparingly in palliative trials (13). Some authors still consider health-related QoL metrics as challenging to assess and accident-sensitive (11). But notably, PROs such as general QoL, symptom severity and self-reported performance status are known to be strong predictors of survival in clinical trials for patients with advanced malignancies (14-16).

Also, routine gathering of PROs in clinical practice results in pronounced benefits for patients not only concerning symptom severity and management and QoL, but also survival, as it has been repeatedly found in clinical trials (17). Therefore, authors and practice guidelines have called for regulators, patient advocates and medical associations to demand the routine implementation of PROs in oncology trials and in routine clinical practice (7,18). Having these instruments become more established in routine clinical practice may increase operational efficiencies, reduce the costs associated with frequency personal contacts with trial centers, and reduce travelling time for patients, which can serve to increase the willingness of patients to enroll in clinical trials. In our opinion, PROs offer a chance to overcome the problem of poor recruitment, which is especially evident in local intervention trials with the intent of symptom control (19).

Findings from the recent systematic review by Fabian *et al.*

In the September 2022 issue of *JAMA Network Open*, Fabian *et al.* presented findings from their very relevant systematic review (1). They investigated the use of PROs as endpoints in palliative radiotherapy trials. In their review, they included 225 trials evaluating a total of 24,281 patients.

Approximately half of these assessed trials implemented PROs as one of their outcomes. Specifically, 45 trials (20%) used a PRO as a primary end point and 71 trials (31%) used at least one PRO among their secondary end points. However, reporting of PROs substantially varied between treated sites. For example, PROs were used 3 to 10 times more often in trials examining radiotherapy for metastases or thoracic disease compared to trials for pelvic, abdominal, central nervous system (CNS), and head and neck cancers, even though it is known that these cancer sites are very often associated with a severe symptom burden and impairment of QoL. These findings are contradictory to the reports of earlier systematic reviews, such as from Howell *et al.* (20). Howell *et al.* reported that PROs were captured most often in brain and head and neck cancers (82% and 77%, respectively), and much less in thoracic and breast trials (19% and 38%, respectively). This difference remains unexplained, and an author inquiry did not yield further ideas to explain this difference, although trial inclusion criteria are likely a primary driver of this difference.

Among the 116 trials reporting PROs in the report by Fabian *et al.*, the Numeric Rating Scale and Visual Analogue Scale are the most commonly used (38 trials), although the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire C30 (32 trials) and trial-specific unvalidated measures (25 trials) were also used frequently.

Interestingly and correlating to the increasing awareness for the value of PROs in the scientific, clinical and regulatory communities, PROs became more commonly used as a secondary end point in trials that were published in more recent years [odds ratio (OR), 1.04; 95% CI, 1.00–1.07; P=0.03]. Disappointingly, the use of PROs as the primary endpoint did not increase over time.

Also disappointing was the finding that adherence to the relevant reporting guideline [Consolidated Standards of Reporting Trials (CONSORT) PRO extension] (21) was often insufficient. Specifically, the mean [standard deviation (SD)] adherence score was 46.2% (19.6%) for trials with PROs as primary end point and 31.8% (19.8%) for trials with PROs as a secondary end point. Notably, not a single trial cited the CONSORT-PRO extension. As a limitation to this finding, it should be noted that Fabian *et al.* also included trials that were not randomized controlled trials (RCTs), but, the CONSORT statement was specifically designed for RCTs.

PROs: in the context of the field and implications for the future

Just prior to the publication by Fabian *et al.* (1), Howell *et al.* (20) examined the utilization of PROs within National Clinical Trials Network (NCTN) Cooperative Group Radiation Oncology trials. They examined trials published in the last 20 years and identified 101 studies, but their main results were quite similar. The slightly higher rate

of PROs utilization found in their work (56% compared to 52% by Fabian *et al.*) can be explained by the greater focus on PROs among NCTN studies and more recent trial inclusion (no time limits are reported in the eligibility criteria by Fabian *et al.*).

The question is now whether the glass of wine is half (52%) full or half empty. Of course, when caring for patients in palliative stages of their disease and when including them in clinical trials, QoL and symptom burden, captured by PROs, should always be a major goal of care. Therefore, the sceptical view on the findings would clearly be that the glass is half empty and moreover that the wine in the glass is diluted with a significant amount of water, making it much less tasty than it should be, since the rate of adherence to the CONSORT-PRO extension was rather low.

Yet, a view on previous studies from earlier years may result in a more optimistic view. For example, in 2016, a systematic review (22) examined the use of PROs in RCTs on cancer treatment of advanced, solid tumours. All assessed studies included patients with a median overall survival of less than two years, with the vast majority of patients expiring within 12 months after recruitment. In this review, only 26% of the included trials reported PROs. On average, only 4.4 (SD 2.5) of the 14 CONSORT items were met. Strikingly, only two of the included trials found PROs valuable enough to mention them as an endpoint in the abstract (CONSORT-PRO checklist item 1b). Moreover, these two studies did not report the finding for these PROs in the full text of the primary trial publication. Most of the primary endpoints in the identified trials were surrogate measures of PFS (53%) or overall survival (33%). All of the included trials were primary publications. It is possible, however, that some of investigators for these trials may have published the findings of their PRO endpoint later in a secondary publication (22). From the view of patient needs in palliative phases, this can be problematic because QoL and symptom burden are major goals of care for all these patients and cancer therapies can potentially impair QoL. Therefore, it should be best practice not only to capture cancer- and treatment-specific PROs in each trial on disease directed therapy (i.e., radiotherapy), but also to report the results in a timely manner in the primary publication or dedicated QoL manuscript published in close proximity to the primary publication (7,21). This should be mandatory, because this information is of utmost importance to help patients and their clinicians to most easily determine an impression of the possible impact of the studied interventions on the patients' wellbeing (7).

Such an approach is also indirectly supported by the European Society of Medical Oncology (ESMO) Magnitude of Clinical Benefit Scale (23), but in July 2022 the developers of this tool reported ongoing shortcomings of drug-approval trials if this scale was used as a quality benchmark (24).

What may be the reasons for ongoing deficits? First, this may be part of tradition and routine. It has been found that RCTs on cancer therapies still avoid the use of palliative or even end-of-life terminology, seldomly mentioning or discussing the limited life-expectancy and QoL needs of the patients, even in patient populations where life expectancy is less than one year (25). Second, the routine monitoring of PROs has not yet become common practice in many cancer care settings, even though this is encouraged by guidelines, patient advocates and evidence-based findings (17,26,27). Therefore, thirdly, investigators and especially funders of clinical trials may be reluctant to implement PROs in their study because of the fear of patients declining to enroll due to the added participation requirements of completing PROs or of the study generating a considerable rate of missing data if patients do not comply with filling out multi-item questionnaires or miss scheduled study visits (7).

In addition, clinical trials in radiation oncology are less likely than their medical oncology counterparts to have industry funding, potentially since sponsors do not see as great of a chance for new revenue streams (28). This is a heavy burden for radiation oncology trials, as industry sponsorship often increases the chance of successful patient accrual (10). From 2006 to 2014, National Institute of Health-sponsored clinical trials declined by 24%, resulting in a reduced chance of funding radiation trials (29). As the utility of surrogate markers to prove the efficacy of palliative radiotherapy is in its infancy (28), a cheap but reliable endpoint as QoL measured by PROs can strengthen the chances to conduct palliative radiation trials.

Finally, although the US Food and Drug Administration (FDA) conducted a round-table meeting on the use of PROs in 2020, in their Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics statement from 2018, their list of commonly used efficacy endpoints in oncology clinical trials does not even mention QoL or PROs (30). Therefore, it is not astonishing that the list of endpoints in oncological trials shows frequent surrogate outcomes without strong correlation to relevant clinical endpoints and only limited clinical benefit rates, but that QoL and PROs are rare (31).

So what about the glass of wine? As explained above; yes, it tastes quite watered down and needs to be filled. But

"*do not let yourself be tainted with a barren scepticism*" (Louis Pasteur). The scientific and clinical communities are on their way. As Fabian *et al.* (1) reported, the use of PROs and the adherence to reporting guidelines are increasing, and in the long run, study investigators and sponsors will not be able to ignore, but to use the chance of guidance from regulatory authorities such as the European Medicines Agency (EMA) and the FDA, medical associations such as European Organisation for Research and Treatment of Cancer (EORTC) (7) and ESMO (18), and patient advocates (7).

But all these developments and facilitators will be insufficient if we do not prioritize PROs as study endpoints in clinical trials, adopt a culture of openly discussing end-of-life or palliative care in trial publications, and routinely obtain PROs and QoL as part of routine clinical care.

Summary and conclusions

In palliative radiotherapy trials, just as in other studies on cancer therapy, PROs are currently insufficiently used, evaluated and reported as endpoints. This corresponds to the unsatisfactory fact that PROs are not routinely monitored in all cancer care settings. Still, the use of PROs is increasing, and they are expected to play a greater role in trials of advanced cancer patients in the future, which may serve to increase clinical meaningfulness of study results, reduce trial costs, and improve trial enrollment.

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References

1. Fabian A, Domschikowski J, Letsch A, et al. Use and Reporting of Patient-Reported Outcomes in Trials of Palliative Radiotherapy: A Systematic Review. JAMA Netw Open 2022;5:e2231930.
2. Asli LM, Kvaløy SO, Jetne V, et al. Utilization of radiation therapy in Norway after the implementation of the national cancer plan--a national, population-based study. Int J Radiat Oncol Biol Phys 2014;90:707-14.
3. Jones JA, Simone CB 2nd. Palliative radiotherapy for advanced malignancies in a changing oncologic landscape: guiding principles and practice implementation. Ann Palliat Med 2014;3:192-202.
4. Gärtner J, Daun M, Wolf J, et al. Early Palliative Care: Pro, but Please Be Precise! Oncol Res Treat 2019;42:11-8.
5. Nieder C, Haukland EC, Mannsåker B, Dalhaug A. Palliative appropriateness criteria: external validation of a new method to evaluate the suitability of palliative radiotherapy fractionation. Strahlenther Onkol. 2023;199:278-83.
6. Kluzek S, Dean B, Wartolowska KA. Patient-reported outcome measures (PROMs) as proof of treatment efficacy. BMJ Evid Based Med 2022;27:153-5.
7. Bottomley A, Reijneveld JC, Koller M, et al. Current state of quality of life and patient-reported outcomes research. Eur J Cancer 2019;121:55-63.
8. Kovic B, Jin X, Kennedy SA, et al. Evaluating Progression-Free Survival as a Surrogate Outcome for Health-Related Quality of Life in Oncology: A Systematic Review and Quantitative Analysis. JAMA Intern Med 2018;178:1586-96.
9. Trapani D, Tay-Teo K, Tesch ME, et al. Implications of Oncology Trial Design and Uncertainties in Efficacy-

Safety Data on Health Technology Assessments. Curr Oncol 2022;29:5774-91.
10. Pasalic D, Tang C, Jagsi R, et al. Association of Industry Sponsorship With Cancer Clinical Trial Accrual. JAMA Oncol 2020;6:1625-7.
11. Blumenthal GM, Kluetz PG, Schneider J, et al. Oncology Drug Approvals: Evaluating Endpoints and Evidence in an Era of Breakthrough Therapies. Oncologist 2017;22:762-7.
12. Smith N, Fu AC, Fisher T, et al. Oncology drugs and added benefit: insights from 3 European health technology assessment agencies on the role of efficacy endpoints. J Med Econ 2022;25:1-6.
13. Kordecka A, Walkiewicz-Żarek E, Łapa J, et al. Selection of Endpoints in Clinical Trials: Trends in European Marketing Authorization Practice in Oncological Indications. Value Health 2019;22:884-90.
14. Ediebah DE, Quinten C, Coens C, et al. Quality of life as a prognostic indicator of survival: A pooled analysis of individual patient data from canadian cancer trials group clinical trials. Cancer 2018;124:3409-16.
15. Gotay CC, Kawamoto CT, Bottomley A, et al. The prognostic significance of patient-reported outcomes in cancer clinical trials. J Clin Oncol 2008;26:1355-63.
16. Howdon D, van den Hout W, van der Linden Y, et al. Replacing performance status with a simple patient-reported outcome in palliative radiotherapy prognostic modelling. Clin Transl Radiat Oncol 2022;37:137-44.
17. Basch E, Schrag D, Henson S, et al. Effect of Electronic Symptom Monitoring on Patient-Reported Outcomes Among Patients With Metastatic Cancer: A Randomized Clinical Trial. JAMA 2022;327:2413-22.
18. Di Maio M, Basch E, Denis F, et al. The role of patient-reported outcome measures in the continuum of cancer clinical care: ESMO Clinical Practice Guideline. Ann Oncol 2022;33:878-92.
19. Buergy D, Riedel J, Sarria GR, et al. Unfinished business: Terminated cancer trials and the relevance of treatment intent, sponsors and intervention types. Int J Cancer 2021;148:1676-84.
20. Howell JN, Anker CJ, Walker AJ, et al. Analysis of Patient-Reported Outcome Utilization Within National Clinical Trials Network Cooperative Group Radiation Oncology Trials Over the Past 2 Decades. Int J Radiat Oncol Biol Phys 2021;109:1151-60.
21. Calvert M, Blazeby J, Altman DG, et al. Reporting of patient-reported outcomes in randomized trials: the CONSORT PRO extension. JAMA 2013;309:814-22.
22. Weingärtner V, Dargatz N, Weber C, et al. Patient reported outcomes in randomized controlled cancer trials in advanced disease: a structured literature review. Expert Rev Clin Pharmacol 2016;9:821-9.
23. Cherny NI, Sullivan R, Dafni U, et al. A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be anticipated from anti-cancer therapies: the European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2017;28:2901-5.
24. Cherny NI. An appraisal of FDA approvals for adult solid tumours in 2017-2021: has the eagle landed? Nat Rev Clin Oncol 2022;19:486-92.
25. Gaertner J, Weingärtner V, Lange S, et al. The Role of End-of-Life Issues in the Design and Reporting of Cancer Clinical Trials: A Structured Literature Review. PLoS One 2015;10:e0136640.
26. Skåre TS, Midtbust MH, Lund JÅ, et al. Barriers and Facilitators When Implementing Electronic Patient-Reported Outcome Measures at a Municipal Cancer Care Unit: A Qualitative Study. Cancer Nurs. 2022. [Epub ahead of print]. doi: 10.1097/NCC.0000000000001120.
27. Nguyen H, Butow P, Dhillon H, et al. A review of the barriers to using Patient-Reported Outcomes (PROs) and Patient-Reported Outcome Measures (PROMs) in routine cancer care. J Med Radiat Sci 2021;68:186-95.
28. Jairam V, Yu JB, Aneja S, et al. Differences in Funding Sources of Phase III Oncology Clinical Trials by Treatment Modality and Cancer Type. Am J Clin Oncol 2017;40:312-7.
29. Giacalone NJ, Milani N, Rawal B, et al. Funding Support and Principal Investigator Leadership of Oncology Clinical Trials Using Radiation Therapy. Int J Radiat Oncol Biol Phys 2018;102:34-43.
30. U.S. Food & Drug Administration. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Accessed February 1, 2023. Available online: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics
31. Walia A, Haslam A, Prasad V. FDA validation of surrogate endpoints in oncology: 2005-2022. J Cancer Policy 2022;34:100364.

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