Supplemental Online Content

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(9):e2231930. doi:10.1001/jamanetworkopen.2022.31930

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This supplemental material has been provided by the authors to give readers additional information about their work.
The databases Pubmed/Medline, EMBASE, Cochrane Library, and “ClinicalTrials.gov” were searched. Screening was performed independently by two authors. Included records that belonged to the same trial were merged and counted as one study. Abbreviations: NIH, National Institutes of Health, PRO, patient-reported outcome.
Logistic regression analysis of the use of a patient-reported endpoint (1 = yes, 0 = no) as dependent variable and year of publication as independent variable. Panel A shows the use of PRO as primary endpoint in randomized trials clearly stating their endpoint (n = 64). Panel B shows the use of PRO as secondary endpoint in all randomized trials (n = 100). Panel C shows the use of PRO as primary endpoint in non-randomized trials clearly stating their endpoint (n = 81). Panel D shows the use of PRO as secondary endpoint in all non-randomized trials (n = 125). Grey bullets represent data points. Gray shading around each line represents the respective 95% confidence interval. A p-value < .05 was considered statistically significant. Abbreviations: PRO, patient-reported outcome; EP, endpoint.
eFigure 3. Treated Sites in Published Trials of Palliative Radiotherapy Including Patient-Reported Outcomes as Primary (n=45) or Secondary End Points (n=71)

Abbreviation: CNS, central nervous system; PRO, patient-reported outcome
etTable 1. Summary Parameters of the Multiple Regression Models

| Model Summary         | Model „extension adherence score“ | Model „total CONSROT PRO adherence score“ |
|-----------------------|----------------------------------|------------------------------------------|
| Number of observations| 108                              | 108                                      |
| F(6,101)              | 6.660                            | 9.669                                    |
| Prob > F              | <0.001                           | <0.001                                   |
| R-squared             | 0.283                            | 0.365                                    |
| Adj. R-squared        | 0.241                            | 0.328                                    |
| Durbin-Watson-Stat.   | 1.946                            | 1.966                                    |
| Variable entry        | Simultaneous entry of prespecified variables<sup>a</sup> |                                          |

<sup>a</sup>the independent variable “trial phase” was not used due to low case numbers and potential collinearity to the included independent variable “randomization”
**eTable 2. Factors Associated With the Degree of Patient-Reported Outcome Reporting in Trials of Palliative Radiotherapy**

“Extension adherence score” and “total CONSORT-PRO adherence score” are dependent variable and trial characteristics are independent variables in two separate multiple regression models. In this models, the variable “year of publication” was modified to “date of publication > 2013” which represents the publication date of the CONSORT-PRO extension.

| Independent variables                     | Dependent variable: “extension adherence score” | Dependent variable: “total CONSORT-PRO adherence score” |
|-------------------------------------------|--------------------------------------------------|--------------------------------------------------------|
| (Constant)                                | B       | Lower 95% CI | Upper 95% CI | p       | B       | Lower 95% CI | Upper 95% CI | p       |
| Date of publication > 2013 (Yes)          | 2.022   | -5.688       | 9.733        | 0.604   | 3.393   | -2.890       | 10.767       | 0.255   |
| PRO as primary endpoint (Yes)             | 9.381   | 1.819        | 16.942       | **0.016** | 12.342  | 5.646        | 19.038       | <.001   |
| Randomization                             | -0.415  | -7.743       | 8.573        | 0.920   | -1.158  | -8.383       | 6.067        | 0.751   |
| Multicenter (Yes)                         | 7.514   | -0.425       | 15.453       | 0.320   | 7.290   | 0.259        | 14.321       | **0.042** |
| Modality of radiotherapy (BT)             | 17.077  | 6.091        | 28.063       | **0.003** | 14.511  | 4.782        | 24.240       | **0.004** |
| Patient number                            | 0.028   | 0.007        | 0.050        | **0.010** | 0.033   | 0.012        | 0.050        | **0.002** |

Abbreviations: B, regression coefficient; BT, Brachytherapy CI confidence interval

**eTable 3. Summary Parameters of the Multiple Regression Models**

| Model Summary                      | Model „extension adherence score“ | Model „total CONSORT-PRO adherence score“ |
|------------------------------------|----------------------------------|-------------------------------------------|
| Number of observations             | 108                              | 108                                       |
| F(6,101)                           | 6.713                            | 9.626                                     |
| Prob > F                           | <0.001                           | <0.001                                    |
| R-squared                          | 0.285                            | 0.364                                     |
| Adj. R-squared                     | 0.243                            | 0.326                                     |
| Durbin-Watson-Stat.                | 2.180                            | 2.273                                     |
| Variable entry                     | Simultaneous entry               |                                           |

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### eTable 4. Characteristics of Ongoing Trials Registered on ClinicalTrials.gov With Patient-Reported Outcomes as End Points

Percentages may not add up to 100% (35 registrations) due to rounding error, missing information in registered studies, or multiple values per study.

|                                | Ongoing registered trials with PRO (n=35) |
|--------------------------------|-----------------------------------------|
|                                | % (No.)                                 |
| **Study design**               |                                         |
| Multicenter                    | 49 (17)                                 |
| **Phase**                      |                                         |
| I                              | 4 (9)                                   |
| I/II                           | 9 (3)                                   |
| II                             | 31 (11)                                 |
| III                            | 20 (7)                                  |
| Exploratory                    | 9 (3)                                   |
| Not stated                     | 31 (11)                                 |
| **Randomized**                 | 54 (19)                                 |
| **Funding by industry**        | 14 (5)                                  |
| **Location**                   |                                         |
| N-America                      | 51 (18)                                 |
| Europe                         | 29 (10)                                 |
| Asia                           | 14 (5)                                  |
| Oceania                        | 3 (1)                                   |
| Multiple                       | 3 (1)                                   |
| **Radiotherapy**               |                                         |
| Modality                       |                                         |
| EBRT                           | 74 (26)                                 |
| SRS/SBRT                       | 17 (6)                                  |
| Other                          | 6 (2)                                   |
| EBRT with BT                   | 3 (1)                                   |
| BT                             | -                                       |
| Conc. systemic Th.             | 17 (6)                                  |
| Immunoth. <sup>a</sup>         | 9 (3)                                   |
| Targeted Th. <sup>a</sup>      | 6 (2)                                   |
| Chemotherapy                   | 3 (1)                                   |

<sup>a</sup>Includes combination with chemotherapy

Abbreviations: BT, brachytherapy; conc., concurrent; EBRT, external beam radiotherapy; PRO, patient-reported outcome; SRS/SBRT, radiosurgery/stereotactic body radiotherapy
eFigure 4. Treated Sites in Ongoing, Registered Trials of Palliative Radiotherapy Including Patient-Reported Outcomes

| Site                      | Frequency (%) |
|---------------------------|---------------|
| Metastasis                | 37            |
| Thoracic                  | 20            |
| Abdominal                 | 14            |
| Pelvic                    | 9             |
| Head/Neck                | 6             |
| Visceral                  | 6             |
| Hematologic/Lymphatic     | 3             |
| Cutaneous                 | 3             |
| Pediatric                 | 3             |

Abbreviation: CNS, central nervous system
Clinical endpoints and patient-reported outcomes in trials of palliative radiotherapy: protocol of a systematic meta-research analysis

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Registration
This study will be registered in the “Open Science Framework” (www.osf.io) of the “Center for Open Science”.

Author contribution
AF, JD and DK wrote the protocol. AF, JDo, OW, DK, CS, and JDu will be engaged in screening the eligible literature, data extraction and analysis, and drafting a manuscript. Statistical support by S. Freitag-Wolf, statistician, is acknowledged.

Financial Support
Financial support by an unrestricted grant from the non-commercial, academic “Kiel Oncology Network” is acknowledged.
Amendments

Amendments from v1 (27.Feb.2021) to v2 (11.May.2021) are highlighted in yellow. The amendments were introduced at “title/abstract screening” stage.

The amendment from v2 (11.May.2021) to v3 (23.June.2021) is highlighted in green. The amendment was introduced at “full text screening” stage prior to data extraction.
1. Introduction

1.1. Rationale

Palliative radiotherapy is frequently employed in patients suffering from advanced cancers in order to alleviate symptoms and improve health-related quality of life [1] (definition of relevant terms displayed in appendix 1). Multiple prospective studies on palliative radiotherapy have been published in the last decades. Clinical endpoints of prospective clinical trials include “patient-centered clinical endpoints” (overall survival, health-related quality of life, self-reported symptom burden) or “tumor-centered clinical endpoints” (e.g. progression-free survival, local control, radiographic response rate) [2][3]. As most patients face a limited prognosis in terms of survival, the employment of “patient-centered clinical endpoints” in trials of palliative radiotherapy is desirable. Specifically, the impact of palliative radiotherapy on health-related quality of life and symptom burden is paramount as it is for any other palliative care intervention [4]. Health-related quality of life and symptom burden should be measured by patient-reported outcomes (PRO) and in a standardized manner by validated patient-reported outcome measures (PROM) [5].

Palliative radiotherapy is used in various settings including the treatment of patients with symptomatic metastases (e.g. bone or brain metastases) or symptomatic incurable primary cancers (e.g. head and neck cancer or lung cancer). Early guidelines on trials for palliative radiotherapy of bone metastases have fostered the use of “patient-centered clinical endpoints” including patient-reported outcomes in this scenario [6]. In other scenarios, however, “patient-centered clinical endpoints”, namely patient-reported outcomes, seem to have been employed less frequently and systematically as demonstrated by our group for studies of palliative radiotherapy for incurable head and neck cancers (Fabian et al. 2020, manuscript submitted).

To date, we lack a systematic overview of the distribution of endpoints employed in clinical trials of palliative radiotherapy across tumor entities. A broader knowledge on the distribution of endpoints chosen in these trials will establish a status quo, help to identify potential gaps concerning “patient-centered clinical endpoints”, and foster future patient-centered research.

1.2. Objectives

The primary objective is to determine the distribution of endpoints chosen in prospective trials of palliative radiotherapy. For this purpose, the rate of studies that employed a “patient-centered clinical endpoint” vs. a “tumor-centered clinical endpoint” as primary endpoint will be analyzed.
Furthermore, the distribution of specific primary and secondary endpoint categories (e.g. overall survival) will be assessed. The distribution of patient-reported outcomes will be highlighted. These rates and distributions will be assessed in the context of prespecified independent variables, for example study design or year of publication (see 2.6 statistical analysis plan).

A co-primary objective is to determine the methodological quality of patient-reported outcome employment in respective studies per CONSORT-PRO reporting guideline [7]. The CONSORT-PRO scores will be assessed in the context of prespecified independent variables, for example study design or year of publication.

The secondary objective is to investigate the distribution of endpoints in ongoing studies per “ClinicalTrials.gov”.

2. Methods
This prospectively planned analysis focusses on patterns in research itself rather than on effect sizes of outcomes in individual studies. Therefore, we perceive this analysis as “meta-research” [8]. Nevertheless, a systematic literature review is the basis of this analysis and the “preferred reporting items for systematic reviews and meta-analysis (PRISMA)” reporting guidelines are followed closely where appropriate [9,10].

2.1.1 Eligibility criteria
The eligibility criteria define studies suitable for final assessment and data extraction according to this study’s objectives.
Inclusion criteria:
- Palliative radiotherapy (including external beam radiotherapy or brachytherapy) as integral part of the study or control treatment
- Cancer patients in a palliative treatment setting
- Clinical trial (per NIH definition [11])
- Trial includes at least one clinical endpoint
Exclusion criteria:

- Oligometastatic treatment setting if single-arm trial of locally curative/ablative therapy
- Treatment with curative intent
- Supportive medication (e.g. anti-emetics during radiotherapy) or validation of outcome assessment tools as focus of the study
- Abstract format only (e.g. conference talk or poster)
- Publication language other than English

2.1.2 Comments on eligibility criteria

The terms “palliative” and/or “incurable”, as required for a study’s inclusion, need to be stated and/or defined by the respective study authors.

In case the study population consists of patients with oligometastatic disease (as defined by the respective study authors) the study will only be included for analysis if palliative radiotherapy with non- ablative dosage serves as a control arm. For example, if a study tests stereotactic body radiotherapy compared to palliative radiotherapy in a two-arm trial, this study will be included in case the other eligibility criteria are met. Conversely, if a study consists of a single-arm trial of patients with oligometastatic disease planned to undergo stereotactic body radiotherapy as ablative treatment modality, this study will not be included.

Systemic therapy given concurrently to a palliative radiotherapy regimen, as defined by the authors, is no reason for exclusion.

This paragraph is to further explain the context of eligibility without introducing any change concerning eligibility criteria. The NIH-definition of a “clinical trial” will be strictly applied in the context of palliative radiotherapy. This means that palliative radiotherapy (“palliative” as defined by the respective author) will be considered as the intervention in the context of the NIH-definition. The NIH-definition as applied in this analysis is based on four key questions: [11]

1. Does the study involve human participants?
2. Are the participants prospectively assigned to an intervention?
3. Is the study designed to evaluate the effect of the intervention on the participants?
4. Is the effect being evaluated a health-related biomedical or behavioral outcome?

For example, if a study mentions palliative radiotherapy as optional in a “standard of care” control arm while the experimental arm investigates a different intervention (e.g. ablative SBRT),
this study will not be included. Furthermore, observational studies will be largely excluded by this definition as they usually not prospectively assign a patient to an intervention.

2.2. Information sources and search strategy
Sources to screen for eligible studies from 1990 to and including 2020 are PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL). The reason for the limitation in time is to focus on more recent and therefore more relevant changes in the choice of endpoints and employment of PROs by trials. Furthermore, PROs were less established before that period. The search strategy is presented in “appendix 2”. Duplicates will be removed. Furthermore, the trial register “ClinicalTrials.gov” will be screened for ongoing trials (“Recruiting”, “Not yet recruiting”, “active, not recruiting”, “suspended”, “enrolling by invitation”). The search will be conducted by a professional librarian.

2.3. Study records
Search results of the different databases will be merged by a librarian and uploaded to “Covidence”. The software “Covidence” will be employed to manage records. First, at least two authors will independently screen studies based on title and abstract for potential inclusion eligibility. Second, full text will be retrieved. Third, at least two authors will independently judge eligibility based on full text. In case of divergent interpretations concerning eligibility, consensus will be reached by discussion with other co-authors.

2.4. Data extraction, outcomes and prioritization
Data from studies will be extracted based on full text publication. Data collection forms will be pilot-tested for usability and completeness. For this purpose, two authors will independently extract data into prespecified data collection forms of 15 eligible articles. In case of sufficient inter-rater concordance, data extraction of the remaining articles will be continued separately by the authors due to the expected amount of eligible studies and data to extract. At least two authors will independently extract data into prespecified data collection forms. Discrepancies will be resolved by discussion among co-authors. Endpoints will be assessed per study in case of multiple publications. For example, if there is a publication on efficacy and a separate publication of the same study on quality of life, this will be regarded as one “study”.

Protocol v3, 23.June.2021
The first form will serve to collect general data as well as endpoints of included studies (variables displayed in appendix 3). In case of multiple co-primary endpoints, all endpoints will be counted as primary endpoints. All endpoints will be defined as secondary endpoints if no clear primary endpoint is defined in the reflective study. The endpoints will be counted per category (patient-centered vs. tumor-centered) and subcategory (e.g. overall survival, health-related quality of life, progression-free survival etc.) as stated in each individual included study (for definitions see appendix 1, for variables see appendix 5).

The second form will be used for studies that employed patient-reported outcomes as an endpoint. The quality level of PRO employment in individual studies will be assessed per CONSORT-PRO reporting guideline as surrogate [7]. Although the CONSORT-PRO guideline is dedicated to randomized trials, its items are equally important for non-randomized trials. This was confirmed by peer review prior to registration of this protocol. There are no dedicated PRO-reporting guidelines for non-randomized studies.

A third form will be used for endpoints in ongoing trials per “ClinicalTrials.gov”.

2.5 Evaluation and statistical analysis plan
Descriptive statistics and testing will be used as appropriate including percentages and means or medians and quartiles.

2.5.1 Primary objective
Independent variables and subgroups for the comparison of trials using “patient-centered clinical endpoints” vs. “tumor-centered clinical endpoints” as primary endpoint include:

- Study design (dedicated phase I vs. II vs III, randomized vs. non-randomized, multi- vs. mono-center)
- Tumor entity (per specific entities, bone metastases vs. other (due to published guidelines for radiotherapy trials of bone metastases)),
- Modality of radiotherapy (external beam radiotherapy vs. brachytherapy)
- Sample size (Number of patients per study)
- Year of publication
The same independent variables will be considered for display of the distribution of specific endpoints (e.g. overall survival) per primary or secondary endpoint.

2.5.2 Co-primary objective

The quality level of PRO employment in individual studies will be assessed per CONSORT-PRO reporting guideline as surrogate [7]. Although the CONSORT-PRO guideline is dedicated to randomized trials, its items are equally important for non-randomized trials. This was confirmed by peer review prior to registration of this protocol. There are no dedicated PRO-reporting guidelines for non-randomized studies.

Our study adopts without changes a previously described scoring system for the CONSORT-PRO guideline [12]. Accordingly, values for the “CONSORT-PRO score” (max. score = 7 points) and for the “total CONSORT-PRO score” (max score = 14 or 15 points, respectively if PRO secondary or primary endpoint) will be evaluated per study. In case a study employs multiple different PROMs, the overall highest score per CONSORT-PRO item will be used to calculate the summary score. Summary scores will be expressed as percentages of adhered CONSORT-PRO items.

Independent variables for CONSORT-PRO scores for comparisons will include:
- Endpoints status of PRO (primary vs. secondary endpoint)
- Study design (randomized vs. non-randomized, dedicated phase I vs II vs III, multi- vs. mono-center)
- Sample size (Number of patients per study)
- Modality of radiotherapy (external beam radiotherapy vs. brachytherapy)
- Year of publications

Adherence frequencies to each individual item of the CONSORT-PRO guideline will be displayed in percentages per endpoint status of PRO (primary vs. secondary endpoint). Adherence rates will be categorized in poor (≤ 49%), moderate (50-79%), or good (≥ 80%) as described previously [12].
2.5.3 Secondary objective

The assessment of endpoint distribution in ongoing trials per “clinicalTrials.gov” will be performed on an exploratory basis using descriptive statistics.

3. Abbreviations

PRO, patient-reported outcome; PROM, patient-reported outcome measure

4. References

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5. Appendices

5.1 Definition of relevant terms

| Term                              | Definition[13]                                                                                                                                 |
|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Clinical endpoint                 | A characteristic or variable that reflects how a patient feels, functions, or survives. [14]                                                    |
| Clinical trial                    | A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes. [11] |
| Health-related quality of life    | A multidimensional concept that usually includes self-report of the way in which physical, emotional, social, or other domains of well-being are affected by a disease or its treatment. [13] |
| Patient-reported outcome (PRO)    | An outcome reported directly by patients themselves and not interpreted by an observer; PROs may include patient assessments of health status, quality of life, or symptoms. [13] |
| Patient-centered endpoint         | Clinically meaningful endpoint. Including: overall survival, patient-reported outcome for health-related quality of life or symptom burden. [2,3] |
| Patient-reported outcome measure (PROM) | Instrument to measure PROs (e.g. multi-item questionnaires)                                                                                     |
| Primary outcome/end point         | The most important outcome in a trial, providing the most clinically relevant evidence directly related to the primary objective of the trial. [13] |
| Secondary outcome/end point       | Outcomes prespecified in the protocol to assess additional effects of the intervention. [13] All endpoints if no primary endpoint is defined (see 2.4) |
| Tumor-centered endpoints          | (Surrogate) Endpoint that result (in part) of radiographical, biochemical, or clinical tumor activity and aim to substitute or complement patient-centered endpoints. [2,3] Including but not limited to: progression-free |
survival, disease-free survival, recurrence-free survival, event-free survival, failure-free survival, local control/recurrence, radiographic/clinical (other than patient-reported)/biochemical tumor response rate, remission rate, time to new treatment.

| PICOS    | Layer | Search string (exemplified for PubMed/Medline)                                                                                                                                                                                                 |
|----------|-------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Population | #1    | Palliative care[MeSH] OR Terminally Ill[Mesh] OR palliat*[title/abstract] OR incurable*[title/abstract]                                                                                                                                    |
| Intervention | #2   | radiotherapy[MeSH] OR radiotherapy[title/abstract] OR “radiation therapy” [title/abstract] OR radiotherap*[title/abstract] OR radiation[title/abstract] OR irradiat*[title/abstract] OR brachytherapy[title/abstract] OR chemoradiotherap*[title/abstract] OR radiochemotherap*[title/abstract] OR chemoradiat*[title/abstract] |
| Comparator | not applicable |
| Outcome   | not specified |
| Study type | #3    | prospective study [MeSH] OR clinical study[publication type] OR clinical trial[publication type] OR prospective*[tw] OR trial[title/abstract] OR phase[title/abstract]                                                            |
|           | #4    | #1 AND #2 AND #3                                                                                                                                                                                                                      |

5.2 Search strategy

5.3 Variables included in data extraction form 1 – “included studies”

| Category      | Variables                                                                                                                                                                                                 |
|---------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| General       | first author, year, location                                                                                                                                                                               |
| Study design  | phase, arms, randomization, specific indication, specific radiotherapy regimen, number of centers, concurrent antineoplastic systemic per protocol, control arm of oligo-metastatic cancer study, patient number, age, performance status, study sponsor (“industry” if at least one sponsor from industry; otherwise “academic”) cancer entity |
| Endpoint category | primary, secondary                                                                                                                                                                                        |
| Endpoint type | overall survival, health related quality of life per patient reported outcomes, symptom control per patient reported outcomes (including symptomatic response)                                             |
| Category                  | Variables                                                                                           |
|--------------------------|-----------------------------------------------------------------------------------------------------|
| General                  | first author, year                                                                                  |
| Study design             | randomization, CONSORT-PRO cited, name of PROM, number of PROMs                                     |
| CONSORT-PRO checklist    | scoring as described in [12]                                                                          |

### 5.4 Variables included in data extraction form 2 – “CONSORT-PRO”

| Category                  | Variables                                                                                           |
|--------------------------|-----------------------------------------------------------------------------------------------------|
| General                  | study identifier, location, tumor entity, start date, status, planned patient number, actual patient number, study design |
| Endpoint category        | primary, secondary                                                                                  |
| Endpoint type            | overall survival, health related quality of life per patient reported outcomes, symptom control per patient reported outcomes (including symptomatic response rate), progression free survival, disease-free survival, recurrence-free survival, local control, toxicity, objective response rate, radiographic response rate, biochemical response rate, toxicity, change in performance status, feasibility, other |

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eAppendix 2. References of Included Published Trials of Palliative Radiotherapy and Trial Registrations

The reference list of published trials includes trials with multiple publications which were merged to one record. Therefore, it exceeds the number indicated in the PRISMA flow chart.

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