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CRITICAL REVIEW

Patient-Reported Outcomes Following Magnetic Resonance-Guided Radiation Therapy for Prostate Cancer: A Systematic Review and Meta-Analysis

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Purpose: This systematic review provides an overview of literature on the impact of magnetic resonance–guided radiation therapy (MRgRT) on patient-reported outcomes (PROs) in patients with prostate cancer (PC).

Methods and Materials: A systematic search was performed in October 2023 in PubMed, EMBASE, and Cochrane Library. The Patient, Intervention, Comparison, Outcomes, and Study design (PICOS) framework was used to determine eligibility criteria. Included were studies assessing PROs following MRgRT for PC with a sample size >10. Methodological quality was assessed using the Cochrane's Risk of Bias in Nonrandomized Studies - of Interventions and Cochrane's risk of bias tool for randomized trials. Relevant mean differences (MDs) compared with pre-RT were interpreted using minimal important differences. Meta-analyses were performed using random-effects models. Between-study heterogeneity was assessed using the I^2 statistic.

Results: Eleven observational studies and 1 randomized controlled trial (n = 897) were included. Nine studies included patients with primary PC with MRgRT as first-line treatment (n = 813) and 3 with MRgRT as second-line treatment (n = 84). Substantial risk of bias was found in 5 studies. European Organization for Research and Treatment Quality of Life Questionnaire (EORTC QLQ) core 30 (C30) and EORTC QLQ prostate cancer module (PR25) scores were pooled from 3 studies, and

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Expanded Prostate Cancer Index Composite (EPIC)-26 scores were pooled from 4 studies. Relevant MDs for the urinary domain were found with the EPIC-26 (MD, −10.0; 95% CI, −12.0 to −8.1; $I^2 = 0\%$) and the EORTC QLQ-PR25 (MD, 8.6; 95% CI, −4.7 to 22.0; $I^2 = 97\%$), both at end-RT to 1-month follow-up. Relevant MDs for the bowel domain were found with the EPIC-26 (MD, −4.7; 95% CI, −9.2 to −0.2; $I^2 = 82\%$) at end-RT or 1-month follow-up, but not with the EORTC QLQ-PR25. For both domains, no relevant MDs were found after 3 months of follow-up. No relevant MDs were found in the general quality of life domains of the EORTC QLQ C30.

Conclusions: MRgRT for PC results in a temporary worsening of patient-reported urinary and bowel symptoms during the first month after treatment compared with pre-RT, resolving at 3 months. No clinically relevant changes were found for general quality of life domains. These results provide important information for patient counseling and can serve as a benchmark for future studies. © 2024 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Introduction

Patient-reported outcomes (PROs) are essential for the evaluation of new cancer treatments because they contribute substantially to our understanding of the impact of new cancer treatments on patients' health and well-being.[1,2] PROs offer valuable insights into treatment effectiveness and potential side effects that are not apparent through traditional clinical measures alone. Moreover, PROs play an important role in cost-effectiveness and cost-benefit studies, in which the added costs are compared with the incremental health benefits.

Hybrid magnetic resonance–guided radiation therapy (MRgRT) systems are able to acquire high-quality magnetic resonance (MR) images while simultaneously delivering radiation therapy (RT).[3,4] MRgRT allows for the application of online adaptive RT and gating strategies to improve accuracy. The improved accuracy of MRgRT enables safe reduction of treatment margins, potentially reducing toxicity and improving quality of life (QoL).

The MRI-Guided Stereotactic Body Radiotherapy for Prostate Cancer (MIRAGE) trial investigated the reduction of 4-mm margins with a conventional computed tomography–guided RT (CTgRT) to 2-mm margins with MRgRT in the treatment of patients with localized prostate cancer. A significant reduction in genitourinary and gastrointestinal toxicity and a significant reduction in patient-reported bowel symptoms were found.[5] Interestingly, patient-reported irritative and obstructive urinary symptoms did not significantly change. However, the trial was not powered to find a statistically significant effect on PROs. Also, in interim analysis, the sample size was reduced because a clear benefit was shown for the intervention arm. An overview of all available studies with a larger sample size conducted in various countries and institutes might give a better understanding of the impact of MRgRT on PROs for this patient group.

The aim of this systematic review and meta-analysis was to provide a comprehensive overview of the current literature on PROs after MRgRT for patients with prostate cancer. Hereby, we provide a benchmark for evaluating the effects of novel MRgRT treatment strategies (eg, dose-escalation, additional boosting, or ultrahypofractionation) in this specific context.

Methods and Materials

This review was registered in the International Prospective Register of Systematic Reviews database of the National Institute for Health Research (CRD42021255457). The Preferred Reporting Items for Systematic Review and Meta-Analysis were followed.[6]

Search strategy

PubMed, EMBASE, and Cochrane Libraries were systematically searched for all available records published until October 12, 2023. The search strategy included keywords, synonyms, and Medical Subject Heading (MeSH) terms related to "MRgRT," "cancer," and "PROs" (Table E1). After deduplication, titles and abstracts and, subsequently, full-texts of original articles were screened independently by 2 reviewers (JW and LD or TL). In case of conflict on eligibility, consensus was achieved through discussion. References of included articles were checked for potentially relevant publications that were missed in the initial search. In case of multiple eligible publications describing identical PRO measures (PROMs) in overlapping patient cohorts, the article providing the most extensive follow-up data on PROs was included.

Study selection

Studies were considered eligible if (1) the study reported on patients with prostate cancer who received MRgRT on a hybrid system, irrespective of disease stage; (2) the study

Table 1 Patients, Intervention, Comparison, Outcome, Study design (PICOS) table

Patients	Adult men with prostate cancer
Intervention	Magnetic resonance–guided radiotherapy
Comparison	Any
Outcome	Patient-reported outcomes
Study design	Any

population consisted of more than 10 patients; and (3) outcomes included PROs. The Patient, Intervention, Comparison, Outcomes, and Study design (PICOS) framework was used to determine eligibility criteria (Table 1).[7] Apart from case reports, all study designs were considered eligible. Conference abstracts were excluded. Language was restricted to English.

Quality assessment

Cochrane's Risk of Bias in Nonrandomized Studies - of Interventions tool was used to assess the quality of included nonrandomized studies.[8] Cochrane's risk of bias tool for randomized trials was used for randomized studies.[9] Overall risk of bias was scored as the highest judgment in any bias domain. The classification of a particular score per domain was predefined and can be found in Table E2. In short, the risk of bias due to missing data was scored as serious when 30% to 50% of PROs was missing on a particular point in time and critical when >50% was missing. The risk of bias in selection of the reported results was scored as serious when PROs were reported in subgroups of the entire patient cohort only or if only a selection of PROM domains was presented. Risk of bias assessment was used to put study findings into perspective, not to exclude studies based on risk of bias.

Data collection and analysis

Items extracted from the included studies were study characteristics (sample size, study design, country, enrollment period, PROM used, timing of assessment during follow-up, rate of completed questionnaires of initial sample size, statistical analysis, and outcome estimate for interpretation of changes in PRO scores over time), patient characteristics (study population and age), and treatment characteristics (type of RT system, dose and fractionation, treatment margins, treatment strategies including adaptation workflow and motion management, and concurrent therapy). Outcomes of interest were changes in PRO scores measured with a validated PROM at different time points within the first year after MRgRT compared with pre-RT scores. Changes in PRO scores were presented as in the original study, and the mean difference (MD) was calculated when not presented. MDs were considered clinically relevant when they were larger than minimal important differences (MIDs) selected from literature, irrespective of statistical significance.[10-15] The hormonal domain was excluded from this review because this domain assesses symptoms mainly determined by the use of androgen deprivation therapy (ADT) and does not show the impact of MRgRT. A meta-analysis was considered appropriate when 3 or more studies with a homogeneous patient population assessed the same PROM within a month or less apart. MDs between pre-RT and scores at each moment of follow-up were pooled for each domain of a particular PROM separately. A meta-analysis was performed with a random-effects model with the inverse variance method using ReviewManager (RevMan) version 5.3. Heterogeneity within the meta-analysis was assessed using the I^2 statistic. An I^2 of 0% to 35% was defined as insignificant heterogeneity, 35% to 55% as low heterogeneity, 55% to 80% as moderate heterogeneity, and 80% to 100% as high heterogeneity.[16]

Results

The systematic search resulted in 12 studies eligible for inclusion (Fig. 1).[5,17-27]

Quality assessment

The overall risk of bias varied (Table E3) and was considered critical in 5 studies.[21,22,24-26] This was mainly due to concerns regarding participant selection, missing data, and selection of the reported results. Although PROs were collected prospectively, participant selection was retrospective in 5 studies.[17,21,22,24,27] The risk of bias due to missing data was considered serious or critical in 4 studies.[21,22,24,25] The risk of bias due to selection of the reported result was critical in 1 study because PRO results were presented in undefined categories.[26]

Study characteristics

Included studies were 1 randomized controlled trial (RCT) and 11 prospective observational cohort studies (Table 2). In total, 9 different PROMs were used.[14,28-35] The rate of completed questionnaires at a time point varied between 17% and 100% (Table E4). Methods used to establish a relevant difference in PRO scores over time were statistically significant changes ($p < .05$), effect size, MID, and categorization of scores.

Patient and treatment details

Of 12 studies focusing on patients with prostate cancer, 9 studies reported on treatment of primary prostate cancer (Table 2).[5,17,18,21-25,27] Three studies included patients with previous treatment: 1 after previous RT and 2 after prostatectomy.[19,20,26] Of those 3, 2 studies included patients with biochemical recurrences,[20,26] and 1 study additionally included patients with unfavorable pathologic features after prostatectomy.[19] Seven studies included only patients with localized prostate cancer, of whom the majority of patients had intermediate-risk disease (37%-97%). Two studies also included patients with low-volume metastatic prostate cancer.[17,18] Use of ADT varied between 6% and 83%. The delivered radiation dose to primary prostate cancer varied between 35 and 40 Gy in 5 to 20 fractions. Four studies integrated a boost to the intraprostatic dominant lesion (IDL).

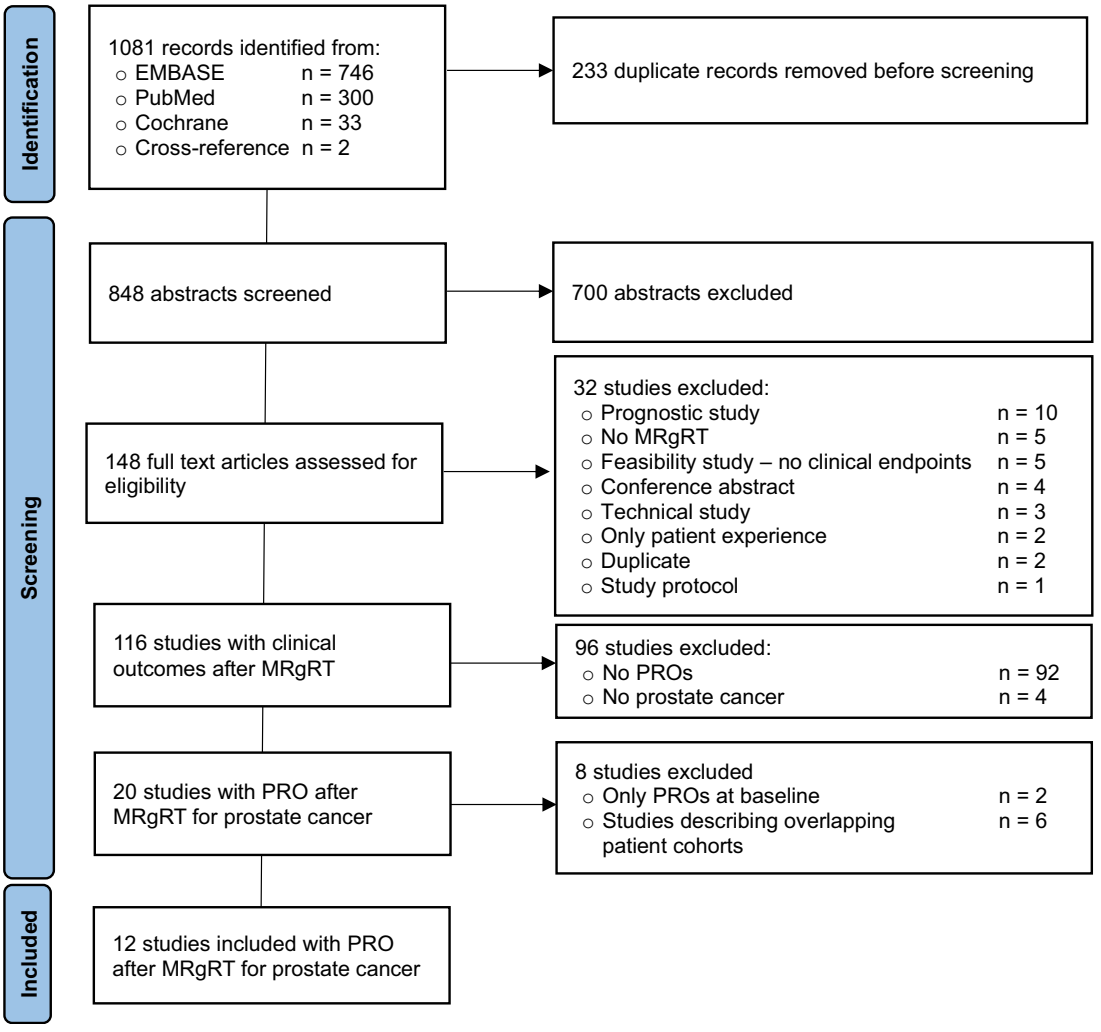

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis diagram. *Abbreviations*: MRgRT = magnetic resonance–guided radiation therapy; PROM = patient-reported outcome measure.

Recurrent prostate cancer was treated with doses ranging from 27.5 to 73 Gy in 5 to 35 fractions.

PROs

General PROMs

Three studies presented European Organization for Research and Treatment Quality of Life Questionnaire core 30 (EORTC QLQ-C30) domains (Fig. 2).[17,23,25] One study found a decline in social functioning and an increase in pain and diarrhea at end-RT (Table E5).[23] Moreover, this study showed worsening of fatigue at the end of RT, 6 weeks after treatment, and 6 months after treatment. One study reported worsening of insomnia at end-RT and an improvement of social function at 2, 5, and 8 months of follow-up.[17]

Prostate-specific PROMs

Three studies used the EORTC QLQ prostate cancer module (PR25) questionnaire[17,23,25]; 5 studies used the Expanded Prostate Cancer Index Composite (EPIC)-26 questionnaire[5,17-19,24]; 1 study used the EPIC-50 questionnaire[21]; 2 studies used the International Consultation on Incontinence Questionnaire (ICIQ)[17,26]; 8 studies used the International Prostate Symptom Score (IPSS) questionnaire[5,17,19,20,22,23,26,27]; and 1 study used the International Index of Erectile Function (IIEF)-5 questionnaire (Tables E6-E8).[17]

Urinary domain

For patients with primary prostate cancer, 6 of 6 studies found a relevant worsening in the urinary domain at end-RT or 1 month of follow-up (Table E6).[5,17,18,21,23,24] At 2 to 3 months' follow-up, 1 of 5 studies reported relevant worsening.[23] At 5 to 6 months' follow-up, 1 of 5 studies reported relevant worsening,[22] and 1 study reported relevant improvement.[18] At 10 to 12 months of follow-up, 1 of 4 studies reported a relevant improvement.[21] Of patients with MRgRT as second-line of treatment, 1 of 3 studies showed an increase in proportion of moderate symptoms at end-RT to 1 month of follow-up.[26]

Table 2 Study, patient, and treatment characteristics

Author, year	n	Study design*	Country	Enrollment	PROM	Timing PROMs during FU	Study population, n (%)	Risk category (of localized), n (%)†			Age (y), median (IQR)‡	ADT, n (%)	RT system	Dose (Gy/fractions)	Margins (mm)
								High risk	IM risk	Low risk					
Alongi et al,[17] 2022	100	Single-center	Italy	2019-2020	IPSS,[14] EORTC-QLQ-C30,[28] EORTC-QLQ-PR25,[29] EPIC-26,[32] ICIQ-SF,[30] IIEF-5[31]	End-RT, 2 mo, 5 mo, 8 mo	96 (96) Localized, 4 (4) low-volume metastatic	2 (2)	60 (60)	34 (34)	71 (52-84)	32 (32)	Unity	35/5 (55%), 36.25/5 (45%)	5 + dorsal 3§
Kishan et al,[5] 2023	79	RCT, Single-center	United States	2020-2021	EPIC-26,[32] IPSS[14]	1 mo, 3 mo	74 (94) Localized, 5 (6) N + disease	20 (27)	54 (73)		71 (68-75)	49 (62)	MRIdian	40/5, SIB IDL boost 42 (n = 19, 24%)	2§
Leeman et al,[18] 2022	22	Single-center	United States	2020-2021	EPIC-26,[32] PROMIS[33]	End-RT, 3 mo	13 (59) Localized, 9 (41) low-volume metastatic	2 (9)	9 (41)	2 (9)	70 (50-85)	8 (62)	MRIdian	36.25/5	3§
Ma et al,[19] 2022	31	Multicenter	United States	2018-2021	EPIC-26,[32] IPSS[14]	1 mo, 3 mo, 6 mo	Postprostatectomy‖				68 (50-82)	16 (52)	MRIdian	30-34 on the prostate bed, optional SIB to 40, 25 on nodes/5	3
Michalet et al,[20] 2022	37	Single-center	France	2019-2020	IPSS[14]	6 mo, 12 mo	Biochemical recurrence after previous RT				75 (56-93)	8 (21)	MRIdian	27.5/5 (n = 6, 16%), 30/5-6 (n = 30, 81%), 38.7/9 (n = 1, 3%)	3
Poon et al,[21] 2021	51	Single-center	Hong Kong	2020-2021	EPIC-50[34]	1 mo, 4 mo, 7 mo, 10 mo, 13 mo	Localized	18 (35)	29 (57)	4 (8)	72 (mean) 7.7 (SD)	30 (59)	Unity	Low/intermediate risk: 36.25/5, IDL boost 40, high risk: 40/5 + pelvic nodes 25	5 + dorsal 3§
Sandoval et al,[22] 2021	35	Single-center	United States	2019-2020	IPSS[14]	FU1 (1 mo), FU2 (4 mo), FU3 (10 mo)¶	Localized	0 (0)	34 (97)	1 (3)	70 (51-82)	9 (26)	MRIdian	36.25/5 (urethra max 35)	3§
Tetar et al,[23] 2021	101	Single-center	NL	2016-2018	EORTC QLQ-C30,[28] EORTC QLQ-PR25,[29] IPSS[14]	End-RT, 6 wk, 3 mo, 6 mo, 9 mo, 12 mo	Localized	60 (59)	37 (37)	4 (4)	72 (55-88)	84 (83)	MRIdian	36.25/5 (urethra max 35)	3§
Teunissen et al,[24] 2022#	293	Multicenter	NL	2020-2022	EPIC-26[32]	1 mo, 3 mo, 6 mo, 9 mo, 12 mo	Localized	47 (16)	217 (74)	29 (10)	70 (mean) 6 (SD)	40 (14)	Unity	36.25/5 (83%), 62/20 (16%), other (1%)	5
Teunissen et al,[25] 2023#	425	Multicenter	NL	2019-2021	EORTC QLQ-C30,[28] EORTC QLQ-PR25[29]	3 mo, 6 mo, 12 mo	Localized	27 (7)	337 (82)	47 (11)	70 (51-85)	347 (18)	Unity	36.25/5	5 (n = 355, 84%), 5 + dorsal 3 (n = 70, 16%)
Wegener et al,[26] 2022	16	Single-center	Germany	2018-NR	PRO-CTCAE,[35] IPSS,[14] ICIQ[30]	During-RT, end-RT	Biochemical recurrence after radical prostatectomy				66 (55-77)	6 (38)	Unity	66/33 (38%), 66.5-70/35 (SIB) (56%), 66.5/70/73.4 (SIB) (6%)	6-10 + dorsal 5-8§
Willigenburg et al,[27] 2022#	130	Single-center	NL	2020- 021	IPSS[14]	1 mo, 3 mo, 6 mo, 9 mo, 12 mo	Localized	7 (5)	109 (84)	14 (11)	69 (mean) 6 (SD)	8 (6)	Unity	36.25/5	5§

Abbreviations: ADT = androgen deprivation therapy; BL = baseline; EORTC = European Organization for Research and Treatment; EPIC = Expanded Prostate Cancer Index Composite; FU = follow-up; ICIQ-SF = International Consultation on Incontinence Questionnaire-Short Form; IDL = intraprostatic dominant lesion; IIEF-5 = International Index of Erectile Function-5; IM = intermediate; IPSS = International Prostate Symptom Score; NL = the Netherlands; NR = not reported; PRO-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PROM = patient-reported outcome measure; PROMIS, Patient-Reported Outcomes Measurement Reporting System; QLQ-C30 = Quality of Life Questionnaire core 30; QLQ-PR25 = Quality of Life Questionnaire prostate cancer module; RCT = randomized controlled trial; RT = radiation therapy; SIB = simultaneously integrated boost.

* All were prospective observational studies unless stated otherwise.

† Risk according to the National Comprehensive Cancer Network.

‡ Unless stated otherwise.

§ Measured from clinical target volume of the prostate gland.

‖ Biochemical recurrence, high Decipher genomic classifier score, or adverse pathologic features at prostatectomy.

¶ Timing between brackets are the median assessments of the follow-up visits.

\# These studies report on overlapping patient cohorts; because they report different PROMs, they were included in this review. Only the largest study was included to calculate the total number of included patients.

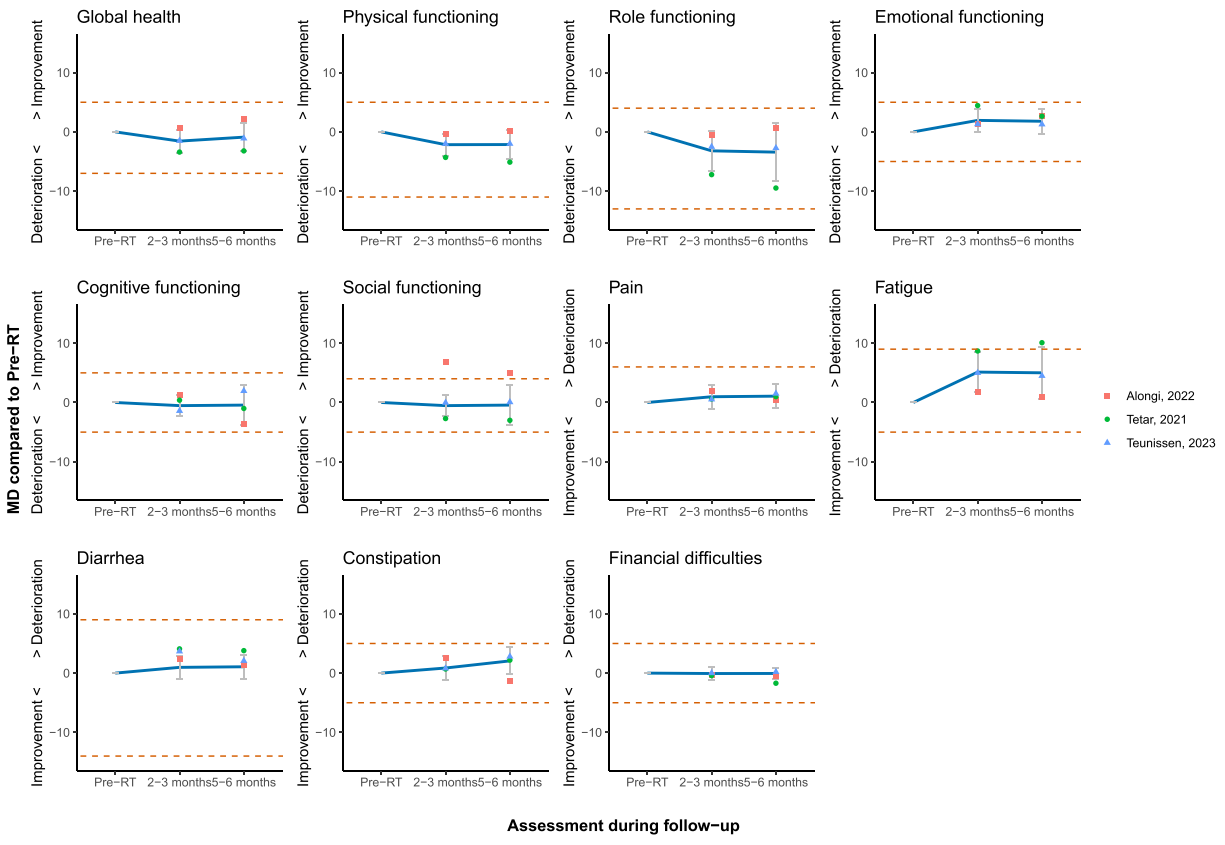

Fig. 2. Meta-analysis of the general patient-reported outcomes assessed with the European Organization for Research and Treatment Quality of Life Questionnaire core 30 in patients treated with magnetic resonance–guided radiation therapy (RT) for localized prostate cancer. The blue line presents the pooled mean differences compared with pre-RT, with a 95% CI in gray. The red dashed line represents the applicable minimal important difference per domain obtained from the literature.[10] When unavailable, a minimal important difference of 5 was considered relevant. Mean differences of individual studies are plotted in a pink square,[17] green circle,[23] and blue triangle.[25]

For the incontinence domain in patients with primary prostate cancer, 1 of 4 studies reported worsening,[5] and 1 reported an improvement in treatment at end-RT to 1 month of follow-up.[18] At 2 to 3 months, 1 of 4 studies reported a worsening.[5] At 10 to 12 months of follow-up, 1 of 2 studies reported a worsening.[25]

Bowel domain

Relevant worsening of the bowel domain in patients with primary prostate cancer was reported in 4 of 6 studies at end-RT to 1 month of follow-up (Table E7).[5,21,23,24] At 5 to 6 months of follow-up, 1 of 4 studies reported worsening.[23] The only study including patients with MRgRT as a second line of treatment reported relevant worsening of symptoms at end-RT to 1-month follow-up.[19]

Sexual domain

Two of 5 studies reported a relevant worsening in the sexual domain at end-RT to 1 month of follow-up (Table E8).[23,24] At 2 to 3 months, 2 of 4 studies reported relevant worsening.[23,25] At 5 to 6 months and 10 to 12 months, 2 of 3 studies reported relevant worsening.[23,25] One study reported sexual domain in patients with MRgRT as second-line of treatment, in which no relevant change was found.[19]

Meta-analysis

Studies that included outcomes of patients treated for primary prostate cancer were included in a meta-analysis. Three studies were included for the EORTC QLQ-C30,[17,23,25] 3 studies for the EORTC QLQ-PR25,[17,23,25] and 4 studies for the EPIC-26.[5,17,18,24]

Pooled PROs did not show relevant changes compared with pre-RT for EORTC QLQ-C30 domains (Fig. 2, Fig. E1). For the urinary domain, a clinically relevant difference was found with the EORTC QLQ-PR25 (MD, 8.6; 95% CI, −4.7 to 22.0; $I^2 = 97\%$) and with the EPIC-26 urinary irritative/obstructive domain (MD, −10.0; 95% CI, −12.0 to −8.1; $I^2 = 0\%$), both between pre-RT and end-RT to 1-month follow-up (Fig. 3, Figs. E2 and E3). At 2 to 3 months and 5 to 6 months after MRgRT, the difference compared

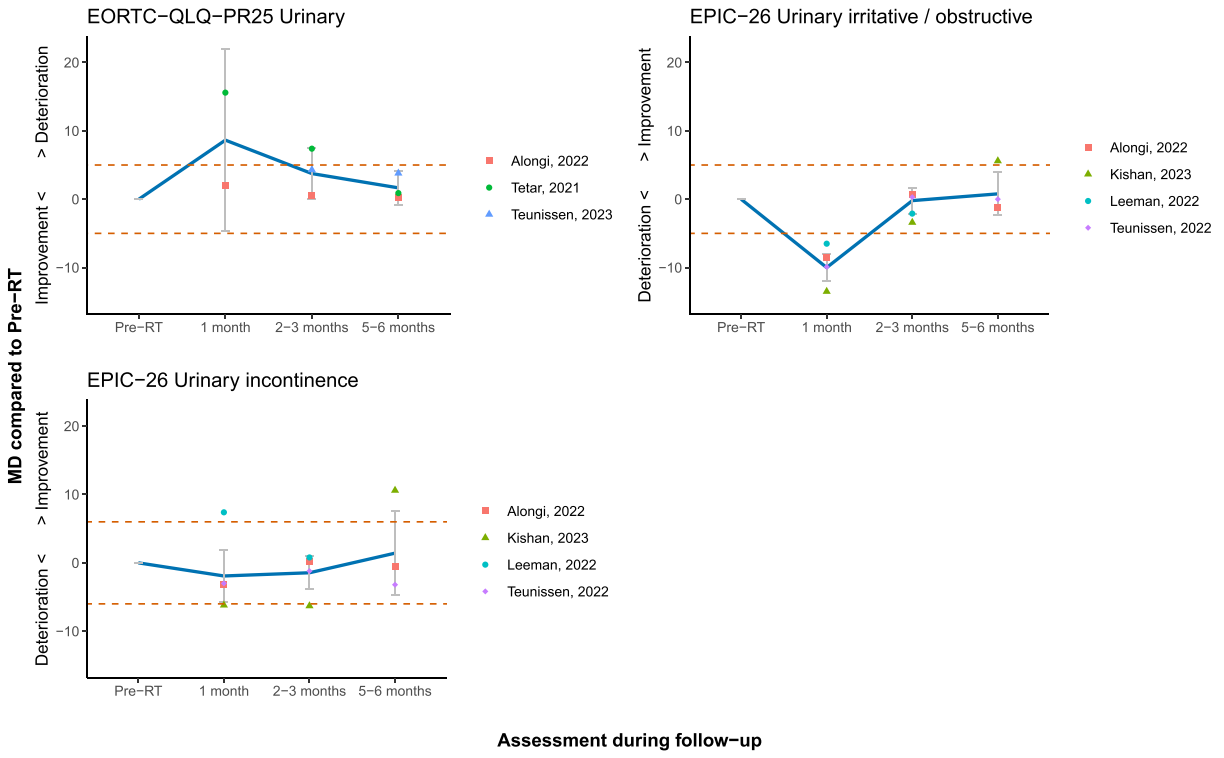

Fig. 3. Meta-analysis of the patient-reported outcomes assessing urinary domain in patients treated with magnetic resonance−guided radiation therapy (RT) for localized prostate cancer. The blue line presents the pooled mean differences (MDs) compared with pre-RT, with a 95% CI in gray. The red dashed line represents the applicable minimal important difference per domain obtained from the literature.[11,15] MDs of individual studies are plotted in a pink square,[17] green circle,[23] green triangle,[5] blue triangle,[25] blue circle,[18] and purple diamond.[24] Note that the direction of MDs for improvement and deterioration is opposite for the European Organization for Research and Treatment Quality of Life Questionnaire prostate cancer module (EORTC-QLQ-PR25) and the Expanded Prostate Cancer Index Composite (EPIC)-26.

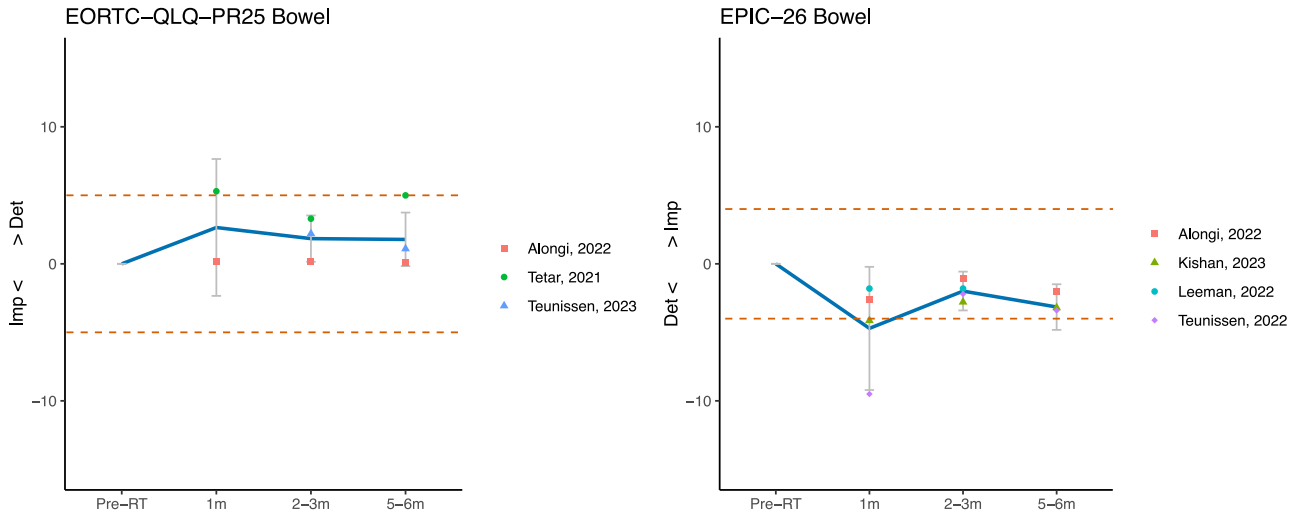

Fig. 4. Meta-analysis of the patient-reported outcomes assessing bowel domain in patients treated with magnetic resonance−guided radiation therapy (RT) for localized prostate cancer. The blue line presents the pooled mean differences (MDs) compared with pre-RT, with a 95% CI in gray. The red dashed line represents the applicable minimal important difference per domain obtained from the literature.[11,15] MDs of individual studies are plotted in a pink square,[17] green circle,[23] green triangle,[5] blue triangle,[25] blue circle,[18] and purple diamand.[24] Note that the direction of MDs for improvement and deterioration is opposite for the European Organization for Research and Treatment Quality of Life Questionnaire prostate cancer module (EORTC-QLQ-PR25) and the Expanded Prostate Cancer Index Composite (EPIC)-26.

with pre-RT was not clinically relevant. For the bowel domain, a clinically relevant difference was found with the EPIC-26 (MD, −4.7; 95% CI, −9.2 to −0.2; $I^2 = 82\%$) between end-RT to 1-month follow-up. This was not found with the EORTC QLQ-PR25 (Fig. 4, Figs. E2 and E3).

Discussion

This systematic review and meta-analysis shows that MRgRT for primary prostate cancer results in a temporary clinically relevant deterioration of urinary symptoms measured in the first month after treatment compared with pre-RT, measured with the EORTC-QLQ-PR25 (MD, 8.6; 95% CI, −4.7 to 22.0) and the EPIC-26 (MD, −10.0; 95% CI, −12.0 to −8.1), both larger than the respective MID. Pooled results of the urinary symptoms returned to values less than the MID compared with pre-RT at 3 months following MRgRT. Results on bowel symptoms were inconsistent, depending on the PROMs used. General QoL domains remained stable over time.

To our knowledge, this is the first systematic review and meta-analysis to present (pooled) PROs after MRgRT. The assessment of longitudinal changes in PROs is of great importance to patients because it provides insights into what to expect from their treatment and can help in patient counseling and shared decision making. The meta-analysis improves the precision and power of findings because PROs are currently mainly reported in small, single-center studies.

Previously, Jackson et al[36] published a systematic review of EPIC-26 scores from 1585 patients with localized prostate cancer treated with stereotactic CTgRT. Weighted averages were presented, which showed a significant decline in urinary scores at the end-RT. This is similar to the current study, in which all included studies for primary prostate cancer showed a relevant worsening of urinary symptoms assessed with either EORTC QLQ-PR25, EPIC-26, EPIC-50, or IPSS questionnaires. One study that did not find a relevant worsening of urinary symptoms delivered RT with a lower dose (ie, 30-34 Gy) because the indication was salvage RT. This might explain their findings. The pattern of initial clinically relevant deterioration in urinary symptoms was also found in our pooled analyses. For EORTC QLQ-PR25 scores, however, the 95% CI around the MD was rather large, reflecting a higher degree of uncertainty.

The weighted average PROs of the EPIC-26 bowel domain showed in the study by Jackson et al[36] showed a significant, temporary deterioration after RT. The presented meta-analysis also showed a clinically relevant temporary deterioration of the EPIC-26 bowel domain, whereas this was not found for the EORTC QLQ-PR25 bowel domain. Inconsistencies between the EPIC-26 and EORTC QLQ-PR25 could be explained by the measurement properties of the respective PROMs, which were previously investigated by the Prostate Cancer Diagnosis and Treatment Enhancement Through the Power of Big Data in Europe (PIONEER) consortium.[37] The consortium reported a moderate internal consistency for the EORTC QLQ-PR25 compared with a high internal consistency for the EPIC-26. Nevertheless, the EORTC QLQ-PR25 was determined to have a higher structural validity and was, therefore, recommended to be part of the core outcome set for assessment of PROs in patients with prostate cancer.[37] Another explanation for the difference in variance could be the larger pooled sample size for EPIC-26.

Furthermore, Jackson et al[36] presented a pooled decline in the EPIC-26 sexual domain for 1188 patients. It is unclear how patients treated with ADT were handled in their analysis, which is important because ADT has a large impact on sexual and hormonal domains of QoL.[38] In the current review, heterogeneity in handling of patients treated with ADT limited the possibility of a quantitative analysis for sexual domains. Some individual studies reported a deterioration over time, whereas others showed stable PROs.

It is important to highlight that Jackson et al[36] pooled PROs after CTgRT, whereas the current study focuses on MRgRT. Unfortunately, the study by Jackson et al[36] lacked information on the exact pooled scores and the baseline characteristics of the subgroup in which PROs were presented. This limited the ability to perform an in-depth comparison of pooled PROs between treatment modalities. With increased visibility, MR guidance has the ability to decrease treatment margins with the goal of reducing toxicity. For localized prostate cancer, the benefit of using an MR-Linac to treat with 2-mm margins over 4-mm margins with CTgRT was shown in the MIRAGE RCT, in which 156 patients were randomized.[5] MRgRT resulted in a significant reduction of acute grade ≥2 clinician-reported genitourinary toxicity (24.4% vs 43.4%) and gastrointestinal toxicity (0.0% vs 10.5%). Interestingly, the PROs of the IPSS and the urinary irritative/obstructive domain of the EPIC-26 did not show significant differences between CTgRT and MRgRT, whereas the bowel domain of the EPIC-26 did show significant differences between both arms. The moderate-to-poor correlation between clinician-reported National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) and PROs was described previously.[39,40] Symptoms might have been managed properly with adequate therapy, diminishing the difference in toxicity from a patient's perspective. Discrepancy between clinician- and patient-reported side effects might also be attributed to response shift, recall bias in patients, or lack of blinding of clinicians. Nevertheless, it does show that PROs and clinician-reported outcomes are complementary endpoints, which emphasizes the additional value of measuring PROs.

Included studies delivered MRgRT through 2 commercial devices, the Unity (Elekta AB) and MRIdian (ViewRay Systems Inc). There are 2 major technical differences. First is the strength of the MR field: the Unity is equipped with a 1.5-T magnet, and the MRIdian has a 0.35-T magnet. A second difference is the availability of adaptive strategies. At time of writing, gating was being implemented for the Unity, but previously, only online adaptation was available. For the

MRIdian, gating was available from clinical introduction. It is unclear whether these technical differences are clinically relevant, and therefore, both devices were handled as 1 treatment entity in this systematic review. Although the MRIdian was developed and brought on the market by ViewRay Inc, it was recently purchased by a new company, ViewRay Systems, Inc. Although there was previously uncertainty regarding the continuation and future of the MRIdian, ViewRay Systems, Inc is currently providing support for existing users and plans to resume development and sales.

It remains challenging to determine to what extent longitudinal changes in PROs are clinically relevant. An overview of all methods that can be used was published by Crosby et al.[41] Briefly, 2 groups of methods can be identified: (1) anchor-based methods use other measures or PROMs to determine an MID, and (2) distribution-based methods determine a meaningful change based on the statistical variance of the outcome, such as significance or effect sizes. In 7 of the 15 studies included, a change in PROs over time was considered clinically relevant if the difference was statistically significant. However, this method might be misleading because statistical significance is highly dependent on sample size. A large sample size with small differences could be incorrectly interpreted as clinically relevant based on statistical significance. Statistical significance alone does not provide much information about the clinical relevance of the change. Three studies used effect sizes, calculated as the difference in score divided by the SD of the baseline score. Nevertheless, as shown in this systematic review, SDs differ largely among studies, even with similar sample sizes. For example, Alongi et al[17] reported a baseline SD of 25.2 for the EORTC QLQ-C30 domain on social functioning, whereas this was 13.6 for Tetar et al.[23] When using effect sizes for the interpretation of PRO changes over time, a similar absolute difference could be interpreted as clinically relevant for Tetar et al[23] and not relevant for Alongi et al.[17] An alternative approach used in this review involves MIDs reported by the literature. MIDs establish a cutoff value based on the smallest change in score of a particular domain, which patients perceive as beneficial. This value serves as a minimal threshold of clinical importance. A disadvantage of this approach is its arbitrary threshold. Yet, emerging research aims to establish MIDs with greater precision.[10] This was most extensively investigated for the EORTC QLQ-C30, where Musoro et al[10] established an MID per PROM domain and cancer type. MIDs for additional PROMs used in this review were the EPIC-26, estimated based on patients treated for prostate cancer[15]; the MID of the IPSS, estimated based on patients with benign prostate hyperplasia[14]; the MID of the IEFF-5, estimated based on patients with erectile dysfunction[12]; and the MID of the ICIQ-Sort Form, estimated based on women with stress incontinence.[13] The MID was not available for the EORTC QLQ-PR25 and was retrieved from a landmark trial.[11] Because Musoro et al[10] showed that MIDs could differ per cancer type and per domain, interpretation of MIDs based on other indications should be done with care because its generalizability is yet unclear. Consequently, it is important to not only report the proportion of patients with changes in score that exceed the MID but also include the raw scores to show valuable nuances.

Limitations of this review should be acknowledged. First, a critical risk of bias was found in 5 of the included studies.[21,22,24-26] This was mainly due to the proportion of missing data, reported as critical risk of bias when >50% of data were missing at any point during follow-up. It is important to highlight that critical risk of bias due to missing data was only found from 9 months of follow-up or more. Before this, completion rates were higher. This reduces the risk of bias due to missing data on outcomes reported during early follow-up. One study performed a linear mixed model analysis, whereas the remaining studies performed a complete case analysis, introducing risk of bias. Whether this bias resulted in an overestimation or underestimation of the reported outcomes is unclear because the mechanism of missing data was not explained. Another limitation was the heterogeneity of included studies, which limited the possibility of proper comparison of all studies and all PROs. Three main sources of heterogeneity were identified: heterogeneity in handling of subgroups with ADT use, heterogeneity in prostate cancer stage with differences in treatment prescription, and heterogeneity in PROMs used. Heterogeneity in handling of subgroups treated with ADT prevented the meta-analysis of the sexual domain. Heterogeneity of study population was most profound in 3 studies that treated patients with prostate cancer recurrences, which resulted in the exclusion of these studies from the meta-analysis. Still, the remaining studies showed some differences in the inclusion of low-volume metastatic disease, dose, IDL boost, and margins. Heterogeneity of PROMs used was most profound in the reporting of urinary symptoms (EORTC QLQ-PR25, EPIC-26, EPIC-50, ICIQ-Short Form, and IPSS). Two PROMs were specifically developed for patients treated with prostate cancer, ie, the EPIC-26 and EORTC QLQ-PR25.[42] However, their outcomes cannot be directly compared because of differences in specifications of subdomains and outcome scoring. As previously mentioned, the PIONEER consortium investigated measurement properties of PROMs for prostate cancer to establish consensus on the PROMs of choice. This should prevent heterogeneity in future research, thereby enabling comparison of studies and the synthesis of robust aggregated evidence.

Although the impact of MRgRT on PROs is suggested to be minimal or temporary, further reduction of side effects and improvement of QoL for patients is an important topic of investigation. It is hypothesized that this could be achieved by increasing the precision of MRgRT. The Dose De-escalation in Prostate Radiotherapy Using the MRL (DESTINATION) study (NCT05709496) investigates the feasibility of high-precision toxicity-minimizing RT on an MR-Linac for patients with intermediate-risk localized prostate cancer. Treatment consists of 5 fractions with 30 Gy to the prostate without a margin and 45 Gy to the dominant lesion with a 4-mm margin. This review sets an important benchmark for future development and hypothesis-generating studies.

In conclusion, PROs of patients with prostate cancer treated with MRgRT show a relevant temporary deterioration in the urinary and bowel domain after treatment compared with pre-RT, which improved at 3 months after treatment. General domains of QoL scores did not show relevant change over time. These findings are important to aid patient counseling, support cost-effectiveness studies, and serve as a benchmark for future interventional studies.

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