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ORIGINAL ARTICLE

Patient-Reported Outcomes 12 Years after Localized Prostate Cancer Treatment

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Abstract

BACKGROUND Long-term patient-reported outcomes are needed to inform treatment decisions for localized prostate cancer.

METHODS Patient-reported outcomes of 1643 randomly assigned participants in the ProtecT (Prostate Testing for Cancer and Treatment) trial were evaluated to assess the functional and quality-of-life impacts of prostatectomy, radiotherapy with neoadjuvant androgen deprivation, and active monitoring. This article focuses on the outcomes of the randomly assigned participants from 7 to 12 years using mixed effects linear and logistic models.

RESULTS Response rates exceeded 80% for most measures. Among the randomized groups over 7 to 12 years, generic quality-of-life scores were similar. Among those in the prostatectomy group, urinary leakage requiring pads occurred in 18 to 24% of patients over 7 to 12 years, compared with 9 to 11% in the active monitoring group and 3 to 8% in the radiotherapy group. In the prostatectomy group, 18% reported erections sufficient for intercourse at 7 years, compared with 30% in the active monitoring and 27% in the radiotherapy groups; all converged to low levels of potency by year 12. Nocturia (voiding at least twice per night) occurred in 34% in the prostatectomy group compared with 48% in the radiotherapy group and 47% in the active monitoring group at 12 years. Fecal leakage affected 12% in the radiotherapy group compared with 6% in the other groups by year 12. The active monitoring group experienced gradual age-related declines in sexual and urinary function, avoiding radical treatment effects unless they changed management.

Professor Donovan, Professor Hamdy, Professor Lane, Ms. Young, Professor Metcalfe, and Professor Neal contributed equally to this article.

**A complete list of investigators in the ProtecT trial is provided in the Supplementary Appendix, available at evidence.nejm.org.*

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CONCLUSIONS ProtecT provides robust evidence about continued impacts of treatments in the long term. These data allow patients newly diagnosed with localized prostate cancer and their clinicians to assess the trade-offs between treatment harms and benefits and enable better informed and prudent treatment decisions. (Funded by the UK National Institute for Health and Care Research Health Technology Assessment Programme projects 96/20/06 and 96/20/99; ISRCTN number, ISRCTN20141297; ClinicalTrials.gov number, NCT02044172.)

Introduction

Most men diagnosed with low- or intermediate-risk clinically localized prostate cancer can expect to live 15 years or longer after diagnosis.[1] Robust evidence is therefore needed about the adverse effects of treatment modalities on sexual, urinary, and bowel function as well as quality of life over the short, medium, and long term to inform decision-making. Providing accurate information about adverse effects of treatment is critical to avoid later regret about treatment decisions.[2,3] Patients newly diagnosed with localized prostate cancer need to choose their initial treatment after weighing the risks of adverse effects of treatment against risks of cancer progression and low likelihood of dying of prostate cancer.[1] The U.K. National Institute for Health and Care Research–supported ProtecT (Prostate Testing for Cancer and Treatment) trial compared prostatectomy (mostly open retropubic), radiotherapy (external beam, 74 Gray in 37 fractions with neoadjuvant androgen deprivation), and active monitoring (surveillance with prostate-specific antigen [PSA] tests every 6 months and annual clinical review). ProtecT participants completed patient-reported outcome measures (PROMs) at 6 months and then annually. The primary analysis provided evidence that each treatment strategy produced a distinct profile of impact on sexual, urinary, and bowel function and related quality of life at 6 years, without differences between the groups in overall physical or mental health.[4]

Treatments have evolved since ProtecT participants were treated (2001 to 2009), but observational studies initiated to evaluate treatments received since 2010 (including robot-assisted laparoscopic radical prostatectomy, active surveillance, intensity-modulated radiotherapy, and brachytherapy) confirmed similar short-term adverse-effect profiles up to 3 or 5 years after intervention[5-9] compared with the ProtecT 6-year PROMs.[4] The ProtecT trial provides a randomized comparison of the impacts of major treatment modalities. Here we focus on the comprehensive range of PROMs completed annually by ProtecT trial participants over 7 to 12 years postrandomization to show the adverse effects of prostatectomy, radiotherapy, and active monitoring over the long term and thus enable better-informed treatment decisions.

Methods

ProtecT TRIAL PARTICIPANTS AND PROMs

Following population-based PSA testing and 10-core biopsy under ultrasound guidance, 1643 study participants diagnosed with clinically localized prostate cancer were randomly assigned between 2001 and 2009: 545 to active monitoring, 553 to radical prostatectomy, and 545 to radiotherapy with neoadjuvant androgen deprivation.[10] Details of the ProtecT trial recruitment methods, baseline findings, and prespecified PROMs outcomes up to 6 years were published previously.[4,11,12] The study flowchart and details of treatments and clinical outcomes are included in Hamdy et al.[1] The ProtecT study was designed by J.L.D., F.C.H., and D.E.N. The authors vouch for the data analysis and fidelity to the protocol available with the full text of this article at evidence.nejm.org. J.L.D. wrote the first draft of the paper and all authors contributed to the final version. Institutions, sponsor, and funder had no role in the data analysis or writing the article.

PROMs, completed at 6 months and then annually by participants, were scored and analyzed according to a prespecified analysis plan[13] and presented in four key domains, as shown in Table 1 and described previously.[4] This method of presentation did not include a threshold for identifying clinical relevance so that patients and clinicians could reach their own judgments about the meaningfulness of the effects. Measures used were the International Consultation on Incontinence Questionnaire (ICIQ; scores range from 0 [least affected] to 21 [most affected]),[14] International Continence Society male Short Form (ICSmaleSF; scores range from 0 [least affected] to 24 [most affected]),[15] Expanded Prostate Index Composite (EPIC; scores range from 0 [most affected] to 100 [least affected]),[16] Medical Outcomes study Short Form (SF-12; scores range from 0 [most affected] to 100 [least affected]),[17] Hospital Anxiety and Depression Scale (HADS; scores range from

Table 1. Patient-Reported Outcome Measure Domains and Key Items.*
Domain 1: Urinary function and quality of life using ICIQ,[14] ICSmaleSF,[15] and EPIC[16] **Key item**: EPIC pad-use item (Fig. 1B)[16]
Domain 2: Sexual function and quality of life using EPIC[16] **Key item**: EPIC item on erections firm enough for intercourse (Fig. 2A)[16]
Domain 3: Bowel function and quality of life using EPIC[16] **Key items**: EPIC items on loose stools, fecal incontinence, and bloody stools (Fig. 3C–E)[16]
Domain 4: Generic health status, anxiety, depression, and cancer-related quality of life using SF-12,[17] HADS,[18] and EORTC QLQ-C30[19]

* Table S1A–D includes all EPIC summary and subscale scores, ICSmaleSF subscale and item scores, ICIQ subscale and item scores, HADS subscale scores, and EORTC QLQ-C30 global, functional, and symptom scores. Detailed descriptions of the scales are provided in each of the respective supplementary tables. EORTC QLQ-C30 denotes European Organization for Research and Treatment of Cancer Core questionnaire; EPIC, Expanded Prostate Index Composite; HADS, Hospital Anxiety and Depression Scale; ICIQ, International Consultation on Incontinence Questionnaire; ICSmaleSF, International Continence Society male Short Form; and SF-12, Medical Outcomes Study 12-Item Short Form General Health Survey.

0 [least affected] to 21 [most affected]),[18] and European Organization for Research and Treatment of Cancer Core questionnaire (EORTC QLQ-C30; scores range from 0 to 100 with least/most affected varying by the specific subscale as indicated).[19] Some measures/items were added after feasibility study completion, and others were removed from a later version of the study questionnaire that was revised to reduce duplication and respondent burden (Fig. S1 in the Supplementary Appendix). This led to fewer responses in years 10 to 12 for specific measures (Table 2 and Table S1A–D).

STATISTICAL ANALYSES

The current analysis extends the previous 6-year findings[4] and focuses on follow-up of all participants from 7 to 12 years. Participants were analyzed according to their original randomly assigned allocation, with summary statistics presented by randomly assigned group. Two-level mixed-effects models were employed with each participant as the higher level and repeated measurements at the lower level to accommodate intraindividual correlations between the repeated measures. Two-level mixed effects linear and logistic models were used for continuous and binary responses, respectively. For each outcome, evidence was evaluated against the null hypothesis of equal average response across the three allocated groups in postrandomization means/odds over 7 to 12 years of follow-up. All models included, as covariates, the stratification/minimization variables used in the random allocation: age and log-transformed PSA at baseline (continuous variables) and Gleason score ($\leq$6, 7, or $\geq$8) and nine study centers (dummy variables). Means or odds ratios are presented for

Table 2. Response Rates for Exemplar Outcome Measures.

	Completed Questionnaire/Expected* Questionnaire (%)			
Time Point	ICIQ Score†	EPIC Sexual Function Subscore‡	EPIC Pad-Use Item‡	ICSmaleSF Nocturia Item§
Baseline	1243/1539 (81%)	725/1012 (72%)	753/1012 (74%)	1623/1643 (99%)
6 months	1407/1571 (90%)	1014/1140 (89%)	1052/1140 (92%)	1438/1637 (88%)
1 year	1385/1612 (86%)	1032/1214 (85%)	1080/1214 (89%)	1433/1633 (88%)
2 years	1380/1624 (85%)	1132/1362 (83%)	1186/1362 (87%)	1425/1625 (88%)
3 years	1389/1614 (86%)	1260/1479 (85%)	1301/1479 (88%)	1416/1614 (88%)
4 years	1384/1602 (86%)	1328/1544 (86%)	1364/1544 (88%)	1421/1602 (89%)
5 years	1384/1589 (87%)	1367/1587 (86%)	1392/1587 (88%)	1407/1589 (89%)
6 years	1369/1572 (87%)	1352/1572 (86%)	1360/1572 (87%)	1394/1572 (89%)
7 years	1372/1556 (88%)	1328/1556 (85%)	1349/1556 (87%)	1380/1556 (89%)
8 years	1326/1532 (87%)	1290/1532 (84%)	1339/1532 (87%)	1356/1532 (89%)
9 years	1296/1510 (86%)	1259/1510 (83%)	1299/1510 (86%)	1319/1510 (87%)
10 years	1214/1401 (87%)	1175/1401 (84%)	1279/1491 (86%)	1281/1491 (86%)
11 years	993/1160 (86%)	968/1160 (83%)	1180/1464 (81%)	1195/1464 (82%)
12 years	765/891 (86%)	747/891 (84%)	1133/1440 (79%)	1117/1440 (78%)

* Expected counts are the number of men for whom an assessment point falls after the introduction of the stated measure. EPIC and ICIQ measures were reduced after 2018 and participants with assessment points after this were excluded from the expected counts. Participants who died were excluded from expected counts after their date of death.

† ICIQ[14] introduced October 1, 2001. EPIC denotes Expanded Prostate Index Composite; ICIQ, International Consultation on Incontinence Questionnaire; and ICSmaleSF, International Continence Society male Short Form.

‡ EPIC[16] introduced March 1, 2005.

§ The ICSmaleSF[15] question was included in all questionnaires from the initiation of study.

prostatectomy or radiotherapy versus active monitoring alongside confidence intervals (CIs) for the between-group comparisons. The widths of the CIs have not been adjusted for multiplicity and so intervals should not be used in place of hypothesis tests.

Baseline measures were not included as covariates because some questionnaires were introduced after the study started, as explained above. Baseline levels of PROMs were presented previously and shown to be comparable across allocated groups.[12] Participants with at least one postrandomization measure were included in the longitudinal analyses. Missing data were not imputed because mixed-effects models provide unbiased estimates of treatment comparisons under the assumption that the values of any missing measurements are unrelated to the risk of those data being missing (conditional on the data that are observed). This assumption cannot be formally tested, but the similarly high rate of PROMs completion across the three groups minimizes the risk of misleading results in any realistic circumstances.

Secondary analyses included prespecified interactions between allocated groups and age (<65 vs. ≥65 years) or cancer risk-stratification group (low vs. intermediate/high) at baseline for key PROMs. An exploratory analysis also used a mixed effects model to investigate levels of sexual dysfunction and urinary leakage among those allocated to active monitoring who either remained on active monitoring throughout or changed management and received a radical treatment at any time during follow-up. Stata version 17.0 was used for analyses.

Results

Completion of PROMs questionnaires exceeded 80% for most measures and time points (Table 2). Details of the ProtecT study's clinical outcomes and change of management are reported in Hamdy et al.[1] For context here, by 7 years 249 of 545 (46%) in the active monitoring group had received a radical treatment compared with 481 of 550 (88%) in the prostatectomy group and 484 of 544 (89%) in the radiotherapy group.[1] By 12 years, receipt of radical treatment had increased to 59%, 90%, and 92%, respectively.[1]

Patient-reported outcomes of key measures in the four prespecified functional and quality-of-life domains are portrayed graphically in Figures 1–4 with error bars denoting the 95% CIs. Comparisons between the three groups for the period 7 to 12 years are shown in Table S1A–D. Scores/percentages of all PROMs throughout the study from baseline to 12 years are also shown in Table S1A–D in the Supplementary Appendix.

DOMAIN A: URINARY FUNCTION AND QUALITY OF LIFE

Data for the groups in the follow-up period from 7 to 12 years for all prespecified urinary function and related quality-of-life measures are shown in Figure 1A–G and Table S1A. In the prostatectomy group, the percentage of participants reporting wearing one pad or more per day was 18% at 7 years, rising to 24% by year 12, compared with 9 to 11% in the active monitoring group and 3 to 8% in the radiotherapy group (Fig. 1B). Urinary leakage with a moderate-to-large interference with life was reported by 15% in the prostatectomy group compared with 11% in the active monitoring group and 7% in the radiotherapy group by year 12 (Fig. 1C and Table S1A).

Urinary voiding difficulties are shown in Figure 1E. Nocturia (at least twice per night) continued to increase gradually in all groups in years 7 to 12, with 37 to 48% of participants in the active monitoring and radiotherapy groups experiencing nocturia compared with 27 to 34% in the prostatectomy group (Fig. 1G). All urinary symptoms, including leakage, had "somewhat" or "a lot" of impact on quality of life among 7 to 11% in the active monitoring and prostatectomy groups compared with 5 to 7% in the radiotherapy group (Fig. 1F).

DOMAIN B: SEXUAL FUNCTION AND QUALITY OF LIFE

Continuing functional declines and differences between the groups could be seen in all prespecified sexual function measures from 7 to 12 years (Fig. 2A and 2C and Table S1B). In year 7, 18% of participants in the prostatectomy group had erections firm enough for intercourse compared with 30% in the active monitoring and 27% in the radiotherapy groups (Fig. 2A). Although all groups converged to a similarly low level of potency by year 12 (13 to 17%; Fig. 2A), each group exhibited a different profile of decline. Sexual/erectile function was retained most and for the longest in the active monitoring group. Levels of sexual/erectile function were lower in the radiotherapy group and lowest in the prostatectomy group.

Differences between the groups were also reflected in related quality-of-life measures (Fig. 2B, 2D, and 2E).

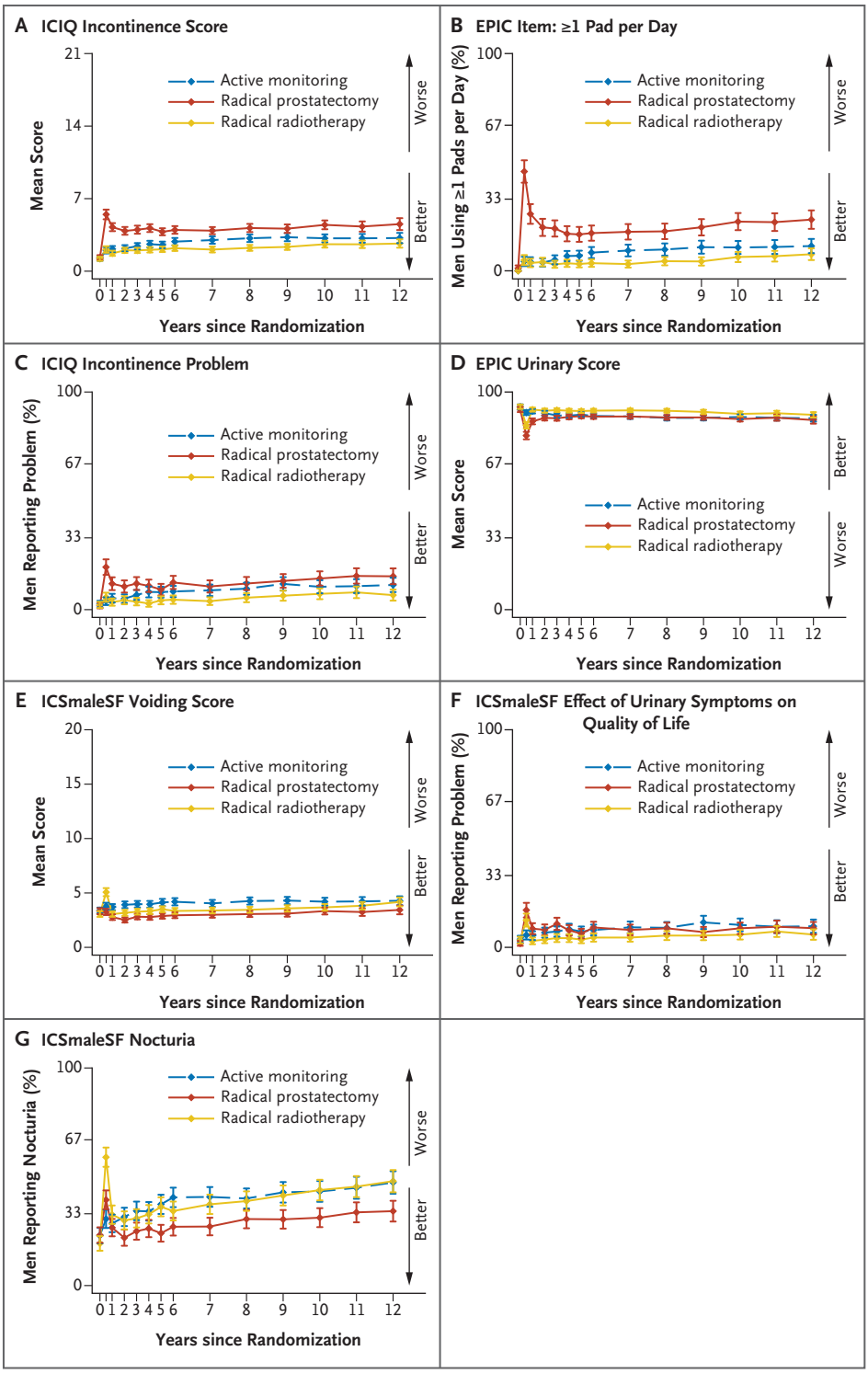

Figure 1. Outcomes for Urinary Function and Impact on Quality of Life.

Shown are the effects of treatments on urinary leakage and voiding symptoms and quality of life. The International Consultation on Incontinence Questionnaire (ICIQ) urinary incontinence scores, shown in Panel A, range from 0 to 21. Panel B shows the percentage of men who used one or more absorbent pads per day for urinary leakage, as assessed by the Expanded Prostate Cancer Index Composite (EPIC) instrument. In Panel C, the percentages shown are for men who reported a moderate-to-severe problem with urinary leakage, as assessed by the ICIQ. The EPIC urinary scores, shown in Panel D, comprise several urinary symptoms, including leakage; scores are formed by linear transformation of raw scores and range from 0 to 100. The International Continence Society male Short Form (ICSmaleSF) voiding scores, shown in Panel E, range from 0 to 20. Panel F shows the percentage of men reporting that urinary symptoms affected their quality of life somewhat to a lot and Panel G, the percentage of men reporting nocturia at least two times per night — both as assessed by the ICSmaleSF. I bars represent 95% confidence intervals.

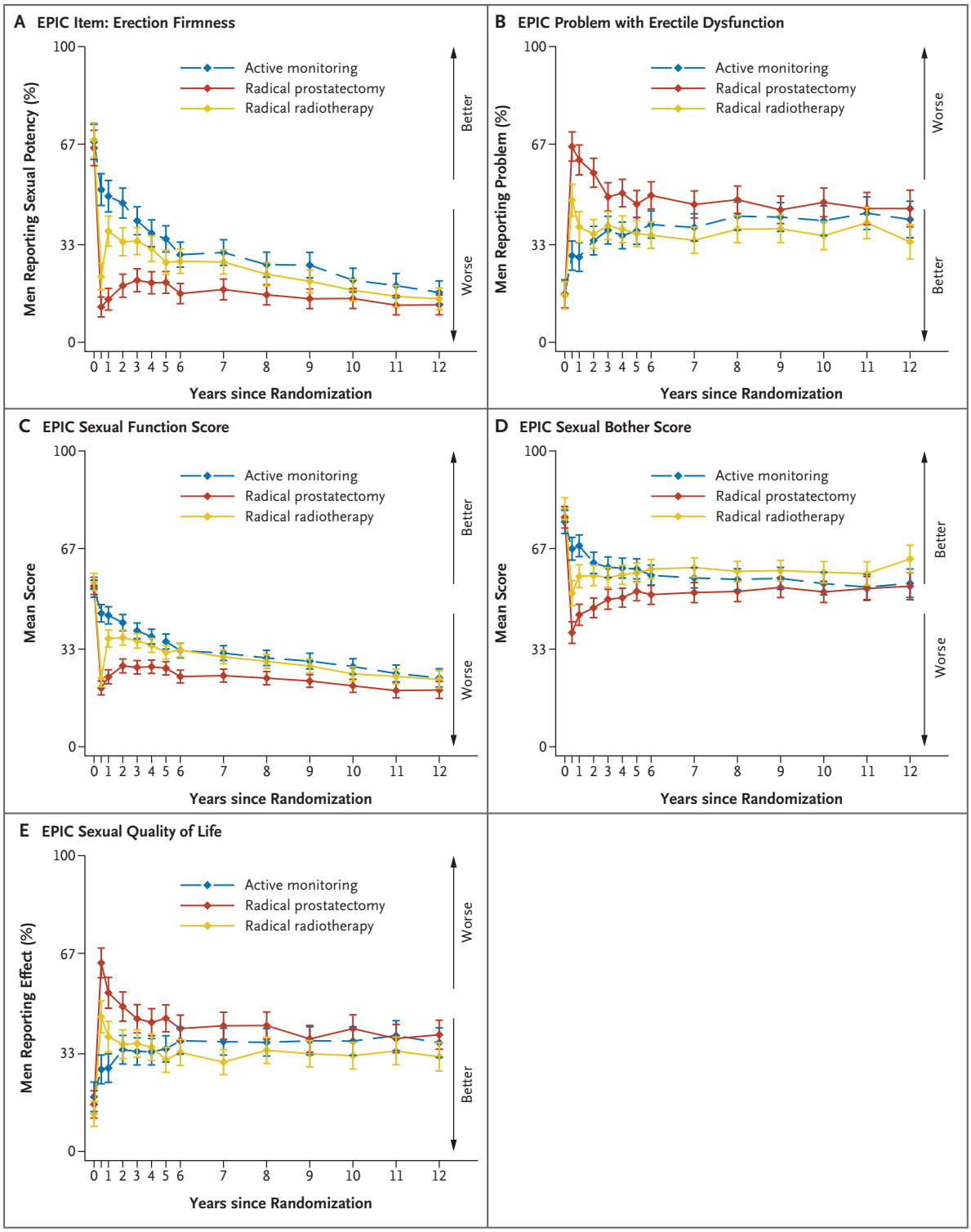

Figure 2. Outcomes for Sexual Function and Impact on Quality of Life.

Shown are the effects of treatments on sexual function (including erectile dysfunction) and quality of life according to the Expanded Prostate Cancer Index Composite (EPIC) instrument. Panel A shows the percentage of men reporting erections firm enough for intercourse. In Panel B, the percentages are for men who reported a moderate-to-severe problem with erectile dysfunction. The EPIC sexual function and bother scores, shown in Panels C and D, range from 0 to 100. In Panel E, the percentages are for men who reported a moderate-to-severe effect of sexual dysfunction on quality of life. I bars represent 95% confidence intervals.

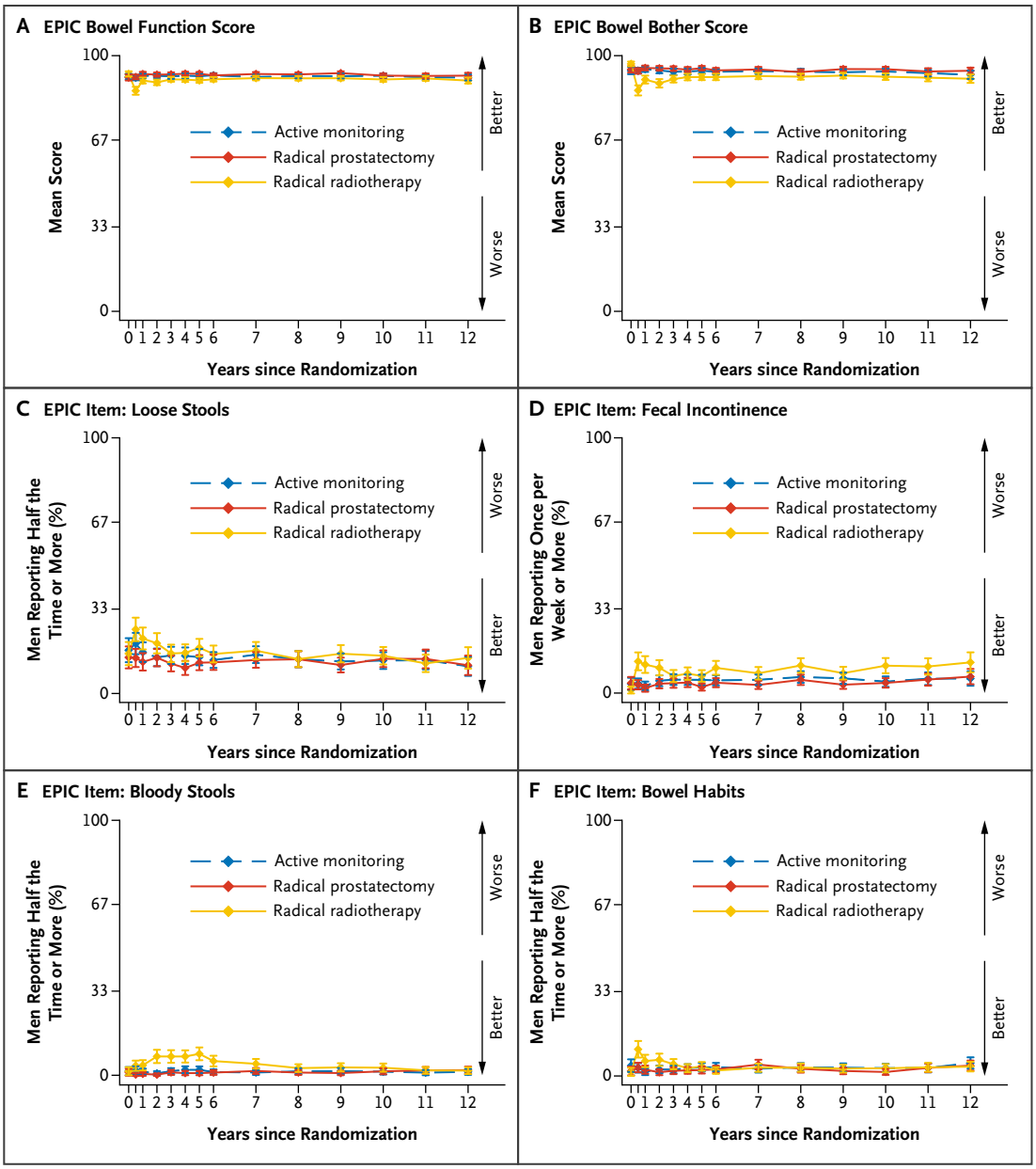

Figure 3. Outcomes for Bowel Function and Impact on Quality of Life.

Shown are the effects of the treatments on bowel function and quality of life. In Panels A and B, the Expanded Prostate Cancer Index Composite (EPIC) bowel function and bowel bother scores range from 0 to 100. In Panel C, the percentages are for men who reported having loose stools half the time or more. In Panel D, the percentages are for men who reported having fecal leakage at least once per week. In Panel E, the percentages are for men who reported having bloody stools half the time or more. In Panel F, the percentages are for men who reported a moderate-to-severe effect on bowel habits. I bars represent 95% confidence intervals.

Moderate-to-severe impact was reported by 42% in the prostatectomy group, 37% in the active monitoring group and 30% in the radiotherapy group at year 7 (Fig. 2E). Levels of impact remained relatively stable, even though sexual function continued to decline in all groups over time.

DOMAIN C: BOWEL FUNCTION AND QUALITY OF LIFE

Although there was a suggestion of worse outcomes for overall bowel function (Fig. 3A) and bowel-related bother (Fig. 3B) in the radiotherapy group, absolute differences were very small (Table S1C). However, fecal leakage

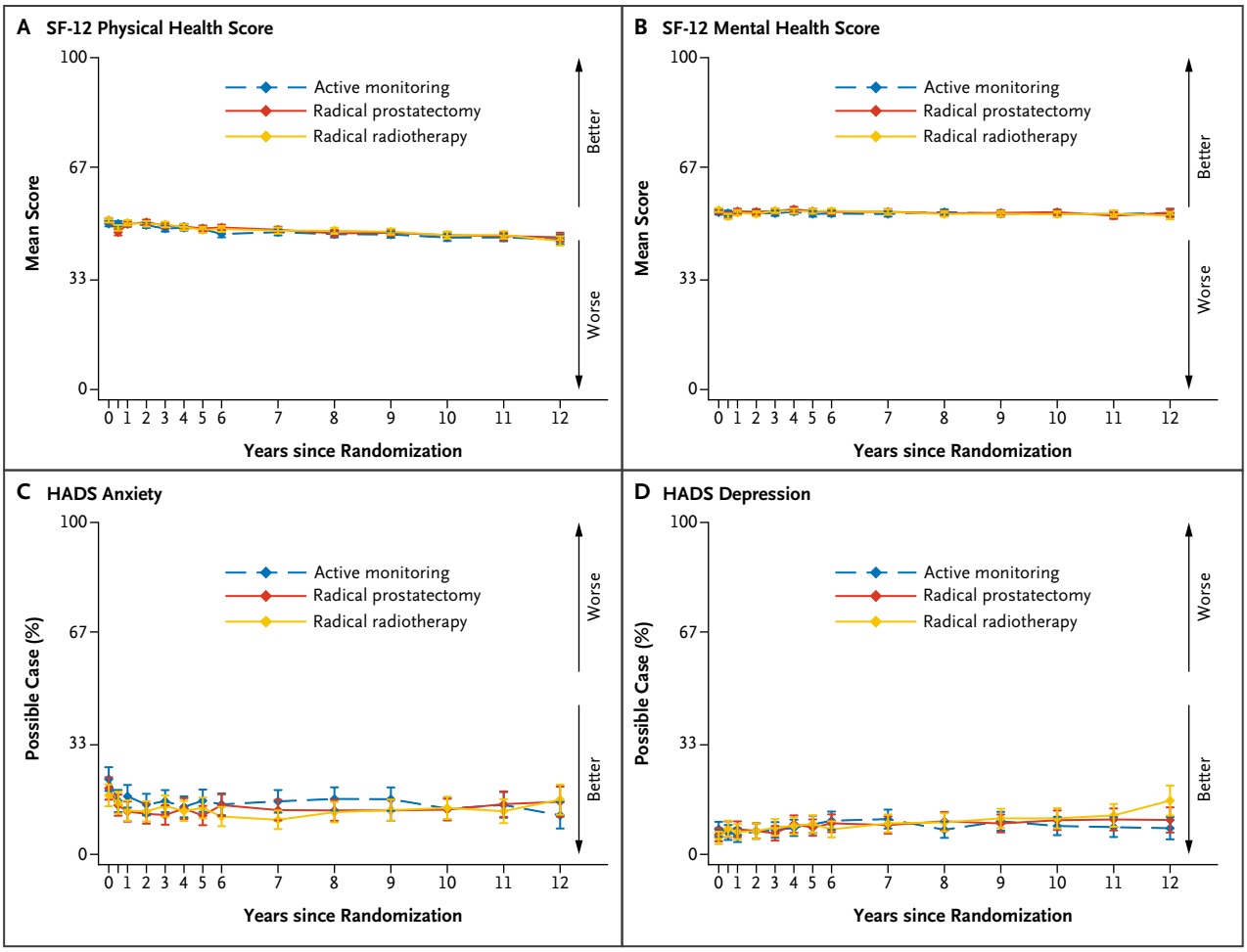

Figure 4. Outcomes for Health-Related Quality of Life.

Shown are the effects of treatments on health-related quality of life. Medical Outcomes Study 12-Item Short Form General Health Survey (SF-12) physical health scores (Panel A) and mental health scores (Panel B) range from 0 to 100. "Possible case" indicates the percentages of patients assessed by the Hospital Anxiety and Depression Scale (HADS) and found with scores suggesting clinically significant cases of anxiety (Panel C) and depression (Panel D). I bars represent 95% confidence intervals.

(more than once per week) increased gradually in the radiotherapy group to affect twice as many participants in the radiotherapy group (12%) compared with 6% in the prostatectomy and active monitoring groups by year 12 (Fig. 3D). In contrast, the passing of blood in stools, previously worse in the radiotherapy group, resolved, becoming similar to that in the other groups in years 7 to 12. The incidence of loose stools and the impact of bowel habits on quality of life appeared similar across the groups in years 7 to 12 (Fig. 3C and 3F).

DOMAIN D: GENERIC/HEALTH-RELATED QUALITY OF LIFE

All groups reported similar levels of physical or mental health, anxiety, depression, and cancer-related quality of life at 5 and 10 years (Table S1D). A gradual decline over time in physical health in all groups (Fig. 4A) was not seen for mental health (Fig. 4B). Although anxiety and depression fluctuated they remained at similar levels throughout (Fig. 4C and 4D).

SECONDARY ANALYSES

The differential effects on pad use for urinary leakage across groups less than 65 and 65 or more years of age are given in Table S2A. During years 7 to 12 of follow-up, use of one or more pads per day was reported in 10 to 13% of younger men and 7 to 12% of older men in the active monitoring group, compared with 15 to 22% of younger men and 23 to 27% of older men in the prostatectomy group.

When considering these data it is important to understand that 34% (117/340) of younger men in the active monitoring group changed management to prostatectomy compared with 15% (31/205) among those 65 years of age or older. There was no evidence of differential effects on other PROMs or subgroups according to cancer risk stratification (Table S2B).

With 12 years of follow-up, in an exploratory analysis, 3% of participants in the active monitoring group who remained on active monitoring throughout and did not receive a radical treatment had urinary leakage, defined as use of one or more pads per day, compared with 16% among those who had received a radical treatment (odds ratio [radical treatment vs. staying on active monitoring] 32.5; 95% CI: 6.5, 162.9) (Table S3). Similarly, erections firm enough for intercourse were reported by 23% of participants in the active monitoring group who remained on active monitoring throughout and did not receive a radical treatment compared with 14% among those who had received a radical treatment (odds ratio [radical treatment vs. staying on active monitoring] 0.20; 95% CI: 0.08, 0.48) (Table S3).

Discussion

This complete 12-year follow-up of patient-reported outcomes in the ProtecT randomized trial provides robust and detailed evidence about the long-term impacts of prostatectomy, radiotherapy, and active monitoring on urinary, sexual, and bowel function and related quality of life. The immediate and short-term effects of treatments have been well-documented,[4,6-8] but some authors concluded that most effects were attenuated by 2 to 5 years.[6,8] However, this long-term analysis has revealed that for some patients effects on sexual, urinary, and bowel function persist and can worsen over time — an important new consideration for treatment decision-making.

Urinary leakage continued to affect the prostatectomy group most over 7 to 12 years of follow-up, with twice as many participants (18 to 24%) requiring pads compared with active monitoring (9 to 11%) and three times as many (3 to 8%) as in the radiotherapy group. Urinary leakage in the active monitoring group was related to the 59% allocated to this group who changed to a radical treatment by year 12 (Table S3), particularly among younger participants, who were more likely to change to prostatectomy than radiotherapy (Table S2A). While sexual function reached a similarly low level in all groups by year 12 each group exhibited a very distinct profile of impact over time. The prostatectomy group experienced the worst impact on sexual function throughout, with minimal recovery after the initial impact of surgery and then a further slow decline from a low level during years 7 to 12. The radiotherapy group experienced an immediate and expected reduction in sexual function from neoadjuvant treatment with androgen deprivation, with some recovery but then a gradual decline over time. The active monitoring group retained more sexual function for longer but also experienced a gradual decline over time. Lower-urinary-tract symptoms including nocturia were less apparent in the prostatectomy group compared with the other groups; removal of the prostate likely relieved preexisting bladder outflow obstruction. In the radiotherapy group, fecal leakage worsened in the longer term, reported by 12% in the radiotherapy group compared with 6% in the other groups by year 12.

These findings need to be considered in the context of changes in treatments since ProtecT completed recruitment in 2009. Several trials and cohort studies investigated whether more modern treatment techniques produced different PROMs profiles compared with the ProtecT 6-year analysis but found similar impacts over their 2- to 5-year follow-up periods. For example, almost identical effects on urinary leakage, voiding, and sexual function were found for robot-assisted/laparoscopic procedures[5-9] compared with open surgery in ProtecT.[4] Similar PROMs profiles were also found for contemporary active surveillance compared with low-intensity active monitoring in ProtecT, even with different patient selection and surveillance methods.[6-8] Profiles for intensity-modulated radiotherapy techniques and brachytherapy did find less impact in the first year and after treatment without hormones, but among those treated with neoadjuvant androgen deprivation, impacts were similar to those found in ProtecT.[6-8] The increased fecal leakage found in ProtecT was beyond the shorter follow-up in the cohort studies, and there is further need to investigate later effects, including whether image guidance using magnetic resonance imaging linear accelerators and hydrogel spacers reduce bowel toxicity in the longer term.[20]

Although observational cohort studies concluded that little change was seen in PROMs after 2 years[8] and that treatment effects had attenuated by 5 years,[6] this ProtecT analysis at 7 to 12 years shows that harms were experienced in the long term. Urinary leakage requiring pads persisted and increased to affect 24% of men in the prostatectomy group by year 12. Sexual function profiles continued to be

best in the active monitoring group and worst in the prostatectomy group — until the groups converged around year 12. There was an increase in fecal leakage in years 7 to 12 in the radiotherapy group. Previous long-term studies had also found some decrements in urinary and sexual function among prostate cancer survivors,[21] including when compared with controls.[22] It is accepted that there is a need for lengthy follow-up of the clinical outcomes of localized prostate cancer because of the protracted natural history of the disease. In parallel, lengthy follow-up of patient-reported outcomes is also required, and now available, to enable full consideration of the trade-offs between the benefits and harms of treatments, particularly in light of the high likelihood of long-term survival.[1] Given the high levels of consensus between the ProtecT results at 6 years and contemporary treatment cohorts with up to 5 years' follow-up, these ProtecT findings provide the comprehensive long-term patient-reported outcome profiles needed to inform current treatment decisions.

Determining the clinical relevance of PROMs is challenging and debated, with suggested methods including setting a target difference of 0.5 of a standard deviation[8] or a specific number of points on scores.[23] These approaches have acknowledged limitations, including a lack of relevance to active surveillance/monitoring and an inability to adapt to variation in perceptions of meaningful differences across a scale or an individual's perception of whether the particular level of change is truly important.[24] Applying the recommended numbers of points[23] at 7 years indicated that clinical relevance was reached only for the difference in urinary leakage between prostatectomy and radiotherapy. This benchmark was also reached for prostatectomy compared with active monitoring at 10 to 12 years, but only because of worsening of leakage in the prostatectomy group rather than changes in the active monitoring group (Table S1A).

In contrast, our approach aims to preserve the meaning of the data by prespecifying comparisons of key PROM items/scores, displaying them graphically over time (Figs. 1–4) and reporting all outcomes with summary statistics (Table S1A–E).[4,13] This allows patients and clinicians to reach their own judgments about the relevance of PROMs based on all available data and respects the rights of patients to use their own values and priorities when considering harms and benefits. This is important because particular scores or items, such as urinary leakage, can "bother" individuals very differently, depending on factors such as their age, occupation, and social activity.[25] It is also important that patients have this information available to avoid the decisional regret associated with a lack of understanding of treatment adverse effects[2,3] and later unmet needs among patients, for example with post-prostatectomy urinary leakage.[26] Further research about the relevance of clinical thresholds to patients and the impact of adverse effects of treatments on individuals who experience them is warranted.

This intention-to-treat analysis provides robust policy-relevant evidence of average effects for comparable groups, but because these included some who did not receive their allocation a treatment-received analysis can help patients to assess their own individual risks.[27] Such an analysis of ProtecT PROMs up to 6 years found greater immediate and more persistent effects following radical treatments and lesser, age-related effects in those remaining on active monitoring.[28] Minimal urinary leakage and longer preservation of sexual function were confirmed in the long term in participants remaining on active monitoring without a radical treatment in an exploratory analysis here (Table S3).

The strengths of ProtecT include its randomized design with balanced groups at baseline enabling unbiased comparisons, generalizable population-based recruitment following PSA testing and follow-up within a comprehensive cohort,[29] a clinically localized patient cohort with at least one third harboring intermediate-risk prostate cancer,[1] implementation of standardized diagnostic and treatment protocols, sustained extremely high response rates over 80% for most measures over 12 years, and comprehensive presentation of validated PROMs. Further details about the representativeness of the ProtecT trial cohort and generalizability of the findings are given in Table S4. Limitations of the study include evolutions in treatments since ProtecT recruitment began, although contemporary treatment studies found similar short-/medium-term results.[6-8] Also, the ProtecT cohort consisted mostly of White participants, although no differences in PROMs were found between ethnic groups in a contemporary diverse cohort.[6]

This long-term follow-up of the ProtecT trial provides robust, mature, and detailed evidence about the effects of treatments on urinary, sexual, and bowel function among patients over 12 years, extending and enriching those reported by short-term studies of contemporary treatments. Prostatectomy continued to cause urinary leakage in 20 to 24% of participants and severely impaired sexual function. Radiotherapy with neoadjuvant androgen deprivation reduced sexual function and caused a late increase

in fecal leakage. With active monitoring, natural age-related declines in sexual function and urinary voiding occurred, with adverse effects of radical treatments avoided unless or until management changed and radical interventions were received. Detailed profiles of patient-reported treatment effects are now available in the short, medium, and long term. Patients newly diagnosed with localized prostate cancer should carefully consider the trade-offs between treatment harms and the risks of prostate cancer progression in the context of low cancer-specific mortality provided by the ProtecT study and discuss these with clinicians to enable well-informed and individualized treatment decisions.

Disclosures

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