Reports of Practical Oncology and Radiotherapy 25 (2020) 442–446

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

The effect of radiation therapy on post-prostatectomy urinary function

David K. Jenkins[a,*], Gregory P. Swanson[a], Sameer G. Jhavar[a], Kristofer R. Wagner[a], Chul S. Ha[b], Wencong Chen[c]

[a] Baylor Scott & White Medical Center - Temple, 2401 S 31stSt, Temple, TX 76508, US
[b] University of Texas Health Science Center San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229, US
[c] Baylor Scott & White Research Institute, 4236 Lowes Dr, Temple, TX 76508, US

ARTICLE INFO

Article history:
Received 4 November 2019
Received in revised form 7 February 2020
Accepted 25 March 2020
Available online 16 April 2020

Keywords:
Prostate
Radiotherapy
Incontinence
Postoperative
Toxicity.

ABSTRACT

Aim: We sought to evaluate the effect of radiation therapy on post-prostatectomy urinary quality of life in prostate cancer patients.
Background: In some men with non-metastatic prostate cancer, radiation therapy is indicated following prostatectomy. The radiation toxicity and quality of life considerations are unique in the post-prostatectomy setting.
Materials and methods: A total of 106 patients receiving post-prostatectomy radiation therapy completed the Expanded Prostate Cancer Index Composite questionnaire before radiation and at 2-year follow-up. The primary outcomes of this study were the urinary domain summary score and subscale scores. Planned analysis was performed based on time interval from prostatectomy to radiation therapy.
Results: Among the 106 patients analyzed, the mean urinary domain summary score worsened at 2-year follow-up after radiation therapy, lowering from 77.23–72.51 ($p = 0.0085$). Similar worsening was observed in the subscales of function ($p = 0.003$), bother ($p = 0.0397$), and incontinence ($p = 0.0003$). Urinary incontinence showed the greatest observable change among subscales. While the summary score worsened ($p = 0.0031$) among patients receiving radiation therapy more than 1 year after prostatectomy, it did not show statistically significant change in those treated 1 year or less after prostatectomy.
Conclusion: Our results demonstrate that post-prostatectomy radiation therapy is associated with modest declines in reportable urinary quality of life. Patients receiving radiation therapy more than 1 year after prostatectomy showed greater worsening of urinary quality of life, which indicates that there may be no functional advantage to delaying radiation therapy beyond the initial postoperative period.

1. Introduction

Radical prostatectomy (RP) is an effective treatment for patients with non-metastatic prostate cancer (PrCa). Adjuvant external beam radiation therapy (EBRT) is recommended to improve biochemical and/or local control after RP, particularly in patients whose radical prostatectomy specimens display high-risk pathological features.[1,2] Salvage EBRT is recommended to improve biochemical, local, and/or distant control in patients who do not undergo adjuvant EBRT and then have biochemical or clinical recurrence of PrCa[3,4] months to years later. The decision to undergo EBRT or pursue surveillance in the adjuvant setting is not straightforward and requires careful consideration of the risks and benefits of both options. Patient quality of life (QOL) is one of the crucial factors that impacts this decision. Quality of life data after adjuvant EBRT are not robust,[5–8] unlike in the definitive EBRT setting where these are well defined and include late toxicities such as urinary frequency, incontinence, irritation, obstruction, or hematuria.[9–14] Despite some data pointing to an improved QOL after adjuvant EBRT,[8] many clinicians choose to defer EBRT to a later time due to concerns over QOL.

The International Prostate Symptom Score (IPSS), developed for use in benign prostatic hypertrophy, is a useful tool to monitor general urinary symptoms and has been validated for clinical use.

Abbreviations: EBRT, external beam radiation treatment; EPIC, Expanded Prostate Cancer Index Composite; IPSS, International Prostate Symptom Score; MID, minimally important differences; QOL, quality of life; RT, radiation therapy.

* Corresponding author.
E-mail addresses: david.jenkins1@bswhealth.org (D.K. Jenkins), swansong@uthscsa.edu (G.P. Swanson), sameer.jhavar@bswhealth.org (S.G. Jhavar), kristofer.wagner@sw.org (K.R. Wagner), hac@uthscsa.edu (C.S. Ha), wencong.chen@bswhealth.org (W. Chen).

https://doi.org/10.1016/j.rpor.2020.03.019
1507-1367/

Table 1
Patient characteristics.

Characteristic	Mean	Median	Range
Age, y	64	65	41–81
Interval between RP and RT, mo	31	16	1–224
Longest available follow-up after RT, mo	29	25	17–52
Radiation dose to prostate bed, Gy	69.94	70.00	68.00–76.60

Abbreviations: RP, radical prostatectomy; RT, radiation therapy.

Among the various existing tools to measure QOL after PrCa treatment, the Expanded Prostate Cancer Index Composite (EPIC) questionnaire is the one that is widely used and validated for evaluating toxicity across various methods of treating PrCa.[15] The purpose of this study is to evaluate whether, and to what degree, EBRT after RP impacts urinary QOL. To achieve this, we retrospectively analyzed QOL data in the urinary function domain as reported in the EPIC questionnaire. This information will aid patients and clinicians in making an informed decision about EBRT vs. surveillance after RP.

2. Materials and methods

Institutional review board approval was obtained prior to conducting a retrospective patient review and the study was conducted in accordance with the ethical standards of the committee on human experimentation. All patients who received post-RP EBRT and completed EPIC questionnaires at baseline and 2-year follow-up comprised the study cohort. Patients completed follow-up questionnaires either at a follow-up visit or by mail. Prior data indicates that urinary QOL measured at the 2-year interval is consistent with longer-term measures of function; therefore, 2-year follow-up is the selected time interval by the institutions studied for obtaining repeat questionnaires.[9] With institutional review board approval, we retrospectively reviewed the questionnaires completed by patients between April 2010 and September 2017.

The primary endpoint measured in this study was the EPIC urinary domain summary score, using questions 23-34.[15] Additionally, the EPIC urinary subscale scores of function (questions 23–27), bother (28–34), incontinence (23, 26–28), and irritative/obstructive (24, 25, 29–33) symptoms were separately measured. The summary and subscale scores were normalized by a Likert scale of 0–100, with higher scores representing better reportable QOL. Supplement Table 1 shows the questions used for the scoring of each subscale.

A secondary endpoint was the IPSS score. Although originally developed for the evaluation of symptoms related to benign prostatic hypertrophy,[16] it is a simple, supplementary tool for evaluating overall urinary function. The EPIC questionnaire allows for the formal inclusion of the IPSS as a non-scored component, but we analyzed it separately. The IPSS is reported on a scale from 0–35. Lower scores represent better reportable urinary function.

Planned analysis was also performed based on the time interval from RP to EBRT. The impression exists that RT retards healing and that earlier treatment may have a greater detriment on ultimate functional outcome. We sought to account for and assess that difference. Analysis was planned for 2 main groups: patients receiving EBRT 1 year or less after RP (early-radiation group) and those receiving EBRT more than 1 year after RP (late-radiation group).

We also report on patients meeting minimally important differences (MID), which are used for identifying clinically meaningful threshold changes in EPIC scores. MIDs were previously developed by the PROST-QA Consortium using EPIC-26[17] and are based on standard deviations and secondary validation with satisfaction questionnaires. The PROST-QA Consortium determined a range of changes for clinical relevance for each subscale. Based on their work, we used the following MIDs to establish meaningful score changes of 6–9 points for the incontinence and 5–7 points for the irritative/obstructive subscales. The PROST-QA Consortium did not report MIDs for the summary score, the function subscale, or the bother subscale. However, based on results of the other subscales, an MID of 6–7 points is considered a reasonable endpoint.

Patients in this cohort were recommended for post-operative radiotherapy due to persistently elevated PSA after prostatectomy, adverse pathologic features or biochemical failure as defined by the generally accepted definition of PSA $\geq$ 0.2 ng/mL.

2.1. Statistical analysis

Descriptive statistics were presented in the analysis. Mean, standard deviation, median, and range were reported for continuous variables. The categorical variables were tabulated by corresponding categories. The differences between EPIC domain and IPSS scores as well as between the early and late-radiation groups from baseline to first follow-up were assessed by Wilcoxon signed rank test. P values of less than 0.05 were considered to indicate statistical significance. All tests were two-sided. No adjustment on multiplicity was made. No imputation on missing data was made. For EPIC and IPSS scores, sensitivity analyses were implemented for the patients whose EPIC urinary domain summary scores were greater than the 25th percentile of all patients. All analyses were performed with the use of SAS software, version 9.4 (The SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

106 patients completed QOL questionnaires at baseline and at 2 year follow-up. The mean patient age was 64 years (range, 41–81 years). The mean time interval from baseline to completion of the follow-up questionnaire was 29 months (range, 17–52 months).

Of the 106 patients, 39 (37 %) and 67 (63 %) were in the early-radiation and late-radiation group, respectively. The mean time interval from RP to EBRT was 6 months and 46 months in the early- and late-radiation groups, respectively (Table 1). All patients received EBRT to a total dose of at least 68 Gy to the prostate bed.

3.2. QOL

A statistically significant decline in the mean IPSS score was seen for the entire cohort from 8.21 at baseline to 9.71 at follow-up ($p = 0.0076$) (Table 2). Similarly, a statistically significant decline in the mean EPIC summary score was seen for the entire cohort from 77.23 at baseline to 72.51 at follow-up ($p = 0.0085$) (Tables 1 and 3). The decline in the mean EPIC summary score was magnified when patients in the lowest (worst) quartile of reported baseline summary scores were excluded, with the mean declining from 86.28 at baseline to 78.42 ($p = 0.0005$).

The mean score significantly declined in three of the four subscales: function ($p = 0.0030$), bother ($p = 0.0397$), and incontinence ($p = 0.0003$) (Table 3). The subscale with the greatest magnitude change was incontinence, which worsened by more than 10 points from 66.49–56.14 ($p = 0.0003$).

In the early-radiation group, the mean EPIC summary score declined from 76.63–74.76, but the change was not statistically significant ($p = 0.5888$) (Supplement Table 2). In the late-radiation group, the mean EPIC summary score also declined but with a greater magnitude (77.58–71.19) and with a statistical significance ($p = 0.0031$).

Table 2
Effect of post-radical prostatectomy radiation on urinary function as measured by the International Prostate Symptom Score.

Patient group (No.)		Mean	Median	Range	P-value
All, 106	Base	8.21	6.0	0–32	0.0076
	Post	9.71	8.0	0–35	
Upper 75th percentile[a], 77	Base	5.94	4.0	0–22	0.0042
	Post	7.89	7.0	0–35	
Early radiation group[b], 39	Base	9.34	7.5	0–32	0.4708
	Post	8.08	7.0	1–26	
Late-radiation group[c], 67	Base	7.56	5.5	0–30	< 0.0001
	Post	10.66	10.0	0–35	

Abbreviations: base, baseline measurement; post, post-radiation 2-year follow-up measurement.
[a] The upper 75th percentile is an evaluation that excludes the patients with the poorest function (lowest 25th percentile) based on the baseline EPIC urinary domain summary score.
[b] The early radiation group is composed of patients receiving radiation therapy 1 year or less after prostatectomy.
[c] The late-radiation group is composed of patients receiving radiation therapy more than 1 year after prostatectomy.

Table 3
Effect of post-prostatectomy radiation on urinary function as measured by Expanded Prostate Cancer Index Composite (EPIC).

Patient Group, No.		Mean	Median	Range	p-value
Urinary Domain Summary Score					
All patients, 106	Base	77.23	80.58	21.50–100	0.0085
	Post	72.51	75.00	6.92–100	
Upper 75th percentile[a], 77	Base	86.28	86.83	67.42–100	0.0005
	Post	78.42	82.67	6.92–100	
Urinary Subscale Scores					
Function	Base	77.76	81.00	11.60–100	0.0030
	Post	72.04	71.80	6.60–100	
Bother	Base	76.83	82.14	28.57–100	0.0397
	Post	72.84	78.57	7.14–100	
Incontinence	Base	66.49	71.00	0.00–100	0.0003
	Post	56.14	58.50	0.00–100	
Irritative/obstructive	Base	85.04	89.29	32.14–100	0.4498
	Post	83.66	85.71	7.14–100	

Abbreviations: base, baseline measurement; post, post-radiation 2-year follow-up measurement.
[a] The upper 75th percentile is an evaluation excluding the patients with the poorest function (lowest 25th percentile) based on the baseline EPIC urinary domain summary score.

Table 4
For each EPIC urinary subscale, the differences between patients in the early and late-radiation groups at baseline (base) and follow-up (post).

	Early radiation group[a]				Late-radiation group[b]			
	Mean	**Median**	**Range**	**p-value**	**Mean**	**Median**	**Range**	**p-value**
Summary Score								
Base	76.63	79.17	21.5–100	0.5888	77.58	82.67	32.58–100	0.0031
Post	74.76	79.92	6.92–100		71.19	73.67	25.67–100	
Subscale								
Function								
Base	75.73	78.40	11.6–100	0.7422	78.96	85.00	26.6–100	0.0001
Post	73.79	78.40	6.6–100		71.01	66.80	35.0–100	
Bother								
Base	77.20	79.17	28.57–100	0.7432	76.61	82.14	28.57–100	0.3663
Post	75.46	85.71	7.14–100		71.32	78.57	14.29–100	
Incontinence								
Base	64.37	66.75	8.25–100	0.4043	67.74	73.00	0–100	< 0.0001
Post	59.39	66.75	0–100		54.25	52.00	0–100	
Irritative/Obstructive								
Base	85.74	89.29	32.14–100	0.8619	84.63	87.50	42.86–100	0.3235
Post	84.98	89.29	7.14–100		82.89	85.71	35.71–100	

[a] The early radiation group is composed of patients receiving radiation therapy 1 year or less after prostatectomy.
[b] The late-radiation group is composed of patients receiving radiation therapy more than 1 year after prostatectomy.

Patients in the early- and late-radiation groups reported worsening QOL in each of the individual urinary subscales (Table 4). In the late-radiation group, the incontinence subscale worsened from 67.74 to 54.25 (13.49 point change, $p < 0.0001$). In the early-radiation group, the incontinence subscale score also decreased from 64.37–59.39 (4.98 point change, $p = 0.4043$).

Forty-nine percent of all patients had meaningful worsening of the incontinence subscale, based on MIDs (Fig. 1). After excluding the 25% of patients with the lowest baseline incontinence scores, the proportion of patients reporting meaningful worsening of incontinence is higher at 56% (Fig. 2). Any improvement in the incontinence subscale score was seen in 25% of all patients. In the early-radiation group, 44% experienced meaningful worsening of incontinence, compared with 52% of the late-radiation group (Fig. 2). Improvement in the incontinence score was seen in 36% of the early-radiation group, compared with 18% of the late-radiation group.

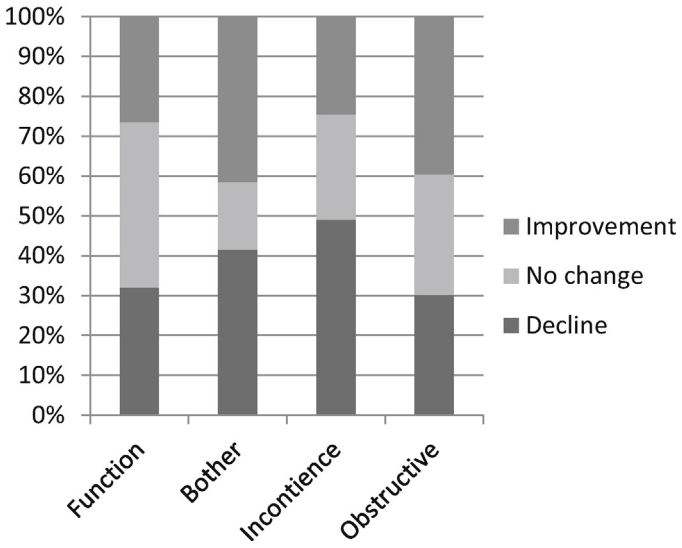

Fig. 1. Proportion of patients reporting change in subscale score. Shown by subscale score are the percentages of all reporting patients experiencing changes in scores from before post-prostatectomy radiation through 2-year follow-up. *Improvement* includes patients reporting any increase in score. *Decline* includes patients reporting a decline in score based on reported Minimally Important Differences specific to each subscale (see Materials and Methods section).

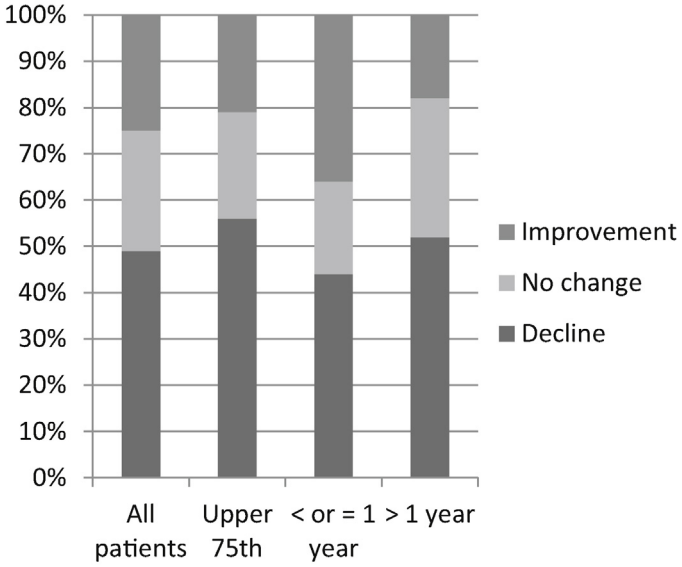

Fig. 2. Proportion of patients reporting change in incontinence subscale score. Shown are the percentages of patients in each group experiencing changes in incontinence subscale score from before post-prostatectomy radiation through 2-year follow-up. Groups displayed include all patients, those receiving radiation 1 year of less after prostatectomy (< or =1 year) or more than 1 year after prostatectomy (> 1 year). *Improvement* includes any patient reporting any increase in score. *Decline* includes any patient reporting a decline in score of 6 or more based on reported Minimally Important Differences (see Materials and Methods section). *Upper 75*th (upper 75th percentile) is an evaluation that excludes the patients with the poorest function (lowest 25th percentile) based on the baseline EPIC urinary domain summary score.

4. Discussion

It is not unexpected that long-term, perceivable functional declines occur after radiation. Ours is one of the first reports to quantify those changes from patients' perspective, specifically in the post-RP setting. The EPIC and IPSS questionnaires provide patient self-assessment of urinary function and QOL. Although follow-up beyond 2 years would be informative, prior data indicates that urinary QOL measured at the 2-year interval is consistent with longer-term measures of function.[9] Thoughtful work has been done to determine the degree of functional change that would be meaningful to the patient.[17] MIDs have helped establish threshold changes in scores that represent clinically meaningful changes. Across the subscales, a score in the 5- to 9-point range appears to be a clinically meaningful change (see Methods section), with some slight variation across the different subscales. The decline in the EPIC urinary domain summary score we observed for the entire cohort (77.23–72.51) barely approaches the lower end of that threshold—a difference that can mostly be accounted for by changes in the incontinence subscale. Specifically, a borderline decrement existed in the function subscale, which is heavily influenced by urinary control, but did not exist in the bother or irritative/obstruction subscales.

Arguably, from the patient's perspective, the biggest life-altering change occurs in the incontinence subscale. Not surprisingly, the baseline mean score (66.49) reflects a significant impact from surgery. Other series[9] that look at pre- and postoperative differences find that the incontinence subscale score declines from > 90 at baseline to approximately 50 at 2 months and 60–70 at 6 months, which is similar to our baseline levels. In our series, we found that EBRT lowered the mean score from 66.49–56.14. This change easily exceeds the MID threshold (6–9 points) for significance but, in perspective, is only a minor further decline from what has occurred with RP.

It is surprising and, therefore, interesting that patients treated in the first year after RP fared better with incontinence than those treated later. This was similar across the other subscale scores where the late-radiation group consistently reported a greater magnitude of change compared with the early-radiation group. Conventional thinking has been that EBRT will have a greater detriment on function the earlier it is delivered, ostensibly because of impairment on healing. This scenario may be true in the first 2 months after RP because prior studies have shown that most of the improvement in continence occurs as previously noted.[9] Our inability to demonstrate a greater detriment to earlier versus later treatment may be that the median time to EBRT was 6 months in our early-radiation group. It appears that a delay of just 2–3 months after RP is an adequate interval to prevent healing impairment. The fact that the early-radiation group fares better overall than the late-radiation group may be due to ongoing active healing that is able to overcome any further detrimental effects on healing influenced by EBRT. Another possibility is that any worsening of the incontinence subscale in the early-radiation group was overshadowed by the postsurgical improvement in continence that is known to occur. We were limited in this study in our ability to further subdivide patients based on time intervals from RP to EBRT (e.g., < 3 months, 3–6 months, and 6–12 months) while still maintaining robust patient numbers in each group.

Our current practice is to recommend immediate post-operative radiation in patients with a persistently elevated PSA or other adverse pathologic features such as seminal vesicle invasion, extraprostatic extension or positive surgical margins. In patients with only minimal adverse features, such as an undetectable PSA with a focal positive margin, we discuss the alternative of close PSA surveillance. Given the findings presented here, we can more confidently counsel these patients that deferring radiotherapy until a PSA recurrence does not appear to significantly reduce the risks of urinary toxicity from post-operative radiotherapy.

5. Conclusions

We have documented through patient assessment that permanent urinary function changes exist after post-RP EBRT. Overall,

the changes are modest in the EPIC urinary domain summary score and across the specific subscales of function, bother, and irritative/obstruction. The greatest changes are in the incontinence subscale. Although clearly meaningful, the changes are considerably less in absolute magnitude compared with the changes occurring after RP. These findings should be beneficial to patients and clinicians as they consider the risks and benefits of post-RP EBRT.

Funding source declaration and disclosure

The authors have no funding sources to disclose.

7. DECLARATIONS OF INTEREST

None.

Acknowledgements

The authors would like to thank Angela Rutherford, Medical Writer at Baylor Scott & White Health Research Institute for helping to prepare this manuscript.

References

1. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: Long-term followup of a randomized clinical trial. *J Urol*. 2009;181:956–962.
2. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96–02/AUO AP 09/95 trial. *Eur Urol*. 2014;66:243–250.
3. Stish BJ, Pisansky TM, Harmsen WS, et al. Improved metastasis-free and survival outcomes with early salvage radiotherapy in men with detectable prostate-specific antigen after prostatectomy for prostate cancer. *J Clin Oncol*. 2016;34:3864–3871.
4. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2007;25:2035.
5. Corbin KS, Kunnavakkam R, Eggener SE, Liauw SL. Intensity modulated radiation therapy after radical prostatectomy: Early results show no decline in urinary continence, gastrointestinal, or sexual quality of life. *Pract Radiat Oncol*. 2013;3:138–144.
6. Abuodeh YA, Naghavi AO, Juan T-H, et al. Quality of Life after post-prostatectomy intensity modulated radiation therapy to the prostate bed with or without the use of gold fiducial markers for image guidance or higher total radiotherapy doses. *Int Braz J Urol*. 2017;43:628–637.
7. Ervandian M, Høyer M, Petersen SE, et al. Late urinary morbidity and quality of life after radical prostatectomy and salvage radiotherapy for prostate cancer. *Scand J Urol*. 2017;51:457–463.
8. Moinpour CM, Hayden KA, Unger JM, et al. Health-related quality of life results in pathologic stage C prostate cancer from a Southwest Oncology Group trial comparing radical prostatectomy alone with radical prostatectomy plus radiation therapy. *J Clin Oncol*. 2008;26:112–120.
9. Sanda MG, Dunn RL, Michalski J, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. *N Engl J Med*. 2008;358:1250–1261.
10. Chipman JJ, Sanda MG, Dunn RL, et al. Measuring and predicting prostate cancer related quality of life changes using EPIC for clinical practice. *J Urol*. 2014;191:638–645.
11. Donovan JL, Hamdy FC, Lane JA, et al. Patient-reported outcomes after monitoring, surgery, or radiotherapy for prostate cancer. *N Engl J Med*. 2016;375:1425–1437.
12. Hamdy FC, Donovan JL, Lane JA, et al. 10-year outcomes after monitoring, surgery, or radiotherapy for localized prostate cancer. *N Engl J Med*. 2016;375:1415–1424.
13. Barocas DA, Alvarez J, Resnick MJ, et al. Association between radiation therapy, surgery, or observation for localized prostate cancer and patient-reported outcomes after 3 years. *JAMA*. 2017;317:1126–1140.
14. Chen RC, Basak R, Meyer AM, et al. Association between choice of radical prostatectomy, external beam radiotherapy, brachytherapy, or active surveillance and patient-reported quality of life among men with localized prostate cancer. *JAMA*. 2017;317:1141–1150.
15. Wei JT, Dunn RL, Litwin MS, et al. Development and validation of the expanded prostate cancer index composite (EPIC) for comprehensive assessment of health-related quality of life in men with prostate cancer. *Urology*. 2000;56:899–905.
16. Barry MJ, Fowler FJ, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. *J Urol*. 1992;148:1549–1557.
17. Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the expanded prostate cancer index composite short form. *Urology*. 2015;85:101–106.