A systematic review of expanded prostate cancer index composite (EPIC) quality of life after surgery or radiation treatment

Tsz Kin Lee, MD,[1] Rodney Henry Breau, MD,[2] Ranjeeta Mallick, PhD,[3] Libni Eapen, MD[4]

[1]Department of Radiation Oncology, Christchurch Oncology Centre, Christchurch, New Zealand
[2]Division of Urology, The Ottawa Hospital/University of Ottawa, Ottawa, Ontario, Canada
[3]Clinical Epidemiology Program, The Ottawa Hospital - General Campus, Ottawa, Ontario, Canada
[4]Department of Radiation Oncology, The Ottawa Hospital Cancer Centre, Ottawa, Ontario, Canada

LEE TK, BREAU RH, MALLICK R, EAPEN L. A systematic review of expanded prostate cancer index composite (EPIC) quality of life after surgery or radiation treatment. *Can J Urol* 2015;22(1):7599-7606.

Introduction: *The Expanded Prostate Cancer Index Composite (EPIC) is a validated and widely adopted instrument that measures patient quality of life. This study aims to describe and compare patient quality of life in the bowel, urinary, and sexual domains across different prostate cancer treatments.*

Materials and methods: *A systematic review of English articles published prior to 2012 was conducted. Peer reviewed articles reporting longitudinal EPIC data in a statistically analyzable form with clearly defined time points were included. Articles were assessed by content experts to ensure optimal treatment quality.*

Screening of studies and extraction of data were completed using a predefined data abstraction tool. Data on bowel, urinary, and sexual domains were documented. Scores in each domain range from a low of 0 to a high of 100.

Results: *Twenty-six articles, representing 8302 patients, were included. All treatments were associated with short term or long term reductions in urinary, bowel, and sexual domains. Surgery patients had better post-treatment bowel quality of life; however, average declines were small regardless of treatment. Post-treatment urinary incontinence scores were lower for surgery patients; while radiation patients had worse urinary irritation. Average urinary bother and function were similar between treatment groups at 18 months post-treatment. Surgery patients had better baseline sexual function. A greater decline in sexual function was observed in surgery patients compared to radiation patients.*

Conclusions: *Prostate cancer treatments have different impacts on patient quality of life and function. The magnitude of difference between treatment-related adverse effects may be important to patients when choosing therapy.*

Key Words: prostate cancer, EPIC, quality of life

Introduction

Prostate cancer is the second most frequently diagnosed non-skin cancer, with an estimated incidence of 220,800 and mortality of 27,540 in the United States in 2015.[1]

The introduction of prostate-specific antigen (PSA) testing in the mid 1980s has contributed to increased diagnosis in younger men.[2] A recent Surveillance Epidemiology and End Result (SEER) cohort study revealed increased incident diagnoses among men under age 50 and a decrease among men over 70.[3] A majority of young prostate cancer patients with clinically localized disease will pursue curative treatment options such as radical prostatectomy or prostate radiation.[4] When patients choose between treatments, they consider probability of cure and treatment-related adverse effects on quality of life

Accepted for publication October 2014

Address correspondence to Dr. Rodney Henry Breau, Surgical Oncology, Division of Urology, The Ottawa Hospital/University of Ottawa, 501 Smyth Road, Ottawa, ON K1H 8L6 Canada

and function.[5] Unfortunately, most studies comparing post-treatment quality of life are not randomized, and methods to assess these outcomes are inconsistent.

The Expanded Prostate Cancer Index Composite (EPIC) is a validated 50-item questionnaire. Unlike previous questionnaires, EPIC addressed urinary, bowel, sexual, and hormonal domains, with higher scores representing better function and less bother.[6] EPIC has been freely available since 2000, is commonly used in North America, and has been validated in several languages.

Materials and methods

To perform a systematic review of the literature to describe and compare patient quality of life across different prostate cancer treatment methods based on the EPIC quality of life instrument.

Search strategy

A literature search of English articles was performed from databases within EMB reviews, Ovid MEDLINE(R) in-process and other non-indexed citations, and OVID MEDLINE(R). There were no publication-year limitations. Titles and abstracts were screened and full manuscripts that met inclusion criteria were obtained. Additional articles were identified by manually examining reference lists for retrieved publications.

Eligibility criteria

To allow for analysis and temporal comparisons, EPIC data must have been reported at specific time points after prostate cancer treatment. We arbitrarily chose 0 (prior to treatment), 1, 3, 6, 9, 12, and 18 months after treatment. If the data were reported at other times, they were allocated to the nearest pre-specified interval. For example, if data were reported at 2 months after treatment, they were grouped with data from other studies that presented 3 months post-treatment. To allow for pooled estimates, studies were required to report sample size, mean, and standard deviation. Studies with patients treated with neoadjuvant, adjuvant, or salvage androgen deprivation were included. However, hormone domain outcomes were not analyzed because the duration of hormone therapy was often not specified.

To be included in this review, articles must have reported detailed treatment information. Eligible prostatectomy approaches were open, laparoscopic, or robot-assisted. Nerve sparing technique has an adverse impact on postoperative sexual well-being. Therefore, to include a "typical" surgical patient experience, sexual domain scores from surgical data were only used if at least 75% of patients in the series received bilateral nerve sparing surgery. This number is selected based on two large prospective surgical series, each with over 1000 patients, where 68% and 76.5% received bilateral nerve sparing prostatectomy.[7,8]

In order to include articles with radiation treatment techniques more accessible and widely used throughout the world, external beam radiation must have been delivered using standard fractionation with photon beam, and brachytherapy must have been delivered using low-dose rate with iodine or palladium. Alternate delivery techniques such as hypofractionation, proton radiation, and high dose rate brachytherapy or other radioactive sources were excluded. All articles were reviewed by a urologist and/or a radiation oncologist to confirm that the treatment technique was of acceptable quality.

Lastly, to include the largest number of quality of life data for analysis while avoiding potential data duplication, such as updates on the previous published data from a single institution, articles from the same authors or institutions were reviewed together. Unless different treatment techniques were used, or the data were from a different study inclusion period, the study with the largest sample size was used, while data from the potential redundant studies were excluded. For example, if one study included patients treated with radical prostatectomy from 2003 to 2007, while another from the same institution included patients from 2005 to 2008, the study with the larger sample size was abstracted.

Statistical analysis

No individual patient data was obtained. Mean EPIC domain scores from each article were summarized using means and standard deviations. For each treatment method, time-specific domain scores were compared to baseline using t-tests. Similarly, comparisons between treatment modality at baseline and 18 months post-treatment were performed using t-tests. All tests were two-sided with $p < 0.05$ considered statistically significant. No adjustment was made for multiple testing.

Results

The electronic search strategy and review of references identified 172 articles that were then reviewed by hand. Of these, 41 articles fulfilled the inclusion criteria, with 31 reviewed by RHB and 18 reviewed by LE to determine if the study was of adequate treatment

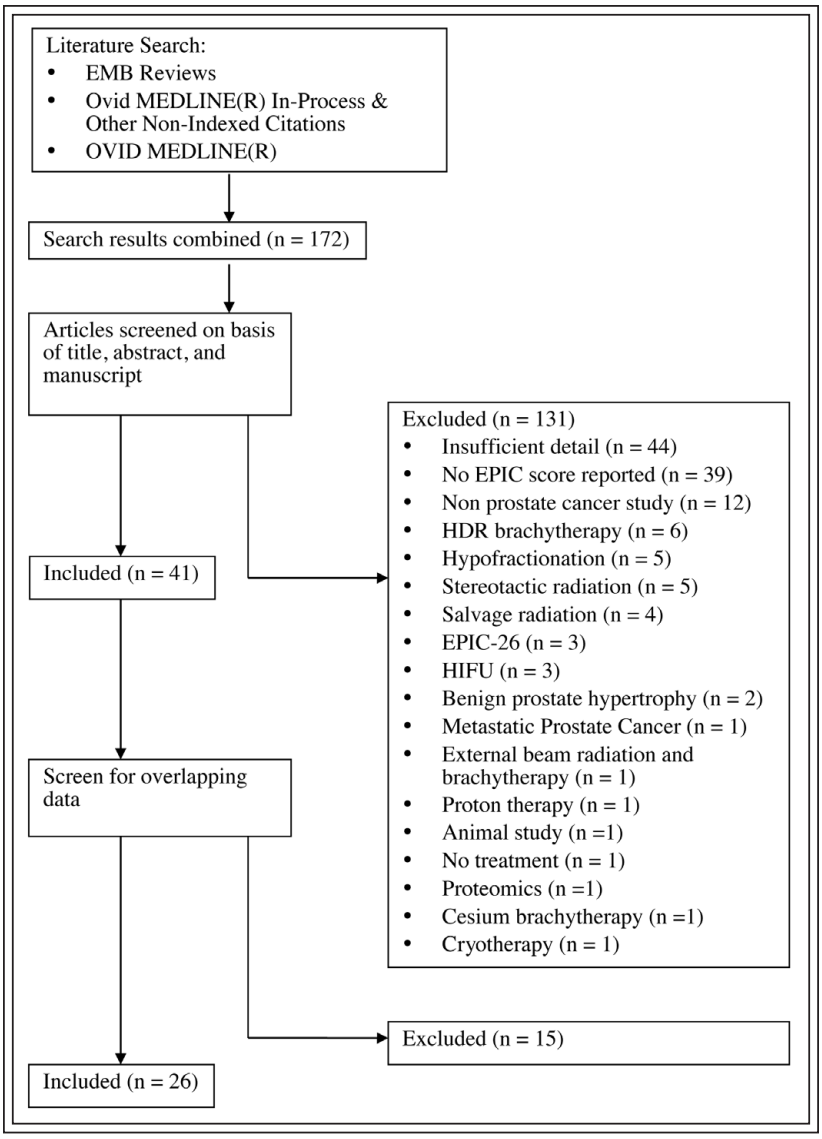

Figure 1. Flow diagram of study selection.

quality, Figure 1. Fifteen articles were excluded because of duplicate data, resulting in final inclusion of 26 articles evaluating a total of 8302 patients, Table 1. No studies were published prior to 2003. One month post-treatment data was not presented in any studies evaluating external beam radiation or brachytherapy.

A larger proportion of external beam radiation (3 of 7) and brachytherapy (5 of 9) cohorts used neoadjuvant, concurrent, and/or adjuvant androgen deprivation therapy compared to 4 of 19 radical prostatectomy cohorts. The proportion of patients in each cohort using androgen deprivation therapy ranged from 3% to 75%. None of the radiation cohort stratified quality of life outcomes based on androgen therapy usage. The details on androgen therapy, such as choice of medication, timing, and duration, were often not reported clearly. Urinary and bowel domain scores represented all patients, while the sexual domain scores only include cohorts where more than 75% had received bilateral nerve sparing techniques.

Bowel domain

Within the radical prostatectomy group, bowel bother, bowel function, and bowel summary scores decreased within the first month of surgery and returned to baseline by 6 months post-surgery ($p > 0.05$ in all domains; Figure 2). Within the external beam radiation and brachytherapy groups, bowel bother and bowel function score decreased by 3 months and never returned to baseline. Bowel summary score for the external beam radiation group also decreased significantly starting at 3 months and remained decreased; while for the brachytherapy group, it returned to baseline at 12 months.

By 18 months post-treatment, mean decline in bowel domain scores were small regardless of treatment, Figure 2. In the pooled analysis, the baseline bowel domain scores were similar between treatment groups (all $p > 0.05$). However, by 18 months, radical prostatectomy patients had higher average scores than the radiation groups (all $p < 0.05$).

Urinary domain

For the radical prostatectomy group, urinary bother, function, continence, irritation, and summary scores all decreased significantly immediately after treatment, Figure 3. Urinary bother returned to baseline by 18 months while urinary irritation improved compared to baseline by 12 months ($p = 0.002$). Average urinary continence scores did not return to baseline by 18 months (-17.7; 95%CI -20.5, .15.1; $p < 0.001$). Average urinary summary score decreased minimally from 89.5 to 87.8 ($p = 0.03$).

Within the external beam radiation group, urinary bother and function scores decreased 3 months post-treatment and returned to baseline by 18 months. Urinary continence (-10.1, 95%CI -13.1, -7.1; $p < 0.001$)

TABLE 1. **Characteristics of studies included**

Author	Year	n	Study design	Country	Treatment
Merrick et al	2003	195	Retrospective cohort	USA	BT
Yang et al	2004	109	Prospective cohort	USA	RP
Pinkawa et al	2006	60	Prospective cohort	Germany	BT
Tseng et al	2006	90	Prospective cohort	USA	RP
Symon et al	2006	50	Prospective cohort	USA	RP + EBRT
Mikhail et al	2006	100	Prospective cohort	USA	RP
Tseng et al	2007	402	Prospective cohort	USA	RP
Frank et al	2007	443	Retrospective cohort	USA	RP + EBRT + BT
Kübler et al	2007	265	Prospective cohort	USA	RP
Ferrer et al	2008	614	Prospective cohort	Spain	RP + EBRT + BT
Hashine et al	2009	184	Prospective cohort	Japan	RP + BT
Anderson et al	2009	263	Retrospective cohort	USA	BT
Thong et al	2010	71	Retrospective cohort	Netherland	EBRT
Freire et al	2009	447	Prospective cohort	USA	RP
Rice et al	2010	665	Prospective cohort	USA	RP + EBRT + BT
Parker et al	2011	382	Prospective cohort	USA	RP
Levinson et al	2011	568	Retrospective cohort	USA	RP
Crook et al	2011	168	RCT	Canada	RP + BT
Kowalczyk et al	2011	610	Retrospective cohort	USA	RP
Willis et al	2012	282	Prospective cohort	USA	RP
Wang et al	2012	1745	Retrospective cohort	USA	RP
Pinkawa et al	2012	67	Prospective cohort	Germany	EBRT
Pinkawa et al	2012	61	Retrospective cohort	Germany	BT
Hutchinson et al	2012	116	Retrospective cohort	USA	RP
Kimura et al	2012	329	Retrospective cohort	USA	RP
Vainshtein et al	2012	16	Prospective cohort	USA	EBRT

BT = brachytherapy; RP = radical prostatectomy; EBRT = external beam radiation

and irritation (-9.9; 95%CI -12,-7.8; $p < 0.001$) scores declined up to 18 months postoperative. Urinary summary scores decreased minimally from 95.5 to 93.4 ($p = 0.009$).

For the brachytherapy group, urinary bother, continence, function, and irritation all decreased from baseline and improved slowly over time. By 18 months, most of the urinary domains had only small declines from baseline.

Between treatment groups, there were small differences in baseline urinary domains. By 18 months post-treatment, patients treated with radical prostatectomy had worse urinary continence but less urinary irritation compared to radiation groups. Overall, average urinary function and quality of life was close to baseline by 18 months, regardless of treatment method.

Sexual domain

For the radical prostatectomy group, average sexual bother, function, and summary scores declined following surgery, improved over time, but did not return to baseline by 18 months, Figure 4. For the external beam radiation group, sexual quality of life and function declined over time. Brachytherapy patients had an initial decline in sexual bother, which then plateaued at 18 months post-treatment. Average sexual function and summary scores did not

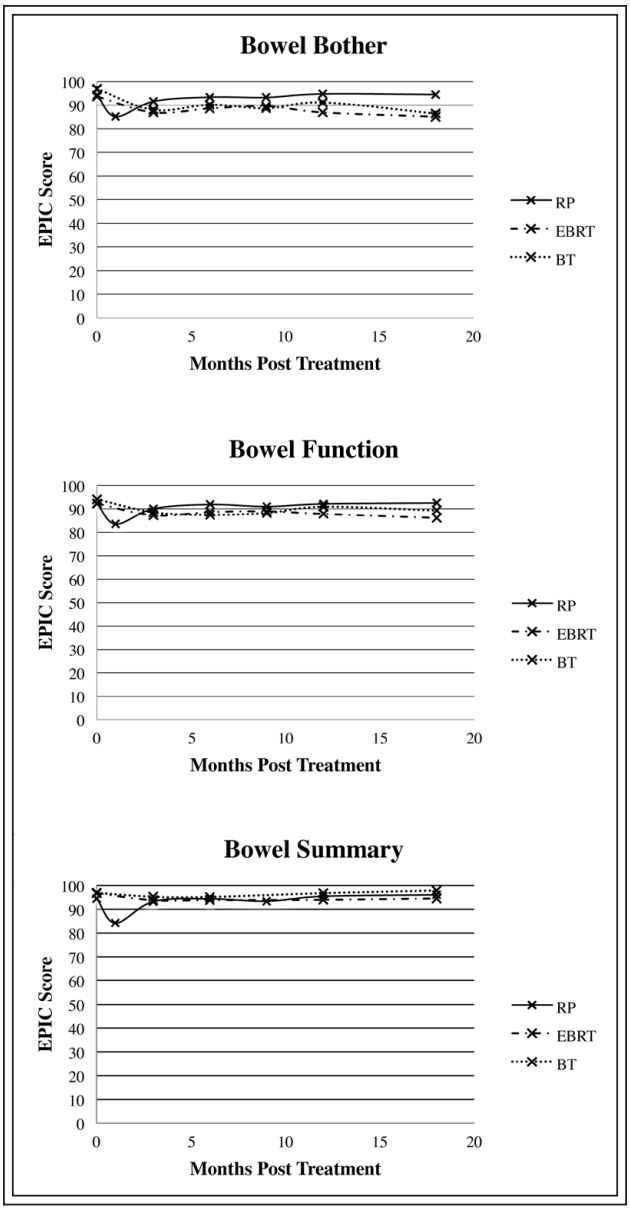

Figure 2. EPIC bowel scores at specific time points.

change significantly from baseline. Overall, radical prostatectomy patients had higher baseline sexual function and quality of life, but by 18 months these domain scores were similar, regardless of treatment group ($p > 0.05$).

Only 3 of the 19 studies evaluating radical prostatectomy patients and 2 of the 13 radiation studies (external beam radiation and/or brachytherapy) reported post-treatment use of erectile function aids, such as phosphodiesterase 5 inhibitors. Among these studies, the percentage of patients who pursued erectile dysfunction aids ranged from 6% to 93%.

Discussion

Management options for localized prostate cancer include active surveillance, watchful waiting, radical prostatectomy, external beam radiation, and brachytherapy. Post-treatment quality of life is an important consideration for patients, especially those with favorable risk prostate cancer who are likely to be cured or live for many years unaffected by their disease. In this study, we systematically reviewed the literature and summarized available data from publications that used the EPIC questionnaire to evaluate prostate cancer patients.

For the bowel domain, the overall trend was that despite the acute decrease in scores for prostatectomy patients within the perioperative period, there was minimal long term impact. Among patients treated with radiation, there was a small reduction in bowel quality of life and function that did not return to baseline. This finding is similar to other studies that utilize assessment tools such as the University of California-Los Angeles Prostate Cancer Index (UCLA-PCI).[9,10] Quality of life related to bowel function overall is better after radical prostatectomy, when compared to external beam radiation or brachytherapy.

All three treatments reviewed have an effect on urinary domains. Radical prostatectomy had the largest negative effect on urinary continence, while brachytherapy and external beam radiation had the largest negative impact on urinary irritation. Therefore, the urinary side effect profile is different between surgery and radiation. These findings are consistent with publications using the EPIC-26.[11]

Many surgical series indicate better sexual quality of life recovery with bilateral nerve sparing.[12,13] For this study, the sexual domain data was based on "typical" prostatectomy cohorts where greater than 75% patients have received bilateral nerve preservation, in the hope to reflect practice in contemporary urological centers of excellence. Inclusion of cohorts with low prevalence of nerve sparing may inaccurately represent function outcomes for surgical patients. Among the included studies, brachytherapy has the least impact on sexual quality of life. Negative effects from radical prostatectomy and external beam radiation on sexual domain are long lasting. Considering that radical prostatectomy cohorts had better pre-treatment function compared to external beam radiation and brachytherapy cohorts, brachytherapy has the most favorable side effect profile on sexual domain, followed by external beam radiation, and then radical prostatectomy.

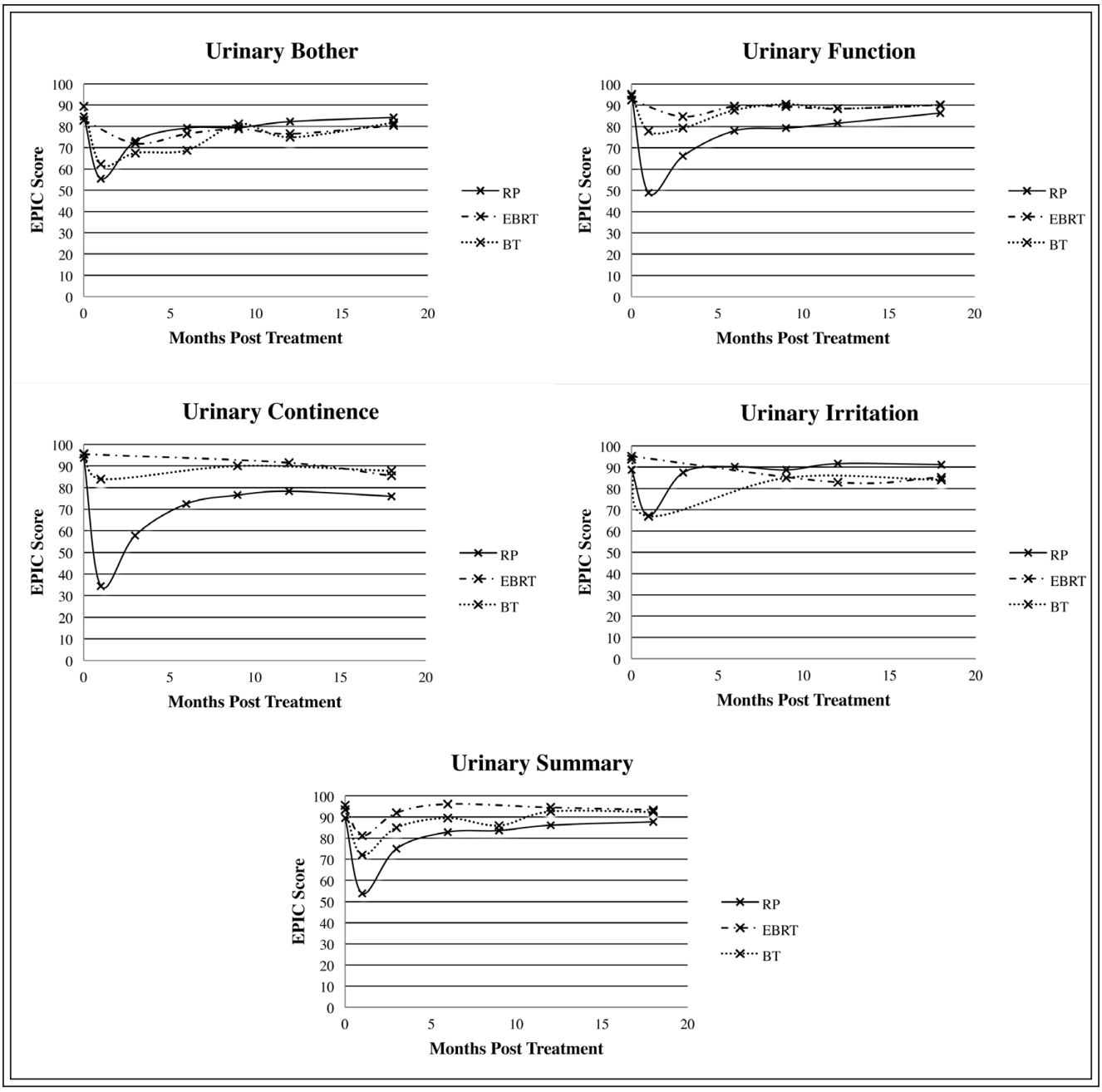

Figure 3. EPIC urinary scores at specific time points.

Only one of the identified articles, SPIRIT, was a randomized controlled trial, which compared quality of life post radical prostatectomy and brachytherapy.[14] Sixty-six and 102 men were treated with radical prostatectomy and brachytherapy, respectively. Although some patients were not randomly assigned to their treatment, the authors have shown that side effects were not statistically different between those who were randomly assigned and those who followed their preference. Patients in the two treatment groups were similar in baseline characteristics including preoperative PSA, comorbidity, and potency. After median follow up of 5.2 years, brachytherapy patients had higher quality of life scores in the sexual domain, with mean score difference of 13.3. This difference was similar to the difference observed between non-randomized patient cohorts (difference of 11.4).

One of the main limitations of this study was short follow up. At the time of publication, the majority of the articles do not report EPIC data beyond 2 years

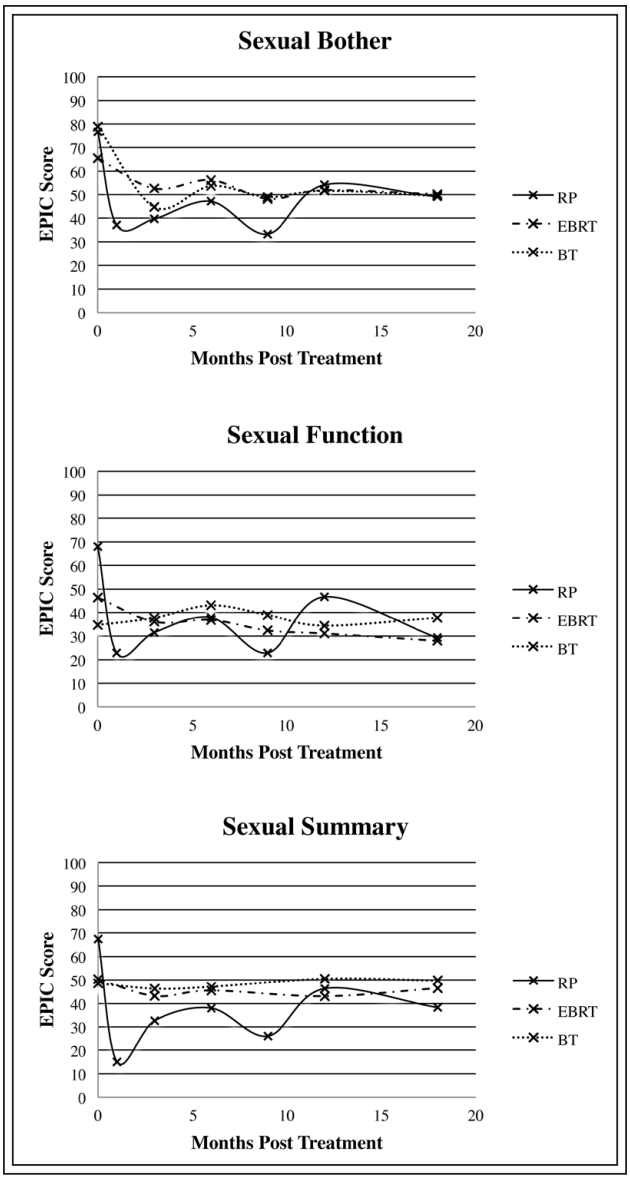

Figure 4. EPIC sexual scores at specific time points.

post-treatment. The recently updated Prostate Cancer Outcomes Study (PCOS) has shown that differences in urinary, bowel, and sexual domains between treatment methods decrease over the long term.[15] Another limitation of this study was that the majority of the data was from North American institutions. Only 5 of the 26 articles originated from Europe and Asia. Given that prostate cancer post-treatment quality of life differs based on race and socio-economical status, the results from included studies may not be generalizable to post-treatment quality of life in different populations throughout the world.[16-18] We were also unable to assess adverse events associated with androgen deprivation, which could be significant for some individuals. Lastly, lack of information about post-treatment interventions such as post-surgery radiation and aids for erectile function and incontinence limited our ability for more detailed or sub-group analysis.

Conclusion

In conclusion, findings from this review are consistent with the published literature using other quality of life instruments. Post-radiation bowel side effect outcomes are less favorable compared radical prostatectomy, with a low probability of returning to baseline. The overall impact on urinary quality of life is similar between surgical and radiation treatment, however, urinary incontinence is most prominent after radical prostatectomy and urinary irritative symptoms are most prominent in patients treated with radiation. On average, brachytherapy was associated with the least impact in sexual quality of life and function. □

References

1. American Cancer Society: Cancer Facts and Figures 2015. http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/index.
2. Shao YH, Demissie K, Shih W et al. Contemporary risk profile of prostate cancer in the United States. *J Natl Cancer Instit* 2009; 101(18):1280-1283.
3. Li J, Djenaba JA, Soman A et al. Recent trends in prostate cancer incidence by age, cancer stage, and grade, the United States, 2001-2007. *Prostate Cancer* 2012;2012:691380.
4. Kim J, Ebertowski J, Janiga M et al. Many young men with prostate-specific antigen (PSA) screen-detected prostate cancers may be candidates for active surveillance. *BJU Int* 2013;111(6):934-940.
5. Sidana A, Hernandez DJ, Feng Z et al. Treatment decision-making for localized prostate cancer: what younger men choose and why. *Prostate* 2012;72(1):58-64.
6. Wei J, Dunn R, Litwin M 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(6):899-905.
7. Harris CR, Punnen S, Carroll PR. Men with low preoperative sexual function may benefit from nerve sparing radical prostatectomy. *J Urol* 2013;190(3):981-986.
8. Sivarajan G1, Prabhu V, Taksler GB et al. Ten-year outcomes of sexual function after radical prostatectomy: results of a prospective longitudinal study. *Eur Urol* 2014;65(1):58-65.
9. Huang GJ, Sadetsky N, Penson DF. Health related quality of life for men treated for localized prostate cancer with long-term follow up. *J Urol* 2010;183(6):2206-2212.
10. Gore JL, Kwan L, Lee SP et al. Survivorship beyond convalescence: 48-month quality-of-life outcomes after treatment for localized prostate cancer. *J Natl Cancer Instit* 2009; 101(12):888-892.

11. 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(12):1250-1261.
12. Rabbani F, Stapleton AM, Kattan MW et al. Factors predicting recovery of erections after radical prostatectomy. *J Urol* 2000; 164(6):1929-1934.
13. Catalona WJ, Carvalhal GF, Mager DE et al. Potency, continence and complication rates in 1,870 consecutive radical retropubic prostatectomies. *J Urol* 1999;162(2):433-438.
14. Crook JM, Gomez-Iturriaga A, Wallace K et al. Comparison of health-related quality of life 5 years after SPIRIT: Surgical Prostatectomy Versus Interstitial Radiation Intervention Trial. *J Clin Oncol* 2011;29(4):362-368.
15. Resnick MJ, Koyama T, Fan KH et al. Long-term functional outcomes after treatment for localized prostate cancer. *N Engl J Med* 2013;368(5):436-445.
16. Chornokur G, Dalton K, Borysova ME et al. Disparities at presentation, diagnosis, treatment, and survival in African American men, affected by prostate cancer. *Prostate* 2011;71(9): 985-997.
17. Rice K, Hudak J, Peay K et al. Comprehensive quality-of-life outcomes in the setting of a multidisciplinary, equal access prostate cancer clinic. *Urology* 2010;76(5):1231-1238.
18. Namiki S, Carlile RG, Namiki TS et al. Racial differences in sexuality profiles among American, Japanese, and Japanese American men with localized prostate cancer. *J Sex Med* 2011;8(9):2625-2631.