

Scientific Article

Urinary quality of life outcomes in men who were treated with image-guided intensity-modulated radiation therapy for prostate cancer

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Abstract

Purpose: Quality of life (QoL) outcomes play a major role in the treatment selection for prostate cancer (CaP). We evaluated the urinary QoL outcomes in men who were treated with image-guided intensity-modulated radiation therapy (IG-IMRT) for CaP.

Methods and materials: We enrolled men who were diagnosed with CaP and underwent IG-IMRT in a large urological group practice into a prospectively maintained database. The typical radiation treatment dosage to prostates and seminal vesicles was 8100 cGy in 45 fractions. Urinary QoL was self-assessed using the standardized incontinence grade and International Prostate Symptom Score (IPSS) at baseline and at each follow-up visit. We evaluated the cumulative incidence of urinary incontinence and changes in both continence and IPSS over time.

Results: Of the 3602 men who were eligible for analysis, 3086 (85.7%) had no urinary incontinence; 479 (13.3 %) had minimal incontinence (no requirement for pads), and 37 (1.0 %) had significant urinary incontinence that required the use of pads or interfered with activities of daily living, at baseline. After a median follow-up of 24 months (range: 12.0-41.0 months), these numbers were 80.6%, 17.4%, and 2.0%, respectively. Radiation therapy appeared to have a beneficial effect on some men: 54.1% of men with minimal incontinence became completely continent of urine during follow-up. Of those with significant urinary incontinence, 29.7% reported resolution and 27.0% reported improved symptoms with no requirement for pads. Of the 1276 men with moderate IPSS, the mean IPSS decreased from 12 to 9.8 at the time of the last follow-up ($P < .001$). Similarly, of the 233 men with severe IPSS, the mean IPSS decreased from 24 to 13 at the time of the last follow-up ($P < .001$).

Conflict of interest: None.

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Conclusion: IG-IMRT for clinically localized CaP is associated with a relatively low incidence of urinary incontinence. Although unexplained, IG-IMRT seems to improve symptoms in some men with baseline urinary incontinence and moderate-to-severe IPSS.

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Introduction

Prostate cancer (CaP) is the most common solid-organ malignancy diagnosed in men in the United States and accounted for an estimated 27,540 deaths in 2015.¹ The choice of treatment for patients who are diagnosed with CaP depends on the promise of oncologic control with minimal potential for side effects or complications. Available options for the treatment of clinically localized CaP include active surveillance, radical prostatectomy, brachytherapy, and external beam radiation therapy with or without hormone therapy. A key concern for most men who face this decision is the possible loss of urinary control or urinary incontinence.

Radical prostatectomy is one recommendation for clinically localized CaP in men with an estimated life expectancy of 10 years or more who do not qualify for active surveillance.² This procedure, however, is associated with life-changing complications and quality of life (QoL) issues for patients and their spouses, such as erectile dysfunction and urinary incontinence.³ Resnick et al.⁴ reported that patients who undergo prostatectomy were more likely to have urinary incontinence at 2 years, compared with patients who had radiation therapy (odds ratio, 6.2; 95% confidence interval [CI]: 1.9-20.3), and 5 years (odds ratio, 5.1; 95% CI: 2.3-11.4). The incidence of erectile dysfunction and urinary incontinence remained unchanged even after the introduction of laparoscopy with or without robotic assistance. On the other hand, with the introduction of image guidance, external beam radiation therapy has demonstrated a lower risk of short- and long-term toxicities compared with older radiation techniques while significantly delivering higher doses of radiation to the prostate.⁵⁻⁹ In this article, we report on the urinary QoL outcomes in a large cohort of men who underwent image-guided intensity modulated radiation therapy (IG-IMRT) for clinically localized CaP.

Methods and materials

This is a retrospective study based on deidentified data derived from our Mount Sinai Hospital institutional review board-approved database. We treated 3602 men with clinically localized CaP using IG-IMRT at our multispecialty practice between March 31, 2008 and

September 28, 2012. Baseline clinical characteristics and pathologic data were collected prospectively. Patients typically underwent a standard 12-core prostate biopsy for various indications including but not limited to elevated or increasing prostate-specific antigen levels or abnormal digital rectal examination findings. After a diagnosis of CaP, patients were staged according to the National Comprehensive Cancer Network guidelines.² Patients then participated in shared decision-making consultations with radiation oncologists and urologists and were counseled on the appropriate management options available, including observation, active surveillance, radical prostatectomy (open, laparoscopic, or robotic-assisted laparoscopic), radiation therapy (brachytherapy and/or external beam), and androgen deprivation therapy (ADT). The urologists and radiation oncologists had previously designed and implemented a clinical pathway in which all men with CaP that was very low risk per the National Comprehensive Cancer Network guidelines were urged to select active surveillance as their best choice.

The data of the 3602 patients included in this report are only from those who chose IG-IMRT. Exclusion criteria for IG-IMRT included history of radiation to the pelvis and active inflammatory bowel disease. Participants with a history of urinary incontinence at baseline were not excluded from the analysis. Radiation therapy was administered under image guidance and typically at dosages of 180 cGy per fraction to a total dose of 8100 cGy (45 fractions total). Radiation therapy was delivered to the prostate in 137 patients (3.8%); to the prostate and seminal vesicles in 3007 patients (83.5%); and to the prostate, seminal vesicles, and pelvic lymph node regions in 458 patients (12.7%) at the discretion of the treating radiation oncologist and based on the clinical stage and risk for advanced disease. Fiducial markers were placed in all patients before the initiation of treatment. Daily cone beam computed tomography (CBCT) imaging was used to accurately deliver targeted radiation therapy. Typically, a cone down of the seminal vesicles or pelvic nodal regions would be performed after reaching a dose of 4500 cGy in daily fractions. Routinely, we employed more stringent dose constraints on the bladder than those of Radiation Therapy Oncology Group protocols (RTOG0815). Specifically, our target goal is a bladder D10 <7200 cGy and a bladder D50 <4000 cGy. Based

on available evidence and at the discretion of the radiation oncologist, ADT in the form of neoadjuvant, concomitant, and/or adjuvant treatment was utilized.

The primary outcome of interest in this analysis was overall urinary function and urinary incontinence, which was self-reported by the study participants both at the time of the initial consultation (before initiation of the radiation therapy) and at each follow-up visit during or after radiation treatment. Incontinence was reported with use of a standardized incontinence grading system and assessed by the patient, who checked off the appropriate score describing degree of incontinence (Appendix A), which was then entered into the electronic medical record. The score options were G0 (totally continent), G1 (minor incontinence that does not require pads), G2 (significant incontinence that requires pads), and G3 (incontinence that interferes with everyday life activities).

Overall urinary function was self-assessed by patients in a similar fashion by checking off International Prostate Symptom Score (IPSS) boxes at baseline and at the time of each follow-up visit. Total IPSS were entered in the electronic medical record for each patient at the time of each visit. Urinary bother scores were not included in the majority of IPSS scores. Men with IPSS scores of 0 to 7, 8 to 19, and 20 to 35 were deemed mildly, moderately, and severely symptomatic, respectively. Participants were seen in follow-up at 1 month after radiation therapy and every 6 months thereafter. Participants' self-assessment of urinary incontinence and completed IPSS questionnaires were collected at each follow-up visit. We evaluated the cumulative incidence of urinary incontinence, change in incontinence grade, and IPSS over time. Chi-square and t-tests were used for comparisons, and 2-sided *P* values were reported at .05 level of significance.

Results

A total of 3602 patients with a mean age of 71.3 years (range: 47-94 years) met the eligibility criteria for this analysis. The median follow-up period was 24 months (range: 12.0-41.0 months). The clinical characteristics and pathological features of the cohort are summarized in Tables 1 and 2. As illustrated in Table 2, 46.7% of men received neoadjuvant, concomitant, and/or adjuvant ADT for a mean duration of 11.2 months (range: 1.0-12.0 months). At baseline, 3086 patients (85.7%) reported no urinary incontinence (G0), 479 patients (13.3%) had G1 urinary incontinence, and 37 patients (1.0%) had G2 or G3 urinary incontinence (Fig 1). At the end of the follow-up, the proportions of men with G0, G1, and G2 or G3 urinary incontinence were 80.6%, 17.4%, and 2.0%, respectively.

The prevalence of significant urinary incontinence, defined as any incontinence that requires the use of pads

or interferes with activities of daily living (G2 and G3 combined), was 1.0% at baseline (Fig 1). The cumulative incidence of significant urinary incontinence was 1.4% over a median duration of 24.0 months (Fig 2a), which was not significantly different from the baseline prevalence (*P* = .171). In this subgroup of men (G0; *n* = 3086), 85.4% of patients remained continent (G0) whereas 13.2% of patients developed dribbling that did not require the use of pads at the end of follow-up (Fig 2a).

As shown in Figure 2b, among patients who had dribbling of urine that did not require the use of pads at baseline, 259 (54.1%) had a complete resolution (G0) of their symptoms at the end of follow-up. However, 208 (43.4%) in this group still reported dribbling (G1), and 12 (2.5%) progressed to significant urinary incontinence (G2 or G3). Due to the small number of participants with significant urinary incontinence (G2 and G3) at baseline (*n* = 37), they were combined for a subgroup analysis. As shown in Figure 2c, 16 patients (43.4%) in this subgroup reported no change in their symptoms. However, 11 (29.7%) reported complete resolution of incontinence, and the remaining 10 (27.0%) reported improved symptoms without the need for pads. Although not statistically significant, participants with urinary incontinence who did not require pads at baseline (G1) were more likely to develop significant urinary incontinence during follow up compared with those who were continent of urine at baseline (2.5% vs. 1.4%, respectively; *P* = .066; Fig 2a and b).

Baseline self-reported IPSS was identified as mild (0-7) in 2092 men (58.1%), moderate (8-19) in 1276 men (35.4%), and severe (20-35) in 233 men (6.5%; Fig 3). The mean IPSS for each subgroup is also presented in Figure 3. In 2092 men with mild IPSS at baseline, the mean IPSS increased from 3.5 to 5.4 at the end of follow up. However, in the 1276 men with moderate IPSS at baseline, the mean IPSS decreased from 12 to 9.8 at the time of the last follow up visit (*P* ≤ .001). Similarly, in the 233 men with severe IPSS at baseline, the mean IPSS decreased from 24 to 13.4

Table 1 Clinical characteristics and pathological features of participants who underwent IG-IMRT for prostate cancer

Variable	Value (Range/%)
Mean age (yr)	71.3 (47-95)
Mean pretreatment PSA (ng/dL)	7.1 (0.01-130.5)
Mean recent PSA (ng/dL)	2.4 (0.0-372)
Gleason grade	
≤6	1667 (46.3%)
7	1460 (40.5%)
8-10	475 (13.2%)
Mean number of positive cores	3.7 (1-18)
Perineural invasion	665 (18.5%)

IG-IMRT, image-guided intensity-modulated radiation therapy; PSA, prostate-specific antigen.

Table 2 Treatment of participants who underwent IG-IMRT for prostate cancer

Variable	Value (Range/%)
Hormone therapy	1683 (46.7%)
Mean duration of hormone therapy (months)	11.2 (1.0-12.0)
Radiation target	
Prostate only	137 (3.8%)
Prostate, SV	3007 (83.5%)
Prostate, SV, Nodes	458 (12.7%)

IG-IMRT, image-guided intensity-modulated radiation therapy; SV, seminal vesicles.

at the time of the last follow-up visit ($P \leq .001$). Although there was no clinically significant difference between the mean IPSS reported at baseline and at the end of follow-up (7.9 vs. 7.5), we observed an improvement in IPSS for patients who had moderate or severe IPSS prior to IG-IMRT (Fig 3). Radiation target volume or addition of ADT did not modify the effect of IG-IMRT on IPSS in any of the 3 categories (data not shown).

Lower urinary tract symptoms that were reported by the study participants included dysuria in 145 men (4.0%) pre-IMRT and 264 (7.3%) post-IG-IMRT. The pain level that was associated with urination was reported as mild by 709 patients (19.7%), moderate by 127 patients (3.5%), severe (i.e., interferes with ADL) by 24 patients (0.7%), and disabling by 5 patients (0.1%). However, 2737 men (76.0%) had no pain whatsoever. Hematuria was reported by 43 men (1.2%) prior to treatment and by 82 (2.3%) after IG-IMRT. Prior to undergoing IG-IMRT, 669 men (18.6%) were taking medications for urination and 1,389 (38.6%) were taking medications to aid urination after IG-IMRT.

Discussion

Radiation therapy, with or without androgen deprivation, is an established treatment option for patients with clinically localized CaP. Some of the advantages of radiation therapy over radical prostatectomy include avoidance of significant bleeding, need for transfusion, other surgical and anesthesia-related complications, and rare requirement for hospital stay. In addition, functional outcomes as measured by urinary incontinence rate and erectile dysfunction remain an important factor that guides patients and their urologists in making treatment decisions. In our study, we estimated the cumulative incidence of significant urinary incontinence after IG-IMRT at 1.4%, which was unchanged from baseline (1.0%; $P = 0.171$). We also found that urinary incontinence in some men improved, and urinary QoL measured by IPSS improved significantly in men with moderate-to-severe scores at baseline.

A relatively low incidence of urinary incontinence is an advantage of radiation therapy delivered with imaging guidance. In an analysis of 129 patients with low- and intermediate-risk CaP who were treated with high-dose hypofractionated radiation therapy (dose = 66 Gy; 22 daily fractions of 3 Gy), Patel et al.¹⁰ reported Grade ≥ 2 late genitourinary (GU) toxicities of 33% at a median follow-up of 90 months and 1.5% at 116 months. In our cohort, however, we reported a cumulative incidence of significant urinary incontinence of 1.4% after a median follow-up of 24 months, which was not statistically significantly different from the prevalence of significant urinary incontinence of 1.0% at baseline ($P = .171$). A possible explanation for the low rate of incontinence in our cohort compared with the rate reported by Patel et al.¹⁰ could be the use of fiducial markers and daily CBCT in

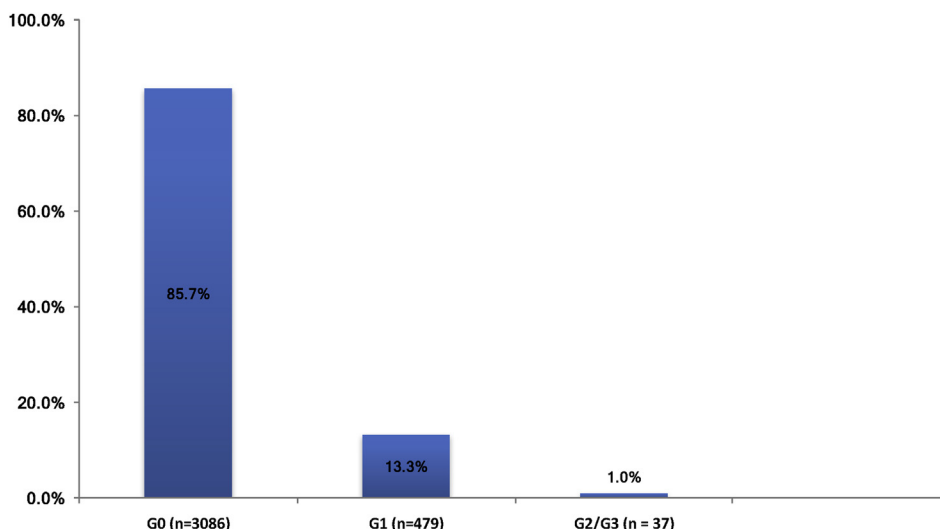


Figure 1 Baseline urinary continence status of participants who undergo image-guided intensity-modulated radiation therapy for prostate cancer.

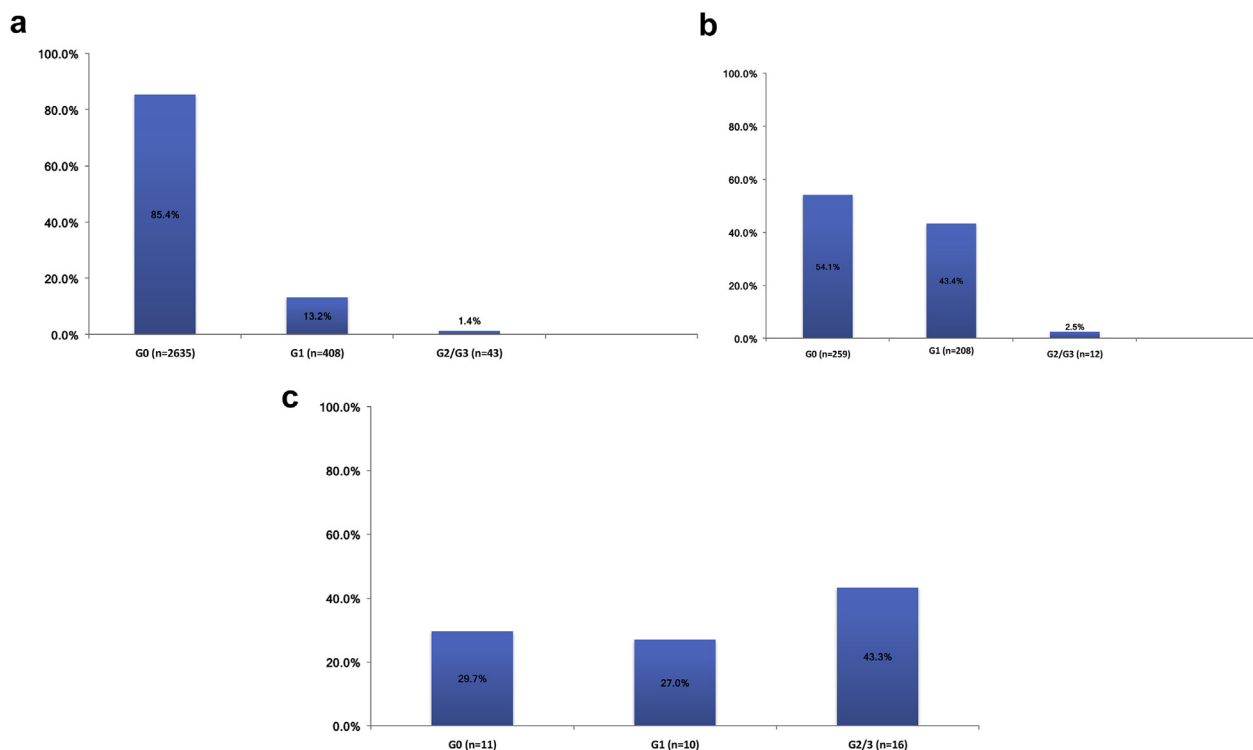


Figure 2 Urinary continence status of participants treated with image-guided intensity-modulated radiation therapy for prostate cancer at the end of follow up (a) G0 at baseline (n = 3806); (b) G1 at baseline (n = 479); and (c) G2/3 at baseline (n = 37).

our cohort to aid delivery of radiation. Although a daily ultrasound was performed to localize the prostate in the study reported by Patel et al.,¹⁰ use of computed tomography imaging in the delivery of radiation has the promise of more accurately delineating tissue planes and allowing focused and/or targeted delivery of radiation while sparing normal tissues, including neurovascular bundles.^{11,12}

Several studies have evaluated the impact of radiation therapy on urinary function and QoL using the IPSS

questionnaire with up to 40% of Grade 1 to 3 toxicities reported.¹³⁻¹⁶ In an assessment of late GU toxicity and QoL after radiation therapy in 268 patients with CaP who received follow-up for a median duration of 5 years, Ghadjar et al.¹³ reported 20% Grade 2 and 1% Grade 3 late toxicities and no change in overall QoL index. The authors also reported an overall median increase in median IPSS sum of 3. Conversely, in a cohort of 337 participants, Jerezek-Fossa et al.¹⁷ reported that there was

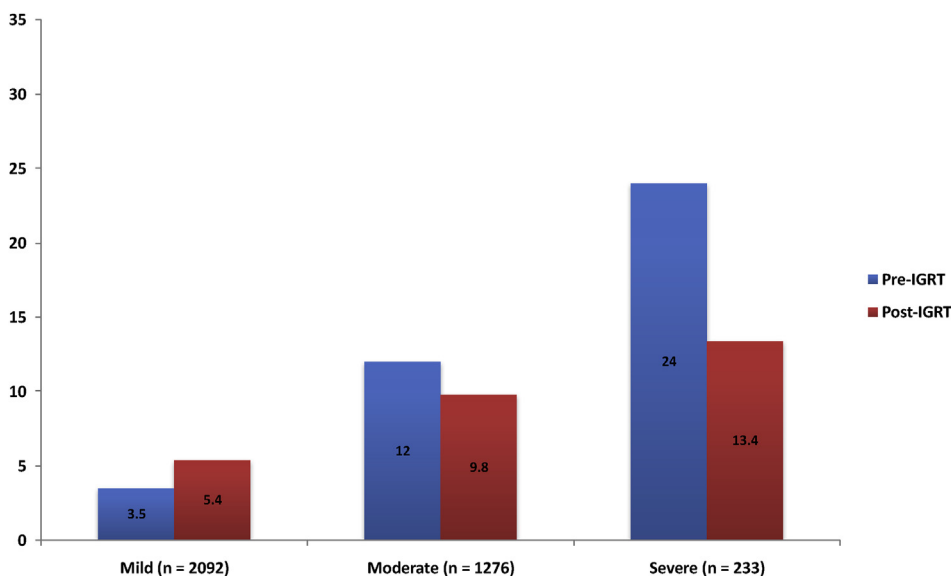


Figure 3 Mean international prostate symptom score (IPSS) pre- and post-image-guided intensity-modulated radiation therapy by severity of IPSS at baseline.

no change in urinary symptom-related QoL in participants who underwent image-guided radiation therapy for CaP. However, this was after a median follow-up of 19 months in a relatively small cohort of patients.¹⁷ To our knowledge, our cohort represents the largest reported incidence of urinary incontinence after IG-IMRT. Although the mean IPSS at the end of follow-up was not significantly different from baseline in our cohort (7.9 vs. 7.5), we reported a significant decrease in IPSS of men with moderate or severe IPSS at baseline. Similar to our results, Malik et al.¹⁶ reported a decline in mean IPSS score of -3.6 to -6.9 points during follow-up after radiation therapy for CaP ($P < .05$). Our findings highlight the possible benefit of IG-IMRT compared with radiation delivery without imaging guidance. Also, to our knowledge, our study represents the largest cohort in literature to examine urinary QoL after radiation treatment for CaP.

An interesting finding in our cohort is the proportion of patients with improved incontinence symptoms and IPSS after radiation therapy. For example, 54.1% of participants with G1 incontinence at baseline became completely continent, and men with moderate or severe IPSS reported a significant improvement after radiation therapy (Fig 2b and 3). The observed improvement in symptoms may be explained by shrinkage in prostatic tissue due to radiation effect, treatment effect on cancer-related symptoms, the use of urinary-directed medications, and—less likely—regression toward the mean. Given that urinary incontinence was self-reported by the study participants, it is also possible that cancer control (decreasing prostate-specific antigen) after radiation therapy may have had a placebo effect on the patients' incontinence symptoms. However, we observed the same effect in participants who had significant urinary incontinence that required the use of pads (G2 and G3) at baseline, of whom 29.7% became completely continent of urine after radiation therapy for CaP. While further studies are needed to explore the impact of radiation therapy on the improvement of urinary incontinence or QoL, our results may be useful to counsel patients who are considering radiation therapy to treat CaP.

Limitations

Our study is not without limitations. First, we did not evaluate the acute toxicity effect of radiation, which includes temporary bladder and/or bowel symptoms. Kuban et al.¹⁸ reported a Grade ≥ 2 gastrointestinal toxicity rate of 13% to 26% and a GU toxicity rate of 8% to 13%, depending on whether participants received low or high doses of radiation. Their analysis showed that a reduction in the amount of radiation to the rectum could lower the complication rate, which we were able to achieve in our cohort with daily computed tomography imaging guidance to guide radiation delivery. Second, the treatment period of

8 to 9 weeks may render radiation therapy less attractive to patients compared with radical prostatectomy, which typically requires an average hospital stay of 4 days or less. Therefore, patient counseling must include a detailed discussion of what each treatment option involves, and a risk–benefit analysis should be performed. Third, the results of our study may not extrapolate to 10 to 15 years posttreatment. Resnick et al.⁴ reported that participants who underwent a prostatectomy were more likely to have urinary incontinence at 2 years than participants who had radiation therapy (odds ratio, 6.2; 95% CI: 1.9–20.3) and 5 years (odds ratio, 5.1; 95% CI: 2.3–11.4). However, they showed that this difference in incidence of urinary incontinence seemed to disappear at 15 years of follow-up. One may argue that health-related QoL issues are more important to younger men than to older men, rendering radiation treatment more attractive to younger patients with CaP. In a recent randomized control study, surgery was reported to have the worst outcome on urinary continence compared with radiation therapy or monitoring.¹⁹

Conclusion

Image-guided intensity modulated radiation therapy remains a valid option for the treatment of patients with clinically localized CaP. In the largest cohort of men reported in the literature, we demonstrated a relatively low incidence of significant urinary incontinence associated with IG-IMRT. We also reported improvements in urinary QoL in men with moderate or severe IPSS at baseline. These findings may be used by clinicians to counsel eligible patients who are diagnosed with primary localized CaP regarding treatment options. However, studies with large sample sizes such as ours with a longer follow-up duration are needed to evaluate how urinary function after IG-IMRT evolves in the long term.

Supplementary Data

Supplementary material related to this article can be found at <http://dx.doi.org/10.1016/j.adro.2016.10.005>.

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