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Scientific Article

Building a High-Dose-Rate Prostate Brachytherapy Program With Real-Time Ultrasound-Based Planning: Initial Safety, Quality, and Outcome Results

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Abstract

Purpose: Growing evidence supports the efficacy and safety of high-dose-rate (HDR) brachytherapy as a boost or monotherapy in prostate cancer treatment. We initiated a new HDR prostate brachytherapy practice in April 2014. Here, we report the learning experiences, short-term safety, quality, and outcome.

Methods and Materials: From April 2014 to December 2017, 164 men were treated with HDR brachytherapy with curative intent. Twenty-eight men (17.1%) underwent HDR brachytherapy as monotherapy, receiving 25 to 27 Gy in 2 fractions. Men treated with HDR brachytherapy as a boost received 19 to 21 Gy in 2 fractions. Fifty-two men (31.7%) had high-risk disease. HDR procedure times, dosimetry, and response were recorded and analyzed. Genitourinary (GU) and gastrointestinal (GI) toxicities were recorded according to the toxicity criteria of the Radiation Therapy Oncology Group.

Results: Mean HDR procedure times decreased yearly from 179 minutes in 2014 to 115 minutes in 2017. Median follow-up was 18.6 months (range, 3-55 months). At last review, 79% of patients reported returning to baseline GU status, and 100% of patients noted no change in GI status from their baseline. Four patients experienced acute urinary retention. Treatment planning target volume (PTV) was defined as prostate with margins. Dosimetrically, 97.5% of all HDR implants had PTV D90 $\geq$100%, 81.5% had PTV V100 $\geq$95%, 73.6% had maximal urethral doses $\leq$120%, and 77.5% had rectal 1 mL dose $\leq$70% (all but one $\leq$10.8 Gy). The estimated 3-year overall survival was 98.7% (95% confidence interval, 91.4%-99.8%), and disease-free survival was 96.2% (95% confidence interval, 89.5%-98.7%).

Conclusions: The low incidence of GU and GI complications in our cohort demonstrates that a HDR brachytherapy program can be successfully developed as a treatment option for patients with localized prostate cancer.

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Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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Introduction

Nonmetastatic prostate cancer has a long natural history. The American Cancer Society estimates the 5-year overall survival rate for men with locoregional disease is near 100%. The National Institute for Health Research–Supported Prostate Testing for Cancer and Treatment trial found that 10-year prostate cancer-specific survival is nearly 100%, irrespective of the treatment assigned to men with either low- or intermediate-risk disease.[1] Nearly 80% of men with prostate cancer die of other causes.[2] Therefore, maintaining a patient's quality of life and ultimate disease control are the overarching goals of prostate cancer management.

Treatment options for nonmetastatic prostate cancer have traditionally included surgery or radiation, either external beam radiation or brachytherapy. Despite its declined usage in the United States,[3,4] prostate brachytherapy is highly effective in cancer control with comparable, if not fewer, side effects.[5-8] The National Comprehensive Cancer Network guidelines now list prostate brachytherapy as an option, either alone or in combination with external beam radiation, for all disease risk groups. With its advantages of precise dosimetry, no radiation exposure to the providers and to a lesser degree to the patients compared with permanent seed implants, high-dose-rate (HDR) prostate brachytherapy offers a compelling alternative option.[9-13] Because HDR brachytherapy has been used to treat other malignancies, especially gynecologic cancers, many institutions have an HDR program. Expanding its role to prostate cancer treatment maximizes the usage of existing resources, thus reducing the overall cost of maintaining an active HDR program.

With the support of our multidisciplinary team, we initiated HDR prostate brachytherapy in April 2014. After reviewing various HDR protocols, we chose real-time ultrasound-based planning instead of a CT-based one.[14–16] By eliminating patient transfer, real-time ultrasound-based planning allows the entire treatment to be completed in one setting within a shorter timeframe. We observed the treatment process at Odette Cancer Center in Toronto, Ontario, Canada and followed a similar workflow with minor adjustments to fit into our institution practice at that time.[16] Here, we report our initial experience after retrospectively reviewing procedure times, patient side effect profiles, implant quality, and outcome data. Our experience provides support that a quality HDR prostate brachytherapy can be developed following existing successful protocols.

Methods and Materials

Data from 164 patients who had HDR prostate brachytherapy, either as a boost or monotherapy, at our institution from April 2014 to December 2017 were reviewed. All patients had biopsy-proven adenocarcinoma of the prostate without clinical or imaging evidence of metastatic disease. Prostate cancer was classified into low-, intermediate-, or high-risk groups according to National Comprehensive Cancer Network guidelines. Patient characteristics are shown in Table 1.

All patients were asked to perform an enema on the day of the procedure. HDR prostate brachytherapy procedures reported here were performed under spinal anesthesia. An anesthesiologist was responsible for the placement of spinal anesthesia and level of sedation, and was present during the entire procedure. After spinal anesthesia, the patient was placed in the dorsal lithotomy position. The ultrasound probe, attached to a stepper, was placed through the rectum and secured during the entire treatment process. A Foley catheter was then placed. If we were not able to clearly define the urethra on the ultrasound image, we instilled aerated gel into the Foley catheter to improve visualization. Ultrasound images were acquired after a rigid template was secured onto the stepper. Prostate, urethra, and rectum were contoured once images were transferred into the planning system. Planning target volume (PTV) was defined as prostate with 3-mm margins all around, except posteriorly with no margin or with a margin as deemed necessary by the treating physician. A preplan was generated using a standardized pattern of catheter placement with adjustment based on each individual patient's prostate and urethral anatomy, for example in cases of prostate asymmetry or deviated urethra. Plastic afterloading catheters with a metal stylet were then inserted into the prostate gland under ultrasound guidance according to the preplan. The second set of ultrasound images were then acquired. The placement of catheters was verified. The final treatment plan was then optimized based on verified catheter location. The treatment was delivered after transfer cables were connected to the HDR afterloader. Once the treatment was completed, all catheters were removed. A new Foley catheter was placed and the patient was transferred to the recovery room.

All patients were given a single dose of intravenous antibiotics during the procedure. They were discharged with a Foley catheter in place and a 3-day course of oral antibiotics. They were instructed to remove the Foley catheter in the morning the day after the procedure.

When HDR brachytherapy was used as monotherapy, the treatment was delivered in 2 fractions, 12.5 to 13.5 Gy per fraction, 1 week apart. When HDR brachytherapy was used as a boost, the treatment was delivered in 2 fractions, 9.5 to 10.5 Gy per fraction, 1 week apart. External beam phase of treatment doses ranges from 46 to 50 Gy at 2 Gy per fraction. Inclusion of pelvic nodal regions was at the discretion of treating radiation oncologist.

HDR dosimetry and prostate-specific antigen (PSA) response were recorded and analyzed. Genitourinary (GU)

Table 1 Study cohort characteristics

	No.	Percentage
Age, y (48-83)		
Median	68	-
Average	67	-
<70	103	62.8
≥70	61	37.2
PSA (1.06-79)		
Median	6.86	
Average	9.44	
Gleason scores		
3 + 3	13	7.9
3 + 4	63	38.4
4 + 3	36	22.0
3 + 5/4 + 4/4 + 5	52	31.7
Risk grouping		
Low	13	7.9
Favorable intermediate	46	28.0
Unfavorable intermediate	53	32.3
High	52	31.7
Treatment		
HDR monotherapy	28	17.1
Combined radiation	136	82.9
ADT		
Yes	100	61.0
No	64	39.0

Abbreviations: ADT = androgen deprivation; HDR = high-dose-rate; PSA = prostate-specific antigen.

and gastrointestinal (GI) toxicities were recorded according to the toxicity criteria of the Radiation Therapy Oncology Group. Acute toxicity was defined as events in the initial 6 months post-HDR procedure. Overall survival (OS) and prostate cancer disease-free survival (DFS) were estimated using Kaplan-Meier survival analysis. Biochemical recurrence was defined based on American Society for Therapeutic Radiology and Oncology Phoenix definition (PSA nadir + 2 ng/mL).

Procedure time for each HDR implant was calculated based on procedure start and stop time recorded as part of anesthesia event report. The nonparametric Kruskal-Wallis test was used to compare procedure times by year. The χ^2 test was used to compare GU toxicity by year.

Results

A total of 164 men with localized prostate cancer were treated with HDR prostate brachytherapy as either monotherapy (17.1%) or in combination with external beam radiation (82.9%; Table 1). Sixty-one men (37.2%) were 70 or older. Fifty-two men (31.7%) had Gleason Score 8 or 9 (3 + 5, 4 + 4, or 4 + 5) disease. The majority of patients (61%) had androgen deprivation (ADT) with Leuprolide as part of the treatment regimen. Median duration of ADT was 8 months (range, 1-28 months). Five patients had only 1 month of ADT, and 3 had 2 months of ADT for prostate gland downsizing.

HDR implant dosimetry

A total of 314 implants were performed. Of those, 306 (97.5%) had PTV D90 ≥ 100%, and 256 (81.5%) had PTV V100 ≥ 95% (Fig 1). In addition, 231 (73.6%) had maximal urethral doses ≤ 120%, and 243 implants (77.4%) had rectal 1 mL dose ≤ 70% (all but one ≤10.8 Gy).

Treatment toxicity

Within the first month after HDR treatment, 3 patients (all in 2017) developed urosepsis requiring additional antibiotic treatment, and 4 patients developed urinary retention (one man's HDR was done in 2015, one in 2016, and 2 in 2017). All 4 patients with urinary retention had acceptable urinary status (ie, approximate International Prostate Symptom Score <18) before HDR, and their prostate volumes were all <50 mL. At last follow-up, one man had urethal stricture at 5.7 months post HDR, one had grade 2 GU toxicity at 8.3 months, and the other 2 had less than grade 1 GU toxicity at 20.7 and 47.6 months, respectively.

At last review, GU status had returned to baseline in 79% of patients. No patients noted any change in GI status from their baseline (Table 2). As noted earlier, one patient in the entire cohort developed urethral stricture (0.6%).

Learning curve

We started our program slowly to ensure safety. As a group, we were able to master the technique of the procedure very quickly, as shown with significant decreased procedure time by year ($P < .001$, Fig 2). We did not observe significant differences in implant dosimetry during this period (data not shown). No significant difference was noted in acute urinary toxicity over time ($P = .734$, Fig 3).

Oncologic outcome

Median follow-up was 18.6 months (range, 3-55 months). At last review, only one patient (with node positive prostate cancer at diagnosis) died of metastatic disease 1.6 years after treatment. Three patients had disease recurrence but were still alive at last follow-up (2 patients exhibited biopsy-proven prostate-only recurrence, and one with only biochemical recurrence). Estimated DFS at 3 years was 96.2% for the entire group (95% confidence interval [CI], 89.5%-98.7%). Estimated OS at 3 years was 98.7% (95% CI, 91.4%-99.8%; Fig 4).

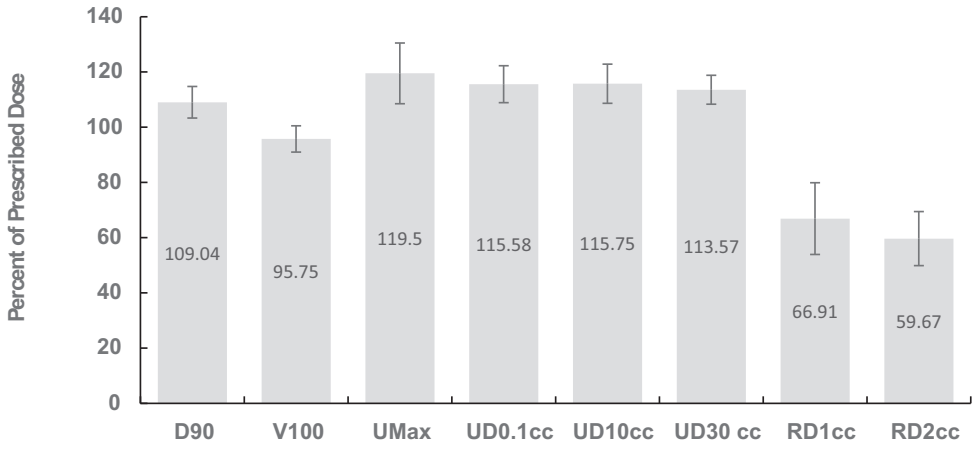

Figure 1 Implant dosimetry. *Abbreviations*: D90 = median percentage of prescribed dose covering 90% of the PTV; V100 = median percentage of planning target volume receiving 100% of prescribed dose; UMax = median maximal urethral dose in percentage of prescribed dose; UD0.1cc = median dose in percentage of prescribed dose to 0.1 mL of urethral; UD10cc = median dose in % of prescribed dose to 10 mL of urethra; UD30cc = median dose in % of prescribed dose to 30 mL of urethral; Rectal 1 mL = median % highest dose of prescribed dose to 1 mL rectum; Rectal 2 mL = median % highest dose of prescribed dose to 2 mL rectum. Error bar: standard deviation.

Discussion

Prostate brachytherapy has proven effectiveness in prostate cancer control with a favorable side effect profile compared with other treatment modalities for a suitable group of patients. There are now many studies with more than 5 years of follow-up supporting the efficacy and safety of HDR prostate brachytherapy either as a boost or monotherapy.[8] With acceptable biologic effective dose,[17] biochemical failure-free survival for low-risk prostate cancer was >95% while treated with HDR as monotherapy[18-22]; biochemical failure-free survival for intermediate- and high-risk prostate cancer was 81% to 98% and 66% to 94% while treated with HDR as a boost, respectively.[23-34] The incidence of late grade 3 or higher GU and GI toxicity was 0% to 14% and 0% to 4%, respectively. More recently, Astrom et al reported their experience of 623 patients treated with combined external

Table 2 Acute and late genitourinary (GU) and gastrointestinal (GI) toxicity

	Grade 1	Grade 2	≥Grade 3
Acute (<6 mo)			
GU	85.5%	8%	2.4
GI	3.2%	0	0
	Increase 1 grade vs BL	Increase 2 grade vs BL	Increase 3 grade vs BL
Late (≥6 mo)			
GU	17.7%	1.9%	0%
GI	0%	0%	0%

Abbreviation: BL = baseline.

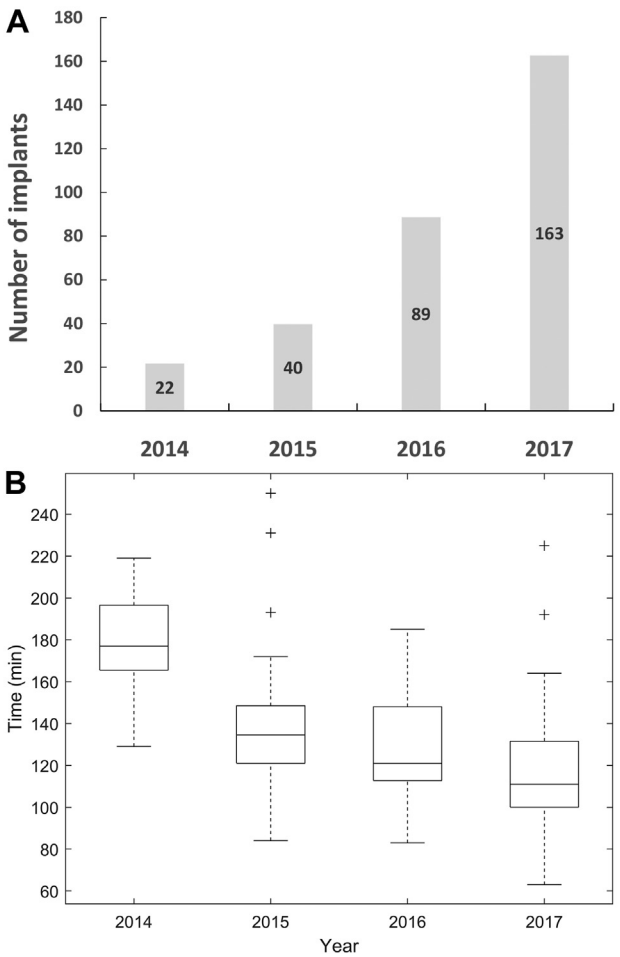

Figure 2 High-dose-rate implants. (A) Number of implants done by year. (B) The nonparametric Kruskal-Wallis test to compare procedure times by year.

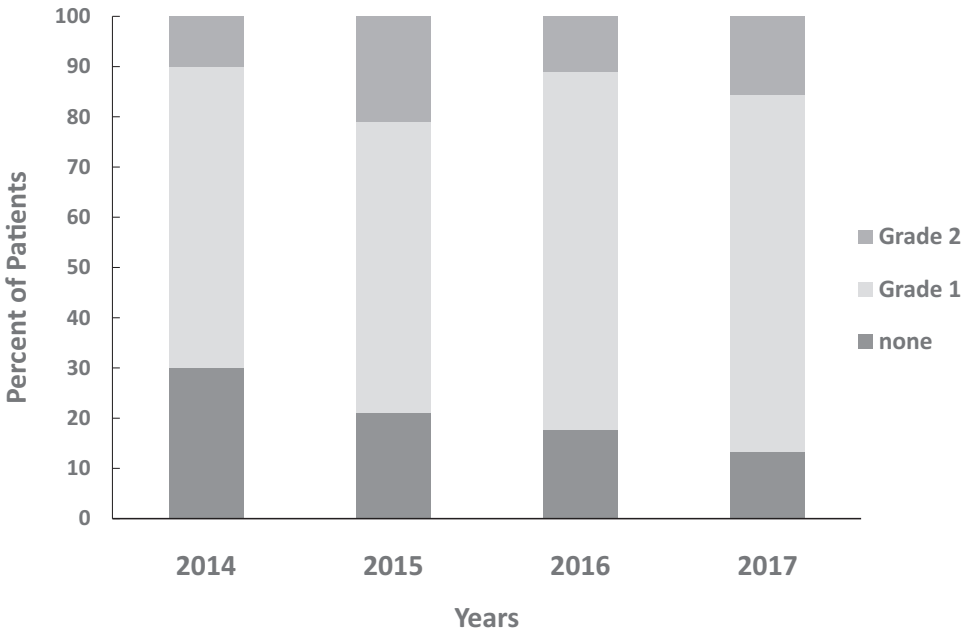

Figure 3 Genitourinary toxicity by year.

beam radiation and HDR boost.[35] With a median follow-up of 11 years, 10-year net probability of PSA relapse was 0% for low-risk disease, 21% for intermediate-risk disease, 33% for high-risk disease, and 65% for very high-risk disease. Grade ≥3 GU and GI toxicity were 4% and 1% at 5 years, and 6% and 1% at 10 years. Martell et al retrospectively reviewed 518 men with intermediate-risk prostate cancer treated with 15 Gy HDR boost in a combined radiation approach.[36] Freedom from biochemical failure was 91% at 5 years with a median follow-up of 5.2 years. No grade 4 or higher late GU toxicity was noted. Grade 3 GU toxicity was 5%. There was no grade 3 or higher late GI toxicity. Strouthos et al reported that 303 patients with high-risk prostate cancer treated with combined radiation with HDR boost yielded 85.7% biochemical control at 72 months, with a median follow-up of 6 years.[37] Late grade ≥3 GU toxicity was 2.5%, and there was no late grade ≥3 GI toxicity. Despite these promising results, brachytherapy utilization has been declining steadily over the years in the United States.[9,10] Such decline has been postulated as multifactorial. One likely reason is that brachytherapy requires specialized expertise and support from other specialties, including radiation physicists, urologists, and anesthesiologists.

With support from the multidisciplinary team, our prostate HDR brachytherapy program went live in April 2014. With a median follow-up of 18.6 months, acute and late GU and GI toxicity in our cohort of patients treated in the initial 3.5 years was comparable with published series using similar dose fractionation schema. Acute urinary retention rate in our cohort was 2.4%, comparable with 1% to 20% reported in the literature.[11-15] Although the follow-up remained short, the estimated 3-year DFS and OS were also comparable with reported studies.[5] In the beginning, the procedure took about 3 hours to complete to meet dosimetric parameters of quality implantation. With time, we became proficient enough to complete an HDR implant in about 2 hours, as we became familiar with the workflow of the planning software and mastered the needle placement/verification techniques while maintaining the quality of implants.

We followed the HDR protocol at Odette Cancer Center in Toronto, Ontario, Canada with minor adaptations to fit our own needs and environment. Although our ultimate goal was to perform HDR brachytherapy under general anesthesia, as it was done at Odette Cancer Center, such a practice would require us to build a brand new HDR brachytherapy suite that met technical and regulatory requirements. We therefore started our HDR treatment with spinal anesthesia. This allowed us to perform HDR in the existing room, requiring minimal additional resources (we used a portable suction machine and oxygen tank in the room). We followed the same work flow as the one at Odette Cancer Center with the following adjustment: in our low-dose-rate brachytherapy protocol, we instilled aerated gel into the Foley catheter to visualize the urethra. We adapted this practice into our HDR protocol only when the urethra was not clearly visualized as a result of the patient's anatomy, or at the time of reconstruction after catheter placement. Unlike Odette Cancer Center protocol, we discharged the patient home with a Foley catheter in place and instructed them to remove it the next morning. This practice was inherited from our low-dose-rate brachytherapy protocol. It remains

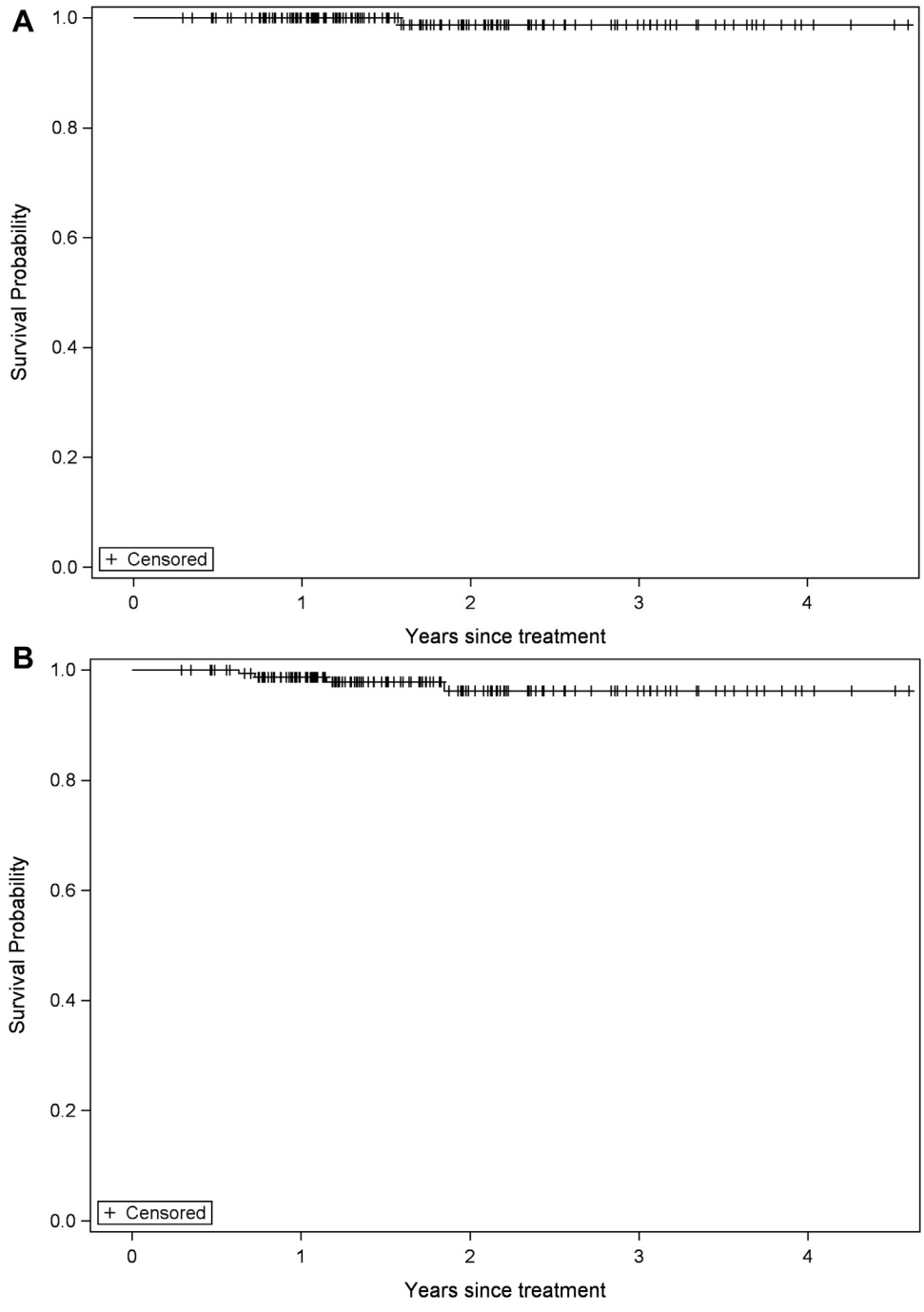

Figure 4 Oncologic outcome. (A) Overall survival. (B) Disease-free survival.

to be tested if such a practice lowers the risk of urinary retention, but at the increased risk of urosepsis.

Our study is not novel, as many have already reported outcomes of real-time ultrasound-based HDR prostate brachytherapy with longer follow-up.[8,35-37] What we have shown here is that it is indeed feasible to start a successful HDR prostate brachytherapy practice by using existing resources based on our learning experiences, implant quality, and initial patient outcomes. Our experience should offer encouragement for others interested in starting their own HDR prostate brachytherapy program.

Conclusions

The quality data, safety outcome, and learning experiences from our new HDR prostate brachytherapy

program has shown that such a program can be successfully implemented in an institution with the support of a multidisciplinary team.

Acknowledgments

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