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Original Article

Patient-Reported Sexual Survivorship Following High-Dose Image-Guided Proton Therapy for Prostate Cancer

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ABSTRACT

Objective: To help guide individualized treatment, we sought to identify baseline predictive factors that impact long-term erectile function following high-dose image-guided radiotherapy (HD-IGRT).
Methods: Potent men with localized prostate cancer treated with radiotherapy alone were enrolled in an institutional review board-approved prospective cohort study. Men received HD-IGRT as primary treatment of prostate cancer. Patient-reported inventories were used to assess erectile function at baseline, 6 months, 2 years, and 5 years after treatment. Long-term potency rates were compared to validated models, and baseline factors were used to create a novel, internally validated nomogram for predicting long-term function.
Results: 1,159 men were treated with HD-IGRT. Among 676 men who were potent at baseline and did not receive hormone therapy, the potency rates at 6 months, 2 years, and 5 years were 81%, 68%, and 61%. Recursive partitioning categorized patients into 3 groups based on two factors: baseline response to EPIC Q57 (ability to have an erection) and pre-existing heart disease. At 5 years, the most favorable group reported "very good" on Q57 and had an 80% potency rate ($n = 137$; $p = 0.83$); the intermediate group reported "good" on Q57 and had no baseline cardiac disease with a 62% potency rate ($n = 145$; $p = 0.86$); and the remaining poor risk group had a 37% potency rate ($n = 117$; $p = 0.19$).
Conclusions: Patient-reported pretreatment sexual function and comorbidities enables stratification and prediction of erectile function. EPIC subset questions with baseline comorbidities may potentially serve as a quick and practical clinical tool for predicting sexual survivorship.
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Sexual survivorship after primary treatment for prostate cancer is an important quality-of-life (QOL) metric for measuring satisfactory outcomes. Among patients surveyed, post-treatment sexual function rates highly among factors when considering treatment decisions [1]. Several high-impact studies have looked at QOL survivorship among men who are impotent or on androgen deprivation therapy (ADT) before treatment [2–8]; few studies, such as the Prostate Cancer Outcomes and Satisfaction With Treatment Quality Assessment (PROSTQA) Consortium, provide a model for predicting post-treatment patient-reported QOL [6,7,9]. Published validated models that do exist require versions of the Expanded Prostate Index Composite (EPIC) questionnaire for pretreatment sexual function score alongside other pretreatment characteristics, which are not always available or feasible in all clinical scenarios [6,7]. The purpose of this analysis was to identify baseline predictive factors of long-term sexual survivorship among a large, homogeneous cohort of potent men treated with high-dose image-guided radiotherapy (HD-IGRT) to develop a more practical model for determining long-term function following curative therapy.

Methods

From August 2006 to May 2010, 1,159 men were enrolled on an institutional review board-approved outcomes tracking protocol and treated for prostate adenocarcinoma with HD-IGRT protons to a median dose of 78 Gy(RBE) (range, 72–82 Gy[RBE]) in 36 to 39 fractions. Patients self-reported sexual QOL using the EPIC questionnaire [10,11] before treatment, every 6 months for 2 years after treatment, and then once annually. Table 1 depicts the patient characteristics and medical comorbidities known to impact erectile

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Table 1
Baseline patient characteristics in 1,005 men treated for prostate cancer with radiotherapy.

Characteristic	Potent at baseline* (n = 676)	Impotent at baseline† (n = 329)	P value
Age, years	64 (range, 41–82)	70 (range, 47–86)	<0.0001
Race			0.9999
White	91% (613 pts)	93% (305 pts)	
Hispanic	2% (16 pts)	0% (1 pts)	
African-American	6% (38 pts)	5% (18 pts)	
Asian/Pacific	1% (8 pts)	2% (5 pts)	
Unknown/other	0% (1pt)	0% (0 pts)	
Body mass index			0.135
<25	24% (162 pts)	20% (66 pts)	
25–29.9	52% (354 pts)	51% (166 pts)	
30–34.9	18% (121 pts)	21% (68 pts)	
35+	6% (39 pts)	9% (29 pts)	
EPIC sexual summary score			<0.0001
100	21% (136 pts)	0% (0 pts)	
68–99	62% (406 pts)	7% (23 pts)	
<67	17% (114 pts)	93% (287 pts)	
Missing	3% (20 pts)	6% (19 pts)	
EPIC sexual function score	72 (range, 17–100)	27 (range, 0–77)	0.0066
EPIC sexual bother score	94 (range, 0–100)	44 (range, 0–100)	<0.0001
IIEF			<0.0001
>22	69% (441 pts)	8% (16 pts)	
17–21	24% (153 pts)	21% (41 pts)	
12–16	6% (38 pts)	35% (67 pts)	
8–11	1% (3 pts)	23% (45 pts)	
5–7	0% (0 pts)	12% (23 pts)	
Missing	6% (41 pts)	42% (137 pts)	
IPSS	6 (range, 0–33)	8 (range, 0–34)	0.0066
T stage			0.5359
T1	75% (510 pts)	74% (242 pts)	
T2	24% (164 pts)	26% (86 pts)	
T3	0% (2 pts)	0% (1 pts)	
Gleason's score			0.4831
4–6	56% (378 pts)	55% (180 pts)	
7	40% (268 pts)	42% (139 pts)	
8–10	4% (30 pts)	3% (10 pts)	
Prostate-specific antigen			0.3871
<10 ng/mL	87% (588 pts)	84% (277 pts)	
10–20 ng/mL	12% (80 pts)	15% (49 pts)	
>20 ng/mL	1% (30 pts)	1% (3 pts)	
Risk group			0.3056
Low	49% (328 pts)	45% (148 pts)	
Intermediate	45% (306 pts)	50% (165 pts)	
High	6% (42 pts)	5% (16 pts)	
Relationship			0.0962
Single	5% (33 pts)	6% (18 pts)	
Divorced/separated	9% (59 pts)	5% (17 pts)	
Married/living together	86% (458 pts)	89% (287 pts)	
Unknown – n/a	5% (36 pts)	2% (7 pts)	
Cardiac comorbidity			0.0001
No	84% (568 pts)	74% (242 pts)	
Yes	16% (107 pts)	26% (87 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Hypertension			<0.0001
Yes	50% (336 pts)	64% (210 pts)	
No	50% (339 pts)	36% (119 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Hypertension medications			<0.0001
Yes	47% (315 pts)	63% (208 pts)	
No	53% (360 pts)	37% (121 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Hyperlipidemia			0.0185
Yes	50% (338 pts)	58% (191 pts)	
No	50% (337 pts)	42% (138 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	

(*continued on next page*)

Table 1 (*continued*)

Characteristic	Potent at baseline* (n = 676)	Impotent at baseline† (n = 329)	P value
Hyperlipidemia medications			0.0128
Yes	54% (308 pts)	54% (178 pts)	
No	46% (367 pts)	46% (151 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Diabetes mellitus			0.0028
Yes	9% (61 pts)	16% (51 pts)	
No	91% (614 pts)	84% (278 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Currently using sexual function aide			0.1367
Yes	14% (96 pts)	18% (59 pts)	
No	86% (579 pts)	82% (270 pts)	
Unknown – n/a	0% (1pt)	0% (0 pts)	
Depression history or medication			0.1178
Yes	8% (51 pts)	11% (35 pts)	
No	92% (625 pts)	89% (294 pts)	
Alpha blocker			0.0844
Yes	15% (101 pts)	19% (64 pts)	
No	85% (575 pts)	81% (265 pts)	
Radiation dose			0.8533
70–72.5 Gy(RBE) at 2.5 Gy(RBE)/fraction	0% (0 pts)	0% (1pt)	
76–78 Gy(RBE) at 2 Gy(RBE)/fraction	85% (572 pts)	84% (276 pts)	
80–82 Gy(RBE) at 2 Gy(RBE)/fraction	15% (104 pts)	16% (52 pts)	

* Patients who responded with a 4 to EPIC Question 59, How would you describe the usual QUALITY of your erections during the last 4 weeks? 1. None at all; 2. Not firm enough for any sexual activity; 3. Firm enough for masturbation and foreplay; or 4. Firm enough for intercourse.
† Patients who responded with 1, 2, or 3 to the above EPIC Question 59.

dysfunction, which were extracted from each patient's initial medical history at consultation.

As part of our typical workflow, sexual health-reported QOL parameters were captured prospectively before the start of HD-IGRT, every 6 months after HD-IGRT for the first year, and then every 6–12 months annually following treatment using the 50-item EPIC, the 5-item International Index of Erectile Function (IIEF), and the International Prostate Symptom Score (IPSS) questionnaires. Patients unable to return to our clinic for follow-up completed either mailed or secure online questionnaires. EPIC questionnaires were answered by 100%, 89%, 82%, 62%, and 83% of eligible men at baseline, 6 months, 2 years, 5 years, and 5+ years after treatment. The EPIC summary and subscales were then calculated and reported using a scale of 0–100 and IIEF scores were calculated and reported by a scale of 5–25, with higher scores indicating better outcomes. For the purposes of this study, potency was defined as an erection "firm enough for intercourse." This endpoint has previously been used in a prospective investigation comparing external-beam radiotherapy, brachytherapy, and prostatectomy [7]. The simulation, planning, and treatment guidelines for prostate cancer have previously been published [10,12]. Cardiac disease was defined as ischemic disease, cardiomyopathy with reduced ejection fraction <35%, arrhythmias, or valvular disease.

Statistics

SAS and JMP software facilitated statistical analysis (SAS Institute, Cary, NC). For baseline potency and post-treatment function rates, univariate association with other categorical prognostic factors was assessed with Fisher's exact test; the Wilcoxon rank sum test was used for continuous prognostic factors. Multiple logistic regression provided multivariate assessment of the ability of several prognostic factors to predict post-treatment erectile function rates.

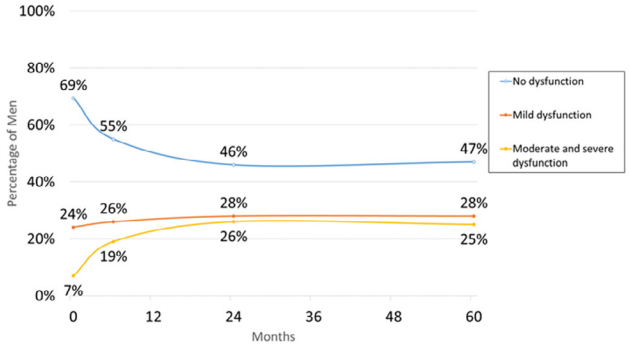
Recursive partitioning analysis (RPA) via a decision-tree method that categorizes missing data as non-informative was used to attempt to identify optimal cut points for predicting erectile function among various prognostic factors. We validated the nomogram through a chi-square analysis of potency rates in this cohort compared to the rates observed for patients treated on another institutional protocol; data were first delineated into the subsets recommended by the decision-tree analysis, and then the chi-square analysis was applied within each subset. A non-significant *P* value signified that the potency rates adequately predicted by the nomogram derived from the original cohort.

Results

Of the 1,159 men analyzed, 154 were excluded from the analysis because of hormone therapy. Table 1 depicts a univariate analysis, with covariate stratification, for potency at baseline comparing the remaining 1,005, including 676 potent and 329 impotent men. Overall sexual summary scores and potency rates for the cohort at baseline, 6 months, 2 years, and 5 years were 67%, 61%, 51%, and 46%. Statistically significant differences arose among several categorical and continuous variables. Among the patient-reported inventory data, baseline EPIC summary score, sexual function and bother, and IIEF significantly differentiated the two groups. For the health-related data, age, cardiac disease, hypertension, hyperlipidemia, and diabetes were statistically significant factors associated with impotency among the 1,005 men. Race, BMI, relationship status, and disease-specific characteristics (T stage, Gleason score, PSA, and overall risk group) were not statistically different in the studied cohort nor were treatment-related factors such as planned radiation dose. At baseline, 14% ($n = 96$) of the potent men were on sexual aides compared to 18% ($n = 59$) of the impotent group.

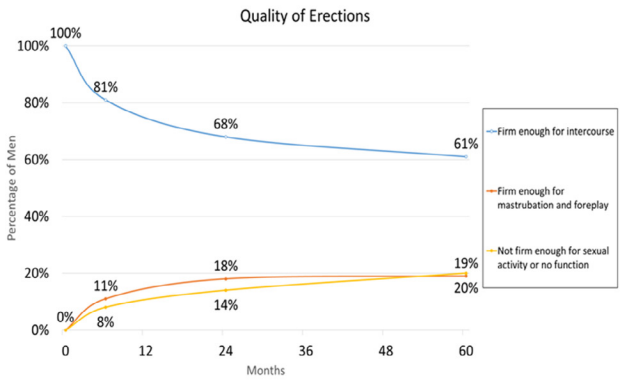
Among the 676 men who were potent at baseline, Fig. 1 demonstrates several of the QOL response rates over 5 years. The potency rates at the follow-up time points of 6 months, 2 years, and 5 years were 81%, 68%, and 61%, respectively. Evaluating potency at 5 years by univariate analysis revealed several pretreatment QOL, patient-specific, disease-specific, and treatment-specific factors potentially associated with potency, as depicted in Table 2. Baseline EPIC sum-

1A



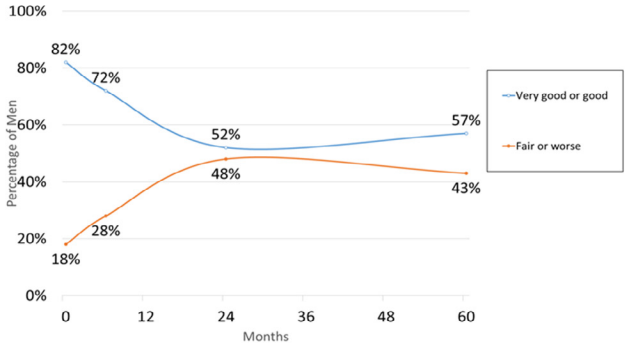
Baseline	6 months	24 months	60 months
N=635	n=560	n=480	n=262

1B



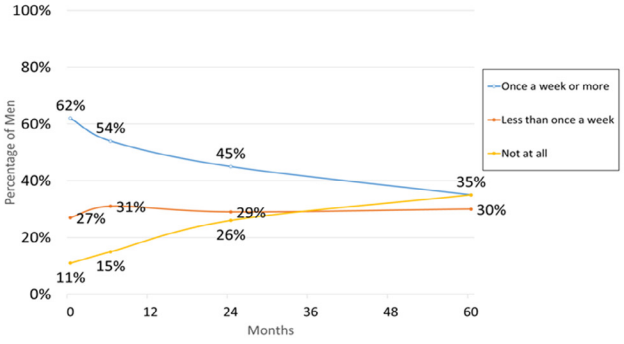
Baseline	6 months	24 months	60 months
N=676	n=603	n=552	n=399

1C



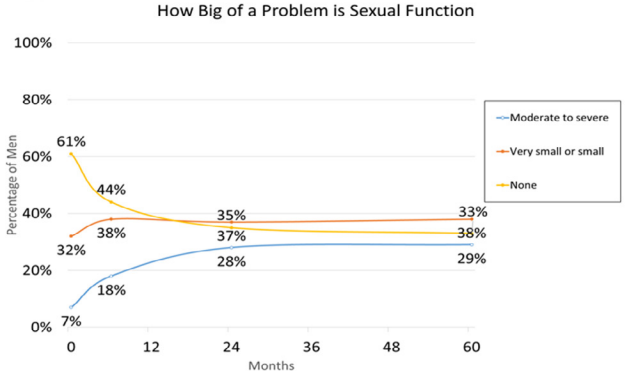
Baseline	6 months	24 months	60 months
N=652	n=575	n=544	n=394

1D



Baseline	6 months	24 months	60 months
N=673	n=600	n=553	n=400

1E



Baseline	6 months	24 months	60 months
N=666	n=599	n=551	n=400

Fig. 1. (a–e) Summary of Erection Quality at baseline, 6 months, 2 years, and 5 years in men who at baseline were able to have an erection firm enough for intercourse. The QOL responses included are International Index of Erectile Function (a), Quality of Erections (b), Ability to Reach an Orgasm (c), Frequency of Intercourse (d), and How Big of a Problem is Sexual Function (e).

Table 2
Univariate analysis of erectile function demonstrated at 5 years for the men with erections firm enough for intercourse at baseline, excluding men on androgen deprivation therapy.

Variable (covariate stratification)	5 years
Age (<50, 50–59, 60–69, 70+ years)	0.0508
Race (White, African-American, Hispanic, other)	0.6836
Baseline EPIC summary score (<67, 68–99, 100)	<0.0001
6-month EPIC summary score (<67, 68–99, 100)	<0.0001
IIEF(yes or no)	<0.0001
Marital status (yes or no)	0.7674
Body mass index (<25, 25–29.9, 30–34.9, 35+)	0.0002
Hyperlipidemia (yes or no)	0.1009
Hyperlipidemia medication (yes or no)	0.0402
Hypertension (yes or no)	0.0054
Hypertension medication (yes or no)	0.0053
Diabetes (yes or no)	0.2272
Cardiac disease (yes or no)	0.0004
Smoker (yes or no)	0.0028
Radiotherapy dose (≥80 Gy)	0.3333
Penile bulb dose (<40 Gy vs > 40 Gy)	0.2334
Clinical T stage (T1 vs T2/T3)	0.3453
Gleason score (2–6, 7, 8–10)	0.4174
Prostate-specific antigen (PSA; <4, 4- <10, 10+)	0.6396
Risk group (low, intermediate, high)	0.4814
Biochemical or clinical progression	0.4144
Depression (yes or no)	0.6538
Alpha blocker (yes or no)	0.378
IPSS (mild, 0–7; moderate, 8–19; severe 20 +)	0.4951
Prostate volume (<30, 30–60, >60 g)	0.1435
Seminal vesicles treated (yes or no)	0.1507
Baseline erectile medication (yes or no)	0.0013
Your ability to have an erection, EPIC Q57	<0.0001
Your ability to reach an orgasm, EPIC Q58	0.0033
How often did you have sexual intercourse, EPIC Q63	0.0007
How big a problem has your sexual function been for you, EPIC Q68	0.1595
Your ability to reach an orgasm, EPIC Q67	0.0702

Abbreviations: EPIC, Expanded Prostate Index Composite; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score.

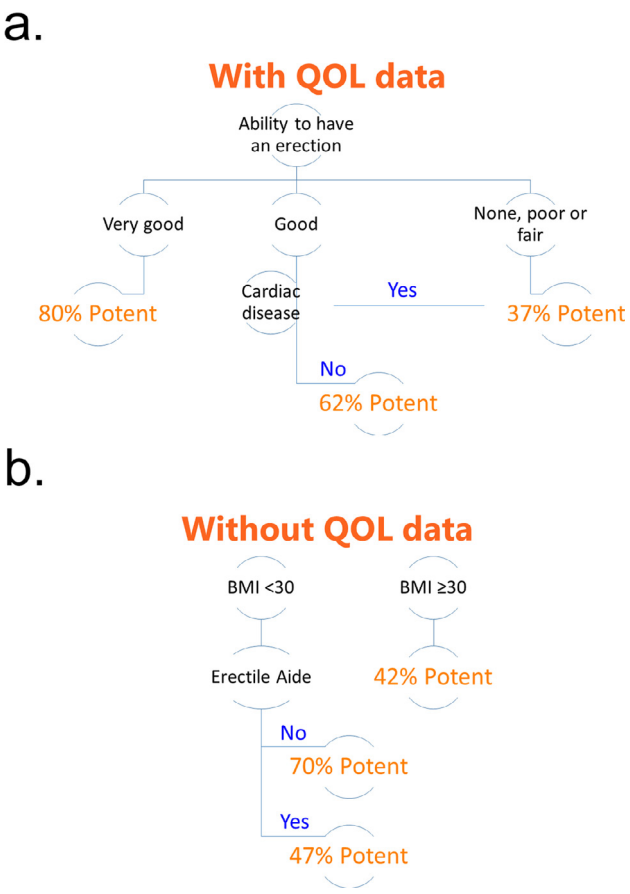


Fig. 2. (a) Five-year recursive partition analysis with quality-of-life data. (b) Five-year recursive partition analysis without quality-of-life data.

mary score, baseline IIEF, 6-month summary score, and baseline subset EPIC questions Q57, Q58, and Q68 were statistically significant. Among the health-related factors assessed, BMI, hypertension, hypertension medications, cardiac disease, >10 pack-year history of smoking, and baseline erectile medication use were statistically significant across all three time points. The *p* value in this category represents a difference in 5-year actuarial potency rates.

Among treatment-related factors, RT dose and seminal vesicle treatment were significant at 6 months and 2 years, but not at 5 years, whereas penile bulb dose was only significant at 2 years. Disease-specific factors were also inconsistent among the various time points. While Gleason's score and risk group were only significant at 6 months, PSA was significant at 2 years, and biochemical progression and clinical T stage were not significant at any of the time intervals. Results regarding biochemical progression-free survival have been previously reported for this cohort; rates were 99%, 94%, and 74% in low-risk, intermediate-risk, and high-risk men, respectively [12].

As illustrated in Fig. 2a, for the RPA, patients were categorized into 3 groups based on two factors (1): baseline response to EPIC Q57, How would you rate each of the following during the last 4 weeks: Your ability to have an erection? (from very poor to none to very good) and (2), pre-existing heart disease. These results were validated against a cohort of men treated on a prospective hypofractionation study ($N = 167$) for whom 5-year follow-up was available for 67% ($n = 112$) [14]. At 5 years, the most favorable group reported "very good" on Q57 and had an 80% potency rate ($n = 137$; $p = 0.83$); the intermediate group reported "good" on Q57 and had no baseline cardiac disease with a 62% ($n = 145$; $p = 0.86$) potency rate; and the remaining poor risk group had a 37% potency rate ($n = 117$; $p = 0.19$).

Fig. 2b shows an RPA based on patient comorbidities at predicting potency at 5 years using BMI and erectile medication use. Men with a BMI below 30 and no erectile medication use had a 5-year potency rate of 70% ($p = 0.68$), which dropped below 50% ($p = 0.25$) with a BMI above 30 or erectile medication use at baseline. There was no statistically significant difference among the 3 potency group compared to the hypofractionated internal cohort as well.

Discussion

Recently published multi-institutional, randomized studies have shown that in patients with low- and intermediate-risk prostate cancer radiotherapy and prostatectomy can yield equivalent oncologic clinical outcomes [14]. For these patients, treatments with more favorable long-term toxicity profiles have become increasingly relevant to the treatment decision-making process. When surveyed about QOL outcomes, men rank sexual function as one of their greatest concerns [1]. Some studies show that a decline in sexual function is the most common cause of disease-specific distress in men with prostate cancer [15]. With the goal of aiding men in their treatment decision-making, we sought to develop a model to predict 5-year erectile function after HD-IGRT. Similar models have included impotent men and those on ADT at baseline, but fewer provide a model for predicting patient-reported QOL [6,7,9]. Our analysis provides patient-reported outcomes in a large cohort of potent men treated with HD-IGRT without ADT.

Despite the importance of post-treatment sexual function to men, comparisons across studies that attempt to interpret and apply patient-specific data to localized therapy decisions are challenging owing to how potency is defined, a lack of understanding about whether non-localized prostate cancer therapies, such as ADT, can cause transient or even permanent impotence [16], and patient-related factors such as co-morbidities or natural aging. For instance, it is well-known that erectile function declines sharply after age 60 years, and the median age of prostate cancer at diagnosis is 66 years [17]. Even in the present data set, as shown in Table 1, there is a 6-year difference in median age when comparing men who are potent to those impotent at baseline. Alongside age, several other co-morbidities are significantly associated with a higher rate of impotency at baseline.

For these reasons, we analyzed a highly selected, homogeneous group of men representing the ideal scenario for modeling erectile function. Not surprisingly, many of the baseline risk factors we included—age, cardiac disease, hypertension and antihypertensive medications, hyperlipidemia and hyperlipidemia medications, diabetes mellitus, and IPSS—were statistically different at baseline between potent and impotent men. Our findings are consistent with other studies investigating factors associated with impotence [17–23].

At 5 years, most men in our cohort could experience erections firm enough to have intercourse, reach orgasm, which compares favorably to the 5-year potency rates following prostatectomy or even active surveillance. At 2 years, the potency rate in the present cohort was 68% compared to 40%, 58%, and 63% for surgery, external-bream radiotherapy, and brachytherapy in the PROSTQA study. Those in the most favorable group per our novel nomogram reported an 80% potency rate at 5 years (n = 137). The median age of our cohort was 64 years compared to 60, 70, and 66 years for surgery, external-beam radiotherapy, and brachytherapy in the PROSTQA study [7]. In a similar study to ours, Spratt et al reported a 78% 2-year erectile function rate. Of note, they investigated a vessel-sparing technique whereas we included the posterior neurovascular bundle within the planning target volumes [24]. As aforementioned, any comparisons between cohorts must factor in age as this is one of the most established risk factors for erectile dysfunction [17].

While men in the present series also experienced an initial decline at 6 months, for which the EPIC summary score was associated with 2- and 5-year function on MVA, these findings are not isolated to patients treated with radiotherapy. Donovan et al found that even men under active surveillance see a decline in potency at 6 months, from 68% to 52%. Nevertheless, potency rates in the present series are higher across all time points even in comparison to the active surveillance cohort on the ProtecT study. The surgical results reported in this investigation were as low as 12% at 6 months [5]. While some functional outcomes may differ with more conventional techniques, like the robot-assisted laparoscopic approach, recently published randomized level 3 data suggest otherwise at 6 months, 1 year, and 2 years between the two surgical modalities [25].

Similar to the PROSTQA external-beam radiotherapy group, we also demonstrated that better pretreatment sexual functioning score was associated with a greater likelihood of functional erections. In contrast to the PROSTQA and some other QOL studies, however, we did not observe a consistent association between lower PSA level or lower-risk category and potency [6,7,9]. An explanation for the latter is that our analysis excluded patients who received planned hormone therapy; however, over 50% of our patients had intermediate- or high-risk disease. Cardiac disease, BMI, hypertension, hyperlipidemia medication use, cardiac disease, smoking status, and baseline erectile function medication use were significant at 5 years.

While numerous studies demonstrate a correlation between potency and penile bulb dose the radiation-related factors we analyzed—total dose, dose to the penile bulb (p = 0.23), and treatment volume included the seminal vesicles (p = 0.15)—were not statistically significant at 5 years after treatment on univariate analysis. Roach et al. published an analysis of the association of impotence and penile bulb dose on men treated on a prospective multi-institutional study [26,27]. They found a statistically significant increase in impotency among the 83 men who received doses above 52.5 Gy as compared to the 75 treated with less dose (48% vs 32%). While we did not observe a dose–response relationship nor a threshold for increased impotence at the 2- and 5-year intervals, the median dose in the present series was only 14 Gy (range, <1–73 Gy) with less than 2% of patients receiving doses equal to 52.5 Gy or above.

Patient-reported QOL inventories were highly predictive across all time points was baseline and 6-month QOL. This finding was not isolated to EPIC summary scores alone but also EPIC subset questions and IIEF, which is consistent with a recent publication from the PROSTQA group demonstrating that smaller versions of the EPIC questionnaire can be used to model 2-year erectile function [6,7].

The variables shown in the univariate analysis were used to generate an RPA with several nomograms with and without QOL inputs (Fig. 2a). We specified our model to predict a 5-year endpoint. The most clinically meaningful patient co-morbidities at 5 years were BMI and erectile medication use. Men with a BMI below 30 and no erectile medication use had a 5-year potency rate of 70%, which dropped below 50% with BMI 30 or erectile medication at baseline.

Fig. 2b shows the nomogram combining QOL and co-morbidities since models that include QOL are both meaningful and simple to use in the clinic. The results of both nomograms were validated against the 5-year results of a cohort of men treated on a hypofractionation protocol [13]. When compared to the PROSTQA model, the proposed model requires only 2 EPIC subset questions [6,7]. An added strength of the nomogram is that it may be useful in those treated with similar hypofractionated regimens of 72.5 at 2.5 Gy(RBE) equivalence with the increasing use of this practice pattern.

Strengths and limitations

As with other QOL studies, ours is limited by measurement and follow-up biases [28]. The results of the present study are limited to specific subset domains of QOL and the follow-up rate is in-line with several well-funded multi- and single-institution reports. Even the highest-quality patient-reported QOL studies have a follow-up rate of approximately 85% at 2- and 5-year endpoints. The strength of our analysis is that it is comprised of the largest known cohort of sexual function data prospectively collected using a validated measurement of potency in patients undergoing highly-conformal radiotherapy [2,5,7,29]. A limitation of the internal validation is the power of the analysis to detect differences among the two cohorts as there were only 167 potent men available for baseline comparison, and these men were treated with hypofractionation.

Among men who are potent before treatment for prostate cancer, 68% and 61% retain potency at 2 and 5 years, respectively, following highly conformal radiotherapy. Stratifying potent men by pretreatment sexual function and comorbidities can help predict erectile function at 2 and 5 years in those treated with radiotherapy without ADT. A nomogram including specific EPIC subset questions and baseline comorbidities may serve as a quick and practical clinical tool for predicting sexual survivorship, but further external validation is needed.

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Conflicts of interest

The authors have no conflicts of interest to disclose.

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