Biochemical failure-rate and preservation of erectile function after prostate seed brachytherapy in early-onset prostate cancer

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Introduction: *To analyze biochemical failure-free survival and erectile dysfunction (ED) in younger men treated with prostate seed brachytherapy (PB).*

Materials and methods: *Included were patients ≤ 55 years treated with PB. Erectile function at baseline and after treatment were assessed using the physician-reported CTCAE version 4.0. Biochemical failure (BF) was defined according to the Phoenix Consensus definition (PSA nadir + 2 ng/mL). The log-rank test (Kaplan-Meier method) and cox-regression analysis was used to calculate BF-free survival.*

Results: *Between July 2005 and November 2020, a total of 137 patients ≤ 55 years (range 44-55 years old) were treated with PB. Median follow up was 72 months. Twenty percent had Gleason 3+4 disease and 6% a PSA >10 ng/mL. Median prostate volume was 34 cc. Actuarial biochemical failure free survival at 5, 7, and 10 years, were 98%, 95% and 89%, respectively. Five patients received local salvage treatment. On multivariate analysis, CAPRA-score (HR 4.46, 95%CI 1.76-11.33, p = 0.002) and the dosimetric measure D90 > 130 Gy (p = 0.03) were predictive of BF. Five deaths occurred in our cohort, two due to cardiovascular reasons and three due to another malignancy. At baseline, all patients were able to have erections with or without medication. At 5 years and 7 years after PB, 80% and 64% of patients had little or no ED (erections without the need for medication) respectively.*

Conclusion: *In young-onset patients treated with PB, failure rates are similar to their older counterparts. Sexual function decreases with time, even in patients with good sexual function.*

Key Words: prostate brachytherapy, early-onset prostate cancer, sexual function

Introduction

Low dose seed prostate brachytherapy (PB) is a well-established treatment option for localized prostate cancer with favorable oncologic outcomes, namely a 5 year cancer-specific survival of 90%-95%.[1] Because results are comparable to surgery and external beam radiation therapy,[2,3] {Cozzi, 2017 #1075}{Goy, 2016 #1076}decisions regarding treatment choice is often based on treatment-related toxicity.[4] This is especially true in younger men with longer life expectancies, who often wish to maintain their sexual function after treatment.[4] In the literature, the definition of "young" varies greatly but most would recognize that early-onset prostate cancer could be defined as patients ≤ 55 years.[5-7]

The incidence of prostate cancer in men ≤ 55 years has increased in the last 20 years, more aggressive cancers have a higher cause-specific mortality in younger patients than in men aged 80 or older. This points to a possible novel clinical subtype of prostate cancer in young men.[7]

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Given the paucity of data on oncologic outcome and sexual function after treatment for early-stage cancers, the aim of this study is therefore to report contemporary results of biochemical failure-free survival and erectile dysfunction (ED) in these men treated with PB.

Materials and methods

Data source

Patients were assessed and identified using a prospectively maintained institutional database. The study was approved by the institution's ethics committee (CER 19.369). No signed informed consent was necessary.

Outcomes of interest

Erectile function was assessed using the standardized physician-reported measure called the Common Terminology Criteria for Adverse Event Scale (CTCAE) version 4.0.): Grade 0 (normal erection), Grade 1 (ED, but without the need for oral pharmacologic or mechanical assistance), Grade 2 (ED with the need for oral pharmacologic or mechanical assistance), and Grade 3 (ED refractory to oral pharmacologic or mechanical assistance). ED was defined as a CTCAE grade 2 or 3 function. Biochemical failure (BF) was defined according to the Phoenix definition (prostate specific antigen (PSA) nadir + 2 ng/mL).[8] Cancer of the Prostate Risk Assessment (CAPRA) score was calculated and used as a prognostic factor to predict for BF.[9] Its score includes information from the PSA, Gleason score, clinical T stage, biopsy results and age. Its predictive ability for 5-year BF in patients treated with external-beam radiotherapy and brachytherapy has been shown recently with AUC for 5-year BCR prediction for patients treated with seed brachytherapy of 0.63.[10]

Study population

We identified 137 patients with early onset (aged ≤ 55 years) prostate cancer treated with PB between July 2005 and November 2020. No patient received androgen deprivation therapy (ADT). Per institutional policy, all low risk cancer were eligible for PB. Patients with intermediate risk cancer were eligible if they had either Gleason score 3+4 disease in a maximum of 50% of biopsies and a PSA < 10 or a PSA ≤ 12 and Gleason 6 disease.

Two physicians performed all implantation via 3-D trans-rectal ultrasound-guided intraoperative interactive planning. The dose prescribed was 144 Gy-160 Gy. Implant quality and dosimetry were evaluated by pelvic CT-scan around 30 days post-implantation. Dosimetry was ascertained for V100 (percentage of prostate receiving 100% of the prescribed dose), V150 (volume of prostate receiving 150% of the prescribed dose) and D90 (minimum dose covering 90% of prostate volume).

Patient characteristics

Complete medical history was obtained, and physical examination undertaken at the first consultation. Patient's age, prostate volume, Gleason score and PSA level were then recorded. Baseline ED according to CTCAE v4.0 was reported. Finally, familial history of prostate cancer was ascertained. All patients were followed up after implantation at 1 month and then at 3 to 6 months intervals. Some patient had their clinical follow up at other centers. For these patients, only PSA follow up was obtained. Potency was assessed during each follow up at our hospital only.

Statistical analysis

Kaplan-Meier analysis (log-rank test) was used for actuarial biochemical failure-free analysis and to calculate potency rates. Potency was defined as having no ED or a maximum grade 1 toxicity (defined as ED, but without the need for oral pharmacologic or mechanical assistance). Multivariate analysis, cox regression analysis was used. Statistical analysis was done using SPSS 26.0 for Windows (IBM SPSS, Chicago, IL, USA).

Results

Between July 2005 and November 2020, a total of 137 patients were treated with a median follow up of 72 months. Seventy-five patients had a clinical follow up of at least 2 years and 43 of at least 5 years to assess erectile function. Median age (range) was 54 (44-55) years. Twenty percent had Gleason 3+4 disease. 6% had a PSA > 10 ng/mL. Median prostate volume was 34 cc. Table 1 summarizes the baseline characteristics and dosimetric parameters 1 month after brachytherapy. Nine patients experienced a recurrence. Actuarial biochemical failure free survival at 5, 7 and 10 years were 98%, 95% and 89%, respectively. Four patients with a recurrence were treated with focal high-dose brachytherapy and one patient underwent prostatectomy. Imaging or biopsies of the prostate were so far negative in the other patients. Five deaths occurred in our cohort, two of them were due to cardiovascular cause and three to another malignancy. No death was due to prostate cancer. So far, no secondary cancer in the rectum or bladder was detected in these patients.

TABLE 1. **Patient baseline characteristics and dosimetric parameters**

Characteristic	Median	IQR	range	%
Age	54	51-55	44-55	
CAPRA	2	2-3	0-4	
IPSS	3.5	1-6	0-20	
Gleason score				
6				79
3+4				20
4+3				1
PSA				
< 6				56
≥ 6-10				39
≥ 10-20				6
Sexual function at baseline[3]				
0				75
1				19
2				6
3				0
Nadir ≤ 0.2				60
Nadir ≤ 0.5				74
Follow up (months)	72	37-106.5	4-180	
Prostate volume (cc)	33.8	27.2-43.6	14.9-71.4	
Dosimetry at day 30				
D90[1] (Gy)	165.8	151.4-182.5		
D90[1] < 130 Gy				7
V100[2] (%)	95.7	92.1-98.3		
Diabetes	n = 11			8
Hypertension	n = 47			34
Hypercholesterolemia	n = 41			30

[1]D90 = dose in Gy that covers 90% of the prostate volume at day 30 after the implant on CT-scan based dosimetry 1 month after brachytherapy
[2]V100 = percentage of prostate volume of that receives 100% of the prescription dose at day 30 after the implant on CT-scan based dosimetry
[3]Sexual function CTCAE classification = 0 (normal, no ED); 1 (ED, but without need for pharmacologic or mechanical assistance); 2 (ED with the need for oral pharmacologic or mechanical assistance); 3 (ED refractory to oral pharmacologic or mechanical assistance); CAPRA = Cancer of the Prostate Risk Assessment; IPSS = International Prostate Symptom Score

Univariate and multivariate analyses testing biochemical failure free survival after prostate brachytherapy

TABLE 2. **Multivariate analysis to predict for BR**

Factor	HR	95%CI	p value
CAPRA	4.46	1.76-11.33	0.002
D90 > 130 Gy	0.16	0.03-0.85	0.03

On univariate analysis, CAPRA score ($p = 0.001$), PSA ($p < 0.001$), and D90 > 130 Gy ($p = 0.04$) were associated with better BF-free-survival. Age ($p = 0.25$) and Gleason score ($p = 0.9$) were not. Of note, only two patients with D90 > 130 Gy had a BF. Table 2 depicts the multivariate analysis to predict for BF. CAPRA score and D90 > 130 Gy remained statistically-significant predictors for BF.

Erectile function

At time of analysis, 110 patients had follow up data on erectile function. Median follow up was 43 months

TABLE 3. **Sexual function score over time for patients with no erectile dysfunction or grade 1 erectile dysfunction at baseline before treatment**

Years since brachytherapy	n =	Grade of erectile function	
		% erections 0-1	% erections 0-2
2 years	75	94	96
3 years	61	89	96
4 years	52	86	96
5 years	43	80	96
6 years	33	76	93
7 years	24	63	90

(IQR 17.3-74.8). At baseline, all patients had either no ED or achieved an erection with PDE5 inhibitors (CTCAE V4.0 grade ≤ 2). At the time of last evaluation, 51% had normal erectile function (grade 0), 23% had abnormal function but not needing medication (grade 1), 15% needed medication (grade 2), and 12% were unable to achieve a sufficient erection despite medication (grade 3). Table 3 illustrates sexual function score over time since brachytherapy for all patients and number of patients at each time-point.

Of the patients with a baseline function of 0-1 (no erectile dysfunction or erectile dysfunction not needing medication), 5 years after PB, with 46 patients available for analysis, 80% patients still had no or little (grade 1) ED.

After 7 years, the rate was 64% of 32 analyzed patients. Because of the small number of patients, the following analysis predicting for ED 0-1 at last follow up has to be regarded as purely exploratory. Only baseline sexual function was borderline predictive (HR 0.60, 95% CI 0.36-1.01, p = 0.053) but not age as a continuous variable (p = 0.16), hypercholesterolemia (p = 0.86), diabetes (p = 0.90) or hypertension (p = 0.15).

Discussion

Our study reports favorable biochemical failure-free survival outcomes after PB for early-onset prostate cancer patients of 98% at 5 years, 95% at 7 years and 89% at 10 years. At 5 years and 7 years after PB, 80% (n = 46) and 64% (n = 32), of patients had little or no ED (erections without the need for medication) respectively.

Comparison of BF with other series is difficult because of different strategies combining PB with either external beam radiotherapy or ADT. Our series of 137 patients is the largest PB report in patients aged ≤ 55 years. Gómez-Iturriaga Piña et al[11] reported in 2010 on a cohort of 94 patients using the same inclusion criteria for age. Only 2% had Gleason 7 disease and none had received ADT. At 7 years of follow up, they reported a biochemical control (Phoenix definition) of 98.9%. Ninety-three percent of their patients maintained satisfactory erections, but 47% used PDE5 inhibitors. Using an inclusion criterion of age ≤ 54 years, Merrick et al[12] reported on 108 patients with localized prostate cancer treated with PB. At 8 years, they had a biochemical control (PSA ≤ 0.40 ng/ml) of 96% and 100% in their low risk and intermediate risk groups, respectively. These results are better than ours, probably due to the fact that 43 out of 44 patients with intermediate risk cancer received additional external-beam radiotherapy. None of their or our patients received ADT.

In patients ≤ 60 years old, Prada et al showed that 94% of their 270 patients had no biochemical failure after 5 years, but the comparison to our patients is limited by the fact that 24% of their cohort received adjuvant ADT, and patients had less aggressive disease with only 8% of treated patients with Gleason 7 disease and another 8% a PSA 10-20 ng/mL.[13]

In an earlier paper by our group we found that advanced age, pre-PB potency, and vascular comorbidities (hypertension, diabetes and dyslipidemia) were predictors of potency.[14] This current analysis corroborates our previous study as well as others that age is an important predictor of ED after PB.[15] The preservation of potency and the efficacy of the treatment were the most important factors in the provider–patient interactions of young patients (< 60 years).[16] This further illustrates why PB remains an attractive treatment modality, especially in young patients. Our results for ED compare favorably to data after robotic prostatectomy from our institution.[17]

Using the Erectile Hardness Scale (EHS) to assess rigidity sufficient for sexual intercourse, with grade 3 meaning rigidity sufficient for sexual intercourse, but not fully rigid and grade 4 meaning fully rigid. When excluding patients with baseline ED (SHIM < 12), in the patients with a mean age of nearly 59 years, 73.3% had an EHS of 3 or 4 at 2 years. Our potent patients at baseline had no or ED without need for pharmacologic or mechanical assistance in 94%.

The decline of erectile function after brachytherapy has to be compared to the natural decline of erectile function with age. The natural evolution of ED in patients has been well studied. The Men's Attitudes to Life Events and Sexuality (MALES) study showed that men aged 50-59 had 20%-25% probability to show each a progression or a regression of ED 3 years later.[18] Direct comparison of erectile function with other publications is difficult because most studies use different definitions of ED but most use a physician or self-assessment measuring erectile stiffness. Other include only patients with normal baseline erectile function in their analysis. Gómez-Iturriaga Piña et al[11] found in their patients ≤ 55 years old after a median follow up of a bit more than 5 years that 93.5% had preserved erectile function with 47% using medication. This compares well to our patients. With a median follow up that was 20 months shorter, 15% needed medication and only 12% were unable to have a sufficient erection. Keyes et al[19] found that the crude 7-year rate of patients ≤ 55 years having erectile functioning with or without medication was 80%.

Most patients with early-onset prostate cancer have no known predisposing germ-line component. We found that of the 106 patients for whom the family history was available, 34% had a first-degree relative with prostate cancer. Patients with early-onset prostate cancer often have androgen receptor-type rearrangements and multiple recurrent genomic aberrations that act directly or indirectly to dysregulate the androgen receptor pathway.[5] In a study investigating the risk of prostate cancer in familial and hereditary syndromes, men with a history of familial and hereditary prostate cancer were associated with a 3 to 4-fold increase in relative risk of early-onset prostate cancer (diagnosis at age ≤ 55 years).[20] Also, genetic variants associated with increased risk of prostate cancer in genome-wide association studies are found more often in early-onset prostate cancer men.[21] Despite these genetic variants, younger patients don't seem to have more aggressive cancers. Patients ≤ 50 years had less aggressive clinico-pathological features than older patients.[22,23]

A weakness of this present study is that a number of patients didn't have a clinical follow up in our department and therefore didn't have their erectile function assessed.

Conclusion

In patients ≤ 55 years treated with prostate seed brachytherapy, biochemical control is good, despite the probability of often harboring genetic variants. The chances of preserving erectile function are equally good with about only one fifth of patients needing medication or having no erections at all 5 years after brachytherapy. □

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