Comparison of external beam radiotherapy versus permanent seed brachytherapy as monotherapy for intermediate-risk prostate cancer – a single center Canadian experience

Guila Delouya, MD,[1,2] Carole Lambert, MD,[1,2] Jean-Paul Bahary, MD,[1,2] Marie-Claude Beauchemin, MD,[1,2] Maroie Barkati, MD,[1,2] Cynthia Ménard, MD,[1,2] Daniel Taussky, MD[1,2]

[1]Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal, Hôpital Notre-Dame, Montréal, Québec, Canada
[2]CRCHUM-Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Montréal, Québec, Canada

DELOUYA G, LAMBERT C, BAHARY J-P, BEAUCHEMIN M-C, BARKATI M, MENARD C, TAUSSKY D. Comparison of external beam radiotherapy versus permanent seed brachytherapy as monotherapy for intermediate-risk prostate cancer – a single center Canadian experience. *Can J Urol* 2017;24(3):8822-8826.

Introduction: *We tested different classification systems in order to separate intermediate-risk prostate cancers into prognostic groups. We then examined which groups were most suited for either prostate seed brachytherapy (PB) or external beam radiotherapy (EBRT).*

Materials and methods: *We selected patients with D'Amico intermediate-risk prostate cancer who were treated exclusively with either PB or EBRT. Patients were excluded if they had received androgen deprivation therapy in combination with EBRT or a follow up of < 30 months without recurrence. The Kaplan-Meier method was used to compare groups.*

Results: *Our sample consisted of 475 patients treated from July 2002-September 2013. Median follow up for patients without biochemical failure (BF) was 56 months (interquartile range 44-78); 222 patients (47%) were treated with PB exclusively (D90 interquartile range 145-176 Gy) and 253 (53%) with EBRT exclusively (dose interquartile range 76-80 Gy). The rate of BF was significantly lower in patients treated with PB (5.4%) than in patients treated with EBRT (14.2%) (p = 0.036, log-rank test).*

Upon univariate analysis, significant predictors of BF included the number of unfavorable intermediate-risk factors (0, 1, 2, 3) (p = 0.024) as well as the Cancer of the Prostate Risk Assessment (CAPRA) score (p = 0.002). After adjusting for the type of treatment, only the CAPRA score remained predictive (p = 0.025). For patients with a CAPRA score of 0-2, those with PB fared better than those treated with EBRT (p = 0.042). This difference disappeared in patients with a CAPRA score of 3-5 (p = 0.5).

Conclusions: *Using our current selection criteria for monotherapy, we found that PB or EBRT as monotherapy are equally effective treatment options for intermediate-risk prostate cancer.*

Key Words: intermediate-risk prostate cancers, prostate seed brachytherapy, external beam radiotherapy, CAPRA-score

Introduction

The use of low-dose-rate permanent seed brachytherapy (PB) as monotherapy in intermediate-risk prostate cancer is well established.[1] However, there is still debate over which patients are good candidates for PB, and the role of androgen deprivation therapy (ADT) in these patients is not well understood.[2] Hence, treatment selection is variable and primarily depends on patient preferences and the physician's judgment.[3]

PB monotherapy is usually reserved for favorable intermediate-risk prostate cancer patients. What constitutes an intermediate-risk cancer that is unsuitable for PB monotherapy is still debated. Zumsteg et al[4] proposed a new definition of favorable and unfavorable intermediate-risk prostate cancer:

Accepted for publication February 2017

Address correspondence to Dr. Guila Delouya, Department of Radiation Oncology, Centre Hospitalier de l'Université de Montréal – Hôpital Notre-Dame, 1560 Sherbrooke St. E., Montreal, QC H2L 4M1 Canada

Patients with unfavorable intermediate-risk have either a primary Gleason pattern of 4, a percentage of positive biopsy cores ≥ 50%, or multiple intermediate-risk factors (cT2b–c, prostate-specific antigen (PSA) 10–20 ng/mL, Gleason score 7). Zumsteg et al[4] studied a cohort of more than 1000 patients with intermediate-risk prostate cancer in which patients had been treated with external beam radiotherapy (EBRT) of ≥ 81 Gy with or without ADT. Unfavorable intermediate-risk patients had worse prognoses even though they comprised the subgroup that was most treated with the addition of ADT.

Merrick et al[5] tested this new definition in a cohort of patients treated with PB as monotherapy or in combination with EBRT and/or ADT. They found that this definition successfully discriminated between patients with different prognoses.[5]

In this study, we examined a large cohort of patients from a single institution. We tested different classification systems to determine which factors best discriminate intermediate-risk cancers into different prognostic groups. We then examined which treatment (PB or EBRT) best applies to each prognostic group.

Material and methods

Patients included in this study were those with D'Amico intermediate-risk prostate cancer (clinical stage T2b, and/or PSA between 10 and 20 ng/mL, and/or Gleason score of 7), treated exclusively with PB to a dose of 144 Gy or with EBRT to a dose of either 76-80 Gy in 1.8-2.0 Gy daily fractions or 60 Gy in 20 fractions. The D90 (minimum dose to 90% of prostate volume) at day 30 was 160 Gy (IQR 145-176 Gy). The median dose for EBRT (IQR) was 78 Gy (76-80 Gy), and 17% of patients received 60 Gy in 20 fractions. We excluded any patient treated with a neo-adjuvant or treated concomitantly with ADT, as well as all patients treated with a combination of EBRT and PB. We also excluded patients without any recurrence and a follow up of < 30 months following treatment. We defined biochemical failure (BF) according to the Phoenix definition (nadir PSA + 2).[6]

Following criteria proposed by Zumsteg and al,[4] favorable intermediate-risk patients were defined as those with clinical T1c-T2a disease, Gleason ≤ 3 + 4 = 7, and < 50% of positive biopsy cores with a PSA ≤ 10 ng/mL. All other patients were considered as unfavorable intermediate-risk prostate cancer.

TABLE 1. **Patient characteristics (n = 475)**

Characteristic	All patients (n = 475)	EBRT (n = 253)	PB (n = 222)	p value
Age in mean (SD)	68.1 (6.4)	68.5 (6.5)	67.5 (6.2)	0.095[1]
Gleason 4+3	18%	26%	8%	< 0.001[2]
PSA > 10 ng/mL	24%	29%	19%	0.013[2]
≥ 50% positive cores on biopsy	40%	23%	55%	< 0.001[2]
Two D'Amico risk factors	11%	3%	17%	< 0.001[2]
Favorable/unfavorable[1]	47/53%	30/70%	69/31%	< 0.001[2]
Number of unfavorable factors[1]				< 0.001[2]
0	48%	30%	69%	
1	36%	44%	27%	
2	15%	25%	4%	
3	1%	2%	0%	
CAPRA score				< 0.001[2]
2	20%	11%	30%	
3	37%	28%	47%	
4	26%	31%	20%	
5	11%	19%	2%	
6	6%	10%	1%	
7	1%	2%	0%	

[1]according to Zumsteg et al.[4]
SD = standard deviation; EBRT = external beam radiotherapy; PB = prostate brachytherapy; PSA = prostate-specific antigen; CAPRA = cancer of the prostate risk assessment

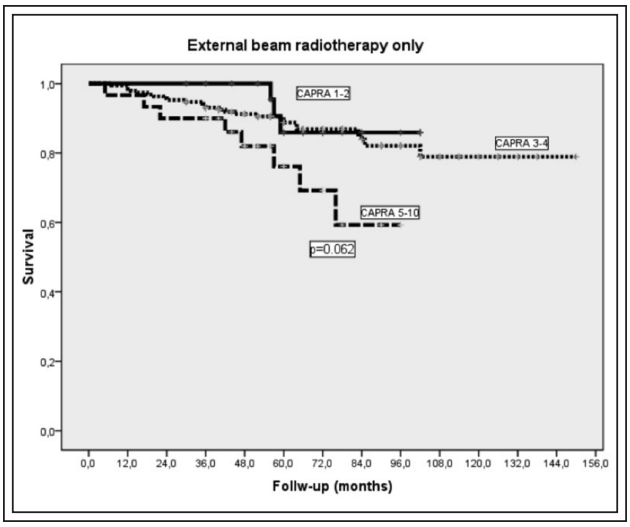

Figure 1. Biochemical recurrence for external beam radiotherapy and risk definition from the CAPRA score.

Survival analyses were performed using the Kaplan-Meier method and comparisons were made using the log-rank test. A multivariate analysis was performed using Cox regression analysis. Statistical significance was defined as p values ≤ 0.05. Analyses were performed using SPSS 17.0 for Windows (IBM SPSS, Chicago, IL, USA).

Results

We identified 475 patients treated from July 2002-September 2013. Median age was 68.5 years (interquartile range [IQR] 63-73). The cohort was divided into 222 patients (47%) treated exclusively with PB and 253 (53%) patients treated exclusively with EBRT. Patients treated with EBRT had more frequent unfavorable risk features according to all the analyzed intermediate-risk definitions, Table 1.

Biochemical failure

Median follow up for patients without BF was 56 months (IQR 44-78). Median time to BF was 44.5 months (IQR 22.25-61.5).

Patients treated with PB had significantly less BF (5.4%) than patients treated with EBRT (14.2%) (p = 0.036, log-rank test).

Four year biochemical recurrence-free survival was 96% for PB and 91% for EBRT. At 7 years, the rates were 91% and 83%, respectively. Upon univariate analysis, significant predictors of BF included the number (0,1,2,3) of unfavorable intermediate-risk factors as defined by by Zumsteg et al[4] (p = 0.024;), as well as the Cancer of the Prostate Risk Assessment (CAPRA)[7] score (p = 0.002; see Figure 1).

In various multivariate models that had been adjusted for the type of treatment, Table 2, only the CAPRA score remained predictive (p = 0.025). Neither unfavorable risk factors nor the type of treatment remained predictive in multivariate models, although a statistical trend (p = 0.06) was observed for the Zumsteg classification.

For patients with a CAPRA score of 0-2, those who had PB had better biochemical failure-free survival (BFFS) (p = 0.042) than those treated with EBRT. There was no difference between treatments for patients with a CAPRA score of 3-5 (p = 0.5). There was only one patient treated with PB with a CAPRA score of > 5.

We next examined which classification system best predicts BF. We found that CAPRA score (AUC 0.63, p = 0.003) was a better predictor of BF than the Zumsteg classification (AUC = 0.56, p = 0.17) or the number of unfavorable factors (AUC = 0.57, p = 0.09).

Discussion

In this paper we examined the treatment of intermediate-risk prostate cancer. For these patients, there are no

TABLE 2. **Multivariate models adjusted for type of treatment**

Model	HR	95% CI	p value
1. Number of unfav. factors	1.17	0.80-1.70	0.42
Type treatment (PB versus EBRT)	0.53	0.26-1.01	0.08
2. Zumsteg classification (Fav. versus Unfav.)	1.2	0.65-2.2	0.56
Type treatment (PB versus EBRT)	0.52	0.26-1.03	0.06
3. CAPRA score (continuous)	1.33	1.04-1.70	0.025
Type treatment (PB versus EBRT)	0.65	0.32-1.35	0.25

HR = hazard ratio; CI = confidence interval; EBRT = external beam radiotherapy; PB = prostate brachytherapy; CAPRA = cancer of the prostate risk assessment; Fav = favorable; Unfav = unfavorable

clear guidelines to date concerning the minimum dose of EBRT, when and whether concomitant ADT is recommended, and whether PB should be prescribed alone or in combination with EBRT. We studied patients with intermediate-risk prostate cancer treated exclusively with either PB or EBRT. Our results from a retrospective large cohort suggest that both treatments yield very similar results when adjusted for the different stratification models for intermediate-risk cancers. However, we did find a small but significant advantage for patients with a CAPRA score of < 3 treated with PB.

It is difficult to generalize our results for other centers. We believe that our results show that our selection criteria for either PB or EBRT monotherapy are reasonable, because after adjusting for risk factors, results were very similar for both treatments. Based on our results, we believe that the advantage of PB in intermediate-risk cancers reported in previous publications can be explained by the fact that patients with EBRT usually had more unfavorable risk factors. Indeed, when we adjusted our cohort for unfavorable risk factors, the statistical difference between EBRT and PB vanished.

Recent Canadian guideline recommendations published by Rodrigues et al[8] indicate that there is no difference in efficacy between low-dose-rate PB and EBRT for the treatment of intermediate-risk cancers. However, the adverse effect profile is noticeably different (e.g. more sexual impotency and rectal morbidity with EBRT). These guidelines emerged from a systematic review of studies that included different treatment modalities such as EBRT alone or in combination with low- or high-dose-rate brachytherapy. In our single center study, patients were all treated exclusively with either PB or EBRT, without the use of ADT. Most patients (83%) were treated with standard daily fractionation (1.8-2.0 Gy per fraction). In a different propensity-matched Canadian study, Rodrigues et al[9] compared 231 low-dose-rate PB patients with 265 EBRT patients that had intermediate-risk prostate cancer. They showed a statistically significant improvement in BFFS for PB compared with EBRT (HR 4.58, 95% CI 1.82-11.51, p = 0.001). Vassil et al[10] examined intermediate-risk prostate cancer patients and found a slightly higher freedom from biochemical failure (FFBF) for PB patients (5 year FFBF at 90%) when compared to EBRT patients (5 year FFBF at 86%), but this difference was not significant (p = 0.969).

Although randomized trials are the ideal method of defining the current standard of care, patient accrual can be difficult as exemplified by the SPIRIT study, which was unsuccessful at accumulating patients to compare PB with surgery. No prospective randomized trials published to date have directly compared the efficacy of radiation treatment modalities such as PB and EBRT, either alone or in combination. Consequently, treatment selection is quite challenging for the physician and patients.

We compared the Zumsteg definition of unfavorable intermediate-risk cancers with the CAPRA score definition. Although both definitions discriminated well in univariate analysis, we found an advantage for the CAPRA score definition in our cohort. In a study by Krishnan et al, our center previously showed that the CAPRA scoring system can be applied to PB and EBRT patients to predict BF in multivariate analyses.[11] In that study, the authors compared the BF of patients treated with low-dose-rate PB to those treated with EBRT. When stratified to the CAPRA scoring system, results showed that PB patients had a significantly lower BF than EBRT patients. In this present study, we utilized a much longer follow up and restricted our analysis to intermediate-risk cancers only. We did not find a difference in outcome for patients treated with PB when compared to those treated with EBRT.

Another reason why our results may not be generalizable is because we rarely offer PB monotherapy to patients with Gleason 4+3 disease or to patients with Gleason 7 and a PSA > 10 ng/mL. These patients are offered PB as a boost to EBRT.

Our practice to exclude patients with Gleason 7 (4+3) is based on several retrospective studies. For instance, Bittner et al found a small but statistically significant advantage in biochemical progression-free survival and a trend towards improved cancer specific survival in patients with a primary Gleason pattern of 3.[12] However, Stock and Stone showed that the primary Gleason pattern in Gleason 7 disease shows no significant effect on BF when treated with PB.[13] We also excluded patients using ADT to avoid confounding its effect with radiation treatment.

Other limitations of this study include its retrospective nature and the lack of toxicity data. Our results may change with longer follow up.

Conclusion

We found that our selection criteria for PB or EBRT monotherapy resulted in equally effective results for intermediate-risk prostate cancer. We showed that the different prognostic groups within the intermediate-risk population are best characterized with the CAPRA score. □

References

1. Frank SJ, Grimm PD, Sylvester JE et al. Interstitial implant alone or in combination with external beam radiation therapy for intermediate-risk prostate cancer: a survey of practice patterns in the United States. *Brachytherapy* 2007;6(1):2-8.
2. Lo AC, Morris WJ, Lapointe V et al. Prostate-specific antigen at 4 to 5 years after low-dose-rate prostate brachytherapy is a strong predictor of disease-free survival. *Int J Radiat Oncol Biol Phys* 2014;88(1):87-93.
3. Nguyen CT, Kattan MW. Development of a prostate cancer metagram: a solution to the dilemma of which prediction tool to use in patient counseling. *Cancer* 2009;115(13 Suppl):3039-3045.
4. Zumsteg ZS, Spratt DE, Pei I et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013;64(6):895-902.
5. Merrick GS, Butler WM, Galbreath RW et al. Stratification of brachytherapy-treated intermediate-risk prostate cancer patients into favorable and unfavorable cohorts. *J Contemp Brachytherapy* 2015;7(6):430-436.
6. Roach M 3rd, Hanks G, Thames H et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: recommendations of the RTOG-ASTRO Phoenix Consensus Conference. *Int J Radiat Oncol Biol Phys* 2006;65(4):965-974.
7. Cooperberg MR, Freedland SJ, Pasta DJ et al. Multiinstitutional validation of the UCSF cancer of the prostate risk assessment for prediction of recurrence after radical prostatectomy. *Cancer* 2006;107(10):2384-2391.
8. Rodrigues G, Yao X, Loblaw DA et al. Low-dose rate brachytherapy for patients with low- or intermediate-risk prostate cancer: A systematic review. *Can Urol Assoc J* 2013;7(11-12):E783-E787.
9. Smith GD, Pickles T, Crook J et al. Brachytherapy improves biochemical failure-free survival in low- and intermediate-risk prostate cancer compared with conventionally fractionated external beam radiation therapy: a propensity score matched analysis. *Int J Radiat Oncol Biol Phys* 2015;91(3):505-516.
10. Vassil AD, Murphy ES, Reddy CA et al. Five year biochemical recurrence free survival for intermediate risk prostate cancer after radical prostatectomy, external beam radiation therapy or permanent seed implantation. *Urology* 2010;76(5):1251-1257.
11. Krishnan V, Delouya G, Bahary JP et al. The Cancer of the Prostate Risk Assessment (CAPRA) score predicts biochemical recurrence in intermediate-risk prostate cancer treated with external beam radiotherapy (EBRT) dose escalation or low-dose rate (LDR) brachytherapy. *BJU Int* 2014;114(6):865-871.
12. Bittner N, Merrick GS, Butler WM et al. Gleason score 7 prostate cancer treated with interstitial brachytherapy with or without supplemental external beam radiation and androgen deprivation therapy: is the primary pattern on needle biopsy prognostic? *Brachytherapy* 2013;12(1):14-18.
13. Stock RG, Berkowitz J, Blacksburg SR et al. Gleason 7 prostate cancer treated with low-dose-rate brachytherapy: lack of impact of primary Gleason pattern on biochemical failure. *BJU Int* 2012; 110(9):1257-1261.