Robotic prostatectomy versus brachytherapy for the treatment of low risk prostate cancer

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Introduction: *To compare oncological and functional results of robot-assisted radical prostatectomy (RARP) and brachytherapy (BT) with a single-center prospective randomized study.*

Materials and methods: *From January 2012 to January 2014, 165 patients with low risk prostate cancer, prostate volume ≤ 50 g, normal urinary (IPSS ≤ 7 and mean flow rate ≥ 15 mL/sec) and erectile functions (IIEF-5 > 17) were enrolled and randomly assigned to the RARP or BT group. Our end points included the comparison of biochemical recurrence-free survival rates, urinary function (IPSS and EPIC scores) and potency rates (IIEF-5 score) at different time points during the first 2 years after surgery between the two groups.*

Results: *The biochemical recurrence-free survival rates were 96.1% and 97.4% for the BT and RARP groups, respectively ($p = 0.35$). Significantly higher IPSS scores were assessed in the BT than in the RARP group at all the postoperative time points ($p < 0.05$). Significantly higher continence rates were assessed in the BT than in the RARP group during only the first 6 months of follow up ($p < 0.05$). Significantly lower potency rates were assessed in the BT than in the RARP group at all the postoperative time points ($p < 0.05$).*

Conclusions: *Our data showed similar biochemical recurrence-free survival rates after BT and RARP. BT patients confirmed constantly higher rates of urinary symptoms while only reporting better continence rates for the first 6 months after surgery. RARP patients reported higher potency rates than BT patients during all the follow up period.*

Key Words: prostate cancer, robotic prostatectomy, prostate brachytherapy, prostatectomy incontinence, erectile dysfunction

Introduction

Today, the evidence on treatment effectiveness for low risk prostate cancer is still poor due to the lack of randomized trials providing comparative data regarding the different surgical and not surgical options. As such, the treatment decisions are still based largely on patient preference and/or physician experience. Among the surgical therapies, radical prostatectomy (RP) and brachytherapy (BT) are accepted options for low risk prostate cancer. Comparative retrospective studies regarding radical retropubic prostatectomy (RRP) versus BT demonstrated similar biochemical recurrence rates with different postoperative complications.[1-4] Prospective or randomized trials comparing these two procedures are very few and their results are often limited by poor recruitment.[5-7] In the last 10 years, robot-assisted radical prostatectomy (RARP) has largely replaced RRP as a less invasive and more effective procedure producing better and earlier recovery of urinary continence and potency.[8,9] However, very few retrospective studies have compared RARP with BT and randomized studies comparing these two techniques do not exist at this time.[10,11]

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Based on these findings, we aim to contribute to this field by comparing the oncological and functional results of BT and RARP in a single-center, prospective randomized study.

Materials and methods

The study lasted from January 2012 to January 2016 with an enrolment phase in the first 2 years. It was conducted in accordance with the Good Clinical Practice Rules and the ethical principles of the Declaration of Helsinki. The procedures have been approved by a local ethics committee.

Inclusion criteria

Eligible patients were all males referred to our institution with low risk prostate cancer (clinical stage T1c or T2a, PSA value ≤ 10 ng/mL and Gleason sum ≤ 6),[12] prostate volume ≤ 50 g, normal urinary (IPSS ≤ 7 and mean flow rate ≥ 15 mL/sec) and erectile functions (IIEF > 17).[13,14] Table 1 shows patients' characteristics.

Exclusion criteria

Exclusion criteria included large median lobes, previous radiation therapy, hormonal therapy, pelvic surgery and transurethral prostate resection.

Randomization

After signing a specific informed consent form, patients were randomized into either RARP or BT groups using a computer-generated 1-to-1 simple randomization list.

Justification of sample size

The sample size of our study was calculated to recognize significant differences (a level < 0.05) of approximately 25% between the incidence proportions of tested outcome with an adequate power (1 – b = 80%). These conditions require a total of 75 + 75 = 150 observations. Considering an acceptable exclusion or lost-to-follow-up rates of 20%-25%, we enrolled 50 extra patients for each group.

Preoperative evaluation

Before surgery, all patients underwent history, physical examination, routine laboratory tests and transrectal ultrasound guided needle biopsy. Furthermore, they were invited to fill in the International Prostate Symptom Score (IPSS), the International Index of Erectile Function (IIEF-5) and the Expanded Prostate Cancer Index Composite (EPIC) questionnaires.[13-15]

Surgical techniques and postoperative schedule

Bilateral nerve sparing procedures were performed on all of the RARP patients by a single skilled surgeon according to Mottrie's technique.[16] BT was performed by an experienced team, which included a urologist from our group, a radiation therapist and a primary care physician, through a transperineal template-guided peripheral loading real-time technique and seeds of I-125.[17]

RARP patients were discharged after performing cystography with catheter removal and pelvic floor muscle rehabilitation, usually the fifth-sixth day after surgery, while BT patients were discharged the day after surgery after performing routine radioactive controls, pelvic radiography and assessment of the residual urine

TABLE 1. **Comparison of preoperative characteristics between the two groups of patients**

Patient characteristics	RARP group	BT group	p value
Age, years, mean (SD)	62.6 ± 6.0	63.0 ± 5.4	0.31
Clinical stage, no. (%)			
T1c	69 (69.0%)	67 (67.0%)	0.37
T2a	31 (31.0%)	33 (33.0%)	0.36
Gleason score at biopsy, median	5.8 ± 0.4	5.9 ± 0.1	0.35
PSA, ng/mL, mean ± SD	6.6 ± 1.9	7.2 ± 2,5	0.09
Prostate volume, mL, mean ± SD	39.2 ± 8.4	36.3 ± 7.6	0.13
IPSS score, mean ± SD	3.2 ± 2.2	3.1 ± 2.2	0.40
Flow rate (Q max), mL/sec, mean ± SD	19.3 ± 6.4	19.4 ± 6.6	0.39
IIEF score, mean ± SD	22.0 ± 2.1	22.0 ± 2,1	0.41
EPIC score, mean ± SD	0 ± 0	0 ± 0	-

RARP = robot-assisted radical prostatectomy; BT = brachytherapy; PSA = prostate-specific antigen; IPSS = International Prostate Symptom Score; IIEF = International Index of Erectile Function; SD = standard deviation; EPIC = Expanded Prostate Cancer Index Composite

voiding by ultrasonography. Phosphodiesterase type 5 (PDE-5) inhibitor therapy was proposed to all patients while alpha blocker drugs were also administered to BT patients for 1 year after surgery.

Postoperative evaluation

Both groups of patients were monitored as recommended by the European Association of Urology.[18] In particular, the follow up consisted of a clinical evaluation and prostate-specific antigen (PSA) level determination at 3, 6, 9 and 12 months after surgery; every 6 months for the following 2 years and annually thereafter. Furthermore, the patients were invited to fill in the IPSS, IIEF-5 and EPIC questionnaires at every follow up visit.[13-15]

Biochemical recurrence (BCR) was defined, in RARP patients, as the detection of a PSA value > 0.2 ng/mL in at least two consecutive measurements while, in BT patients, as a PSA increase ≥ 2 ng/mL higher than the PSA nadir value independent of the serum concentration of the nadir.[19,20]

The evaluation of the urinary function included the assessment of continence and urinary disorders. Continence was defined using a single question from the EPIC questionnaire: ''How many pads of adult diapers per day did you usually use to control leakage?'' Patients were defined as continent if they did not use any pads. Urinary disorders were assessed using the IPSS questionnaire. Potency was evaluated using the IIEF-5 questionnaire and was defined as the ability to achieve and maintain satisfactory erections for sexual intercourse with or without the use of PDE-5 inhibitors (IIEF score ≥ 17).[13-15] Patients dependent on intracavernous injections were not considered potent.

Patients who had undergone adjuvant radiotherapy or hormonal treatment were excluded from the PSA outcomes analysis and functional evaluation.

Data

Demographics, preoperative characteristics, perioperative and postoperative parameters and follow up data of all the patients were prospectively collected in a customized database and then analyzed.

End points

Our end points included the comparison of biochemical recurrence-free survival rates, urinary function, continence and potency rates at the different time points during the first 2 years follow up among the BT and RARP groups of patients.

Statistical analysis

Means and standard deviations were used to report continuous variables. Frequencies and proportions were used for categorical variables. The means were compared using the Student's t-test and the Mann-Whitney test. Frequencies and proportions were compared using the χ^2 test. Any p value < 0.05 was considered significant.

Results

The two groups were comparable in terms of preoperative characteristics, Table 1.

Figure 1 shows the study flow diagram. Four patients in the RARP group and three patients in the BT group were lost to follow up. Two patients in the RARP group underwent adjuvant radiotherapy due to finding pT3b tumors at the definitive pathological evaluation and were excluded from the outcomes assessment. Lastly, 77 and 79 patients were evaluable in the RARP and BT groups, respectively.

Regarding the oncological outcomes, a biochemical recurrence was assessed in three BT and two RARP patients corresponding to biochemical recurrence-free survival rates of 96.1% and 97.4%, respectively (p = 0.35).

Regarding urinary function, significantly higher IPSS scores were assessed in the BT group than the RARP group, at all postoperative time points (p = < 0.05), Figure 2. Significantly higher continence rates were assessed in the BT group, although only during the first 6 months of follow up (p = < 0.05), Figure 3. Regarding erectile function, significantly lower potency rates were assessed in the BT group than in the RARP group of patients at all postoperative time points (p = < 0.05), Figure 4.

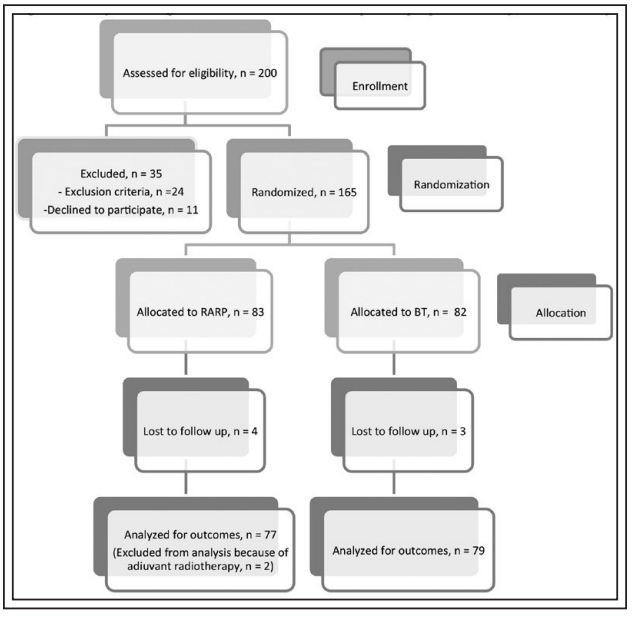

Figure 1. Study flow diagram. RARP = robot-assisted laparoscopic prostatectomy; BT = brachytherapy

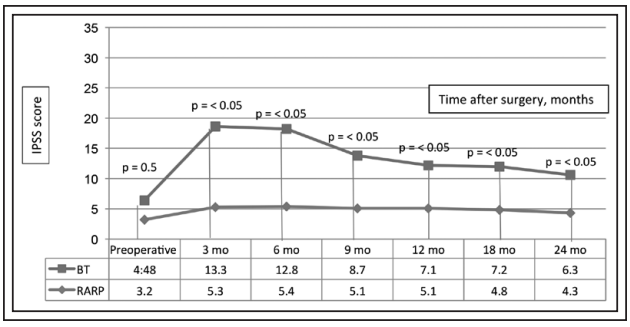

Figure 2. Mean IPSS score and statistical differences between the two groups at the different time points.

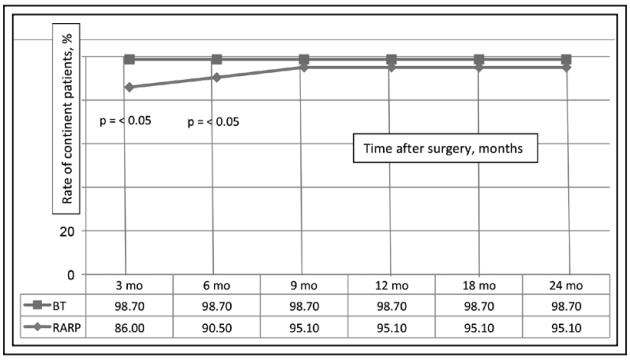

Figure 3. Continence rates and statistical differences between the two groups at the different time points.

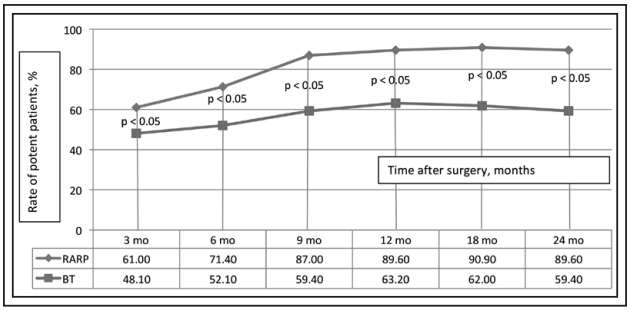

Figure 4. Potency rates and statistical differences between the two groups at the different time points.

Discussion

The surgical management of low risk prostatic cancer is an open debate in literature due to the lack of randomized controlled trial information, especially since the introduction of minimally invasive techniques in urological practice. Some papers have been published comparing laparoscopic techniques or BT with RRP showing similar mid to long term oncological outcomes and very attractive functional results.[1-3,21,22] Today, although RRP should still be considered the gold standard by which these surgical managements are also compared during long term follow up, BT and laparoscopic procedures, particularly RARP, have become the standards of care at many centers worldwide.

These aspects influenced the aim of the present study, which was to compare oncological and functional results of RARP versus BT in the treatment of low risk prostatic cancer. In fact, very few retrospective studies have compared these two different procedures and, to our knowledge, no single prospective study has been reported in literature providing a low level of evidence on this topic.[10,11] To contribute to this field, we planned a prospective randomized trial involving two groups of patients with comparable demographic and preoperative characteristics.

Regarding the oncological aspects, our results did not demonstrate any difference in terms of biochemical recurrence-free survival rates between the two groups at 2 years follow up. This aspect was rather expected in this particular low risk group of patients and seem to suggest similar oncological outcomes for the treatment of localized prostate cancer after both procedures, as reported during medium to long term follow up after RRP and BT.[10,23,24] However, we know very well that our 2 year follow up is short and these data must be confirmed in the future before making any oncological conclusions.

On the other hand, we think that interesting data could derive from the evaluation of follow up functional outcomes.

Concerning urinary function, BT patients reported a significantly higher rate of continence for the first 6 months but also a significantly higher rate of urinary symptoms during the 2 year follow up with respect to RARP patients. The higher probability of maintaining continence and developing urinary symptoms after BT compared to the other surgical procedures has already been reported in literature even many years after surgery.[2,3,25,26] Our data confirmed these higher and longer lasting urinary symptoms but also showed a better continence rate among BT patients only during the first 6 months of follow up, with respect to RARP patients.

Regarding sexual function, despite a decrease in postoperative IIEF-5 scores with respect to the preoperative values among both groups, significantly higher potency rates were assessed among RARP than BT patients during the entire follow up period. Also this aspect is not in accordance with the literature. In fact, although the published studies reported a decrease in sexual function during the first 12-24 months after

all surgical procedures, they generally showed a quicker and better recovery of sexual function after BT compared to the other treatments, probably due to no immediate damage of the neurovascular bundles.[3,4,21,26,27]

However, some considerations should be made regarding these mentioned outcomes. Usually, these data were derived from retrospective studies based on overall quality of life questionnaire assessments, which did not include specific evaluations of urinary and sexual functions. Furthermore, the majority of them still considered RRP as the only type of prostatectomy and did not evaluate the impact of the reported advantages of RARP, in terms of earlier recovery of continence and potency, in the comparison with the other techniques.[2-4,8,9,25-28] In this setting, our study, which prospectively compared BT to RARP for the first time, showed new and different outcomes. In fact, our data downsized the reported benefits of BT in terms of conservation of continence confirming the higher rate of postoperative urinary symptoms with respect to the RARP procedure. Furthermore, our outcomes highlighted an advantage of RARP in terms of recovery of potency with respect to BT. These aspects could be related to the technical characteristics of robotic surgery which has been reported to allow a more accurate apical dissection, a more effective urethrovesical anastomosis and better preservation of the neurovascular bundles producing earlier and better functional outcomes and a more favorable profile in the comparison with the other surgical procedures including BT.[28-30]

This study was not free of limitations. In fact, the number of enrolled patients was relatively small, even if validated by statistics. However, difficulties in the development of such a randomized study have already been reported in literature.[5,6] Additionally, 2 years is not an adequate period of time to reach any oncological conclusions. On the contrary, the main strengths of the present paper are the strict preoperative selection, which produced no significantly different baseline characteristics of the patients, the prospective randomized profile, the use of validated questionnaires and classifications and the adequate follow up period for the evaluation of functional results.

Conclusion

Our data showed similar biochemical recurrence-free survival rates after BT and RARP at 2 years follow up. BT patients confirmed constantly higher rates of urinary symptoms while only reporting better continence rates for the first 6 months after surgery. RARP patients reported higher potency rates than BT patients during all the follow up period. These aspects, which could be related to the reported advantages of robotic surgery in terms of shorter and better recovery of functional outcomes with respect to BT, should be taken into consideration during patient counseling for the treatment of low risk prostatic cancer. □

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