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Radical Transurethral Resection of the Prostate: A Possible Radical Procedure Against Localized Prostate Cancer with Almost No Postoperative Urinary Incontinence

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1. Introduction

Current radical surgery against localized prostate cancer (PCa), such as open (Memmelaar, 1949; Reiner & Walsh, 1979; Walsh & Donker, 1982), laparoscopic (Schuessler et al., 1997; Abbou et al., 2000; Guillonneau et al., 2003) or robot-assisted prostatectomy (Binder & Kramer, 2001; Menon et al., 2002; Menon et al., 2004), has a possible risk to injure supporting structures that surround and support the prostate as well as the external sphincter and the neurovascular bundle. As a result, postoperative stress urinary incontinence develops and continues in about 10% of patients (Stanford et al., 2000; Lepor et al., 2004; Namiki et al., 2009; Menon et al., 2007). Many procedures were introduced to improve the recovery of postoperative sexual function and urinary incontinence: bladder neck suspension or reconstruction (Poon et al., 2000), reconstruction of the rhabdosphincter (Rocco et al., 2007), periurethral suspension of the dorsal vein complex/urethral complex (Patel et al., 2009) and preservation of the neurovascular bundle (Kaiho et al., 2005), but have failed to solve the problems completely until now.

The idea of a transurethral approach to resect almost total prostate tissues containing prostate cancer dates back to around 1990 (Valdivia Uría & López López, 1989; Reuter et al., 1991). The technique did not significantly increase the operative morbidity and mortality compared with transurethral resection of the prostate (TURP) for benign prostate hyperplasia (BPH), and was suggested to be a valid alternative in some patients with prostate cancer. And a recent report concluded that localized prostate cancer could be resected transurethrally as radical as open surgery (Reuter et al., 2008).

We thought that the transurethral approach to treat prostate cancer might bring better clinical results in the era of more improved resectoscope and more sensitive PSA test for the follow-up examination. We applied the transurethral technique to manage prostate cancer with the intention to eliminate almost all prostate tissues that contained localized cancer. As we already reported (Morita & Matsuura, 2009), radical transurethral resection of prostate cancer (RTUR-PCa) against localized prostate cancer has a possibility to minimize the injury to the external sphincter because an operator is able to recognize it clearly during the operation. With a minimal injury to the supporting structures of the prostate, we think that urinary continence can be reserved in RTUR-PCa at least at a
similar rate in transurethral resection of the prostate for BPH. Urinary incontinence after TURP is reported to occur in 0.4 – 3.3 % of the patients (Holtgrewe et al., 1989; AUA Practice Guidelines Committee, 2003).

2. Patients and methods

2.1 Patients

Between December 2003 and December 2007, a total of 222 radical transurethral resection of prostate cancer were performed under spinal anesthesia in 170 patients with clinical stages of T1 or T2. Clinical stages were determined according to the UICC TNM staging system of 1997. We informed the patients that the procedure was not a current standard radical method of management, and those who refused this procedure were excluded from the study. We also excluded patients with serious comorbidities that might affect their lives by standard TURP. Patients who gave a written informed consent were eligible for the study in the order they were given a diagnosis of localized prostate cancer. Institutional review board approved the TUR-PCa program after the preliminary study. Clinical stage was determined mainly by digital rectal examination and transrectal ultrasonography combined with the result of needle biopsy. We selected the patients to be checked for metastasis by eliminating patients with a minimum risk of metastasis according to Partin nomogram (Partin et al., 1993) and other reports on bone metastasis (Oesterling, 1991; Oesterling, 1993). Ultrasound guided transrectal needle biopsy was performed on 123 patients under caudal block, excluding the patients who were given a diagnosis of PCa after transurethral resection of the prostate for BPH. We obtained a total of 14 samples per case from the peripheral and transition zone including far lateral part, dividing the prostate into base (2 cores), upper middle part (2 cores), lower middle part (6 cores) and apex (4 cores), and we marked at the dorsal end. Patients ranged from 52 to 91 years old (mean ± SD: 72.9 ± 7.3, median: 74.0), preoperative PSA 1.5 to 100.5 ng/mL (mean ± SD: 10.38 ± 11.95, median: 6.2). Out of 170 patients, 20 patients were lost to follow-up, leaving 150 patient included in this study. Clinical stages were as follows: T1b: 39 cases, T1c: 88 cases, T2: 23 cases. The present study includes the patients who were given a diagnosis of prostate cancer after TURP for BPH and on antiandrogen therapy. Thirty-five patients with a clinical stage of T1b were on oral antiandrogen (chlormadinone acetate) therapy for a mean period of 72.1 weeks with the longest case for 12 years preoperatively. In 11 patients with a clinical stage of T1c, oral antiandrogen was administered for the period between 5 and 47 months (mean 23.0 months). In the other patients, oral antiandrogen was administered for 1 to 2 weeks just before RTUR-PCa, with no hormonal therapy being done after the operation.

2.2 Operative procedures

One authorized urologist (M.M.) performed all the operations. We used a standard TURP setup with an irrigation pressure of 80 cmH₂O and an irrigation rate of 250 ml/min using D-sorbitol solution. After a rough resection of almost all the transition and central zone, we tried to resect and fulgurate the peripheral zone as completely as possible, especially where cancer was detected by biopsy. The resection was continued until adipose tissue, venous sinus or the external sphincter was identified. But we did not resect prostate tissues until adipose tissue was exposed all around the operative field. We aggressively fulgurated the area adjacent to where adipose tissue was exposed because the remaining
prostate tissue could be considered a thin layer. We especially paid attention not to distend the bladder too much to prevent a high irrigation pressure and a resultant TUR syndrome. Special attention was paid to avoid the injury to Santorini’s plexus and the rectum. The procedure was started from the 12 o’clock position, dividing the prostate into 6 parts, and resected specimens were collected separately to examine the distribution of cancer. The seminal vesicle was partially resected at its attached part to the prostate between the 4 and 8 o’clock positions to determine the invasion of cancer. Finally the verumontanum was resected to achieve the complete resection of prostate tissue. A bag catheter was removed on the third postoperative day.

Fig. 1. As radical TUR proceeds, adipose tissue and the external sphincter can be seen.

2.3 Follow-up
Postoperative PSA was measured every two months starting two months after the initial operation. PSA failure was diagnosed when PSA showed a consecutive rise over 0.2 ng/mL. This was also applied to the indication of the second RTUR-PCa. But when the PSA level reached a plateau between 0.2 and 1.0 ng/mL, we did not think immediately that the patients were in a treatment failure.

3. Results
3.1 Results of RTUR-PCa
The mean follow up period of 150 patients was 45.1 ± 13.1 months (median: 43.9, range: 11 - 72 months). The operation time ranged between 60 and 125 min. (mean 80 min.), and the resected tissue weight was between 4.0 and 63.0 grams (mean ± SD: 15.1 ± 8.5, median: 14.0). The preoperative mean PSA value was 9.4 ± 9.7 ng/mL (median: 6.0, range: 1.5 to 66.3), with an unknown value in one patient. Pathological stages were as follows: pT2a: 60 cases, pT2b: 84, pT3: 5, pT4: 1 (Table 1). And Gleason score were: 4: 3 cases, 5: 7, 6: 35, 7: 67, 8: 17, 9: 21
Out of 20 patients who were lost to follow up, eight patients went for treatments elsewhere, five patients refused the second RTUR-PCa, and seven patients did not return to the clinic after their discharge. Three out of 8 patients who went to other hospitals underwent open radical prostatectomy. No malignant cells were detected pathologically in the residual prostate tissue in one patient, and no prostate tissue was found in the other two patients. Seven patients died during the follow-up period: three died of pneumonia, another of heart disease, of cerebrovascular accident, and of gastric cancer, and the last of biliary duct cancer, but there was no prostate cancer-related death. At present, ninety-seven patients have stable PSA after the first RTUR-PCa.

### Table 1. Results of RTUR-PCa grouped by pathological stage

<table>
<thead>
<tr>
<th>Pathological Stage</th>
<th>Total Patients</th>
<th>Patients treated with 1 operation</th>
<th>Patients treated with 2 operations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Patient</td>
<td>No. Patient</td>
<td>Latest PSA Mean (SD)</td>
</tr>
<tr>
<td>pT2a</td>
<td>60</td>
<td>45</td>
<td>0.080 (0.138)</td>
</tr>
<tr>
<td>pT2b</td>
<td>84</td>
<td>53</td>
<td>0.071 (0.106)</td>
</tr>
<tr>
<td>pT3</td>
<td>5</td>
<td>3</td>
<td>0.001</td>
</tr>
<tr>
<td>pT4</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Results of RTUR-PCa grouped by Gleason’s score

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Total Patients</th>
<th>Patients treated with 1 operation</th>
<th>Patients treated with 2 operations</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>3</td>
<td>0</td>
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<tr>
<td>5</td>
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<tr>
<td>9</td>
<td>21</td>
<td>13</td>
<td>8</td>
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The second TUR-PCa was performed in 46 patients between 5 and 51 months (mean 16.8) after the first operation. The resected tissue weight was between 5.0 and 14.0 grams (mean ± SD: 6.6 ± 1.3, median: 6.0). No cancer cells were detected pathologically in 13 patients (28.3%). PSA failure was diagnosed in 9 patients who underwent the second RTUR-PCa. These patients showed high preoperative mean PSA value of 22.4 ng/mL (7.7 to 55.5 ng/mL) and PSA values did not fall significantly after the second RTUR-PCa. In the other 36 patients PSA levels stabilized after the second operation showing PSA ≤ 0.01: 19 cases, ≤ 0.02: 4, ≤ 0.03: 2, ≤ 0.1: 7, ≤ 0.2: 1, ≤ 0.3: 1, ≤ 0.5: 2.

3.2 Overall results
PSA failure finally developed in 16 patients (10.7%) in the most recent follow-up. Preoperative PSA levels in these patients ranged from 7.3 to 55.5 ng/mL (mean 21.9), and Gleason scores were 7 in 8 patients, 8 in 2, and 9 in 6 (Table 1, 2). In the other 134 patients, PSA values stabilized as follows: PSA ≤ 0.01: 55 cases, ≤ 0.02: 18, ≤ 0.03: 10, ≤ 0.04: 3, ≤ 0.1: 22, ≤ 0.2: 10, ≤ 0.7: 16.

Non-Recurrent Rate (Clinical stage)

Fig. 2. Actuarial biochemical non-recurrence rate of each clinical stage

In all cases studied, the actuarial biological non-recurrence rate for each clinical stage were as follows: T1b: 0.97 at 72 months, T1c: 0.92 at 66 months, T2: 0.65 at 64 months (Fig. 2). The actuarial biological non-recurrence rate for pT2a at 66 months and pT2b at 72 months were 0.92 in both groups (Fig. 3).
Non-recurrence rate of each risk group according to D’Amico classification (D’Amico et al., 1998) are shown in Fig. 4. PSA failure did not develop in the low-risk group of 34 patients (stage T1c, T2a and PSA level ≤ 10 ng/mL and Gleason score ≤ 6). Biological non-recurrence rate was 91.4% in the intermediate-risk group of 70 patients (stage T2b or Gleason score of 7 or 10<PSA level ≤ 20 ng/mL) and 78.3% in the high-risk group of 46 patients (stage T2c or PSA level > 20 ng/mL or Gleason score ≥ 8) respectively.

![Non-Recurrence Rate (Pathological stage)](image)

**Fig. 3.** Actuarial biochemical non-recurrence rate of each pathological stage (pT2a, solid line; pT2b, dotted line)

### 3.3 Learning curve

In some of the patients that underwent the first operation until March 2006, the PSA level did not show a sufficient drop. The operative technique became proficient and stable after that time, resulting in an acceptable clinical outcome (Fig. 5). Only 8 cases needed the second operation in 73 cases (p<0.0001 compared with cases before March 2006, chi square test) including 7 cases of PSA failure and 2 cases that was lost to follow-up, yielding more cases with lower PSA level as follows: PSA≤0.01: 31 cases, ≤0.02: 15, ≤0.03: 4, ≤0.04: 2, ≤0.1: 8, ≤0.2: 4, ≤0.6: 3. Nadir PSA levels were 0.013 ± 0.026 ng/mL (median, 0.004; range, 0.001-0.149 ng/mL) at 2.8 ± 1.4 months (median, 2; range, 2 - 8 months) postoperatively.
Non-Recurrence Rate (Risk group)

Fig. 4. Actuarial biological non-recurrence rate of each risk group

Fig. 5. Latest PSA and the time of operation

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3.4 Complications

3.4.1 Urinary incontinence

We evaluated stress urinary incontinence by asking patients the postoperative status of urinary leak on a cough or a sneeze and needs for a urinary pad. Urinary incontinence was seen in 35% of the patients when a bag catheter was removed on the third postoperative day. Incontinence soon improved until the third postoperative week, and no patients need a urinary pad at all at the third postoperative month.

3.4.2 Other postoperative complications

There were no patients in whom water intoxication developed or who needed transfusions perioperatively. Bladder neck contracture, which developed three to four months postoperatively, was the most frequent complication (49 cases, 32.7%). Other complications included pubic osteitis (2 cases), bladder tamponade (2 case), acute epididymitis (3 case), pulmonary embolism (1 case), and rectourethral fistula (1 case). Erectile function was preserved after the first operation in 26 (60.5%) of the evaluated 38 sexually active patients. After the second operation only 1 out of 9 patients preserved erectile function probably due to the injury of the neurovascular bundle by excessive resection and fulguration during TUR-PCa.

Figure 6 shows an urethrocystogram 3 weeks after the operation. The seminal vesicle is clearly visualized with no extravasation from the prostate bed. Marked expansion of the prostate bed may indicate that most prostate tissues were removed by the procedure.

Fig. 6. Postoperative urethrocystogram (left anterior oblique)

3.5 Focal TUR-PCa: Report of a case

A 78-year-old man, who had a history of acute myocardial infarction and cerebral infarction and was on anticoagulation therapy, visited our clinic with a complaint of frequency with
urge incontinence. An estimated prostate volume was 33.0 cm$^3$ by transrectal ultrasonography (TRUS). We started the treatment by giving alpha-blocker. His PSA at first visit was 4.20 ng/mL, and became slightly elevated to 5.47 ng/mL after two months. Transrectal prostate biopsy revealed prostate cancer confined in the right lobe. Gleason scores were 6 (3 + 3) in two out of 14 cores. He underwent standard TURP of the transition and central zone, and then we made a deeper resection of the peripheral zone of the right lobe. The operation took 80 minutes with no blood transfusion and water intoxication, and the resected weight was 27.0 g. A bag catheter was removed on the third postoperative day. The patient complained of mild dysuria that improved after two weeks, but did not complained of urinary incontinence. His erectile function had been lost preoperatively. Pathological examination confirmed prostate adenocarcinoma of Gleason score of 6 (3 + 3) in the right lobe. PSA values measured every two months were stable between 0.04 and 0.09 ng/mL till 48 postoperative weeks. The PSA values indicate the efficacy of focal TUR-PCa though final evaluation of the treatment in this patient must need longer time.

4. Discussions

4.1 Radical TUR-PCa

4.1.1 Results and complications

Transurethral resection of the prostate is now ranked as a palliative therapy used mainly to relieve obstruction caused by prostate cancer. We advanced the transurethral technique and applied it to the complete ablation of prostate tissue (RTUR-PCa). Five and 10-year biochemical recurrence-free survival rates of radical prostatectomy are reported 70-84% (M. Han et al., 2003; Zinzcke et al., 1994; Catalona & Smith, 1994) and 52-82% (M. Han et al., 2003; Zincke et al., 1994; Catalona & Smith, 1994; Hull et al., 2002; Pound, 1997; Roehl, et al., 2004) respectively. Our result is comparable with that of radical prostatectomy, though the number of patients and the follow-up period are not sufficient to evaluate the procedure finally at this time. The operative technique may be more difficult than that of the standard TURP and needs more experience to become proficient. Extravasation of irrigation fluid is sure to occur during the operation, but no patients experienced water intoxication with the lowest irrigation pressure, and no patients needed blood transfusion. These suggest that the procedure can be performed safely. But much safer operation may be possible with the use of a bipolar TUR system. The postoperative course is usually uneventful and all patients could void immediately after the removal of indwelling catheters on the third postoperative day. Urinary incontinence was temporary, disappearing within 3 months. By the transurethral technique, continence can be reserved because the operator can easily detect the external sphincter, and supporting structures surrounding the prostate therefore allow the urethra to remain intact. The most excellent results of postoperative continence after radical prostatectomy are reported 93.0 % as to open prostatectomy (Walsh et al., 2000), 97.4 % as to laparoscopic surgery (Christopher et al., 2011) and 98.0 % as to robot-assisted surgery (Patel et al., 2005). And there seems no difference among the procedures when a surgeon becomes proficient. In the present study, the most frequent postoperative complication was bladder neck contracture, which had been expected because of an aggressive bladder neck resection to achieve radicality. But bladder neck contracture was easily treated by neck incision using an optical urethrotome under caudal block on a day surgery basis.
Dissemination of cancer cells may occur and affect the prognosis of patients. But the impact of TURP on the clinical outcome in patients with PCa is controversial (Levine et al., 1986; Zelefsky et al., 1993; Pansadoro et al., 1991). One report concludes that extensive TURP did not worsen the prognosis of patients with PCa (Trygg et al., 1998).

The effect of chlormadinone acetate on postoperative PSA must be considered in the present study. We could not find any reports that describe the duration of the suppressive effect of chlormadinone acetate in patients with prostate cancer. But in patients with prostate hyperplasia given 50 mg/day of chlormadinone acetate for 16 weeks, PSA levels are reported to return to the baseline levels 16 weeks after discontinuation (Noguchi et al., 2000). In this study the effect of preoperative hormonal therapy on the most recent PSA levels, therefore, can be minimum and negligible.

4.1.2 PSA failure and the second RTUR-PCa

In open or laparoscopic radical prostatectomy, residual cancer relates with PSA failure. RTUR-PCa is probably less invasive than radical prostatectomy and more flexible in the point that the second operation can be indicated and easily done to eliminate residual cancer when PSA shows a successive rise. The second RTUR-PCa was required in 46 patients. But this is considered just a technical issue because the need for the second operation has decreased as the surgeon has become experienced. There were no malignancies reported by pathologists in 13 out of 46 cases, although it is not clear whether cancer did not actually exist or missed to be detected in the specimens of the second operation. PSA failure is usually defined as a progressive rise over 0.2 ng/mL (Schild et al., 1996; Pound et al., 1999; Freedland et al., 2003). We took a careful watching policy if PSA level reached a plateau between 0.2 and 1.0 ng/mL, not regarding as PSA failure. But the second RTUR-PCa must be considered and easily performed when PSA levels start to rise continuously after the first operation.

4.1.3 Some considerations to reduce urinary incontinence and erectile dysfunction

We were able to obtain satisfactory postoperative PSA levels by RTUR-PCa comparable with open radical prostatectomy. But we recently started to think that, after a considerable number of the procedures, minimal residual prostate tissue at the part where cancer was not detected by biopsy might not necessarily prevent the radicality of the disease in carefully selected patients. We performed prostate biopsy to get information about the localization of cancer. The results of cancer localization from operative specimens were consistent with those from biopsy specimens in 46.7%. Information about the localization of cancer from biopsy specimens is very helpful to plan the manner of resection. Although an experienced resectionist can remove almost all prostate tissues transurethrally, aggressive resection can be applied where the cancer was detected by biopsy to achieve the radicality of the operation. Erectile function was preserved in about 60% of the patients in the present study. Preservation of the cavernous nerve can be achieved by leaving some prostate tissue not to be resected around the 4 or 8 o’clock position not to injure the nerve. When PSA levels rise postoperatively, removal of residual prostate tissue is possible by the second RTUR-PCa. Because the open radical prostatectomy is likely to damage the supporting tissue around the prostate and the urethra, improvement of urinary incontinence and erectile function after the operation remains limited (Stanford et al., 2000). RTUR-PCa, therefore, can provide urinary continence at least to the same degree as TURP for BPH. RTUR-PCa may be also a breakthrough to prevent the development of erectile dysfunction.
4.2 Focal TUR-PCa

4.2.1 The idea of focal therapy for prostate cancer

Currently, the two main options for the radical treatment of localized prostate cancer are radical prostatectomy (Memmelaar, 1949; Reiner & Walsh, 1979; Walsh & Donker, 1982; Schuessler et al., 1997; Abbou et al., 2000; Guillonneau et al., 2003; Binder & Kramer, 2001; Menon et al., 2002; Menon et al., 2004) and irradiation therapy (Zelefsky et al., 2002; Wahlgren et al., 2007), but post-treatment morbidities that annoy the patients include urinary incontinence and erectile dysfunction as to operative therapy, and urinary frequency, difficult urination, erectile dysfunction and rectal hemorrhage as to irradiation therapy. On the other hand, active surveillance policy or watchful waiting, which is an ultimate non-invasive procedure, is also accepted to care for the patients with low risk cancer (Bill-Axelson et al., 2008; Wilt et al., 2009). But active surveillance seems still difficult in the point to select a suitable patient, and the patient may feel anxiety about cancer progression.

4.2.2 Current options of focal therapy

Recently introduced concept of focal ablative therapy (Moul et al., 2009; Polascik et al., 2008; Eggener et al., 2007) based on the accumulated pathological and clinical findings after radical prostatectomy, may be the third idea to treat patients with localized prostate cancer. Focal therapy may contribute to minimize morbidities such as incontinence or erectile dysfunction by trying to destruct minimum prostate tissues with cancer in it. The reported rate of postoperative urinary incontinence decreased as the improvement of equipment and technique as follows: 1 to 3 % in cryotherapy (Long et al., 1998; K.R. Han et al., 2003; Hubosky et al., 2007; Polascik et al., 2007; Dhar et al., 2010) and 0.8 % in HIFU (Uchida et al., 2009). The procedures are less invasive and repeatable, and other radical procedures can be applied when necessary after the focal therapy. One of the most important points at issue concerning the focal therapy lies in the selection of the most suitable candidate. Prostate cancer is often multifocal, and then the location of cancer must be properly diagnosed preoperatively. Because current imaging technique cannot detect a tiny focus of cancer, mapping biopsy technique is reported using a template (Onik & Barzell, 2008; Crawford et al., 2005; Furuno et al., 2004) to get information about the precise location of cancer focuses. Procedures of focal therapy, such as cryotherapy (Onik et al., 1993; Cohen et al., 1995; Zisman et al., 2001; Babaian et al., 2008) and high intensity focused ultrasound (HIFU) (Madersbacher et al., 1995; Thüroff et al., 2003; Poissonnier et al., 2007; Lee et al., 2006), are now still thought to be an experimental one in the point that the evaluation of the efficacy is still controversial because the standard of evaluation using PSA has not been established yet. The other serious drawback of these procedures is that we cannot obtain prostate tissues. The pathological evaluation is limited only to biopsy specimens, which may confuse the results to evaluate the procedure because pathological diagnosis by operation specimen is sometimes different from that by biopsy specimen.

4.2.3 Advantages of transurethral resection

We think transurethral resection as a focal therapy for localized prostate cancer has advantages over cryotherapy or HIFU. We can control the resection of prostate tissues precisely under direct vision. We can also obtain specimens for pathological examination. PSA is applied to the follow-up examination and there remains a possibility to carry out the
second TUR to aim at the radical treatment in case of PSA failure. In a patient with prostate cancer confined to one lateral lobe by biopsy, aggressive resection and fulguration can be done in the affected lobe, and appropriate non-radical resection can be applied in the other lobe only to check for cancer tissues (Morita & Matsuura, 2011). Control of prostate cancer, as a result, may be possible preserving urinary continence and erectile function.

5. Conclusion

Recent introduction of PSA into the health check up program in Japan resulted in a marked increase of patients with early stage prostate cancer. These patients were treated until now by open or laparoscopic prostatectomy, irradiation therapy including external beam irradiation and brachytherapy, hormonal therapy, watchful waiting and high intensity focused ultrasound. From the present study with the longest follow-up patients of 6 years, RTUR-PCa can be an effective treatment option for the radical treatment of prostate cancer, although the results of much longer follow up with more cases remain to be studied. To avoid the possibility of overdiagnosis and/or overtreatment, less invasive focal TUR-PCa, can be also a suitable option of focal ablative therapy with less postoperative morbidity in carefully selected patients.

6. References


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Prostate Biopsy represents the standard procedure for diagnosing Prostate Cancer. This procedure can be performed transrectally, through perineum or occasionally through the urethra. Although the procedures of Prostate Biopsy are covered in numerous publications, there is still a need for gathering different aspects and methods in one source. Hopefully, this book will help physicians in their effort to provide the best treatment for their patients.

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