Effects of preoperative dutasteride treatment in holmium laser enucleation of the prostate

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Abbreviations: BPH, benign prostatic hyperplasia; CIC, clean intermitted catheterization; HoLEP, holmium laser enucleation of the prostate; IPSS, International Prostate Symptom Score; MRI, magnetic resonance imaging; PVR, postvoid residual urine; Q_{max}, maximum urinary flow rate; Q_{ave}, average urinary flow rate; QOL, quality

of life; TRUS, transrectal ultrasonography; TUR-P, transurethral resection of the prostate; TZ, transitional zone; UTI, urinary tract infection

Abstract

Objectives When performing holmium laser enucleation of the prostate, finding and maintaining an appropriate plane on the surgical capsule of the prostate for decapsulation are vital for safe and quick surgery. However, it is not always easy to identify this surgical surface.

Methods Enrolled in this study were 116 men diagnosed as having benign prostate hyperplasia who underwent holmium laser enucleation of the prostate between January 2010 and September 2013. The difficulty of decapsulating the surgical capsule was evaluated retrospectively according to newly defined criteria using surgical videos (grade I, least difficult; grade IV, most difficult). We investigated the factors influencing decapsulation difficulty.

Results Evaluable video recording was possible in 99 of 116 patients. Decapsulation difficulty was grade I in 32 patients, grade II in 31 patients, grade III in 20 patients, and grade IV in 16 patients.

Preoperative dutasteride therapy was the only factor increasing the difficulty in decapsulation of the surgical capsule of the prostate by holmium laser enucleation.

Conclusions Although preoperative dutasteride therapy effectively reduces intraoperative blood loss, surgeons with limited experience should be careful with the

use of dutasteride because its administration increases surgical difficulty.

Key words: Dutasteride; Laser Therapy; MRI, Prostate; Urologic Surgical Procedures

Introduction

Although the primary treatment for benign prostatic hyperplasia (BPH) is drug therapy with α1-adrenoceptor blockers, anti-androgen drugs are frequently combined for patients with relatively severe BPH. Moreover, as recommended by the treatment guidelines for BPH, surgery is often indicated when patients with large BPH present with acute urinary retention or progressive symptoms[1].

Transurethral resection of the prostate (TUR-P) has long been the gold standard surgical treatment of BPH. However, because of low blood loss, low incidence of hyponatremia, and short operative time even in cases of large prostate, holmium laser enucleation of the prostate (HoLEP) has become more prevalent in recent years[2-4]. In fact, HoLEP has become the first surgical choice for BPH at our clinic because many studies have reported excellent postoperative outcomes, due in part to improvements in the device and laser output. In our clinical practice, we experienced many HoLEP cases in which dissection of the surgical capsule was difficult, and therefore we retrospectively investigated the factors influencing its difficulty in this study.

Methods

Patients

Of the patients who were diagnosed as having BPH and underwent HoLEP between January 2010 and September 2013, 116 were enrolled in this study after excluding the initial 100 patients to minimize the learning curve effect. Preoperatively, all patients received α1-adrenoceptor blockers and underwent transrectal ultrasonography (TRUS) to measure transitional zone (TZ) volume in the prostate. The same surgeon (RS) performed all procedures.

Evaluation items

Using clinical records, we investigated age at the time of surgery, history of acute urinary retention, preoperative administration of dutasteride over 3 months, preexisting urinary tract infection or bladder stones, clean intermitted catheterization (CIC), indwelling urinary catheter, TUR-P, and prostate hyperthermia therapy.

International Prostate Symptom Score (IPSS), quality of life (QOL) score, postvoid residual urine (PVR), maximum urinary flow rate (Q_{max}), and average urinary flow rate (Q_{ave}) were evaluated before and 3 months after HoLEP.

Surgical HoLEP procedure

HoLEP was performed in all patients under general anesthesia using the VersaPulse

Select 80W Laser (2.4 J at 30 Hz; LUMENIS Co. Ltd., Tokyo, Japan) and SlimLine fiber laser (550 μm; LUMENIS Co. Ltd.). Retrograde enucleation was performed as the standard surgical method using the three-lobe technique[5,6]. Morcellation was performed using the VersaCut Morcellator (LUMENIS Co. Ltd.), and prostate tissue was resected after enucleation and morcellation. After recording total tissue weight, specimens were subjected to pathological examination.

The resection rate (%) was defined as the total weight of the resected prostate (g)/TZ volume (ml) in TRUS × 100, and resection efficiency (g/min) was defined as the total weight of the resected prostate (g)/enucleation time (min). Enucleation time was defined as the time needed for laser irradiation, enucleation, and hemostasis, but not morcellation.

Evaluating difficulty in decapsulation of the surgical capsule

Three evaluators (KN, YK, and SS) blinded to patient information evaluated a surgical video and jointly determined the level of difficulty in decapsulating the surgical capsule. Decapsulation difficulty was classified into four grades using a newly established system based on the proportion of the adenoma surface that could be decapsulated easily at the time of enucleation, with a clear view of the surface and without making an

incision through the tissue between the adenoma and capsule, with the exception of incisions in the mucus layer or those made to reach the capsule: Grade I difficulty, ≥75% of the surface; grade II, ≥50%; grade III, ≥25%; and grade IV, <25%. The higher the grade, the more difficult the decapsulation of the surgical capsule. A set of representative video images are shown in Figure 1. To standardize the grading of decapsulation difficulty, representative videos of grades I to IV were prepared and explained by RS. In preliminary work, 3 evaluators were requested to grade 20 videos that were not used in this study. The grading was identical for 18 of the videos. The discrepancy in grading the other 2 videos was minimal, with one video graded as II, II, and III and the other as II, III, and III. In these cases, the grade was determined by the decision by the majority.

Statistics

Statistical analysis was performed in StatView version 5.0 (SAS Institute Inc., Cary, NC). The Kruskal-Wallis test was used to analyze the correlations between background factors and the level of decapsulation difficulty, and the Mann-Whitney U test was used to analyze preoperative dutasteride administration vs age, weight of resected prostate, enucleation rate, and decline of postoperative levels of serum hemoglobin (Hb). In addition, contingency table analysis was performed to investigate the association

between preoperative dutasteride administration and the proportion of grade III/IV patients. Significance was set at $p<0.05$.

This study was approved by the Institutional Review Board of Dokkyo Medical University. All study procedures conformed to the provisions of the Declaration of Helsinki as revised in Tokyo (2008).

Results

Evaluable video recording was possible in 99 of 116 patients. Decapsulation difficulty was grade I in 32 patients, grade II in 31 patients, grade III in 20 patients, and grade IV in 16 patients. The grades of decapsulation difficulty given by the 3 evaluators were identical in 89 patients. In the remaining 10 patients, the decapsulation difficulty was determined by the decision by the majority. There were no cases where all 3 evaluators assigned different grades."

Dutasteride was administered for 3 to 30 months (mean 8.4 months).

In all four groups, decapsulation difficulty did not correlate with age, history of acute urinary retention, CIC, indwelling urinary balloon catheter, TUR-P, prostate hyperthermia therapy, urinary tract infection or bladder stones, prostate resection rate, or enucleation efficiency. Decapsulation difficulty in all four groups correlated with only dutasteride administration. The fraction of patients with preoperative dutasteride

administration did not differ significantly between the grade I and II groups. However, the incidence of patients treated with dutasteride before HoLEP increased in accordance with the decapsulation difficulty (Table 1).

Association of preoperative administration of dutasteride with patient age or resected prostate weight

We compared resection weight, enucleation efficiency, decline in postoperative Hb, and incidence of decapsulation difficulty in grade III/IV patients according to whether they received dutasteride or not (Table 2). The number and mean age of patients with and without dutasteride administration was 36 patients aged 71.8 years and 63 patients aged 67.3 years, respectively, indicating the patients administered dutasteride were older. No significant differences were observed in resection weight or enucleation efficiency. The reduction in Hb was significantly lower in patients administered dutasteride than in those not administered it, with median postoperative Hb levels of 0.3 g/dl and 0.6 g/dl, respectively. The incidence of grades III/IV was significantly higher in patients with preoperative dutasteride administration.

Median values (standard deviation) of IPSS, QOL score, PVR, Q_{max}, and Q_{ave} before surgery were 20.9 (7.9), 4.9 (1.1), 124.5 ml (109.6), 6.9 ml/s (4.0), and 2.7 ml/s (1.6),

respectively. These values were 6.5 (5.1), 1.5 (1.4), 24.2 ml (29.1), 19.3 ml/s (9.6), and 9.9 ml/s (5.1), respectively, at 3 months after surgery. HoLEP improved subjective and objective urinary symptoms.

Discussion

A good understanding of the surgical capsule of the prostate is essential when operating for BPH. In particular, finding a good plane for decapsulation in HoLEP, where decapsulation is the main surgical technique, is key for establishing a sense of orientation in the operative field and for achieving good enucleation efficiency.

In this study, we analyzed the correlation between decapsulation difficulty and the factors influencing the internal structure of the prostate. The results revealed preoperative administration of dutasteride as the only factor increasing the difficulty of decapsulation. A previous study reported that after the administration of dutasteride, the glandular epithelium of the prostate shrinks due to the reduction in the thickness of the epithelium[7]. Finasteride, another 5α-reductase inhibitor, is known to induce apoptosis of the glandular epithelium cells and prostate cancer cells[8-10]. Therefore, it is possible that normal capsular structures are destroyed as the structure of the prostate changes, causing inflammation and adhesions. Some BPH patients underwent magnetic

resonance imaging (MRI) before and after the administration of dutasteride, and findings revealed that the surgical capsule was clearly visible before the administration and became unclear after 18 months of dutasteride therapy. These histological changes are shown on representative MRI images in Figure 2.

The decapsulation difficulty in this study was enhanced by the preoperative administration of dutasteride, without affecting surgical time, weight of the resected prostate, or resection efficiency. This is presumably because regardless of decapsulation difficulty, surgeons with a certain level of surgical skill can orient themselves properly in the operative field to perform enucleation, provided they can locate the surgical capsule at a couple of points and make a proper incision between them. When the surface for decapsulation is difficult to identify, it is also difficult to orient in the operative field, resulting in an accidental incision into the adenoma or increased risk of perforation through the surgical capsule outside the decapsulation plane. For these reasons, institutions lacking staff appropriately trained in HoLEP procedures should avoid the preoperative administration of dutasteride, which makes the decapsulation difficult.

Preoperative dutasteride therapy significantly suppressed the postoperative decline in Hb[11]. However, the decline in Hb in patients administered dutasteride preoperatively

was minimal and did not influence the difficulty of the surgical procedures. Similarly, preoperative administration of finasteride was shown to reduce intraoperative blood loss during TUR-P[12, 13]. In addition, Suzuki et al. reported that blood loss during HoLEP was significantly reduced in patients with preoperative dutasteride administration compared to those without[14].

This study has some limitations. One was that no universal criteria were available for evaluating decapsulation difficulty. To overcome this limitation and add objectivity to this study, surgical videos were retrospectively and cooperatively evaluated by 3 evaluators blinded to patient information. Another limitation was that decapsulation difficulty was evaluated subjectively by the evaluators. In preliminary work, 20 surgical videos were separately evaluated by 3 evaluators. The grades were identical for 90% of the videos. Therefore, the use of this grading system in this study was considered appropriate.

As with α1-adrenoceptor blockers, dutasteride is considered a useful treatment drug for BPH and is recommended as the grade-A treatment drug in many countries. Particularly in Japan, where finasteride is currently not approved for marketing, the clinical application of dutasteride is expected to increase since it is the only 5α-reductase inhibitor available. Although the primary treatment method for BPH is drug therapy,

some BPH patients need to undergo surgery because the combination therapy with α1-adrenoceptor blockers and anti-androgens is not effective[15, 16]. Therefore, we anticipate that the number of HoLEP candidates who have been previously treated with dutasteride will gradually increase. Furthermore, because dutasteride shrinks the prostate, it is often used in patients with a larger prostate. Compared with TUR-P, HoLEP is often indicated for a larger prostate, due to a short operative time, low blood loss, and a low incidence of hyponatremia. For these reasons, the proportion of patients with a history of dutasteride therapy among patients indicated for HoLEP is likely to increase. Expert surgeons overcome decapsulation difficulty due to dutasteride administration by imagining the correct decapsulation plane and then finding the surgical capsule by multidirectional dissection.

In summary, this study investigated the factors influencing the difficulty in dissecting the surgical capsule in BPH patients during HoLEP and revealed that the preoperative administration of dutasteride was the contributing factor. Because it is anticipated that more patients with a history of dutasteride therapy will be indicated for HoLEP, surgeons with little experience should exercise caution when treating such patients.

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Figure legend

Figure 1. Representtive video images illustrating the difficulty in decapsulation of the surgical capsule.

a. The plane for decapsulation could be idenfied clearly. The decapsulation of the surgical capsule could be done easily.

b. The plane for decapsulation could not be identified clearly. Surgical capsule adhered to surface of adenoma.

When the decapsulation was done with clear dissecting plane like Fig. 1 a. in ≥75% of the surface of the adenoma, the difficulty of decapsulation was graded as Grade I.

Figure 2 Images of the surgical capsule (arrows)

a. The surgical capsule is clearly visible before dutasteride administration. b. The surgical capsule is unclear 18 months after dutasteride administration.

Table 1. Background factors and level of difficulty in decapsulation of the surgical capsule

	I	II	III	IV	
No. of patients	32	31	20	16	
Median age (years)	68.1	69.0	68.5	71.6	n.s.
Acute urinary retention	15 (47)	19 (61)	8 (40)	7 (43)	n.s.
Previous dutasteride therapy*	4 (13)	7 (22)	11 (55)	14 (88)	p<0.001
Previous CIC	3 (9)	2 (6)	2 (10)	2 (13)	n.s.
Indwelling urinary catheter	8 (25)	9 (29)	3 (15)	4 (25)	n.s.
TUR-P/hyperthermia therapy	2 (6)	1 (3)	0 (0)	0 (0)	n.s.
UTI/urinary stone	0 (0)	5 (16)	2 (10)	0 (0)	n.s.
Resection rate (%)	0.98	0.82	0.89	0.86	n.s.
Enucleation rate (g/min)	0.80	0.72	0.59	0.66	n.s.

Numbers in parentheses indicate percentages. *I vs. II, n.s.; I vs. III, P<0.05.; I vs. IV, P<0.05; II vs. III, P<0.05; II vs. IV, P<0.05; III vs. IV, P<0.05.

Abbreviations: CIC, clean intermitted catheterization; TUR-P, transurethral resection of the prostate: UTI, urinary tract infection

Table 2. Preoperative administration of dutasteride and factors associated with holmium laser enucleation of the prostate

	Dutasteride not administered (n=63)	**Dutasteride administered** (n=36)	
Resection (g)	41 (5–160)	35 (10–90)	n.s.
Enucleation (g/min)	0.6 (0.1–2.3)	0.6 (0.1–1.7)	n.s.
Hemoglobin reduction	0.6 (0–4.1)	0.3 (0–1.4)	P<0.05
Decapsulation difficulty level III/IV (%)	21.9	76.9	P<0.05

Numbers in parenthesis indicate ranges

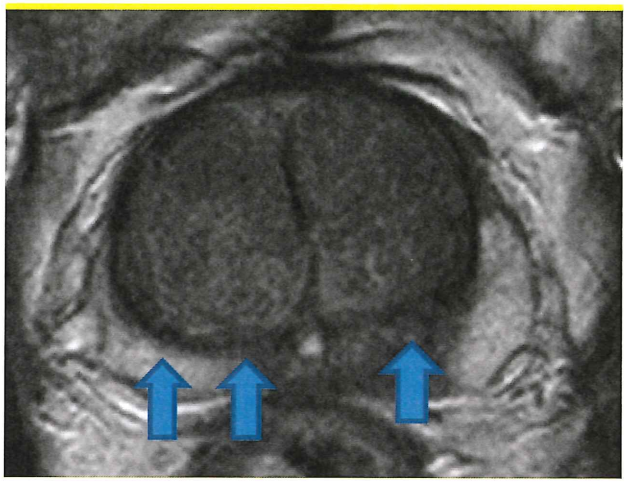


Fig. 2a

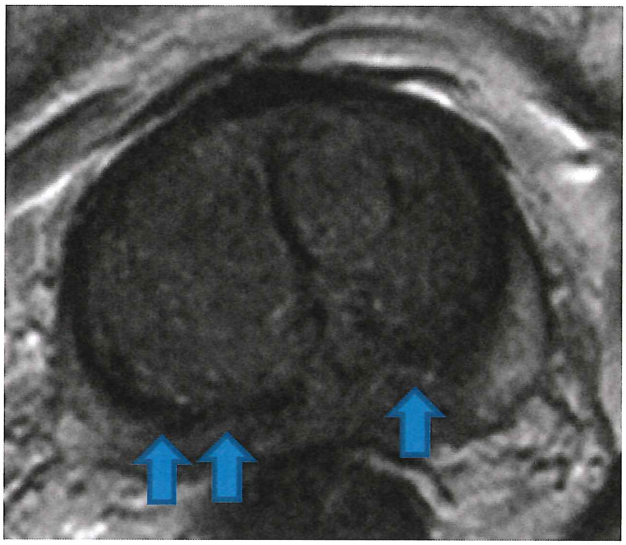
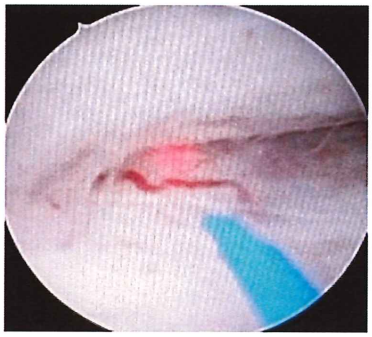


Fig. 2b



A：剥離良好な面

B：剥離不良な面

Figure 1