ORIGINAL ARTICLE

Does mechanical morcellation of large glands compromise incidental prostate cancer detection on specimen analysis? A pathological comparison with open simple prostatectomy

Vincent Misraï[1] · Sébastien Kerever[2] · Marie Pasquie[1] · Benoit Bordier[1] · Julien Guillotreau[1] · Julien Palasse[3] · Virginie Guillotreau[4] · Enrique Rijo[5] · Sébastien Vincendeau[6] · Romain Huet[6] · Romain Mathieu[6] · Benoit Peyronnet[6] · Nathalie Rioux-Leclercq[7] · Eva-Maria Compérat[8]

Abstract

Objective This study sought to compare the incidental prostate cancer (iPCa) detection rate between pathological specimens from green laser enucleation of the prostate (GreenLEP) and open simple prostatectomy (OSP).

Materials and methods In two institutions, the charts of all consecutive patients who underwent OSP between January 2005 and December 2010 were retrospectively reviewed, and the data of all consecutive patients who underwent GreenLEP with tissue morcellation between July 2013 and January 2018 were also collected. Preoperative demographics and pathological findings were recorded. iPCa detection rate was retrospectively compared between the GreenLEP and OSP groups in a propensity score model, including all predetermined variables: Age, preoperative PSA level and prostate volume.

Results Of 738 patients, 402 were included in the propensity-score matching analysis, and they were equally distributed among groups. The overall iPCa detection rates were similar in both groups (9.9% vs. 8.5%; $p = 0.73$), and there were no statistically significant differences in terms of tumour stage, Gleason score or the rate of clinically significant iPCa, although the number of cassettes analysed was significantly higher in the morcellation group than in the OSP group. No predictive factors for iPCa were identified.

Conclusions The results of the present study suggest that the mechanical morcellation of large glands had no influence on iPCa detection. Compared with a specimen from standard OSP, a large morcellated tissue sample allows adequate pathological evaluation and does not alter a pathologist's ability to detect iPCa.

Keywords Benign prostatic obstruction · Enucleation · Histology · Prostate cancer · Prostate-specific antigen

✉ Vincent Misraï
v.misrai@clinique-pasteur.com

1 Department of Urology, Clinique Pasteur, 31300 Toulouse, France

2 Lariboisière University Hospital, ECSTRA Team, CRESS, Epidemiology and Statistics Centre, and University Denis Diderot, Paris, France

3 Department of Pathology, S.O. Path, Toulouse, France

4 Department of Pathology, Les Feuillants, Toulouse, France

5 Department of Urology, Hospital Quirón Salud, Barcelona, Spain

6 Department of Urology, Rennes Hospital, Rennes, France

7 Department of Pathology, Rennes Hospital, Rennes, France

8 Department of Pathology, Tenon Hospital, AP-HP, University Pierre and Marie Curie, Paris, France

Introduction

Prostate cancer (PCa) can be diagnosed incidentally on pathological examination of a benign prostatic hyperplasia (BPH) specimen. Incidental prostate cancer (iPCa) is an ancillary phenomenon of BPH surgery and has to be managed, according to EAU guidelines on localised prostate cancer [1]. With the introduction of PSA screening and the broad diffusion of multiparametric magnetic resonance imaging (mpMRI) combined with the use of targeted prostate biopsies, the iPCa detection rate has decreased dramatically over the last 30 years from 16–20% to less than 10% of histologic specimens after transurethral resection of the prostate (TURP) [2]. The surgical management of benign prostatic obstruction (BPO) has evolved over the last decade from TURP and open simple prostatectomy

🖄 Springer

(OSP) to laser ablation [3] and endoscopic enucleation of the prostate (EEP) using various energy sources [4, 5]. These minimally invasive endoscopic procedures have raised concerns regarding iPCA detection owing to the lack of a specimen (ablative techniques) [6, 7] or due to potential changes in tissue samples caused by mechanical morcellation and laser energy [8]. In the most recent studies, the incidence of iPCa was reported to range from 2.5% to 13% of patients who underwent holmium laser enucleation of the prostate (HoLEP) [9–11] or thulium enucleation of the prostate (ThuLEP) [12]; there was no significant difference in the incidence of iPCA detected with HoLEP and ThuLEP compared to that detected with TURP, despite established discrepancies between these techniques in terms of the weight of adenomatous tissue removed [13]. Transurethral tissue morcellators have significantly evolved over time to improve morcellation efficiency [14]. However, it remains unclear whether mechanical morcellation provides adequate tissue samples for a correct pathological examination or conversely if morcellation hinders proper pathological assessment and is associated with a risk of underdiagnosis of iPCa compared to OSP, in which adenoma specimens can be evaluated as a whole. The aim of the present study was to evaluate and compare iPCa detection with OSP and green laser enucleation (GreenLEP) for prostates larger than 80 ml.
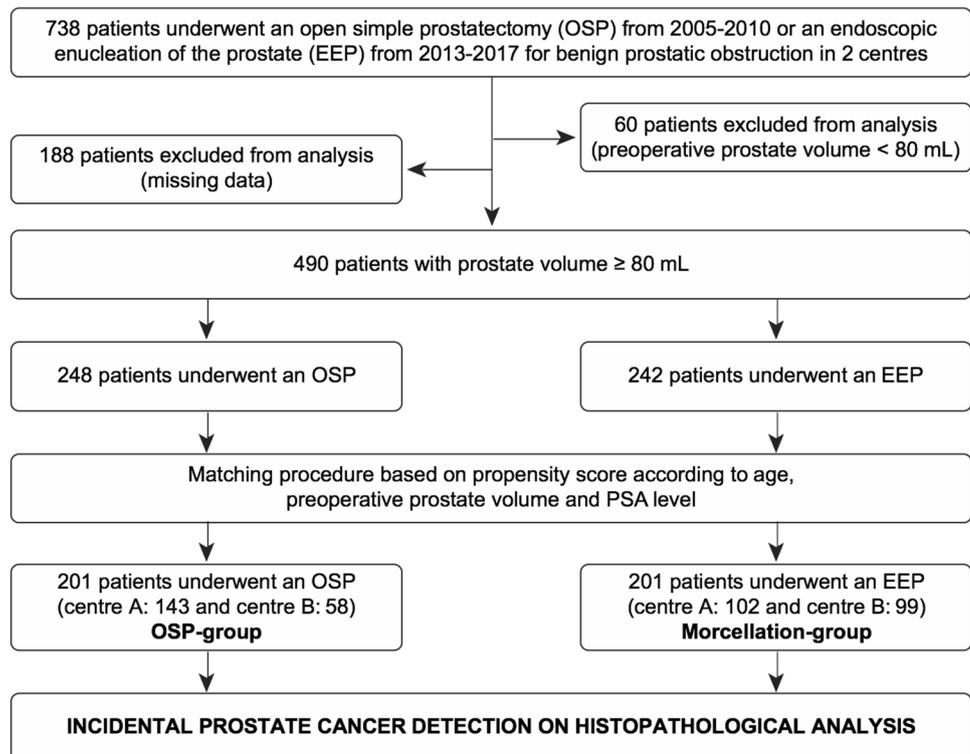
Patients and methods

Study population and surgical procedures

A total of 738 consecutive patients with BPO who were treated in two centres with either OSP ($n = 393$; from January 2005 to December 2010) or GreenLEP ($n = 345$; from July 2013 to January 2018) were retrospectively identified (Fig. 1).

The data of all consecutive patients who underwent GreenLEP were collected. Prior to surgical intervention, all patients underwent the same evaluation, and the following parameters were retrospectively assessed: prior medical history, clinical examination findings, medications [including 5-alpha reductase inhibitors (5ARIs)], prostate volume as determined using transrectal ultrasound (TRUS), and prostate-specific antigen (PSA) level (corrected $\times 2$ for patients taking 5ARIs). Patients with a PSA level ≥ 4 ng/ml or an abnormal finding on digital rectal examination underwent prostate magnetic resonance imaging (MRI) and a targeted (for PIRADS ≥ 3) and randomised ultrasound-guided prostate biopsy prior to GreenLEP. All GreenLEP procedures were performed by two seasoned surgeons (VM and SV) for patients with a prostate volume ≥ 80 ml according to the surgical technique described by Gomez Sancha who mentored them in their learning phase [15]. An oscillating morcellator (reference 2208, Piranha, Wolf) with disposable V_{max} or

Fig. 1 Study flow diagram

738 patients underwent an open simple prostatectomy (OSP) from 2005-2010 or an endoscopic enucleation of the prostate (EEP) from 2013-2017 for benign prostatic obstruction in 2 centres

60 patients excluded from analysis (preoperative prostate volume < 80 mL)

188 patients excluded from analysis (missing data)

490 patients with prostate volume ≥ 80 mL

248 patients underwent an OSP

242 patients underwent an EEP

Matching procedure based on propensity score according to age, preoperative prostate volume and PSA level

201 patients underwent an OSP (centre A: 143 and centre B: 58) **OSP-group**

201 patients underwent an EEP (centre A: 102 and centre B: 99) **Morcellation-group**

INCIDENTAL PROSTATE CANCER DETECTION ON HISTOPATHOLOGICAL ANALYSIS

reusable blades was used for each morcellation procedure in both centres. The use of a morcellator allows retrieval of tissue in a dedicated specimen container suitable for histological analysis.

All consecutive patients who underwent OSP for an enlarged prostate ≥ 80 ml in the same two departments were retrospectively reviewed. Patients with a PSA level ≥ 4 ng/ml or an abnormal finding on digital rectal examination underwent prostate MRI and a targeted and randomised ultrasound-guided prostate biopsy prior to surgery.

The following parameters were collected for both types of surgeries: patient age, preoperative PSA level, preoperative prostate volume determined by TRUS, and history of prostate biopsy. The postoperative tissue weight, histological analysis of each specimen, histological evaluation and number of cassettes were assessed. Patients with a prior history of PCa, missing data or preoperative prostate volume less than 80 ml were excluded from the analysis. Conversely, patients with abnormal MRI findings but negative targeted/randomised biopsies were not excluded. A flow diagram of the inclusion of the study patients is shown in Fig. 1. Histopathological analysis and reports were made in accordance with the reports recommended by the *International Collaboration on Cancer Reporting* (*ICCR*) at each centre (http://www.iccr-cancer.org). Morcellated tissue analysis: eight initial cassettes of tissue plus 1 cassette per each additional 10 g of tissue beyond that were submitted for analysis. Simple prostatectomy analysis: prostatic tissue was weighted and sectioned at 3–5-mm intervals.

Statistical analysis

Data are expressed as median and quartiles (1; 3) for continuous variables, and numbers and percentages for nominal variables. The main outcome measure was the incidental prostate cancer (iPCa) detection rate between pathological specimens from green laser enucleation of the prostate GreenLEP and open simple prostatectomy OSP [16]. Given the observational nature of the data, surgical management allocation was not randomly allocated in the study population. The risk of allocation bias caused by the presence of confounders was handled using PS matching. Using PS matching, the causal effect of the exposure on the outcome could be more precisely estimated assuming a set of identifiable and causal assumptions. The PS was estimated from the observed data using a logistic regression model, including a set of variables selected among available baseline variables. Each patient treated with GreenLEP was matched to one OSP control with similar PS using the nearest neighbour approach, with no replacement and a caliper size of 0.2. In this approach, each GreenLEP subject was matched to the nearest OSP subject within a specified maximum difference in the PS between two matched subjects (so-called caliper). Covariate balance between the two groups before and after PS matching was assessed using the mean standardised differences (MSDs). An absolute MSD < 10% was considered to support the assumption of balance between the groups [16]. All P values were two-tailed, and $p < 0.05$ was considered significant. All statistical analyses were performed using R statistical software with the statistical package MatchIt for the matching process (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

In the original sample, patient appears to be different in many characteristics including preoperative prostate size and PSA level.

A total of 402 patients (201 in each group) were included in the PS-matched population. After PS matching, all major differences were appropriately balanced between groups, including 143 and 58 patients who underwent OSP at centres A and B, respectively, and 102 and 99 patients who underwent GreenLEP at centres A and B, respectively.

The median weight of the retrieved specimen was similar in both groups (80 g [65–100 g] vs. 75 g [58–100 g]; $p = 0.46$). Preoperative prostate biopsies were more commonly performed in the OSP group (38.4% vs. 23.5%; $p = 0.003$) (Table 1).

Detection of iPCa

The iPCa detection rates did not differ significantly between patients who underwent GreenLEP + morcellation and those who underwent OSP (9.9% vs. 8.5%; $p = 0.73$). However, the morcellated tissue was randomly sampled from a significantly greater number of cassettes in the morcellation group than in the OSP group (15 [10–15] vs. 12 [10–12]; $p < 0.0001$). No tissue thermal artefacts were reported on any of the histological reports of patients in the morcellation group.

The majority of patients with iPCa were diagnosed with stage T1a disease (75% in the OSP group vs. 76% in the morcellation group; $p = 0.85$) and a Gleason score of 6 (65% in the OSP group vs. 82.3% in the morcellation group; $p = 0.85$). The rate of clinically significant iPCa (stage T1b and/or Gleason score ≥ 7) was similar in both groups and was reported to be 35% and 20% in the OSP and morcellation groups, respectively. The postoperative PSA level decreased significantly and similarly from baseline in both groups independent of the iPCa findings.

Table 1 Patient's baseline characteristics and oncologic outcomes

	OSP group		Morcellation group		p value
Age	201	69 [66; 75]	201	68 [63; 74]	0.3
Preoperative PSA (ng/ml)	201	6.6 [4.4; 9.9]	201	7.4 [4; 11]	0.27
Preoperative prostatic volume (ml)	201	110 [100; 140]	201	120 [100; 140]	0.36
Use of 5-ARI	200	14%	201	23.8%	0.015
Preoperative prostate biopsies	143	38.4%	102	23.5%	0.003
Incidental prostate cancer on specimen analysis	201	9.9%	201	8.5%	0.73
Weight of specimen (g)	201	80 [65; 100]	201	75 [58; 100]	0.46
Number of cassettes	141	12 [10; 12]	150	15 [10; 15]	< 0.0001
Tumour stage	201		201		0.85
T1a		15		13	
T1b		5		4	
Gleason score	201		201		0.69
6 (3 + 3)		13		14	
7 (3 + 4)		6		3	
8 (4 + 4)		1		0	
2-Month PSA (ng/ml)	47	0.86 [0.44; 1.5]	138	0.7 [0.38; 1.3]	0.19
6-Month PSA (ng/ml)	79	0.84 [0.54; 2]	69	0.73 [0.44; 1.1]	0.14
Adjuvant therapies (n)	199	20	201	17	
Active surveillance		13		15	0.85
Radical prostatectomy		1		2	
External beam therapy and/or hormonotherapy		6		0	

Predictive factors for iPCa

Patients who were diagnosed with iPCa and those who had benign pathological findings were similar in terms of age, preoperative PSA (6.8 ng/ml [4.1; 10] vs. 8.1 ng/ml [4.9; 12]; $p = 0.81$) and prostatic volume, use of 5-ARIs, negative preoperative prostate biopsies (19.7% vs. 18.9%; $p = 0.45$), weight of the specimen retrieved, and number of cassettes analysed (Table 2).

Discussion

Morcellation of intravesical adenoma is currently a standard procedure following most endoscopic enucleation techniques involving a laser energy source. Although several series have suggested that laser endoscopic enucleation of small–medium-sized glands combined with mechanical morcellation has no influence on iPCa detection compared to iPCA detection following TURP [8, 12, 13], our study is the first to report that morcellated

Table 2 Predictive factors for incidental prostate cancer

	Benign hyperplasia		Incidental prostate cancer		p value
Centres	365		37		0.07
A	230	63%	18	48.6%	
B	135	37%	19	51.4%	
Age	365	70 [65; 76]	37	72 [63; 77]	0.86
Preoperative PSA (ng/ml)	365	6.8 [4.1; 10]	37	8.1 [4.9; 12]	0.81
Preoperative negative prostate biopsies	72	19.7%	7	18.9%	0.45
Preoperative prostatic volume (ml)	365	110 [100; 140]	37	100 [100; 130]	0.15
Use of 5-ARI	364	18.4%	37	15.9%	0.84
Weight of specimen (g)	365	80 [61; 100]	37	73 [61; 98]	0.3
Number of cassettes	262	12 [10; 12]	29	12 [12; 15]	0.11
2-Month PSA drops (%)	365	91 [82; 95]	36	86 [76; 93]	0.02
6-Month postoperative positive prostate biopsies	365	1.9%	37	0%	

specimens were adequate for obtaining an accurate histological examination compared to specimens obtained from OSP. Of the 201 patients who underwent EEP and mechanical morcellation, 8.5% were diagnosed with iPCa, which is in accordance with the 8.1–13% iPCa detection rate previously reported in most updated HoLEP series. Elkoushy et al. reported that patient age and PSA density independently predicted iPCa after HoLEP. To perform the most accurate comparison, we chose to match the baseline characteristics of the OSP and morcellation groups. To our knowledge, none of the previous published series adjusted for important confounders, such as PSA level [13], age [13, 17], prostate volume [13, 17], or weight of the specimen retrieved [18]. The weight of specimen retrieved was similar in our report but differed significantly from that reported in most studies depending on the type of surgery performed and the intention of the surgeon to remove the transitional zone entirely or partially [8, 12, 13, 18]. The wide range of the iPCa detection rate might be mainly caused by difference in baseline patient characteristics and by the extent of surgical prostatic desobstruction in these studies [18]. In this current study, the surgical goal was always to remove the adenoma anatomically either in an open or endoscopic manner to make a valuable comparison between open and endoscopic techniques.

Although Trpkov et al. [19] reported that when minimal cancer was found in the first six cassettes obtained during transurethral resection, additional sampling did not change the initial Gleason score or tumour volume; the number of cassettes reported in this study was greater 10 and was significantly higher in the morcellation group than in the OSP group. Better identification of the peripheral zone of the adenoma during OSP specimen analysis might explain this difference. However, pathologists did not report tissue thermal artefacts during histological analysis of the enucleated specimens. Naspro et al. compared changes in tissue specimens obtained after HoLEP and monopolar transurethral resection (mTURP) and reported that the sample quality was impaired similarly with both techniques due to coagulation and vaporisation effects [8]. These results contrast with our findings. The lack of thermal injuries may be at least partially attributable to the procedure itself. GreenLEP is a blunt enucleation using a resectoscope to separate the adenoma from the outer prostatic margins, and laser energy is mainly delivered to the capsule for coagulation [15, 20]. In addition, the type of morcellator (herein an oscillating morcellator) does not seem to play a role as the rate of iPCa detection reported here was comparable with previous series using a reciprocating morcellator (Lumenis, Yokneam, Israel) [11].

We assume that the histological analysis was reliable enough and robust, as there was a very low postoperative 6-month re-biopsy rate (1.9%) in the subgroup of patients diagnosed with BPH. To our knowledge, this rate was not provided in most recent studies comparing HoLEP to TURP [8, 13, 18].

Although the propensity-score matching analysis involved 402 patients, we have to acknowledge some limitations. First, the data from patients in both groups came from a retrospective evaluation, and histological analyses were not reviewed for the purposes of the study. Second, the baseline patient characteristics differed significantly in terms of 5ARI use, which may be considered a drawback regardless of the treatment duration even though no significant difference was found in the iPCa subgroup analysis. The extensive use of preoperative mpMRI in recent years must be taken into account, and the comparison between patients who were treated with endoscopic enucleation and those who were treated with OSP 7 years ago might be questioned. Finally, the 6-month follow-up was not long enough in the Green-LEP group to assess for a possible increased rate of PCa diagnosed during consecutive postoperative years, which was ultimately the only way to ensure that morcellation did not alter the detection of iPCa on pathological examination.

Conclusions

The results of the present study suggest that the mechanical morcellation of large glands does not influence the detection of iPCa. A large morcellated tissue sample allows adequate histological evaluation and does not alter the pathological detection of iPCa compared with a specimen from standard OSP. Further studies following the postoperative diagnosis of PCa over a longer follow-up period are needed to confirm our findings.

Compliance with ethical standards

References

1. Mottet N, Bellmunt J, Bolla M (2017) EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. Eur Urol 71:618–629
2. Mai KT, Isotalo PA, Green J, Perkins DG, Morash C, Collins JP (2000) Incidental prostatic adenocarcinomas and putative premalignant lesions in TURP specimens collected before and after the introduction of prostrate-specific antigen screening. Arch Pathol Lab Med 124:1454–1456
3. Bachmann A, Tubaro A, Barber N et al (2014) 180-W XPS green-Light laser vaporisation versus transurethral resection of the prostate for the treatment of benign prostatic obstruction: 6-month

safety and efficacy results of a European multicentre randomised trial–the GOLIATH study. Eur Urol 65:931–942

4. Cornu JN, Ahyai S, Bachmann A et al (2015) A systematic review and meta-analysis of functional outcomes and complications following transurethral procedures for lower urinary tract symptoms resulting from benign prostatic obstruction: an update. Eur Urol 67:1066–1096

5. Herrmann TR (2016) Enucleation is enucleation is enucleation is enucleation. World J Urol 34:1353–1355

6. Biers SM, Oliver HC, King AJ, Adamson AS (2009) Does laser ablation prostatectomy lead to oncological compromise? BJU Int 103:454–457

7. Voigt S, Huttig F, Koch R et al (2011) Risk factors for incidental prostate cancer—who should not undergo vaporization of the prostate for benign prostate hyperplasia? Prostate 71:1325–1331

8. Naspro R, Freschi M, Salonia A et al (2004) Holmium laser enucleation versus transurethral resection of the prostate. Are histological findings comparable? J Urol 171:1203–1206

9. Otsubo S, Yokomizo A, Mochida O et al (2015) Significance of prostate-specific antigen-related factors in incidental prostate cancer treated by holmium laser enucleation of the prostate. World J Urol 33:329–333

10. Elkoushy MA, Elshal AM, Elhilali MM (2015) Incidental prostate cancer diagnosis during holmium laser enucleation: assessment of predictors, survival, and disease progression. Urology 86:552–557

11. Bhojani N, Boris RS, Monn MF, Mandeville JA, Lingeman JE (2015) Coexisting prostate cancer found at the time of holmium laser enucleation of the prostate for benign prostatic hyperplasia: predicting its presence and grade in analyzed tissue. J Endourol 29:41–46

12. Carmignani L, Macchi A, Ratti D et al (2015) Are histological findings of thulium laser vapo-enucleation versus transurethral resection of the prostate comparable? Pathol Oncol Res 21:1071–1075

13. Herlemann A, Wegner K, Roosen A et al (2017) "Finding the needle in a haystack": oncologic evaluation of patients treated for LUTS with holmium laser enucleation of the prostate (HoLEP) versus transurethral resection of the prostate (TURP). World J Urol 35:1777–1782

14. Misrai V, Bordier B, Guillotreau J (2017) Assessment of the learning curves for intravesical adenoma morcellation using Piranha((c)) device during endoscopic enucleation. Prog Urol 27:33–37

15. Gomez SF, Rivera VC, Georgiev G, Botsevski A, Kotsev J, Herrmann T (2015) Common trend: move to enucleation-Is there a case for GreenLight enucleation? Development and description of the technique. World J Urol 33:539–547

16. Austin PC (2009) Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. Biom J 51:171–184

17. Helfand BT, Anderson CB, Fought A, Kim DY, Vyas A, McVary KT (2009) Postoperative PSA and PSA velocity identify presence of prostate cancer after various surgical interventions for benign prostatic hyperplasia. Urology 74:177–183

18. Rosenhammer B, Lausenmeyer EM, Mayr R, Burger M, Eichelberg C (2018) HoLEP provides a higher prostate cancer detection rate compared to bipolar TURP: a matched-pair analysis. World J Urol 1:10. https://doi.org/10.1007/s00345-018-2353-0

19. Trpkov K, Thompson J, Kulaga A, Yilmaz A (2008) How much tissue sampling is required when unsuspected minimal prostate carcinoma is identified on transurethral resection? Arch Pathol Lab Med 132:1313–1316

20. Peyronnet B, Robert G, Comat V et al (2017) Learning curves and perioperative outcomes after endoscopic enucleation of the prostate: a comparison between GreenLight 532-nm and holmium lasers. World J Urol 35:973–983