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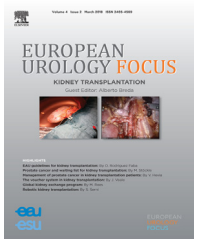

Original Article – Prostate Cancer

Initial Experience with Radical Prostatectomy Following Holmium Laser Enucleation of the Prostate

Alexander Kretschmer[a,*], *Elio Mazzone*[b], *Francesco Barletta*[b], *Riccardo Leni*[b], *Isabel Heidegger*[c], *Igor Tsaur*[d], *Roderick C.N. van den Bergh*[e], *Massimo Valerio*[f], *Giancarlo Marra*[g], *Veeru Kasivisvanathan*[h], *Alexander Buchner*[a], *Christian G. Stief*[a], *Alberto Briganti*[b], *Francesco Montorsi*[b], *Derya Tilki*[i,j], *Giorgio Gandaglia*[b], *on behalf of the EAU-YAU Prostate Cancer Working Party*

[a] *Department of Urology, Ludwig-Maximilians University of Munich, Munich, Germany;* [b] *Division of Oncology/Unit of Urology, Urological Research Institute, IRCCS Ospedale San Raffaele, Milan, Italy;* [c] *Department of Urology, Medical University Innsbruck, Innsbruck, Austria;* [d] *Department of Urology and Pediatric Urology, Mainz University Medicine, Mainz, Germany;* [e] *Department of Urology, St. Antonius Hospital, Utrecht, The Netherlands;* [f] *Department of Urology, CHUV, Lausanne, Switzerland;* [g] *Department of Urology, San Giovanni Battista Hospital, University of Turin, Turin, Italy;* [h] *Division of Surgery and Interventional Science, University College London, London, UK;* [i] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [j] *Department of Urology, University Hospital-Hamburg Eppendorf, Hamburg, Germany*

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Abstract

Background: Although an increasing number of prostate cancer (PCa) patients received holmium laser enucleation of the prostate (HoLEP) previously for benign prostatic obstruction (BPO), there is still no evidence regarding the outcomes of radical prostatectomy (RP) in this setting.
Objective: To assess functional and oncological results of RP in PCa patients who received HoLEP for BPO previously in a contemporary multi-institutional cohort.
Design, setting, and participants: A total of 95 patients who underwent RP between 2011 and 2019 and had a history of HoLEP were identified in two institutions. Functional as well as oncological follow-up was prospectively assessed and retrospectively analyzed.
Intervention: RP following HoLEP compared with RP without previous transurethral surgery.
Outcome measurements and statistical analysis: Patients with complete follow-up data were matched with individuals with no history of BPO surgery using propensity score matching. Complications were assessed using the Clavien-Dindo scale.
Results and limitations: The median follow-up was 50.5 mo. We found no significant impact of previous HoLEP on positive surgical margin rate (14.0% [HoLEP] vs 18.8% [no HoLEP], $p = 0.06$) and biochemical recurrence-free survival (hazard ratio 0.74, 95% confidence interval [CI] 0.32–1.70, $p = 0.4$). Patients with a history of HoLEP had increased 1-yr urinary incontinence rates after RP. After adjusting for confounders, no significant impact of previous HoLEP was found (odds ratio [OR] 0.87, 95% CI 0.74–1.01; $p = 0.07$). Previous HoLEP did not hamper 1-yr erectile function recovery (OR 1.22, 95% CI 1.05–1.43; $p = 0.01$). Limitations include retrospective design and small sample size.

* Corresponding author. Department of Urology, Ludwig-Maximilians-University, Marchioninistrasse 15, Munich 81377, Germany. Tel.: +49 89 4400-0; Fax: +49 89 4400-5444.
E-mail address: Alexander.kretschmer@med.uni-muenchen.de (A. Kretschmer).

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Conclusions: RP after previous HoLEP is surgically feasible, with low complication rates and no negative impact on biochemical recurrence–free survival. However, in a multivariable analysis, we observed significantly worse 1-yr continence rates in patients after previous HoLEP.

Patient summary: In the current study, we assessed the oncological and functional outcomes of radical prostatectomy in patients who underwent holmium laser enucleation of the prostate (HoLEP) previously due to prostatic bladder outlet obstruction. A history of HoLEP did not hamper oncological results, 1-yr continence, and erectile function recovery.

1. Introduction

Holmium laser enucleation of the prostate (HoLEP) represents an emerging treatment option in the setting of patients with benign prostatic obstruction (BPO). Several recent meta-analyses demonstrated that this surgical approach is characterized by shorter catheterization time and hospital stay, reduced blood loss, and fewer perioperative complications compared with standard transurethral resection of the prostate (TURP) [1,2]. This held true particularly in patients under anticoagulant and/or antiplatelet therapies [3]. Although there is compelling evidence that radical prostatectomy (RP) can be performed safely after TURP, patients who received previous surgery for BPO might be at a higher risk of experiencing worse oncological and functional outcomes [4,5]. These assumptions might also apply to individuals with a history of HoLEP since one might hypothesize that previous transurethral prostate surgery and, in some cases, concomitant prostate capsule perforation increase inflammation and tissue fibrosis, and ultimately lead to more challenging surgical procedures, resulting not only in decreased oncological outcomes, but, possibly, also in worse functional outcomes [6,7]. Several intraoperative pitfalls have been described, including a floppy prostatovesicular junction [8], thickened bladder walls, and impaired identification and consecutive preservation of residual urethral length [4,9]. In addition, HoLEP usually results in a more radical removal of the transitional zone compared than standard TURP, with only a smaller prostate volume being left. Thus, anatomical and functional alterations in the internal sphincter complex might be more distinct in these patients than in post-TURP patients [9]. To date, there is little evidence regarding oncological and functional outcomes of patients treated with RP following HoLEP. We hypothesized that technical features of the laser enucleation of the prostate as well as the observation that patients undergoing HoLEP typically have larger prostate volumes than those treated with TURP might impact the feasibility, safety, and efficacy of RP after HoLEP. In the face of such a paucity of data, we evaluated the oncological and functional results of RP in a contemporary multicentric cohort of patients with a history of HoLEP for BPO.

2. Patients and methods

2.1. Study design and participants

A total of 1438 consecutive patients who underwent open or robot-assisted RP between 2011 and 2019 at two tertiary care centers were identified. The exclusion criteria encompassed cT4, cN1, and cM1 disease as well as patients who had a history of any other previous surgery for benign prostate enlargement other than HoLEP. HoLEP was performed in both centers as previously described [10].

After approval by a local ethics committee, patient-reported outcomes were prospectively retrieved by sending questionnaires through mail to eligible patients. Erectile dysfunction was assessed via the validated International Index of Erectile Function (IIEF-5) questionnaire [11]. Continence was assessed by daily pad usage. Continence recovery was defined as use of no pads; erectile function recovery was defined as an IIEF-5 score of $\geq$22 as previously described [12]. Biochemical recurrence was defined as a prostate-specific antigen (PSA) level of $\geq$0.2 ng/mL for two consecutive times. Regarding perioperative patient education, patients were instructed to perform pelvic floor muscle training and were offered phosphodiesterase type 5 inhibitors on demand for penile rehabilitation. Ninety-day complications were assessed using the Clavien-Dindo scale [13].

2.2. Statistical analysis

For a retrospective analysis, we generated a 1:4 propensity score–matched cohort limited to patients with complete follow-up (n = 43 [HoLEP]; n = 138 [no HoLEP]). Matching variables represented age, prostate volume (based on the weight of the pathological RP specimen), and pT stage. Based on PSA levels, biochemical recurrence–free survival (bRFS) was calculated. Multivariable Cox regression and logistic regression models were used to identify predictors of, respectively, oncological and functional outcomes after adjusting for hypothesized potential confounders. A p value of $<$0.05 was considered to be statistically significant.

3. Results

3.1. Patient characteristics in unmatched cohort

Baseline characteristics, pathological features, and oncological and functional outcomes were initially compared between patients with (n = 95) and without previous HoLEP for BPO (n = 1343). Individuals with previous HoLEP were older (69 vs 63 yr, $p < 0.001$), their pre-RP prostate volume was smaller (34 vs 51 ml, $p < 0.001$) and in line, and their median PSA values were lower (6.3 vs 3.9 ng/mL, $p < 0.001$). We found statistically significantly increased positive surgical margin (PSM) rates for patients with previous HoLEP compared with patients without HoLEP (20.0% vs 17.7%, $p < 0.001$). In addition, we found significantly decreased 1-yr continence recovery rates for patients with previous HoLEP (81.4% vs 68.4%, p = 0.02). Detailed patient characteristics of the unmatched cohorts are summarized in Table 1.

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Table 1 – Patient characteristics of the unmatched patient cohort.

Variable		Overall	No HoLEP before RP N = 1343; 93%	HoLEP before RP N = 95; 7%	p value
Prostate volume (ml)	Median	50	51	34	<0.001
	IQR	40–63	41–64	24–44	
Age at RP (yr)	Median	64	63	69	<0.001
	IQR	58–68	58–68	63–72	
Surgical approach, n (%)	ORP	417 (30.4)	910 (70.4)	34 (44.2)	0.01
	RARP	953 (69.6)	383 (29.6)	43 (55.8)	
Nerve-sparing procedure, n (%)		1098 (78.2)	1047 (78.3)	51 (76.1)	6
Follow-up (mo)	Median	32	31	37	0.905
	IQR	15–60	15–60	13–60	
PSA at diagnosis (ng/mL)	Median	6.3	6.3	3.9	<0.001
	IQR	5–9	5–9	2–8	
pT stage, n (%)	pT2c	912 (63.5)	847 (63.1)	65 (69.1)	0.495
	pT3a	365 (25.4)	345 (25.7)	20 (21.3)	
	≥pT3b	160 (11.1)	151 (11.2)	9 (9.6)	
pN stage, n (%)	pN0	1000 (69.7)	929 (69.4)	71 (74.7)	0.194
	pN1	155 (10.8)	150 (11.2)	5 (5.3)	
	pNx	279 (19.5)	260 (19.4)	19 (20.0)	
Pathological GG, n (%)	≤7	1200 (83.7)	1128 (84.0)	72 (80.0)	0.304
	8–10	233 (16.3)	215 (16.0)	18 (20.0)	
Perioperative complications, n (%)		288 (20.9)	272 (20.3)	16 (39.0)	0.006
Postoperative ADT, n (%)	None	1289 (92.1)	1210 (92.2)	79 (91.9)	0.444
	Adjuvant	91 (6.5)	84 (6.4)	7 (8.1)	
	Salvage	19 (1.4)	19 (1.4)	0 (0.0)	
Postoperative radiotherapy, n (%)	None	1167 (82.4)	1089 (81.8)	78 (90.7)	0.041
	Adjuvant	173 (12.2)	165. (12.4)	8 (9.3)	
	Salvage	77 (5.4)	77 (5.8)	0 (0.0)	
Positive surgical margins, n (%)	None	1181 (82.1)	1105 (82.3)	76 (80.0)	<0.001
	Focal	138 (9.6)	119 (8.9)	19 (20.0)	
	Multifocal	119 (8.3)	119 (8.3)	0 (0.0)	
1-yr UC recovery, n (%)	No	239 (19.2)	969 (81.4)	39 (68.4)	0.023
	Yes	1008 (80.8)	221 (18.6)	18 (31.6)	
1-yr EF recovery, n (%)	No	742 (59.3)	711 (59.5)	31 (54.4)	0.491
	Yes	510 (40.7)	484 (40.5)	26 (45.6)	

ADT = androgen deprivation therapy; EF = erectile function; GG = Gleason grade; HoLEP = holmium laser enucleation of the prostate; IQR = interquartile range; ORP = open RP; PSA = prostate-specific antigen; RARP = robot-assisted RP; RP = radical prostatectomy; UC = urinary continence.

3.2. *Outcomes after propensity score matching*

3.2.1. *Patient characteristics*

To account for measurable confounders, we subsequently generated a 1:4 propensity score–matched cohort of patients with complete follow-up ($n = 138$ [no HoLEP]; $n = 43$ [HoLEP]). Matched cohorts were well balanced without statistically significant differences in preoperative tumor characteristics including Gleason grade (GG; $p = 0.6$), pT stage ($p = 0.6$), pN stage ($p = 0.3$), and nerve-sparing procedures ($p = 0.1$). There were no statistically significant differences in comorbidities such as coronary heart disease ($p = 0.1$) and diabetes mellitus ($p = 0.2$). The median follow-up was 50.5 mo (interquartile range [IQR]: 24–84) for patients without previous HoLEP and 44 mo (IQR: 13–73) for patients with previous HoLEP ($p = 0.1$). The median time between HoLEP and RP was 15 mo (IQR: 4.5–35.5). Detailed patient characteristics of the unmatched cohorts are summarized in Table 2.

3.2.2. *Oncological outcomes*

Regarding oncological outcomes, we found comparable PSM rates (14.0% [HoLEP] vs 18.8% [no HoLEP], $p = 0.06$). Six-year bRFS estimates were 86% for patients with previous HoLEP and 75% for patients without previous HoLEP ($p = 0.44$; Fig. 1). In the multivariable Cox regression analysis adjusted for age, pT stage, GG, and pN stage, previous HoLEP was not associated with bRFS (hazard ratio 0.74, 95% confidence interval [CI] 0.32–1.70, $p = 0.4$). Detailed results of the multivariable analysis for bRFS are summarized in Table 3.

3.2.3. *Functional outcomes*

Regarding functional outcomes, continence recovery was observed in 65.1% (HoLEP) versus 79.0% (no HoLEP) of the patients ($p = 0.09$). However, in multivariable logistic regression models adjusted for age, prostate volume, postoperative androgen deprivation therapy, radiotherapy, preoperative lower urinary tract symptoms, surgical approach, and nerve-sparing extent, previous HoLEP was not an independent predictor of unfavorable 1-yr continence recovery (odds ratio [OR] 0.87, 95% CI 0.74–1.01, $p = 0.07$; Table 4). Instead, we found unfavorable continence recovery for patients with postoperative androgen deprivation therapy ($p = 0.05$) and larger prostate volume ($p = 0.02$).

Regarding erectile function recovery, previous HoLEP surgery was associated with increased 1-yr erectile function recovery (OR 1.22, 95% CI 1.05–1.43, $p = 0.01$; Table 4). In addition, we found a significant impact of preoperative IIEF

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Table 2 – Patient characteristics of the matched patient cohort.

Variable		Overall	No HoLEP before– RP *N* = 138; 76%	HoLEP before –RP *N* = 43; 24%	*p* value
Volume prostate (ml)	Median	36	37.8	34	0.06
	IQR	30–46	30–48	27–41.5	
Age at RP (yr)	Median	67	66.5	69	0.1
	IQR	63–71	63–71	63–71	
Follow-up (mo)	Median	48	50.5	44	0.1
	IQR	24–84	24–84	13–72.5	
Preoperative IPSS	Median	7	7	6	0.8
	IQR	3–12	3–12	4–13	
Preoperative IIEF	Median	51	54	25	<0.001
	IQR	18–64	26–65	11–54	
PSA at diagnosis (ng/mL)	Median	5.7	6.5	4.2	<0.001
	IQR	4–9	5–9	2–7	
pT stage, *n* (%)	pT2c	115 (63.5)	89 (64.5)	26 (60.5)	0.6
	pT3a	51 (28.2)	39 (28.3)	12 (27.9)	
	≥pT3b	15 (8.3)	10 (7.2)	5 (11.6)	
pN stage, *n* (%)	pN0	134 (74)	105 (76.1)	29 (67.4)	0.3
	pN1	14 (7.7)	11 (8)	3 (7)	
	pNx	33 (18.2)	22 (15.9)	11 (25.6)	
Pathological GG, *n* (%)	≤7	150 (82.9)	116 (84.1)	34 (79.1)	0.6
	8–10	31 (17.1)	22 (15.9)	9 (20.9)	
Postoperative ADT, *n* (%)	No	168 (92.8)	128 (92.8)	40 (93)	0.6
	Adjuvant	10 (5.5)	7 (5.1)	3 (7)	
	Salvage	3 (1.7)	3 (2.2)	0 (0)	
Postoperative radiotherapy, *n* (%)	No	149 (82.3)	109 (79)	40 (93)	0.06
	Adjuvant	19 (10.5)	16 (11.6)	3 (7)	
	Salvage	13 (7.2)	13 (9.4)	0 (0)	
Positive surgical margins, *n* (%)	No	149 (82.3)	112 (81.2)	37 (86)	0.06
	Focal	18 (9.9)	12 (8.7)	6 (14)	
	Multifocal	14 (7.7)	14 (10.1)	0 (0)	
Surgical approach, *n* (%)	ORP	72 (39.8)	52 (37.7)	20 (46.5)	0.5
	RARP	109 (60.3)	86 (62.3)	23 (53.5)	
Nerve sparing, *n* (%)	No	52 (28.7)	45 (32.6)	7 (16.3)	0.003
	Unilateral	22 (12.2)	11 (8)	11 (25.6)	
	Bilateral	107 (59.1)	82 (59.4)	25 (58.1)	
UC recovery, *n* (%)	No	44 (24.3)	29 (21)	15 (34.9)	0.09
	Yes	137 (75.7)	109 (79)	28 (65.1)	
EF recovery, *n* (%)	No	110 (60.8)	87 (63)	23 (53.5)	0.3
	Yes	71 (39.2)	51 (37)	20 (46.5)	

ADT = androgen deprivation therapy; EF = erectile function; GG = Gleason grade; HoLEP = holmium laser enucleation of the prostate; IIEF = International Index or Erectile Function; IPSS = International Prostate Symptom Score; IQR = interquartile range; ORP = open RP; PSA = prostate-specific antigen; RARP = robot-assisted RP; RP = radical prostatectomy; UC = urinary continence.

score ($p = 0.001$), age at RP ($p = 0.03$), larger prostate volume ($p = 0.03$), and bilateral nerve sparing ($p = 0.007$).

The time interval between HoLEP and RP was not associated with significantly worse continence ($p = 0.99$) or erectile function outcomes ($p = 0.57$).

3.2.4. *Complications*

Assessing the safety of the procedure, we did not find significant differences in total postoperative complication rates (22.6 [no HoLEP] vs 20.9 [HoLEP], $p = 1.0$) as well as complications stratified by Clavien-Dindo score, as displayed in Table 5 [13].

4. Discussion

In the current study, we provide the largest contemporary patient cohort supporting the safety and effectiveness of RP in patients with a history of HoLEP for BPO. Recently, Abedali et al [14] published their experience of 27 patients who underwent RARP following HoLEP, and found similar continence outcomes but inferior erectile function to those in patients without previous HoLEP.

In our unmatched cohort, we observed significant differences regarding patient age as well as prostate volume, variables that have been shown to influence functional outcomes after RP [15]. This fact highlights the obligation for adequate matching in order to improve generalizability of the findings. In the current study, we present data from an unmatched as well as a propensity score–matched cohort. Although patients who underwent HoLEP before RP had worse urinary continence recovery rates, than their counterparts who did not receive HoLEP, in the univariate but not in the multivariate analysis, RP was associated with comparable oncological outcomes and erectile function recovery. Several studies previously attempted to assess the outcomes after TURP, and mixed results were obtained so far. In a recent meta-analysis, Liao and colleagues [5]

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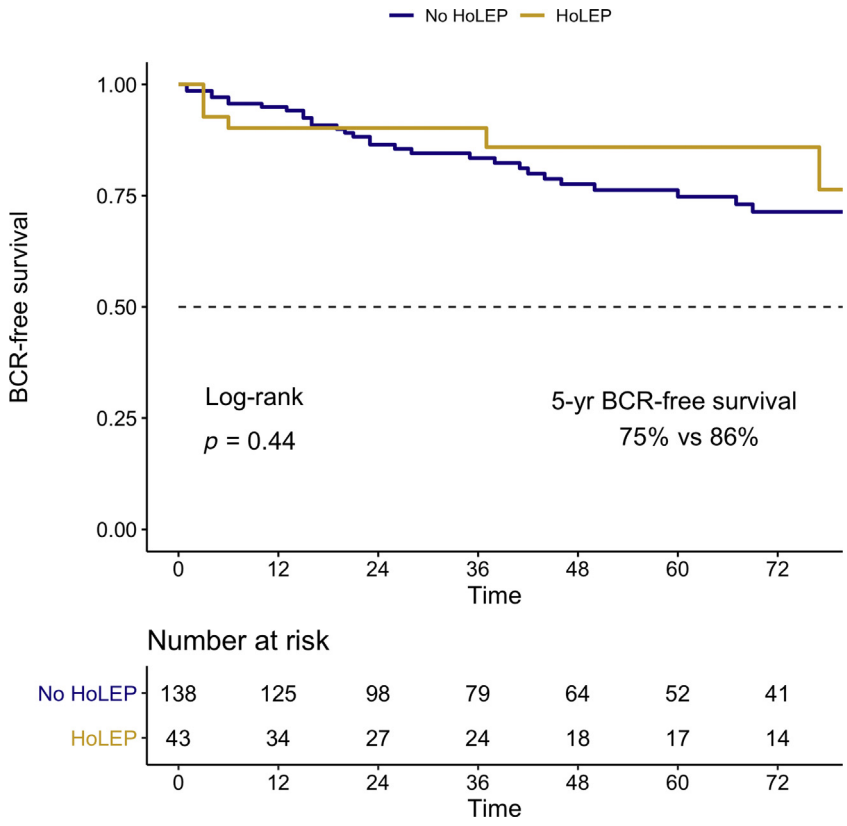

Fig. 1 – Biochemical recurrence (BCR)-free survival in patients with and without previous holmium laser enucleation of the prostate (HoLEP).

found significantly higher PSM rates for patients undergoing RP after previous TURP, which differs from the results of the current study. For instance, Jaffe et al [16] analyzed the outcomes of 118 patients who underwent laparoscopic RP following TURP and found higher PSM rates for patients with previous TURP. However, the largest study investigating oncological outcomes of RP after TURP to date did not show significant differences in bRFS between both subgroups [17]. Similarly, our bRFS rates do not show any significant differences in univariable and multivariable analyses. Based on these preliminary results, performing RP after previous HoLEP is feasible and oncologically safe.

Table 3 – Multivariate Cox regression for the endpoint biochemical recurrence–free survival.

Variable	Measure	HR	95% CI		*p* value
Pre-RP HoLEP	No	Ref.			
	Yes	0.74	0.32	1.70	0.4
Pathological GG	≤7	Ref.			
	8–10	3.64	1.67	7.91	0.001
Age at RP		1.024	0.970	1.080	0.3
pT stage	pT2c	Ref.			
	pT3a	0.89	0.39	2.06	0.7
	pT3b	1.46	0.36	5.93	0.5
pN stage	pN0	Ref.			
	pN1	1.62	0.42	6.13	0.4
	pNx	0.80	0.30	2.16	0.6

CI = confidence interval; GG = Gleason grade; HoLEP = holmium laser enucleation of the prostate; HR = hazard ratio; Ref. = reference; RP = radical prostatectomy.

With regard to functional outcomes after previous transurethral surgical desobstruction, it has to be stated that there is conflicting evidence to date. Colombo et al [7] investigated 88 patients after TURP between 1999 and 2003, and found continence rates of up to 86% after 12 mo. In the current study, we observe decreased continence recovery rates for patients with previous HoLEP in the univariate analysis. This is in line with the findings of Pompe et al [17] where the authors found a significantly increased risk for urinary incontinence 3 and 12 mo after RP, and worse erectile function recovery rates. In the multivariate analysis, however, we were not able to confirm previous HoLEP as an independent predictor of worse 1-yr continence outcomes. In general, it has to be emphasized that direct comparisons of urinary continence between previously published studies are limited by different definitions of continence as well as varying time points of continence assessment.

Regarding 1-yr erectile function recovery, we found even increased recovery probability for patients with previous HoLEP. Several hypotheses have been generated for decreased continence outcomes after previous transurethral BPO surgery, including floppy prostatovesicular junctions [8]; thickened bladder walls, and impaired identification and consecutive preservation of residual urethral length [4,9]; and anatomical and functional alterations in

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Table 4 – Multivariate logistic regression for the endpoints 1-yr continence recovery and 1-yr potency recovery. P values <0.05 are highlighted in bold.

Variable	Measure	Continence recovery				Potency recovery			
		OR	95% CI		*p* value	OR	95% CI		*p* value
Pre-RP HoLEP	No	Ref.				Ref.			
	Yes	0.87	0.74	1.01	0.07	1.22	1.05	1.43	**0.01**
Preoperative IPSS	Score	0.994	0.985	1.004	0.2	–			
Preoperative IIEF	Score	–				1.004	1.001	1.008	**0.03**
Postoperative RT	No	Ref.				Ref.			
	Yes	0.93	0.83	1.05	0.2	1.03	0.88	1.20	0.7
Postoperative ADT	No	Ref.				Ref.			
	Yes	0.80	0.65	0.99	**0.046**	0.87	0.67	1.12	0.2
Age at RP (yr)		0.995	0.984	1.005	0.2	0.972	0.957	0.987	**0.001**
pT stage	pT2c	Ref.				Ref.			
	pT3a	0.90	0.77	1.04	0.4	0.92	0.80	1.07	0.3
	pT3b	1.09	0.85	1.39	0.3	0.92	0.72	1.18	0.5
Prostate volume (cc)		0.995	0.991	0.999	**0.02**	0.995	0.991	0.999	**0.03**
Surgical approach	Open	Ref.				Ref.			
	Robot assisted	1.12	0.99	1.26	0.061	1.05	0.93	1.18	0.3
Nerve sparing	No	Ref.				Ref.			
	Unilateral	0.82	0.66	1.02	0.08	1.04	0.83	1.28	0.7
	Bilateral	0.97	0.84	1.14	0.7	1.23	1.06	1.42	**0.007**
Postoperative PDE5 inhibitor use	No	–				Ref.			
	Yes					1.15	0.96	1.37	0.1

ADT = androgen deprivation therapy; CI = confidence interval; HoLEP = holmium laser enucleation of the prostate; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; OR = odds ratio; PDE5 = phosphodiesterase type 5; Ref. = reference; RP = radical prostatectomy; RT = radiotherapy.

Table 5 – Perioperative complications based on the Clavien-Dindo classification for patients with and without holmium laser enucleation of the prostate (HoLEP) in the propensity score matched cohort.

	Perioperative complications, *n* (%)						*p* value
	None	Clavien I	Clavien II	Clavien III	Clavien IV	Clavien V	
No HoLEP	120 (87.0)	5 (3.6)	11 (8.0)	2 (1.5)	0 (0.0)	0 (0.0)	0.1
HoLEP	34 (79.1)	4 (9.3)	2 (4.7)	2 (4.7)	1 (2.3)	0 (0.0)	

the internal sphincter complex [9]. Regarding erectile function recovery, it has been postulated that identification and preservation of the neurovascular bundle might be limited after transurethral BPO surgery due to periprostatic fibrosis and inflammation [18]. While our results might indicate that these artifacts might be less profound in our contemporary post-HoLEP subcohort, given the increased 1-yr erectile function recovery in the multivariate analysis, these results have to be interpreted with caution given the rather small sample size of this respective cohort. Importantly, we observed similar rates of bilateral nerve sparing to, but higher rates of unilateral nerve sparing than, no nerve sparing in our previous HoLEP subcohort, indicating that nerve sparing might not generally be hampered after previous HoLEP.

In line with the recent findings, we did not observe a significant impact of the time interval between HoLEP and RP in our matched patient cohort [19].

The current study is not devoid of limitations. First, the retrospective nature and the small sample size of the propensity score–matched cohort have to be addressed, leading to potential underpower of our analyses. In particular, comorbidities such as coronary heart disease, diabetes, and body mass index have not been included in the multivariable analysis in order to avoid overfitting of the model. The current study was based on questionnaire retrieval instead of hypothetically more informative physical examination and personal interview-based follow-up. In addition, continence definition was based on pad usage only. Future studies should also include objective data from validated questionnaires such as the International Consultation of Incontinence Questionnaire—Short Form (ICIQ-SF) [20]. Furthermore, the current study focuses on 1-yr continence and erectile function outcomes only, and future studies should elaborate the improvement of functional outcomes over time in patients with previous HoLEP surgery. Lastly, future studies will also need to address the association between prostate volume before enucleation and outcomes after RP.

5. Conclusions

Despite its inherent limitations, our study gives important novel insights into surgical and functional outcomes in a distinct patient cohort, which are hypothesized to increase in the nearer future. These findings have direct clinical

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impact since they inform the preoperative patient education processes, which have been shown to correlate positively with postoperative patient satisfaction [21].

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Study concept and design: Kretschmer, Tilki, Gandaglia.
Acquisition of data: Kretschmer, Mazzone, Barletta, Leni.
Analysis and interpretation of data: Kretschmer, Mazzone, Buchner, Gandaglia.
Drafting of the manuscript: Kretschmer, Mazzone, Gandaglia.
Critical revision of the manuscript for important intellectual content: Heidegger, Tsaur, van den Bergh, Valerio, Marra, Kasivisvanathan, Stief, Briganti, Montorsi, Tilki.
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