Initial experience with radical prostatectomy following Holmium laser enucleation of the prostate (HoLEP)

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Abstract:

Although an increasing number of Prostate Cancer (PCa) patients received Holmium laser enucleation of the prostate (HoLEP) for benign prostatic obstruction (BPO), there is still no evidence regarding the outcomes of radical prostatectomy (RP) in this setting. Thus we aimed to assess functional and oncological results of RP in PCa patients who previously received HoLEP for BPO in a contemporary multi-institutional cohort. Overall, 95 patients who received RP between 2011 and 2019 and had a history of HoLEP were identified in two institutions. Patients with complete follow-up data (n=43) were matched with individuals without history of BPO surgery in a 1:4 propensity-score matching (n=138). Median follow-up was 50.5 months. We found no significant impact of previous HoLEP on positive surgical margin rate (14.0% [HoLEP] vs. 18.8% [no HoLEP]), p=?) and biochemical recurrence-free survival (hazard ratio 0.74, 95% CI 0.32–1.70, p=0.4). Patients with a history of HoLEP had an increased risk of urinary incontinence (defined as no wet pads per day) after RP compared to those without previous BPO surgery after adjusting for confounders (odds ratio [OR]: 0.83, 95% confidence interval [CI]: 0.71–0.96; p=0.01). A history of HoLEP did not have significant impact on erectile function recovery (OR: 0.74, 95%CI: 0.32–1.70; p=0.4).

Patient summary: In the current study, we assessed the oncological and functional outcomes of RP in patients who underwent previous HoLEP due to prostatic bladder outlet obstruction. Although a history of HoLEP did not hamper oncologic results, worse urinary continence results were observed in this setting.

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Holmium laser enucleation of the prostate (HoLEP) represents an emerging treatment option in the setting of patients with benign prostatic obstruction (BPO). A recent meta-analysis demonstrated that this surgical approach is characterized by shorter catheterization time and hospital stay, reduced blood loss, and fewer blood transfusions compared to standard transurethral resection of the prostate (TURP). This held true particularly in patients with large prostates and those receiving anticoagulant and/or antiplatelet therapies [1]. Although there is compelling evidence that radical prostatectomy (RP) can be safely performed after TURP, patients who received previous surgery for BPO might be at higher risk of experiencing worse oncological and functional outcomes [2, 3]. These assumptions might apply also to individuals with a history of HoLEP. To date there is no 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 compared to 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 oncologic and functional results of RP in a contemporary multicentric cohort of patients with a history of HoLEP for BPO.

A total of 1,438 consecutive patients that underwent open or robot-assisted RP between 2011 and 2019 at two tertiary care centers were identified. Baseline characteristics, pathologic features, oncological and functional outcomes were compared between patients with (n=95) and without previous HoLEP for BPO (n=1343). We then generated a 1:4 propensity score matched cohort limited to patients with complete follow-up [n=43 (HoLEP), n=138 (no HoLEP)]. Matching variables were represented by age, prostate volume based on RP specimen, and pT stage. Patients with cT4, cN1 and cM1 disease were excluded from further analysis. Continence recovery was defined as use of no pads, erectile function recovery was

defined as IIEF-5 score of ≥22 [4]. Based on PSA retrieval, 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 potential confounders.

Patient characteristics of the unmatched and matched cohorts are summarized in Table 1. We identified 95 patients with previous HoLEP in the unmatched patient cohort. Individuals with previous HoLEP were older (69 vs. 63 yrs, p<0.001) and pre-RP prostate volume was smaller (34 vs. 51ml, p<0.001). We found clinically comparable albeit statistically significantly increased positive surgical margin rates for patients with previous HoLEP compared to patients without HoLEP (20.0 vs. 17.7%, p<0.001). In addition, we found significantly decreased continence recovery rates for patients with previous HoLEP (81.4 vs. 68.4%, p=0.02). To account for meaurable confounders, we subsequently generated a 1:4 propensity score matched cohort of 181 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 score (GG) (p=0.6), pT stage (p=0.6) and pN stage (p=0.3). Median follow-up was 50.5 months (interquartile range [IQR]: 24-84) for patients without previous HoLEP and 44 months (IQR: 13-73) for patients with previous HoLEP (p=0.1). Regarding oncological outcomes, we found comparable positive surgical margin rates (14.0% [HoLEP] vs. 18.8% [no HoLEP]) with higher rates of multifocal positive margins in the no-HoLEP subgroup (10.1% vs. 0.0%, p=0.06). 6-yr bRFS estimates were 86% for patients with previous HoLEP and 75% for patients without previous HoLEP (p=0.44; figure 1). In multivariable Cox regression analysis adjusted for age, pT stage, Gleason grade, and pN stage, previous HoLEP was not associated with bRFS (hazard ratio 0.74, 95%CI 0.32–1.70, p=0.4). Detailed results of the multivariable analysis for bRFS are summarized in supplementary table 1.

Regarding functional outcomes, continence recovery was observed in 65.1% (HoLEP) vs. 79.0% (no HoLEP) of the patients after XX months post- surgery. (p=0.09). However, in multivariable logistic regression models adjusted for age, prostate volume, postoperative androgen deprivation therapy and radiotherapy, previous HoLEP was associated with unfavorable continence recovery (odds ratio [OR] 0.83, 95%CI 0.71–0.96, p=0.01; supp. table 2). Conversely, higher erectile function recovery rates were observed for patients with previous HoLEP, although not reaching statistical significance (univariable analysis 46.5 vs 37.0%, p=0.3; multivariable analyses OR 1.12, 95%CI 0.95–1.31, p=0.1; supp. table 2).

In the current study, we provide first evidence supporting the safety and effectiveness of RP in patients with a history of HoLEP for BPO. Although patients who underwent HoLEP before RP had worse urinary continence recovery rates as compared to their counterparts who did not receive surgery for BPO, RP was associated with comparable oncologic outcomes and erectile function recovery in this setting. Several studies previously attempted to assess outcomes after TURP and mixed results were provided so far. In a recent meta-analysis, Liao and colleagues found significantly higher positive surgical margin rates for patients undergoing RP after previous TURP, which differs to the results of the current study [3]. However, the largest study investigating oncologic outcomes of RP after TURP to date did not show significant differences in bRFS between both subgroups [5]. Similarly, our bRFS survival rates after a median follow-up of more than 4 years 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. It has been postulated that previous transurethral surgery increases inflammation and tissue fibrosis and ultimately leads to more challenging surgical procedures resulting not only in decreased oncological but, possibly, in worse functional outcomes. In the current study, we observe decreased continence recovery rates for patients with previous HoLEP. This is in line with the findings of Pompe et al. where

the authors found a significantly increased risk for urinary incontinence 3-month as well as 12-month after RP as well as worse erectile function recovery rates [5]. The continence rates have to be interpreted with caution since patient cohorts as well as continence definitions vary between most studies and generalizability is therefore often hampered.

Despite its inherent limitations, given the retrospective nature and the small sample size, our study gives important novel insights in surgical and functional outcomes in a distinct patient cohort. These findings have direct clinical impact since they inform the preoperative patient education processes, which has been shown to correlate with postoperative patient satisfaction [6].

Take home messages:

We provide data from a propensity score-matched population of patients who underwent RP with or without previous HoLEP. In multivariable analyses, no differences in biochemical recurrence-free survival and positive surgical margin rates were found, however, previous HoLEP was an independent predictor of worse continence outcomes.

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Figure legends:

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

	Unmatched cohort	Matched cohort

Variable		Overall	No HoLEP pre-RP N=1343; 93%	HoLEP pre-RP N=95; 7%	p value	Overall	No HoLEP pre-RP N=138; 76%	HoLEP pre-RP N=43; 24%	p value	
Volume Prostate [ml]	**Median**	50	51	34	<0.001	36	37.8	34	0.06	
	IQR	40 - 63	41 - 64	24 - 44		30-46	30-48	27-41.5		
Age at RP [yrs]	**Median**	64	63	69	<0.001	67	66.5	69	0.1	
	IQR	58 -68	58 - 68	63 - 72		63-71	63-71	63-71		
Surgical approach [n (%)]	**ORP**	417 (30.4)	910 (70.4)	34 (44.2)	0.010	70 (38.7)	50 (36.2)	20 (46.5)	0.5	
	RARP	953 (69.6)	383 (29.6)	43 (55.8)		111 (61.3)	88 (63.8)	23 (53.5)		
Follow-up [mo]	**Median**	32	31	37	0.905	48	50.5	44	0.1	
	IQR	15 - 60	15 - 60	13 - 60		24-84	24-84	13-72.5		
pT stage [n (%)]	**pT2c**	912 (63.5)	847 (63.1)	65 (69.1)		115 (63.5)	89 (64.5)	26 (60.5)		
	pT3a	365 (25.4)	345 (25.7)	20 (21.3)	0.495	51 (28.2)	39 (28.3)	12 (27.9)	0.6	
	≥pT3b	160 (11.1)	151 (11.2)	9 (9.6)		15 (8.3)	10 (7.2)	5 (11.6)		
pN stage [n (%)]	**pN0**	1000 (69.7)	929 (69.4)	71 (74.7)		134 (74)	105 (76.1)	29 (67.4)		
	pN1	155 (10.8)	150 (11.2)	5 (5.3)	0.194	14 (7.7)	11 (8)	3 (7)	0.3	
	pNx	279 (19.5)	260 (19.4)	19 (20.0)		33 (18.2)	22 (15.9)	11 (25.6)		
path. GG [n (%)]	**<=7**	1200 (83.7)	1128 (84.0)	72 (80.0)	0.304	150 (82.9)	116 (84.1)	34 (79.1)	0.6	
	8-10	233 (16.3)	215 (16.0)	18 (20.0)		31 (17.1)	22 (15.9)	9 (20.9)		
Postoperative ADT [n (%)]	**None**	1289 (92.1)	1210 (92.2)	79 (91.9)	0.444	168 (92.8)	128 (92.8)	40 (93)	0.6	
	Adjuvant	91 (6.5)	84 (6.4)	7 (8.1)		10 (5.5)	7 (5.1)	3 (7)		
	Salvage	19 (1.4)	19 (1.4)	0 (0.0)		3 (1.7)	3 (2.2)	0 (0)		
Postoperative Radiotherapy [n (%)]	**None**	1167 (82.4)	1089 (81.8)	78 (90.7)	0.041	149 (82.3)	109 (79)	40 (93)	0.06	
	Adjuvant	173 (12.2)	165. (12.4)	8 (9.3)		19 (10.5)	16 (11.6)	3 (7)		
	Salvage	77 (5.4)	77 (5.8)	0 (0.0)		13 (7.2)	13 (9.4)	0 (0)		
Positive surgical margins [n (%)]	**None**	1181 (82.1)	1105 (82.3)	76 (80.0)	<0.001	149 (82.3)	112 (81.2)	37 (86)	0.06	
	Focal	138 (9.6)	119 (8.9)	19 (20.0)		18 (9.9)	12 (8.7)	6 (14)		
	Multifocal	119 (8.3)	119 (8.3)	0 (0.0)		14 (7.7)	14 (10.1)	0 (0)		
UC recovery [n (%)]	**No**	239 (19.2)	221 (18.6)	18 (31.6)	0.023	44 (24.3)	29 (21)	15 (34.9)	0.09	
	Yes	1008 (80.8)	969 (81.4)	39 (68.4)		137 (75.7)	109 (79)	28 (65.1)		
EF recovery [n (%)]	**No**	742 (59.3)	711 (59.5)	31 (54.4)	0.491	110 (60.8)	87 (63)	23 (53.5)	0.3	
	Yes	510 (40.7)	484 (40.5)	26 (45.6)		71 (39.2)	51 (37)	20 (46.5)		

Table 1. Patient characteristics of the unmatched and matched patient cohort that was included in the current study (ADT = androgen deprivation therapy, EF = erectile function, GG = Gleason grade, HoLEP = holmium laser enucleation of the prostate, RP= radical prostatectomy, UC = urinary continence).

Variables	Measure	

		HR	95% CI		P value
Pre-RP HoLEP					
	No	Ref			
	Yes	0.74	0.32	1.70	0.4
Path. 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

Supp. Table 1. Multivariate Cox regression for the endpoint biochemical recurrence free survival (GG = Gleason grade, HoLEP = holmium laser enucleation of the prostate, HR = hazard ratio, RP= radical prostatectomy).

Variable	Measure	Continence recovery			Potency recovery		
		OR	95% CI	p	OR	95% CI	p

HoLEP pre-RP									
	No	Ref.				Ref.			
	Yes	0.83	0.71	0.96	0.01	1.12	0.95	1.31	0.1
Postoperative RT									
	No	Ref.				Ref.			
	Yes	0.92	0.81	1.03	0.2	1.05	0.93	1.19	0.4
Postoperative ADT									
	No	Ref.				Ref.			
	Yes	0.80	0.65	0.98	0.04	0.84	0.68	1.06	0.1
Age at RP	Years	0.994	0.984	1.004	0.2	0.972	0.961	0.983	<0.001
pT stage									
	pT2c	Ref.				Ref.			
	pT3a	0.94	0.81	1.09	0.4	0.94	0.80	1.10	0.4
	pT3b	1.12	0.88	1.44	0.3	0.83	0.64	1.08	0.2
Prostate volume	cc	0.995	0.991	1.000	0.049	0.994	0.990	0.999	0.02

Supp. Table 2. Multivariate regression for the endpoint continence recovery and potency recovery (ADT = androgen deprivation therapy, GG = Gleason grade, HoLEP = holmium laser enucleation of the prostate, OR = odds ratio, RP= radical prostatectomy).