ORIGINAL PAPER

Preoperative multiparametric prostate magnetic resonance imaging: a safe clinical practice to reduce incidental prostate cancer in Holmium laser enucleation of the prostate

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Introduction Purpose of the study was to investigate the correlation of a preoperative multiparametric magnetic resonance imaging of the prostate (mpMRI) in patients with a suspicion of prostate cancer and eligible for Holmium Laser Enucleation of the Prostate (HoLEP).
Material and methods Data of 228 patients who had undergone HoLEP was selected and retrospectively analyzed from a multicentric database. All patients presented with a raised serum PSA and/or an abnormal digital rectal examination (DRE). Prostate cancer (PCa) was excluded either with a negative mpMRI (group 'NEGATIVE MRI' n = 113) or a standard biopsy (group 'NO MRI' n = 115). Preoperative characteristic surgical and histological outcomes were confronted. A univariate and multivariate logistic regression model was performed to investigate independent predictors of incidental Prostate Cancer (iPCa).
Results Both groups presented with no statistical differences in preoperative characteristics besides previous acute urinary retention rates and post-voided residual volume, found to be higher (27.8% vs. 14.2% and median 120cc vs. 80cc) in NO MRI and NEGATIVE MRI respectively.
No differences were registered in surgical time, removed tissue, catheterization time, hospital stay and complications rate.
Statistically lower rate of iPCa (p = 0.03) was detected in the NEGATIVE MRI group (6.2%) in comparison with NO MRI group (14.8%). In multivariate logistic regression only presence of a preoperative negative mpMRI correlated (p = 0.04) as an independent predictive factor (OR 2.63; 95% CI: 1.02–6.75).
Conclusions A negative mpMRI might be a useful tool to be included in a novel preoperative assessment to patients eligible for HoLEP with a suspicion of PCa in order to avoid an incidental PCa.

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INTRODUCTION

Benign prostate enlargement (BPE) with related bladder outlet obstruction (BOO) and affected quality of life (QoL) is one of the most common non-malignant disease in aging men [1]. Secondary bothersome lower urinary tract symptoms (LUTS) represent therefore a non-irrelevant clinical and social burden [2] and surgical treatment is required when medical therapy fails to relieve symptoms and avoid adverse events [3].
Holmium laser enucleation of the prostate (HoLEP) demonstrated to be safe, efficient, time durable [4, 5], less invasive compared to open surgery and capable to be applied in all prostate sizes [6]. HoLEP permits to retrieval of adequate tissue, comparable to

open surgery and transurethral resection of prostate (TURP) [7, 8], in order to detect an incidental prostate cancer (iPCa) [9, 10].

Diagnosis of prostate cancer might represent a heavy burden in a patient's quality of life [11] and its exclusion might be necessary whenever an abnormal digital rectal examination (DRE) and/or a raised serum PSA are present prior to the surgical management of BPE. Prostate biopsy is commonly performed in order to exclude prostate cancer, leading sometimes to false negative results [12, 13].

During the last years, several novel imaging techniques such as MRI and PET/TC [14] were introduced in clinical practice as a diagnostic tool for PCa diagnosing and staging. Magnetic resonance imaging (MRI) has shown to be a remarkable tool in PCa diagnosis and especially combining functional studies, multiparametric MRI of the prostate (mpMRI) improves the identification of PCa foci with high accuracy [15, 16]. Evidences suggest that mpMRI could both reduce unnecessary biopsies and lead to less false- negative biopsies directly targeting any suspicious lesion found [17].

The purpose of our study was to investigate the correlation between a negative preoperative mpMRI and iPCa rates in patients who had undergone HoLEP with clinical suspicion of prostate cancer.

MATERIAL AND METHODS

Population and study design

Data was retrospectively analyzed from a multicentric prospective database of patients eligible for surgery due to symptomatic BPE who underwent to Holmium laser enucleation of the prostate (HoLEP) between January 2017 and June 2018. Indications for surgical treatment were persistent bladder outflow obstruction (BOO) symptoms, International Prostatic Symptoms Score (IPSS) higher than 8, peak urinary flow (Qmax) ≤15 ml/s, non-responsiveness to medical therapies [α-blockers and/or 5α-reductase inhibitors (5-ARIs)], acute and chronic urinary retention or renal function impairment due to BOO.

Patients with pre-operative suspicion of a prostatic tumor and younger than 75 years old (total PSA >4 ng/mL and/or abnormal DRE) were selected form the database pool. In the study cohort a pre-interventional Prostatic cancer (PCa) exclusion was carried out through either a negative mpMRI (after adequate explanations of risks and benefits, refusing the procedure) or a negative transrectal ultrasound guided random biopsy (TRUS-GB). When TRUS-GB

was performed 10 or 12 cores were taken based on the prostate volume.

Multiparametric MRI was conducted with a 1.5 T whole body scanner (Achieva XR; Philips Medical Systems, Best, Netherlands) without endorectal coil and with a 32-channels phased-array surface coil. Obtained morphological and functional studies consisted in turbo spin echo (TSE) T2-weighted sequences in sagittal, axial and coronal planes, diffusion weighted imaging (DWI) and dynamic contrast- enhanced MRI (DCE-MRI). Each mpMRI was exclusively performed in one of the two involved centers and evaluated according to PI-RADS-v2, based on the European Society of Urogenital Radiology (ESUR) guidelines for the evaluation and reporting of prostate mpMRI [18], by two high experienced uro-radiologists and mpMRIs with PI-RADS-v2 Score <3 were considered negative.

Collected pre-operative data included age, total PSA, DRE, prostate and adenoma volume either at mpMRI or at transrectal ultrasound, PSA density, Qmax, IPSS, Quality of Life Score (QoL), post-voided residual volume (PRV), drug assumption, previous acute urinary retention.

Following peri- and post-operative clinical and pathological parameters were evaluated: surgical time, removed tissue weight, catheterization time, hospital stay, peri-operative complications, presence of incidental prostate cancer (iPCa), pT stage and International Society of Urological Pathology (ISUP) Grade Group of each iPCa.

Surgical procedure

HoLEP was conducted in either of the two centers by four experienced surgeons with the Lumenis Versa Pulse™ Holmium laser set at 2.0 J and 60 Hz (maximum power of 120 W) and a 26Fr continuous-flow Storz laser resectoscope delivering laser energy with a 550-μm fiber. The procedure was performed based on Gilling's technique [19] and the Lumenis VersaCut™ Morcellator System was used to remove the enucleated prostatic lobes. At the end of the surgery a 20F three-way catheter was indwelled with continuous flow irrigation until the next morning. Catheter was removed at second post-operative day if no hematuria or other complication had intercurred.

Statistical analysis

Patients were divided in two groups, 'NEGATIVE MRI' (n = 113) and 'NO MRI' (n = 115) based on the presence of the negative mpMRI prior to surgery. Mean with standard deviations (SD) and median val-

ues with interquartile ranges (IQR) were respectively reported for normally distributed and non-normally distributed continuous variables, while frequencies with proportions (%) were used for categorical variables. Differences between the two groups was analyzed with the student t-test and Mann-Whitney U test for continuous data, and the chi-square test for categorical values.

A univariate and multivariate logistic regression model was used in order to investigate if any preoperative factors (age, PSA, prostate volume, adenoma volume, removed tissue, PSA density >15, presence of a preoperative mpMRI) could be associated with iPCa in patients eligible for HoLEP surgery with a suspect of PCa.

IBM SPSS 22 with a 2-sided significance level set at P <0.05, was employed for statistical analysis.

RESULTS

Overall, preoperative characteristics are listed in Table 1. In summary, 113 (NEGATIVE MRI) and 115 (NO MRI) men underwent HoLEP with preoperative negative mpMRI and negative prostate biopsy, respectively.

We found no significant differences between the two groups concerning age at surgery, PSA, prostate volume, adenoma volume and PSA density (Table1). Digital rectal examinations and drugs assumptions were found to be similar in the two groups whereas a higher rate of previous acute urinary retentions episodes were found in the NO MRI group: 32 (27.8%) versus 16 (14.2%) [p = 0.01].

Both cohorts, as expected, presented moderate LUTS based on the IPSS (median value 18.5; IQR 15.75 – 23),

Table 1. *Study cohort patients' characteristics*

	Overall (n = 228)	Negative MRI (n = 113)	No MRI (n = 115)	p value
Age, years Mean (SD)	64.9 (7.3)	63.7 (7.3)	65.6 (7.2)	0.65
PSA, ng/ml Mean (SD)	7.09 (3.9)	7.6 (4.0)	7.4 (3.7)	0.75
DRE, n (%) Negative Positive	184 (80.7) 44 (19.3)	96 (85.0) 17 (15.0)	88 (76.5) 27 (23.5)	0.11
Prostate volume, cc Mean (SD)	86.9 (34.4)	95.3 (44.8)	86.6 (44.4)	0.14
Adenoma volume, cc Mean (SD)	54.5 (28.4)	61.9 (36.2)	52.7 (36.5)	0.06
PSA Density, ng/ml/cc Mean (SD)	0.09 (0.06)	0.09 (0.04)	0.09 (0.07)	0.37
PSA Density > 0.15 ng/ml/cc, n (%) No Yes	192 (84.2) 36 (15.8)	99 (86.1) 16 (13.9)	93 (82.3) 20 (17.7)	0.23
Qmax, mL/sec Median (IQR)	8.0 (6.7–9.8)	8.0 (6.7–9.8)	8.8 (6.1–9.9)	0.85
IPSS score Median (IQR)	18.5 (15.75–23)	18 (17–22)	19.5 (15–25.5)	0.84
QoL score Median (IQR)	4 (3–5)	4 (3–5)	4 (3–5)	0.75
PRV, cc Median (IQR)	66 (0–189)	120 (60–320)	80 (20–130)	0.02*
Drug assumption, n (%) No Alfa blocker 5-ARI 5-ARI + alfa-blocker	66 (28.9) 68 (29.8) 10 (4.4) 84 (36.9)	37 (32.7) 32 (28.3) 1 (0.9) 43 (38.1)	29 (25.2) 36 (31.3) 9 (7.8) 41 (35.7)	0.07
Previous acute urinary retention, n (%) No Yes	180 (78.9) 48 (21.1)	97 (85.8) 16 (14.2)	83 (72.2) 32 (27.8)	0.01*

Continuous variables are shown as mean (SD) and median (IQR) values based on their distribution while categorical as number (%). Statistically significant values are considered as p value <0.05.

PSA – prostate specific antigen; DRE – digital rectal examination; Qmax – maximum peak urinary flow; IPSS – international prostate symptoms score; QoL – quality of life; PRV – post-void volume; 5-ARI – 5-aromatase receptor inhibitor

with an affected quality of life and a relevant bladder outflow obstruction with decreased peak urinary flow (Qmax). A superior preoperative post-voided residual volume was recorded in NEGATIVE MRI patients (120 cc, IQR 60–320) compared to NO MRI patients (80 cc, OQR 20–130).

As shown in Table 2, the surgical time, removed tissue weight, catheterization time, hospital stay, and perioperative complications were comparable between the two groups.

At a final pathology examination of the resected tissue, statistically lower rate of iPCa (p = 0.03) was detected in the NEGATIVE MRI group (6.2%) in comparison with the NO MRI group (14.8%). No significant differences on pT stage and the International Society of Urological Pathology (ISUP) Grade Group in iPCa stratification were detected with pT1a stage and ISUP Grade Group I (Gleason Score 3+3) 100% versus 88.2% (p = 0.34) and 85.7% versus 88.2% (p = 0.86) respectively in NEGATIVE MRI and NO MRI group.

At univariate analysis, only age (p = 0.04) and presence of a preoperative negative MRI (p = 0.03) were correlated with iPCa whereas at multivariate analysis only presence of a preoperative negative MRI correlated (p = 0.04) as an independent predictive factor (OR 2.63; 95% CI: 1.02–6.75) (Table 3).

DISCUSSION

Holmium laser enucleation of the prostate is a modern non-invasive surgical technique which allows to efficiently manage BOO with safe and long-term results, as shown by several authors including a randomized trial [5]. Differently to other BPE laser surgery, HoLEP performs an endoscopic prostate enucleation and therefore final specimen histology might reveal sometimes iPCa.

Elkoushy et al. [20] showed that oncological management of iPCa is usually carried out by active surveillance [21, 22]; however, sometimes a radical prostatectomy or radiotherapy is required, negatively impacting the patient's quality of life [23]. Therefore, an accurate diagnostic investigation is required each time a PCa suspicion is raised when a BPE surgery is indicated.

In our study, the role of a preoperative negative mpMRI was investigated as a diagnostic tool in order to exclude PCa before submitting to HoLEP a patient with a suspicion of PCa. A group of patients undergone to HoLEP after a negative mpMRI were compared to a group of patients undergone to HoLEP without a pre- surgery mpMRI. In this group systematic prostate biopsy was used to exclude the presence of PCa. Pre- surgery assessments and peri-

Table 2. *Surgical and histological outcomes*

	Overall (n = 228)	NEGATIVE MRI (n = 113)	NO MRI (n = 115)	p value
Surgery time (min) Mean (SD)	86.5 (32.4)	89.3 (29.1)	94.7 (35.1)	0.11
Removed tissue (gr) Mean (SD)	47.1 (27.7)	48.1 (29.4)	45.6 (26.0)	0.32
Catheterization time (days) Median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	0.83
Hospital stay (days) Median (IQR)	2 (2–2)	2 (2–2)	2 (2–2)	0.73
Peri-operative complications, n (%) No Grade* 1 Grade* 2	209 (91.7) 18 (7.9) 1 (0.4)	103 (91.2) 10 (8.8) 0 (0.0)	106 (92.2) 8 (7.0) 1 (0.8)	0.53
Histopathology (%) Negative iPCa	204 (89.5) 24 (10.5)	106 (93.8) 7 (6.2)	98 (85.2) 17 (14.8)	0.03*
pT Stage (%) pT1a pT1b	22 (91.7) 2 (8.3)	7 (100.0) 0 (0.0)	15 (88.2) 2 (11.8)	0.34
ISUP Grade Group (%) Group I Group II	21 (87.5) 3 (12.5)	6 (85.7) 1 (14.3)	15 (88.2) 2 (15.8)	0.86

Continuous variables are shown as mean (SD) and median (IQR) values based on their distribution while categorical as number (%). Statistically significant values are considered as p value <0.05.
pT – stage pathologic T stage; ISUP – International Society of Urological Pathology

Table 3. *Uni and multivariate logistic regression*

Variables	Univariate		Multivariate	
	p value	OR (95% CI)	p value	OR (95% CI)
Age [continuous] (years)	0.04*	1.02 (0.97–1.03)	0.12	1.02 (0.95 – 1.12)
PSA [continuous] (ng/mL)	0.43	1.02 (0.92–1-13)	0.45	1.07 (0.93 – 1.15)
Prostate Volume [continuous] (cc)	0.81	0.99 (0.98–1.01)		
Adenoma Volume [continuous] (cc)	0.90	0.99 (0.98–1.01)		
Removed Tissue [continuous] (gr)	0.45	1.01 (0.98–102)		
PSA density > 15 [yes vs. no] (ng/mL/cc)	0.81	0.84 (0.23–3.06)		
Presence of a preoperative negative mpMRI (yes vs no)	0.03*	2.62 (1.04–6.61)	0.04*	2.63 (1.02 – 6.75)

Statistically significant values are considered as p value <0.05.
OR – odds ratio, CI – confidence interval, PSA – prostate specific antigen, mpMRI – multiparametric Magnetic Resonance Imaging

operative outcomes had no statistical significative differences showing that the two groups were homogeneous.

The wide range of iPCa after HoLEP in the available literature (8.1–15%) might be due to the different and various baseline patients' characteristics [9, 10, 24, 25]. Including the only patient with a raised PSA and/or an abnormal DRE, our study cohort represents a selected population although those parameters might be altered when large prostates and BOO symptoms are present [26, 27].

HoLEP is suitable for all prostate volume, especially for the large prostate as it is shown by the two group's median prostate volume >80 cc. Herlemann et al. [25] found in their HoLEP study arm 40% of iPCa despite a negative preoperative prostate biopsy highlighting that a different diagnostic pre-surgical path is needed for those patients.

In our experience, mpMRI proved to be a valuable diagnostic tool not only to program a precise nerve sparing in patients scheduled for radical prostatectomy [28], but also to exclude PCa in patient at risk before undergoing to HoLEP, since the iPCa rate in the NEGATIVE MRI group was significantly lower as compared to NO MRI group (6.2% vs. 14.8%). However, no differences in terms of pT stage and ISUP Grade Group were found. Preoperatively, assessing a patient without a mpMRI leads to an iPCa rate which is similar to the upper limit evidenced in the literature. On the other hand, our data suggests that a preoperative negative mpMRI might reduce iPCa leading to a rate smaller than the lowest available in the literature.

Several parameters (older patients, preoperative PSA, smaller prostate volume, PSA density, preoperative biopsy) were pointed in various publications to be identified as predictor of iPCA. Only age and

PSA density demonstrated as strong risk factor for iPCa in cohort of patients undergone to HoLEP. Bhojani et al. [10] reported only age as an independent predictive factor for iPCa in uni- and multivariate analysis while Herlemann et al. [25] and Elkoushy et al. [20] found in their regression analyses PSA density as an independent predictor of iPCa with 0.15 ng/mL/cc and 0.092 ng/mL/ cc cut-off value respectively. Our multivariate logistic regression analysis (Table 3) showed that only the presence of negative mpMRI corelated as an independent predictive factor suggesting a different diagnostic approach to patients eligible for HoLEP with a PCa suspicion.

The main limitation of the study is due to its retrospective nature. Secondly, the two analyzed groups were not matched and lastly prostate volume stratification with 80cc cut-off was not feasible. Moreover, due to the lack of follow-up data, we are unable to assess the impact of the different proportions of iPCa between the two group on long-term oncologic outcomes.

Despite these limitations, our study represents the first multicentric data available of mpMRI employed in the preoperative assessment to exclude the presence of PCa for patients with clinical suspicion of PCa, who had undergone HoLEP. However, in order to deeply investigate the role of mpMRI in this population, prospective randomized trials and further study are needed to assess the potential oncologic benefit of mpMRI by reducing the occurrence of iPCa during HoLEP.

CONCLUSIONS

Patients eligible for holmium laser enucleation of the prostate with a suspicion of prostate cancer (PCa) might need a different preoperative assess-

ment in order to avoid an incidental PCa. Our findings suggest that a negative multiparametric magnetic resonance imaging of the prostate might be a useful tool to be included in a novel approach to obstructed patients with a raised serum PSA and/ or a suspect digital rectal exam leading to low rates of incidental PCa.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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