

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

Angelo Porreca¹, Marco Giampaoli¹, Lorenzo Bianchi², Daniele D'Agostino¹, Daniele Romagnoli¹, Federico Mineo Bianchi², Alessandro Del Rosso¹, Paolo Corsi¹, Riccardo Schiavina², Walter Artibani¹, Eugenio Brunocilla²

¹Abano Terme Hospital, Department of Urology, Abano Terme (PD), Italy

²Department of Urology, University of Bologna, Bologna, Italy

Number ID: 1943/2019/01
Type: Original Basic Research And Clinical Articles
Domain: Urological oncology
Corresponding author: Marco Giampaoli; email: giampaoli.marco85@gmail.com
Conflicts of interest: The authors declare no conflicts of interest.
Key Words: magnetic resonance imaging, incidental prostate cancer, Holmium laser enucleation of the prostate, benign prostate enlargement

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)

Materials and methods Data of 228 patients undergone to HoLEP was selected and retrospectively analyzed from a multicentric database. All patients presented a raised serum PSA and/or an abnormal digital rectal examination (DRE). Prostate cancer 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. Univariate and multivariate logistic regression model was performed to investigate independent predictors of incidental Prostate Cancer (iPCa)

Results Both groups presented 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 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

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 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 size(6). HoLEP allows to retrieve and 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 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 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 technique such as MRI e PET/TC (14) were introduced in clinical practice as diagnostic tool for PCa diagnosing and staging. Magnetic Resonance Imaging (MRI) has shown to be 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 undergone to 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 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 (alfa blockers and/or 5 α -reductase inhibitors 5-ARI), acute and chronic urinary retention or renal function impairment due to BOO.

Patients with pre-operative suspicion of 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 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 next morning. Catheter was removed at second post-operative day if no hematuria or other complication had intercurrent.

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 values 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 two groups was analysed with student t test and Mann-Whitney U test for continuous data, and chi-square test for categorical values.

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. Overall, 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 rates 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), with 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 surgical time, removed tissue weight, catheterization time, hospital stay, and perioperative complications were comparable between the two groups. At 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 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 showed by several authors including a randomized trial (5). Differently to other BPE laser surgery, HoLEP perform 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 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 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 perioperative 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 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 large prostate as it is shown by the two group's median prostate volume > 80cc. 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 patient without a mpMRI lead to an iPCa rate which is similar to the upper limit evidenced in the literature. On the other hand, our data suggest 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 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 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 correlated 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 of its retrospective nature. Secondly the two analyzed groups were not matched and lastly prostate volume stratification with 80cc cut-off were not feasible. Moreover, due to lacking follow up data we are not able to assess the impact of different proportion 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, underwent to 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 HoLEP with a suspicion of PCa might need a different preoperative assessment in order to avoid an incidental PCa. Our findings suggest that a negative mpMRI might be a useful tool to be included in a novel approach to obstructed patients with a raised serum PSA and/or a suspect DRE leading to low rates of iPCa

REFERENCES

1. De Ridder D, Roumeguère T, Kaufman L. Urgency and other lower urinary tract symptoms in men aged ≥ 40 years: a Belgian epidemiological survey using the ICIQ-MLUTS questionnaire. *Int J Clin Pract.* 2015 Mar;69(3):358-65.
2. Martin SA, Haren MT, Marshall VR, Lange K, Wittert GA, Members of the Florey Adelaide Male Ageing Study. Prevalence and factors associated with uncomplicated storage and voiding lower urinary tract symptoms in community-dwelling Australian men. *World J Urol.* 2011 Apr;29(2):179-84.
3. Gravas S., Bach T., Bachmann A., Drake M., Gacci M., Gratzke C., Madersbacher S., Mamoulakis C., Tikkinen K.A.O. S-O. Guidelines on the management of non-neurogenic male lower urinary tract symptoms (LUTS) [Internet]. 2018. Available from: <https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/>
4. Krambeck AE, Handa SE, Lingeman JE. Experience with more than 1,000 holmium laser prostate enucleations for benign prostatic hyperplasia. *J Urol.* 2013 Jan;189(1 Suppl):S141-145.
5. Lourenco T, Pickard R, Vale L, Grant A, Fraser C, MacLennan G, et al. Alternative approaches to endoscopic ablation for benign enlargement of the prostate: systematic review of randomised controlled trials. *BMJ.* 2008 Jun 30;337:a449.
6. Elshal AM, Mekkawy R, Laymon M, Barakat TS, Elsaadany MM, El-Assmy A, et al. Holmium laser enucleation of the prostate for treatment for large-sized benign prostate hyperplasia; is it a realistic endourologic alternative in developing country? *World J Urol.* 2016 Mar;34(3):399-405.
7. Naspro R, Freschi M, Salonia A, Guazzoni G, Girolamo V, Colombo R, et al. Holmium laser enucleation versus transurethral resection of the prostate. Are histological findings comparable? *J Urol.* 2004 Mar;171(3):1203-6.
8. D'Addessi A, Porreca A, Foschi N, Racioppi M. Thick loop prostatectomy in the endoscopic treatment of benign prostatic hyperplasia: results of a prospective randomised study. *Urol Int.* 2005;74(2):114-7.
9. Nunez R, Hurd KJ, Noble BN, Castle EP, Andrews PE, Humphreys MR. Incidental prostate cancer revisited: Early outcomes after holmium laser enucleation of the prostate. *Int J Urol.* 2011;18(7):543-7.
10. Bhojani N, Boris RS, Monn MF, Mandeville JA, Lingeman JE. 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.* 2014 Jul 21;29(1):41-6.
11. Noale M, Maggi S, Artibani W, Bassi PF, Bertoni F, Bracarda S, et al. Pros-IT CNR: an Italian prostate cancer monitoring project. *Aging Clin Exp Res.* 2017 Apr;29(2):165-72.
12. Jones JS. Saturation biopsy for detecting and characterizing prostate cancer. *BJU Int.* 2007 Jun;99(6):1340-4.
13. Serefoglu EC, Altinova S, Ugras NS, Akincioglu E, Asil E, Balbay MD. How reliable is 12-core prostate biopsy procedure in the detection of prostate cancer? *Can Urol Assoc J J Assoc Urol Can.* 2013 Jun;7(5-6):E293-298.
14. Vagnoni V, Brunocilla E, Bianchi L, Porreca A, Borghesi M, Pultrone CV, et al. State of the art of PET/CT with 11-choline and 18F-fluorocholine in the diagnosis and follow-up of localized and locally advanced prostate cancer. *Arch Esp Urol.* 2015 Apr;68(3):354-70.
15. Rhudd A, McDonald J, Emberton M, Kasivisvanathan V. The role of the multiparametric MRI in the

- diagnosis of prostate cancer in biopsy-naïve men. *Curr Opin Urol*. 2017 Sep;27(5):488-94.
16. Porpiglia F, Manfredi M, Mele F, Cossu M, Bollito E, Veltri A, et al. Diagnostic Pathway with Multiparametric Magnetic Resonance Imaging Versus Standard Pathway: Results from a Randomized Prospective Study in Biopsy-naïve Patients with Suspected Prostate Cancer. *Eur Urol*. 2017;72(2):282-8.
 17. Schiavina R, Vagnoni V, D'Agostino D, Borghesi M, Salvaggio A, Giampaoli M, et al. "In-bore" MRI-guided Prostate Biopsy Using an Endorectal Nonmagnetic Device: A Prospective Study of 70 Consecutive Patients. *Clin Genitourin Cancer*. 2017;15(3):417-27.
 18. Weinreb JC, Barentsz JO, Choyke PL, Cornud F, Haider MA, Macura KJ, et al. PI-RADS Prostate Imaging - Reporting and Data System: 2015, Version 2. *Eur Urol*. 2016 Jan;69(1):16-40.
 19. Gilling PJ, Kennett K, Das AK, Thompson D, Fraundorfer MR. Holmium laser enucleation of the prostate (HoLEP) combined with transurethral tissue morcellation: an update on the early clinical experience. *J Endourol*. 1998 Oct;12(5):457-9.
 20. Elkoushy MA, Elshal AM, Elhilali MM. Incidental Prostate Cancer Diagnosis During Holmium Laser Enucleation: Assessment of Predictors, Survival, and Disease Progression. *Urology*. 2015 Sep;86(3):552-7.
 21. Schiavina R, Borghesi M, Brunocilla E, Romagnoli D, Diazzi D, Giunchi F, et al. The biopsy Gleason score 3+4 in a single core does not necessarily reflect an unfavourable pathological disease after radical prostatectomy in comparison with biopsy Gleason score 3+3: looking for larger selection criteria for active surveillance candidates. *Prostate Cancer Prostatic Dis*. 2015 Sep;18(3):270-5.
 22. Grasso AA, Cozzi G, DE Lorenzis E, et al (2016) Multicenter analysis of pathological outcomes of patients eligible for active surveillance according to PRIAS criteria. *Minerva Urol Nefrol* 68:237-241
 23. Porreca A, Noale M, Artibani W, Bassi PF, Bertoni F, Bracarda S, et al. Disease-specific and general health-related quality of life in newly diagnosed prostate cancer patients: the Pros-IT CNR study. *Health Qual Life Outcomes*. 2018 Jun 13;16(1):122.
 24. Rivera ME, Frank I, Viers BR, Rangel LJ, Krambeck AE. Holmium Laser Enucleation of the Prostate and Perioperative Diagnosis of Prostate Cancer: An Outcomes Analysis. *J Endourol*. 2014 Feb 2;28(6):699-703.
 25. Herlemann A, Wegner K, Roosen A, Buchner A, Weinhold P, Bachmann A, et al. "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*. 2017 Nov;35(11):1777-82.
 26. Marks LS, Dorey FJ, Rhodes T, Shery ED, Rittenhouse H, Partin AW, et al. Serum prostate specific antigen levels after transurethral resection of prostate: a longitudinal characterization in men with benign prostatic hyperplasia. *J Urol*. 1996 Sep;156(3):1035-9.
 27. Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology*. 1999 Mar;53(3):581-9.
 28. Schiavina R, Bianchi L, Borghesi M, Dababneh H, Chessa F, Pultrone CV, et al. MRI Displays the Prostatic Cancer Anatomy and Improves the Bundles Management Before Robot-Assisted Radical Prostatectomy. *J Endourol*. 2018 Apr;32(4):315-21.

Attached tables:

1. Table1CEJU iPCa in Negatve MRI preHoLEP.docx
2. Table2CEJU iPCa in Negatve MRI preHoLEP.docx
3. Table3CEJU iPCa in Negatve MRI preHoLEP.docx

Table1CEJU iPCa in Negative MRI preHoLEP.docx

Failed conversion of the file to PDF preview. The table preview will be prepared by the editorial office within 24 hours.

Table2CEJU iPCa in Negative MRI preHoLEP.docx

Failed conversion of the file to PDF preview. The table preview will be prepared by the editorial office within 24 hours.

Table3CEJU iPCa in Negative MRI preHoLEP.docx

Failed conversion of the file to PDF preview. The table preview will be prepared by the editorial office within 24 hours.