Incidental prostate cancer at holmium laser enucleation of prostate

Asaf Shvero, MD,[1,2] Seth Teplitsky, MD,[3] Edward Kloniecke, MD,[1]
Akhil K. Das, MD[1]

[1]Department of Urology, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania, USA
[2]Department of Urology, Sheba Medical Center, Ramat-Gan, Israel. Affiliated with Tel Aviv University, Tel Aviv, Israel
[3]Department of Urology, University of Kentucky, Lexington, Kentucky, USA

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Introduction: *The purpose of this study was to describe the current incidence, risk factors, and management of incidental diagnosis of prostate cancer (iPCa) among patients who underwent holmium laser enucleation of prostate (HoLEP) and have no history of prostate cancer.*
Materials and methods: *We conducted a retrospective review of all patients who underwent HoLEP in our institution between 2013-2020. All patients were offered a PSA screening according to the latest guidelines. We gathered demographic data, perioperative information, and pathologic evaluation. For patients diagnosed with iPCa, we gathered work up, management, and oncologic outcome. We then conducted a univariate and multivariate analysis to find predictive factors for the diagnosis of incidental cancer.*
Results: *The cohort included 777 patients, among them 55 (7.1%) patients with iPCa. The median age of the entire cohort was 71 years, median PSA was 3.9 mg/dL, and median prostate volume of 96 mL. Of those with iPCa, 34 (61.8%) patients had grade-group (GG) 1. Larger prostate size was found to be protective against iPCa, with a 13% risk reduction for every increment of 10 mL in prostate size. For prostates smaller than 100 mL, iPCa rate was 12.6%. Older age and smaller prostate volume were found to predict GG2-and-above iPCa.*
Conclusions: *iPCa at HoLEP is rare, with clinically significant cancer being even rarer. Smaller preoperative prostate was found to be a predictive factor for iPCa. Our results provide an insight into the current risk and predictive factors to iPCa and can be used to guide surgeons and patients in the preoperative recommendations and informed consent process.*

Key Words: prostate cancer, laser surgery, transurethral prostatectomy

Introduction

Holmium laser enucleation of the prostate (HoLEP) is one of the most prominent modalities for the treatment of benign prostatic enlargement. HoLEP employs a holmium laser to enucleate the adenoma off its surgical capsule in a transurethral endoscopic approach. HoLEP is prostate-size independent and can be used for enucleation of prostates over 100 g, which has traditionally been a limitation of other endoscopic BPH treatment modalities like transurethral resection of the prostate (TURP).[1] After enucleation, morcellation is performed to enable extraction of the prostatic tissue, and prostatic chips are sent for pathologic evaluation. In doing so, HoLEP can identify prostate cancer in the transition zone of the prostate, where the adenoma lies, in a rate similar to open prostatectomy and even higher than TURP.[2,3]

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Address correspondence to Dr. Asaf Shvero, Department of Urology, Thomas Jefferson University Hospital, 1025 Walnut Street, Suite 1100, Philadelphia, PA, 19107 USA

Prostate cancer is the second most common type of cancer among men, accounting for 15% of diagnosed cases of cancer. Current estimates show that 1 out of 9 North American men will be diagnosed with prostate cancer at some point in their lifetime,[4] and about 5% of prostate cancers appear in the transition zone.[5] Although PSA screening is a well-known tool for early detection of prostate cancer, it carries potential risks, and is still an area of controversy,[6,7] with most men not undergoing PSA screening.[8] It is estimated that in the post-PSA era incidence of incidental prostate cancer has been decreased by 50%, and the probability to find incidental diagnosis of prostate cancer (iPCa) during TURP before PSA screening was as high as 31%.[9] Also, PSA testing as a part of the work up of lower urinary tract sympotoms (LUTS) before prostate-reduction procedures is also an area of controversy and is not performed in all cases.[6,7] Given these data, it is not surprising that prostate cancer can be incidentally discovered in the pathologic evaluation of prostatic tissue after HoLEP. On the other hand, if prostate cancer is not detected in the pathological specimen, that does not mean the patient is cancer-free, since only the transitional zone is resected during HoLEP, while most prostate cancers lie in the peripheral zone.

Though HoLEP has been discussed in the literature for more than 20 years, few large studies regarding incidental prostate cancer in a large cohort were published. The purpose of this study was to describe the current incidence, risk factors, and management of incidental diagnosis of prostate cancer among patients who underwent HoLEP and have no history of prostate cancer.

Materials and methods

After institutional board approval, we conducted a retrospective review of all patients who underwent HoLEP between January 2013 and October 2020. We excluded patients with a history of prostate cancer.

All patients who underwent HOLEP in our institution were offered PSA screening according to the latest AUA guidelines. Every man with suspected prostate cancer was offered continued work up including a prostate biopsy. Preoperative prostate size was estimated in mL, by one of the following: transrectal ultrasound, MRI, CT, pelvis US, or cystoscopy. HoLEP procedures were performed or supervised by a single fellowship-trained surgeon with a trainee (fellow/senior resident) participating in most cases. First, a rigid 22FR cystoscopy was performed to evaluate the urethra, prostatic lobes, and bladder (for strictures, stones, or tumors). Then a 26FR continuous flow cystoscope sheath was introduced followed by a 550-micron laser fiber with holmium laser settings of 2J/50Hz. After enucleation of the lobes of the adenoma, they were pushed into the bladder, followed by meticulous hemostasis to the prostatic fossa. Then morcellation was performed using a 26FR offset nephroscope, and a morcellator unit. At the end of the procedure, a 24FR 3-way urethral catheter was inserted with continued bladder irrigation. Patients typically had their urethral catheter removed the following day and were discharged after a voiding trial. All prostatic tissue was sent for pathologic evaluation.

After surgery, all patients diagnosed with prostate cancer were recommended a repeat biopsy after a period of recovery from the surgery. After the repeat biopsy active surveillance was recommended or a referral to the multidisciplinary uro-oncologic team at our institution to be counseled on the different treatment options. Patients who chose active surveillance were followed up with regular serum PSA measurements, digital rectal examination, and prostate biopsies when indicated as a part of the surveillance protocol or as a complementary diagnostic procedure. The repeat biopsy was performed after a recovery period from the HoLEP procedure.

We gathered demographic data, operative and perioperative information, pathologic evaluation, and functional outcome an all the cohort. For patients diagnosed with incidental prostate cancer, we gathered work up, management, and oncologic outcome as well. Tumors were graded using Grade Groups (GG) 1-5.

Statistical analyses

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS v23.0, SPSS Inc.). We divided the cohort into two groups: patients diagnosed with BPH versus patients diagnosed with iPCa and subgroup analysis of GG2-and-above iPCa. We used chi-square and student's t-test to compare binary/nominal and continuous variables. Multivariate analysis was performed using binary logistic regression to find factors associated with a diagnosis of incidental prostate cancer. Statistical significance was considered at $p < 0.05$.

Results

Our database of patients who underwent HoLEP included 801 patients. We excluded 10 patients without an available pathologic report and 14 with a history of prostate cancer before surgery. The cohort included 777 patients, among them 55 patients with iPCa (7.1%). The median age of the entire cohort was

TABLE 1. **Pathologic evaluation of patients with iPCa. Gleason Group 4 was not encountered**

Parameter	Value
Patients, n	55
Gleason group, n (%), %tissue involved, median, IQR	
GG1, n (%)	34 (61.8%)
% tissue involved, median, IQR	2% (1-5)
GG2, n (%)	10 (18.2%)
% tissue involved, median, IQR	5% (5-7.25)
GG3, n (%)	3 (5.5%)
% tissue involved, median, IQR	10% (5-95)
GG5, n (%)	8 (14.6%)
% tissue involved, median, IQR	50% (32.5-75)
GG2 and above, n (%)	21 (38.2%)

71 years (IQR 65-77), preoperative PSA was a median of 3.9 mg/dL (1.9-7), and median prostate size was 96 mL (60-140). Pathologic evaluation of patients with iPCa is given in Table 1. Thirty-four patients (61.8%) were diagnosed with GG1, while 21 (38.2%) had GG2 and above. Out of the entire cohort of 777 patients, 2.7% were diagnosed with GG2 and above.

Predictors for iPCa

Comparison between preoperative parameters in the benign versus iPCa groups is given in Table 2. Univariate analysis yielded a significant difference between the benign and iPCa groups in BMI, with a median of 27.4 versus 25.8 respectively ($p = 0.045$), and prostate size, with a median of 100 mL versus 66 respectively ($p < 0.001$). After introducing these variables into multivariate binary regression analysis, only prostate size remained significant. Prostate size was found to be protective against iPCa, with a 2% risk reduction for every 1ml increment in prostate size, which translates into a 13% risk reduction for an increment of 10 mL in prostate size. Other parameters such as functional measurements, PSA, 5-ARI treatment, and age – were not found to predict iPCa in our cohort.

TABLE 2. **Comparison between patients who underwent HoLEP and had incidental prostate cancer versus BPH**

Parameter	BPH	Incidental cancer	Univariate analysis	Multivariate analysis		
			p value	p value	OR	95% CI
Patients, n	722	55				
Age, yrs, median (IQR)	71 (65-77)	72 (66-78)	0.337	0.601	1.014	0.96-1.06
BMI, median (IQR)	27.4 (24.5-30.6)	25.8 (22.7-30.5)	**0.045**	0.228	0.947	0.87-1.03
Medical treatment-5-ARI, n (%)	412 (57.1%)	36 (65.5%)	0.225			
Prostate size, mL, median (IQR)	100 (60-146.75)	66 (45.7-103.5)	**< 0.001**	**0.002**	**0.986**	**0.98-0.99**
PSA (ng/mL), median (IQR)	3.9 (1.8-7.0)	3.8 (2.6-6.6)	0.270	0.589	1.002	0.99-1.01
PSA density (ng/mL^2)	0.045 (0.025-0.075)	0.059 (0.04-0.13)	0.388			
Non-invasive uroflow						
Peak urine flow (mL/s), median (IQR)	6 (3-11)	5 (3-11)	0.656			
Mean urine flow (mL/s), median (IQR)	3 (2-4)	3 (2.6-3.9)	0.925			
Post-void residual volume	150 (58-333)	197 (79-420)	0.353			
Symptoms assessment						
AUA symptoms score, median (IQR)	19 (13-25)	20 (13.5-25.5)	0.705			
QoL, median (IQR)	4 (3-5)	3 (2.5-4)	0.573			
Previous prostate biopsy, n (%)	N/A	10 (18.2%)	N/A			

TABLE 3. **Factors associated with GG2 (Grade Group 2) and above prostate cancer in HoLEP patients**

Parameter	BPH + GG1	≥ GG2	Univariate analysis p value	Multivariate analysis p value	OR	95% CI
Patients, n	756	21				
Age, years, median (IQR)	71 (65-77)	77 (69-81)	**0.013**	**0.004**	**1.18**	**1.05-1.33**
BMI, median (IQR)	27.4 (24.4-30.6)	24.7 (22.6-30.5)	0.147			
Medical treatment - 5-ARI, n (%)	437 (57.8%)	10 (47%)	0.620			
Prostate size, mL, median (IQR)	100 (60-145)	50 (34-77.5)	**< 0.001**	**0.001**	**0.956**	**0.93-0.98**
PSA (ng/mL), median (IQR)	3.8 (1.9-6.9)	4.2 (3.6-12)	0.091			
PSA density (ng/mL^2)	0.046 (0.026-0.074)	0.15 (0.07-0.42)	**< 0 .001**	0.407	1.11	0.86-1.44

For prostates 100 mL and larger iPCa rate was only 4.9%, and for prostates smaller than 100 mL, iPCa rate was 12.6%. We then tried to find factors associated with pathology of GG2-and-above iPCa, and compared these cases with the rest of the cohort (BPH + GG1), Table 3. Older age (OR 1.18) and smaller prostate volume (OR 0.956) were found to predict GG2-and-above iPCa compared to BPH + GG1.

Oncologic outcome

Oncologic outcome is given in Table 4. Out of the 55 patients with iPCa, 10 were lost to follow up or continued follow ups at a hospital closer to their residence and not in our institution. We followed up on 45 patients for a median of 15 months. Thiry-one patients (68.9%) were put on active surveillance protocol, 3 patients chose watchful waiting (6.7%) and 11 patients (24.4%) had an intermediate/high/

TABLE 4. **Oncologic outcome of patients with iPCa (incidental prostate cancer)**

Parameter	Value
Patients, n	45
Follow up time, months, median (IQR)	15 (8.25-38.5)
Intermediate/high risk, metastatic disease - referred to oncologic treatment, n (%)	11 (24.4%)
Watchful waiting, n (%)	3 (6.7%)
Active surveillance, n (%)	31 (68.9%)
Monitor with PSA and DRE only, n (% of AS)	6 (19.4%)
Monitor with prostate biopsies, n (% of AS)	25 (80.6%)
Underwent at least one biopsy, n	19
Pathologic progression on repeat biopsy, n (% of AS)	5 (16.1%)
Pathologic progression of subsequent biopsies, n (% of AS)	1 (3.2%)
Time to progression, months, median (IQR)	16 (9-20)
Treatments received	
Any treatment, n (%)	12 (26.7%)
Hormonal	10
Radiation	5
Chemotherapy	1
Radical prostatectomy	2
Death from prostate cancer, n (%)	3 (4.3%)
Death from other causes, n (%)	3 (4.3%)

risk disease or metastatic disease and were referred to our multidisciplinary oncologic team for oncologic treatment plan. Three patients were referred to oncologic treatment but did not receive it due to death from other causes (2 patients) or due to more urgent treatment (1 patient with duodenal cancer). Six patients that were on active surveillance had progressed pathologically (6/31 19.3% of patients on active surveillance) and received treatment (3 received hormonal + radiation treatment, one received hormonal treatment only, one underwent a radical prostatectomy, and one was treated in a hospital closer to his home). Seven patients were diagnosed with metastatic disease, 6 of them on initial work up (5 with GG5 and 1 with GG3), and one 44 months after initial diagnosis. Three of them died of their disease during follow up.

Among the patients that were put on an AS protocol, 6 (19.4%) chose not to undergo a prostate biopsy and follow up initially with a PSA test and a DRE only.

Discussion

HoLEP is currently a guideline endorsed procedure for prostate enlargement due to LUTS, and is suitable for prostates in all sizes.[10,11] By performing enucleation with the holmium laser, damage to targeted and surrounding prostatic tissue during HoLEP is minimal. Also, by maintaining good visualization of the surgical capsule, the vast majority of the adenomatous tissue can be removed. And so, pathologic evaluation and detection rate of iPCa was shown to be equal or better than TURP and open prostatectomy.[2,3,12] Although the vast majority of prostate cancers do not lie in the transition zone, iPCa rates after HoLEP were reported to be 5.6%-9.5%.[13-15] This rate is surely influenced by PSA screening rate, preoperative PSA testing, and other risk factors such as a family history of prostate cancer, for which early detection may be pursued. In our cohort, we found a 7.1% iPCa detection rate which is similar to other studies,[13-15] and 2.7% with GG2 and above (10 patients with GG2, 3 with GG3, and 8 with GG5). We looked for preoperative predictive factors of iPCa such as age, BMI, PSA, LUTS, and 5-ARI treatment, Tables 3 and 4.

Prostate volume

We found that preoperative prostate volume is associated with iPCa with medians of 66 mL and 100 mL for the iPCa and BPH groups, respectively (p = 0.002). Higher prostate volume was found to protect from prostate cancer with an odds ratio (OR) of 0.986 for 1 mL, which translates into a reduction of the risk by 13.2% for every increment of 10 mL in prostate volume. Among prostates < 100mL, iPCa rate was 12.6% (1 in every 8 men). Smaller prostate volume was even more strongly associated with GG2-and-above iPCa, with a risk increment of 37% for every decrement of 10 mL in volume. Bhojani et al[15] did not find prostate volume to be a predictor for iPCa with a mean size of 85.2 mL among 103 patients in the iPCa group, compared to 101.4 mL among 1169 patients in the benign group. Preoperative PSA was found to be a significant predictor for iPCa. Elkoushy et al[13] found prostate size to be smaller in the iPCa group (85 mL versus 95 mL) but it was not found to be a predictor for iPCa. PSA density was found to be a predictor for iPCa (OR 3.62). These risk factors are dependent on the preoperative approach for PSA local screening policies among urologists and primary care physicians, and a shift in the rate and characteristics of the population with iPCa is expected.

Preoperative PSA

Serum PSA is an established sensitive marker for the presence of prostate cancer and is a main tool for early cancer detection.[6,7] In our cohort, we found no difference in preoperative PSA between the BPH and iPCa groups (median of 3.9 versus 3.8 in the BPH and iPCa groups respectively), and BPH + GG1 and GG2-and-above groups (median of 3.8 versus 4.2, p = 0.091, respectively). Others have found preoperative PSA to be a significant predictor for iPCa.[16] In our practice, we work up every elevation in PSA if we measure it, including prostate biopsy, in accordance with recent guidelines. Therefore, it is not surprising that in the subgroup of iPCa, PSA levels were not significantly higher than the BPH group. 5-ARI treatment, which is known to reduce PSA by 50% after 1 year of treatment[17] and could be a potential bias, was used at a similar proportion in the malignant and benign groups (57.1% versus 65.5%, p = 0.227, in the BPH and iPCa groups respectively). PSA density, which was found to be a predictor for iPCa by others,[13,16] was not found to associated with iPCa in our cohort (0.045 versus 0.056, p = 0.338, for the benign and iPCa groups respectively, and 0.046 versus 0.15, p = 0.407 in the BPH + GG1 versus GG2-and-above groups respectively). Since a higher preoperative PSA density would be most commonly followed by work up for prostate cancer before surgery, this finding is not surprising.

Age

We found age to be associated with GG2-and-above iPCa (median 71 versus 77, p = 0.004, 1.18, in the BPH + GG1 versus GG2-and-above groups respectively). Age

was not found to be a associated with iPCa (median 71 versus 72, p = 0.337, in the benign versus iPCa groups, respectively). Elkoushy et al[13] found older age to be a strong predictor for iPCa (OR 1.27), similar to Bhojani et al,[15] who found age to be a predictor for iPCa as well (OR 1.07). Age is a well-established risk factor for prostate cancer, but PSA screening is not uniformly recommended for men above the age of 70 or with a life expectancy < 15 years.[6,7] Therefore, there are older men who did not underwent PSA screening nor preoperative PSA testing and maybe diagnosed with iPCa. As prostate cancer prevalence rises with age, iPCa at HoLEP is expected to rise as well.

Oncologic outcome

Follow up was available for 45 patients out of 55, at a median of 15 months. Since we are a referral center for HoLEP, we often treat patients that do not live in proximity of our institution and some of them preferred to be followed up on closer to their home. In total, 68.9% of these 45 patients with available follow up, were offered an active surveillance protocol, and 87.1% of them remained eligible for active surveillance during the follow up period. Six patients (19.4%) chose to follow up with a PSA test and a DRE only, while 25 (80.6%) chose to undergo a repeat biopsy and follow up biopsies accordingly. Grade progression occurred in 6 patients under active surveillance (19.4%). Other groups have reported similar rates of eligibility for active surveillance after HoLEP (76%-90%).[13,14] In our cohort, 5 out of the 19 patients that had a repeat biopsy had upgrading (26.3%). When performing HoLEP, we resect only the transitional zone of the prostate, which holds only 5% of cases with prostate cancer.[5] This pathological specimen does not give us any information about the peripheral zone, and in light of the high rate of upgrading in these cases, a biopsy of the peripheral zone should be recommended to all patients. After that repeat biopsy the patient can be risk-stratified and managed accordingly.

In total, 26.7% of patients with iPCa were referred to treatment for their prostate cancer after HoLEP. For the patients that did receive treatment for prostate cancer, HoLEP was not a contraindication for any of the treatments either local or systemic. In total, 1.5% of the entire cohort, required treatment for prostate cancer right after HoLEP. This low rate reflects the safety of HoLEP in light of the current practice of PSA testing.

Study limitations

First, since we report on the incidence and predictive factors, the study is retrospective in nature. Second, because of the relative rarity of iPCa, this group is relatively small. Third, since the procedures and preoperative management were done by a single surgeon, the results may rely on local screening and early prostate cancer detection policies, and may therefore differ from other institutions. Although, this may be looked at as an advantage since there is no variability in these approaches. Moreover, all procedures were performed in a high-volume academic center, where clinical practices reflect the current state-of-art.

Conclusions

Incidental prostate cancer at HoLEP is relatively rare finding, with clinically significant cancer being even rarer. Small preoperative prostate volume was found to be a predictive factor for iPCa, with 1 in every 8 men with a prostate under 100 mL, diagnosed with iPCa. Prostate size and older age were found to predict clinically significant cancer. Our results provide an insight into the current risk and predictive factors to iPCa and can be used to guide surgeons and patients in the preoperative recommendations and informed consent process. □

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