How holmium laser enucleation of the prostate reduces bladder radiation in prostate cancer radiotherapy

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ABSTRACT

Introduction: Off-target delivery of radiotherapy to the bladder and rectum is a major source of morbidity from radiotherapy (RT) for the treatment of prostate cancer (PCa). Holmium laser enucleation of the prostate (HoLEP) has the ability to dramatically reduce prostate volume among men with benign prostatic hyperplasia (BPH). We sought to determine if the prostate volume reduction among men with BPH would result in a reduction in off-target radiotherapy delivery to the bladder and rectum during RT for PCa.
Methods: We performed a retrospective study among men who underwent HoLEP from 2015−2025 at our institution for BPH with a prostate volume >80 mL and who had both incidentally obtained preoperative and postoperative computed tomography (CT) of the pelvis. A hypothetical external beam radiation therapy (EBRT) prostate plan (70 Gy in 28 fractions) was performed on the pre- and post-HoLEP CT. Outcomes included the volume of bladder and rectum exposed to radiation.
Results: A total of 176 men underwent HoLEP with a preoperative CT from 2015−2025, of whom, 11 met study criteria. The median volume of bladder exposed to 70 Grey decreased after HoLEP from 26.1 cc to 15.9 cc (p=0.004); median volumes for rectum exposed to radiation did not change significantly.

Conclusions: HoLEP dramatically reduces off-target radiation dose to the bladder, but not to the rectum during PCa RT. Performing HoLEP prior to PCa RT radiotherapy may provide benefits in limiting bladder-related RT toxicity.

INTRODUCTION

Holmium laser enucleation of the prostate (HoLEP) is a surgical procedure to alleviate lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH). BPH is one of the most common conditions to affect men aged 60 and older and produces LUTS through compression of the prostatic urethra due to age-related enlargement of the prostate.[1] Prostate cancer (PCa) is often co-morbid with BPH or can contribute to LUTS.[2] Unique to HoLEP is the ability to reduce the size of the prostate to degrees much higher than what is achieved by transurethral resection of the prostate (TURP), the most common treatment for BPH.[3] Randomized controlled trials comparing HoLEP to TURP demonstrate superior quantity of tissue resected;[4] additionally when compared to open simple prostatectomy, HoLEP approaches urinary outcomes and longevity of effect at similar rates.[5] Additionally, the size reduction of HoLEP can be measured using conventional computed tomography (CT) of the abdomen and pelvis.[6]

Off target radiotherapy is defined as adjacent organ exposure to radiation and remains the source of substantial morbidity associated with radiotherapy for PCa; off target exposure of the rectum and bladder to radiotherapy directed to the prostate has been associated with colitis, cystitis, including hemorrhagic cystitis.[7] It remains unexplored whether the reduction of size produced by HoLEP can result in reduction in off target radiation delivered to bladder and rectum.[8] We performed a retrospective study in which patients who underwent HoLEP and had a incidentally acquired pre- and post-operative CT of the pelvis underwent a hypothetical external beam radiotherapy (EBRT) plan for PCa, and compared the volume of rectum and bladder exposed to radiotherapy to determine if prostate size reduction by HoLEP was associated with changes in the volume of rectum and bladder exposed to radiation.

METHODS

Patient population and study design

We conducted a retrospective, cross-sectional study of men (ages > 18 years old) who underwent HoLEP between 2015-2025 at our institution for BPH with a prostate volume > 80 mL and who incidentally obtained a pre-operative and post-operative computed tomography (CT) of the pelvis. This study received approval from our institutional research subjects review board. A list of patients who had undergone HoLEP for BPH was extracted from our prospectively maintained HoLEP database;[9] data collected from this dataset included demographic information, prostate volume as measured by CT, specimen weight, pre-operative and post-operative prostate specific antigen (PSA), intra-operative features such as operative time, enucleation time (defined as time during adenoma enucleation), morcellation time, and laser energy administered. Additional data was collected through review of the electronic medical record, pathologic records, and radiology reports. Patients were included if they had an incidentally acquired CT prior to HoLEP and after HoLEP within 2 years of HoLEP; patients were excluded if they had an indwelling hip prosthesis, if the bladder and rectal volume were disproportionate by more than 50% between the pre-operative and post-operative CT, or if the CT slice thickness was >3mm.

Operative technique
HoLEP at our center was performed by three fellowship-trained endourologists as described previously.[3] In brief, we perform an en-bloc enucleation with early apical release using a Moses 2.0 holmium laser (Boston Scientific, Marlborough, MA) or Litho 150 (Quanta, Samarate, Italy) at a standard setting of 2 J and 50 Hz.[10,11] Following enucleation, hemostasis is achieved using laser fulguration at 1 J and 20 Hz using long pulse width or with bipolar transurethral resectoscope at the surgeon’s discretion. Morcellation was performed with a Piranha morcellator (Richard Wolf, Knittlingen, Germany).

Image interpretation and planning
All contouring and RT planning was completed in Eclipse v18.0 (Varian, Palo Alto, CA). Normal tissue structures were contoured using AutoContour v2.6.2 (Radformation, New York, NY) and reviewed by a medical physicist. All clinical target volume (CTV) and subsequent planning target volume (PTV) structures were contoured by radiation oncology residents and reviewed by an attending radiation oncologist. A dose of 70 Gy was prescribed to the PTV in 28 fractions. Beam geometry was set the same for all plans; two full volumetric modulated arc therapy (VMAT) arcs with collimator angles of 30 and 330 degrees on a TrueBeam linear accelerator (Varian) with isocenter fixed to center of PTV structure. Plan objectives were generated using a RapidPlan (Varian) prostate model and no manual adjustments to the objectives or optimization process were made. Final dose calculations were completed using Acuros v15.6 (Varian) with a resolution of 0.2 cm.

Statistical analyses
We calculated median pre-operative and post-operative bladder and rectal volumes exposed to radiotherapy in the hypothetical EBRT plan and compared the paired values using the Wilcoxon matched-pairs signed-rank test.[12] Sensitivity analyses were performed using the relative volume of bladder and rectum exposed to radiation, as a percentage. All tests were 2-sided with a significance level of $p < 0.05$. All statistical analyses were performed in Stata v18.5 (StataCorp, College Station, TX); figures were generated in Stata or Prism v10 (GraphPad, Boston, MA).

RESULTS
During the study period, 176 men underwent HoLEP for BPH; of which only 11 (mean age of surgery, 70.5 ± 6.7 yrs) met the study criteria and were included in the study. Of the 176 men, 23

men had a incidentally obtained pre-operative and post-operative CT of the pelvis. Indications for CT included urinary stone disease, trauma, and emergency department presentation for abdominal pain. Patients were further excluded for >20% difference in rectal and bladder volume between pre- and post-operative CT (n=9), for presence of an indwelling hip prosthetic (n=1), or if the CT slice thickness was >3 mm (n=1). Clinical, demographic and operative features are described in Table 1. The median decrease in PSA from pre-operative (4.2, inter-quartile range (IQR): 3.1-6.6 ng/dL) to post-operative state (0.5, IQR: 0.2-1.2 ng/dL) was 2.9 (1.9-5.2) ng/dL. The median specimen weight extracted during surgery was 80 (IQR: 55-103) g. Median time from pre-operative CT to HoLEP was only 2.8 (IQR: 1.6-4.2) months and median time from HoLEP to post-operative CT was 2.5 (IQR: 0.6-12.7) months. The median decrease in prostate volume as measured by CT was 67.2 (IQR: 52.7-114.8) mL; median pre-operative prostate volume was 123.2 (IQR: 98.5-139.1) mL and median post-operative prostate volume was 43.2 (30.3-80.8) mL. Review of pathological records failed to identify any clinically significant prostate cancer (PCa, defined as grade group 2 or higher). Two patients were diagnosed with grade group 1 PCa, and were managed with active surveillance or watchful waiting. No patients underwent any local prostate cancer therapy. The distribution of prostate volume pre- and post-HoLEP is provided in Supplementary Figure S1.

Table 2 and Figure 1 compare the volume of adjacent organs (e.g., bladder or rectum) and their exposure to radiotherapy (between 40-70 Gy) before and after HoLEP. At the prescription dose of 70 Gy, exposed bladder volume decreased from 26.1 (IQR: 21.3-32.2) cc to 15.9 (IQR: 7-21.1) cc, a median decrease of 13 (IQR: 5.6-15.6) cc (p=0.004; Table 2A, Figure 1A). At 40 Gy, the effect on bladder exposure is even greater, with exposed bladder volume decreasing from 65.4 (IQR: 54.1-78.5) cc to 33.8 (19.7-43.3) cc; a median decrease of 33.4 (IQR: 13.8-44.0) cc (p=0.004). However, exposed rectal volume appears to be similar before and after HoLEP (Table 2B, Figure 1B). Axial and sagittal views of an hypothetical 70 Gy radiotherapy plan are provided in Figure 2, which demonstrates the reduction in exposed bladder volume after HoLEP but similar exposure of the rectum to radiation given prostate pelvic geometry. A sensitivity analysis was performed on the relative volume of exposed prostate/rectum, which found similar results (Supplementary Table S2). We furthermore examined the distribution of exposed bladder and rectum volume pre- and post-operation by prostate volume, and found that following HoLEP the distribution appeared to be left-shifted, implying that smaller adjacent organ volumes were exposed to radiation with smaller prostates (Supplementary Figure S3).

DISCUSSION

In this study, we found that HoLEP produces large size reductions in the prostate size. Furthermore, EBRT planning results in reduced exposure of the bladder to radiation, while the rectum receives a similar dose of radiation regardless of prostate size. We postulate that the prostate-rectum interface is consistent as prostate size varies, which would explain the consistent radiotherapy dose pre- and post-HoLEP. In contrast, the prostate-bladder interface is highly dependent on prostate size, and reduction in prostate size results in dramatic reduction in bladder radiation exposure. Patients with enlarged prostates planning to undergo radiotherapy may benefit from HoLEP for prostate size reduction, in order to reduce exposed bladder volume to radiation.

Bladder and rectal toxicities are well established adverse effects of PCa radiotherapy; previous retrospective studies have demonstrated that bladder volumes < 200 mL have been associated with an increased risk of acute and late-term urinary toxicity, suggesting that volume of bladder exposure to radiation is a factor in the severity of urinary toxicity.[13-16] A retrospective study of 80 patients undergoing prostate radiotherapy found that increased bladder volumes, in particular those greater than 180 mL and even 350 mL, were associated with fewer urinary toxicity in both acute and long term follow up.[14] Unfortunately, the relationship between prostate volume and urinary toxicity was not assessed in those earlier studies of bladder toxicity after radiotherapy. Our study demonstrates that exposed bladder volume is associated with prostate size during radiotherapy planning, and efforts to decrease very enlarged prostates (e.g. > 100 mL) to less than 50 mL can have a beneficial effect on exposed bladder volume and subsequent urinary toxicity.

Few studies have reported on the association between prostate size and associated bladder toxicity. A survey study of 204 patients undergoing prostate radiotherapy attempted to dichotomize patients with small and large prostates and examined the degree of urinary toxicity as a function of quality of life. They found counter-intuitively that patients with larger prostates (median volume 59 mL (IQR: 44-151)) had lower rates of urinary toxicity compared to patients with smaller prostates (median volume 31 mL (IQR: 11-43)); however their median prostate size distribution appears to have considerable overlap, which may explain their results.[17] In contrast, our population had a much larger median prostate volume (123 cc; IQR 99-139) which decreased to 63 cc (IQR: 30-80) following HoLEP; with subsequent reduction in exposed bladder volume.

We found that reducing prostate size reduces the volume of bladder exposed to radiation, but the volume of rectum exposed to radiation was similar across prostate sizes. We hypothesize that this reflects similarity of the prostate-rectum interface across prostate sizes, as well as a highly variable prostate-bladder interface across prostate sizes. A small, prospective trial of 20 patients who underwent radiation planning with margin reduction at the prostate-rectum and prostate-bladder interface found that patients who underwent margin reduction had clinically meaningful reduced urinary toxicity compared to patients who did not undergo margin reduction, suggesting that margin reduction is helpful limiting radiation associated toxicity.[18] We did not directly measure prostate-rectum or prostate-bladder interface in this study, although attention to the prostate-bladder/rectum interface maybe a significant factor in future studies regarding prostate size reduction for radiation.

Previous studies have examined the impact of TURP on urinary toxicity following various forms of radiation.[18-20] A retrospective, propensity-score matched cohort of 50 patients who had undergone TURP were matched with 50 patients who did not undergo TURP, all of whom underwent stereotactic body radiation therapy (SBRT) and found that a history of TURP had increased the rate of GU toxicity. However, patients were not matched on prostate size but rather diabetes mellitus and volume of RT.[18] To our knowledge, this is the first study to examine the impact of HoLEP prior to RT, and to determine whether size reduction had a hypothetical benefit on urinary toxicity. Furthermore, given the increased volume of tissue resected in HoLEP and superior and durable LUTS outcomes of HoLEP,[4,5] we expect that among men with very enlarged prostates, HoLEP prior to RT will reduce urinary toxicity compared to earlier reports on TURP prior to RT. However, it remains unexplored the degree to which HoLEP will reduce urinary toxicity in men with very enlarged prostates, or if men with very enlarged prostates without ongoing LUTS should undergo HoLEP prior to RT. We also acknowledge that long-term PCa outcomes remain unexplored in men who undergo HoLEP, although men who undergo HoLEP with PCa may experience higher intra-operative bleeding.[21] A meta-analysis of a 4 retrospective series found that men who underwent HoLEP with subsequent RT did not have higher rates of urethral stenosis or incontinence compared to men who did not undergo HoLEP.[22]

Limitations of our study include its retrospective and hypothetical nature. Given that CT scans were obtained incidentally, variation in pre-operative and post-operative CT scan bladder and rectal filling can result in variation of our main outcome, exposed organ volume to radiation. Furthermore, we had to exclude the majority of patients within our HoLEP cohort given the requirement for incidentally obtained pre- and post-operative CT of the pelvis. Strengths of our study include its novel implementation of a new surgical technique on RT and the use of formally trained dosimetrist and radiation oncologists to perform the RT planning and measure adjacent organ RT exposure. Lastly, a follow up study is needed to determine whether urinary outcomes are improved with a pre-RT HoLEP compared to men with enlarged prostates receiving RT.

CONCLUSIONS

We found that prostate size reduction by HoLEP resulted in reduced exposure of the bladder to radiation, but not the rectum, in a retrospective, hypothetical cross-sectional study. Men with enlarged prostates who undergo HoLEP prior to RT may experience fewer RT-associated urinary toxicity compared to men who did not undergo HoLEP. This investigation remains exploratory given its hypothetical nature and its findings are relevant for a future, prospective clinical trial or cohort study to investigate the impact of pre-RT HoLEP on downstream urinary toxicity.

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Conflicts of interest: *Dr.Quarrier has been a HoLEP proctor and consultant for Cook Medical,, Coloplast Medical, and Richard Wolf Medical. All other named authors have no conflicts of interest, financial or otherwise, to declare.*

FIGURES AND TABLES

Figure 1. Volume of bladder (A) or rectum (B) exposed to varying (70−40 Gy) levels of radiotherapy prior to HoLEP and after HoLEP. HoLEP: holmium laser enucleation of the prostate.

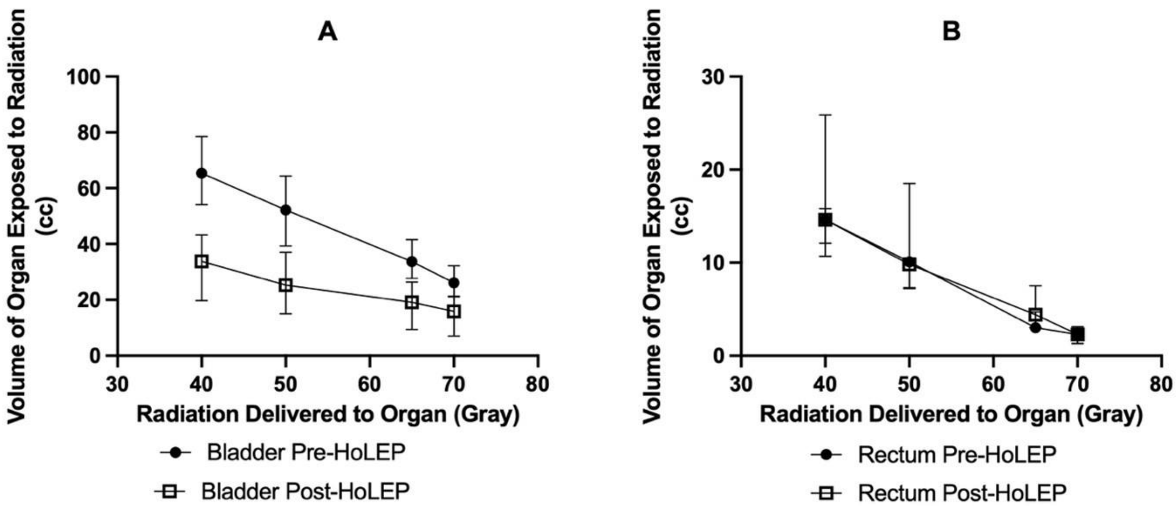

Figure 2. Sagittal (A, C) and axial (B, D) computed tomography (CT) of the pelvis with radiotherapy planned pre-HoLEP (A, B) and post-HoLEP (B, D). Isodose lines are provided with 100.0% (red line) referring to 70 Gy. HoLEP: holmium laser enucleation of the prostate.

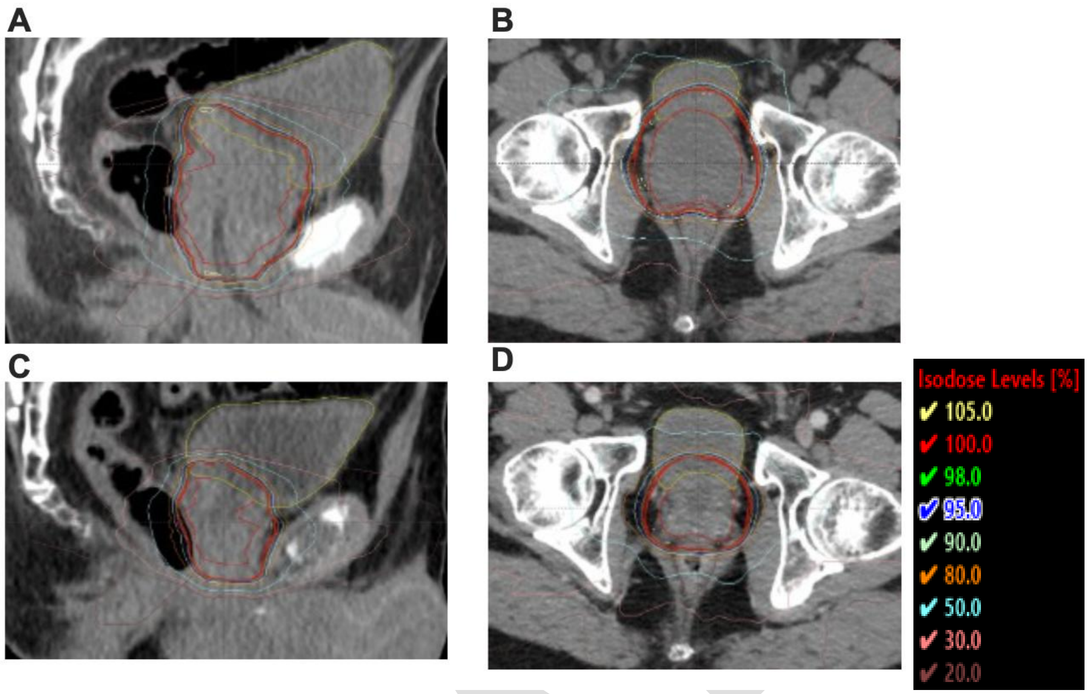

Table 1. Demographic, clinical, and operative features of men who underwent HoLEP with incidental preoperative and postoperative CT scans of the abdomen/pelvis (N=11).	
Characteristic	**Total population N=11**
Age at surgery, mean, SD, yrs	70.5, 6.7
Pre-operative PSA, median (IQR), ng/dL	4.2 (3.1−6.6)
Post-operative PSA, median (IQR), ng/dL	0.5 (0.2−1.2)
Median change in PSA (IQR), ng/dL	2.9 (1.9−5.2)
Median specimen weight (IQR), g	80 (55−103)
Median operative time (IQR), min	116 (87−140)
Median enucleation time (IQR), min	71 (55−92)
Median morcellation time (IQR), min	15 (8−20)
Median laser energy administered (IQR), kJ	235 (175−265)
Preoperative CT slice thickness, n (%), mm	
2.0	7 (63.6)
2.5	2 (18.2)
3.0	2 (18.2)
Postoperative CT slice thickness, n (%), mm	
2.0	7 (63.6)
2.5	2 (18.2)

3.0	2 (18.2)
Median time from pre-op CT to HoLEP (IQR), mo	2.8 (1.6−4.2)
Median time from HoLEP to post-op CT (IQR), mo	2.5 (0.6−12.7)
Median preoperative prostate volume (IQR), mL*	123.2 (98.5−139.1)
Median postoperative prostate volume (IQR), mL*	43.2 (30.3−80.8)
Change in prostate volume, median (IQR), mL**	67.2 (52.7−114.8)

*Prostate volume was measured by CT. **Change in prostate volume was calculated as the difference between the preoperative and postoperative prostate volume. CT: computed tomography; HoLEP: holmium laser enucleation of the prostate; IQR: interquartile range 25th–75th percentile; PSA: prostate-specific antigen; SD: standard deviation,

Table 2. Volume of bladder (A) or rectum (B) exposed to varying (70-40 Gy) levels of radiotherapy prior to HoLEP and after HoLEP							
A	**Preoperative exposed bladder volume (cc)**		**Postoperative exposed bladder volume (cc)**		**Change in exposed bladder volume (cc)***		
Gray	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**p**
70	26.1	21.3−32.2	15.9	7−21.1	13	5.6−15.6	0.004
65	33.7	27.7−41.5	19.1	9.4−26.4	18	7.7−19.8	0.003
50	52.2	39.3−64.4	25.3	15.0−37.0	25.5	8.9−32.1	0.004
40	65.4	54.1−78.5	33.8	19.7−43.3	33.4	13.8−44.0	0.004
B	**Preoperative exposed rectal volume (cc)**		**Postoperative exposed rectal volume (cc)**		**Change in exposed rectal volume (cc)***		
Grey	**Median**	**IQR**	**Median**	**IQR**	**Median**	**IQR**	**p**
70	2.3	1.3−3.1	2.3	1.3−2.7	0.3	-0.7−0.5	0.8
65	5.1	3−7.5	4.4	3.0−4.7	0.4	-0.6−1.5	0.4
50	10.1	7.3−18.5	9.8	7.2−10.5	1	-0.9−3.5	0.1
40	14.6	12.1−25.9	14.6	10.7−15.8	2	-0.3−7.3	0.06

p refers to the Wilcoxon signed-rank test. *Change in bladder or rectal volume was calculated as the difference between the preoperative and postoperative organ volume; a negative sign indicates an increase from the preoperative to the postoperative organ volume. HoLEP: holmium laser enucleation of the prostate; IQR: interquartile range.