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Original Article

Results of Phase 1 study on cytoreductive radical prostatectomy in men with newly diagnosed metastatic prostate cancer

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ABSTRACT

Background: Preclinical and retrospective data suggest that cytoreductive radical prostatectomy may benefit a subset of men who present with metastatic prostate cancer (mPCa). Herein, we report the results of the first planned Phase 1 study on cytoreductive surgery.
Methods: From four institutions, 36 patients consented to the study. However, four did not complete surgery because of rapid disease progression (n = 3) and another because of an intraoperatively discovered pericolonic abscess. Men with newly diagnosed clinical mPCa to lymph nodes or bones were eligible. The primary endpoint was the rate of major perioperative complications (Clavien-Dindo Grade 3 or higher) occurring within 90 days of surgery.
Results: The mean age at surgery was 64.0 years. The 90-day overall complication rate was 31.2% (n = 10), of which two (6.25%) were considered major complications: one acute tubular necrosis requiring temporary dialysis and one death. In men with more than 6 months of follow-up, 67.9% had prostate specific antigen nadir ≤0.2 ng/mL, while one patient experienced a rapid rise in prostate specific antigen and another a widely disseminated disease that resulted in death 5 months after surgery. Altogether, these results demonstrate that cytoreductive radical prostatectomy is safe and surgically feasible in selected patients who present with mPCa . Yet, there may be a small subset of patients in whom surgery may cause a significant harm.
Conclusion: Therefore, cytoreductive surgery in men with mPCa should be limited to clinical trials until robust data are available.

1. Introduction

Prostate cancer is the most common noncutaneous malignancy and the third leading cause of cancer deaths in American men.[1] Since the introduction of prostate specific antigen (PSA)–based screening, most of cancers are diagnosed at a localized stage. However, the incidence of metastatic prostate cancer (mPCa) has risen in recent years, and in part, secondary to the recommendation against PSA-based prostate cancer screening. [2] The treatment of mPCa has evolved over time, as androgen deprivation therapy (ADT) alone via medical or surgical castration no longer represents the optimal first-line treatment in men with extensive metastatic disease. Specifically, results from the CHAARTED and STAMPEDE clinical trials shifted the treatment paradigm to include docetaxel

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chemotherapy in combination with ADT in this setting. [3,4] Despite these advances, the prognosis of mPCa remains dismal.

Primary tumor control improves clinical outcomes when combined with systemic therapy for metastatic disease in several disease processes, such as renal cell carcinoma, colon cancer, and ovarian cancer.[5-7] While surgery or radiation remains the standard of care for localized prostate cancer, the role of cytoreductive radical prostatectomy (CRP) is not clear. The perception that surgery in men with mPCa is futile has historically limited its use, although advances in surgical technique and cancer staging have led to the reconsideration of its role. Results from a few recent retrospective studies indicate a survival benefit for CRP. Specifically, data obtained from the Surveillance Epidemiology and End Results (SEER) database showed the 5-year overall survival to be significantly higher in patients who underwent CRP when compared to those who did not have a local therapy.[8] These findings were reproduced after a similar analysis of the Munich Cancer Registry.[9] Moreover, a retrospectively designed feasibility and case-control study by Heidenreich et al and the more recent prospective series by Poelaert et al demonstrated that CRP was safe in well-selected men, with complication rates comparable to those undergoing radical prostatectomy (RP) for high-risk localized disease.[10,11] In this framework, we report the results of the first planned Phase 1 study to evaluate the safety and feasibility of CRP in men with newly diagnosed mPCa.

2. Materials and Methods

2.1. Patients

Eligible men had biopsy-proven adenocarcinoma of the prostate and evidence of lymph node (LN) or bone metastasis by magnetic resonance imaging/computed tomography, bone scan, or biopsy (cN1, cM1a, or cM1b). The Response Evaluation Criteria in Solid Tumors (RECIST) criteria was applied for all LN metastases. Exclusion criteria were prior local therapy, visceral metastasis, known spinal cord compression, or Eastern Cooperative Oncology Group Performance Scale ≥ 2.

Patients were recruited from four institutions in the United States and Asia. The local institutional review boards at each participating institution approved this study. All patients gave signed informed consent. Identical study protocol and informed consent were used for all participating sites. The study was registered at each of the three participating countries: NCT02458716 (USA), UMIN000021303 (Japan), and KCT0002633 (South Korea).

2.2. Treatment

Men who met all eligibility criteria were offered either robot-assisted RP or conventional open retropubic RP, with the surgical approach determined by a consultation between the surgeon and patient. The minimum number of prostatectomies performed annually by the participating surgeon at each institution was 100. Extended pelvic LN dissection as defined by the National Comprehensive Cancer Network (NCCN) guideline was carried out in all patients.[12] Best systemic therapy was determined by the treating medical oncologists.

2.3. Statistical methods and study design

The primary endpoint was the rate of major perioperative complications occurring within 90 days of CRP, assessed using the Clavien-Dindo (CD) grading system.[13] Major complications were defined as CD Grade 3 or higher. Additional perioperative outcomes assessed were minor complications (CD Grade 1 and 2), estimated blood loss, total operating time, length of hospital stay, and status of continence and potency. Continence was defined as being pad-free after surgery and potency, the ability to complete sexual activity in more than half of the attempts with or without PDE5 inhibitor use. Potency, continence, and voiding symptoms were assessed using validated self-administered questionnaires—Sexual Health Inventory for Men, Expanded Prostate Cancer Index Composite, and the American Urological Association Symptoms Score (AUAss)—administered prior to and after surgery. In men with more than one complication, the event with the highest severity was considered as the final outcome.

The secondary endpoints were time to PSA nadir and time to rising PSA while on ADT. PSA was measured at 1 and 3 months following surgery, then every 3 months thereafter. Biochemical disease progression was defined using the Prostate Cancer Clinical Trials Working Group 2 definition.[14]

We aimed to recruit 50 patients for this Phase 1 study. The reported overall incidence of complications following RP ranges as high as 26.9% and the rate of major complications 6.7%.[15,16] Following the more technically difficult salvage RP for radio-recurrent disease, the highest major complication rate published was 33%.[17] Therefore, we proposed that a rate of major complications less than 25% would be considered acceptable.

To minimize risk to the participating patients, continuous interim analysis was planned after each patient that accrued following the 10th patient. Early termination of the study was to be triggered if the posterior probability of the major complication rate being greater than 25% was greater than 90%. A one-sided binomial test was used to compare the rates to the hypothesized value.

A two-sided paired *t* test was used to compare preoperative and postoperative variables. For all statistical analyses, a P value <0.05 was considered statistically significant. Analyses were performed with Stata statistical software.

3. Results

A total of 36 patients consented to the study between June 2015 and April 2017. Three patients were unable to undergo surgery because of rapid disease progression to spinal cord compression, and one patient's surgery was aborted immediately because of extensive intraabdominal adhesions and a colonic abscess that was discovered intraoperatively. Thirty-two patients completed the study protocol. Although the study was initially approved to accrue 50 patients and early stopping rule was only in place for high complication rates, we found the major complication rate to be very low during the planned continuous monitoring phase of the study after the 10th patient. For example, by patient #23, the major complication rate met our predefined definition of acceptable safety, with a 96% posterior probability that the major complication rate would be less than 25%. Therefore, the study closed early with the consent of all participating institutions. Table 1 describes patient demographics and preoperative data.

The mean age of patients at the time of surgery was 64.0 years. Mean PSA at the time of diagnosis was 75.5 ng/mL (range 5 – 418 ng/mL). Eleven men (35.5%) had a biopsy Gleason score of ≤ 7 (one with Gleason score 6), while 20 men (64.5%) had biopsy Gleason score ≥ 8; in one patient, biopsy Gleason score was not available because he proceeded to surgery based on the diagnosis from LN biopsy. Preoperatively, six men (18.75%) had cT1 disease, while 13 (40.6%) men had each cT2 and cT3 disease. Clinical metastases to pelvic LNs (N1), distant LNs (M1a), and bones (M1b) were reported in 17 (53.1%), 3 (9.4%), and 20 (62.5%) patients, respectively. Before surgery, 12 men (37.5%) had neoadjuvant systemic therapy consisting of bilateral orchiectomy (n = 1), leuprolide (n = 4), leuprolide + bicalutamide (n = 2) or leuprolide + docetaxel

(n = 4), or paclitaxel (n = 1). The mean PSA before surgery was 24.9 ng/mL (range <0.1 to 63.4 ng/mL) in patients who had neoadjuvant therapy; in men who were treatment-naïve before surgery, mean preoperative PSA was 28.3 ng/mL (range 5.1 to 287.0 ng/mL).

Table 2 contains the perioperative data. All surgeries were performed robotically. Pathologic analysis revealed a Gleason score of 7 in 10 patients (31.25%) and ≥8 in 22 patients (68.75%); there were no Gleason score 6 pathologically. Furthermore, 26 patients (81.25%) had ≥ pT3a disease. Pelvic LN dissection confirmed a node-positive disease in 20 patients (62.5%), while positive surgical margins were found in 21 men (65.6%). The mean operative time was 262.3 minutes (range 110–550 min), and the mean estimated blood loss was 267.7 mL (range 50–950 mL).

At the time of this manuscript preparation, all 32 patients were eligible for the primary endpoint analysis with more than 90 days of follow-up (median 214.5 days). Overall, 10 perioperative complications were observed within 90 days following surgery, including two major complications (6.25%) (Table 3). The major complications were acute tubular necrosis of the kidney requiring 3 days of dialysis starting on postoperative Day 2 (CD Grade 4a) and one death (CD Grade 5). The lone mortality occurred in a patient who was discharged from the hospital on postoperative Day 2 in stable condition. He expired on postoperative Day 4 from an unknown cause. Postmortem examination was refused by the family. There were eight minor complications, of which five were CD Grade 1, and three were CD Grade 2.

Surgeons reported a more technically difficult surgery in patients who had neoadjuvant taxol-based chemotherapy. However, this subjective opinion could not be verified because the sample size was only five. Comparison of complication rates between patients who had neoadjuvant treatment against those who did not revealed a higher risk in the neoadjuvant group (29.4 vs 41.7%), but the difference was not statistically significant ($P = 0.2253$) (Fig. 1).

We are not yet able to completely assess the oncologic secondary endpoints. To date, 28 patients (87.5%) have reached at least 6 months of follow-up, and 19 of these men (67.9%) had a PSA nadir of less than or equal to 0.2 ng/mL (Fig. 2). Of these patients, 11 did not receive any neoadjuvant therapy. On the other hand, in one patient, PSA continued to rise after surgery. Specifically, PSA on diagnosis was 84 ng/ml; at 4 months after surgery, the level was 1539 ng/ml on ADT. Additionally, one patient developed rapidly progressing liver metastases despite of PSA nadir of 0.96 ng/ml and died 177 days after surgery.

Finally, CRP was associated with a significant decrease in the reported sexual function of men (Fig. 3A). Mean Sexual Health Inventory for Men score decreased from 11.5 preoperatively to 4.7 following surgery ($P = 0.0018$). In contrast, we found a trend toward improved patient self-reported urinary function as the mean AUAss decreased from 12.0 to 8.6. However, this result was not statistically significant ($P = 0.1172$) (Fig. 3B). As for urinary continence, only 50% of men reported that they did not require any pads for urinary leakage at 6 months. When stratified by neoadjuvant treatment status, the 6-month continence rate was slightly lower in the neoadjuvant group, but results were not statistically significant (47% vs 33.33%, $P = 0.7833$).

Table 1
Preoperative patient characteristics.

Sample size	32
Age (yr), mean (range)	64.0 (50-73)
PSA diagnosis (ng/ml), mean (range)	75.5 (5-418)
Biopsy Gleason score, n (%)	
6	1 (3.2%)
7	10 (32.3%)
8	7 (22.6%)
9	12 (38.7%)
10	1 (3.2%)
Clinical T stage, n (%)	
cT1	6 (18.7%)
cT2	13 (40.6%)
cT3	13 (40.6%)
Clinical N and M stage, n (%)	
N1M0	7 (21.9%)
N1M1a	3 (9.4%)
N1M1b	7 (21.9%)
N0M1a	0 (0%)
N0M1b	15 (46.9%)
Neoadjuvant treatment, n (%)	
Orchiectomy	1
Leuprolide	4
Leuprolide + bicalutamide	2
Leuprolide + docetaxel	4
Leuprolide + paclitaxel	1
Total	12 (37.5%)

PSA, prostate specific antigen.

Table 2
Surgical outcomes.

OR Time (min), mean (range)	262.3 (110-550)
EBL (mL), mean (range)	267.7 (50-950)
Hospital stay (days), mean (range)	3.2 (1-13)
[a)]Pathologic T stage, n (%)	
pT2	6 (18.75%)
pT3a	6 (18.75%)
pT3b	20 (62.5%)
Pathologic N stage, n (%)	
N0	12 (37.5%)
N1	20 (62.5%)
Pathologic Gleason score, n (%)	
7	10 (31.25%)
8	2 (6.25%)
9	19 (59.4%)
10	1 (3.1%)
Positive surgical margin, n (%)	
Positive	21 (65.6%)
Negative	11 (34.4%)
PSA nadir < 0.2 ng/mL	19/28 (67.9%)

OR, operating room; PSA, prostate specific antigen.
[a)] In one patient, biopsy Gleason score not available because surgery was performed based on lymph node biopsy.

4. Discussion

In the present study, we report the outcome of the first planned Phase 1 study on the safety and feasibility of CRP in men who present with an mPCa. Several key findings in our trial will aid in the design of future trials for men with metastatic disease undergoing surgery in the cytoreductive setting.

First, in the hands of experienced surgeons, the overall complication rate appears to be similar between CRP and RP carried out for patients with a localized disease. Second, the early incontinence rate (6 months postoperatively) was relatively high at

Table 3
Complication grades and descriptions.

Clavien-Dindo Grade 1, symptom (n)	Urinary anastomotic leak (4)
	Severe abdominal pain (1)
Clavien-Dindo Grade 2, symptom (n)	Paralytic ileus (1)
	DVT/PE (1)
	Postop bleeding, anemia (1)
Clavien-Dindo Grade 3	0
Clavien-Dindo Grade 4, symptom (n)	ATN of kidney requiring dialysis (1)
Clavien-Dindo Grade 5, symptom (n)	Death (1)
Minor (<3), *n* (%)	8 (25.0%)
Major (>3), *n* (%)	2 (6.25%)
Total complication rates, *n* (%)	10 (31.25%)

DVT, deep vein thrombosis; PE, pulmonary embolism; ATN, acute tubular necrosis.

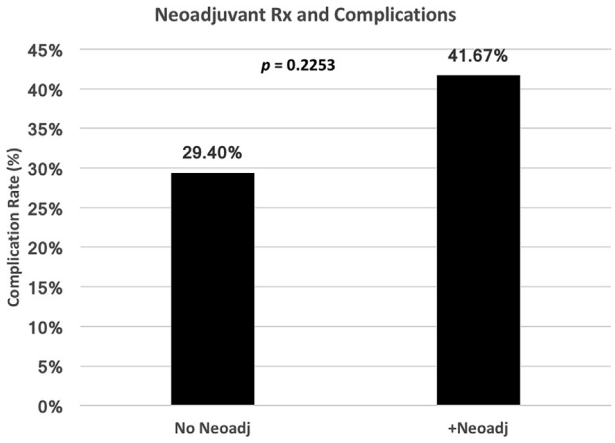

Fig. 1. Complication rates based on neoadjuvant treatment status. There was no statistical difference ($P = 0.2253$).

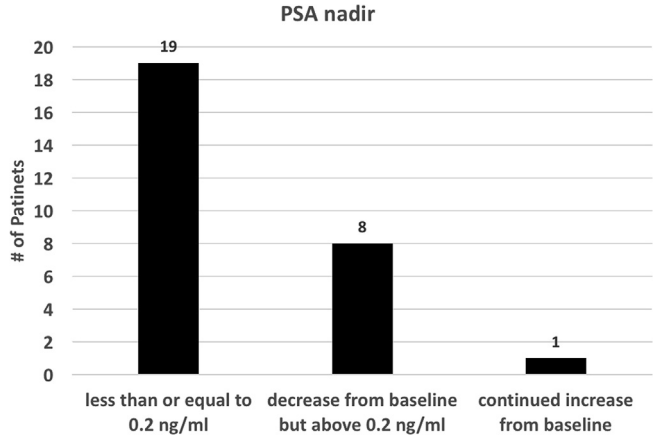

Fig. 2. PSA nadir with more than 6 months of follow-up after surgery. Of 28 patients with more than 6 months of follow-up, 27 demonstrated decrease in PSA. However, in one patient, PSA continued to rise.
PSA, prostate specific antigen.

50%. Third, neoadjuvant treatment, especially taxol-based chemotherapy, may increase the risk of postsurgery complications and incontinence. Fourth, there is a subset of patients whose disease may progress rapidly despite surgery. Fifth, in addition to potential oncologic benefit, CRP may improve quality of life. Collectively, these findings have been incorporated into our recently designed multiinstitution international phase 2/3 study that aims to assess the efficacy of CRP in men with newly diagnosed mPCa (SIMCAP, **S**urgery **in** **M**etastatic **C**arcinoma of **P**rostate, NCT03456843).

Our understanding of the role of cytoreductive surgery for mPCa continues to evolve. Several retrospective studies now suggest that there is an oncologic benefit associated with local tumor control.[8,9] Further support stems from observations of RP in the setting of LN-positive disease.[18] As it is often considered a systemic process, RP was routinely abandoned when positive LNs were found intraoperatively, and patients were instead started on hormonal therapy. However, this treatment practice was challenged after it was demonstrated that completion of RP in the setting of LN-positive disease may produce a survival benefit. For example, Engel et al. evaluated 938 LN-positive patients from the Munich Cancer Registry and found that patients who had a completed RP had an improved 10-year overall survival compared with those in whom surgery was aborted (63.8% vs. 28.2%, respectively).[19] Surgical extirpation of the primary tumor was thus believed advantageous in LN-positive disease, when micrometastatic deposits are thought to exist.

Despite evidence to suggest CRP may be beneficial, an absence of prospective data has limited its implementation into routine clinical practice. Culp et al. identified 8185 men from the Surveillance Epidemiology and End Results database with mPCa between 2004 and 2010 and found that CRP was performed in 245 of these men.[8] The authors found that the 5-year overall survival was significantly higher in those men who had CRP compared to those who had no local therapy (67.4% vs. 22.5%, $P < 0.001$). Interestingly, this difference in survival was most pronounced in patients with visceral metastases who underwent CRP, suggesting that even patients with the poorest prognoses may benefit from surgery. Other retrospective analyses have reported similar oncologic benefits associated with CRP at both the institutional and population-based level.[9,10,20,21] In this study, we found that 67.9% of men with more than 6 months of follow-up had a PSA nadir <0.2 ng/mL after surgery with concomitant systemic therapy. This is notable, as a low PSA nadir during ADT is associated with superior prostate cancer (PCa)-specific outcomes.[22-24] Although it can be argued that this result is due to ADT, it should be noted that the fraction of patients who reached PSA <0.2 ng/ml following chemohormonal therapy with ADT and docetaxel after 6 and 12 months in the landmark CHAARTED study were only 32% and 27.7%, respectively.[3] Therefore, the decline in PSA observed in the present study may be a reflection of the added therapeutic value of combining CRP with ADT. Further clinical trials with extended follow-up are warranted to clarify any oncologic benefit of CRP.

We also found two patients who experienced a dramatic disease progression following surgery. In one patient, PSA rose from 84 to

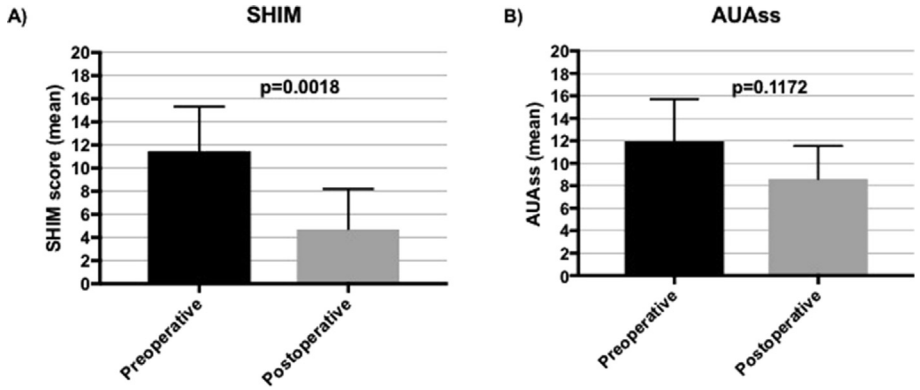

Fig. 3. Plots of pair analysis (preoperative vs. postoperative value) for functional outcome parameters. (A) SHIM (Sexual Health Inventory for Men). (B) AUAss (American Urologic Association symptom score. The results demonstrated a significant decline in sexual function ($P = 0.0018$). As for the voiding symptoms, there was a trend for an improvement after surgery ($P = 0.1172$).

1539 ng/ml over a 4-month period. In the second patient, PSA decreased significantly, but liver metastases developed rapidly, and the patient eventually died from disease in 177 days. Collectively, the outcome of these two patients suggest that CRP may cause a significant harm in some men with mPCa. It will be important in future trials to identify this subgroup of men with mPCa who despite CRP will progress rapidly.

In addition to a lack of prospective data on oncologic outcomes, few reports have analyzed the safety of CRP. With this gap in knowledge, CRP cannot yet be investigated aggressively. To this end, we believe our study is the first planned prospective analysis of the safety and feasibility of CRP. We show that the major complication rate for patients who underwent CRP is 6.25%, which is consistent with previous retrospective series.[10,20,25] Previously, we compared and reported complication rates of CRP compared to RP for localized disease from four institutions. We found longer operative times and slightly higher estimated blood loss (EBL) in patients who underwent CRP but comparable rates of major complications (4.41% vs. 2.17%).[10,25] In that report and in the one by Heidenreich et al., no CD Grade 4 or 5 complications were observed.[10,25] This is in contrast to the present study, in which there were one CD Grade 4a and one CD Grade 5 complications. Notwithstanding, we believe these complication rates are reasonable and advocate prospective efficacy trials.

Reported 12-month urinary continence for all localized PCa were 69-96% across contemporary studies in a recent meta-analysis.[26] In a study by Pompe et al., functional outcomes for 4041 NCCN very high-risk or high-risk patients were retrospectively analyzed.[27] After 12 months, 60.5% of patients did not report wearing any pads for urinary incontinence. Furthermore, 38.4% of those patients were pad-free 3-months after surgery. Our finding that 50% of the men were pad-free after 6 months is encouraging. Because urinary function can be expected to improve with time during the first year after RP,[28] we anticipate that a longer follow-up of our cohort may yield results in urinary symptoms and continence rates to at least approach those of patients following surgery for high-risk localized PCa. In addition, it should be pointed out that the statistical trend for an improved urinary function based on the AUAss suggests that CRP may ameliorate local voiding symptoms. Indeed, local urinary symptoms in patients with a mPCa are likely to be severe. Accordingly, even if the higher rate of urinary incontinence rate after CRP remains true after a longer follow-up period, it is entirely possible that CRP offers a better quality of life by removing urinary obstructive and irritative symptoms. For example, patient #1 in this trial presented with urinary retention requiring suprapubic tube. After CRP, he is tube-free but wears 1 ppd. In this patient, his quality of life is clearly improved after surgery.

Currently, a few randomized clinical trials assessing the impact of local therapy in men with mPCa are ongoing. In the United States, a randomized Phase II trial comparing best systemic therapy or best systemic therapy in addition to either radiation or RP is underway. The primary outcome will be progression-free survival. In Europe, the g-RAMPP study, currently recruiting, is randomizing men with up to five bone metastases to receive ADT plus RP or ADT alone with the goal of completing analysis by 2025. Most recently, we have opened the SIMCAP study that will accrue patients from 27 institutions across five countries (USA, Japan, South Korea, Hong Kong, and Singapore). Over 4 years, 190 patients will be randomized 1:1 between CRP + best standard of care vs best standard of care. Being a Phase 2/3 design, SIMCAP trial will automatically expand to a full Phase 3 study with the overall survival being the primary endpoint if the initial cohort of 190 patients demonstrate the predefined improvement in the primary endpoint of failure-free survival (PSA progression, clinical progression, radiographic progression, or death from prostate cancer).[4] Collectively, these studies will likely add to our growing understanding of the clinical efficacy of CRP.

Our study presents the first planned prospective evidence that CRP is safe and feasible in men with mPCa. However, several limitations warrant mention. First, there was no standardized systemic treatment protocol before and after surgery. Second, different surgeons performed procedures across several institutions. Third, the results may not be generalized to all urologists as the participating surgeons in this study were experienced with more than 100 radical prostatectomies annually. Indeed, the observation that the mean operative time of 262.3 min was much longer than the expected duration in men with localized disease and the relatively low 6-month continence rate confirm that CRP is a technically challenging procedure that should be limited to select expert surgeons at high-volume institutions. Finally, the relatively small sample size and lack of control group typical of Phase 1 study makes any extrapolation of data to the population difficult. Nonetheless, we believe CRP is acceptable to be conducted within the scope of a clinical trial by experienced surgeons.

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Conflicts of interest

None of the authors declare competing financial interests.

CRediT authorship contribution statement

Bertram E. Yuh: Data curation, Formal analysis, Investigation, Writing - original draft. **Young Suk Kwon:** Data curation, Formal analysis, Formal analysis. **Brian M. Shinder:** Data curation, Formal analysis. **Eric A. Singer:** Data curation, Formal analysis. **Thomas L. Jang:** Data curation, Formal analysis. **Sinae Kim:** Data curation, Formal analysis, Formal analysis. **Mark N. Stein:** Data curation, Formal analysis. **Tina Mayer:** Data curation, Formal analysis. **Anna Ferrari:** Data curation, Formal analysis. **Nara Lee:** Data curation, Formal analysis. **Rahul R. Parikh:** Data curation, Formal analysis. **Nora Ruel:** Data curation, Formal analysis. **Wun-Jae Kim:** Data curation, Formal analysis. **Shigeo Horie:** Data curation, Formal analysis, Investigation, Writing - original draft. **Seok-Soo Byun:** Data curation, Formal analysis, Investigation, Writing - original draft. **Thomas E. Ahlering:** Data curation, Formal analysis, Investigation, Writing - original draft. **Isaac Yi Kim:** Data curation, Formal analysis.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2018.10.002.

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