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Radical prostatectomy for patients with high-risk, very-high risk, or radiographic suspicion for metastatic prostate cancer: Perioperative and early oncologic results from the MUSIC statewide collaborative

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Abstract

Objective: High-risk (HR) prostate cancer (CaP) patients are at greatest risk for occult metastases and disease progression. Radical prostatectomy (RP) provides benefit, but remains of unknown oncologic value compared with other options. We investigated outcomes of RP for HR, very-high-risk (VHR), or metastatic CaP.

Methods: Included are 1,635 patients undergoing RP between January 2012 and December 2018 (prior to widespread availability of CaP-specific PET imaging). VHR CaP was defined as having ≥2HR features, >4cores of biopsy Gleason ≥4+4, or primary Gleason pattern 5. Metastatic CaP was defined by radiographic evidence of N1 and/or M1 CaP and grouped as $cN1M_{any}$ and cN0M1. Pre-treatment, perioperative, and early oncologic data were compared. Patient/tumor characteristics were compared according to risk groups using Chi-squared and Wilcoxon rank-sum tests. Kaplan-Meier analysis of cancer progression and multivariable analyses were performed.

Results: Length of stay >2days and readmission following RP was 10.8% and 5.5% for patients with HR or higher CaP. Median time to progression was 3.9 months (IQR:1.6−13.9), and 2-year progression-free probability was 67% for HR, 53% for VHR, 51% for $cN1M_{any}$, and 58% for cN0M1. In multivariable analysis, VHR (hazard ratio:1.70; $P < 0.0001$) and $cN1M_{any}$ (1.96, $P < 0.0001$) were highly significant predictors of progression, while cN0M1 was not ($P = 0.54$), compared with non-metastatic HR CaP. Limitations include selection biases and imprecision of imaging methodologies.

Conclusions: Most patients with HR or higher CaP remain progression-free 2 years after RP, with acceptable perioperative outcomes. Progression-free survival was similar in cN1 and VHR patients, better with non-metastatic HR CaP, and between these for cN0M1 patients indicating the imprecise clinical staging occurring with conventional imaging modalities alone.

Keywords: Biochemical recurrence free survival; High-risk; Metastatic prostate cancer; Prostate cancer; Prostatectomy

1. Introduction

Most deaths from prostate cancer (CaP) are in patients with high-risk (HR) CaP, whether localized, locally advanced, or metastatic at diagnosis [1]. Features associated with recurrence and death from CaP have been well studied, and the risk factors associated with oncologic risk are clear. Many of these patients have micrometastatic disease at the time of diagnosis, with previously occult metastases now often identifiable through advanced PET imaging [2]. Conventional imaging modalities, including CT abdomen/pelvis and MRI pelvis to detect lymph node metastases (N1), and bone scan to detect bony metastases

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(M1) have proven problematic, with relatively low sensitivity and specificity [3−5]. Our recent analysis of MUSIC patients demonstrated sensitivity/specificity for detection of N1 of 8.9%/98.3% for CT and 14.3%/98.8% for MRI, which fall within the previously reported ranges of 5% to 77% for sensitivity and 75% to 100% for specificity [4,6]. The interpretation and response to concerning imaging studies can be complex.

To manage HR CaP, primary multimodal therapy has been proposed for decades, with strategies combining local and systemic therapies in various combinations and sequences. Current guidelines, such as those from NCCN, support radical prostatectomy (RP), external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT), and clinical trials as options for HR CaP [7]. Patients with extraprostatic disease (advanced CaP), including those with lymph node metastases (N1) and/or distant metastases (M1), have the poorest prognosis of all [7−9]. Although local treatment was previously not thought to be indicated for men with advanced CaP, there is now phase 3 data supporting the benefit of pelvic RT in some men with advanced disease [10−13]. NCCN guidelines recommend initial therapy with EBRT and ADT for patients with N1 cancer who have >5 year expected survival or are symptomatic [7]. For patients with low-volume, metastatic, hormone-sensitive CaP (mHSPC), local therapy with EBRT should be considered along with systemic therapy [7,11,14]. While there is no level I evidence from prospective randomized clinical trials, several retrospective cohorts do exist to support RP with pelvic lymph node dissection (PLND) in HR and very high-risk (VHR) patients with CaP. There is also some data to support RP with PLND in HR in N1 and M1 disease, and its role in such patients remains a critical area of investigation, with randomized controlled trials such as SWOG 1802 ongoing at present (NCT03678025) [15,16].

Even in the absence of level I evidence, RP/PLND is sometimes offered for patients with possible or confirmed N1 and M1 disease in clinical practice. As a substantial proportion of HR patients undergoing prostatectomy have occult metastases, it is increasingly relevant to evaluate HR, N1, and M1 patients together in order to understand differences in surgical and oncological outcomes [2]. There have been a number of reports examining the safety of RP and retrospective data surrounding oncological impact for such patients [17,18]. In this study, we retrospectively investigated the perioperative and oncologic outcomes of patients with HR, VHR, or metastatic CaP undergoing RP alone or in combination with other treatments. Using data from the MUSIC registry, we hypothesize that such patients can undergo treatment safely despite the likelihood that they have increased risk of cancer progression. We also sought to better understand the cN0M1 disease state, as conventional imaging can lead to false positive findings particularly when suspicious lesions cannot be (or are not) biopsied.

2. Materials and methods

2.1. Michigan urological surgery improvement collaborative (MUSIC)

MUSIC is a statewide, physician-led quality improvement consortium (https://musicurology.com). Patient data are entered prospectively by trained medical record data abstractors at respective sites throughout the state of Michigan. Participating practices represent a broad spectrum of academic and community practices, representing approximately 90% of the urologists in Michigan. Each MUSIC practice obtained an exemption or approval for collaborative participation from a local institutional review board.

2.2. Study population

Between January 1, 2012 and December 31, 2018, >23,000 patients with CaP had information available for classification according to D'Amico risk group and TNM staging. Gleason scores and/or ISUP grade groups were assigned protocol at each participating site. During this timeframe, very few patients underwent CaP-specific PET imaging; clinical staging was performed using a combination of CT abdomen/pelvis, bone scan, and MRI pelvis [4]. Patients were excluded if they were surveilled without definitive therapy for CaP, underwent any definitive treatment for CaP other than RP (e.g., EBRT, ADT, chemotherapy), or received neo-adjuvant therapy prior to RP. Included are 8,476 patients that underwent RP, of which >95% were robot-assisted RP. Pre-operative and all post-operative PSA levels were obtained for all patients; those without a recorded PSA >30 days after surgery were excluded (n = 91). We examined PSA≥0.1 at the initial post-operative determination as evidence of persistence of PC after surgery. Biochemical recurrence (BCR) was defined as any PSA≥0.2 more than 30 days after surgery [7,14]. Receipt of additional therapies for CaP, including EBRT, ADT, chemotherapy, and/or other therapies was recorded within the MUSIC registry, and is an outcome of the present analysis. A composite endpoint of cancer progression, defined as PSA≥0.2 at least 30 days after surgery or initiation of salvage therapy (secondary treatment for PSA ≥0.1 ng/ml) was used for Kaplan-Meier analyses.

2.3. Exposure variables

Patients were classified according to NCCN risk groups as low, intermediate, high, and very-high (Appendix). Patients were also classified according to TNM classification as non-metastatic ($T_{any}N0M0$), regional metastatic disease with or without distant metastases ($T_{any}N1M_{any}$), and distant metastatic only ($T_{any}N0M1$). HR CaP patients without preoperative imaging (bone scan, abdominopelvic CT, or MRI) were excluded (n = 202).

2.4. Outcomes

The primary outcome was cancer progression, censored at the earlier of the date when of the first PSA≥0.2 (more than 30 days after RP) or secondary treatment for PSA ≥0.1 ng/ml. Secondary outcomes consisted of pathologic endpoints, including the presence/absence of extraprostatic extension (EPE), seminal vesical invasion (SVI), positive lymph nodes (N1) and positive surgical margins (PSM); and perioperative events, including those previously defined in MUSIC as "notable observable and trackable events after surgery" (NOTES) [19].

2.5. Statistical analysis

Clinical characteristics of patients were compared by NCCN risk groups using the Chi-squared test for categorical variables and Wilcoxon rank-sum test for continuous measures. Times to progression following treatment were illustrated with Kaplan-Meier curves. Multivariable logistic (for adverse pathology) and Cox (for time to progression) regression models were used to compare the difference in outcomes between the 3 risk groups (high, very high, metastatic), with Bonferroni correction used to adjust for multiple comparisons. Covariates accounted for during the analysis included age, race, preoperative PSA, clinical T stage, and Charlson comorbidity index. All the analyses were done using SAS 9.4 (SAS Institute), and statistical significance was set at 0.05.

3. Results

The final cohort consisted of 8,476 men who underwent RP in a MUSIC practice between January 2012 and December 2018, and the median length of follow-up after RP was 29.7 months (IQR: 16, 48). Of the 8,476 patients included in this analysis, 1,837 (21.7%) patients were classified as high-risk, very high-risk, or nodal/distant metastatic. Of these, 757 (8.9%) were localized HR, 925 (10.9%) were localized VHR, and 155 (1.8%) were N1 and/or M1. The median age at diagnosis was 63 years (IQR 58-68) and the median PSA was 5.9 ng/ml (IQR: 4.5, 8.4). Patient characteristics categorized by CaP risk group are given in Table 1.

After excluding the HR or higher CaP patients lacking pre-operative imaging, these patients (n = 1,635) were grouped into 4 categories: high-risk without metastasis (HR), very-high-risk without metastasis (VHR), CaP with clinical suspicion for LN metastases with or without suspicion for distant metastases ($N1M_{any}$), and CaP with clinical suspicion for metastatic disease (N0M1). Overall, 79.6% of patients had PSA ≤20, 95.0% had clinical stage T1-T2 disease, and 52.2% had grade group 4 PC. The distribution of PSA, cTNM stage, and grade groups for patients falling into these 4 categories is indicated in Supplementary Table 1. Of note, the vast majority of VHR patients had >4 cores with GG4-5 cancer (97.1%); only 12.1% had PSA>20, 11.8% had primary pattern 5 PC, and 4.5% had clinical T3-T4 PC. The groups of patients with HRN0M0 and N0M1 disease had similar cT stages and grade groups, with fewer patients having PSA>20 in the N0M1 group (7.4% vs. 32.3%). Perioperative and pathologic outcomes of RP according to these 4 CaP risk groups are reported in Table 2.

3.1. Perioperative outcomes

The type of operation performed for HR, VHR, N0M1, and $N1M_{any}$ subgroups was similar. There were no significant differences in rates of PLND or nerve-sparing across the 4 cohorts (Table 2). PLND was performed in nearly all patients (96.8%), and bilateral nerve-sparing was recorded in a minority of cases, including 42.0% of HR patients, 38.8% of VHR patients, 48.8% of $N1M_{any}$ patients, and 46.4% of N0M1 patients. There were also no differences in length-of-stay (LOS) across the 4 groups. Only 10.8% of the patients had an extended LOS (>2 days), and readmission within 30 days occurred in only 5.5% of these patients overall. Evaluation of NOTES revealed no statistically significant difference across the 4 groups for readmission, rectal injury, extended LOS, excessive blood loss, extended drain placement (beyond hospital discharge), extended catheter placement (more than 15 days), and catheter replacement.

3.2. Pathologic outcomes

Variation in pathologic outcomes was observed across the CaP risk groups, with HR patients having the most favorable outcomes of the 4 groups, and the poorest outcomes occurring in the VHR and $N1M_{any}$ cohorts (Table 2). The rates of EPE were 48.3% in HR, 66.4% in VHR, 62.8% in $N1M_{any}$, and 56.5% in N0M1 ($P < 0.001$); rates of SVI were 19.1% in HR, 34.4% in VHR, 41.9% in $N1M_{any}$, and 24.6% in N0M1 ($P < 0.001$). Pathologic evidence of N1 disease was present in 6.9% in HR, 14.3% in VHR, 29.1% in $N1M_{any}$, and 10.1% in N0M1 ($P < 0.001$). Of note, 70.9% of patients with clinical N1 disease identified in the true pelvis on CT and/or MRI were pN0 at RP/PLND.

3.3. Oncologic outcomes

Table 3 details post-RP oncologic outcomes. An undetectable initial PSA (<0.1) was obtained in >67% of patients overall, including 74.2% of HR, 63.3% of VHR, and 48.8% of $N1M_{any}$ patients. Interestingly, 73.5% of N0M1 patients also had an initial PSA<0.1, including 90% of those with low- or intermediate-risk disease, 68% of those with HR, and 64% of those with VHR disease. Differences were also seen in the use of adjuvant and salvage treatments across the 4 CaP risk groups, with most patients receiving no further treatment after surgery. The rates of adjuvant treatment, particularly ADT, were highest in the $N1M_{any}$ group (18.7%).

Table 1
Characteristics of CaP patients undergoing RP, grouped according to risk group.

Variable	All RP	All high risk	High risk without mets	Very high risk without mets	All metastatic (N1 and/or M1)	*P* value
No. patients	8,476	1,837	757	925	155	
Age, y	63.0 (58.0−68.0)	65.0 (60.0−69.0)	65.0 (60.0−69.0)	65.0 (60.0−69.0)	63.0 (59.0−68.0)	0.155
Race						
White	6353 (75.0%)	1366 (74.4%)	572 (75.6%)	693 (74.9%)	101 (65.2%)	0.044
African-American	1114 (13.1%)	250 (13.6%)	89 (11.8%)	128 (13.8%)	33 (21.3%)	
Other	202 (2.4%)	47 (2.6%)	19 (2.5%)	25 (2.7%)	3 (1.9%)	
Unknown	807 (9.5%)	174 (9.5%)	77 (10.2%)	79 (8.5%)	18 (11.6%)	
BMI, units	28.7 (25.8−31.9)	29.1 (26.1−32.4)	28.7 (25.8−32.1)	29.3 (26.3−32.7)	29.2 (26.8−32.6)	0.021
Charlson comorbidity index						
CCI = 0	6,264 (73.9%)	1,288 (70.1%)	527 (69.6%)	653 (70.6%)	108 (69.7%)	0.990
CCI = 1	1,383 (16.3%)	349 (19.0%)	146 (19.3%)	174 (18.8%)	29 (18.7%)	
CCI ≥ 2	828 (9.8%)	200 (10.9%)	84 (11.1%)	98 (10.6%)	18 (11.6%)	
Prostate volume, cm^3	35.0 (26.0−46.6)	35.2 (26.9−47.0)	36.1 (27.0−49.3)	35.0 (26.1−46.0)	35.0 (27.7−48.3)	0.170
Clinical T stage						
T1	6,084 (72.2%)	1,043 (57.1%)	471 (62.5%)	482 (52.3%)	90 (58.4%)	<0.001
T2	2,231 (26.5%)	668 (36.5%)	217 (28.8%)	397 (43.1%)	54 (35.1%)	
T3/4	117 (1.4%)	117 (6.4%)	65 (8.6%)	42 (4.6%)	10 (6.5%)	
PSA, ng/ml	5.9 (4.5−8.3)	7.7 (5.3−15.0)	8.0 (5.2−21.9)	7.5 (5.3−12.3)	9.0 (5.9−15.2)	0.003
PSA group						
< 10	6,757 (82.6%)	1,104 (62.4%)	428 (58.3%)	589 (66.4%)	87 (59.2%)	<0.001
10 to 20	1,070 (13.1%)	310 (17.5%)	77 (10.5%)	196 (22.1%)	37 (25.2%)	
20 to 50	306 (3.7%)	306 (17.3%)	206 (28.1%)	81 (9.1%)	19 (12.9%)	
> 50	48 (0.6%)	48 (2.7%)	23 (3.1%)	21 (2.4%)	4 (2.7%)	
Biopsy grade group						
GG1	1,530 (18.1%)	43 (2.3%)	34 (4.5%)		9 (5.8%)	<0.001
GG2	3,599 (42.5%)	134 (7.3%)	106 (14.0%)		28 (18.2%)	
GG3	1,824 (21.5%)	139 (7.6%)	118 (15.6%)		21 (13.6%)	
GG4	957 (11.3%)	957 (52.2%)	378 (50.1%)	518 (56.0%)	61 (39.6%)	
GG5	561 (6.6%)	561 (30.6%)	119 (15.8%)	407 (44.0%)	35 (22.7%)	
Preoperative imaging						
BS with/without CT/MRI	2,214 (26.1%)	1,476 (80.3%)	575 (76.0%)	777 (84.0%)	124 (80.0%)	<0.001
CT/MRI only	1,149 (13.6%)	159 (8.7%)	65 (8.6%)	63 (6.8%)	31 (20.0%)	
No imaging	5,113 (60.3%)	202 (11.0%)	117 (15.5%)	85 (9.2%)		

RP = radical prostatectomy; BMI = body mass index; PSA = prostate specific antigen; GG = grade group; BS = bone scan; CT = computed tomography of pelvis +/- abdomen; MRI = magnetic resonance imaging of pelvis +/- abdomen. *P* values are for the 3-way comparisons of the HR, VHR, and metastatic CaP groups according to the Chi-squared test.

Adjuvant treatments of any type were only given to 20.6% of HR, 28.2% of VHR, 30.2% of $N1M_{any}$ patients, and 21.7% of N0M1 ($P = 0.002$).

Cancer progression occurred in 718 patients overall, at a median time of 3.9 months (IQR: 1.6−13.9). For patients not experiencing this endpoint, median follow-up is 24.6 months (IQR: 13.7−42.0). Cancer progression was detected in 223 HR, 425 VHR, 43 $N1M_{any}$, and 27 N0M1 patients, a pattern consistent with the observed pathologic outcomes reported in Table 2. Salvage treatments of any type were given to 15.6% of HR, 25.7% of VHR, 22.1% of $N1M_{any}$, and 13.0% of N0M1 patients ($P = 0.001$). Kaplan-Meier estimates indicate that the 2-year progression-free probabilities are 67% for HR, 53% for VHR, 51% for $N1M_{any}$, and 58% for N0M1 (Fig. 1).

Evaluation of patients with distant metastases (M1) who underwent RP did not reveal incrementally worse oncologic outcomes compared to HR, VHR, and N1M0 patients (Supplemental Fig. 1). The likelihood of recurrence for the N1M1 group was more similar to the N1M0 group than the N0M1 group, supporting grouping these together as $N1M_{any}$. Recurrence in the N0M1 group was between the HR and VHR groups, and better than in the $N1M_{any}$ group (Fig. 1). In addition, differences in survival were seen when evaluating patients with and without metastases according to their CaP risk group (Supplemental Fig. 2). Two-year progression-free probabilities are 76% for LR/IR with metastases, 67% for HR without metastases, 53% for VHR without metastases, and 45% for HR/VHR with metastases.

3.4. Predictors of cancer progression after RP

Several factors displayed a statistically- significant association with cancer progression among HR or higher CaP

Table 2
Perioperative and pathologic outcomes of RP for high-risk CaP.

Variable	All high risk	High risk without mets	Very high risk without mets	$N1M_{any}$	N0M1	*P* value
No. patients	1635	640	840	86	69	
Nerve sparing						
Bilateral	669 (40.9%)	269 (42.0%)	326 (38.8%)	42 (48.8%)	32 (46.4%)	0.245
Unilateral	292 (17.9%)	126 (19.7%)	143 (17.0%)	12 (14.0%)	11 (15.9%)	
None	541 (33.1%)	189 (29.5%)	303 (36.1%)	27 (31.4%)	22 (31.9%)	
N/A	133 (8.1%)	56 (8.8%)	68 (8.1%)	5 (5.8%)	4 (5.8%)	
PLND	1568 (96.8%)	609 (95.9%)	816 (97.8%)	78 (95.1%)	65 (94.2%)	0.079
Pathological N1	196 (12.0%)	44 (6.9%)	120 (14.3%)	25 (29.1%)	7 (10.1%)	<0.001
Surgical grade group						
GG1	22 (1.4%)	13 (2.0%)	5 (0.6%)	2 (2.4%)	2 (2.9%)	<0.001
GG2	275 (17.0%)	147 (23.1%)	100 (12.1%)	16 (18.8%)	12 (17.6%)	
GG3	520 (32.2%)	220 (34.6%)	253 (30.5%)	23 (27.1%)	24 (35.3%)	
GG4	270 (16.7%)	120 (18.9%)	126 (15.2%)	10 (11.8%)	14 (20.6%)	
GG5	530 (32.8%)	135 (21.3%)	345 (41.6%)	34 (40.0%)	16 (23.5%)	
EPE	960 (58.7%)	309 (48.3%)	558 (66.4%)	54 (62.8%)	39 (56.5%)	<0.001
SVI	464 (28.4%)	122 (19.1%)	289 (34.4%)	36 (41.9%)	17 (24.6%)	<0.001
Positive margin	711 (43.5%)	250 (39.1%)	388 (46.2%)	45 (52.3%)	28 (40.6%)	0.014
NOTES						
Readmission within 30 d	81 (5.5%)	31 (5.5%)	42 (5.5%)	5 (6.2%)	3 (4.8%)	0.98
Rectal injury	2 (0.1%)	0 (0.0%)	2 (0.3%)	0 (0.0%)	0 (0.0%)	0.60
Length of hospital stay >2 d	152 (10.4%)	57 (10.1%)	80 (10.6%)	9 (11.1%)	6 (9.5%)	0.98
Excessive blood loss	62 (4.5%)	20 (3.8%)	34 (4.8%)	3 (4.1%)	5 (8.5%)	0.38
Drain remains at hospital discharge	69 (4.7%)	22 (3.9%)	42 (5.5%)	3 (3.7%)	2 (3.2%)	0.55
Catheter duration >15 d	88 (6.0%)	38 (6.8%)	42 (5.6%)	7 (8.6%)	1 (1.6%)	0.25
Catheter replacement	42 (3.1%)	13 (2.5%)	24 (3.4%)	4 (5.1%)	1 (1.7%)	0.52

LOS = length of stay; PLND = pelvic lymph node dissection; GG = grade group; EPE = extraprostatic extension; SVI = seminal vesicle invasion; PSA = prostate specific antigen; NOTES = Notable Observable and Trackable Events after Surgery. *P* values are for the 4-way comparisons of the HR, VHR, N1Many and N0M1 subgroups according to the Chi-squared test or Fisher's exact test.

Table 3
Oncologic outcomes after RP for HR CaP.

Variable	All high risk	High risk without mets	Very high risk without mets	$N1M_{any}$	N0M1	*P* value[a]
No. patients	1,635	640	840	86	69	
Initial PSA post-RP						
< 0.1	1,090 (67.2%)	471 (74.2%)	527 (63.3%)	42 (48.8%)	50 (73.5%)	<0.001
≥ 0.1	531 (32.8%)	164 (25.8%)	305 (36.7%)	44 (51.2%)	18 (26.5%)	
Cancer Progression[b]						
No	917 (56.1%)	417 (65.2%)	415 (49.4%)	43 (50.0%)	42 (60.9%)	<0.001
Yes	718 (43.9%)	223 (34.8%)	425 (50.6%)	43 (50.0%)	27 (39.1%)	
Adjuvant treatment						
None	1,225 (74.9%)	508 (79.4%)	603 (71.8%)	60 (69.8%)	54 (78.3%)	0.002
RT only	244 (14.9%)	92 (14.4%)	135 (16.1%)	9 (10.5%)	8 (11.6%)	
ADT only	128 (7.8%)	32 (5.0%)	80 (9.5%)	12 (14.0%)	4 (5.8%)	
Both	33 (2.0%)	7 (1.1%)	19 (2.3%)	4 (4.7%)	3 (4.3%)	
Other treatment	5 (0.3%)	1 (0.2%)	3 (0.4%)	1 (1.2%)	0 (0%)	
Salvage treatment						
None	1,291 (79.0%)	540 (84.4%)	624 (74.3%)	67 (77.9%)	60 (87.0%)	<0.001
RT only	222 (13.6%)	74 (11.6%)	128 (15.2%)	13 (15.1%)	7 (10.1%)	
ADT only	92 (5.6%)	18 (2.8%)	69 (8.2%)	4 (4.7%)	1 (1.4%)	
Both	24 (1.5%)	7 (1.1%)	14 (1.7%)	2 (2.3%)	1 (1.4%)	
Other treatment	6 (0.4%)	1 (0.2%)	5 (0.6%)	0 (0%)	0 (0%)	

RP = radical prostatectomy; RT = radiation therapy; ADT = androgen deprivation therapy.
[a] *P* values are for the 4-way comparisons of the HR, VHR, N1Many, and N0M1 groups according to the Chi-squared test or Fisher's exact test.
[b] Cancer progression was defined as any PSA≥0.2 more than 30 days after surgery (BCR) or any secondary treatment for a post-operative PSA ≥0.1 ng/ml.

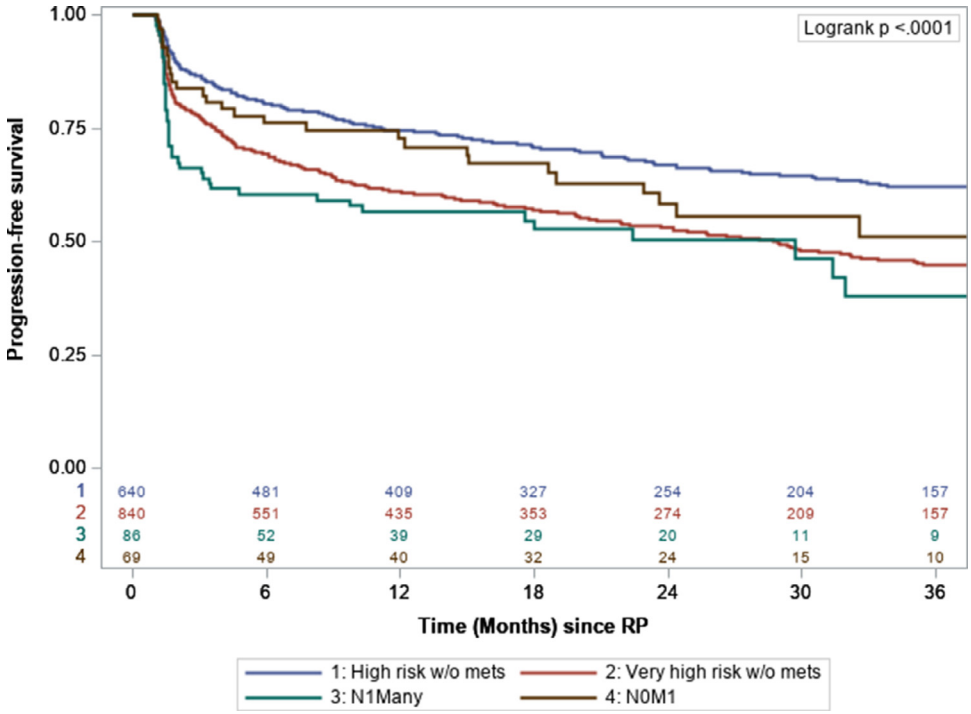

Fig. 1. Kaplan-Meier curves depicting the time to cancer progression after RP for patients in the HR, VHR, $N1M_{any}$, and N0M1 groups. Progression-free probability was significantly different between the 4 groups ($P < 0.0001$). Estimates of progression-free survival at 2 years are 67, 53%, 51%, and 58% in these 4 groups, respectively.

patients in multivariable analysis (Table 4). The VHR and $N1M_{any}$ risk groups were strongly associated with BCR when compared to HR with hazard ratios of 1.70 (95% confidence interval: 1.44,2.01) for VHR ($P < 0.0001$) and 1.96 (95% CI: 1.50,2.74) for $N1M_{any}$ ($P < 0.0001$). There was no statistical difference observed between N0M1 and localized HR (hazard ratio: 1.14 (95% CI: 0.75,1.72), $P = 0.544$). African American race was an additional significant predictor of BCR ($P < 0.0001$), while age and comorbidity were not, in this analysis controlled for surgeons through random effects.

Table 4
Multivariable analysis on factors associated with cancer progression.

	HR	95% CI	P
Group (ref: HR without mets)			
VHR without mets	1.70	(1.44, 2.01)	<0.0001
N_1M_{any}	1.96	(1.40, 2.74)	<0.0001
N_0M_1	1.14	(0.75, 1.72)	0.544
Race (ref: White)			
African-American	1.54	(1.25, 1.89)	<0.0001
Other	0.99	(0.61, 1.59)	0.957
Unknown	0.80	(0.59, 1.09)	0.154
Comorbidity (ref: CCI=0)			
CCI=1	1.03	(0.85, 1.25)	0.727
CCI≥2	1.18	(0.93, 1.49)	0.176
Age	0.99	(0.98, 1.00)	0.243
BMI	0.99	(0.98, 1.01)	0.220

Note: also controlled for surgeon through random effects.

We next examined the individual risk factors contributing to the HR grouping (PSA >20, cT3-T4, GG4-5, GG4-5 in >4 cores, Primary Gleason 5, N1/M1) (Supplementary Table 1). The majority of patients had >1 risk factor, with 40.1%, 43.9%, 13.9%, and 2.1% having 1, 2, 3, or 4 to 5 of these factors, respectively. The number of risk factors was a strong predictor of progression-free survival (Supplementary Fig. 3). Two-year progression-free probabilities are 69% for 1, 56% for 2, 42% for 3, and 31% for 4 to 5 risk factors.

4. Discussion

The use of RP in clinically node positive and metastatic CaP remains controversial and without level I evidence. Several studies have reported that VHR patients undergoing RP are at significantly greater risk of adverse oncologic outcomes compared to HR patients, and this is now reflected in the NCCN guidelines for CaP [7,10-12,14,15]. These outcomes include increased rates of nodal metastases, positive surgical margins, and CaP-specify mortality [7,10,11,14,15]. Other studies have shown that patients with higher-grade CaP (Gleason Score 9−10) undergoing RP tend to develop metastases sooner and have lower overall survival [20,21]. Although use of PSMA-PET is becoming more widespread and being performed earlier in the clinical evaluation of HR and advanced CaP patients, it has not been routinely available to U.S. urologists. Clinical-decision making, with or without PSMA-PET imaging, can

be challenging in patients that may (or may not) have metastatic CaP based on upfront diagnostic imaging.

Several retrospective studies have demonstrated favorable outcomes and better overall survival when using local treatment for metastatic CaP [11,13,15-18,21]. Multiple studies have also emphasized the possible benefit of RP as part of a multimodal approach for control and treatment of metastatic CaP [15−18]. The current literature appears to indicate that patients with HR and VHR CaP are candidates to undergo either RP/PLND or RT and ADT [10,11,13-17,21-23]. Therefore, it is important to continue investigating and provide the best available evidence regarding local treatment for HR and higher-risk CaP. In this study, we were able to explore this topic further.

One of the findings in our study is that there are differences in the pathologic and oncologic outcomes after RP across 4 subgroups of CaP patients. For example, rates of EPE (48.3% in HR vs 66.4% in VHR vs 62.8% in $N1M_{any}$ vs 56.5% in N0M1) and cancer progression (34.8% vs 50.6% vs 50.0% vs 39.1%) were greater in VHR N0M0 and metastatic CaP patients, than in HR N0M0 patients.

Clinical features of patients with clinical N1 disease ($N1M_{any}$) were very similar to those of VHR patients (Table 2). Pathologic outcomes were also similar for the $N1M_{any}$ and VHR cohorts in terms of surgical GG5 disease (40.0% vs. 41.6%) and EPE (62.8% vs. 66.4%), but with higher rates of SVI (41.9% vs. 34.4%) and pathologic N1 disease (29.1% vs. 14.3%) with $N1M_{any}$. Additionally, rates of cancer progression were similar in these 2 groups of patients, with rates of progression estimated to be 51.0% with $N1M_{any}$ and 53.0% with VHR at 2 years using Kaplan-Meier methodology. It is likely that occult metastatic disease went undetected in many patients that underwent only conventional imaging for staging. In addition, many patients with clinical suspicion of N1 disease were not actually found to have pathologic N1 disease at RP, as we have demonstrated previously [4]. Clinical judgment should be used when cN1 disease is suspected based on conventional imaging, and confirmation with PSMA-PET prior to surgery, and extended PLND that includes the suspicious nodal basins, are recommended strongly in this situation. Adjuvant systemic therapy (ADT +/- chemotherapy) should be offered to those with pN1 disease; of note, the observed use of adjuvant and salvage treatments across MUSIC were relatively low in these patients, particularly after considering the observed rates of cancer progression. This is an ongoing QI initiative within our collaborative at present; and we have not yet evaluated the impact of adjuvant treatments in HR patients.

Despite HR or higher CaP patients having worse survival probabilities overall when compared to low-risk and intermediate-risk CaP patients, a high proportion of patients in the 4 evaluated subgroups had an undetectable PSA after surgery: 74.2% of HR, 63.3% of VHR, 48.8% of $N1M_{any}$, and 73.5% of N0M1 (Table 3). Surgery therefore appears to be a reasonable choice for selected patients after a thorough shared-decision making session. Of note, the N0M1 patients experienced more favorable outcomes than would be expected for a population of patients with metastatic disease. The fact that N0M1 patients did better than N1M0 patients indicates that many of these patients did not actually have metastatic cancer. False positives on conventional imaging are more likely to occur with conventional imaging than PSMA PET imaging and can lead to inappropriate clinical management, whether by over-treatment or by under-treatment [2,4]. These findings bring into question the quality of the imaging modalities used at diagnosis, adding further support for CaP-specific PET imaging in high-risk patients at the time of CaP diagnosis [24]. Given its superior sensitivity and specificity, PET imaging enables more accurate classification of the cancer as localized vs. nodal and/or metastatic [2,25-28]. Additional clinical trials incorporating PSMA PET in high-risk CaP are needed to help guide optimal initial management of these patients. When such imaging cannot be obtained, these data suggest that select patients with clinical suspicion of N0M1 may be considered for RP, as many may not truly have metastatic disease. When cM1 disease is suspected, one key takeaway from these findings and our previous work is that biopsy to establish a diagnosis of metastatic CaP should be strongly considered [4].

Similarly, pelvic lymph node dissection or biopsy is advised when cN1 disease is present on conventional imaging or PSMA-PET. Despite early data with PSMA-based imaging suggesting comparatively high sensitivity, such as a 2020 meta-analysis reporting a weighted sensitivity of 59% (range: 23%−100%) [29], more recent studies suggest a sensitivity of about 40%. Four recent studies comparing 68Ga-PSMA-11 with pelvic nodal dissection reported similar sensitivities of 0.42 ($n = 97$), 0.41 ($n = 117$), 0.38 ($n = 208$), and 0.40 ($n = 277$) [24,30-32]. While these values are clearly better than the sensitivity of about 0.23 reported with CT and MRI, care should continue to be exercised when deciding upon a course of action as not every enlarged or "hot" LN harbors CaP and pN1 disease is often found in clinically-negative LNs.

There are several limitations to our findings. First, as a retrospective study, selection bias plays a large role in determining which of these patients undergo RP. Our findings cannot be used to support RP for all men with advanced CaP; the majority of men with metastatic CaP seen in MUSIC practices did not undergo (and were not considered) for RP. Additional known and unknown biases, including patient and urologist preferences for treatment, have an important impact on the nature of this study. Second, the heterogeneity in type and quality of imaging obtained in patients followed in the MUSIC registry is an inherent limitation. As mentioned above, the poor operating characteristics of conventional imaging modalities are a major finding and limitation of this work. In addition, the absence of pre-treatment imaging for staging in 202 high-risk CaP patients (11% of 1837) is a

quality concern. Such patients were excluded from analysis as they could not be classified into the 4 risk groups. A third limitation is our use of cancer progression, a composite endpoint based on elevated post-operative PSA values and the use of salvage treatments, rather than cancer-specific survival, as an outcome. Duration of follow-up and number of events are inadequate to evaluate that endpoint at the present time. Another limit on the interpretability of these data is that 25.1% and 21.0% of the 1,635 included patients received adjuvant treatments and salvage treatments, respectively. These additional therapies complicate analysis of the progression-free probability after RP. The reported results are not presented to advocate for RP alone for such patients, but to provide information regarding patients that choose to undergo RP, many of whom received a multimodal treatment course.

5. Conclusion

Across practices participating in MUSIC, more than 1,600 patients with HR or higher CaP have been managed with RP, including 155 with clinical suspicion of nodal and/or distant metastases. The perioperative outcomes, including length of stay and 30-day readmission rates, are indistinguishable across all of the high-risk groups assessed in this study. Many patients with HR and/or advanced CaP have evidence of cancer progression and receive additional treatments after RP. Our results provide contemporary evidence regarding the use of RP in patients at high risk for or with clinical suspicion of metastatic CaP, and we would encourage participation in clinical trials evaluating the benefit of RP, and other forms of local treatment, together with systemic therapies moving forward. We greatly anticipate the results of such trials to provide definitive evidence regarding potential benefit to various combinations of localized and systemic therapies in this setting.

Declaration of competing interest

None.

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Supplementary materials

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