Pelvic Lymph Node Dissection at Radical Prostatectomy for Intermediate Risk Prostate Cancer: Assessing Utility and Nodal Metastases Within a Statewide Quality Improvement Consortium

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OBJECTIVE To assess which patients with intermediate-risk PCa would benefit from a pelvic lymph node dissection (PLND) across the Michigan Urological Surgery Improvement Collaborative, given the discrepancy in recommendations. AUA guidelines for localized prostate cancer (PCa) state that PLND is indicated for patients with unfavorable intermediate-risk and high-risk PCa and can be considered in favorable intermediate-risk patients. NCCN guidelines recommend PLND when risk for nodal disease is ≥2%.

METHODS Data regarding all robot-assisted radical prostatectomy (RARP) (March 2012-October 2020) were prospectively collected, including patient, and surgeon characteristics. Univariate and multivariate analyses of PLND rate and lymph node involvement (LN+) were performed.

RESULTS Among 8,591 men undergoing RARP for intermediate-risk PCa, 80.2% were performed with PLND (n = 6883), of which 2.9% were LN+ (n = 198). According to the current AUA risk stratification system, 1.2% of favorable intermediate-risk PCa and 4.7% of unfavorable intermediate-risk PCa demonstrated LN+. There were also differences in the LN+ rates among the subgroups of favorable (0.0%-1.3%), and unfavorable (3.5%-5.0%) categories. Additional factors associated with higher LN+ rates include ≥50% cores positive, ≥35% involvement at any core, and unfavorable genomic classifier result, none of which contribute to the favorable/unfavorable subgroups.

CONCLUSION These data support PLND at RARP for all patients with unfavorable intermediate-risk PCa. Our data also indicate patients with favorable intermediate-risk prostate cancer at greatest risk for LN+ are those with ≥50% cores positive, ≥35% involvement at any core, and/or unfavorable genomic classifier result. UROLOGY 165: 227–236, 2022. © 2022 Elsevier Inc.

Pelvic lymph node dissection (PLND) at the time of robot-assisted radical prostatectomy (RARP) is the current gold standard for assessing nodal metastasis. While the diagnostic value of PLND is undebatable, the therapeutic value of PLND is controversial.[1] Furthermore, PLND may be associated with worse intraoperative and perioperative outcomes, including intraoperative risks of ureteral injury, vascular injury, and obturator nerve injury, and postoperative risks of lymphocele and deep vein thrombosis.[2-4] The long-term sequelae of lymphocele in particular are becoming more clear and of increasing concern in recent years.[3,5-7] PLND is also associated with increased operative time, length of stay (LOS), and healthcare costs.

While several studies have examined PLNDs role in high-risk prostate cancer (PCa),[1,4,8] evidence regarding the role of PLND in intermediate-risk (IR) PCa is limited.[9] IR PCa is defined by the American Urological Association (AUA) as meeting one or more of these criteria: Prostate Specific Antigen (PSA) 10-<20 ng/mL or Grade

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American Urological Association (AUA) risk stratification for clinically localized IR PCa				
Intermediate Risk	PSA 10-<20 ng/ml *or* Grade Group 2-3 *or* clinical stage T2b-T2c			
	Favorable	Grade Group 1 with PSA <10 *and* cT2b-T2c		
		Grade Group 1 with PSA 10-<20		
		Grade Group 2 with PSA <10 *and* cT1-T2a		
	Unfavorable	Grade Group 2 with PSA 10-<20 *and* cT1-T2a		
		Grade Group 2 and cT2b-T2c		
		Grade Group 3 with PSA < 20		
National Comprehensive Cancer Network (NCCN) stratification for clinically localized IR PCa				
Intermediate Risk	Has no high- or very high-risk features and has one or more intermediate-risk factors (IRF): • PSA 10-20 ng/mL • Grade Group 2 or 3 • T2b-T2c		Favorable intermediate	• 1 IRF *and* • Grade Group 1 or 2 *and* • <50% biopsy cores positive
			Unfavorable intermediate	• 2 or 3 IRFs *and/or* • Grade Group 3 *and/or* • ≥50% biopsy cores positive
MUSIC risk stratification for clinically localized IR PCa				
Intermediate Risk	Has no high- or very-high-risk features, no clinical* T3-T4 disease, no clinical** evidence of N1 or M1 disease, and has one or more IRF: • PSA 10-20 ng/mL • Grade Group 2 or 3 • Clinical Stage T2b – T2c			
FAVORABLE-INTERMEDIATE RISK				
F-IR1	Grade Group 1 with PSA <10 *and* cT2b-T2c			
F-IR2	Grade Group 1 with PSA 10-<20			
F-IR3	Grade Group 2 with PSA <10 *and* cT1-T2a			
UNFAVORABLE-INTERMEDIATE RISK				
U-IR1	Grade Group 2 with PSA 10-<20 *and* cT1-T2a			
U-IR2	Grade Group 2 and cT2b-T2c			
U-IR3	Grade Group 3 with PSA < 20			

Figure 1. Classification and subclassification of clinically localized intermediate-risk prostate cancer (IR PCa) according to AUA, NCCN, and MUSIC. *Based on standard clinical evaluation of the prostate by digital rectal exam and/or radiographic suspicion of T3/T4 disease on MRI or CT (when performed). **Based on initial standard clinical evaluation for IR PCa, which may or may not have included radiographic evaluation with CT, MRI, bone scan, x-ray or none of the above. During the time-frame of the study, PSMA-PET was not readily available.

Group (GG) 2-3 or clinical stage T2b-c (Fig. 1).[10]. The National Comprehensive Cancer Network (NCCN) risk stratification for IR PCa is similar, but also includes stratification based on <50% or ≥50% biopsy cores positive for F-IR, and U-IR respectively.[11]

Given limitations in preoperative imaging,[12] nomograms are the most widely used tool for considering PLND preoperatively. Commonly used nomograms include the Partin tables,[13,14] the MSKCC nomogram,[15] and the D'Amico risk classification,[16] which were all created using data with a large proportion of low-risk patients, while the Briganti nomogram,[17,18] in contrast, had a higher proportion of high-risk patients. These nomograms thus may not be as helpful for assessing risk in an IR PCa cohort.[8]

Surgical guidelines for IR PCa vary, but all base their recommendations on the patient's preoperative risk of lymphatic metastases. The NCCN, for example, recommends PLND when the nomogram-predicted risk of harboring metastatic disease is ≥2%.[11] The European Association of Urology (EAU) guidelines cite even more stringent criteria, recommending PLND when estimated risk of LN+ exceeds 5%.[19] The AUA guidelines, on the other hand, state PLND can be considered for F-IR PCa, and is recommended for U-IR PCa.[10] However, each of these guideline recommendations is based primarily on expert opinion, rather than upon a preponderance of evidence.

In order to better inform guidelines regarding PLND at RARP for IR PCa, we examined PLND performance, and LN+ rates across the Michigan Urological Surgery Improvement Collaborative (MUSIC).

METHODS

Michigan Urological Surgery Improvement Collaborative (MUSIC)

MUSIC is a statewide, physician-led quality improvement consortium.[20] 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.

Patient Population

We conducted a HIPAA compliant and IRB-approved retrospective analysis of data stored within the MUSIC registry. Initially

considered were all patients undergoing RARP for clinically localized PCa. Patients with locally-advanced or metastatic disease on clinical staging (ie, cT3-4, cN1, or cM1) were not included. All patients in the registry who had undergone RARP were examined regardless of risk category for comparison between the no PLND and PLND groups; subsequently low-risk and high-risk patients were excluded as they are not the focus of this study. All patients in the MUSIC registry who underwent RARP for F-IR and U-IR PCa were included. IR for this study was defined broadly in line with both AUA and NCCN guidelines (PSA 10-20 ng/mL or GG2-3 or clinical stage T2b-T2c). We modified and specified criteria for each of the 6 AUA subgroups to ensure that high-risk and non −localized PCa patients were excluded (Fig. 1)and labeled the 6 subgroups accordingly. In our analyses, we compared all F-IR patients with all U-IR patients, and further considered the 6 subgroups individually. Patients not undergoing PLND were removed from the analyses of LN+. Genomic classifiers were classified as unfavorable as follows: Prolaris predicted mortality risk ≥3%, Oncotype DX high-grade disease >20%, and Decipher biopsy score ≥0.45), and favorable if these criteria were not met, as previously described.[21,22]

Statistical Analyses

The primary outcome of interest was LN+ rates at time of PLND. We first compared demographic and clinical characteristics for patients in whom PLND was performed and not performed and examined preoperative parameters in LN positivity rate for IR PCa patients. A multivariable logistic regression model was then fitted to evaluate the association between LN+ rate and preoperative variables of interest. Age, pre-operative PSA, most recent biopsy GG, number of positive cores, maximum percentage of cancer involvement of an individual core, PI-RADS score, and genomics testing result were evaluated as predictors of LN positivity. Abdominopelvic computerized tomography (CT) and multiparametric magnetic resonance imaging (mpMRI) were categorized according to presence or absence of suspicion for LN metastases. All statistical testing was performed at the 5% significance level using SAS v9.3 (SAS Institute Inc., Cary, NC).

RESULTS

We identified all men within the MUSIC registry who underwent RARP with or without PLND from March 2012 through October 2020. Among 13,665 patients undergoing RARP, 10,987 patients (80.4%) underwent PLND. Performance of PLND (Supplementary Table 1) and LN+ (Supplementary Table 2) were significantly associated with AUA risk group, PSA, clinical stage, biopsy GG, number of positive cores, percentage of cores positive, and greatest cancer involvement at individual core (P <.001 for each). Percentage of biopsy cores positive strongly predicted LN+ with rates of 1.9%, 3.2%, and 8.2% for <25%, 25%-49%, and ≥50% cores positive, respectively (P <.001). Maximum core involvement also strongly predicted LN+ with rates of 1.5%, 3.4%, and 8.8% for <35%, 35% to 65%, and >65%, respectively (P <.001).

After removing the patients not meeting inclusion criteria, 8591 IR patients were identified, of whom 6883 patients (80.2%) underwent PLND (Table 1). The decision to perform PLND was associated with U-IR (vs F-IR), and with higher MUSIC IR subgroup, PSA levels, clinical staging, biopsy GG, number of positive cores, percentage of positive cores, higher percentage cancer involvement of an individual core, PI-RADS score, and genomic testing result (P <.001 for each). There were no significant differences in notable outcomes and trackable events after RP with or without PLND (Supplementary Table 3). For example, extended LOS was 7.6% without PLND and 6.5% with PLND (P = .14), while readmission rates were 3.5% without PLND and 4.6% with PLND (P = .054).

Of the 6883 IR PCa patients undergoing PLND, 198 (2.9%) had LN+ disease at the time of surgery (Table 2). Higher PSA value, clinical T stage, biopsy GG, number of positive cores, percentage of positive cores, greatest cancer involvement at individual core, U-IR, and higher MUSIC IR subgroup were each associated with LN+ disease (P <.001 for each). Pre-operative genomic testing was available for a subset of these patients (n = 1179, 13.7%). Unfavorable genomic testing result was significantly associated with LN+ disease (P = .003). Notably, of 176 patients with a favorable genomic testing result, no patients (0%) had LN+ disease. These patients included 130 F-IR and 46 U-IR patients, 24 patients with PSA 10-20, 13 patients with clinical T2b-c disease, and 25 patients with GG3 disease. Age (P = .052), race (P = .16), comorbidity (P = .25), and PI-RADS score (P = .37) were not significantly associated with LN+ disease. Other information obtained from preoperative mpMRI was not examined as patients were excluded if there was concern for extraprostatic extension (EPE) or seminal vesical invasion (SVI) (cT3) or concerning nodes (cN1) on mpMRI. A higher percentage of biopsy cores positive for PCa strongly predicted LN+ in these IR patients; 0.8%, 2.0%, and 4.8% LN+ rates for <25%, 25%-49%, and ≥50% percent of biopsy cores positive, respectively (P <.001). Maximum core involvement also strongly predicted LN+ with rates of 0.8%, 2.4%, and 4.9% for <35%, 35% to 65%, and >65% core involvement, respectively (P <.001). Regarding grade group, rates of 0.4%, 1.9%, and 5.0% were seen for IR PCa patients with GG1, GG2, and GG3, respectively (P <.001).

Among patients categorized with AUA F-IR disease, the LN+ rate was 1.2% overall, while for AUA U-IR, the LN+ rate was 4.9% overall. Analysis of the 3 subgroups of F-IR disease demonstrated that 0% with F-IR1 (n = 72); 0.5% with F-IR2 (n = 205), and 1.3% with F-IR3 (n = 3275) had LN+ disease. Factors associated with LN+ in F-IR patients included greatest cancer involvement of an individual core (P = .001) (Supplemental Table 4). For U-IR subgroups, rates of LN+ PCa were 3.5% for U-IR1 (n = 606); 4.6% of U-IR2, (n = 366); and 5.0% for U-IR3, (n = 2329). Pairwise comparisons within the F-IR subgroups (F-IR1/F-IR2 vs F-IR3) or U-IR subgroups (U-IR1 vs U-IR2; U-IR2 vs U-IR3; U-IR1 vs U-IR3) were not statistically significant but may be clinically significant. Factors associated with LN+ in U-IR patients included percentage of biopsy cores positive and greatest cancer involvement of an individual core (P <.001). Of 373 U-IR patients with preoperative genomic classifier testing, LN + was 6.7% following an unfavorable result (n = 22 of 327) and 0% following a favorable result (0 of 46), but this did not quite reach statistical significance (P = .07). PLND was more commonly performed for IR PCa patients with higher risk group (Table 3a). Greatest cancer involvement of an individual core and percentage of cores positive were the strongest independent predictors of PLND performance (Table 3a). African American race also independently predicted PLND performance (OR 1.30, CI 1.01, 1.66, P = .04) while age, other races, and comorbidity were not demonstrated as independent predictors of PLND performance.

Multivariable analysis of LN+ (Table 3b) showed, outside of MUSIC risk stratification groups, that greatest cancer

Table 1. Characteristics of 8,591 intermediate risk PCa patients undergoing RARP with or without PLND.

	No PLND	PLND	*P*-Value
No. patients	1708	6883	
Age			
<55	189 (17.8%)	872 (82.2%)	.007
55-65	827 (21.3%)	3052 (78.7%)	
>65	692 (19.0%)	2959 (81.0%)	
Race			
White	1352 (20.9%)	5125 (79.1%)	<.001
African American	202 (19.0%)	859 (81.0%)	
Other	43 (18.9%)	185 (81.1%)	
Unknown	111 (13.5%)	714 (86.5%)	
Comorbidity			
CCI = 0	1246 (19.9%)	5009 (80.1%)	.937
CCI = 1	291 (19.9%)	1172 (80.1%)	
CCI ≥ 2	169 (19.4%)	702 (80.6%)	
Intermediate Risk group			
F-IR	1317 (27.0%)	3552 (73.0%)	<.001
U-IR	390 (10.6%)	3301 (89.4%)	
Intermediate Risk subgroups			
F-IR1: GG1 with PSA<10 and T2b-c	33 (31.4%)	72 (68.6%)	<.001
F-IR2: GG1 with PSA 10-<20	97 (32.1%)	205 (67.9%)	
F-IR3: GG2 with PSA<10 and T1-2a	1187 (26.6%)	3275 (73.4%)	
U-IR1: GG2 with PSA 10-<20 and T1-2a	82 (11.9%)	606 (88.1%)	
U-IR2: GG2 with T2b-c	71 (16.2%)	366 (83.8%)	
U-IR3: GG3 with PSA<20	237 (9.2%)	2329 (90.8%)	
PSA			
<10	1501 (21.2%)	5581 (78.8%)	<.001
10-20	207 (13.7%)	1302 (86.3%)	
Clinical staging			
T1	1394 (21.4%)	5122 (78.6%)	<.001
T2	314 (15.1%)	1761 (84.9%)	
Biopsy Grade Group			
GG1	129 (31.8%)	277 (68.2%)	<.001
GG2	1341 (23.9%)	4277 (76.1%)	
GG3	237 (9.2%)	2329 (90.8%)	
No. positive cores			
≤2	569 (30.0%)	1327 (70.0%)	<.001
3-5	739 (21.5%)	2704 (78.5%)	
≥6	399 (12.4%)	2819 (87.6%)	
% biopsy cores positive			
<25%	598 (28.3%)	1513 (71.7%)	<.001
25%-49%	698 (21.5%)	2555 (78.5%)	
≥50%	411 (12.9%)	2779 (87.1%)	
Greatest cancer involvement			
<35%	782 (27.9%)	2021 (72.1%)	<.001
35%-65%	557 (20.0%)	2229 (80.0%)	
>65%	368 (12.4%)	2611 (87.6%)	
PI-RADS score			
0-2	17 (17.9%)	78 (82.1%)	<.001
3	30 (21.6%)	109 (78.4%)	
4	71 (14.4%)	423 (85.6%)	
5	25 (6.0%)	390 (94.0%)	
Genomic testing result			
Favorable	205 (53.8%)	176 (46.2%)	<.001
Unfavorable	302 (37.8%)	496 (62.2%)	

PCa, prostate cancer; RARP, robot-assisted radical prostatectomy; PLND, pelvic lymph node dissection; CCI, Charleston comorbidity index; GG, grade group; PSA, prostate specific antigen.

involvement of an individual core was the best predictor (>65% core positive: OR 4.58, CI 2.60, 8.08, P <.001). Other independent predictors of LN+ included ≥50% cores positive (OR 1.71, CI 1.03, 2.85, P = .039) and age >65 (OR 1.98, CI 1.12, 3.52, P = .019. Race and comorbidity were not demonstrated to be independent predictors of LN+.

Favorable IR PCa With LN+

To identify subsets of F-IR patients with greatest likelihood of LN+ PCa, we next reviewed the factors associated with LN+ disease (Table 2) in each of the 43 LN+ F-IR PCa patients. Sixteen of the pN1 patients had upgraded GG at surgical pathology. Thirty-nine patients (90.7%) had ≥35% involvement of an

Table 2. Factors associated with LN+ for 6,883 intermediate-risk patients undergoing RARP and PLND.

	N0	N1	*P*-Value
No. patients	6685	198	
Age			
<55	857 (98.3%)	15 (1.7%)	.052
55-65	2966 (97.2%)	86 (2.8%)	
>65	2862 (96.7%)	97 (3.3%)	
Race			
White	4981 (97.2%)	144 (2.8%)	.160
African American	832 (96.9%)	27 (3.1%)	
Other	175 (94.6%)	10 (5.4%)	
Unknown	697 (97.6%)	17 (2.4%)	
Comorbidity			
CCI = 0	4875 (97.3%)	134 (2.7%)	.253
CCI = 1	1131 (96.5%)	41 (3.5%)	
CCI ≥ 2	679 (96.7%)	23 (3.3%)	
Intermediate risk group			
F-IR	3509 (98.8%)	43 (1.2%)	<.001
U-IR	3147 (95.3%)	154 (4.7%)	
Intermediate Risk subgroups			
F-IR1: GG1 with PSA<10 and T2b-c	72 (100%)	0 (0%)	<.001
F-IR2: GG1 with PSA 10-<20	204 (99.5%)	1 (0.5%)	
F-IR3: GG2 with PSA<10 and T1-2a	3233 (98.7%)	42 (1.3%)	
U-IR1: GG2 with PSA 10-<20 and T1-2a	585 (96.5%)	21 (3.5%)	
U-IR2: GG2 with T2b-c	349 (95.4%)	17 (4.6%)	
U-IR3: GG3 with PSA<20	2213 (95.0%)	116 (5.0%)	
PSA			
<10	5447 (97.6%)	134 (2.4%)	<.001
10-20	1238 (95.1%)	64 (4.9%)	
Clinical staging			
T1	4998 (97.6%)	124 (2.4%)	<.001
T2	1687 (95.8%)	74 (4.2%)	
Biopsy Grade Group			
GG1	276 (99.6%)	1 (0.4%)	<.001
GG2	4196 (98.1%)	81 (1.9%)	
GG3	2213 (95.0%)	116 (5.0%)	
No. positive cores			
≤2	1310 (98.7%)	17 (1.3%)	<.001
3-5	2650 (98.0%)	54 (2.0%)	
≥6	2692 (95.5%)	127 (4.5%)	
% biopsy cores positive			
<25%	1492 (98.6%)	21 (1.4%)	<.001
25%-49%	2503 (98.0%)	52 (2.0%)	
≥50%	2654 (95.5%)	125 (4.5%)	
Greatest cancer involvement			
<35%	2005 (99.2%)	16 (0.8%)	<.001
35%-65%	2175 (97.6%)	54 (2.4%)	
>65%	2483 (95.1%)	128 (4.9%)	
PI-RADS score			
0-2	76 (97.4%)	2 (2.6%)	.708
3	107 (98.2%)	2 (1.8%)	
4	415 (98.1%)	8 (1.9%)	
5	378 (96.9%)	12 (3.1%)	
Genomic testing result			
Favorable	176 (100%)	0 (0%)	.003
Unfavorable	472 (95.2%)	24 (4.8%)	

LN+, lymph node involvement; RARP, robot-assisted radical prostatectomy; PLND, pelvic lymph node dissection; CCI, Charleston comorbidity index; GG, grade group; PSA, prostate specific antigen.

individual core. Of the remaining 4 patients, 1 patient had >1 year (16 months) between his initial biopsy and RARP/PLND and 3 had no risk factors identified. Other high-risk features included 36 with ≥25% cores involved, 3 with PI-RADS 5 at mpMRI, and 2 with unfavorable genomic classifier results. The single F-IR patient with biopsy GG1 PCa had PSA 10-<20, cT2b, 4 of 12 positive cores (33%), 90% core involvement, and was upgraded to 663 at surgical pathology (pT3aN1). If PLND was restricted to only F-IR patients with ≥35% involvement of an individual core, 39 of the 43 patients would be identified (90.7%); if patients were selected for PLND based on 2 or more of these factors, 36 of 43 would be identified (83.7%).

Table 3a. Multivariable analysis for performance of PLND for intermediate risk PCa patients.

Variable	OR	95% CI	*P*-Value
Age (ref: <55)			
55-65	0.85	(0.67, 1.09)	.202
>65	0.78	(0.60, 1.00)	.052
Race (ref: White)			
African American	1.30	(1.01, 1.66)	.04
Other	0.89	(0.55, 1.44)	.635
Unknown	1.24	(0.91, 1.69)	.173
Comorbidity (ref: CCI = 0)			
CCI = 1	0.90	(0.74, 1.11)	.34
CCI ≥ 2	0.99	(0.76, 1.28)	.922
Risk group (ref: F-IR3: GG2 with PSA<10 and cT1-2a)			
F-IR1: GG1 with PSA<10 and cT2b-c	0.26	(0.14, 0.50)	<.001
F-IR2: GG1 with PSA 10-<20	0.49	(0.34, 0.72)	<.001
U-IR1: GG2 with PSA 10-<20 and cT1-2a	4.28	(3.09, 5.92)	<.001
U-IR2: GG2 with cT2b-c	2.41	(1.67, 3.49)	<.001
U-IR3: GG3 with PSA<20	8.93	(7.19, 11.09)	<.001
% cores positive (ref: <25%)			
25%-49%	1.70	(1.40, 2.06)	<.001
≥50%	2.71	(2.17, 3.39)	<.001
Greatest % cancer involvement (ref: <35%)			
35%-65%	1.45	(1.20, 1.74)	<.001
>65%	1.81	(1.46, 2.24)	<.001

PLND, pelvic lymph node dissection; PCa, prostate cancer; CCI, Charleston comorbidity index; GG, grade group; PSA, prostate specific antigen. This is a multivariable analysis which is also controlled for surgeon through random effect.

DISCUSSION

There is relative agreement regarding the value of PLND at RARP for patients with high-risk localized and locally advanced PCa and limited value to PLND for those with low-risk PCa. For localized IR PCa, the recommendations vary based on respective guidelines. The decision to perform PLND at RARP is therefore, left to the discretion of the patient, and his urologic surgeon. There is limited contemporary evidence to assist decision-making regarding PLND for IR PCa patients. To provide a framework for this discussion, we assessed LN+ disease in 6883 IR PCa patients who underwent RARP and PLND within MUSIC. The overall LN+ rate was 2.9%, with 1.2% in F-IR, and 4.7% in U-IR PCa patients.

Surgical guidelines offer varying recommendations about the role of PLND at RARP for IR PCa. The NCCN recommends PLND when the nomogram-predicted risk of LN+ is ≥2%,[11] while the EAU guidelines recommend

Table 3b. Multivariable analysis for LN+ at time of PLND for intermediate-risk PCa patients.

Variable	OR	95% CI	*P*-Value
Age (ref: <55)			
55-65	1.68	(0.95, 2.96)	.074
>65	1.98	(1.12, 3.52)	.019
Race (ref: White)			
African American	0.97	(0.62, 1.53)	.908
Other	1.80	(0.89, 3.63)	.100
Unknown	0.84	(0.49, 1.45)	.541
Comorbidity (ref: CCI = 0)			
CCI = 1	1.06	(0.73, 1.54)	.769
CCI≥2	1.06	(0.65, 1.71)	.821
Risk group (ref: F-IR3: GG2 with PSA<10 and cT1-2a)			
F-IR1/F-IR2: GG1 with PSA 10-<20 or cT2b-c	0.56	(0.08, 4.15)	.569
U-IR1: GG2 with PSA 10-<20 and cT1-2a	2.65	(1.53, 4.57)	<.001
U-IR2: GG2 with cT2b-c	3.11	(1.71, 5.64)	<.001
U-IR3: GG3 with PSA<20	3.55	(2.45, 5.13)	<.001
% cores positive (ref: <25%)			
25%-49%	0.97	(0.56, 1.66)	.904
≥50%	1.71	(1.03, 2.85)	.039
Greatest % cancer involvement (ref: <35%)			
35%-65%	2.64	(1.47, 4.73)	.001
>65%	4.58	(2.60, 8.08)	<.001

LN+, lymph node involvement; PLND, pelvic lymph node dissection; PCa, prostate cancer; CCI, Charleston comorbidity index; GG, grade group; PSA, prostate specific antigen. This is a multivariable analysis which is also controlled for surgeon through random effect.

PLND when risk of LN+ is >5%.[19] How these guidelines would play out using MUSIC data are illustrated in Supplemental Table 5. If NCCN criteria (PLND for ≥2% only) were used, 3552 of 6883 patients (51.8%) with IR PCa would have avoided PLND; 78.2% of LN+ disease would be identified (154 detected and 43 missed cases). In contrast, using the EAU criteria (PLND for >5% only), 4524 PLND would be avoided (66%) with 116 LN+ cases detected and 81 LN+ cases missed. The AUA guidelines, meanwhile, recommend that PLND is performed for U-IR PCa, and can be considered for F-IR PCa patients undergoing prostatectomy.[10] Our data indicate that the AUAs recommendation to perform PLND for U-IR PCa is more consistent with the NCCN criteria than the EAU guidelines. We also noted differences in the LN+ rates among the 3 subgroups of F-IR and U-IR: 0.0%-1.3% for F-IR1 to F-IR3 and 3.5%-5.0% for U-IR1 to U-IR3, supporting the current subgroups. Although the pairwise comparisons within F-IR or U-IR groups were not statistically significant, the heterogeneity in LN+ rates may be clinically relevant. If subsequent studies confirm our findings, adjustments to the current F-IR, and U-IR definitions may be in order. GG1 disease, even with PSA < 20 or cT2b/2c disease (F-IR1/F-IR-2), seems better characterized as low-risk (rather than F-IR), if other groups validate these data. And only 1 of 3 U-IR subgroups (GG3 with PSA < 20, U-IR3) met the EAU cut point of 5% in our cohort. Our data confirm the combination of PSA, clinical stage, and biopsy GG into F-IR and U-IR subgroups is a reliable method of distinguishing subgroups of patients with relatively higher and lower rates of LN+ PCa.

In addition, we identify several clinical factors not accounted for in the AUA risk stratification system that were associated with LN+ rates. These other factors include percentage of positive biopsy cores, greatest cancer involvement of an individual core, and unfavorable genomic classifier result. Notably, no patients with favorable genomic testing result had LN+ at PLND. Few patients in this cohort underwent genomic testing, suggesting that genomic testing offers currently underutilized value in shared decision-making for patients with borderline risk of LN+. As indicated in previous studies,[18,23,24] the percentage of positive biopsy cores was a significant predictor of LN+, with ≥50% positive cores demonstrating a 4.5% risk of LN+ in IR PCa patients overall, and 6.8% of U-IR patients. On multivariable analysis, ≥50% cores positive was also seen to be an independent predictor of LN+ (odds ratio: 1.71, $P = .039$). In contrast to these previous studies, however, increasing percentages of an individual core's cancer involvement was found to be an even stronger independent predictor of LN+. Involvement of >65% of any core was associated with LN+ rates of 4.9% overall and 7.2% of U-IR patients. In multivariable analysis, both 35%-65% (odds ratio: 2.64, $P = .001$) and >65% (odds ratio: 4.58, $P < .001$) were independently associated with LN+ rates. These data suggest patients with F-IR PCa may be considered for PLND if they have ≥35% involvement at any core, ≥50% positive cores, and/or unfavorable genomic classifier result. However, none of these factors led to a ≥2% LN+ for F-IR PCa (Supplemental Table 4). On the other hand, using the 2% risk of LN+ recommended by the NCCN, PLND can avoided in all F-IR patients and potentially also be avoided in select U-IR patients, such as those with <35% involvement of an individual core and/or favorable genomic testing result (Supplemental Table 4).

Similar to previous studies indicating disappointing sensitivity and accuracy in detecting nodal disease with preoperative CT and mpMRI imaging,[12] our data indicate no association between PI-RADS score at preoperative mpMRI and LN+ disease in patients with clinically localized, IR PCa patients. Recent work by Wibmer et al suggests that incorporating EPE and SVI into mpMRI risk stratification more strongly predicts oncologic outcomes than PI-RADS scores alone.[25] Since we excluded all cT3 patients (including those with concern for EPE and SVI on mpMRI prostate), as well as patients with cN1 disease, it is perhaps not surprising that PI-RADS score did not predict LN+ in our IR patient population. It is also possible that our study was underpowered to detect an effect of PI-RADS score, as only 14.5% (n =1000) of 6883 IR patients had a preoperative mpMRI.

Within MUSIC, PLND is being performed in many patients in whom the benefit of detecting LN+ disease is very low. Our previous data indicated that nearly 60% of low-risk patients underwent PLND,[3] and our current data indicate rates between 67.9%, and 73.4% for the F-IR subgroups. Only nine patients of 1478 (0.6%) with F-IR1 (GG1) had LN+, indicating that these patients have little to benefit from PLND. Given the disparity between PNLD performed and LN+ in F-IR1 and F-IR2 (and LR groups), all of which have GG1 disease only, also reported in previous studies,[26-28] there is a significant opportunity for quality improvement by limiting unnecessary low yield PLND for GG1 PCa. Even the most common F-IR subgroup (F-IR3: GG2, PSA < 10, T1-T2a) had a LN+ rate of only 1.3%.These findings suggest that subdividing the F-IR category into subgroups has clinical value, an alternative to subdividing F-IR into subgroups would be to recategorize F-IR1 and F-IR2 as low risk..

Although previous studies have indicated worse intraoperative and postoperative outcomes with PLND performance,[2-7] interestingly, within the MUSIC database, we did not make the same observation. Although readmission rates were slightly higher with PLND, no statistically significant difference was seen in any intraoperative, and postoperative outcomes on univariate or multivariate analysis. In fact, the proportion of patients with excessive blood loss, and extended LOS were higher when a PLND was not performed. This suggests that selection bias may play a role in some surgeons' decisions regarding PLNDs, particularly those that perform PLND after the RARP has been completed rather than at the beginning of the procedure. Further evaluation regarding surgeon preference and decision making with regards to PLND is warranted.

This study is impacted by the inherent limitations of retrospective registry studies. One of the greatest strengths of MUSIC is that it includes real-world data from patients undergoing RARP by >90% of the urologists in Michigan. This, however, leads to some unaddressable limitations including non—uniform practices in terms of when to perform PLND and the extent of PLND. As reported previously,[27] the data regarding each PLND did not include the number of nodes removed, total or by side, or description of the template of the procedure. Some surgeons performed a more limited PLND, raising the possibility that LN+ rates could have been higher if extended PLND was routinely performed. Additionally, although dedicated uropathologists reviewed all the RP specimens, no centralized pathologic review was performed, so interobserver variability may be a potential confounder, as is the case for most studies aside from clinical trials. Single-institution studies may provide data to complement ours, but ideally, a multi-institutional prospective, randomized trial would best determine the value of PLND for IR PCa. However, to our knowledge no such trial is currently recruiting or ongoing. Acknowledging these limitations, our results generally support the use of PLND uniformly for U-IR PCa, and only sparingly for select patients with F-IR PCa.

CONCLUSION

Our data support the sub-stratification of IR PCa into favorable and unfavorable groups, and performance of PLND for unfavorable IR. This practice meets with the recommendations of various guideline organizations that have recommended cutoffs of ≥2%->5% risk of LN+ at PLND. Risk factors outside the AUA stratification system that were found to significantly increase the risk of LN+ include ≥50% cores positive, ≥35% involvement at any individual biopsy core, and/or unfavorable genomic classifier result. Even so, none of these risk factors met the ≥2% LN+ rate in favorable IR PCa, suggesting that PLND can frequently be omitted.

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SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.urology.2022.01.049.

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EDITORIAL COMMENT

The evolution of risk stratifications for prostate cancer reflects advances in anatomic (radiographic), pathologic, and molecular (genomic classifications) understandings. These parameters, combined with traditional "bedside" evaluations of clinical T stage, and PSA values, allow for better sharing of clinical decisions with patients. In this issue of the Gold Journal, investigators MUSIC investigators (Michigan Urological Surgery Improvement Collaborative) sought to improve patient selection criteria for PLND in patients with favorable and unfavorable intermediate risk (F-IR, U-IR) disease by analyzing over 6,800 men who underwent RALP and pelvic lymph node dissection (PLND). Despite some limitations, the authors have made an important contribution to further understanding the multitude of factors that help define the decision to add PLND to RALP.

The authors compare differing criteria for performing PLND according to pelvic lymph node positivity risk using AUA, NCCN, or EAU guidelines, but advance them several steps further by adding parameters, readily available in clinical practice, into actionable recommendations.

The results are both informative and provide a further refinement - likely to be consequential — of these categories that now expand IR into 6 subcategories. ("Splitters" will rejoice; "lumpers" will frown). Additional parameters that were evaluated and informative include genomic classifiers, percent positivity of individual cores, and percent of total cores positive.

There are several noteworthy practice changes that if confirmed, could help inform more appropriate use of next generation imaging agents such as PSMA. The authors note that currently 68%-73% of men with F-IR undergo PLND; yet only one of >5000 men of the subset with Grade Group 1 and PSA <20 ng/mL had positive nodes. Those of MUSIC F-IR subgroup with GG2, PSA <10 ng/mL, and T1-T2a had a positive node rate of 1.3%, less than suggested trigger point of 2% positive rate from existing guidelines. The authors suggest that utilizing these subset parameters may lessen the need for low yield PLND. Conversely, in a very small subset of patients with a favorable Decipher, Prolaris or Oncotype genomic classifier, positive nodes were not found in both F-IR, and U-IR patients. This observation needs more study and would be important if tested and confirmed prospectively.

With regard to the morbidity of PLND, readmission rates were slightly higher in those patients undergoing PLND, but other parameters such as length of stay, and blood loss were not adversely impacted. Importantly, this dataset did not capture the boundaries of PLND or number of nodes removed, which is a loose surrogate for quality of PLND. We know that the extent and quality of PLND is highly variable between surgeons yet directly correlates with both morbidity and the likelihood of identifying positive nodes (ref 3-7 in article). This information, as well as the impact of delayed complications from PLND will be crucial in answering future questions regarding PLND in this patient population.

Of note, the Michigan data were collected, and analyzed prior to the availability of axumin or PSMA next generation imaging modalities. We hope future MUSIC evaluations will incorporate these newer diagnostic scans into their registries, thus providing both validation of their current data and enable, in the future, more precision in determining the need for PLND for this very heterogenous population of IR patients.

CONFLICT OF INTEREST

Neither Dr Marc B. Garnick or Dr Andrew A. Wagner have any conflicts or financial disclosures to make in association with this editorial submission.

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AUTHOR REPLY

Subdividing "intermediate-risk" (IR) prostate cancer (PC) patients is one of the most important tasks in PC management, as some of these cancers behave in a manner that resembles other "low-risk" PCs, while others are most similar to "high-risk" PC. Two important steps have been the replacement of "Gleason 7″ PC with Gleason 3 + 4 (Grade group 2) and Gleason 4 + 3 (Grade group 3), and subsequently the creation of favorable IR (F-IR) and unfavorable IR (U-IR) PC subgroups. As mentioned by Drs. Garnick and Wagner, one important ramification of the F-IR, and U-IR split is to identify patients that would most benefit from pelvic lymph node dissection (PLND). As we enter an era of broader use of prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging and genomic testing, Michigan Urological Surgery Improvement Collaborative (MUSIC) plans to provide evidence regarding the likelihood of clinical node positive disease in U-IR (and high-risk) patients and its value as a pre-surgical study. We hope the supplementary data provided by novel radiographic and genomic studies will aid the urologic "lumpers" to further define the barrier between F-IR and U-IR PC and are sure these modalities

will allow "splitters" to collect new data to further characterize disease and influence treatment decisions in more and more patients moving forward.

CONFLICT OF INTEREST

The authors have no conflicts of interest.

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