ARTICLE

Clinical Research

Predictive role of node-rads score in patients with prostate cancer candidates for radical prostatectomy with extended lymph node dissection: comparative analysis with validated nomograms

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BACKGROUND AND OBJECTIVES: The Reporting and Data System (RADS) have been used in the attempts to standardize the results of oncological scans in different scenarios, such as lymph nodes, adding configuration criteria to size determination. We analyze the predictive value of preoperative Node-RADS determination at imaging for pelvic lymph node (PLN) involvement in cases of prostate cancer (PC) considered for radical prostatectomy (RP) with extended lymph node dissection (eLND) and we compare it with validate predictive nomograms (MSKCC, Briganti and Gandaglia).

METHODS: 150 patients with a histological diagnosis of PC (high risk or intermediate with an estimated risk for pN+ higher than 5% using the Briganti or 7% using the Gandaglia nomogram) submitted for RP with an ePLND from 2018 and 2021 were retrospectively examined. Node-RADS determination was performed in all cases using the preoperative magnetic resonance (MR), performed by a radiologist blinded for pathologic results and compared with the MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019 nomograms.

RESULTS: PLN involvement at final pathology (pN+) was found in 36/150 (24.0%) of cases and the mean percentage of positive LNs in pN+ cases was 15.90 ± 13.40. The mean number of PLNs removed at RP was similar ($p = 0.188$) between pN0 (23.9 ± 8.0) and pN+ (25.3 ± 8.0) cases. Considering a Node RADS 4–5 positive and a Node RADS 1–2 negative, the PPV was 100% and the NPV was 79.6%. A Node RADS score 4–5 showed a lower sensitivity (0.167 versus 0.972, 1.000, 0.971, 0.960 respectively), a higher specificity (1.000 versus 0.079, 0.096, 0.138, 0.186 respectively) and a similar AUC (0.583 versus 0.591, 0.581, 0.574, 0.597 respectively) when compared to MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019 nomograms.

CONCLUSIONS: Our evaluation suggests that Node RADS score, combining configuration criteria to size determination could improve specificity in terms of pathologic PLN prediction but a very low sensitivity has been also described.

Prostate Cancer and Prostatic Diseases; https://doi.org/10.1038/s41391-022-00564-z

INTRODUCTION

In non-metastatic PC patients selected for radical prostatectomy (RP), EAU guidelines [1, 2] recommend reserving an extended (e) PLND in all high risk cases and in intermediate risk PC cases with an estimated risk for pN+ higher than 5% using the Briganti [3] or 7% using the Gandaglia [4] nomogram.

Recently, a systematic review suggested that the association of ePLND during RP failed to improve survival [5] and a randomized clinical trial showed no significant differences in terms of oncological outcomes between an extended and a limited PLND [6]. At now, the risk of patients for positive PLNs is mainly estimated on the basis of validated nomograms such as the Briganti, Gandaglia or the MSKCC [3, 4, 7, 8]. These nomograms showed similar diagnostic accuracy in predicting PLNs invasion and a risk for LNs involvement over 5% for the Briganti 2012 and over 7% for MSKCC and Gandaglia 2017 nomograms can be used to select candidates for eLND at RP [2]. These nomograms were developed in a pre-magnetic resonance and random biopsy setting and this situation has been updated using the Gandaglia 2019 nomogram [7] based on mpMR and MR-targeted biopsy. On

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Received: 25 February 2022 Revised: 24 May 2022 Accepted: 10 June 2022
Published online: 22 June 2022

the basis of the Gandaglia 2019 nomogram [7] a risk of nodal metastases over 7% can be used to identify cases for an ePLND during RP [2] which would result in missing 1.5% of patient with LNs involvement.

Several studies evaluated morphologic criteria at imaging using computed tomography (CT) or MR to predict PLN involvement from PC, however at now there is no consensus although nodal size is generally accepted [9]. LN size evaluation using short- or long-axis diameter or volume showed to be a poor predictor for the presence of malignancy [9, 10]. Recently the Reporting and Data System (RADS) have been used in the attempts to standardize the reporting of oncological scans in different scenarios. For example, BI-RADS is recommended for the detection of breast cancer using x-ray mammography [11], LI-RADS for the evaluation of hepatocellular carcinoma using MR and PIRADS for the MR detection of PC [12]. Node-RADS has been proposed to enhance the reporting of regional or distant LN in cancer patients by [1] adding configuration criteria to size determination, [2] improving standardization in LN reporting at CT or MR imaging [12]. The Node-RADS 1.0 has been proposed at any anatomical site to standardize reporting of cancer involvement of LNs at imaging and scoring the categories of size and configuration so to obtain a 5-point category score. At now no clinical results in PC cases submitted to RP have been presented in the literature.

Aim

Aim of the present study is to analyze the predictive value of preoperative Node-RADS determination at imaging in terms of PLN involvement in cases of PC (high risk or intermediate with an estimated risk for pN+ higher than 5% using the Briganti [3] or 7% using the Gandaglia [7] nomogram) considered for RP with eLND and to compare it with validate predictive nomograms (MSKCC, Briganti and Gandaglia).

MATERIALS AND METHODS

This is a retrospective analysis on PC patients (high or intermediate risk with an estimated risk for pN+ higher than 5% using the Briganti [3] or 7% using the Gandaglia [7] nomogram) submitted to RP with an ePLND following recommendation of EAU guidelines. A real-life situation is analyzed.

Population

Patients with a histological diagnosis of prostatic adenocarcinoma submitted for RP with an ePLND as primary therapeutic option in our departments from 2018 and 2021 were consecutively enclosed in the analysis and retrospectively examined. The protocol was approved by our internal ethical committee and all patients gave their informed consensus for each procedure. All diagnostic and therapeutic procedures reflected our routine clinical practice in departments at high volume for the management of PC disease. Inclusion criteria were: histological diagnosis of prostatic adenocarcinoma; no distant metastases at clinical staging; high risk or intermediate risk disease with an estimated risk for pN+ higher than 5% using the Briganti [3] or 7% using the Gandaglia [7] nomogram incorporating mpMR- targeted biopsies; RP as chosen primary treatment decision after multidisciplinary discussion of treatment options and presentation to the patient; anatomical ePLND with removal of the obturator, internal iliac, external iliac lymph nodes associated to RP. Exclusion criteria were androgen deprivation therapies, chemotherapies, pelvic radiation therapies or treatments with other agents that could influence prostate tumor growth and diffusion.

From January 2018 to January 2021, 150 consecutive patients with PC corresponding to our inclusion and exclusion criteria were submitted to radical prostatectomy with eLND and were included in the present analysis.

Characteristics of the whole population of 150 cases is described in Table 1. All cases were submitted to a standard random 14-cores biopsy of the prostate. In cases submitted to mMR, PIRADS v2 score was defined and in cases with PIRADS score 3–5, random biopsy was associated to targeted

Table 1. Characteristics of the whole population included in the study.

Number cases	150
Age (years)	65.90 ± 6.30; 67: (48–74)
BMI	26.34 ± 3.50; 25: (21.6–38.8)
Risk class (D'Amico)	
- Low risk	0 (0.0%)
- Intermediate risk	26 (17.4%)
- High risk	124 (82.6%)
Preoperative total PSA (ng/ml)	16.40 ± 13.10; 13.0: (3.4–66.0)
PSAD	0.25 ± 0.16; 0.19: (0.04–0.59)
Prostate volume (cc)	46.0 ± 19.10; 40.0: (22.0–90.0)
mMR PIRADS score total cases	(data in 96 cases)
PIRADS 2	2 (2.0%)
PIRADS 3	10 (10.5%)
PIRADS 4	50 (52.0%)
PIRADS 5	34 (35.5%)
Prostate Tumor size (mm) at mMR	12.8 ± 4.8; 12.0: (5.0–30.0)
Clinical T staging	
T1c	17 (11.4%)
T2	120 (80.0%)
T3a	7 (4.6%)
T3b	6 (4.0%)
Clinical N staging	
N0	136 (90.6%)
N1	14 (9.4%)
Biopsy outcomes	
% positive samples PC	61.89 ± 26.3; 59.0: (8.0–100.0)
% positive clinical significant PC	55.67 ± 29.5; 50.0: (8.0–100.0)
Max % PC tissue per core	59.64 ± 27.3; 50.0: (5.0–100.0)
ISUP grading at biopsy	
1	8 (5.3%)
2	22 (14.7%)
3	46 (30.7%)
4	54 (36.0%)
5	20 (13.3%)
Nomograms results (% estimated risk for N+)	
MSKCC	32.50 ± 19.03; 30.0: (4.0–83.0)
Briganti 2012	25.01 ± 18.60; 18.5: (4.0–85.0)
Gandaglia 2017	42.10 ± 24.70; 40.0: (4.0–93.0)
Gandaglia 2019	23.99 ± 18.90; 18.0: (4.0–82.0)
Percentage of patients with estimated risk for N + at nomogram over the cut-off	
MSKCC (>7%)	93.3%
Briganti 2012 (>5%)	93.0%
Gandaglia 2017 (>7%)	89.3%
Gandaglia 2019 (>7%)	84.3%
Number of suspected lymph node at imaging	2.28 ± 1.60; 2: (1–5)

Table 1. continued

Lymph node size at preoperative imaging	
<10 mm	115 (76.7%)
≥10 mm	35 (23.3%)
Node Rads score (1–5) at imaging	
1	109 (72.7%)
2	28 (18.6%)
3	7 (4.7%)
4	6 (4.0%)
5	0 (0%)
Surgical technique at radical prostatectomy	
- Laparoscopic	84 (56.0%)
- Robotic assisted	48 (32.0%)
- Open	18 (12.0%)
Pathological stage (T)	
pT2	53 (35.4%)
pT3a	64 (42.6%)
pT3b	32 (21.4%)
pT4	1 (0.6%)
Pathological stage (N)	
N0	114 (76.0%)
N+	36 (24.0%)
Number Lymph nodes removed at surgery	
- Total cases	24.20 ± 8.01; 23: (11–45)
- N + cases	25.30 ± 8.08; 23: (14–45)
- N0 cases	23.90 ± 8.04; 23: (11–45)
Percentage positive lymph nodes in pN + cases	15.90 ± 13.40; 11.4: (4.1–66.6)
ISUP grading at surgery	
1	6 (4.0%)
2	28 (18.6%)
3	51 (34.0%)
4	30 (20.0%)
5	35 (23.4%)
Surgical margin at surgery (R)	
- Negative	109 (72.7%)
- Positive	41 (27.3%)
PNI at surgery	
- Positive	73 (48.6%)
- Negative	77 (51.4%)
Cribriform/IDC at surgery	
- Positive	26 (17.4%)
- Negative	124 (82.6%)
Postoperative total PSA (ng/ml) (90 days from surgery)	0.29 ± 1.39; 0.02: (0.01–4.0)
Biochemical progression (number of cases and %)	26 (17.3%)
Time to biochemical progression (months)	8.04 ± 11.70; 3.0 (3–28)

Mean ± SD, median, (range). Number of cases (%).

samples on the sites indicated by mMRI. Before surgery, clinical staging and risk category (D'Amico and EAU classification) assessment was homogeneously performed following EAU guidelines [2].

Node-RADS determination

The evaluation of LNs results was performed in an assessment category scored between 1 and 5 which reflects the level of suspicious for involvement by PC: −1 = very low; −2 = low; −3 = equivocal; −4 = high; −5 = very high. The interpretation of the radiologist was guided through a 3-level flowchart (Supplementary Fig. 1) with level 1 and 2 addressing size and configuration criteria respectively and level 3 providing the results of Node-RADS score [12]. Size criterion divides nodal sizes in normal (when the shorter diameter is <10 mm), enlarged (between normal and bulk criteria) and bulk (longest diameter >30 mm). Configuration criterion is obtained from the summed numerical values from three sub-categories of texture, border and shape. Texture refers to the internal structure of lymph nodes (homogeneous, heterogeneous, focal necrosis and extended necrosis). Border refers to possible extranodal extension of the disease (smooth, irregular). Shape refers to geometric shape and the delineation of fatty hilum (preserved fatty hilum, oval or spheric without fatty hilum).The radiologist must choose one feature from each sub-category with a minimum configuration score of 0 and a maximum of 5.

Evaluation was performed by a radiologist with high level (more than 15 years) experience in MR imaging and staging for PC (VP), blinded for pathologic postoperative results.

Nomogram evaluation

In each case the MSKCC [8], Briganti 2012 [3], Gandaglia 2017 [4] and Gandaglia 2019 [7] nomograms were evaluated using preoperative clinical and pathological parameters and determining the probability for LN involvement with PC. In particular, as previously described: the MSKCC nomogram based on preoperative PSA, clinical stage, primary and secondary biopsy Gleason and negative and positive biopsy cores; the Briganti 2012 nomogram based on pretreatment PSA, clinical stage, primary and secondary biopsy Gleason score and percentage of positive cores; the Gandaglia 2017 based on preoperative PSA; clinical stage, biopsy Gleason grade, percentage of positive cores with the highest and with the lowest grade disease; the Gandaglia 2019 based on pretreatment PSA, clinical stage, grade group at MR-targeted biopsy, maximum diameter of the index lesion at mpMR, and percentage of cores with clinically significant PC at systematic biopsy.

Pathologic evaluation

All histological specimens from prostatic biopsy and RP were analyzed by our uro-pathologists with a long experience in PC field. In particular, the outcome of interest in our study was lymph node involvement defined as the presence of positive pelvic lymph nodes for PC at final pathology. Fat tissue containing lymph nodes was fixed in 10% buffered formalin, cut at 3 micro-m, stained with haematoxylin-eosin and in selected cases using immunohistochemical staining. Number of lymph nodes removed at surgery and percentage of positive LNs for PC in pN+ cases was reported. Localization of positive LNs was not systematically performed and it was available only in few cases.

Surgical procedure

As routine clinical practice in our Departments, every procedure was performed using a standard robotic assisted (RARP), laparoscopic (LRP) intraperitoneal or an open retropubic approach and performed by surgeons who had the most expertise (more than 10 years and more than 500 procedures) in each approach, consistent with best practice. Extended lymph node dissection (eLND) was performed in all cases including bilateral removal of the nodes overlying the external iliac artery and vein, the nodes within obturator fossa and the nodes medial and lateral to the internal iliac artery.

Statistical analysis and outcomes

For statistical evaluation STATA 1.7 Statistics program was used. For the comparison of quantitative data and pairwise intergroup comparisons of variables a Mann Whitney test was performed. For comparison of qualitative data Fisher's Exact test and chi-square test were used. Pearson correlation analysis was also performed. Univariate and multivariate Cox proportional analysis considering clinical and pathological parameters were used. We tested the accuracy of Node-RADS score in comparison with the available nomograms MSKCC, Briganti and Gandaglia for predicting LN involvement defined at final pathology. Regression coefficients were used to calculate the risk of LN positivity according to each model and the discrimination accuracy of these models was quantified using the area under the receiver operating characteristic (ROC) curve (AUC). Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the different clinical variables in predicting pathologic LN status were evaluated. Statistical significance was fixed at $p < 0.05$.

RESULTS

Characteristics of the whole population

Our population is represented by 150 cases with histological diagnosis of prostate cancer, submitted to radical prostatectomy with an extended pelvic lymph node dissection following the recommendations of EAU guidelines. Baseline characteristics of the whole population are described in Table 1. In particular the indication for an ePLND was based on a preoperative classification of high-risk PC in 124 (82.6%) and of intermediate risk PC in 26 (17.4%) cases. All 26 cases with intermediate risk PC had an estimated risk for pN+ higher than 5% using the Briganti [3] and higher than 7% using the Gandaglia [7] nomogram incorporating mpMR- targeted biopsies. Considering nomograms results as continuous variables without cut-off determination, in the 150 cases (high and intermediate risk), mean estimated % risk for pN+ showed some differences among MSKCC (32.50 ± 19.03), Briganti 2012 (25.01 ± 18.60), Gandaglia 2017 (42.10 ± 24.70) and Gandaglia 2019 (23.99 ± 18.90) nomograms (Table 1).

Most of cases were submitted to a laparoscopic (56.0%) or robotic assisted (32%) RP and the mean number of LNs removed was 24.20 ± 8.01 with similar ($p = 0.188$) values between pN0 (23.90 ± 8.04) and pN+ (25.30 ± 8.08) cases. PLN involvement at final pathology (pN+) was found in 36/150 (24.0%) cases and the mean percentage of positive LNs in pN+ cases was 15.90 ± 13.40 (Table 1). Unfortunately, localization of positive LNs at final pathology analysis was not described in most of cases and simply classified as left or right.

The retrospective evaluation of MR preoperative imaging showed a Node RADS score distribution with 91.3% of score 1–2 (very low + low risk), 4.7% of score 3 equivocal risk) and 4.0% of score 4–5 (high + very high risk) (Table 1).

Comparison in clinical and pathologic parameters between pN0 and pN+ cases

In our population, 36/150 (24.0%) of cases showed a LNs involvement (pN+) at final pathology (Table 2). The number of PLNs removed at RP was similar ($p = 0.188$) between pN0 (23.9 ± 8.0) and pN+ (25.3 ± 8.2) cases. Clinical parameters such as age, risk classification, PIRADS distribution and biopsy outcomes were not significantly ($p > 0.50$) different between pN0 and pN+ cases (Table 2). On the contrary preoperative PSA and the maximal percentage of PC tissue per biopsy core were significantly higher ($p < 0.004$) in pN+ (mean value 17.40 ± 14.41 ng/ml and 70.3 ± 23.89 respectively) when compared to pN0 (mean value 11.6 ± 10.10 ng/ml and 55.6 ± 26.7 respectively) cases. Considering nomograms results as continuous variable without cut-off determination, none of the four preoperative nomograms (although mean values were always higher in pN+ than in pN0 group) showed percentages of estimated risk for pN+ significantly ($p > 0.1$) different between pN0 and pN+ cases (Table 2).

The percentage of Node RADS score 1–2 (low and very low risk) remained high independently to pN status (95.6% in pN0 and 77.7% in pN1), whereas a higher percentage of score 4–5 (high and very high risk) was found in pN+ (16.7%) than in pN0 (0%) cases ($p < 0.01$). The percentage of equivocal Node RADS score 3 cases was similar (5.6% and 4.4%) between pN+ and pN0 cases (Table 2, Fig. 1). Also the number of suspected LNs at imaging significantly differed ($p > 0.01$) between pN0 (mean 1.20 ± 0.44) and pN+ (mean 2.87 ± 1.55) cases (Table 2).

Correlation among pathologic pN status and the other parameters

In our population, Pearson correlation analysis showed no statistically significant correlation between pN result and each of the four nomograms examined as a continuous variable ($p > 0.1$) whereas a statistically significant ($p < 0.01$) correlation was found with preoperative PSA ($r = 0.2155$) and Node RADS score ($r = 2904$) at preoperative MR. Different pathologic parameters at RP

Table 2. Characteristics of the populations on the basis of pN results.

Pathological lymph node status	pN0	pN1	P value
Number cases	114	36	–
Age (years)	66.10 ± 6.44; 68.0: (48–74)	65.50 ± 6.42; 66.0: (50–74)	0.306
BMI	26.0 ± 2.41; 25.5: (23–34.5)	26.30 ± 3.50; 25.6: (22–38.8)	0.280
Risk Class (D'Amico)			
- Low risk	0 (0.0%)	0 (0%)	0.267
- Intermediate risk	21 (18.9%)	5 (13.8%)	
- High risk	93 (81.1%)	31 (86.2%)	
Preoperative total PSA (ng/ml)	11.60 ± 10.10; 9.0: (1.4–66.0)	17.40 ± 14.41; 11.9 (3.5–64.3)	0.004
PSAD	0.21 ± 0.16; 0.15: (0.04–0.59)	0.42 ± 0.07; 0.41: (0.36–0.5)	0.359
Prostate volume (cc)	44.60 ± 20.40; 37.0: (22.0–90.0)	52.30 ± 12.50; 52.0: (40.0–65.0)	0.272
mMR PIRADS score	(data on 71 cases)	(data on 25 cases)	
PIRADS 2	2 (2.8%)	0 (0%)	
PIRADS 3	9 (12.7%)	1 (4.0%)	0.279
PIRADS 4	34 (47.8%)	16 (64%)	
PIRADS 5	26 (36.7%)	8 (32%)	
Prostate Tumor size (mm) at mMR	13.90 ± 6.08; 12.0:(5.0–30.0)	13.90 ± 5.97; 13.0: (7.0–27.0)	0.489
Clinical T staging			
T1c	17 (14.9%)	0 (0%)	
T2	87 (76.4%)	32 (88.8%)	
T3a	6 (5.2%)	2 (5.6%)	0.004
T3b	4 (3.5%)	2 (5.6%)	
Clinical N staging			
N0	108 (94.7%)	28 (77.8%)	
N1	6 (5.3%)	8 (22.2%)	0.001
Biopsy outcomes:			
% positive samples PC	58.90 ± 26.93; 57.0: (8.0–100)	61.40 ± 29.08; 61.05: (11.1–100)	0.318
% positive clinical significant PC	53.10 ± 29.3; 50.0: (8.0–100)	51.20 ± 30.65; 48.5: (10.5–100)	0.372
Max % PC tissue per core	55.60 ± 26.76; 50.0: (5.0–100)	70.30 ± 23.89; 66.7: (31.2–100)	0.001
ISUP grading at biopsy:			
1	7 (6.1%)	1 (2.8%)	
2	14 (12.2%)	8 (22.3%)	
3	35 (30.7%)	11 (30.5%)	0.330
4	43 (37.8%)	11 (30.5%)	
5	15 (13.2%)	5 (13.9%)	
Nomograms results (% estimated risk for N+)			
MSKCC	31.20 ± 19.34; 28.0: (4–83)	36.50 ± 17.69; 34.0: (7–71)	0.074
Briganti 2012	24.10 ± 19.17; 17.0: (4–82)	27.30 ± 17.96; 20.0: (7–85)	0.199
Gandaglia 2017	40.20 ± 25.16; 38.0: (4–93)	46.70 ± 23.34; 45.0: (5–90)	0.096
Gandaglia 2019	22.40 ± 18.89; 16.0: (4–82)	27.70 ± 20.19; 21.0: (4–78)	0.145
Percentage of patients with estimated risk for N + at nomogram over the cut-off			
MSKCC (>7%)	92.1%	97.2%	0.143
Briganti 2012 (>5%)	90.4%	100%	0.029
Gandaglia 2017 (>7%)	86.2%	97.1%	0.038
Gandaglia 2019 (>7%)	80.2%	96%	0.039
Number of suspected lymph node at imaging	1.20 ± 0.44; 1.0 (1–2)	2.87 ± 1.55; 3.0 (1–5)	0.040
Lymph node size at preoperative imaging			
<10 mm	111 (97.3%)	4 (11.1%)	<0.01

Table 2. continued

Pathological lymph node status	pN0	pN1	*P* value
≥10 mm	3 (2.7%)	32 (88.9%)	
Node Rads score (1–5) at imaging			
1	105 (92.1%)	4 (77.7%)	
2	4 (3.5%)	24 (0%)	
3	5 (4.4%)	2 (5.6%)	
4	0 (0%)	6 (16.7%)	<0.01
5	0 (0%)	0 (0%)	
Surgical technique at radical prostatectomy			
- Laparoscopic	72 (63.1%)	12 (33.4%)	
- Robotic assisted	29 (25.5%)	19 (52.7%)	0.007
- Open	13 (11.4%)	5 (13.9%)	
Pathological stage (T)			
pT2	50 (43.9%)	3 (8.3%)	
pT3a	46 (40.3%)	18 (50.0%)	<0.001
pT3b	17 (14.9%)	15 (41.7%)	
pT4	1 (0.9%)	0 (0%)	
Number Lymph nodes removed at surgery	23.90 ± 8.04; 23.0: (11–45)	25.30 ± 8.08; 23.0: (14–45)	0.188
ISUP grading at surgery			
1	6 (5.2%)	0 (0%)	
2	22 (19.3%)	6 (16.7%)	0.039
3	39 (34.3%)	12 (33.3%)	
4	25 (21.9%)	5 (13.8%)	
5	22 (19.3%)	13 (36.2%)	
Surgical margin at surgery (R)			
- Negative	87 (76.3%)	22 (61.1%)	
- Positive	27 (23.7%)	14 (38.9%)	<0.001
PNI at surgery			
- Negative	53 (46.5%)	14 (38.9%)	
- Positive	61 (53.5%)	22 (61.1%)	0.063
Cribriform/IDC at surgery			
- Negative	97 (85.1%)	10 (27.8%)	
- Positive	17 (14.9%)	26 (72.2%)	0.040
Postoperative total PSA (ng/ml) (90 days from surgery)	0.13 ± 0.34; 0.02: (0.01–2.4)	0.79 ± 2.71; 0.02: (0.01–4.0)	0.007
Biochemical progression (number of cases and %)	17 (14.9%)	9 (25%)	0.082
Time to biochemical progression (months)	10.80 ± 13.60; 8.0: (3–24)	3.37 ± 1.76; 3.0: (3–6)	0.048

Mean ± SD, median, (range). Number of cases (%).

such as pT stage, ISUP grading, surgical margins but not the number of nodes surgically removed ($r = 0.0793$, $p = 0.334$) significantly correlated with pN status (Supplementary Table 1).

Moreover, Node RADS score significantly correlated either with preoperative PSA ($r = 0.2195$, $p = 0.006$) or with each of the nomograms ($p < 0.01$), showing higher correlation coefficient with Gandaglia 2017 ($r = 0.3240$, $p < 0.001$) and Gandaglia 2019 ($r = 0.3645$, $p < 0.001$) (Supplementary Table 1).

Sensitivity, specificity, PPV,NPV and AUC results in predicting pN status

The performance of Node RADS score and that of the four nomograms in predicting pN status at final pathology is reported in Table 3. In our population a Node RADS score 4–5 (high and very high suspicious) showed a lower sensitivity (0.167 versus 0.972, 1.000, 0.971, 0.960 respectively) and higher specificity (1.000 versus 0.079, 0.096, 0.138, 0.186 respectively) when compared to MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019 at the recommended estimated risk of >5% or >7%. Accuracy in predictive value was higher using Node RADS score 4–5 (0.793) when compared to that of the different nomograms (<0.400). The AUC for the Node RADS, MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019 nomograms were similar with 0.583, 0.591, 0.581, 0.574,0.597 respectively. ROC curve with AUC value for each nomogram and Node RADS score are presented in Fig. 2. In particular, considering a Node RADS 4–5 positive and a Node RADS 1–2 negative, then the PPV was 100% and the NPV was 79.6%. No cases (0%) with Node RADS 4–5 and 79.6% of score 1–2 showed negative PLN (pN0) at final pathology. On the contrary 100% of Node RADS 4–5 and 20.4% of score 1–2 showed pathologic PLN (pN+) involvement. If we consider only lymph node size (<10 mm versus ≥10 mm) at preoperative imaging as indicator for pN+, PPV was 91.4% and NPV was 96.5%).

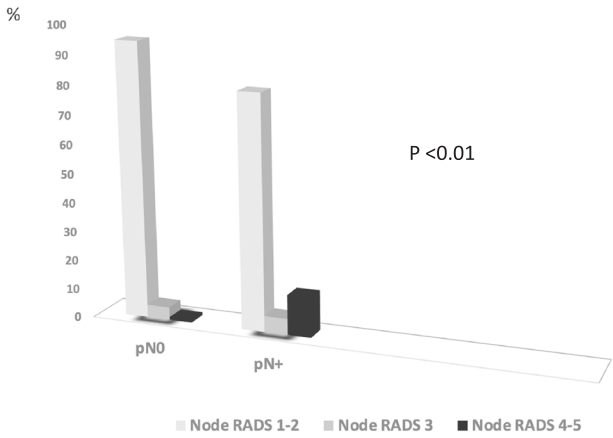


Fig. 1 Bar-chart showing Node RADS score distribution (percentage of cases) between pN0 and pN+ cases. Node RADS score classified as: 1–2 (low and very low risk); 3 (equivocal); 4–5 (high and very high risk). $P < 0.01$.

Logistic regression analysis: predictors for pN+ result at final pathology

Table 4 shows a logistic regression analysis carried out to identify predictors of positive PLN involvement at final pathology (pN+) in our population submitted to RP with ePLND. At the univariate analysis the risk of pN+ significantly increased according to pT stage ($p = 0.004$) and Node RADS ($p = 0.024$); in particular it increased 39.9 times in Node RADS score 4–5 when compared to Node RADS score 1–2 ($p = 0.024$). According to the different nomograms, the risk of pN+ increased 3.0 times for a MSKCC estimated risk >7%, 7.9 times for a Briganti 2012 estimated risk >5%, 5.4 times for a Gandaglia 2017 estimated risk >7% and 5.5 times for a Gandaglia 2019 estimated risk >7%, ($p > 0.1$). At the multivariate analysis, only pT stage maintained an independent predictive value in terms of risk for pN+ ($p = 0.005$) whereas Node RADS was at the limit of statistical significance ($p = 0.052$).

DISCUSSION

The evaluation of PLNs at preoperative imaging using CT or MR is mainly based on nodal size that showed to be a poor predictor for PC involvement [9, 10].

As stated by international guidelines [2], the selection of candidates for a RP associated with an ePLND is performed on the basis of risk classes definition and validated nomograms such as the Briganti and Gandaglia [3, 4, 7, 8]. Using a 5% [3] or 7% [4] cut-off in terms of estimated risk for pN+, nomograms identify cases

Table 3. Sensitivity, specificity, positive and negative predictive values (PPV, NPV) and area under the curve (AUC) of different variables in predicting pN+ status at surgery.

	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	AUC (CI 95%)
Node-RADS 4–5	0.167 (0.076–0.324)	1.000 (0.960–1.000)	1.000 (0.960–1.000)	0.792 (0.716–0.852)	0.583 (0.522–0.645)
Node-RADS 3–5	0.222 (0.116–0.384)	0.956 (0.898–0.983)	0.615 (0.532–0.693)	0.796 (0.532–0.693)	0.589 (0.518–0.661)
MSKCC nomogram > 7%	0.972 (0.843–1.000)	0.079 (0.041–0.146)	0.250 (0.185–0.328)	0.900 (0.838–0.941)	0.591 (0.490–0.691)
Briganti 2012 nomogram > 5%	1.000 (0.879–1.000)	0.096 (0.050–0.175)	0.292 (0.217–0.379)	1.000 (0.964–1.000)	0.581 (0.478–0.683)
Gandaglia 2017 nomogram > 7%	0.971 (0.839–1.000)	0.138 (0.080–0.228)	0.312 (0.233–0.403)	0.923 (0.857–0.961)	0.574 (0.466–0.682)
Briganti 2019 nomogram > 7%	0.960 (0.786–1.000)	0.186 (0.111–0.294)	0.296 (0.209–0.400)	0.929 (0.852–0.969)	0.597 (0.472–0.722)

for an ePLND during RP which would result in missing very low percentage (approximately 1.5%) of patient with LNs involvement. However, these selections continue to produce in the clinical practice a relevant percentage of cases submitted to ePLND in which the pathologic evaluation is negative (pN0) for malignancy [13–17] and trials on the validation of these nomograms [4, 7, 8, 18, 19] mainly showed a percentage higher than 50% of patients above the suggested cut-off without LNs involvement after surgery.

The standardized evaluation of RADS have been used in different oncologic scenarios and in particular for PC the PIRADS changed the paradigm in the management of the early diagnosis [20]. The purpose of Node-RADS is to enhance the identification of LNs by adding configuration criteria to size determination at preoperative imaging [12]. Configuration criterion is obtained from the summed numerical values from 3 sub-categories of texture, border and shape. All these sub-evaluations introduce a possible subjective analysis that could be differently interpreted by different users. In our study all Node RADS evaluations were performed by a radiologist with high level experience in MR imaging and staging for PC who described no significant uncertainties in both size and configuration determination. However, the inter-user reproducibility of Node RADS should be investigated in further analyses.

At now no clinical results in PC cases submitted to RP have been presented in the literature and our analysis represents the first focused report. We considered a real-life situation on a population of PC cases considered for RP with ePLND following the actual recommendation of EAU guidelines [2, 21]. Despite our population represented a selected one with higher percentage of high risk (82.6%) than intermediate risk (17.4%) cases and a percentage of approximately 90% of cases with an estimated risk for LN involvement higher than the suggested cut-off at nomograms, at final pathology, on a mean of 24.2 PLDs removed at surgery, 76% of cases were pN0. Similar low percentages (11–20%) of pN+ cases were reported in other recent clinical experiences using an ePLND [18, 19]. The percentage of Node RADS score 1–2 (low and very low risk) remained high independently to pN status (95.6% in pN0 and 77.7% in pN1). At univariate analysis, the risk for pN+ significantly increased in Node RADS score 4–5 when compared to score 1–2 ($p = 0.024$) cases whereas at the multivariate analysis, only pT stage maintained an independent predictive value in terms of risk for pN+ ($p = 0.005$). Node RADS score 4–5 showed a lower sensitivity (0.167 versus 0.972, 1.000, 0.971, 0.960 respectively), higher specificity (1.000 versus 0.079, 0.096, 0.138, 0.186 respectively) and a similar AUC (0.583, 0.591, 0.581, 0.574, 0.597 respectively) when compared to MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019 at the recommended estimated risk. In particular, considering a Node RADS 4–5 positive and a Node RADS 1–2 negative, then the PPV was 100% and the NPV was 79.6%. No cases (0%) with Node RADS 4–5 and 79.6% of score 1–2 showed negative PLN (pN0) at final pathology. On the contrary 100% of Node RADS 4–5 and 20.4% of score 1–2 showed pathologic PLN (pN+) involvement. If we consider only lymph node size (<10 mm versus ≥10 mm) at preoperative imaging as indicator for pN+, PPV was lower (91.4%) but NPV was higher (96.5%).

A large analysis from Hovels et al. [22] determined the pooled diagnostic accuracy of CT and MR using the traditional size criteria in determining LN status. The pooled sensitivity and specificity for CT were 0.42 (95% CI 0.26–0.56) and 0.82 (95% CI 0.80–0.83) respectively whereas for MR were 0.39 (95% CI 0.22–0.56) and 0.82 (95% CI 0.79–0.83) respectively. Our results show that the majority of cases selected for RP with ePLND following actual recommendations, present a low or very low risk at Node RADS evaluation. In case of a preoperative high o very high risk at Node RADS, the probability for a pathologic confirmation of LNs involvement is high, but a Node RADS 1–2 score remain associated with a relevant percentage of pN+ at final pathology.

Strengths and Limitations

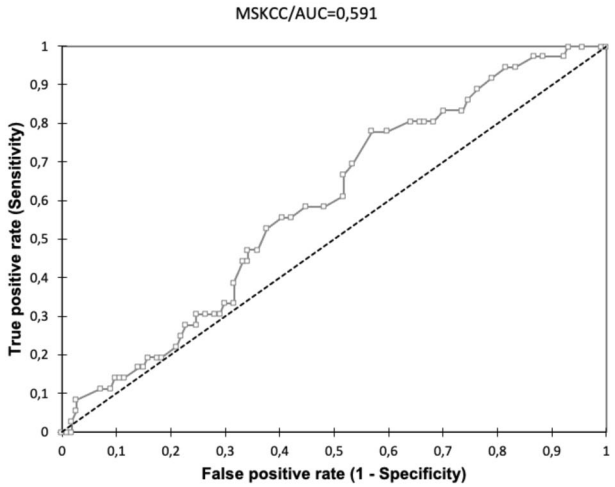
Strengths: (I) the present analysis considered objectives and included results different from previous; (II) a real-life situation based on guidelines recommendation is represented; (III) Node RADS interpretation was performed by an expert in MR imaging and PC, blinded to pathology results; (IV) pathologic results have been used for final comparison.

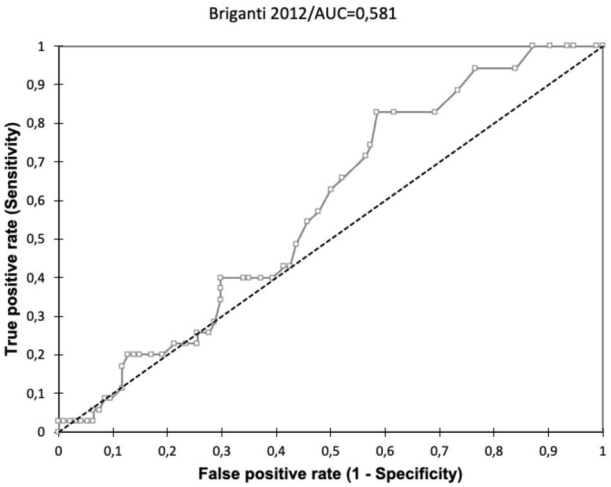
Limitations: (I) this is a retrospective analysis; (II) some data such as localization of positive LNs were not available; (III) the population was selected on the basis of high risk or intermediate with an estimated risk for pN+ at nomograms over the recommended cut—off.

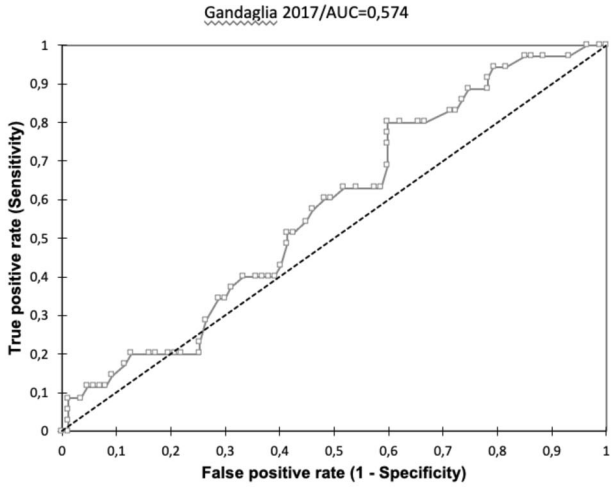
Retrospective analyses were similarly used to initially validate nomograms [3, 4, 7]. We programmed to continue our evaluation with two ongoing trials: a new retrospective multi-center study on a more extended population and a prospective multi-center study with a similar design. The prospective study could better evaluate correspondence between Node RADS and final pathologic results, also in terms of LN localization. It could be also relevant to assess Node RADS performance in a non-selected population. However, pathologic confirmation at surgery is mandatory for this evaluation and recommendations impose to select patients for an ePLND.

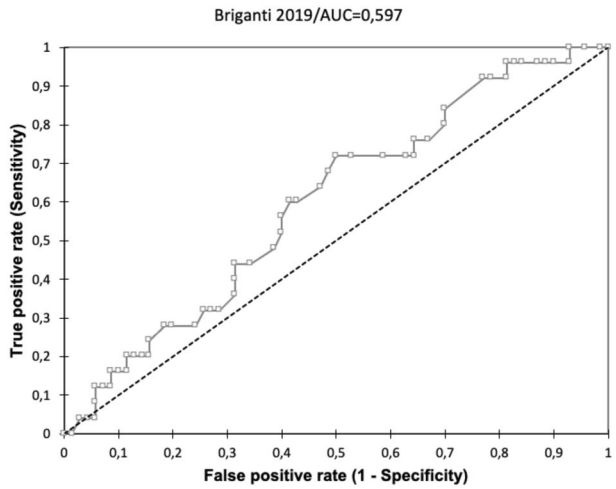
CONCLUSIONS

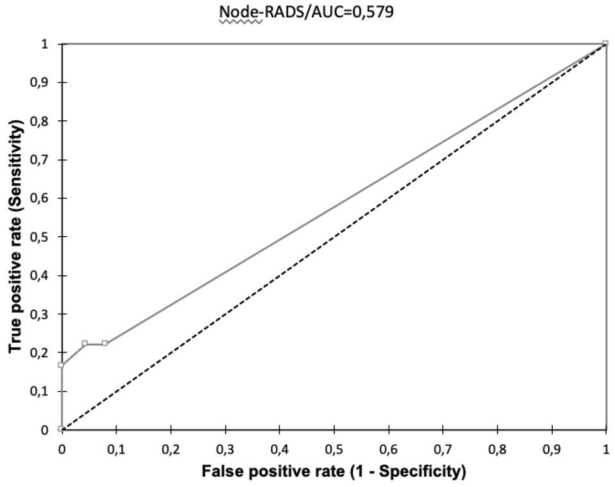
A high percentage of cases selected for RP with ePLND continue to result negative (pN0) for LNs involvement at final pathology. Our evaluation suggests that Node RADS score, combining configuration criteria to size determination at preoperative imaging could improve specificity in terms of pathologic prediction but a very low sensitivity has been also described. Actual imaging, even when using Node-RADS criteria, remains uncertainly useful for driving regional lymph node management











Cut-off	AUC	SE	95% CI	
Briganti 2019_>7%	0,597	0,064	0,472	0,722
Gandaglia 2017_>7%	0,574	0,055	0,466	0,682
Briganti 2012_>5%	0,581	0,052	0,478	0,683
MSKCC_>7%	0,591	0,051	0,490	0,691
Node-RADS (3-5 vs. 1-2)	0,589	0,036	0,518	0,661
Node-RADS (4-5 vs. 1-3)	0,583	0,031	0,522	0,645

AUC comparison	P value
Node-RADS (4-5 vs. 1-3) vs. Node-RADS (3-5 vs. 1-2)	0.8995
Node-RADS (4-5 vs. 1-3) vs. MSKCC_>7%	0.8934
Node-RADS (4-5 vs. 1-3) vs. Briganti 2012_>5%	0.9736
Node-RADS (4-5 vs. 1-3) vs. Gandaglia 2017_>7%	0.8866
Node-RADS (4-5 vs. 1-3) vs. Briganti 2019_>7%	0.8439

AUC comparison	P value
Node-RADS (3-5 vs. 1-2) vs. MSKCC_>7%	0.9744
Node-RADS (3-5 vs. 1-2) vs. Briganti 2012_>5%	0.8993
Node-RADS (3-5 vs. 1-2) vs. Gandaglia 2017_>7%	0.8195
Node-RADS (3-5 vs. 1-2) vs. Briganti 2019_>7%	0.9132

Fig. 2 ROC curve and AUC predicting PLN involvement. Receiver operating characteristic (ROC) curve and relative Area Under the Curve (AUC) in predicting PLN involvement (pN+) of Node RADS and the currently available nomograms MSKCC, Briganti 2012, Gandaglia 2017 and Gandaglia 2019.

Table 4. Logistic regression analysis to identify predictors for positive lymph node (pN+) at RP. Univariate and multivariate analysis. Odds Ratio (OR), 95% Confidential Interval (CI).

		Univariable				Multivariable			
		OR	**95% CI_lower**	**95% CI_upper**	***p* value**	**OR**	**95% CI_lower**	**95% CI_upper**	***p* value**
Preoperative PSA		Ref	–	–	–				
	>10	1792	0.839	3827	0.132				
MSKCC nomogram		Ref	–	–	–				
	>7%	3,00	0.367	24,526	0.305				
Briganti 2012 Nomogram		Ref	–	–	–				
	>5%	7889	0.384	162,183	0.181				
Gandaglia 2017 nomogram		Ref	–	–	–				
	>7%	5440	0.680	43,538	0.110				
Gandaglia 2019 Nomogram		Ref	–	–	–				
	>7%	5474	0.678	44,215	0.111				
Pathologic stage	pT2	Ref	–	–	–	Ref	–	–	–
	pT3a	6522	1.802	23,602	0.004	6338	1743	23,049	0.005
	pT3b	13,889	3.595	53,661	0.0001	10,211	2531	41,200	0.001
ISUP at surgery	1	Ref	–	–	–				
	2	3756	0.148	95,072	0.422				
	3	4114	0.172	98,198	0.382				
	4	2804	0.109	71,957	0.533				
	5	7800	0.324	187,826	0.206				
Node-RADS	1–2	Ref	–	–	–	Ref	–	–	–
	3–5	6.229	1.891	20.515	0.003	3.621	0.988	13.264	0.052
	4–5	39.989	1.636	97.239	0.024				

in most cases, given very low sensitivity and only 4% of patients with positive tests. Further analysis and prospective trials should verify outcomes on Node RADS in PC patients.

DATA AVAILABILITY

Database including all data obtained for this analysis is available with the code: #9645 A at the following mail address for request: alessandro.sciarra@uniroma1.it.

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AUTHOR CONTRIBUTIONS

SL: radiologic evaluation of data. MLP: radiologic evaluation of data. MF: data acquisition and data analysis. FM: pathological analysis. AG: data acquisition. FDG: data analysis and statistical analysis. VC: data acquisition and statistical analysis. ES: data acquisition. GMB: data acquisition. GC: data analysis. LC: data acquisition. AC: data acquisition. AP: data acquisition CDN: data acquisition and data analysis. AT: data acquisition. CL: data acquisition. GF: data acquisition. GDP: data acquisition. SS: study design and concept; drafting of the manuscript. AS: study design and concept; drafting of the manuscript. VP: study design and concept.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41391-022-00564-z.

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