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# Predictors of Lymph Node Invasion in Patients with Clinically Localized Prostate Cancer Who Undergo Radical Prostatectomy and Extended Pelvic Lymph Node Dissection: The Role of Obesity

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**Keywords**
Obesity · Prostate cancer · Clinically localized prostate cancer · Radical prostatectomy · Extended pelvic lymph node dissection · Lymph node invasion · European Association of Urology risk classes

**Abstract**
***Objective:*** In patients with intermediate- and high-risk localized prostate cancer (PCa), improving the detection of occult lymph node metastases could play a pivotal role for therapeutic counseling and planning. The recent literature shows that several clinical factors may be related to PCa aggressiveness. The aim of this study is to investigate the potential associations between clinical factors and the risk of multiple lymph node invasion (LNI) in patients with intermediate- and high-risk localized PCa (cT1/2, cN0, and ISUP grading group >2 and/or prostate-specific antigen (PSA) >10 ng/mL) who underwent radical prostatectomy (RP) and extended pelvic lymph node dissection (ePLND). ***Materials and Methods:*** In a period ranging from January 2014 to December 2018, 880 consecutive patients underwent RP with ePLND for PCa. Among these, 481 met the inclusion criteria and were selected. Data were prospectively collected within an institutional dataset and retrospectively analyzed. Age (years), body mass index (BMI; kg/m$^2$), PSA (ng/mL), prostate volume (mL), and biopsy positive cores (BPC; %) were recorded for each case. BMI and BPC were considered continuous and categorical variables, respectively. The logistic regression models evaluated the association of clinical factors with the risk of nodal metastases. ***Results:*** LNI was detected in 73/418 patients (15.2%) of whom 40/418 (8.3%) harbored multiple LNI (median 2, IQR: 3–4). On multivariate analysis, BMI was independently associated with the risk of multiple

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LNI in the pathological specimen when compared with patients without LNI (OR = 1.147; $p = 0.018$), as well as the percentage of biopsy positive cores (OR = 1.028; $p < 0.0001$) and European Association of Urology high-risk class (OR = 5.486; $p < 0.0001$). BMI was the only predictor of multiple LNI when compared with patients with 1 positive node (OR = 1.189, $p = 0.027$). ***Conclusions:*** In intermediate- and high-risk localized PCa, BMI was an independent predictor of the risk of multiple lymph node metastases. The inclusion of BMI within LNI risk calculators could be helpful, and a detailed counseling in obese patients should be required.



## Introduction

Prostate cancer (PCa) is the second most common cancer in males, and its incidence is increasing worldwide [1]. The European Association of Urology (EAU) Guidelines on PCa classify the disease into low-, intermediate-, and high-risk groups according to the metastatic potential; in addition, patients with high risk are subclassified into clinically localized (cT1–2) or locally advanced (cT > 2 or cN+), while low- and intermediate-risk patients have localized disease only [2, 3].

Radical prostatectomy (RP) is mainly indicated for clinically localized disease, whereas in locally advanced disease it should be considered within the context of a multimodal approach [2]. The indication for extended pelvic lymph node dissection (ePLND) is generally established according to a risk stratification for lymph node invasion (LNI) carried out through statistical predictive tools, given that such events are still underdiagnosed by preoperative diagnostic tools [4, 5]. Roughly, such an indication is posed for almost all the high-risk PCa and a proportion of intermediate risk demonstrating a significant risk of LNI according to the adopted nomogram [2].

In the recent literature, clinical factors such as prostate volume (PV), PCa volume evaluated by the number of positive prostate biopsy cores, and prostate-specific antigen (PSA) have been associated with more aggressive PCa [6, 7]. In addition, over the past 30 years, the prevalence of PCa has mirrored the spread of obesity, potentially reflecting their shared risk factors. Also, an association between obesity and PCa risk was proposed, which may be due to an increase in levels of serum growth factors and inflammatory cytokines resulting in hyperactivation of intracellular transduction pathways with consequent increased anabolic, antiapoptotic, and mitotic activity [8]. According to these findings, a correlation between obesity and more aggressive PCa biology was demonstrated in terms of grade, stage, and cancer-related mortality after surgery [8]. The aim of this study is to evaluate the association between preoperative clinical factors and the risk of multiple LNI in a cohort of patients who underwent RP with ePLND for clinically localized intermediate- and high-risk PCa.

## Materials and Methods

The study was approved by the Institutional Review Board. Data were collected after each patient provided informed signed consent. In a period ranging from January 2014 to December 2018, 880 patients underwent RP at our institution. Data were prospectively entered into our institutional database. For the present study, only patients with intermediate- or high-risk PCa according to EAU risk classes who underwent RP with ePLND were included for analysis, while patients under androgen deprivation therapy were excluded.

Age (years), body mass index (BMI; kg/m$^2$), PSA (ng/mL), PV (mL), and biopsy positive cores (BPC; %) were considered for each case. BMI was considered as categorical variable, based on the WHO classification – normal <25, overweight ≥25 and <30, and obese ≥30 kg/m$^2$[9]); BPC was also categorized using the cutoff of 50% as suggested by the National Comprehensive Cancer Network (NCCN) guidelines [10]. Patients were also classified according to EAU risk classes [2].

Tumor, nodal, and metastatic status was assessed according to the TNM system [2]. Clinical staging was performed according to EAU guideline recommendations. All intermediate- and high-risk patients underwent CT scan and bone scan to assess local extension, lymph-nodal, and distant metastasis; PET-CT scan was used in selected cases, according to clinical preference or to assess suspicious findings on CT and/or PET-CT scan. Imaging studies were interpreted by experienced radiologists and nuclear medicine radiologists. Enlarged pelvic nodes measuring >1 cm in diameter were staged as suspicious for LNI (cN+), and patients were excluded. The metastatic status was investigated by both axial imaging and total bone scans. Patients who were classified as locally advanced according to the EAU system were excluded.

In our institution, a 14-core transperineal prostate biopsy technique was used. In the biopsy specimen report, the number of positive cores was specified for each patient. PV (mL) was measured through transrectal ultrasound (TRUS) by using the formula for an ellipsoid (height × width × length × [π/6]) [11]. Biopsies performed at outside institutions were assessed for the following features: (i) at least 12 biopsy cores, (ii) the reported number of positive cores, and (iii) measurement of PV (mL).

Experienced surgeons performed operations by the robot-assisted RP (RARP) or by the open retropubic RP (RRP) approach. RARP was delivered by the da Vinci Robot System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) and was performed through the transperitoneal approach with anterograde prostatic dissection [12]. RRP was performed according to the technique described by Walsh [13]. The lymph node dissection template included bilateral external iliac (until the crossing of the ureter and the external

**Table 1.** Factors associated with unifocal and multifocal occult LNI of pelvic nodes staged by ePLND in clinically localized PCa including EAU intermediate- and high-risk classes

| Factors | Patient population | No LNI | LNI with one positive node | LNI with >1 positive node | *p* value |
|---|---|---|---|---|---|
| *N* (%) | 481 | 408 (84.8) | 33 (6.9) | 40 (8.3) | |
| Clinical factors | | | | | |
| Age, years, median (IQR) | 65 (61–70) | 65 (61–70) | 67 (62–71.5) | 66 (61.2–71) | 0.560 |
| BMI, kg/m², median (IQR | 25.8 (23.8–28.1) | 25.7 (23.8–27.8) | 25 (24–26.9) | 26.8 (24.7–29.8) | 0.023 |
| PSA, ng/mL, median (IQR) | 7.2 (5.2–10.5) | 6.9 (5.2–9.7) | 7.5 (5.8–11.3) | 14.5 (7.1–24) | <0.0001 |
| PV, mL, median (IQR) | 40 (30–50) | 39.5 (30–50) | 45 (315–62.9) | 40 (35–49.9) | 0.165 |
| BPC, %, median (IQR) | 40 (25–57) | 35.5 (21–50) | 50 (27–77.5) | 57.5 (43–71.7) | <0.0001 |
| Dissected nodes, *n*, median (IQR) | 25 (19–32) | 24 (19–31) | 28 (22.5–36) | 25.5 (18.2–33) | 0.088 |
| ISUP, *n* (%) | | | | | |
| 1 | 43 (8.9) | 36 (8.8) | 3 (9.1) | 4 (10) | <0.0001 |
| 2 | 219 (45.5) | 199 (48.8) | 10 (30.3) | 10 (25) | |
| 3 | 109 (22.7) | 97 (23.8) | 7 (21.2) | 5 (12.5) | |
| 4 | 89 (18.5) | 65 (15.9) | 9 (27.3) | 15 (37.5) | |
| 5 | 21 (4.4) | 11 (2.7) | 4 (12.1) | 6 (15) | |
| Tumor clinical stage, *n* (%) | | | | | |
| cT1 | 287 (58.4) | 247 (60.5) | 13 (39.4) | 21 (52.5) | 0.044 |
| cT2 | 200 (41.6) | 161 (39.5) | 20 (60.6) | 19 (47.5) | |
| EAU risk class, *n* (%) | | | | | |
| Intermediate | 339 (70.5) | 308 (75.5) | 18 (54.5) | 13 (32.5) | <0.0001 |
| High | 142 (29.5) | 100 (24.5) | 15 (45.5) | 27 (67.5) | |
| Pathological factors | | | | | |
| ISUP, *n* (%) | | | | | |
| 1 | 14 (2.9) | 14 (3.4) | 0 (0.0) | 0 (0.0) | <0.0001 |
| 2 | 148 (30.8) | 142 (34.8) | 7 (9.1) | 3 (7.5) | |
| 3 | 151 (31.4) | 140 (34.3) | 3 (21.2) | 4 (10) | |
| 4 | 115 (23.9) | 86 (21.1) | 13 (39.4) | 16 (40) | |
| 5 | 53 (11) | 26 (6.4) | 10 (30.3) | 17 (42.5) | |
| Pathologic tumor stage, *n* (%) | | | | | |
| 2 | 317 (65.9) | 299 (73.3) | 12 (36.4) | 6 (15) | <0.0001 |
| 3a | 70 (14.6) | 60 (14.7) | 4 (12.1) | 6 (15) | |
| 3b | 94 (19.5) | 49 (12) | 17 (51.5) | 28 (70) | |
| Surgical margins, *n* (%) | | | | | |
| Negative | 328 (68.2) | 288 (70.6) | 17 (51.5) | 23 (57.5) | 0.024 |
| Positive | 153 (31.8) | 120 (29.4) | 16 (48.5) | 17 (42.5) | |

LNI, lymph node invasion; ePLND, extended pelvic lymph node dissection; PCa, prostate cancer; IQR, interquartile range; EAU, European Association of Urology; BMI, body mass index; PV, prostate volume; ISUP, International Society of Urological Pathology tumor grade system; PSA, prostate-specific antigen; BPC, biopsy positive cores.

iliac artery), Cloquet's, obturator, and Marcille's lymph node packets, as previously reported [14, 15].

Tumors were classified into grade groups according to the International Society of Urological Pathology (ISUP) tumor grade group system [3]. Our 2 dedicated uropathologists assessed all specimens, which were processed according to the Stanford protocol [16]. Surgical margins were deemed positive when cancer invaded the inked surface of the specimen. Nodal packets were grouped according to a standard template and submitted in separate packages. Lymph nodes were assessed for histopathology after hematoxylin and eosin staining. Immunohistochemical staining was performed when appropriate. In each case, the number of removed lymph nodes and LNI was assessed. Prostate and nodal specimens were then staged using TNM system.

According to the pathology results, LNI was classified as absent (pN0 status) or present (pN1 status). Patients having pN1 were further classified as having one or >1 metastatic nodes.

*Statistical Methods*

Data on continuous variables were reported as medians with interquartile ranges (IQR). Data on categorical variables were presented as frequencies and percentages. Differences among groups (absent vs. present, 1 vs. >1 positive node) were evaluated by the

**Table 2.** Univariate analysis of clinical factors associated with the risk of single and multiple LNI (models I and II)

| | pN0 vs. pN+ | | | More than one positive node vs. no LNI | | | More than one positive node vs. one positive node | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Model I | | | | | | | | | |
| BMI | – | | | 1.170 | 1.049–1.306 | 0.005 | 1.189 | 1.019–1.386 | 0.027 |
| PSA | 1.057 | 1.029–1.086 | <0.0001 | 1.082 | 1.048–1.118 | <0.0001 | 1.076 | 1.014–1.142 | 0.015 |
| BPC | 1.029 | 1.018–1.040 | <0.0001 | 1.033 | 1.019–1.047 | <0.0001 | 1.009 | 0.991–1.208 | 0.315 |
| cT2 | 1.760 | 1.066–2.504 | 0.027 | 1.388 | 0.724–2.663 | 0.324 | 1.207 | 0.465–3.233 | 0.699 |
| Biopsy ISUP >2 | 2.314 | 1.384–3.870 | 0.001 | 2.523 | 1.208–54.973 | 0.008 | 0.588 | 0.231–1.497 | 0.327 |
| Model II | | | | | | | | | |
| BMI | – | | | 1.17 | 1.049–1.306 | 0.005 | 1.189 | 1.019–1.386 | 0.027 |
| BPC | 1.029 | 1.018–1.040 | <0.0001 | 1.033 | 1.019–1.047 | <0.0001 | 1.009 | 0.991–1.028 | 0.315 |
| EAU risk class | | | | | | | | | |
| >Intermediate | 1 | | | 1 | 1 | | 1 | 1 | |
| >High | 4.173 | 2.491–6.991 | <0.0001 | 6.397 | 3.180–12.869 | <0.0001 | 2.492 | 0.961–6.461 | 0.060 |

LNI, lymph node invasion; OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; BPC, biopsy positive cores; EAU, European Association of Urology; ISUP, International Society of Urological Pathology tumor grade system.

Kruskal-Wallis test for continuous variables and by the $\chi^2$ test for categorical parameters. The logistic regression model (univariate and multivariate analysis) was used to evaluate the association between significant clinical factors and the risk of multiple lymph nodes metastases.

In order to evaluate the predictive role of clinical factors on the risk of multiple LNI, 2 sets of models were built: the first studied singularly preoperative predictors including PSA, ISUP, and cTNM, as well as BMI and BPC. The second considered EAU risk classes, BMI, and BPC.

The software used to run the analysis was IBM-SPSS version 20. All tests were two-sided with $p < 0.05$ considered to indicate statistical significance.

## Results

According to the aforementioned inclusion criteria, 481 patients were included in the present study. Demographics are summarized in Table 1. Overall, 339 out of 481 patients were EAU intermediate-risk class (70.5%) and 142 (29.5%) belonged to the EAU high-risk class. RARP with ePLND was performed in 373 cases (77.5%) and RRP with ePLND in 108 cases (21.1%). The median number of removed nodes was 25 (IQR: 19–32); LNI was detected in 73/418 patients (15.2%) of whom 40/418 (8.3%) had multiple LNI (median positive nodes, 2; IQR: 3–4). No significant differences in the median number of retrieved nodes were seen between pN0 and pN+ cases (28 vs. 26, $p = 0.09$, demographics and comparison between pN0 and pN1 patients' groups are reported in online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000510008).

Considering pathological nodal status, BMI with other known clinical factors including PSA, BPC, clinical stage, and ISUP grade group classification was different among patients with N0, pN1 with only 1 positive node, and patients having multiple LNI (Table 1). Patients with multiple LNI were more likely to belong to EAU high-risk class compared with intermediate (67.5% vs. 32.5%; $p < 0.0001$) as detailed in Table 1.

### Univariate and Multivariate Analysis

*Model I*

We investigated the role of BMI and other clinical factors on LNI prediction. We found that PSA (OR: 1.057, $p < 0.0001$), BPC (OR: 1.029, $p < 0.0001$), clinical stage ≥T2 (OR: 1.760, $p = 0.027$), and ISUP grade groups (OR: 2.314, $p < 0.0001$) were predictors of LNI in univariate analysis. On multivariate analysis, PSA (OR: 1.052 $p < 0.0001$), BPC (OR: 1.023, $p < 0.0001$), and ISUP grade groups (OR: 2.182, $p < 0.006$) were predictors of LNI.

When we evaluated the role of clinical factors in predicting multiple LNI, we found that BMI (OR: 1.17, $p = 0.005$), PSA (OR: 1.082, $p < 0.0001$), BPC (OR: 1.033, $p < 0.0001$), and biopsy ISUP (OR: 2.523, $p = 0.008$) were associated with the risk of multiple nodal metastasis compared with patients without LNI in univariate analysis.

**Table 3.** Multivariate analysis of clinical factors associated with the risk of single and multiple LNI (models I and II)

| | LNI vs. no LNI | | | More than one positive node vs. no LNI | | | More than one positive node vs. one positive node | | |
|---|---|---|---|---|---|---|---|---|---|
| | OR | 95% CI | *p* value | OR | 95% CI | *p* value | OR | 95% CI | *p* value |
| Model I | | | | | | | | | |
| BMI | – | | | 1.166 | 1.035–1.313 | 0.012 | 1.221 | 1.040–1.434 | 0.015 |
| PSA | 1.052 | 1.024–1.082 | <0.0001 | 1.081 | 1.046–1.118 | <0.0001 | 1.080 | 1.018–1.115 | 0.010 |
| BPC | 1.023 | 1.012–1.034 | <0.0001 | 1.024 | 1.009–1.039 | 0.002 | – | | |
| cTNM cT2 | 1.618 | 0.942–2.778 | 0.081 | – | | | | | |
| Biopsy ISUP >2 | 2.182 | 1.256–3.791 | 0.006 | 2.559 | 1.175–5.371 | 0.018 | – | | |
| Model II | | | | | | | | | |
| BMI | – | | | 1.147 | 1.024–1.285 | 0.018 | – | | |
| BPC | 1.024 | 1.013–1.035 | <0.0001 | 1.028 | 1.014–1.043 | <0.0001 | – | | |
| EAU risk class | | | | | | | – | | |
| >Intermediate | 1 | | | 1 | 1 | | | | |
| >High | 2.892 | 1.626–5.144 | <0.0001 | 5.486 | 2.662–11.307 | <0.0001 | | | |

LNI, lymph node invasion; OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; BPC, biopsy positive cores; EAU, European Association of Urology.

**Table 4.** Categorized clinical factors associated with the risk of occult multiple LNI of pelvic nodes staged by ePLND in clinically localized PCa including EAU intermediate- and high-risk classes

| | Overall population | Group without LNI | Group with multiple LNI | OR (95% CI) |
|---|---|---|---|---|
| *N* (%) | 448 | 408 (91.1) | 40 (8.9) | |
| BMI | | | | |
| <30 | 398 (88.8) | 367 (92.2) | 31 (7.8) | 1 |
| ≥30 | 50 (11.2) | 41 (82) | 9 (18) | 2.747 (1.120–6.736) |
| BPC | | | | |
| <50% | 279 (62.3) | 266 (95.3) | 13 (4.7) | 1 |
| ≥50% | 169 (37.7) | 142 (84) | 27 (16) | 3.388 (1.650–6.956) |
| EAU risk class | | | | |
| >Intermediate | 321 (71.7) | 308 (95.9) | 13 (4.1) | 1 |
| >High | 127 (28.3) | 100 (78.7) | 27 (21.2) | 6.040 (2.984–12.378) |

LNI, lymph node invasion; ePLND, extended pelvic lymph node dissection; PCa, prostate cancer; OR, odds ratio; CI, confidence interval; BMI, body mass index; BPC, biopsy positive cores; EAU, European Association of Urology.

BMI (OR: 1.189, $p = 0.027$) and PSA (OR: 1.076, $p = 0.015$) were associated with multiple LNI when compared with patients with 1 metastatic node (Table 2). On multivariate analysis, BMI (OR: 1.166, $p = 0.012$), PSA (OR: 1.081, $p < 0.0001$), BPC (OR: 1.024, $p = 0.002$), and ISUP grade group (OR: 2.559 $p = 0.018$) were associated with the risk of multiple LNI compared with patients without LNI; only BMI (OR: 1.080, $p = 0.015$) and PSA (OR: 1.221, $p = 0.01$) were predictors of multiple LNI when compared with patients with 1 metastatic node (Table 3).

*Model II*

Model II evaluates the risk of LNI by BMI through EAU risk classes and BPC. In the model II, we investigated EAU risk classes as well as BMI and BPC in predicting LNI and we found that BPC and EAU high-risk class were associated with the risk pN+ in univariate and multivariate analysis (Tables 2, 3). In addition, we found that BMI (OR: 1.17, $p = 0.005$), BPC (OR: 1.033, $p < 0.0001$), and EAU high-risk class (OR: 6.397, $p < 0.0001$) were predictors of multiple LNI in univariate analysis comparing

with cases without LNI. Only BMI was a predictor of multiple LNI when compared with patients with 1 positive node (OR: 1.189, $p = 0.027$). In multivariate analysis, BMI (OR: 1.147, $p = 0.018$), BPC (OR: 1.028, $p < 0.0001$), and high-risk class (OR: 5.486, $p < 0.0001$) were associated with risk of multiple LNI compared with patients without LNI (Tables 2, 3).

Table 4 shows demographics and multivariate analysis of the patient population including cases with multiple lymph node metastases (8.9%) and patients without LNI. Clinical factors are categorized by EAU risk classes (intermediate/high), BMI categories (nonobese/obese), and BPC (<50%/≥50%). Obese patients (BMI ≥ 30), which made up 11.2% of the population (50 cases), had an almost three-fold risk of harboring multiple lymph node metastases (OR = 2.747; 95% CI: 1.120–6.736) compared with nonobese subjects. Patients with BPC ≥ 50% and patients with EAU high-risk class PCa had a three-fold (OR = 3.388; 95% CI: 1.650–6.956) and six-fold (OR = 6.040; 95% CI: 2.948–12.378) risk of occult multiple nodal metastases, respectively.

## Discussion

Currently, ePLND is the most accurate method of nodal staging in PCa patients, and the number of removed nodes may represent an effective indicator of the quality of ePLND [17]. In clinically localized PCa, EAU guidelines recommend an ePLND in order to have an appropriate nodal stage of the disease whenever it is indicated according to the considered LNI risk nomograms [2]. ePLND should be performed according to a well-defined template that addresses the lymphatic drainage of the prostate during open, laparoscopic, or RARP [2].

Retrospective studies have demonstrated that the number of positive nodes predicted cancer-specific survival in PCa patients who underwent RP and ePLND. In addition, patients with up to 2 positive nodes had better survival compared with cases with >2 positive lymph nodes. Furthermore, the number of positive nodes detected may impact the prognosis and postoperative management [18–21].

The incidence of multiple lymph node metastases along risk groups in clinically localized PCa remains a controversial topic. Heidenreich et al. [22] reported that the incidence of LNI with >1 positive node was 46% compared with cases with only 1 positive node, which was around 54%.

In our study, we found that multiple LNI occurred in 54.8% of all metastatic cases. Also, it was more likely to occur in the high-risk class (67.5%). Furthermore, we showed that tumor and metastatic load were predicted by BPC and PSA, thus confirming the close association between these factors with aggressive tumor biology [6, 7, 23].

In the present study, we have shown that obesity is an independent predictor of multiple nodal invasion in patients with clinically localized intermediate/high-risk PCa. Importantly, we found that obese patients have a three-fold risk of harboring multiple occult lymph node metastases compared with nonobese cases.

The results of our study show that PCa with high occult metastatic load is more likely to occur in obese patients. This may be the result of a complex biological system where interaction of endogenous factors may lead to early progression to occult multiple metastases, which becomes evident by higher PSA levels.

Obesity is a major health concern in Western countries, and its association with aggressive PCa is an emerging critical issue [8, 24]. In the last few years, the prevalence of PCa has mirrored the spread of obesity, reflecting potential shared risk factors. However, there are also some evidence to suggest a causal association between obesity and PCa, related to the increase serum levels of growth factors such as vascular endothelium growth factor, and the deregulation of the insulin growth factors (IGF1)/insulin axis, causing hyperactivation of intracellular transduction pathways with consequent increased anabolic, antiapoptotic, and mitotic activities. In addition, IGF1 promotes mitogenesis and proangiogenesis and inhibits apoptosis facilitating the cancer induction and progression [8]. In overweight or obese patients, dyslipidemia, increased serum concentrations of inflammatory cytokines, and other factors such as interleukine (IL)-6 and IL-8 cause a rise of sex hormone-binding globulin and bioavailable testosterone. Obesity also has a peripherical effect on the hypothalamus-pituitary-testis axis which causes a reduction in systemic androgen levels thought steroid hormone aromatization [25].

All these factors may provide strong stress in the prostatic microenvironment and cause a DNA damage and uncontrolled luminal cell proliferation [26]. Initially, this process promotes neoplastic induction and cancer growth. Later, it provides an increased capacity for extracapsular diffusion and nodal invasion and finally, the loss of hormonal sensitivity [25].

Clinical data have shown that high BMI is associated with a greater incidence of high-grade PCa at the time of

biopsy as well as upgrading and upstaging after surgery. In addition, obese patients show worse intraoperative outcomes during RP performed by open, laparoscopic, or robot-assisted approach, as well as a higher complication rates [8, 27]. On the contrary, Pfitzernmaier et al. [28] found that in 620 PCa patients, the frequency of positive lymph nodes was not statistically different between normal weight, overweight, and obese patients ($p = 0.58$). However, the authors did not specify the number of dissected nodes, as well as the adopted template. Obese patients who have EAU intermediate-risk class PCa presenting with a risk of LNI <5% need careful counseling before surgery because their risk of multiple occult metastases may be elevated and may remain undetected if appropriate ePLND is not planned at time of surgery.

According to our findings, the radiation oncologist who may deliver active treatment to these patients should also consider this adjunctive clinical risk factor that will help in making clinical decisions if radiation of the pelvis is considered with or without androgen blockade. When active surveillance is proposed for obese patients in the EAU intermediate-risk category, an even more close follow-up protocol should be considered because of the high risk of aggressive PCa. More generally, appropriate behavioral dietary habits might prevent obesity, thus reducing the risk of developing aggressive PCa.

In the present study, we investigated a homogeneous contemporary cohort of Caucasian Italian males undergoing RP and ePLND according to a standardized template. The population was large yet it was selected to represent specific categories of the EAU risk group system. Finally, 2 dedicated uropathologists assessed both biopsy and pathological specimens, and biopsy specimens performed outside our institutions were not reviewed by our pathologists.

On the other hand, this is a retrospective study and it suffers of all limitations related to this kind of study. Several surgeons performed ePLND, but each surgeon was experienced in performing open or RARP.

## Conclusions

Among clinical factors, BMI is an independent predictor of the risk of occult multiple lymph node metastases in patients with clinically localized disease, including intermediate- and high-risk classes. BMI has to be considered when evaluating PCa patients presenting with clinically localized disease, and it should be included in LNI risk calculators.

## Statement of Ethics

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

## Conflict of Interest Statement

The authors declare that they have no conflicts of interest.


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## Author Contributions

A. Tafuri: project development, data collection, data analysis and interpretation, and manuscript writing. R. Rizzetto, N. Amigoni, and M. Sebben: data collection, data interpretation, and manuscript writing. A. Shakir: manuscript writing and language and critical revision. A. Gozzo, K. Odorizzi, S. Gallina, A. Bianchi, and Paola Ornaghi: data collection. M. Brunelli, F. Migliorini, S. Siracusano, W. Artibani, and A. Antonelli: supervision and critical revision. A.B. Porcaro: project development, data analysis and interpretation, and manuscript writing.

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