EUROPEAN UROLOGY 75 (2019) 817–825

available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Prostate Cancer

# Which Patients with Clinically Node-positive Prostate Cancer Should Be Considered for Radical Prostatectomy as Part of Multimodal Treatment? The Impact of Nodal Burden on Long-term Outcomes

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**Article info**

***Article history:***
Accepted October 18, 2018

***Associate Editor:***
Giacomo Novara

***Statistical Editor:***
Andrew Vickers

***Keywords:***
Prostate cancer
Radical prostatectomy
Nodal metastases
Node-positive disease
Lymph node dissection

**Abstract**

***Background:*** A role for local therapies including radical prostatectomy (RP) in prostate cancer (PCa) patients with clinical lymphadenopathies has been proposed. However, no data are available to identify men who would benefit from RP in this setting.
***Objective:*** To identify predictors of clinical recurrence (CR) in surgically managed PCa patients with clinical lymphadenopathies.
***Design, setting, and participants:*** We identified 162 patients with lymphadenopathies treated with RP and lymph node dissection at three referral centers.
***Outcome measures and statistical analyses:*** CR was defined as the onset of metastases detected by conventional imaging. Kaplan-Maier analyses assessed time to CR after stratifying patients according to the site of lymphadenopathies and nodal burden. Regression tree analysis stratified patients into risk groups on the basis of their preoperative characteristics.
***Results and limitations:*** Overall, 80% of patients had lymphadenopathies in the pelvis alone and 20% in the retroperitoneum ± pelvis. The median size of positive nodes was 13 mm. A total of 84 patients (52%) received neoadjuvant androgen deprivation therapy and 127 (78%) had pathological lymph node invasion. The median follow-up for survivors was 64 mo. The 8-yr CR-free and CSM-free survival rates were 59% and 80%, respectively. Biopsy grade group and preoperative nodal burden should identify patients more likely to experience CR. While <10% of men with biopsy grade group 1–3 and two or fewer clinical lymphadenopathies developed CR, up to 60% of patients with biopsy grade group 4–5 and retroperitoneal node involvement ultimately experienced CR at 8 yr after RP. The discrimination of the regression tree was 76% according to the area under the receiver operating characteristic curve. Our study is limited by potential unmeasured confounders and the relatively small sample size.

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https://doi.org/10.1016/j.eururo.2018.10.042


***Conclusions:*** Surgery in a multimodal setting might play a role in PCa patients with biopsy grade group 1–3 and/or enlarged nodes in the pelvis. Conversely, grade group 4–5 PCa and lymphadenopathies in the retroperitoneum are associated with worse oncologic outcomes.

***Patient summary:*** Approximately half of prostate cancer patients with clinical lymphadenopathies treated with radical prostatectomy are free from metastases at 8-yr follow-up. Radical prostatectomy with or without systemic therapies might play a role in selected patients with biopsy grade group 1–3 disease and/or enlarged nodes in the pelvis. Conversely, a higher grade group and the presence of lymphadenopathies in the retroperitoneum should identify candidates for systemic therapies upfront.



## 1. Introduction

Clinical lymphadenopathies are detected at diagnosis in a substantial proportion of prostate cancer (PCa) patients [1]. Nonetheless, the optimal management of these individuals still represents a matter of debate in the lack of prospective randomized trials specifically focusing on this population [2]. Over the last decades, patients with clinical lymphadenopathies were deemed as affected by systemic disease and androgen deprivation therapy (ADT) represented the cornerstone of their treatment [3]. A potential role for radiotherapy (RT) in association with ADT has recently been proposed [4–7]. Patients receiving RT ± ADT exhibited better survival than those treated with ADT alone. A similar effect has been observed when radical prostatectomy (RP) was the local treatment delivered [4]. Although local therapies might play a role in selected patients, others might benefit from the administration of systemic therapies upfront [8,9]. Indeed, more than one in four men treated with RP or RT with or without ADT eventually experienced clinical recurrence (CR) at 5-yr follow-up [4,6]. Given the lack of detailed information on the number, size, and site of lymphadenopathies at imaging, none of the available studies identified predictors of CR to assist physicians in identifying patients who could benefit the most from local treatments [4–7]. In the face of this paucity of data, we sought to examine oncologic outcomes for a cohort of patients with detailed data on the site and size of clinical lymphadenopathies. We hypothesized that not all patients share the same prognosis, and that nodal burden at preoperative imaging might predict the risk of recurrence and thus assist physicians in identifying individuals who should be considered for RP ± systemic therapies.

## 2. Patients and methods

### 2.1. Study population

After institutional review board approval, we retrospectively reviewed three prospectively maintained databases for PCa patients treated with RP at three tertiary referral centers (IRCCS Ospedale San Raffaele, Milan, Italy; Mayo Clinic, Rochester, MN, USA; University Hospitals Leuven, Leuven, Belgium) between 2005 and 2017. A total of 23 474 patients were identified. Staging via cross-sectional abdominopelvic imaging was proposed to all patients with intermediate- or high-risk PCa according to the European Association of Urology risk classification [2]. Preoperative radiology reports were reviewed to identify patients with a clinically suspicious lymphadenopathy, defined as the presence of at least one pelvic and/or retroperitoneal lymph node with a short-axis diameter elongated and exceeding 10 mm or rounded and exceeding 8 mm [10,11]. Overall, 162 patients with clinical lymphadenopathies at preoperative imaging who received RP and lymph node dissection (LND) were identified.

### 2.2. Imaging protocols

The minimum requirements for contrast-enhanced abdominal computed tomography (CT) and magnetic resonance imaging (MRI) were as follows. Abdominal contrast-enhanced CT scans were performed with a slice thickness of at least 3.3 mm; CT data were acquired before and after intravenous injection of iodinated contrast media and multiplanar reconstructions were routinely performed [12]. For patients undergoing MRI before surgery, 1.5-T multiparametric MRI with a combined phased array and endorectal coil was performed. The protocol evolved over the study period; common scan elements consisted of multiplanar T2-weighted images (slice thickness at least 2 mm), diffusion-weighted imaging, intravenous (gadolinium) contrast administration with dynamic contrast imaging, T1-weighted images with fat suppression [13], and abdominal T1-weighted imaging and postcontrast imaging extended up to the level of the renal vessels [14]. All CT scans were reviewed by high-volume radiologists. All MRI images were interpreted by experienced dedicated genitourinary radiologists.

### 2.3. Surgical procedures

All patients underwent either open or robot-assisted RP with an anatomically defined extended pelvic LND that included the obturator, internal iliac, and external iliac stations regardless of the presence and site of clinically suspicious lymphadenopathy at preoperative imaging. In selected patients the presacral and common iliac lymph nodes were included in the LND template, as previously described [15,16]. In the case of lymphadenopathies located in the retroperitoneum, retroperitoneal LND that included the para-aortal/paracaval and interaortocaval nodes was performed at the time of RP and pelvic LND [17]. The decision to perform RP and the LND extent were left to the clinical judgment of the treating physician after discussion with each patient regarding the potential benefits and side effects. Lifelong adjuvant ADT was indicated for patients with lymph node invasion (LNI) on final pathology [18]. Selected patients with adverse pathologic characteristics received adjuvant RT plus ADT. Salvage RT with concomitant ADT was administered for either prostate-specific antigen (PSA) persistence or rising PSA after RP [19]. Salvage ADT was administered at the time of CR.

### 2.4. Covariates and endpoints

All patients had data available for PSA at diagnosis, clinical stage according to digital rectal examination, and biopsy grade group. The

number and size of clinical lymphadenopathies as well as their location were retrieved from radiologic reports. The site of lymphadenopathies was categorized as follows: pelvis only (obturator, hypogastric, external iliac, presacral, and common iliac nodes) or retroperitoneum (para-aortal/paracaval and interaortocaval nodes) ± pelvis. Pathologic specimens were processed by dedicated uropathologists. TNM stage was assigned according to the 2002 American Joint Committee on Cancer staging system for PCa. Biopsy and pathologic Gleason scores were categorized in five groups according to the International Society of Urological Pathology 2014 consensus conference [20]. The main endpoint of the study was CR after RP, defined as the onset of metastases in the pelvic and retroperitoneal lymph nodes, bones, parenchymal organs, or soft tissues as identified via conventional imaging. Follow-up time was defined as the time elapsed between RP and CR or last follow-up.

### 2.5. Statistical analyses

Mann-Whitney and $\chi^2$ tests were used to compare differences in medians and proportions, respectively, between patients with and without LNI at final pathology and between individuals with missing data on the number, size, and site of lymphadenopathies and those with complete data. Univariable and multivariable analyses were used to assess predictors of LNI. Kaplan-Meier analyses were used to assess time to CR in the overall population and after stratifying patients according to the number, median size, and location of clinically suspicious lymphadenopathies, as well as time to cancer-specific mortality (CSM) in the overall population. We applied a regression tree method for censored data to generate a risk stratification tool to predict 8-yr CR after surgery with or without additional cancer therapies. This approach uses a standard and a recursive algorithm to sequentially divide patients into two subgroups whereby the separation between the two class-specific survival curves in a pair is maximized [21]. Given the paucity of data on what variables might be predictive of CR among patients with clinical lymphadenopathies undergoing surgery in a multimodal setting, the regression tree analysis included preoperative variables that were significantly associated with CR in univariable Cox regression analyses. Estimates of the area under the receiver operating characteristic (ROC) curve (AUC) were used to test the discrimination of the regression tree–derived risk stratification tool. Finally, univariable and multivariable Cox regression analyses were used to assess predictors of CR in the overall population and the subgroup of patients with pelvic lymphadenopathies after adjusting for administration of additional cancer therapies ($n = 111$).

All statistical tests were performed using R v.3.0.2 (R Project for Statistical Computing; www.r-project.org). All tests were two sided, with the significance level set at $p < 0.05$.

## 3. Results

### 3.1. Baseline characteristics

The median PSA at diagnosis was 16 ng/ml (interquartile range [IQR] 8–35; Table 1). Overall, 121 patients (75%) were evaluated with a CT scan and 41 (25%) with MRI before surgery. The median number of clinically suspicious lymphadenopathies was 1 (IQR 1–2), with a median maximum diameter of 13 mm (IQR 10–20). Overall, 111 patients (80%) had lymphadenopathies at the level of the pelvic stations and 28 (20%) at the level of the retroperitoneal ± pelvic stations on imaging. Overall, 84 (52%) patients received neoadjuvant ADT. The median number of nodes removed at LND was 21 (IQR 14–31) in the overall population and 27 (IQR 18–40) for patients with retroperitoneal lymphadenopathies. A total of 127 patients (78%) had LNI on final pathology. When patients were stratified according to pathologic nodal status, significant differences were observed in the number of clinically suspicious lymphadenopathies, pathologic grade group, and stage between those with pN0 and pN1 disease (all $p \leq 0.03$). Overall, 25, 62, and 23 patients had data missing for the number, maximum diameter, and site of clinical lymphadenopathies, respectively. No differences were observed in age at surgery, preoperative PSA, biopsy grade group, and number of nodes removed at LND between patients with missing data and those who were included in the analyses (all $p \geq 0.1$).

### 3.2. Univariable and multivariable analyses for LNI prediction

On univariable analyses, only biopsy grade group 4–5 (odds ratio [OR] 2.90; 95% confidence interval [CI] 1.34–6.24; $p = 0.01$) and the number of clinically suspicious lymphadenopathies (OR 1.97, 95%CI 1.15–3.36; $p = 0.01$; Table 2) were significantly associated with LNI on final pathology. This was confirmed in multivariable analyses, in which biopsy grade group 4–5 and a higher number of clinically suspicious lymphadenopathies increased the risk of LNI (all $p = 0.01$). A total of 137 patients (102 events) with complete data were included in the multivariable model.

### 3.3. Survival analyses

The median follow-up for survivors was 64 mo (IQR 56–71). Overall, 53 and 27 patients experienced CR and CSM, respectively. The 8-yr CR-free and CSM-free survival rates were 59% (Fig. 1A) and 80% (Fig. 2), respectively. The site of CR was the pelvis, retroperitoneal nodes, bone, and visceral organs in 29%, 12%, 37%, and 22% of patients, respectively. When patients were stratified according to the number of lymphadenopathies on preoperative imaging, the 8-yr CR-free survival rate was 55% for those with two or fewer and 38% for those with more than two lymphadenopathies (Fig. 1B; $p = 0.049$). No differences were observed in 8-yr CR-free survival after stratification according to the median nodal diameter at imaging (38% for <13 mm vs 41% for ≥13 mm; $p = 0.9$; Fig. 1C). When patients were stratified according to the site of the clinical lymphadenopathy, the 8-yr CR-free survival rate was 59% for those with involvement of the pelvic versus 27% for those with retroperitoneal ± pelvic stations involved (Fig. 1D; $p = 0.001$). In univariable Cox regression analyses, PSA at diagnosis, biopsy grade group 4–5, and the number and site of suspicious lymphadenopathies were independent predictors of CR (all $p \leq 0.01$; Table 3). Overall, 131 patients (46 events) with complete data for the site of lymphadenopathies, PSA at diagnosis, biopsy grade group, and number of lymphadenopathies and were included in the regression tree analysis. Three variables were identified to stratify patients according to their risk of CR: biopsy grade group, number of positive nodes, and site of nodal

**Table 1 – Clinical and pathologic characteristics of patients included in the study**

| | pN0 | pN1 | *p* value |
|---|---|---|---|
| Patients, *n* (%) | 35 (22) | 127 (78) | |
| Median age at surgery, yr (IQR) | 65 (57–60) | 63 (58–69) | 0.6 |
| Median year of surgery (IQR) | 2010 (2009–2012) | 2010 (2004–2012) | 0.1 |
| Median PSA at diagnosis, ng/ml (IQR) | 12 (6–28) | 16 (9–39) | 0.2 |
| Clinical stage, *n* (%) | | | 0.2 |
| T1 | 11 (31) | 32 (25) | |
| T2 | 14 (40) | 39 (31) | |
| T3 | 10 (29) | 54 (44) | |
| Biopsy ISUP grade group, *n* (%) | | | 0.06 |
| 1 | 7 (20) | 10 (7.8) | |
| 2 | 7 (20) | 17 (13) | |
| 3 | 6 (17) | 14 (11) | |
| 4 | 8 (23) | 35 (28) | |
| 5 | 7 (20) | 51 (40) | |
| PI technique, *n* (%) | | | 0.3 |
| Computed tomography scan | 25 (71) | 96 (76) | |
| Magnetic resonance imaging | 10 (29) | 31 (24) | |
| Median suspicious nodes on PI, n (IQR) [a] | 1 (1–2) | 2 (1–2) | 0.02 |
| Median $D_{max}$ of suspicious nodes on PI, mm (IQR) [b] | 11 (10–20) | 13 (10–21) | 0.1 |
| Site of suspicious nodes on PI, *n* (%) [c] | | | 0.6 |
| Pelvis | 28 (80) | 83 (80) | |
| Retroperitoneum ± pelvis | 7 (20) | 21 (20) | |
| Neoadjuvant ADT, *n* (%) | 15 (43) | 69 (55) | 0.1 |
| Pathologic ISUP grade group, *n* (%) | | | 0.03 |
| 1 | 4 (13) | 7 (5.8) | |
| 2 | 9 (29) | 15 (12) | |
| 3 | 5 (16) | 11 (8.6) | |
| 4 | 4 (13) | 27 (22) | |
| 5 | 9 (29) | 60 (50) | |
| Pathologic stage, *n* (%) | | | <0.001 |
| pT2 | 18 (51) | 21 (16) | |
| pT3a | 5 (14) | 29 (23) | |
| pT3b | 10 (29) | 69 (54) | |
| pT4 | 2 (5.7) | 8 (6.3) | |
| Positive surgical margins, *n* (%) | 9 (26) | 42 (41) | 0.07 |
| Median nodes removed, *n* (IQR) | 14 (19–26) | 22 (14–33) | 0.4 |
| Median positive nodes, *n* (IQR) | NA | 3 (1–7) | NA |
| Adjuvant ADT, *n* (%) | 11 (31) | 89 (70) | <0.001 |
| Adjuvant RT, *n* (%) | 4 (11) | 23 (18) | 0.2 |
| Salvage ADT, *n* (%) | 8 (23) | 60 (47) | 0.01 |
| Salvage RT, *n* (%) | 2 (5.7) | 21 (16) | 0.2 |

IQR = interquartile range; ISUP = International Society of Urological Pathology; PI = preoperative imaging; $D_{max}$ = maximum diameter; ADT = androgen deprivation therapy; NA = not applicable; RT = radiotherapy.
[a] Data missing for 25 patients.
[b] Data missing for 62 patients.
[c] Data missing for 23 patients.

involvement. The entire cohort was then stratified into five risk groups for 8-yr CR, as shown in Figure 3: (1) very low risk: grade group 1–3 and two or fewer lymphadenopathies on preoperative imaging (8-yr CR 9%); (2) low risk: biopsy Gleason grade 1–3 and more than two lymphadenopathies (8-yr CR 28%); (3) intermediate risk: grade group 4–5 and two or fewer pelvic lymphadenopathies (8-yr CR 32%); (4) high risk: grade group 4–5 and more than two pelvic lymphadenopathies (8-yr CR 35%); and (5) very high risk: grade group 4–5 and any retroperitoneal lymphadenopathies (8-yr CR 59%). The discrimination of the risk stratification tool was 76% according to the ROC-derived AUC.

Multivariable Cox regression analyses confirmed that the site of lymphadenopathies and biopsy grade group were predictors of CR (all $p \geq 0.04$; Supplementary Table 1) even after adjusting for administration of additional cancer therapies (ADT and salvage RT). When considering patients with exclusively pelvic lymphadenopathies, the number of nodal stations with clinical lymphadenopathies (1 vs ≥2) was a predictor of CR after adjusting for confounders (hazard ratio 2.04, 95% CI 1.01–4.12; $p = 0.04$).

## 4. Discussion

The optimal management of patients with clinical lymphadenopathies is still a matter of debate owing to the lack of prospective randomized trials specifically focusing on this population [2]. Several retrospective studies [4,7,22,23] and a subanalysis of the STAMPEDE trial [6] have identified a role for local treatments in this setting. However, the lack of details on the number, size, and site of clinical lymphade-

**Table 2 – Univariable and multivariable logistic regression analyses of the prediction of lymph node invasion in patients with clinically node-positive prostate cancer treated with radical prostatectomy and extended pelvic lymph node dissection**

| | Univariable analyses | | Multivariable analyses [a] | |
|---|---|---|---|---|
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Age | 0.99 (0.94–1.04) | 0.7 | – | – |
| Prostate-specific antigen at diagnosis | 1.00 (0.99-1.01) | 0.4 | – | – |
| Clinical stage | | | – | – |
| T1 | Reference | | | |
| T2 | 0.96 (0.38–2.39) | 0.9 | | |
| T3 | 1.92 (0.73–5.03) | 0.2 | | |
| Biopsy Gleason grade group | | | | |
| 1–3 | Reference | | Reference | |
| 4–5 | 2.90 (1.34–6.24) | 0.01 | 3.31 (1.46–7.59) | 0.01 |
| Number of suspicious nodes on PI | 1.97 (1.15–3.36) | 0.01 | 1.74 (1.01-3.00) | 0.04 |
| Maximum diameter of suspicious nodes on PI | 1.04 (0.98–1.11) | 0.1 | – | – |
| Site of suspicious nodes on PI | | | – | – |
| Pelvis | Reference | | | |
| Retroperitoneum | 1.01 (0.38–2.63) | 0.9 | | |

OR = odds ratio; CI = confidence interval; PI = preoperative imaging.
[a] The model included *n* = 137 patients and *n* = 102 events.

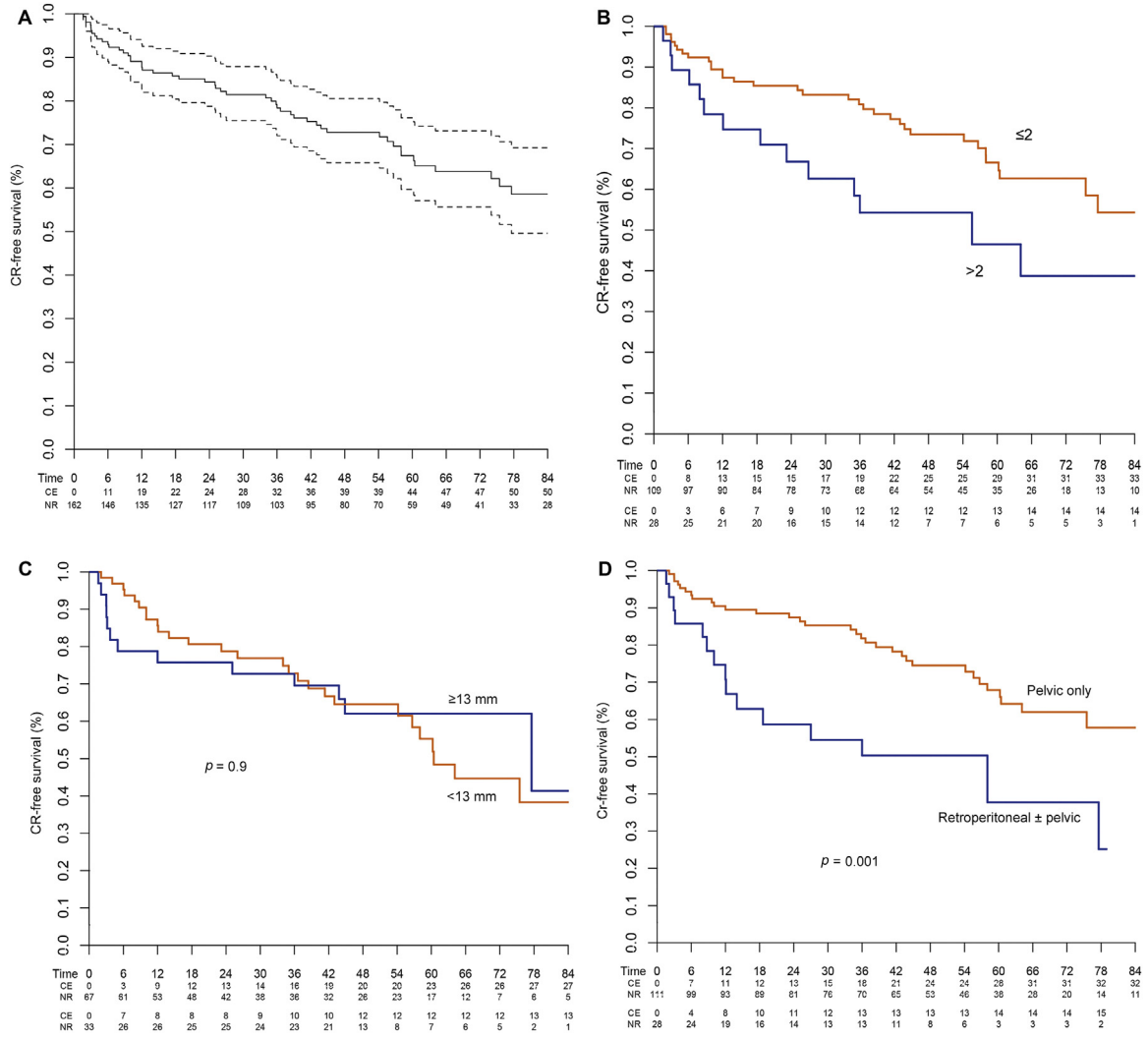


**Fig. 1 – Clinical-recurrence (CR)-free survival (A) in the overall population and after stratifying for (B) the number of clinically suspicious lymphadenopathies, (C) the maximum diameter of suspicious lymphadenopathies, and (D) the site of positive preoperative imaging. CE = cumulative events; NR = number at risk.**

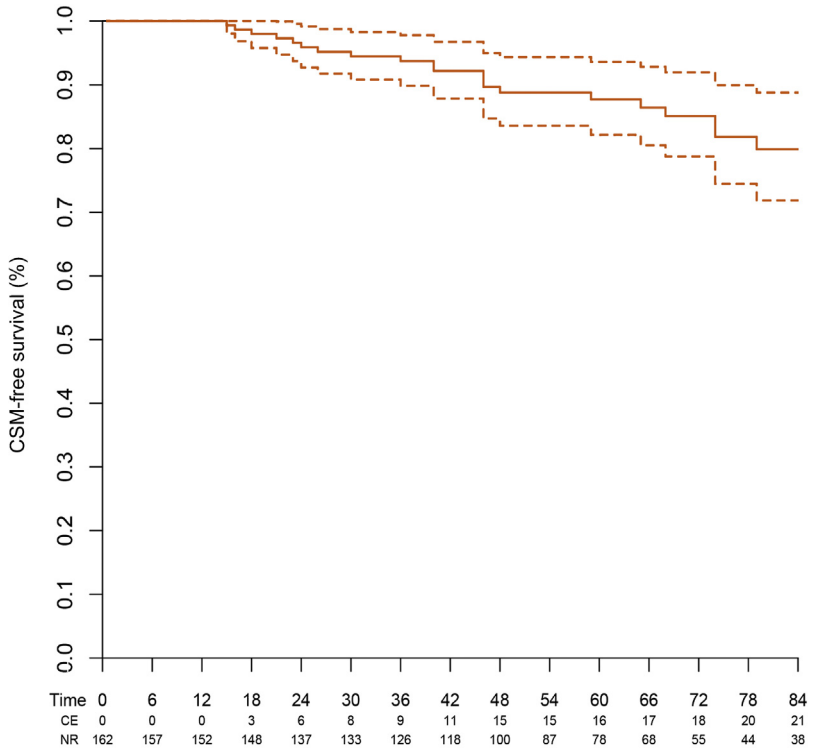


**Fig. 2 – Survival free from cancer-specific mortality (CSM) in the overall population. CE = cumulative events; NR = number at risk.**

**Table 3 – Univariable Cox regression analyses of the prediction of clinical recurrence in patients with clinically node-positive prostate cancer treated with radical prostatectomy and extended pelvic lymph node dissection**

| | HR (95% CI) | *p* value |
|---|---|---|
| Prostate-specific antigen at diagnosis | 1.01 (1.00–1.01) | 0.001 |
| Clinical stage | | |
| T1 | Reference | |
| T2 | 0.94 (0.48–1.85) | 0.9 |
| T3 | 0.72 (0.36–1.42) | 0.7 |
| Biopsy Gleason grade group | | |
| 1–3 | Reference | |
| 4–5 | 2.35 (1.26–4.36) | 0.01 |
| Number of suspicious nodes at preoperative imaging | 1.56 (1.15–2.01) | 0.01 |
| Maximum diameter of suspicious nodes at preoperative imaging | 1.02 (0.99–1.04) | 0.2 |
| Site of suspicious nodes at preoperative imaging | | |
| Pelvis | Reference | |
| Retroperitoneum | 2.54 (1.37–4.72) | 0.01 |

nopathies prevented stratification of outcomes according to nodal burden and identification of men who might benefit the most from local treatments. We hypothesized that not all PCa patients with clinical lymphadenopathies would benefit from surgery or radiotherapy to the same extent. Indeed, while maximizing local and pelvic control might play a role in selected patients, others should be considered for upfront systemic therapies [2,6]. To address this issue, we evaluated a cohort of patients with clinical lymphadenopathies treated with RP and LND with or without additional therapies at three referral tertiary centers for whom data on the size, site, and number of lymphadenopathies detected on preoperative imaging were available.

Several results of our study are noteworthy. First, surgery ± ADT was associated with long-term cancer control in a substantial proportion of patients, with up to 60% free from CR at 8-yr follow-up. Moreover, when patients experienced CR, the site of recurrence was limited to the pelvis in approximately one-third of cases. These individuals typically have a more favorable prognosis than their counterparts with distant metastases [24]. The encouraging long-term oncologic outcomes observed in our cohort are in line with previous studies in which local therapies delivered in addition to systemic treatments led to better recurrence and survival rates [4,6,7,22,23]. Under this light, it should be stressed that surgery was considered in a multimodal setting in which approximately 80% of patients received neoadjuvant or adjuvant ADT. Taken together, these findings suggest that the presence of clinical lymphadenopathies on preoperative imaging should not be invariably considered as a proxy for a systemic disease, and maximizing local and pelvic control as part of a multimodal approach that might include systemic therapies could reduce the risk of distant recurrence during long-term follow-up in selected patients.

Second, not all patients benefit from local therapies to the same extent, so biopsy grade group and the number and site of lymphadenopathies should be used to predict the risk of CR. These variables were included in a regression tree that showed excellent discrimination when predicting the risk of

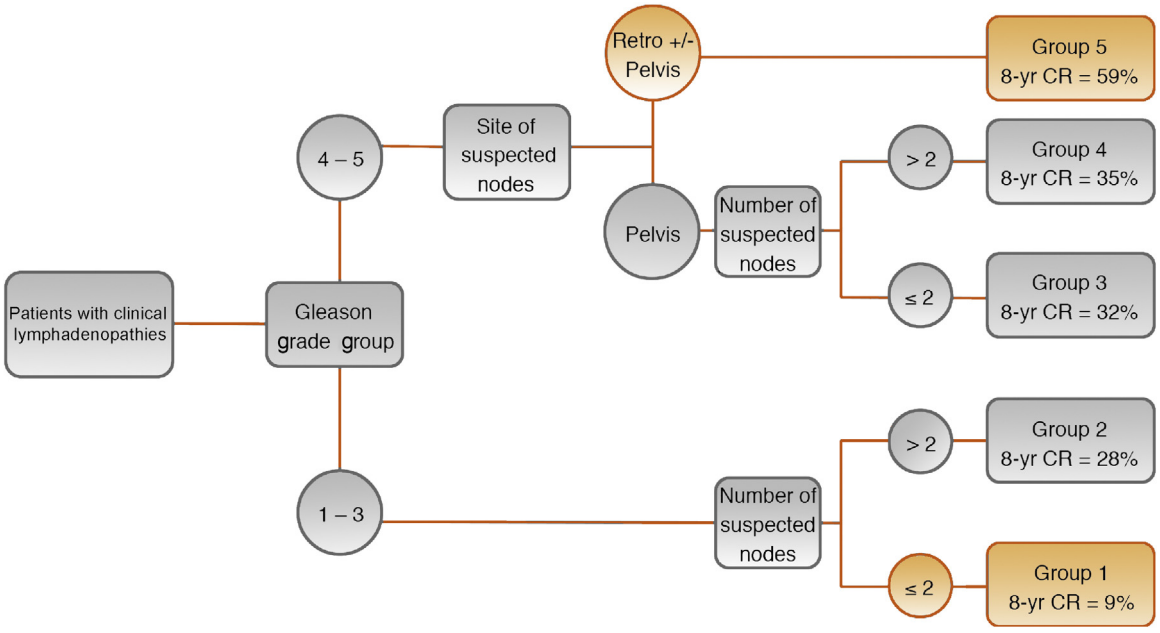


**Fig. 3 – Risk stratification tree assessing 8-yr clinical recurrence (CR) for prostate cancer patients with clinical lymphadenopathies undergoing radical prostatectomy and lymph node dissection.**

CR at 8 yr. This represents the first attempt to stratify patients with clinical lymphadenopathies according to the extent of nodal involvement on preoperative imaging. Nodal burden plays a major role when identifying individuals who should be considered for local therapies. For example, the presence of retroperitoneal involvement was associated with a twofold higher risk of experiencing CR during follow-up as compared to pelvic lymphadenopathies only. Although previous studies proposed a potential role for maximizing local disease control in men with retroperitoneal involvement in both the primary and salvage settings [5,17,25], caution is required when considering local therapies for these patients. The retroperitoneal nodes do not represent primary PCa landing sites and tumor cells typically spread from the pelvic stations to the retroperitoneum [17]. To do so, PCa cells have to acquire specific alterations that eventually lead to a more aggressive disease phenotype [26]. The presence of lymphadenopathies in the retroperitoneal stations should be regarded as a proxy for more aggressive (or systemic) disease. This is in line with the salvage setting, where men with involvement of the retroperitoneal nodes experienced poorer oncologic outcomes compared to those with pelvic recurrence only [5]. Moreover, when considering patients with exclusively pelvic lymphadenopathies, the number of stations with enlarged lymph nodes was an independent predictor of disease recurrence. This confirms the importance of nodal burden in identifying surgical candidates. Conversely, our results show that the size of clinical lymphadenopathies should not be considered in selecting candidates for RP with LND. This is in contrast to observations when considering pathologic data, whereby some authors showed that the size of nodal metastases on final pathology might represent a predictor of disease recurrence and mortality [27–29]. This discrepancy might be explained by the poor performance characteristics of conventional imaging when assessing nodal involvement in PCa patients [10,11]. This is also supported by the observation that not all patients with clinical lymphadenopathies eventually harbor LNI at final pathology, with negative nodes retrieved in approximately 20% of men [4]. Biopsy grade group and the number of lymphadenopathies were the only predictors of LNI and should be considered for identifying individuals more likely to harbor node-positive disease.

From a clinical standpoint, our stratification tool might assist physicians in identifying patients more likely to benefit from local disease control as part of a multimodal approach, and ultimately improving long-term oncologic outcomes and delaying the use of systemic therapies [30]. In particular, patients with grade group 1–3 disease and a single enlarged node limited to the pelvis exhibited more favorable oncologic outcomes after RP with or without systemic therapies, with $<$10% ultimately experiencing CR at 8-yr follow-up. Conversely, approximately 60% of patients with biopsy grade group 4–5 PCa and lymphadenopathies in the retroperitoneum experienced CR after surgery. Our findings could also be used to guide the design of future clinical trials among patients with clinical lymphadenopathies, as the inclusion of men with retroperitoneal involvement might jeopardize the potential effect of local therapies.

Despite several strengths, our study is not devoid of limitations. First, selection bias might have introduced unmeasured confounders, since surgery was proposed for selected patients according to the treating physicians' preference. Moreover, the lack of a control group prevented us from comparing the outcomes for patients treated in our

series with counterparts receiving other therapies, such as RT and/or systemic treatments. Second, owing to the multi-institutional nature of our study and the inclusion of patients treated over a relatively long time period, we relied on review of radiologic reports rather than actual images. In addition, not all patients included in our series had complete data on the number, site, and size of lymphadenopathies on preoperative imaging, so the final number of patients included in our multivariable models was lower than the entire cohort. Third, all patients were evaluated via conventional imaging and none of them was staged using molecular imaging before RP. Although positron emission tomography/CT scans have shown promising results in the detection of node-positive disease [31], this imaging modality is characterized by relatively low sensitivity [32] and its use for nodal staging is still not recommended by clinical guidelines [2]. Finally, the inclusion of patients treated at three different centers might have introduced heterogeneity in staging procedures, surgical therapies, pathologic evaluation, administration of neoadjuvant and adjuvant therapies, and follow-up protocols. No central image or pathology review was performed. However, all preoperative imaging procedures were performed by high-volume radiologists at referral centers. Similarly, all specimens were evaluated by a dedicated uropathologist.

## 5. Conclusions

Not all patients with clinical lymphadenopathies are affected by systemic disease, and RP in a multimodal setting is associated with excellent CR-free survival among patients with biopsy grade group 1–3 and/or enlarged pelvic nodes. Men with grade group 4–5 PCa and retroperitoneal lymphadenopathies exhibited worse oncologic outcomes and might not benefit from the addition of surgery to systemic therapies. The inclusion of these patients in trials assessing the role of local therapies might jeopardize the potential effect of these treatments.

***Author contributions***: Giorgio Gandaglia had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design*: Gandaglia, Briganti.
*Acquisition of data*: Soligo, Battaglia, Muilwijk, Robesti, Barletta, Moschini.
*Analysis and interpretation of data*: Gandaglia, Fossati, Mazzone, Bandini, Briganti.
*Drafting of the manuscript*: Gandaglia, Karnes, Briganti.
*Critical revision of the manuscript for important intellectual content*: Briganti, Joniau, Karnes, Montorsi.
*Statistical analysis*: Gandaglia, Mazzone.
*Obtaining funding*: None.
*Administrative, technical, or material support*: None.
*Supervision*: Briganti, Montorsi, Karnes, Joniau.
*Other*: None.

***Financial disclosures:*** Giorgio Gandaglia certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

***Funding/Support and role of the sponsor:*** None.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.10.042.

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