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

European Association of Urology

Platinum Priority – Prostate Cancer

*Editorial by Christian Stief on pp. 220–221 of this issue*

# More Extensive Pelvic Lymph Node Dissection Improves Survival in Patients with Node-positive Prostate Cancer

*Firas Abdollah* [a], *Giorgio Gandaglia* [a], *Nazareno Suardi* [a], *Umberto Capitanio* [a], *Andrea Salonia* [a], *Alessandro Nini* [a], *Marco Moschini* [a], *Maxine Sun* [b], *Pierre I. Karakiewicz* [b], *Sharhokh F. Shariat* [c], *Francesco Montorsi* [a], *Alberto Briganti* [a,*]

[a] *Division of Oncology/Unit of Urology, URI, IRCCS Ospedale San Raffaele, Milan, Italy;* [b] *Cancer Prognostics and Health Outcomes Unit, University of Montreal Health Centre, Montreal, Quebec, Canada;* [c] *Department of Urology, Medical University of Vienna, Vienna, Austria*

## Article info

***Article history:***
Accepted May 15, 2014

***Keywords:***
Neoplasm recurrence
Prostatic neoplasms/pathology
Prostatic neoplasms/surgery
Prostatic neoplasms/mortality
Lymph node invasion
Lymph node dissection

## Abstract

***Background:*** The role of extended pelvic lymph node dissection (ePLND) in treating prostate cancer (PCa) patients with lymph node invasion (LNI) remains controversial.
***Objective:*** The relationship between the number of removed lymph nodes (RLNs) and cancer-specific mortality (CSM) was tested in patients with LNI.
***Design, setting, and participants:*** We examined data of 315 pN1 PCa patients treated with radical prostatectomy (RP) and anatomically ePLND between 2000 and 2012 at one tertiary care centre. All patients received adjuvant hormonal therapy with or without adjuvant radiotherapy (aRT).
***Outcome measurements and statistical analysis:*** Univariable and multivariable Cox regression analyses tested the relationship between RLN number and CSM rate, after adjusting to all available covariates. Survival estimates were based on the multivariable model; patients were stratified according to RLN number using points of maximum separation.
***Results and limitations:*** The average number of RLNs was 20.8 (median: 19; interquartile range: 14–25). Mean and median follow-up were 63.1 and 54 mo, respectively. At 10-yr, the CSM-free survival rate was 74.7%, 85.9%, 92.4%, 96.0%, and 97.9% for patients with 8, 17, 26, 36, and 45 RLNs, respectively. By multivariable analyses, the number of RLNs independently predicted lower CSM rate (hazard ratio [HR]: 0.93; $p = 0.02$). Other predictors of CSM were Gleason score 8–10 (HR: 3.3), number of positive nodes (HR: 1.2), and aRT treatment (HR: 0.26; all $p \leq 0.006$). The study is limited by its retrospective nature.
***Conclusions:*** In PCa patients with LNI, the removal of a higher number of LNs during RP was associated with improvement in cancer-specific survival rate. This implies that ePLND should be considered in all patients with a significant preoperative risk of harbouring LNI.
***Patient summary:*** We found that removing more lymph nodes during prostate cancer surgery can significantly improve cancer-specific survival in patients with lymph node invasion.


* Corresponding author. Department of Urology, Urological Research Institute, San Raffaele Hospital, University Vita-Salute, Via Olgettina, 60, Milan 20132, Italy. Tel. +39 02 2643 7790; Fax: +39 02 2643 7298.
E-mail address: briganti.alberto@hsr.it (A. Briganti).

http://dx.doi.org/10.1016/j.eururo.2014.05.011
0302-2838/

## 1. Introduction

Radical prostatectomy (RP) is one of the most commonly used treatments for patients with prostate cancer (PCa) [1,2]. However, the benefit of an extended pelvic lymph node dissection (ePLND) is still debated. It is generally accepted that whenever a PLND is indicated, this should be anatomically extended [3]. Such an extensive approach represents the only accurate staging procedure for lymph node invasion (LNI) in PCa [4]. However, the therapeutic impact of this ePLND (if any) is still unclear [5–13].

Results of a recent randomised clinical trial suggested that ePLND could significantly decrease the risk of biochemical recurrence (BCR) after RP in patients with intermediate- or high-risk tumours [6]. However, although BCR risk reduction is an important finding, it does not necessarily translate into better survival. In contrast, several observational reports failed to demonstrate any beneficial impact of ePLND on BCR and/or survival [5,9,13]. There may be two main reasons for this result: (1) use of limited and nonhomogeneous PLND, which might have artificially undermined the role of PLND, and (2) selection of patients at lower risk of dying from PCa. These points are key, since any therapeutic benefit associated with surgical treatments of PCa should be tested using a proper surgical approach (ie, ePLND) in a properly selected population (ie, patients at higher risk of dying from the disease).

To address this issue, we tested the relationship between the number of removed lymph nodes (RLNs) and cancer-specific mortality (CSM) in pN1 patients treated with RP and ePLND.

## 2. Materials and methods

We evaluated the data of 315 M0 pN1 PCa patients treated with RP and ePLND between 2000 and 2012 at one tertiary care centre. Patients were staged preoperatively with pelvic/abdominal computerised tomography or abdominal ultrasound, bone scan, and chest x-ray. Seven surgeons performed RP using a standardised retropubic technique. EPLNDs consisted of excision of fibrofatty tissue along the external iliac vein, the distal limit being the deep circumflex vein and the femoral canal. Proximally, ePLND was performed up to and including the bifurcation of the common iliac artery. Furthermore, all fibrofatty tissue within the obturator fossa was removed to completely skeletonise the obturator nerve. The lateral limit consisted of the pelvic sidewall, and the medial dissection limit was defined by perivesical fat. In all the patients included in our cohort, LNs along the internal iliac vessels were dissected. In some cases, LNs located in the presacral and common iliac areas were also removed.

Postoperatively, all patients received adjuvant hormonal therapy (aHT), which was intended to be lifelong. However, given the retrospective nature of the cohort, it is uncertain whether patients discontinued treatment after a period of androgen-deprivation therapy. Additionally, 147 (46.7%) patients received aRT. ART was administered based on the clinical judgment of each treating physician according to patient and cancer characteristics. Radiation therapy consisted of localised radiation delivered to the prostate and to the seminal vesicle bed with pelvic LN irradiation (whole pelvis radiotherapy). Details of the aRT technique used have been previously published [14]. Adjuvant treatments (both aHT and aRT) were initiated within 90 d from RP. The institutional review board approved the study.

### 2.1. Variable definition

All patients included in this study had complete clinical and pathology data, which consisted of age at surgery, prostate-specific antigen (PSA) value, D'Amico risk group (low- vs intermediate- vs high-risk) [15], pathologic Gleason score (2–7 vs 8–10), pathologic tumour stage (pT2 vs pT3a vs pT3b vs pT4), surgical margin status (negative vs positive), number of removed LNs (RLNs), number of positive lymph nodes, aRT status (no aRT vs aRT), and year of surgery.

### 2.2. Statistical analyses

Descriptive statistics of categorical variables focused on frequencies and proportions. Means, medians, and interquartile ranges (IQR) were reported for continuously coded variables. Chi-square and Mann-Whitney tests were used to compare the statistical significance of differences in proportions and medians, respectively.

Univariable and multivariable Cox regression analyses were used to test the relationship between the number of RLNs and CSM rate, after adjusting for all available covariates. Estimated survival curves were plotted based on the multivariable model results. Survival curves were stratified according to the number of RLNs, using the points of maximum separation, as described by Harrell [16]. The number of RLNs was then dichotomised according to the most informative cut-off predicting CSM. This was obtained applying the chi-square test for every possible cut-off value and choosing the lowest $p$ value. Survival curves were then stratified according to the most informative cut-off for the number of RLNs. Finally, predicted 10-yr survival according to the number of RLNs was plotted for the entire cohort, and after stratification according to Gleason score and aRT status.

All statistical analyses were performed using the R statistical package system (R Foundation for Statistical Computing, Vienna, Austria), with a two-sided significance level set at $p < 0.05$.

## 3. Results

### 3.1. Baseline patient characteristics

Clinical and pathologic demographics of the cohort, stratified by adjuvant treatment status are reported in Table 1. The average PSA value was 24.2 ng/ml (median: 11.2 ng/ml; IQR: 6.9–24.4 ng/ml). Most of the patients included in the study were affected by high-risk disease at diagnosis (60%). Most patients harboured a pT3b disease (66%), and had a pathologic Gleason score 8–10 (57%). Average number of RLNs and positive LNs was 20.8 (median: 19; IQR: 14–25) and 3.3 (median: 2.0; IQR: 1–3), respectively. For all examined variables, there were no statistically significant differences between patients treated with aRT versus without aRT (all $p \geq 0.07$).

### 3.2. Cox regression analyses and survival estimates

At univariable analyses, Gleason score 8–10 (hazard ratio [HR]: 2.9), pT4 (HR: 6.7), aRT treatment (HR: 0.40), and the number of positive LNs (HR: 1.1) were the only predictors of CSM rate (all $p \leq 0.02$) (Table 2). At multivariable analyses, Gleason score 8–10 (HR: 3.3) and a higher number of positive LNs (HR: 1.2) were independently associated with higher CSM rate (all $p \leq 0.006$) (Table 2). Conversely, aRT treatment (HR: 0.26) and a higher number of RLNs