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

European Association of Urology

Platinum Priority – Collaborative Review – Prostate Cancer

*Editorials by Martin Spahn on pp. 200–201 of this issue and by Hagen F. Kennecke and Mira Keyes on pp. 202–203 of this issue*

# The Role of Radical Prostatectomy and Lymph Node Dissection in Lymph Node–Positive Prostate Cancer: A Systematic Review of the Literature

*Georgios Gakis* [a,*], *Stephen A. Boorjian* [b], *Alberto Briganti* [c], *Steven Joniau* [d], *Guram Karazanashvili* [e], *R. Jeffrey Karnes* [b], *Agostino Mattei* [f], *Shahrokh F. Shariat* [g], *Arnulf Stenzl* [a], *Manfred Wirth* [h], *Christian G. Stief* [i]

[a] *Department of Urology, University Hospital Tübingen, Eberhard-Karls University Tübingen, Germany;* [b] *Department of Urology, Mayo Clinic, Rochester, MN, USA;* [c] *Department of Urology, Urological Research Institute, University Vita-Salute San Raffaele, Milan, Italy;* [d] *Department of Urology, University Hospital K.U. Leuven, Leuven, Belgium;* [e] *Clinic of Urology, SJC Modern Medical Technologies, Tbilisi, Georgia;* [f] *Department of Urology, Kantonsspital Lucerne, Lucerne, Switzerland;* [g] *Department of Urology, Weill Cornell Medical College, New York, NY, USA;* [h] *Department of Urology, University Hospital Carl Gustav Carus, Technical University of Dresden, Dresden, Germany;* [i] *Department of Urology, Ludwig-Maximilians-University, Munich-Grosshadern, Germany*

## Article info

***Article history:***
Accepted May 13, 2013
**Published online ahead of print on May 22, 2013**

***Keywords:***
Androgen-deprivation therapy
Imaging
Lymph node positive metastasis
Multimodality
Pelvic lymph node dissection
Prostate cancer
Radical prostatectomy
Radiotherapy



## Abstract

***Context:*** Because pelvic lymph node (LN)-positive prostate cancer (PCa) is generally considered a regionally metastatic disease, surgery needs to be better defined.
***Objective:*** To review the impact of radical prostatectomy (RP) and pelvic lymph node dissection (PLND), possibly in conjunction with a multimodal approach using local radiotherapy and/or androgen-deprivation therapy (ADT), in LN-positive PCa.
***Evidence acquisition:*** A systematic Medline search for studies reporting on treatment regimens and outcomes in patients with LN-positive PCa undergoing RP between 1993 and 2012 was performed.
***Evidence synthesis:*** RP can improve progression-free and overall survival in LN-positive PCa, although there is a lack of high-level evidence. Therefore, the former practice of aborting surgery in the presence of positive nodes might no longer be supported by current evidence, especially in those patients with a limited LN tumor burden. Current data demonstrate that the lymphatic spread takes an ascending pathway from the pelvis to the retroperitoneum, in which the internal and the common iliac nodes represent critical landmarks in the metastatic distribution. Sophisticated imaging technologies are still under investigation to improve the prediction of LN-positive PCa. Nonetheless, extended PLND including the common iliac arteries should be offered to intermediate- and high-risk patients to improve nodal staging with a possible benefit in prostate-specific antigen progression-free survival by removing significant metastatic load. Adjuvant ADT has the potential to improve overall survival after RP; the therapeutic role of a trimodal approach with adjuvant local radiotherapy awaits further elucidation. Age is a critical parameter for survival because cancer-specific mortality exceeds overall mortality in younger patients (<60 yr) with high-risk PCa and should be an impetus to treat as thoroughly as possible.
***Conclusions:*** Increasing evidence suggests that RP and extended PLND improve survival in LN-positive PCa. Our understanding of surgery of the primary tumor in LN-positive PCa needs a conceptual change from a palliative option to the first step in a multimodal approach with a significant improvement of long-term survival and cure in selected patients.


* Corresponding author. Department of Urology, Eberhard-Karls University Tübingen, Hoppe-Seyler Strasse 3, D-72076 Tübingen, Germany. Tel. +49 7071 2985092; Fax: +49 7071 295092.
E-mail address: georgios.gakis@googlemail.com (G. Gakis).

0302-2838/$ – see back matter 
http://dx.doi.org/10.1016/j.eururo.2013.05.033

## 1. Introduction

Positive lymph nodes (LNs) represent a significant adverse prognostic factor in prostate cancer (PCa) and can be associated with systemic metastases [1]. In the past, radical prostatectomy (RP) was frequently aborted when frozen sections showed pelvic LNs to be positive [2]. Recently, despite considerable clinical efforts to improve outcomes in patients with LN-positive PCa, the available systemic treatment options, that is, androgen-deprivation therapy (ADT), systemic chemotherapy, and secondary hormonal manipulation (ie, inhibition of adrenal testosterone synthesis), have not proven to reliably provide long-term survival in most cases [3–5]. In advanced stages, local symptoms (ie, macrohematuria, pain) often develop despite early ADT, which often requires repeated transurethral interventions in those who did not undergo radical extirpative surgery [6]. Due to this dilemma, our understanding of the role of RP in LN-positive PCa is about to change. Today, there are three major issues for which the role of RP in LN-positive PCa needs to be defined.

First, emerging data have challenged the former clinical practice of abandoning RP in the case of intraoperatively detected positive nodes [2] because some studies have demonstrated a reduced risk of local failure after completion of RP [1]. Other studies have even reported that RP in node-positive PCa may contribute to long-term survival in patients with limited LN metastatic disease [7,8].

Second, similar to patients with muscle-invasive bladder cancer (MIBC) for whom an extended pelvic lymphadenectomy (ePLND) at radical cystectomy has been increasingly advocated to provide both improved staging and survival even in LN-positive disease [9], the question arises whether an ePLND also exerts beneficial effects on survival in LN-positive PCa.

Third, the issue of maximizing local and systemic treatment in node-positive PCa based on a multimodal approach with RP/ePLND, local radiotherapy, and ADT needs to be addressed because this may not only be a suitable regimen for improving progression-free survival and avoiding locoregional complications [7] but inherently may also be curative in selected patients.

Beyond these issues, it is of utmost importance to tailor treatment regimens individually by carefully selecting those patients who are most likely to benefit from the multimodal approach while sparing unnecessary side effects for those who will progress despite aggressive treatment. This review provides evidence for the role of RP for these three essential management issues in LN-positive PCa.

## 2. Evidence acquisition

A systematic literature search was performed to identify studies reporting treatment regimens and outcomes in patients with LN-positive PCa undergoing RP between 1993 and 2012. Medline was searched using the controlled vocabulary of the Medical Subject Headings database, along with a free-text protocol using one or several combinations of the following items: *androgen-deprivation therapy, imaging, lymph node positive, metastasis, multimodality, pelvic lymph node dissection, prostate cancer, radical prostatectomy*, and *radiotherapy*. A total of 857 records were initially identified through database research using the following terms: *radical prostatectomy* and *lymph node positive prostate cancer*. Further selection process of studies followed the rules according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis statement [10]. Basically, PICOS were generated to address three specific questions on the role of RP in LN-positive prostate cancer as previously outlined.

These PICOS consisted of the following combinations: Participants: patients with prostate cancer and lymph node metastasis; Interventions: RP, (e)PLND, adjuvant ADT, adjuvant radiotherapy; Comparisons: (1) RP plus (e)PLND versus no RP; (2) RP plus ePLND versus RP with standard PLND; (3) RP plus (e)PLND plus adjuvant ADT versus RP plus (e)PLND; (4) RP plus (e)PLND plus adjuvant ADT plus adjuvant radiotherapy versus RP plus (e)PLND plus adjuvant ADT; Outcomes: survival (progression-free and/or overall survival); Study Design: retrospective versus prospective. Articles referring to these PICOS were assessed according to their level of evidence (LE) based on the Oxford Centre for Evidence-based Medicine levels of evidence [11]. Notably, most data were derived from retrospective studies that inevitably inherit selection biases for which we could not control in this review. The intention of this systematic review is to focus explicitly on the role of RP as a local treatment option in LN-positive PCa because there is no clear head-to-head comparison with other local modalities (ie, radiotherapy) in a randomized setting for patients with LN-positive PCa.

## 3. Evidence synthesis

### 3.1. Should we proceed with radical prostatectomy in lymph node–positive prostate cancer?

One of the most challenging clinical management issues in PCa today is whether to perform RP if diagnostic staging investigation shows enlarged LNs [1]. Cytoreductive surgery in conjunction with systemic treatment has been shown to improve survival in metastatic renal cell carcinoma [12] as well as in many other malignant diseases [13]. In this regard, the question whether to continue or discontinue with RP in the case of positive nodes has been debated in recent decades [2,14]. The first data suggesting a prognostic benefit were reported in a retrospective series of 139 patients staged pN1–N3M0 at RP. In 52 patients it was decided to proceed intraoperatively with RP; in the remaining 87 the procedure was discontinued. The latter group experienced significantly higher progression rates and lower 10-yr cancer-specific and overall survival than the RP-treated group (LE: 3) [15]. These retrospective data are presumably flawed because only patients with minimal LN metastases or no severe comorbidities might have undergone RP and PLND. Thus the question arises whether there is a subgroup of LN-positive patients who profits most from radical surgery, possibly in conjunction with