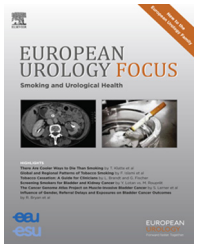
available at www.sciencedirect.com
journal homepage: www.europeanurology.com/eufocus



Platinum Priority – Prostate Cancer
Editorial by XXX on pp. x–y of this issue

Association between Lymph Node Counts and Oncological Outcomes in Lymph Node Positive Prostate Cancer

Philipp Mandel [a,b], ***Maximilian C. Kriegmair*** [c], ***Katharina Bogdan*** [a], ***Katharina Boehm*** [b], ***Lars Budäus*** [a], ***Markus Graefen*** [a], ***Hartwig Huland*** [a], ***Derya Tilki*** [a,b,*]

[a] *Martini-Klinik Prostate Cancer Center, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [b] *Department of Urology, University Hospital Hamburg-Eppendorf, Hamburg, Germany;* [c] *Department of Urology, University Medical Centre Mannheim, Mannheim, Germany*

Article info

Article history:
Accepted February 28, 2016

Associate Editor:
James Catto

Keywords:
Prostate cancer
Radical prostatectomy
Lymph node dissection
Positive lymph nodes

Abstract

Background: While the diagnostic value of pelvic lymph node dissection (PLND) during radical prostatectomy (RP) is undisputed, its therapeutic benefit remains a matter of debate.
Objective: To investigate the association between total and positive lymph node (LN) counts and oncological outcomes in pN1 patients at RP.
Design, setting, and participants: The records of 706 LN-positive patients undergoing RP and PLND between 1998 and 2012 in a single center were analyzed. The median follow-up was 47.8 mo.
Intervention: RP and PLND.
Outcome measurements and statistical analysis: The number of harvested and positive LNs and their influence on biochemical recurrence-free survival, metastasis-free survival, and cancer-specific survival was evaluated using univariate and multivariate Cox regressions. The number of harvested LNs was used as a continuous and dichotomous variable with a cut-off of 13 LNs.
Results and limitations: The mean (median) number of removed LNs was 15.0 (13) and the mean (median) number of positive LNs was 2.4 (1). In multivariate analysis, the number of removed LNs did not significantly influence oncologic outcomes (biochemical recurrence, metastasis-free survival, or cancer-specific survival). The occurrence of metastasis and cancer-specific mortality significantly increased with higher number of positive LNs. The main limitation was the retrospective nature of the study.
Conclusions: While a higher number of positive LNs were significantly associated with worse oncological outcomes, the number of removed LNs was not a significant predictor.
Patient summary: We found that only the number of positive lymph nodes (LNs) but not the total number of removed LNs was a factor adversely influencing oncological outcomes in LN-positive patients undergoing radical prostatectomy.

* Corresponding author. Martini-Klinik Prostate Cancer Center, Martinistrasse 52, 20246 Hamburg, Germany. Tel. +49 4074100; Fax: +49 4074100.
E-mail address: d.tilki@uke.de (D. Tilki).

1. Introduction

Prostate cancer is the most frequent cancer among men in Europe and other developed countries and among the leading causes of death [1,2]. For its treatment, radical prostatectomy (RP) is one of the recommended treatment options for all levels of risk. Pelvic lymph node dissection (PLND) is the most precise staging procedure for possible

http://dx.doi.org/10.1016/j.euf.2016.02.018
2405-4569/

lymph node (LN) metastasis; however, its therapeutic benefit concerning oncologic outcome remains controversial [3–6]. According to the guidelines of the European Urological Association (EAU), whenever a PLND is indicated, an anatomically extended PLND should be performed [7].

To present, Level IB evidence from randomized controlled trials on the oncological role of PLND is lacking. The Prospective Study to Compare a Limited Versus Extended Pelvic Lymphadenectomy During Prostatectomy (NCT01555086) is currently recruiting participants. Several retrospective studies could not show that removing more LNs during RP results in improved oncological outcome in patients with pN0 [8], pN0 or pN1 [9], and pN1 [10] only. In contrast, Abdollah et al. [11] recently reported that a higher number of removed LNs is an independent predictor of a more favorable cancer-specific survival (CSS) in LN-positive patients [11]. All patients included in the study received immediate adjuvant hormonal treatment (ADT). This study was followed by a controversial discussion on potential biases and confounders involved in this type of analysis, including the Will Rogers phenomenon possibly explaining the results [12,13].

It remains questionable whether a higher number of removed LNs, regardless if these additional removed LNs harbor metastases or not, impacts oncologic outcome.

The aim of the present study was to analyze the influence of the extent of PLND according to the number of removed LNs in pN1 patients at RP on biochemical recurrence (BCR), metastasis, and cancer-specific mortality (CSM) in a large single center and to add further information to the controversial ongoing discussion using a dataset of more than 700 LN-positive patients.

2. Materials and methods

2.1. Patient population

From our institutional Martini-Klinik database, we identified 969 out of 15 947 patients who underwent RP at our institution between January 1998 and December 2012 with positive LNs in the final pathology. Information on the number of harvested LNs at PLND was missing in 75 men. Moreover patients who were lost to follow up within 24 mo after RP were excluded (188), which left 706 patients for our analysis. Furthermore, for analysis of BCR, patients with ADT were excluded from regressions (242 patients). All data were collected prospectively into our review board-approved database. Patients were stratified according to the number of removed LNs. Indication to perform PLND was in accordance to respective EAU guidelines applicable at the relevant time and partly based on an individual approach [7].

BCR was defined as a prostate-specific antigen (PSA) level $\geq$0.2 ng/ml and rising after RP in patients without ADT. Metastasis was confirmed with imaging. The cause of death was determined by the treating physicians, by chart review corroborated by death certificates, or by death certificates alone.

After RP, patient follow up consisted of periodical PSA testing and digital rectal examination. Postoperative imaging studies to detect local recurrence or systemic spread were performed according to PSA level, patients' preferences, and further symptoms. Adjuvant hormonal and/ or radiation therapy (RT) was recommended based on further patient and tumor characteristics and according to respective EAU guidelines applicable at the relevant time [7]. Adjuvant treatment was defined as immediate treatment administered within 6 mo after RP with an undetectable PSA ($<$ 0.2 ng/ml), while salvage treatment was defined as treatment administered at a postoperative PSA $\geq$0.2 ng/ml.

2.2. Surgical procedure and histologic evaluation

RP was performed using an open retropubic approach or robotic-assisted laparoscopic approach by high volume surgeons, as previously described [14]. Pathological outcome was assessed using the American Joint Cancer Committee 2002 staging system and tumor grading was classified using the Gleason Grading system [15]. From 2004, the template of PLND was in accordance with the EAU guidelines for anatomically extended PLND and included removal of the nodes overlying the external iliac artery and vein, the nodes within the obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateral to the internal iliac artery [7]. Before 2004, bilateral PLND was not uniformly performed with extended template and mainly included the region of the obturator fossa and along the external iliac artery.

As the pathologic examination of LNs has changed during the study period due to advances in LN metastasis detection via the introduction of complete embedding of fat tissue, an increase in the detection of harvested LNs may have occurred. We introduced dummy variables to control for both the change in PLND template and change in pathologic examination in all multivariate regressions. To control for further unobserved time-dependent variation we included the year of surgery in all regressions.

2.3. Statistical analyses

To check for differences in our respective subsamples Pearson's Chi-square tests and Kruskall-Wallis tests were performed.

To evaluate the association between removed lymph nodes and oncologic outcome (MFS and CSS) Kaplan-Meier curves and uni- and multivariate Cox proportional hazard models adjusting for pre- and postoperative prognosticators were assessed. These prognosticators included age at surgery, preoperative PSA, pathologic Gleason score, pT-stage, surgical margin status, number of positive LNs, year of surgery, neoadjuvant treatment, adjuvant ADT, salvage ADT, adjuvant RT, and salvage RT. Statistical software STATA was used (version 14 for Windows, StataCorp LP, College Station, TX, USA). LN count was used as both, continuous and dichotomous variable. For dichotomization all cut-offs between 5 and 25 removed LNs were analyzed. As all cut-off values of removed LNs showed only insignificant differences on oncological outcomes, we presented the results at a cut-off value of 13 (median of removed LNs).

3. Results

3.1. Patient and tumor characteristics

Patient and tumor characteristics of the entire cohort and stratified by the number of removed LNs (high LN count [$>$ 13] and low LN count [$\leq$ 13]) are summarized in Table 1. In the entire population of LN positive patients, the mean (median) number of removed LN was 15.0 (13) and the mean (median) number of positive LN was 2.4 (1). Next to number of removed LNs and number of positive LNs, LN density (ratio of the number of metastatic LNs to the total number of LNs removed; $p < 0.001$) and Gleason score ($p = 0.002$) were significantly different between patients with a high and low LN count.

Please cite this article in press as: Mandel P, et al. Association between Lymph Node Counts and Oncological Outcomes in Lymph Node Positive Prostate Cancer. Eur Urol Focus (2016), http://dx.doi.org/10.1016/j.euf.2016.02.018