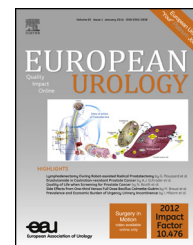


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Platinum Priority – Collaborative Review – Prostate Cancer

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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. Stiefⁱ

^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

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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.

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* 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).

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

antihormonal treatment. In this respect, a prior study addressed the risk of progression in LN-positive patients ($n = 297$) after RP, PLND, and adjuvant ADT, according to the number of affected LNs. Patients with single positive nodes showed more favorable outcomes compared with those with two and or more LNs [16].

Studies in the era of the prostate-specific antigen (PSA) have confirmed that RP improves progression-free survival in patients with LN-positive PCa [1,7]. Still, its beneficial effects on overall survival are not well established. This issue is difficult to tackle because there are no randomized trials that have controlled for the effects of RP on overall survival in patients with limited LN tumor burden. A recent retrospective study evaluated independent parameters for cancer-specific survival in a mixed cohort of 158 patients scheduled for RP between 1992 and 2008. After the intraoperative detection of positive nodes, the decision was made either to continue ($n = 108$) or discontinue ($n = 50$) with the procedure. Multivariate analysis revealed the number of positive nodes and performance of RP independently predicted cancer-specific survival [17] (LE: 3). However, the chance to achieve long-term survival with RP alone for LN-positive stages is limited and has been reported to vary between 10% and 14% [18].

Conversely, in patients with clinically locally advanced PCa (cT3b/4), overstaging is frequent (up to 37%) and should not be ignored in the decision to continue with RP [19] because this might relegate some patients to a conservative treatment approach and deprive them of RP with a potential benefit in survival. A recent population-based database analysis identified 938 LN-positive patients (688 with RP, 250 without RP). The decision to perform RP was based on the results of a frozen section analysis of pelvic nodes. After a median follow-up of 5.6 yr, overall 5-yr and 10-yr survival was significantly higher in patients who were treated with RP (84% and 64%) compared with those with aborted RP (60% and 28%, respectively). In this study, imbalances in the two groups were noted because only 17% with RP had four or more positive nodes versus 28% in the patient group with aborted RP. Nonetheless, in multivariate analysis, adjusted for the number of affected nodes, RP was an independent predictor of survival [7] (LE: 3). In recent years, this suggested survival advantage has encouraged urologists to complete RP, regardless of LN status, and in fact to omit frozen section analysis of nodes [20]. To address this question properly, a formal prospective trial would be the only way to get a final answer to this critical question, but it is unlikely ever to be performed.

3.2. *Is there a survival benefit of performing extended pelvic lymph node dissection in patients with lymph node-positive prostate cancer at radical prostatectomy?*

In MIBC, there has been increasing evidence that ePLND improves recurrence-free survival in patients with limited LN tumor burden [9] (LE: 1b). Therefore, the question that needs to be addressed is whether the eradication of all metastatic or micrometastatic sites improves disease-free survival in node-positive PCa as well [21]. However, a more

meticulous PLND might result in apparently improved survival rates as a result of stage migration and dissection of a micrometastasis that prior to a thorough node dissection would have been undetected—the well-known Will Rogers phenomenon [22,23]. If we compare survival rates in patients with LN-positive PCa who underwent RP and ePLND, we need to take a careful look at the template of LN dissection because a more extended PLND might result in apparently improved survival rates by stage migration. There is some disagreement in the literature regarding the definition of the anatomic extent of an ePLND in PCa. Some authors have reported that an ePLND includes the removal of lymphatic tissue up to the iliac bifurcation [24] (LE: 3); others have included the common iliac and presacral nodes in their ePLND template [25] (LE: 2b).

A recent prospective study investigated the impact of standard versus extended PLND on biochemical progression-free survival (BPFS) in 360 patients with clinically localized PCa undergoing open RP. Patients were randomized 1:1 into both arms. Standard PLND was defined as the removal of lymphatic tissue around the external and obturator region. Extended PLND also included the removal of lymphatic tissue around the internal iliac region up to the common iliac artery excluding the presacral region. With these templates, the median number of retrieved LNs was 10 and 23, respectively. Interestingly, the number of LN-positive patients was significantly different with 10% in the standard group and 22.2% in the extended group, whereas no differences in primary clinicopathologic characteristics were found for both groups (including age, PSA, cT/pT stage, Gleason grade in biopsy and RP specimens, and margin status). The 5-yr BPFS in the standard group and the ePLND group was not different in low-risk patients (90.1% and 91.3%, respectively). By contrast, in intermediate-risk patients, a significant difference was noted (73.1% vs 85.7%; $p = 0.042$) and was most pronounced in high-risk patients (51.1% vs 71.4%; $p = 0.036$) [26] (LE: 2a). These data suggest that LN tumor burden plays a critical role for BPFS in LN-positive PCa. Yet long-term data will inevitably be needed to corroborate these findings in terms of a prognostic benefit for the outcome measure of overall survival.

3.3. *Which are the primary anatomic lymphatic landing sites in lymph node-positive prostate cancer?*

To define the role of RP in LN-positive PCa adequately, the issue of the primary lymphatic landing sites needs to be addressed because the removal of these affected nodes might be essential both for diagnostic and therapeutic purposes. The frequency and distribution of nodal metastases in PCa was recently investigated in a retrospective single-surgeon series of 427 patients treated with RP for localized PCa. Standard PLND included the removal of the external iliac, obturator, and internal iliac nodal chains. With a median number of 16 nodes removed, 35 of the 427 patients (8.2%) were found to have positive nodes. In 37% of these patients, LNs were exclusively located in the external and obturator region. Overall, 80% of the patients showed a maximum of two positive nodes at final

pathologic examination. These data reflect the critical role of performing a thorough PLND in the internal iliac region to enable accurate pathologic LN staging [27]. However, these data do not provide information about the anatomic pathway of lymphatic tumor cell dissemination in the pelvis and retroperitoneum as well as the risk of LN-positive PCa cranial to the boundaries of standard PLND.

In a prospective mapping study of a select group of 19 very high-risk patients (meeting at least two of the following criteria: PSA > 20 ng/ml, cT3, or Gleason score \geq 8), a “radical” lymphadenectomy template was used (including the removal of the external and internal iliac, obturator, presacral, common iliac, para-aortal, interaortocaval, and paracaval nodes) to reveal the lymphatic pathways of the pelvis and retroperitoneum [28] (LE: 3). LN-positive disease was found in 95% of the patients. The most commonly affected landing sites were the obturator (89%) followed by the external iliac (83%), common iliac (77%), internal iliac (44%), and presacral (33%) region. A total of 78% of the patients were found to have metastatic nodes in the para-aortal, interaortocaval, and paracaval region that were only present in patients with positive common iliac nodes and with at least five positive lower pelvic nodes. In addition, no skip lesions were found in the retroperitoneum in the case of negative common iliac nodes [28].

Although this study is limited due to its relatively small number of included patients, it seems to suggest an ascending lymphatic spread from the pelvis to the retroperitoneum in which the internal and the common iliac nodes represent critical landmarks for accurate LN staging, whereas metastatic lymph nodes are less frequent in the presacral region. Based on these data, if we assume that the removal of lymphatic tissue around the common iliac nodes is critical for accurate staging and skip lesions in the retroperitoneum are infrequent in the case of negative common iliac nodes, we need to evaluate additionally the necessity of performing PLND in the presacral region. In other words, do we need a presacral lymphadenectomy for improved staging even in the presence of negative preoperative scans?

The need of a presacral lymph node dissection (LND) in LN-positive PCa has been a matter of debate for many decades [29]. A prospective study evaluated 74 patients with localized PCa and negative computed tomography (CT) scans who were estimated to carry a 10–35% risk of harboring LN-positive or \geq pT3a stage disease [30] (LE: 2b). After technetium Tc 99m nanocolloid injection, a planar scintigraphy and single-photon emission computed tomography (SPECT) scan was conducted preoperatively. A sentinel node (SN) LND followed by a superextended lymphadenectomy was performed in every patient and completed with RP. A total of 470 SNs were scintigraphically detected in the 74 patients with a median number of 6 SNs (calculated interquartile range [IQR]: 2.25–6). With a superextended approach, 91 positive nodes were found in 34 of the 74 patients (46%) (median: 2; IQR: 1–3). More importantly, with an ePLND up to the common iliac chain, 32 of the 34 patients (94%) would have been correctly staged, but in only 26 of the 34 patients (77%) would all

metastatic sites have been removed. This number increased from 77% to 97% when the presacral region was added to the lymphadenectomy template [30]. Similar results were reported in a multimodal mapping study using SPECT techniques of 34 patients with cT1–T2cN0 PCa. An ePLND at least up to the ureteric crossing of the common iliac arteries removed 75% of all primary lymphatic landing sites [31]. Although preoperative SPECT-CT/magnetic resonance imaging (MRI) is highly reliable to detect nonmetastatic sentinel nodes of the prostate and less time consuming than gamma probe-guided SN dissection, both procedures take significantly longer than an upfront ePLND [32].

Altogether, these data suggest that an ePLND up to the common iliac nodal chains is sufficient to stage correctly most of the patients with LN-positive PCa. However, these data show that lymphatic drainage and dissemination patterns are not always congruent in LN-positive PCa and that a SN-driven lymphadenectomy does not reliably detect all positive nodes because there is an invariable distribution of tumor cells along the multiple lymphatic axis in the pelvis. A prospective mapping study of 96 patients with LN-positive PCa undergoing RP and ePLND investigated radio-guided surgery in patients with LN-positive PCa. Based on an SN concept, the major drawback was that when SNs and non-SNs were positive, the non-SNs were located outside the region of sentinel lymphadenectomy in more than half of the patients [33]. In this respect, if we assume that RP in LN-positive PCa provides a survival benefit in node-positive PCa, then maximizing the outcome of the procedure would routinely include the presacral region in the ePLND template in intermediate- to high-risk patients to catch up all metastatic LNs. Nonetheless, even with an ePLND, the risk of undetected residual micrometastatic disease in the retroperitoneum at RP remains considerable because most high-risk patients will remain at high risk of progression in the retroperitoneum despite aggressive secondary treatment with salvage retroperitoneal LN dissection and ADT [34].

3.4. Do functional imaging technologies predict the lymphatic spread?

Despite the studies cited previously, the need and the extent of ePLND in high-risk PCa remains a matter of debate because of the potential risk of residual micrometastatic disease after RP despite a meticulous lymphadenectomy [34,35]. Therefore, an individualized risk-adapted template may represent a more sensible approach in a given patient with high-risk disease. This approach, however, requires cross-sectional imaging techniques that reliably detect minimally enlarged LNs harboring metastatic disease. Large correlation studies in patients who underwent RP with ePLND for locally advanced PCa (with a nomogram-derived risk of LN-positive disease \geq 50%) have shown disappointing sensitivity rates (24%) for conventional abdominopelvic CT scan with an overall accuracy of only 59% [36].

These rates do not seem to alter significantly with the use of choline positron emission tomography (PET)/CT scan methods or MR diffusion-weighted imaging techniques. A

recent study found that both methods were unable to detect metastatic disease reliably even in nodes with histopathologically proven capsular penetration [37]. Although a prospective trial among 132 intermediate- to high-risk patients reported higher sensitivity and positive predictive values for fludeoxyglucose F 18 choline PET/CT in LNs >5 mm of 66% and 82%, respectively, the main limitation of this method is that the detection rate of low-volume and micrometastatic disease is low [38]. A smaller prospective study of 20 patients (with an at least nomogram-based 20% risk of LN-positive disease) who underwent F 18 choline PET/CT prior to RP reported disappointing sensitivity because in none of the 9 patients with LN-positive disease was a single positive LN detectable (median diameter of positive nodes at pathologic examination: 7 mm; range: 0.8–12) [39]. As was demonstrated for the use of choline PET in the setting of biochemical failure after RP [40], we need to realize that the sensitivity of choline PET before RP strongly depends on tumor burden.

The so-called fluorescence-guided SN dissection was recently introduced. After intraprostatic injection of indocyanine green immediately before surgery, this fluorescence-based navigation technique was shown to be superior to radioisotope-guided SN dissection [41,42]. Although promising, the main disadvantage of this technique is the unique technical equipment necessary to perform lymphadenectomy, making the procedure more time-consuming. Radioisotope-guided and SN-driven imaging techniques for detecting lymphatic spread in patients with node-positive PCa are also limited by a relatively low sensitivity.

A recent prospective study investigated whether ultra-small paramagnetic particles of iron oxide on enhanced magnetic resonance imaging (USPIO-MRI) allows for improved detection of metastatic nodes in patients with prostate ($n = 48$) and/or bladder cancer ($n = 19$). A total of 2993 LNs were examined histologically. Sensitivity and specificity for USPIO-MRI were 55% and 85%, respectively, with a diagnostic accuracy of 77%. Most of the missed metastases were <5 mm in the short axis diameter [43]. Whether lymphotropic MRI has the definitive potential to improve the sensitivity of conventional cross-sectional imaging techniques in the preoperative setting awaits further investigation [44].

3.5. Predicting the presence and location of metastatic lymph nodes by nomograms

Because preoperative imaging modalities are not reliable to detect the exact lymphatic spread in high-risk PCa patients, the question remains whether surgeons need to maximize the extent of PLND in every patient to maximize the prognostic advantage or whether there is a possibility to individualize accurately the optimal extent of PLND at RP in a given high-risk patient. Nomograms predicting the risk of LN tumor involvement at RP can guide clinicians to proceed individually with an ePLND. In this respect, nomograms predicting exclusively nonobturator LN involvement represent the first step to tailor the necessity of an ePLND [24].

Further critical issues are the high rate of Gleason score upgrading at RP and interobserver variability reaching up to 36% between biopsy and final Gleason score in RP series [45]. These factors compromise the clinical significance of proposed nomograms. Despite the fact that former nomograms (ie, the Partin tables) were recently updated in a large contemporary RP series to comply with the updated Gleason grading system [46], the results of this study are based on a limited LND template, and the study population contained a small percentage of high-risk PCAs. In this study, main determinants for LN tumor involvement at RP were preoperative PSA value, Gleason score, and clinical stage.

Another nomogram based on a formerly published series of patients who underwent RP with ePLND was recently updated as well. LND included the removal of the external, obturator, and internal regions. The addition of the percentage of positive cores to the three established parameters improved their predictive ability significantly, yielding a high predictive accuracy of 87.6% [47,48]. Nomograms for predicting the presence of metastatic nodes at RP have been already externally validated [49,50].

The use of nomograms certainly helps us to identify which patient harbors metastatic LNs and ultimately needs a thorough lymphadenectomy at RP because the retrieval of at least 20 LNs will derive a 90% probability of correctly staging LN metastases [51]. But is this approach of any real clinical benefit as long as we do not know the exact metastatic sites?

This question is even more important because the number of affected nodes likely predicts cancer-specific survival. A large consecutive series of >700 patients with LN-positive PCa treated with RP, ePLND, and adjuvant treatments reported that patients with more than two positive nodes exhibited significantly inferior survival than those with two or fewer affected nodes [52]. This has also been confirmed in patients treated with RP and ePLND alone until progression [53]. Although ePLND has been shown not to influence functional outcomes (ie, erectile function recovery), after bilateral nerve-sparing RP [54] it seems clinically reasonable to tailor individually the necessity of performing ePLND to the risk of LN tumor involvement according to predictive nomograms.

Recently, the European Association of Urology (EAU) guideline nomogram was externally validated in a cohort of 1520 patients who underwent RP with PLND including the external, obturator, and hypogastric nodes. LN tumor involvement was present in 10.6% of the patients. Theoretically, using a 7% cut-off value to trigger PLND, almost half of all PLNDs could be avoided at the cost of missing 11% of the patients with positive nodes, resulting in a high predictive accuracy of 81% [55]. These data once again suggest that nomograms are useful tools to optimize the extent of PLND.

3.6. Multimodal treatment in lymph node-positive prostate cancer

LN-positive PCa represents a significant adverse prognostic factor and can be associated with systemic metastases [1].

Table 1 – Overview of most recent series reporting survival in patients with high-risk prostate cancer according to treatment regimen

Study	Treatment	Overall survival		Cancer-specific survival		Recurrence-free survival	
		5 yr	10 yr	5 yr	10 yr	5 yr	10 yr
Cheng et al. [16] n = 3463	RP N–	–	–	99	97	77	59
	RP plus ADT (immediate) N+			94	83	74	64
	RP plus ADT (immediate) N+ ≤1			99	94		
Daneshmand et al. [70] n = 235	RP all			–	–	80	65
	RP l/n ≤2	94–96	74–75			81–89	70–73
	RP l/n ≥5	75	49			62	49
Messing et al. [58] n = 98 with pN+	RP plus ADT (immediate)	89	76	96	87	84	70
	RP plus ADT (deferred)	74	54	76	59	30	16
Spiess et al. [60] n = 100	RP plus ADT (immediate vs deferred)	93	74	94	75	–	–
	No statistically significant difference						
Schumacher et al. [53] n = 122	RP all	83.3	52.2	84.5	60.1	–	–
	RP l/n ≤2	92.8–88.5	70.5–71.9	94.9–93.2	72.1–79.1		
	RP plus ADT (33 mo) l/n ≥3	67.7	27.2	67.7	33.4		
Briganti et al. [52] n = 703	RP plus ADT or ADT plus RT	84	67	90	82	71	58
	RP plus ADT or ADT plus RT l/n ≤2			93	85		
	RP plus ADT or ADT plus RT l/n >2			81	73		
	RP plus ADT	–	–	81.4	71.8	65.3	41.7
Da Pozzo et al. [67]	RP plus ADT plus RT			88.4	70.3	73.2	51.0
	RP plus ADT	84	64	94.9	86.2	–	–
Engel et al. [7] n = 938	ADT	60	28	70.5	40.5		
	RP plus ADT	–	–	84	76	77	61
Steuber et al. [17]	ADT			81	46	61	31

ADT = androgen-deprivation therapy, l/n = number of positive nodes; N– = node negative; N+ = node positive; RP = radical prostatectomy; RT = radiotherapy.

Thus multimodal treatment concepts should aim at improving survival. As outlined earlier, ePLND allows for improved nodal staging in high-risk patients and may also affect survival because an impact on PSA progression-free rates has been demonstrated.

Although there is no convincing evidence for the use of neoadjuvant ADT in LN-positive PCa [56], some promising data was published in a phase 2 study on combined neoadjuvant docetaxel and ADT treatment in patients with high-risk PCa [57]. Nevertheless, in contrast to these approaches, adjuvant ADT or bilateral subcapsular orchiectomy has been investigated more extensively for improving local and systemic tumor control in LN-positive PCa [8,58]. Although randomized trials have demonstrated the superiority of lifelong ADT in locally advanced PCa patients treated by local radiotherapy, the appropriate timing and duration of ADT in LN-positive patients after surgery has been a matter of discussion for many years [59].

Whereas retrospective data suggested that a delayed initiation of ADT may result in similar survival rates [60,61], a randomized controlled trial by Messing et al. was set up to investigate survival effects of adjuvant ADT in 98 LN-positive patients after RP (with a median follow-up of 11.9 yr) [58]. The 10-yr overall (76% vs 54%), cancer-specific

(87% vs 59%), and progression-free survival rates (70% vs 16%) were significantly higher in those patients receiving immediate ADT versus deferred treatment (LE: 1b). The results of this study have gained much recognition, but the main limitation of this study was the low number of included patients. In addition, it has to be mentioned that in the control group, treatment was only initiated at clinical progression. In the Early Prostate Cancer Program, an improved progression-free survival among locally advanced PCa patients was most pronounced in the subgroup of LN-positive patients treated with adjuvant bicalutamide versus placebo; only a trend toward improved overall survival was observed ($p = 0.06$) [62,63] (LE: 1b). These results were also confirmed in a meta-analysis [64]. Altogether, the EAU guidelines on prostate cancer do not support the use of adjuvant ADT in LN-positive PCa by level 1 evidence [65].

Escalation of adjuvant treatment by adding local radiotherapy to ADT was shown to improve both cancer-specific and overall survival in matched analyses of >700 patients with LN-positive pT2–T4a PCa regardless of the extent of nodal invasion [66,67] (LE: 3). It should be noted that about 75% of patients had positive resection margins and/or pT3b PCa at final pathology. The positive

effect on survival may probably be explained by the maximization of local control, rather than an improved disease control at the node-positive sites. However, to our knowledge, there has been no reported randomized study to date that has evaluated an overall survival benefit in LN-positive PCa with a trimodal approach using standardized radiation and ADT protocols. Altogether, the current body of evidence suggests the use of a local treatment with RP, ePLND, and adjuvant radiotherapy in selected patients with ADT. Nevertheless, these data will need to be tested in prospective randomized trials. [Table 1](#) lists the most recent series evaluating survival differences in patients undergoing RP with adjuvant ADT/radiotherapy for locally advanced prostate cancer.

3.7. Effect of comorbidities on outcomes in lymph node–positive prostate cancer

Parameters influencing overall survival in LN-positive PCa are poorly understood because reliable long-term data with >10 yr of follow-up from contemporary series are rare. In a recent single-center retrospective series of 193 patients with LN-positive PCa, 94% were treated with immediate ADT. Independent parameters for decreased overall survival were older age (>70 vs <70 yr), a higher number of metastatic nodes (more than two vs two or fewer), and a higher Gleason score (8–10 vs ≤7). The authors of this study concluded that some of the excess mortality in patients with poor-risk LN-positive prostate cancer may be attributed to an increased competing mortality, possibly caused by an interaction between comorbidity and hormonally treated persistent or progressive PCa [68] (LE: 3). These data were confirmed in a multicenter setting of 3828 patients treated with RP and PLND for high-risk PCa in which 5.9% of the patients died from PCa and 14.3% died from other causes. Age (<60 yr) and the Charlson Comorbidity Index were independent predictors of 10-yr overall survival. Other-cause mortality was the leading cause of death in all patients except in the group of patients ≤59 yr of age. These data suggest that long-term cancer-specific mortality represents the leading cause of death in younger patients, which should therefore trigger a more radical local and systemic approach in these patients [69] (LE: 3).

4. Conclusions

RP can improve progression-free and overall survival in LN-positive PCa, although there is a lack of high LE. In younger patients with suspicion of positive LNs in the preoperative staging investigations, RP with ePLND combined with ADT and local radiotherapy should be discussed. Discontinuing surgery in the presence of positive nodes is no longer supported by current evidence, especially in patients with a limited LN tumor burden. Because the lymphatic spread seems to mostly take an ascending pathway from the pelvis to the retroperitoneum in which the internal and the common iliac nodes represent critical landmarks for metastatic distribution, an ePLND up to the common iliac arteries should be offered to intermediate- and high-risk

patients. This improves nodal staging while some therapeutic benefit in progression-free survival might be derived as well from removing all nodal metastatic sites. Postoperative ADT is an integral part of treatment to improve overall survival after RP with timing and duration still under evaluation. The addition of adjuvant radiotherapy in a trimodal approach may further improve outcome but awaits further investigation. Age is a critical parameter for overall survival because cancer-specific mortality exceeds overall mortality in younger patients with high-risk PCa and should therefore guide clinicians to advocate a more radical local and systemic treatment paradigm.

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Study concept and design: Gakis, Stief.

Acquisition of data: Gakis, Boorjian, Briganti, Karazanashvili, Karnes, Joniau, Mattei, Shariat, Stenzl, Wirth, Stief.

Analysis and interpretation of data: Gakis, Boorjian, Briganti, Karazanashvili, Karnes, Joniau, Mattei, Shariat, Stenzl, Wirth, Stief.

Drafting of the manuscript: Gakis.

Critical revision of the manuscript for important intellectual content: Gakis, Boorjian, Briganti, Karazanashvili, Karnes, Joniau, Mattei, Shariat, Stenzl, Wirth, Stief.

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