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The benefits and harms of different extents of lymph node dissection during radical prostatectomy for prostate cancer: a systematic review

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- European Association of Urology Prostate Cancer Guidelines Panel

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1 **Abstract**

2 **Context.** Controversy exists regarding the therapeutic role of pelvic lymph node
3 dissection (PLND) in patients undergoing radical prostatectomy for prostate cancer.

4 **Objective.** To systematically review the relevant literature assessing the relative
5 benefits and harms of PLND on oncological and non-oncological outcomes in
6 patients undergoing radical prostatectomy for prostate cancer.

7 **Evidence acquisition.** Medline, Medline In-Process, Embase, and the Cochrane
8 Central Register of Controlled Trials were searched up to December 2015.
9 Comparative studies evaluating no PLND, limited, standard, and (super)-extended
10 PLND and reporting on oncological and non-oncological outcomes were included.
11 Risk-of-bias and confounding assessments were performed. A narrative synthesis
12 was undertaken.

13 **Evidence synthesis.** Overall, 66 studies recruiting a total of 275,269 patients were
14 included (44 full-text articles and 22 conference abstracts). Oncological outcomes
15 were addressed by 29 studies, one of which was a randomized clinical trial (RCT).
16 Non-oncological outcomes were addressed by 43 studies, three of which were RCTs.
17 There were high risks of bias and confounding across most studies. Conflicting
18 results emerged when comparing biochemical and clinical recurrence, while no
19 significant differences were observed among groups for survival. Conversely, the
20 majority of studies showed that the more extensive the PLND, the greater the
21 adverse outcomes in terms of operating time, blood loss, length of stay and post-
22 operative complications. No significant differences were observed in terms of urinary
23 continence and erectile function recovery.

24 **Conclusion.** Although representing the most accurate staging procedure, PLND and
25 its extension are associated with worse intra-operative and peri-operative outcomes,
26 whereas a direct therapeutic effect is still not evident from the current literature. The
27 current poor quality of evidence indicates the need for robust and adequately
28 powered clinical trials.

29 **Patient summary.** Based on a comprehensive review of the literature, this article
30 summarises the benefits and harms of removing lymph nodes during surgery to
31 remove the prostate for cancer. Although the quality of the data from studies was
32 poor, the review suggests lymph node removal may not have any direct benefit on
33 cancer outcomes and may instead result in more complications. Nevertheless, the
34 procedure is still justified because it enables accurate assessment of cancer spread.

1 **1. Introduction**

2 The current EAU prostate cancer (PCa) guidelines recommend performing
3 extended pelvic lymph node dissection (PLND) in high-risk and intermediate-risk
4 patients when the estimated risk for positive lymph nodes exceeds 5% [1]. However,
5 the therapeutic role of PLND during radical prostatectomy for the management of
6 PCa remains controversial. There are reports suggesting that PLND results in
7 improved pathological staging, and that extending the PLND template may increase
8 its staging accuracy. Nevertheless, the oncological benefit of the procedure is still
9 unclear [2].

10 Historically, the decision to perform a PLND, and on how extensive it ought to
11 be, has been left to the clinical judgment of the surgeon. The lack of clarity regarding
12 the oncological benefit of performing a PLND and the lack of standardised definitions
13 and terminologies regarding the PLND template have led to a wide variety of
14 “experience-based approaches” [3,4], which render any comparisons between them
15 difficult and fraught with uncertainties. It is also unclear whether the PLND outcomes
16 vary between different patient subgroups (i.e. low- vs. intermediate- vs. high-risk
17 localised disease). Furthermore, a PLND may be associated with an increased risk of
18 adverse events, morbidity, length of stay and healthcare costs. However, the
19 assertion that a more extensive PLND leads to higher complication rates has not
20 always been confirmed [5-7].

21 The objective of this systematic review was to evaluate the benefits and harms
22 of PLND, incorporating the comparison between the different PLND extents (i.e. no
23 PLND, limited PLND, standard PLND, extended PLND and super-extended PLND)
24 during radical prostatectomy for PCa, and to identify which patients benefit most from
25 PLND.

1 **2. Evidence acquisition**

2 ***2.1 Search strategy, selection of studies, and data extraction***

3 The protocol for this review has been published
4 (<http://www.crd.york.ac.uk/PROSPERO>; registration number CRD42015024848), and
5 the search strategy is outlined in ***Appendix 1***. Briefly, databases including MEDLINE,
6 Embase and Cochrane Central Register of Controlled Trials were systematically
7 searched. Only English language articles and studies published from January 1980
8 to December 2015 were included. The search was complemented by additional
9 sources, including the reference lists of included studies. Two reviewers (NF and
10 PPW) screened all abstracts and full-text articles independently. Disagreement was
11 resolved by discussion or reference to an independent third party (TVdB and SJ).
12 The review was commissioned and undertaken by the EAU Prostate Cancer
13 Guideline Panel as part of its guideline update for 2017.

14 ***2.2 Types of study designs included***

15 All comparative studies (i.e. randomised controlled trials [RCT] and non-
16 randomised comparative studies [NRCS]) with at least one experimental arm and
17 one control arm were included. Studies with more than two arms were also included.
18 Single-arm case series, case reports, commentaries, reviews and editorial
19 commentaries were excluded. Relevant systematic reviews were scrutinised for
20 potentially relevant studies for inclusion. Studies available as non-full text articles
21 only (e.g. conference abstracts) were eligible for inclusion.

22 ***2.3 Types of participants included***

1 The study population was limited to men above the age of 18 years with
2 histologically proven T1-3 N0 M0 PCa according to the TNM staging system (all
3 versions of the TNM staging system) and who were undergoing radical
4 prostatectomy. Patients with cNx or cMx were accepted for low- and intermediate-risk
5 localised disease. Men with localised disease were further stratified according to the
6 D'Amico classification, if data were available.

7 **2.4 Types of interventions included**

8 The interventions were PLND performed during radical prostatectomy,
9 incorporating all approaches (including open, robotic, or laparoscopic) and the
10 different extents. Due to the expected heterogeneity in defining the extent of PLND
11 across studies, for the purpose of standardisation, the extent of PLND was
12 determined *a priori* based on discussion and consultation with a reference expert
13 panel (EAU Prostate Cancer Guideline Panel) and was categorized as follows
14 (**Figure 1**): (1) No PLND; (2) Limited PLND (IPLND): obturator nodes; (3) Standard
15 PLND (sPLND): obturator and external iliac nodes; (4) Extended PLND (ePLND):
16 obturator, external, and internal iliac nodes; (5) Super-extended PLND (sePLND):
17 ePLND + common iliac, pre-sacral, and/or other nodes; and (6) PLND extent
18 undefined or unclassified. Studies reporting discrepant extents and definitions were
19 reclassified according to the above definitions.

20 **2.5 Type of outcome measures included**

21 The primary outcomes were biochemical recurrence (BCR), clinical recurrence
22 (i.e. development of distant metastasis), cancer-specific survival and overall survival.
23 Secondary outcomes included adverse events or complications reported either as
24 grade of severity (e.g. Clavien) or individual rates, intra-operative and post-operative

1 outcomes including operative time, blood loss, blood transfusion, duration of hospital
2 stay, 30-day readmission rate, 90-day mortality, and functional outcomes including
3 urinary continence and erectile function recovery. Lastly, data regarding the median
4 total number of lymph nodes retrieved and total number of positive lymph nodes in
5 relation to the extent of PLND were also extracted.

6 **2.6 Assessment of risk of bias**

7 The risk of bias (RoB) of RCTs was assessed using the standard Cochrane
8 RoB assessment tool for RCTs, whilst the RoB for NRCS was assessed using the
9 modified Cochrane tool that included additional items to assess confounding bias.
10 This was a pragmatic approach informed by the methodological literature pertaining
11 to assessing RoB in NRCS [8]. A list of important outcome-specific prognostic
12 confounders was defined *a priori* by the EAU PCa guideline panel: clinical stage,
13 pathological stage, pathological Gleason score and adjuvant treatment for
14 oncological outcomes; and age, BMI, performance status and surgical route for non-
15 oncological outcomes. The overall judgement regarding each confounder was based
16 on whether it was measured, if it was balanced across groups and whether any
17 statistical adjustment was made.

18 **2.7 Data analysis**

19 A data extraction form was developed to collect information on study design,
20 participant characteristics, characteristics of interventions, and outcome measures.
21 Two reviewers (NF and PPW) independently extracted data relating to the pre-
22 specified outcomes. Descriptive statistics were used to summarise baseline
23 characteristics data. For time-to-event data (e.g. survival analysis), estimates such as
24 median survival or the percentage event-free (survival rate) at specific time points as

1 reported by authors were extracted. Adjusted and unadjusted hazard ratios (HR) to
2 estimate the size of intervention differences were extracted if available. For
3 categorical data, point estimates reported as proportions (%), risk ratios (RR) and
4 odds ratios (OR) were extracted. For continuous outcomes, mean difference (MD)
5 with corresponding 95% confidence intervals (CI) were extracted. For NRCS, a
6 narrative synthesis of the data was planned. Where possible, dichotomous outcomes
7 comparing the intervention effect were analysed using RR with 95% CI. Means and
8 standard deviations were used to summarise the continuous outcome data and
9 compared using MD and 95% CI.

10 To explore the potential impact of clinical heterogeneity on outcomes,
11 subgroup and sensitivity analyses were planned on the following variables: age, PSA
12 level, and type, schedule and timing (early vs. deferred) of androgen deprivation
13 therapy.

1 **3. Evidence Synthesis**

2 **3.1 Quantity of evidence identified**

3 The study selection process is outlined in the Preferred Reporting Items for
4 Systematic reviews and Meta-analyses (PRISMA) flow diagram (**Figure 2**). In total,
5 4,377 records were identified through database searching, and 3,840 were screened
6 after duplicates removal. Of these, 178 articles were eligible for full-text screening,
7 and 139 conference abstracts were assessed for eligibility. Finally, 66 studies
8 recruiting a total of 275,269 patients met the inclusion criteria (44 full-text papers and
9 22 conference abstracts, with each reporting on a separate study).

10 **3.2 Characteristics of the included studies**

11 Data were included from 66 studies, three of which were RCTs [9-11], four
12 were prospective NRCS [12-15], and the rest were retrospective NRCS [16-74]. The
13 baseline characteristics for all included studies addressing oncological and non-
14 oncological outcomes are shown in **Table 1** and **Table 2**, respectively. The template
15 and extents of PLND performed in the included studies are summarised in
16 **Supplementary Table**: the more extensive the PLND, the higher the rate of pN1
17 disease.

18 **3.2.1 Characteristics of studies reporting on oncological outcomes**

19 Baseline characteristics of studies evaluating oncological outcomes are
20 summarized in **Table 1**. Overall, 29 studies were included. Specifically, 21 studies
21 (15 full-text articles and 6 conference abstracts) compared no PLND vs. any form of
22 PLND, whereas 8 studies (4 full-text articles and 4 conference abstracts) compared
23 IPLND or sPLND vs. ePLND or sePLND.

1 3.2.2 Characteristics of studies reporting on non-oncological outcomes

2 Baseline characteristics of studies evaluating non-oncological outcomes are
3 summarized in **Table 2**. Overall, 43 studies were included. Specifically, 25 studies
4 (18 full-text articles and 7 conference abstracts) compared no PLND vs. any form of
5 PLND, whilst 18 studies (12 full-text articles and 6 conference abstracts) compared
6 IPLND or sPLND vs. ePLND or sePLND.

7 **3.3 Risk of bias and confounding assessment of the included studies**

8 Risk of bias and confounding assessment for each of the individual studies
9 were performed, and the results are presented in **Figure 3a** (studies reporting on
10 oncological outcomes) and **Figure 3b** (studies reporting on non-oncological
11 outcomes). There was high or unclear RoB across most domains. However, some
12 confounding factors were adequately considered through statistical adjustment in a
13 significant proportion of studies, including stage and pathological Gleason score for
14 studies reporting oncological outcomes (**Figure 4a**), and age and BMI for studies
15 reporting on non-oncological outcomes (**Figure 4b**).

16 **3.4 Comparisons of interventions results**

17 **3.4.1 Oncological outcomes**

18 3.4.1.1 No PLND vs. any form of PLND

19 Overall, 21 retrospective comparative studies (15 full-text articles and 6
20 conference abstracts) compared no PLND vs. any form of PLND for oncological
21 outcomes (**Table 3a**). No RCTs were identified for this comparison.

22 Biochemical recurrence

1 Biochemical recurrence was evaluated in 18 studies, in which 5/18 [28%]
2 involved IPLND, 1/18 [5%] sPLND, 3/18 [17%] ePLND, and 9/18 [50%] undefined
3 PLND. Out of these, 16 did not find any statistically significant difference between the
4 two groups [16-18,21,23-25,27-31,33-36]. This negative finding also applied to the
5 various sub-groups of patients (e.g. low-risk disease [23], or pT2, pT3, or pT2 R0
6 disease [24]). On the other hand, counter-intuitive findings were observed in two
7 different retrospective studies regarding the impact of PLND compared with no PLND
8 on BCR [19,22]. Specifically, *Boehm et al* evaluated a cohort of 11,127 patients,
9 including 6,810 pN0 patients and 4,884 pNx patients treated with radical
10 prostatectomy between 1992 and 2011 [19]. Through multivariable Cox regression
11 analysis, pNx was associated with a lower risk of BCR compared to pN0 (HR: 0.81;
12 95% CI: 0.72–0.9; $p < 0.05$). Despite the use of multivariable analysis, the significant
13 baseline differences between the two groups may explain the higher risk of
14 recurrence among pN0 patients. Furthermore, the extent of PLND was not reported.
15 Conversely, *Liss et al* analysed a cohort of 492 patients treated with robotic assisted
16 radical prostatectomy between 2007 and 2011 [22]; 54 received ePLND, 231
17 received sPLND, and 207 did not receive any PLND. At a median follow-up of
18 approximately 1 year, BCR was significantly different among the three groups: 30%
19 vs. 15% vs. 3.4%, respectively ($p < 0.001$). However, when ePLND was compared
20 with sPLND in high-risk patients only, no significant differences were observed
21 ($p = 0.294$).

22 Distant metastasis

23 Distant metastasis following radical prostatectomy were evaluated by two
24 retrospective studies which reported conflicting results [19,23]. *Mitsuzuka et al*
25 analysed a series of 222 low-risk patients and found a metastasis-free survival of

1 100% in both sPLND and no PLND groups at a median follow-up of 60 and 26
2 months, respectively [23]. Conversely, the already mentioned *Boehm et al* study
3 found that no PLND was associated with a lower risk of distant metastasis at
4 multivariable analysis (HR: 0.62; 95 % CI: 0.41, 0.92; p<0.05) [19]. As explained in
5 the previous paragraph, baseline differences among pNx and pN0 patients, and
6 important selection bias may explain this finding.

7 Cancer-specific and overall mortality

8 Cancer-specific and overall mortality were analysed by 6 studies. Of these,
9 PLND was standard in one study [23], while its extension was not reported in the
10 other five studies [19,20,26,27,32]. None of these studies demonstrated any
11 statistically significant differences in cancer-specific mortality [20,23,26,27,32] and
12 overall mortality [19,23] between PLND and no PLND. Mean follow-up was longer
13 than 3 years in five studies, ranging between 4 [19] and 11 years [32]. One
14 conference abstract by *Pokala et al* did not report information about follow-up [27].

15 3.4.1.2 Limited / standard PLND vs. (super)-extended PLND

16 Overall, 8 studies (4 full-text articles and 4 conference abstracts) compared
17 limited / standard PLND vs. (super)-extended PLND for oncological outcomes (**Table**
18 **3b**). One study was a RCT [9].

19 Biochemical recurrence

20 Biochemical recurrence was evaluated by all 8 studies, and conflicting results
21 were observed. In the RCT by *Lestingi et al* which was reported as a conference
22 abstract only, there was no significant difference in terms of BCR between IPLND
23 and ePLND (p=0.39) at a median follow-up of 14.4 and 13.4 months, respectively [9].

1 Similarly, ePLND did not alter BCR rates at a median follow-up of 36 months in a
2 retrospective study by *Kim et al* [40]. Furthermore, ePLND did not provide better
3 biochemical outcome in four comparative studies [39,41,42]. However, all these
4 studies were retrospective in design, and three of them were conference abstracts.
5 Two additional studies did showed a statistically significant benefit of ePLND over
6 limited/standard PLND but only in specific sub-groups of patients: intermediate-risk
7 patients (96% vs. 90%; p=0.017) [38], and pN1 patients with <15% of retrieved nodes
8 affected (43% vs. 10%; p=0.01) [43]. However, counter-intuitive findings were
9 observed in a retrospective study where ePLND was associated with higher risk of 7-
10 year BCR compared with IPLND in pT2 patients only (5% vs. 0%; p=0.01) [37]. This
11 result may reflect the selection bias of the study, as surgeons tended to perform
12 more extensive nodal dissection in higher risk patients.

13 *Distant metastasis*

14 No studies reported on distant metastasis outcome.

15 *Cancer-specific and overall mortality*

16 Cancer-specific mortality was reported in one conference abstract [41] that
17 showed that ePLND did not provide a statistically significant survival benefit over
18 sPLND (p>0.05). However, the median follow-up was 34 months, presumably too
19 short for addressing survival outcomes of prostate cancer.

20 **3.4.2 Non-oncological outcomes**

21 *3.4.2.1 No PLND vs. any form of PLND*

1 Overall, 25 retrospective comparative studies (18 full-text articles and 7
2 conference abstracts) compared no PLND vs. any form of PLND for non-oncological
3 outcomes (**Table 4a**).

4 *Intra-operative and peri-operative outcomes*

5 Data was obtained from 20 retrospective studies regarding operative time,
6 blood loss, and post-operative complications [12,15,19,22,45,48-50,52-63]. Mainly,
7 PLND was associated with a significantly higher risk of lymphocele in the majority of
8 studies that addressed the outcome (12/16 studies). Moreover, a population-based
9 study showed a higher 90-day mortality rate in the PLND group (0.29% vs. 0.20% in
10 case of open surgery and 0.29% vs. 0.13% in case of robotic surgery) without
11 statistical significance being reported by this conference abstract [46]. Conversely, a
12 single institution study did not find any significant difference at multivariable analysis
13 for 30-day readmission rates between the two groups, after adjusting for age at
14 surgery, Charlson comorbidity index, and post-operative complications (OR not
15 reported; $p>0.1$) [47].

16 *Functional outcomes*

17 Three retrospective studies did not find any significant differences between
18 PLND and no PLND regarding urinary continence (OR not reported) [13] and erectile
19 function recovery (OR: 0.95; 95% CI: 0.63, 1.43; $p=0.8$; and HR: 0.9; $p=0.8$) [44,51].

20 *3.4.2.2 Limited / standard PLND vs. (super)-extended PLND*

21 Overall, 18 studies (12 full-text articles and 6 conference abstracts) compared
22 limited / standard PLND vs. (super)-extended PLND for non-oncological outcomes
23 (**Table 4b**). Three were RCTs [9-11].

1 Intra-operative and peri-operative outcomes

2 In comparing IPLND vs. ePLND, one RCT recruited 226 patients with
3 intermediate-risk disease [9], and another RCT recruited 234 patients with high-risk
4 disease [10]. In the study by *Lestingi et al*, ePLND was associated with statistically
5 significant increases in operative time, intra-operative complications, bleeding, and
6 hospital stay ($p < 0.001$), but not with post-operative complications according to the
7 Clavien-Dindo scale ($p = 0.12$). Further details were not reported by the conference
8 abstract [9]. Similarly, in the study by *Schwerfeld-Bohr et al*, ePLND prolonged
9 surgical time by 30 minutes compared with IPLND. In this study, lymphocele
10 development was the only complication which occurred significantly more often after
11 the extended procedure compared with limited PLND (17% vs. 8%) [10]. In another
12 RCT, 123 patients were randomized to either ePLND on the right hemi-pelvis versus
13 IPLND on the left hemi-pelvis. Complications including lymphocele (3% vs. 1%) and
14 lower extremity oedema (3% vs. 2%) occurred more commonly on the side which
15 underwent ePLND compared with IPLND [11].

16 When considering data from 15 retrospective studies, conflicting results were
17 observed. Five studies showed significantly higher intra-operative and post-operative
18 complications in the ePLND group compared with IPLND / sPLND [14,40,70-72],
19 while five studies did not show any statistically significant differences [42,64,66-68].
20 Similarly, the rate of lymphocele was significantly higher in the ePLND group in four
21 studies [40,70,73,74], while no significant differences were observed in four others
22 [42,64,66,67].

23 Functional outcomes

1 One retrospective comparative study did not find any significant differences
2 regarding urinary continence (HR: 1.07; 95% CI: 0.87, 1.31; p=0.5) and erectile
3 function recovery (HR: 1.11; 95% CI: 0.75, 1.63; p=0.6) between ePLND and IPLND
4 [37].

1 **4. Discussion**

2 To date, PLND represents the most accurate staging procedure to assess the
3 presence of lymph node metastasis in PCa patients [2,75]. However, its therapeutic
4 role from an oncological effectiveness perspective remains unclear. The objectives of
5 this systematic review were to determine the benefits and harms of PLND during
6 radical prostatectomy compared with no PLND, how the different extents of PLND
7 compare with one another, and which patients benefit most from PLND.

8 ***4.1 Principal findings***

9 This systematic review, after screening almost 4,000 articles, highlighted
10 important results that deserve attention. Firstly, the overall quality of evidence based
11 on study design and RoB assessment of included studies was low, with most studies
12 judged to be at moderate to high risk of bias. Indeed, out of 67 included studies, only
13 three were RCTs, and four were prospective NRCS, while the rest were retrospective
14 NRCS. Furthermore, anatomical extents of PLND was not specified in more than half
15 of the included studies, highlighting a lack of standardised definitions for extent of
16 PLND in the current literature.

17 Secondly, when considering oncological outcomes, there was no good quality
18 evidence indicating that any form of PLND improves outcomes compared with no
19 PLND. Out of 21 studies, all of which were retrospective in nature, none showed
20 statistically significant differences in favour of PLND when compared with no PLND
21 for BCR, distant metastasis, or survival. Similarly, no good quality evidence was
22 retrieved indicating that ePLND improves oncological outcomes compared with
23 IPLND or sPLND. Data from 13 studies, one of which was a RCT reported as a
24 conference abstract, showed conflicting results; 2 studies (including the RCT)

1 showed no differences in BCR at short-term follow-up; 2 studies showed no
2 differences in BCR between the interventions for the entire cohort, but found that only
3 certain subgroups of patients benefited from an ePLND compared with IPLND /
4 sPLND for BCR; and 9 studies found no significant differences in BCR.

5 Finally, considering non-oncological outcomes, PLND was associated with
6 significantly worse intra-operative and peri-operative outcomes compared with no
7 PLND in 20 retrospective studies. Functional outcomes including urinary continence
8 and erectile function recovery were evaluated in three retrospective studies and no
9 significant differences were observed. Similar results were obtained when comparing
10 IPLND or sPLND with ePLND in 18 studies.

11 Based on current results, the therapeutic benefits of PLND during radical
12 prostatectomy remain unproven. However, two important factors need to be
13 considered:

14 1) PLND may in theory be curative for selected patients, with limited nodal
15 involvement entirely removed at the time of surgery (*direct effect*). In support of this,
16 a recent retrospective study showed that biochemical relapse is likely in patients with
17 limited nodal disease after radical prostatectomy and PLND, however, clinical
18 progression was observed in less than 50% of them [76]. Furthermore, an additional
19 retrospective study showed that the removal of a higher number of lymph nodes in
20 pN1 patients was associated with improvement in cancer-specific survival rate [77].
21 However, such hypotheses still need to be verified by level-1 evidence studies.

22 2) PLND may represent a stratification tool to identify patients who benefit
23 from adjuvant treatments that improve survival outcomes (*indirect effect*). As an
24 example, *Abdollah et al* recently identified specific categories of pN1 patients who

1 benefited from adjuvant radiation therapy combined with adjuvant hormonal therapy
2 [78]. Therefore, more comprehensive and accurate nodal staging through ePLND may
3 indirectly improve pN1 patient prognosis.

4 ***4.2 Implications for clinical practice***

5 The current EAU prostate cancer guidelines recommend performing ePLND in
6 high-risk and intermediate-risk patients for staging if the estimated risk for positive
7 lymph nodes exceeds 5%, and avoiding PLND in low-risk patients. Bearing in mind
8 the low quality of evidence for PLND outcomes from published data, the cautious
9 EAU guidelines statement concerning PLND for treatment is supported by these
10 current findings.

11 Indeed, PLND during radical prostatectomy should not be performed in all
12 patients because of the lack of solid evidence on its oncological benefit and because
13 of the harms that are associated with it. On the other hand, it is equally important not
14 to blindly omit PLND in all patients either for exactly the same reason, which is the
15 lack of solid evidence disproving its oncological benefit.

16 Because an increasing PLND extent improves nodal staging of patients [2,79],
17 it is advisable to always perform an ePLND whenever PLND is indicated. However,
18 ePLND should be avoided when the harms are expected to exceed its possible
19 benefits. Predictive models assessing the risk of lymph node metastasis represent
20 the best available tool to help facilitate decision-making.

21 ***4.3 Implications for further research***

22 The current poor quality of evidence indicates the need for robust and
23 adequately powered clinical trials with appropriate controls, using standardised

1 template definitions, standard operating procedures for pathological work-up, and
2 adequate duration of follow-up in order to determine its therapeutic effectiveness
3 based on oncological outcomes. Results from two on-going prospective studies may
4 improve the level of evidence in the future (NCT01812902, NCT01555086).
5 However, three main factors should be considered when evaluating a RCT in this
6 field:

7 1. The tumour: tumour risk scoring is a fundamental step for the study design
8 and populations with higher risks of lymph node disease should be investigated. As
9 an example, a PLND would be unlikely to have a significant effect when performed in
10 a population of low-risk patients. Therefore, judicious patient selection is mandatory.

11 2. The PLND procedure: the definition and extent of PLND represent other
12 important factors to be considered. Indeed, even if ePLND has shown a superior
13 diagnostic accuracy compared to IPLND, it is unlikely to detect all positive lymph
14 nodes [80]. Furthermore, several surgeon-related factors may importantly influence
15 the final results. As an example, in the SEAL AUO AP 55/09 trial [10] the observed
16 rate of pN1 disease in the ePLND and IPLND group was 15% and 12%, This finding
17 suggests a surgeon-related bias towards more meticulous PLND in the limited group.
18 Therefore, predefined templates should be designed and respected in future studies.

19 3. The pathological examination: pathological evaluation of pelvic lymph nodes
20 remains controversial, with a lack of consensus on the specimen processing and
21 identification of nodes, and heterogeneity in terms of definitions, thresholds, and
22 reporting. Indeed, there is evidence that both the surgeon and the pathologist may
23 influence the number of lymph nodes removed and the number of positive nodes at
24 final pathology [81,82]. Therefore, standard-operating procedures for pathological
25 work-up should be predefined in future studies.

1 In view of the fact that PLND is a morbid procedure which leads to a higher
2 risk of complications, there is a need to consider alternative nodal staging methods,
3 such as sentinel node biopsy [83].

4 **4.4 Limitations and strengths**

5 The current study represents the first systematic review addressing benefits
6 and harms of different anatomical extents of PLND during radical prostatectomy. The
7 review elements were developed in conjunction with a multidisciplinary panel of
8 content experts (EAU Prostate Cancer Guideline Panel), which included a patient
9 representative, and the review was performed robustly in accordance with
10 recognised standards. Limitations include the relatively low quality of the evidence
11 base, with the majority of studies being judged to have moderate to high risk of bias
12 in most domains, especially in relation to oncological outcomes. There was also
13 significant clinical and methodological heterogeneity across studies, with different
14 definitions and thresholds used in terms of describing the PLND procedure. In many
15 instances, the extent of PLND was not described in detail, which made data
16 acquisition, analysis and interpretation difficult. Finally, the so-called *Will Rogers*
17 *phenomenon* should also be taken into account. As an example, in studies focused
18 on pN0 patients, those who received more extensive PLND were better staged and,
19 thus, were more likely to be really free from LNI. Conversely, pN0 patients with a
20 lower number of removed lymph nodes were less accurately staged. The less
21 favourable survival rates observed in these individuals may largely be related to this
22 *phenomenon*. Such limitations indicate that the findings of the review should be
23 interpreted within the appropriate context.

1 **5. Conclusion**

2 The majority of studies showed that PLND and its extensions are associated
3 with worse intra-operative and peri-operative outcomes, whereas a direct therapeutic
4 effect is still not evident from the current literature. The current poor quality of
5 evidence indicates the need for robust and adequately powered clinical trials. In the
6 meantime, because of its recognised staging benefits, extended PLND should be
7 undertaken whenever PLND is indicated in appropriate patients, judiciously selected
8 based on a risk-stratified approach.

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