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Extended Versus Limited Pelvic Lymph Node Dissection During Radical Prostatectomy for Intermediate- and High-risk Prostate Cancer: Early Oncological Outcomes from a Randomized Phase 3 Trial

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Abstract

Background: The role of extended pelvic lymph node dissection (EPLND) in the surgical management of prostate cancer (PCa) patients remains controversial, mainly because of a lack of randomized controlled trials (RCTs).
Objective: To determine whether EPLND has better oncological outcomes than limited PLND (LPLND.
Design, setting and participants: This was a prospective, single-center phase 3 trial in patients with intermediate- or high-risk clinically localized PCa.
Intervention: Randomization (1:1) to LPLND (obturator nodes) or EPLND (obturator, external iliac, internal iliac, common iliac, and presacral nodes) bilaterally.
Outcome measurements and statistical analysis: The primary endpoint was biochemical recurrence–free survival (BRFS). Secondary outcomes were metastasis-free survival (MFS), cancer-specific survival (CSS), and histopathological findings. The trial was designed to show a minimal 15% advantage in 5-yr BRFS by EPLND.
Results and limitations: In total, 300 patients were randomized from May 2012 to December 2016 (150 LPLND and 150 EPLND). The median BRFS was 61.4 mo in the LPLND group and not reached in the EPLND group (hazard ratio [HR] 0.91, 95% confidence interval [CI] 0.63–1.32; $p = 0.6$). Median MFS was not reached in either group (HR 0.57, 95% CI 0.17–1.8; $p = 0.3$). CSS data were not available because no patient died from PCa before the cutoff date. In exploratory subgroup analysis, patients with preoperative biopsy International Society of Urological Pathology (ISUP) grade groups 3–5 who were allocated to EPLND had better BRFS (HR 0.33, 95% CI 0.14–0.74, interaction $p = 0.007$). The short follow-up and surgeon heterogeneity are limitations to this study.
Conclusion: This RCT confirms that EPLND provides better pathological staging, while differences in early oncological outcomes were not demonstrated. Our subgroup analysis suggests a potential BCRFS benefit in patients diagnosed with ISUP grade groups 3–5; however, these findings should be considered hypothesis-generating and further RCTs

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with larger cohorts and longer follow up are necessary to better define the role of EPLND during RP.

Patient summary: In this study, we investigated early outcomes in prostate cancer patients undergoing prostatectomy according to the anatomic extent of lymph node resection. We found that extended removal of lymph nodes did not reduce biochemical recurrence of prostate cancer in the expected range.

1. Introduction

The removal of pelvic lymph nodes, termed pelvic lymph node dissection (PLND), has become an integral part of radical prostatectomy (RP) for prostate cancer (PCa) since the procedure was popularized in the 1980s by Walsh and others [1]. Despite recent advances in imaging, PLND remains the gold standard modality for nodal staging [2].

There remains significant debate about how extensive PLND should be. As demonstrated by many, the odds of finding positive pelvic lymph nodes is proportional to the extent of the PLND [3–7]. However, the diagnostic and therapeutic benefits of more extensive PLND remains an area of controversy [2]. Complicating the matter further, patients who have undergone extended PLND (EPLND) are more likely to be accurately staged as either node-positive or -negative, which makes retrospective observational comparisons of oncological outcomes between limited PLND (LPLND) and EPLND subject to bias; this is often called the Will Rogers phenomenon [8]. Dissection templates vary considerably from one surgeon or study to another. Moreover, many of these studies rely on surrogate endpoints, such as receipt of adjuvant treatments, that are subject to considerable confounding. Finally, we need to consider the surgical risk of performing EPLND, which is associated with longer operative time and higher odds of symptomatic lymphocele, among others [9]. Again, there are very few prospective data on the perioperative safety of EPLND versus LPLND.

Against this backdrop, the American Association of Urology (AUA) and European Association of Urology (EAU) recommend that men with low-risk disease do not need PLND; however, for those with intermediate- and high-risk disease, PLND is indicated and should follow an extended template [10,11].

On the basis of these considerations, we sought to conduct a randomized controlled trial comparing the oncological outcomes of EPLND versus LPLND. We focused the trial on a subset of patients most likely to benefit from EPLND, specifically men presenting with intermediate- and high-risk PCa. We hypothesized that EPLND receipt is associated with better oncological outcomes.

2. Patients and methods

2.1. Study design

In this phase 3 randomized controlled trial, patients with intermediate- or high-risk localized PCa who were candidates for surgical treatment were enrolled between May 2012 and December 2016 at Instituto do Cancer do Estado de Sao Paulo (ICESP; University of Sao Paulo School of Medicine, Sao Paulo, Brazil), an oncological reference center. Recruited patients were prospectively randomized to LPLND or EPLND during RP.

2.2. Study participants

The inclusion criteria were as follows: (1) patients with PCa who were candidates for RP; (2) estimated life expectancy of $\geq$10 yr; (3) D'Amico intermediate risk (cT2b and/or prostate-specific antigen [PSA] 10–20 ng/ml and/or Gleason score 7); (4) D'Amico high risk ($>$cT2b and/or PSA $>$ 20 ng/mL and/or Gleason score $\geq$8); (5) clinically negative lymph node metastases (cN0); and (6) agreement to participate in the study and signing of an informed consent form (ICF). All patients with Gleason 6 disease (International Society of Urological Pathology [ISUP] grade group 1 [GG1]) included in the study cohort had PSA $\geq$ 10 ng/mL and/or palpable disease ($\geq$cT2b).

The exclusion criteria were as follows: (1) previous large abdominal or pelvic surgery; (2) previous prostate surgery; (3) previous hormonal therapy or radiotherapy (RDT) or any other PCa treatment; (4) presence of bone metastases; and (5) presence of another malignant neoplasm.

All patients participating in the study signed the ICF and study was approved by the local research ethics committee.

2.3. Study randomization

Patients were randomized using Research Randomizer software (www.randomizer.org) to undergo EPLND or LPLND in a 1:1 ratio (50-50, no blocks) at the time of RP. Further details of the randomization process are described in the Supplementary material.

2.4. Perioperative management and surgical technique

Patients with D'Amico high-risk or unfavorable intermediate-risk PCa underwent abdominal/pelvic computed tomography (CT) or pelvic magnetic resonance imaging (MRI) for preoperative staging. All patients also underwent a bone scan for preoperative staging.

The EPLND template, defined before conducting the trial, included the obturator, external iliac, internal iliac, common iliac, and presacral regions (nine fields) bilaterally, whereas LPLND was limited to the obturator region bilaterally (two fields). For EPLND, the caudal border was the deep circumflex vein and the femoral canal, the cranial border was the ureter crossing over the common iliac artery, the lateral border was the genitofemoral nerve, and the medial border was the vesical fat [12]. The boundaries for each

dissected lymph node region are described in the Supplementary material.

Surgical specimens of the prostate and pelvic lymph nodes separated by region were submitted for pathological evaluation according to College of American Pathologists protocol and evaluated according to the ISUP recommendations (Supplementary material) [13,14]. No lymph nodes were divided to avoid affecting the count.

Five urologists from the prostate service of ICESP were involved and coordinated the surgical procedures. All surgeons had at least 5 yr of experience in urological oncology at the beginning of the trial and were trained to follow the protocol instructions in terms of lymph node template dissections (open retropubic extraperitoneal approach). As the dissected lymph node regions were sent separately to pathology, a double-check comparing the templates with the histopathological findings was carried out.

After surgery, outpatient appointments and PSA blood tests were scheduled at 1, 3, 6, 12, 18, 24, 30, and 36 mo and then annually. When biochemical recurrence (BCR) was noted, after confirmation of the PSA value, patients were restaged via a bone scan and MRI or CT imaging; positron emission tomography using ^{68}Ga-labelled prostate-specific membrane antigen ligands was not available at our institution during the trial. As a rule, BCR occurrence was taken as an indication for salvage RDT and/or androgen deprivation therapy (ADT) according to AUA/EAU guidelines [10,11], except in patients otherwise indicated by the attending physician. In cases with a slow PSA rise (local recurrence) and the absence of metastases, patients received salvage RDT. In cases with a PSA doubling time of <6 mo and/or metastases, ADT was added (luteinizing hormone–releasing hormone agonists).

The safety and complications data will be reported separately because of space restrictions.

2.5. Endpoints

The primary endpoint was 5-yr BCR-free survival (BRFS); the secondary endpoints were metastasis-free survival (MFS), cancer-specific survival (CSS), and histopathological findings. BCR was defined as a confirmatory postoperative PSA level of ≥0.2 ng/mL. PSA levels were measured in just one laboratory at ICESP. BCR also included PSA persistence, defined as serum PSA ≥ 0.2 ng/mL within 4 wk after surgery, with a second confirmatory measurement ≥0.2 ng/mL within 12 wk postoperatively. BRFS was defined as the time from surgery to PSA ≥ 0.2 ng/mL; all patients with confirmed PSA ≥ 0.2 ng/mL were counted as BCR events. MFS was defined as the time from surgery to radiographic detection of metastases. CSS was defined as the time from surgery to death caused by PCa. Clinical data were prospectively collected from medical records. An internal audit was carried out by a dedicated and independent group to check and validate the data.

2.6. Statistical analysis

The sample size was chosen to detect a 15% improvement in 5-yr BRFS in favor of EPLND. We assumed from previous comparative studies [4,15] a 5-yr BRFS rate of 65% for the LPLND group (80% power; two-sided significance level of $\alpha = 0.05$). Considering the possibility of dropout, enrollment was discontinued at 300 patients in December 2016. Analyses were performed according to the intention-to-treat principle. Additional per-protocol analyses and considerations are provided in the Supplementary material.

For time-to-event endpoints, median survival and 95% confidence intervals (CIs) were estimated using the Kaplan-Meier method. The log-rank test was used to compare treatment groups. The follow-up time in months is defined from the date of surgery until the date of death or the date of last PSA for censored cases.

Subgroup exploratory analyses were performed using forest plots, and hazard ratios (HRs) with 95% CIs were estimated using Cox regression.

Reporting of results was performed according to the CONSORT guidelines for randomized trials. Data analyses were performed using STATA version 16.0 (Stata Corp., College Station, TX, USA). The trial is registered at ClinicalTrials.gov as NCT01812902.

3. Results

3.1. Patients and treatment

Between May 2012 and December 2016, 364 men were assessed for eligibility and 64 were excluded because they did not meet inclusion criteria ($n = 38$), were ruled out by the exclusion criteria ($n = 22$), or declined participation ($n = 4$). Therefore, 300 patients were enrolled, of whom 150 were allocated to EPLND and 150 to LPLND. In the EPLND group, 134 men received EPLND, 12 received LPLND, and four did not receive PLND. In the LPLND group, 137 received LPLND, seven received EPLND, and six did not receive PLND (Fig. 1). Baseline characteristics were well balanced between the two groups (Table 1). Results for the baseline characteristics according to per-protocol analysis are presented in Supplementary Table 1.

3.2. Histopathological findings

The groups were also similar in pathological characteristics, such as Gleason score, ISUP classification, percentage of tumor volume, tumor staging, and rate of positive surgical margins (Table 2). In the entire cohort, 60% had extraprostatic extension, seminal vesicle involvement, or adjacent organ invasion (≥pT3a).

The median number of nodes dissected was 17 (interquartile range [IQR] 13–24) for EPLND and 3 (IQR 2–5) for LPLND ($p < 0.001$). EPLND revealed five times more lymph node metastases (17% [$n = 25$] in the EPLND group vs 3.4% [$n = 5$] in the LPLND group; $p < 0.001$). Lymph node invasion (LNI) was also significantly higher in the EPLND arm in patients with intermediate- and high-risk disease (Table 2).

The histopathological findings were similar in the per-protocol analysis (Supplementary Table 2). Fig. 2 demonstrates the distribution of N1 cases by dissection area for EPLND patients who had at least one positive lymph node.

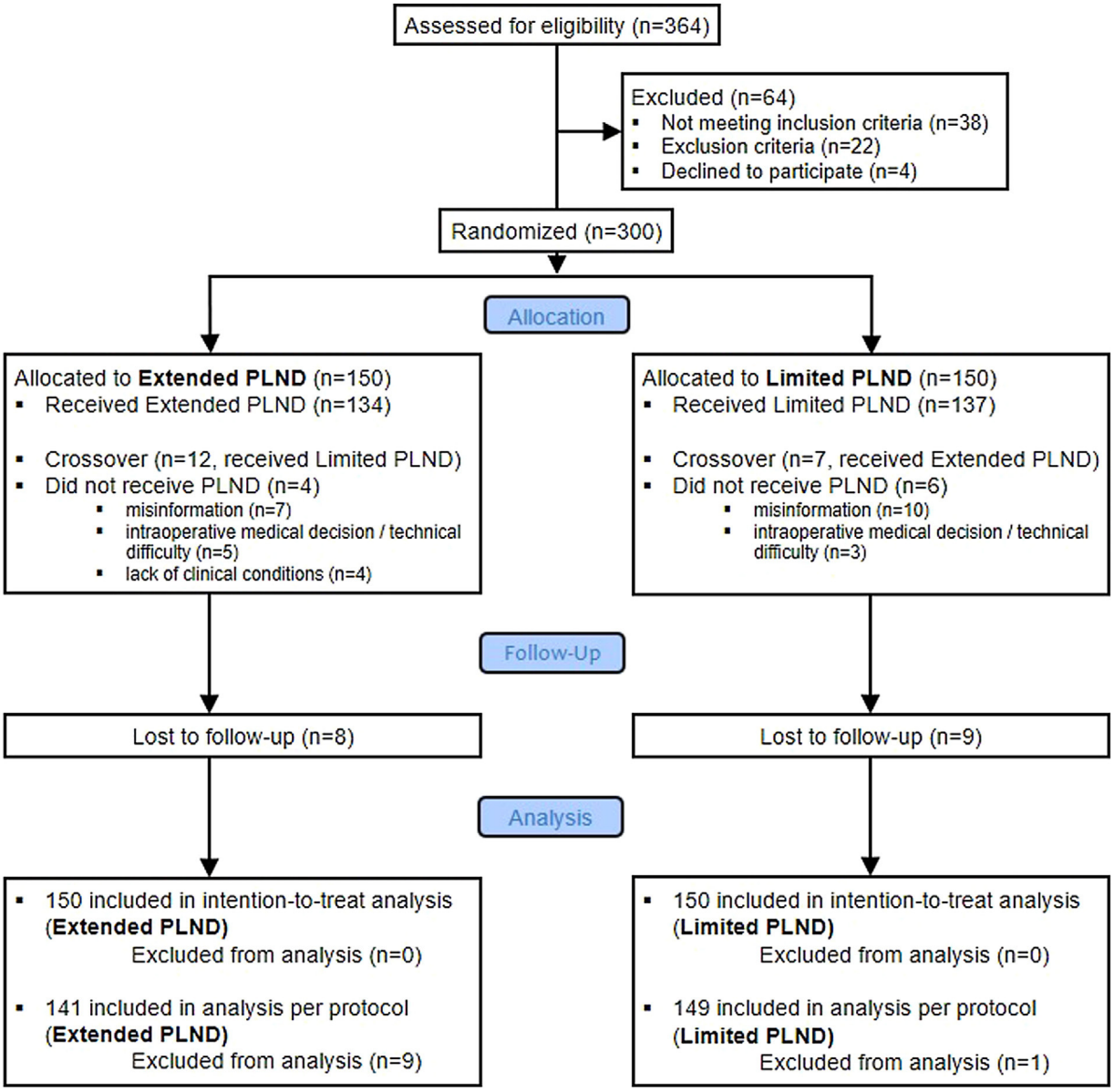

Fig. 1 – CONSORT flow diagram for the trial. PLND = pelvic lymph node dissection. In the overall cohort, the dropout rate was 5.6% of patients (lost to follow-up).

3.3. *Oncological outcomes*

The median follow-up for patients without BCR was 53.9 (IQR 36.1–60.3) mo. At the time of data analysis, 180 patients were free of recurrence: 91 in the EPLND group and 89 in the LPLND group.

EPLND failed to meet the primary (BRFS) and secondary endpoints (MFS, CSS). Median BRFS was 61.4 mo in the LPLND group and was not reached in the EPLND group (HR 0.91, 95% CI 0.63–1.32, $p = 0.6$; Fig. 3A); the results were similar in the per-protocol analysis (Supplementary Fig. 1A). Median MFS was not reached in either group (HR 0.57, 95% CI 0.17–1.8; $p = 0.3$; Supplementary Fig. 2). CSS data were not available because no patient died directly from PCa up to the data cutoff date.

There were also no differences between the groups in RDT receipt, ADT receipt, distant metastases, or death (Table 3 and Supplementary Table 3). Adjuvant RDT (before BCR) was received by only seven patients (one in the EPLND group and six in the LPLND group) for positive margins and/or ≥ pT3a stage. Ninety-three patients had prostate bed irradiation; 15 of them (16%) had additional pelvic irradiation (pN1: $n = 12$). PSA levels at the time of RDT and the RDT doses and fields are summarized in Supplementary Table 4.

Fig. 4 shows a forest plot of the effect of lymph node dissection on BRFS by selected baseline and pathological categories (intention-to-treat analysis). BRFS was better among patients with preoperative biopsy ISUP GG3–GG5 who underwent EPLND (HR 0.33, 95% CI 0.14–0.74;

Table 1 – Baseline characteristics according to randomization[a].

	EPLND	LPLND
Number of patients	150	150
Median age, yr (IQR)	63.4 (59.1–67)	63 (58.8–67.3)
Median body mass index, kg/m^2 (IQR)	27.2 (24.3–29.4) (*N* = 146)	27.7 (24.9–30.6) (*N* = 144)
ASA score, *n* (%)		
1	54 (36)	49 (33)
2–3	96 (64)	101 (67)
Charlson comorbidity index, *n* (%)		
0	114 (76)	114 (76)
≥1	36 (24)	36 (24)
Median prostate-specific antigen, ng/mL (IQR)	10.5 (6.5–17)	10.4 (6.9–13.9)
Preoperative Gleason score, *n* (%)	(*N* = 149)	(*N* = 149)
6 (ISUP GG1)	55 (37)	54 (36)
7 (3 + 4; ISUP GG2)	63 (42)	57 (38)
7 (4 + 3; ISUP GG3)	18 (12)	19 (13)
8 (4 + 4, 5 + 3; ISUP GG4)	8 (5.4)	13 (8.7)
9 (4 + 5, 5 + 4; ISUP GG5)	5 (3.4)	6 (4)
Clinical stage, *n* (%)	(*N* = 145)	(*N* = 146)
T1	82 (57)	76 (52)
T2	31 (21)	33 (23)
T3	32 (22)	37 (25)
Intermediate D'Amico risk, *n* (%)	93 (62)	95 (63)
High D'Amico risk, *n* (%)	57 (38)	55 (37)
Risk of LNI (Briganti nomogram [16]), % (SD)	11 (17) (*N* = 141)	12 (18) (*N* = 144)

EPLND = extended pelvic lymph node dissection; LPLND = limited PLND; IQR = interquartile range; ASA = American Society of Anesthesiologists; ISUP GG = International Society of Urological Pathology grade group; LNI = lymph node invasion; SD = standard deviation.
[a] Numbers differ owing to missing data across variables.

interaction $p = 0.007$, Cox regression). This differential effect was also noted in the per-protocol analysis (HR 0.48, 95% CI 0.21–1.08; Supplementary Fig. 3).

For the subgroup with preoperative biopsy ISUP GG3–GG5 PCa, Fig. 3B shows Kaplan-Meier estimates of BRFS by dissection approach (LPLND or EPLND) in the intention-to-treat analysis. Median BRFS was 12.34 mo in the LPLND group and not reached in the EPLND group (HR 0.48, 95% CI 0.26–0.91; $p = 0.024$, log-rank test). In the per-protocol analysis, the median BRFS was 19.9 mo in the LPLND group

Table 2 – Pathological characteristics according to randomization[a].

Parameter	EPLND	LPLND	*p* value
Prostatectomy Gleason score, *n* (%)			
6 (ISUP GG1)	4 (2.7)	6 (4)	0.8 **
7 (3 + 4; ISUP GG2)	83 (55)	73 (49)	
7 (4 + 3; ISUP GG3)	45 (30)	46 (31)	
8 (4 + 4; ISUP GG4)	2 (1.3)	1 (0.7)	
9, 10 (4 + 5, 5 + 4, 5 + 5; ISUP GG5)	16 (11)	23 (15)	
Median percentage of tumor volume, % (IQR)	16 (10–25)	16 (10–29)	0.5 *
pT stage, *n* (%)			NA
T0	0	1 (0.7)	
T2	61 (41)	57 (38)	
T3a (extraprostatic extension)	67 (45)	64 (43)	
T3b (seminal vesicle involvement)	21 (14)	27 (18)	
T4	1 (0.7)	1 (0.7)	
Positive surgical margins, *n*/*N* (%)	65 (44)	55 (37)	0.2 **
T2 with positive surgical margins	17/61 (28)	12/57 (21)	0.3 **
≥T3 with positive surgical margins	49/89 (55)	43/92 (47)	0.2 *
Number of lymph nodes dissected			<0.001 *
Median, *n* (IQR)	17 (13–24)	3 (2–5)	
Mean, *n* (standard deviation)	18.5 (9.8)	4.5 (4)	
Patients with lymph node metastasis (N+), *n* (%)	25 (17)	5 (3.4)	<0.001 **
D'Amico intermediate risk (N+), *n*/*N* (%)	10/91 (11)	0	0.001 **
D'Amico high risk (N+), *n*/*N* (%)	15/57 (26)	5/55 (9)	0.017 **

EPLND = extended pelvic lymph node dissection; LPLND = limited PLND; IQR = interquartile range; ISUP GG = International Society of Urological Pathology grade group; NA = not assessable.
[a] Data are for the intention-to-treat analysis. For each variable, *n* = 150 and/or 149 in EPLND and/or LPLND.
* Mann-Whitney *U* test.
** χ^2 test.

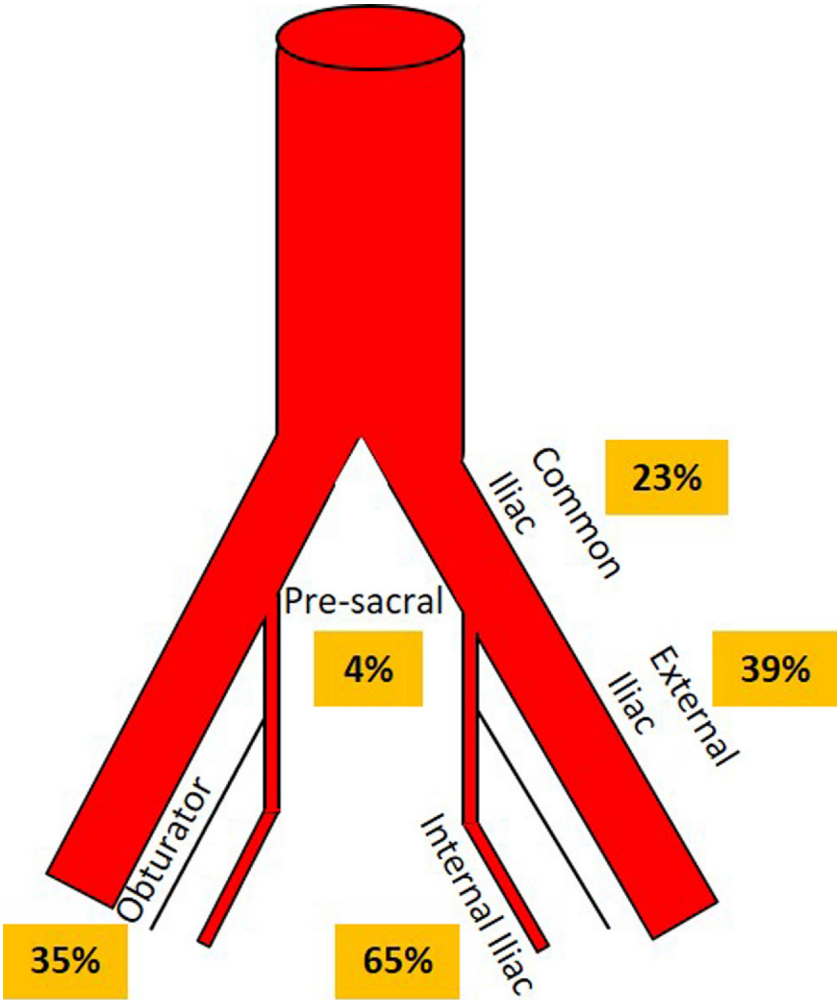

Fig. 2 – Distribution of node-positive patients (N1) undergoing extended pelvic lymph node dissection per region.

and 32.7 mo in the EPLND group (HR 0.79, 95% CI 0.42–1.5; $p = 0.4$; Supplementary Fig. 1B). There were no differences in preoperative biopsy ISUP GG1–GG2 PCa between the groups (Supplementary Fig. 4).

4. Discussion

Before this study, there was limited high-level evidence on the oncological outcomes of EPLND versus LPLND. A recent systematic review comprising 66 comparative studies and 275 269 patients found that the overall quality of evidence was low with moderate to high risk of bias. Most of the studies were retrospective and there was a lack of standardized definitions for the extent of PLND. The comparison of 21 retrospective studies on no PLND versus any form of PLND revealed no significant difference in favor of EPLND for BCR, MFS, or CSS. The comparison of LPLND versus EPLND in terms of BCR showed that 11 of 13 studies did not demonstrate a significant difference between the groups, while two studies showed a benefit from EPLND in specific subgroups: intermediate-risk disease and pN1 with <15% LNI [9]. Both previous studies that demonstrated a benefit in these subgroups had larger cohorts (585 and 4000 patients) than in the present study and the procedures were carried out by only two surgeons in each study.

To address this gap in knowledge, we conducted the first randomized phase 3 trial investigating the therapeutic role of EPLND versus LPLND for intermediate- and high-risk localized PCa in patients undergoing RP. Results from another ongoing trial from Germany comparing LPLND versus EPLND during RP (NCT01555086) are currently awaited. A third trial has recently started recruiting in Switzerland (NCT03921996), but is comparing EPLND versus no PLND during RP for intermediate- and high-risk PCa.

In this trial EPLND failed to show a significant benefit over LPLND with regard to the primary endpoint (BRFS) and the secondary endpoints (MFS, CSS). In terms of histopathological findings, EPLND significantly improved lymph node staging.

Our subgroup analyses, while hypothesis-generating, do suggest that a subset of patients may benefit from EPLND, namely men with ISUP GG3, GG4, or GG5 PCa on

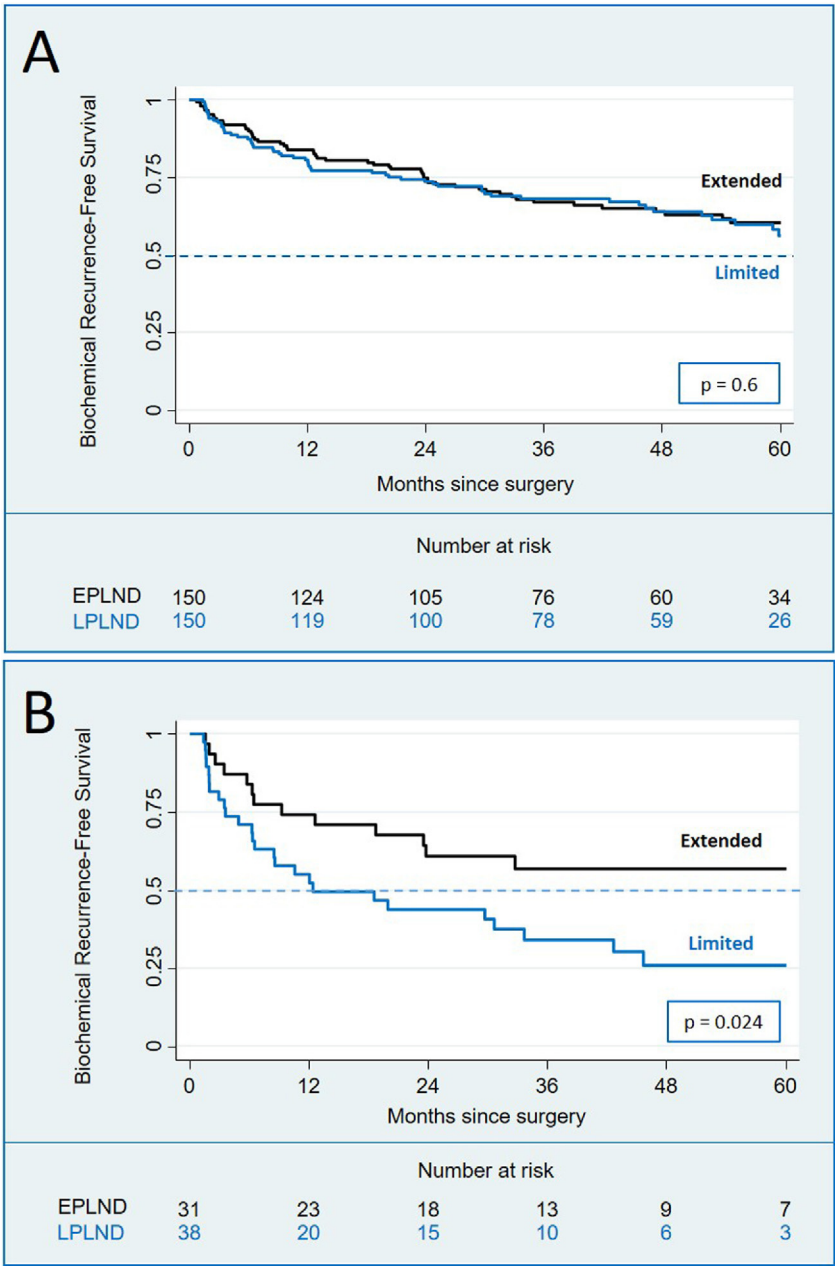

Fig. 3 – Kaplan-Meier estimates of biochemical recurrence–free (BRF) survival in the intention-to-treat analysis according to limited (LPLND) or extended pelvic lymph node dissection (EPLND) in (A) the overall cohort and (B) the subgroup with preoperative biopsy International Society of Urological Pathology grades 3–5.

preoperative biopsy. Considering that current imaging methods for preoperative staging still have low sensitivity for detection of lymph node metastases [17], this finding is important because it may help in preoperative selection of men who might benefit the most from EPLND. These findings help in reconciling the retrospective data suggesting that EPLND may be curative in select patients for whom cancerous lymph nodes are completely removed [18] and published series for salvage lymphadenectomy showing that 9–22% of patients are free of BCR at 5 yr [19]. Some of these patients are affected by systemic disease, but others have true oligorecurrent disease. In the former group, any local therapy would be of limited value, but in the latter group, EPLND could be beneficial, at the very least in postponing the use of systemic treatments.

Messing et al [20] demonstrated that early ADT benefits patients with nodal metastases who have undergone RP and lymphadenectomy in comparison to deferred treatment. More recently, Abdollah et al [21] showed a beneficial impact of adjuvant RDT on survival for patients with pN1 PCa with low-volume nodal disease (two LNIs) in the presence of intermediate- to high-grade non–specimen-confined PCa and those with intermediate-volume nodal disease (three to four LNIs). Nevertheless, considering that

Table 3 – Oncological events (total numbers) according to randomization[a].

Parameter	Patients (*n*)	
	EPLND	LPLND
Biochemical recurrence	54	57
Biochemical persistence after radical prostatectomy	12	19
Salvage lymphadenectomy	0	3
Radiotherapy	39	55 [b]
Salvage radiotherapy	38	48
Adjuvant radiotherapy	1	6
Androgen deprivation therapy	21	28
Salvage androgen deprivation therapy	21	27
Adjuvant androgen deprivation therapy	0	1
Bone metastases	4	7
Death (not prostate cancer–specific)	9	6

EPLND = extended pelvic lymph node dissection; LPLND = limited PLND.
[a] Intention-to-treat analysis. For each variable, $n = 150$.
[b] One patient in the LPLND group received palliative radiation therapy for bone metastases.

adjuvant treatment could affect the primary endpoint of the study (BRFS) and bias might occur in a similar manner to previous studies [9], the majority of patients in the current trial were observed until BCR occurred before salvage treatments were initiated (Table 3). It is possible that by improving staging, another benefit of EPLND is better selection of candidates for adjuvant treatments.

In our cohort, six pN1 patients with only one positive node treated with EPLND are currently free of BCR without any adjuvant treatment, whereas all node-positive patients in the LPLND group have developed BCR. Previous data suggest that patients with a low volume of nodal disease have significantly higher survival rates compared to patients with a larger volume of LNI, regardless of adjuvant treatment. Specifically, Briganti et al [22] reported significantly higher 15-yr CSS rates for patients with two or fewer positive lymph nodes treated with a multimodal approach ($n = 703$; 84% vs 62%; $p < 0.001$). With regard to our study, since these patients represent a small proportion of the total sample, no significant impact on survival was observed.

Regarding surgical margins, in one of the most extensive literature reviews, Novara et al [23] reported specific rates for each stage, supporting the notion that the more extensive the cancer, the greater is the risk of positive margins. In our cohort, >60% of the patients had stage ≥ pT3a advanced PCa and the positive margin rates were within the range reported in the literature and both groups were affected equally.

Some authors have demonstrated that increasing the area of lymph node dissection has oncological benefits [24–26]. However, Preisser et al [27] analyzed data for patients with intermediate- and high-risk PCa who underwent RP with or without PLND and concluded that there was no difference in oncological outcomes, which demonstrates that the role of PLND remains uncertain.

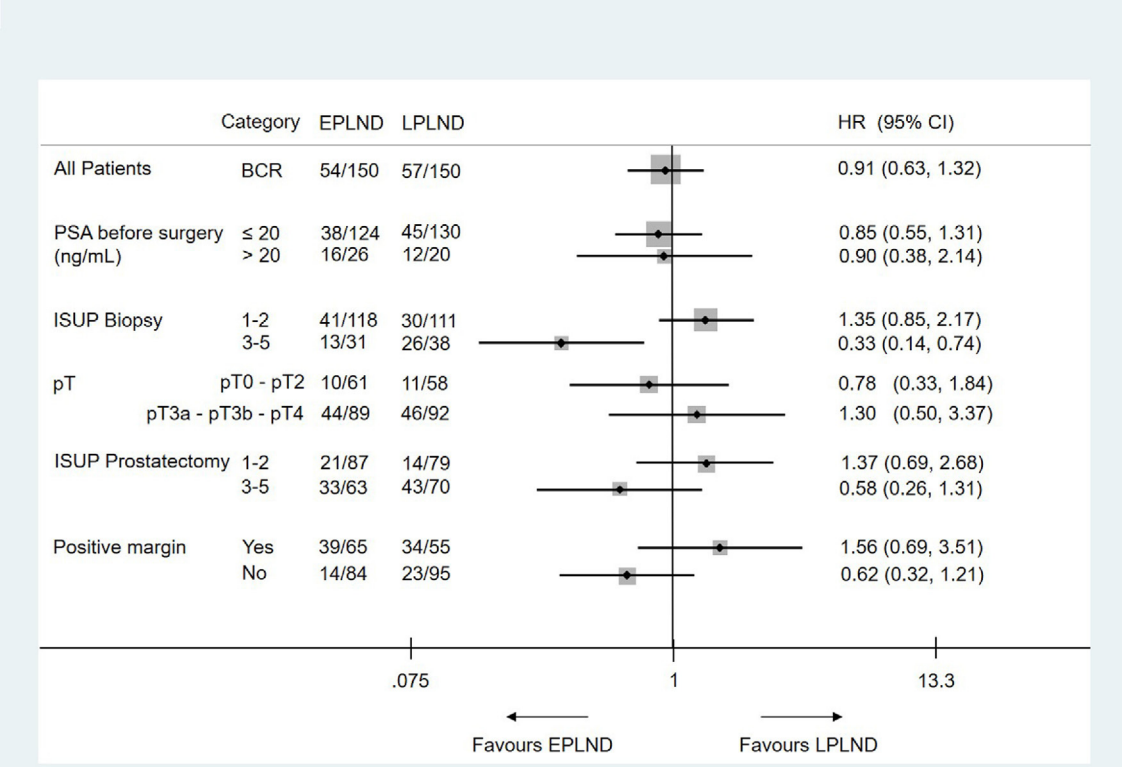

Fig. 4 – Forest plot of the effect of PLND on BCR-free survival by selected baseline and pathological categories in the intention-to-treat analysis. PLND = pelvic lymph node dissection; HR = hazard ratio; CI = confidence interval; EPLND = extended PLND; LPLND = limited PLND; PSA = prostate-specific antigen; ISUP = International Society of Urological Pathology; BCR = biochemical recurrence.

4.1. Strengths and limitations

To the best of our knowledge, this is the first completed randomized controlled trial to compare oncological outcomes between EPLND and LPLND during RP for localized PCa.

Although there was no oncological difference, EPLND improved staging and may be associated with better BRFS among patients with ISUP GG3–GG5 PCa.

The main limitation of this study is the short follow-up time. Results after longer follow-up are awaited to determine whether EPLND is superior to LPLND.

Surgeon heterogeneity was another limitation of our study. To decrease the surgical bias, we standardized the dissection template for both groups before the start of the study. Patients who crossed over or for whom the randomized PLND type was not performed (9.7%) represent potential bias; however, the intention-to-treat and per-protocol analyses were very similar. The primary endpoint is BRFS; after BCR, there was no standardized postoperative management. Positive margins were an independent factor for BCR risk.

5. Conclusions

This randomized controlled trial comparing EPLND and LPLND for men with intermediate- and high-risk localized prostate cancer undergoing RP confirms that EPLND provides better pathological staging, while differences in early oncological outcomes were not demonstrated. Our subgroup analysis suggests a potential BCR-free survival benefit for patients diagnosed with ISUP GG3, GG4, or GG5; however, these findings should be considered hypothesis-generating and further RCTs with larger cohorts and longer follow-up are necessary to better define the role of EPLND during RP.

Author contributions: Jean F.P. Lestingi had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Lestingi, Pontes, Guglielmetti.
Acquisition of data: Lestingi, Guglielmetti, Pontes, Bastos, Sarkis, Faraj, Cordeiro, Coelho.
Analysis and interpretation of data: Lestingi, Guglielmetti, Trinh, Coelho, Pontes, Bastos, Cordeiro, Sarkis, Mitre, Nahas.
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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eururo.2020.11.040.

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