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Review Article

Comparison of perioperative complications for extended vs standard pelvic lymph node dissection in patients undergoing radical prostatectomy for prostate cancer: a meta-analysis

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Abstract: Introduction: Pelvic lymph node dissection (PLND) is widely performed for staging in men undergoing radical prostatectomy (RP) for prostate cancer. Our goal was to synthesize all available evidence and data to evaluate perioperative complications for two templates of PLND, standard (sPLND) vs extended (ePLND), at the time of RP in patients with prostate cancer. Methods: A meta-analysis was performed on relevant literature about complications during PLND. Pubmed, Scopus, WebofScience, and Cochrane Library were systematically searched through July 2021. Meta-analysis was conducted with both fixed-effects and random-effects models to estimate risk ratios (RRs) between treatments. A subgroup analysis was also conducted based on surgery type - open vs robotic. Results: 13 (1 randomized clinical trial and 12 observational studies) studies published between 1997 and 2019 with a total of 7,036 patients were analyzed. Pooled data showed complications in a random-effects model was lower in the sPLND group than the ePLND group (RR, 0.62; 95% CI 0.40-0.97). In a subgroup analysis, neither the open surgery subgroup nor the robotic surgery subgroup showed significant differences in complication rate between sPLND and ePLND. Conclusion: ePLND is associated with a significantly greater risk of perioperative complication compared to sPLND, but not when comparing these templates performed via a robotic approach. Additional studies comparing the complication rates of sPLND and ePLND when utilizing a robotic approach should be conducted.

Keywords: Prostate cancer, extended pelvic lymph node dissection, pelvic lymph node dissection, pelvic lymphadenectomy, complications, radical prostatectomy

Introduction

While pelvic lymph node dissection (PLND) has long been regarded as the gold standard for cancer staging in men with prostate cancer undergoing radical prostatectomy (RP), it remains controversial due to the lack of clear evidence regarding its clinical benefit for patients and the potential for associated morbidity [1, 2]. Some studies have shown that PLND is associated with positive outcomes such as extended survival [3], but other studies have contradicted such findings and concluded that PLND is not associated with improved oncologic outcomes [4, 5]. The National Comprehensive Cancer Network (NCCN) currently recommends PLND for any patients with a greater than 2% chance of lymph node metastasis, and the AUA guidelines recommends PLND for patients with unfavorable intermediate risk or high risk disease [6, 7]. NCCN guidelines note that while no current model predicts the chance of lymph node metastasis with perfect accuracy, nomograms may be used to provide contextualized, individual information [8]. The increased morbidity associated with PLND is also unclear, as complication rates in studies of PLND range from 2% to 18.2% [9, 10].

Determining the benefits and harms of PLND is further complicated by the different templates of PLND used during RP, with the most common being limited, standard, and extended. The exact extent of each template is highly heterogeneous among different studies, but according to the European Association of Urology's (EAU) Prostate Cancer Guideline Panel, a limited template includes obturator lymph nodes, a standard template (sPLND) extends to obturator and external iliac nodes, and an extended template (ePLND) encompasses obturator, external iliac, and internal iliac nodes [11]. The historical shift in surgical approach from open RP with PLND to robotic-assisted laparoscopic RP with PLND also makes standardized assessment of PLND and its outcomes difficult.

The aim of this meta-analysis is to search the available literature for comparative studies evaluating the complications of sPLND vs ePLND, synthesize and analyze their findings as a whole, and report any significant differences in overall complications.

Methods

Literature search

We conducted a comprehensive systematic literature search using four databases updated through July 2021: Pubmed, Scopus, WebofScience, and the Cochrane Library. The search string '("pelvic lymph node dissection" OR "pelvic lymphadenectomy") AND ("prostate cancer" AND "complications")' was used to search each database. The references of included articles were also searched to identify additional relevant documents. If the same cohort or population was used in more than one study, data from the most recent study was utilized. The Rayyan QCRI web app was used to facilitate document screening [12]. The review protocol has not been registered.

Selection criteria

We included comparative studies assessing perioperative complications for standard dissection vs extended dissection at the time of radical prostatectomy in patients with prostate cancer. Included studies must have been designed with at least a limited or standard PLND group and an extended PLND group. Some studies made a distinction between limited PLND (lPLND) and sPLND, but we standardized both of these templates as sPLND. Publication types such as reviews, editorials, and letters were excluded, though conference abstracts were included. If data was unavailable for our outcome measures due to the paper being written in a foreign language or the data being unreported, the study was excluded. The primary outcome of interest was rate of perioperative complications.

Data extraction

Data was extracted, compiled, and reviewed in depth by two reviewers (Kong and Lichtbroun). Any disagreements or concerns were resolved either by discussion or consultation with other researchers (Sterling and Kim). From each study and for each cohort (distinguished according to PLND template), we recorded the first author, year of publication, study design, surgical approach (open, laparoscopic, or robotic), median PSA level, Gleason score, clinical stage, risk stratification, median number of lymph nodes retrieved, lymph node positive rate, rate of overall complications, rate of several specific complications, and surgical method.

Statistical analysis

We performed meta-analysis with both fixed-effects and random-effects models. The heterogeneity statistic I^2 was reported, and the heterogeneity test was performed. Risk ratio (RR) was used to measure the effect of treatments. We also conducted a subgroup analysis to assess the effects of surgical approach on results. We assessed publication bias with a funnel plot and conducted a test for its asymmetry based on a weighted linear regression utilizing efficient score and score variance. Statistical analyses were conducted using R version 4.0.2 (https://www.r-project.org/) and package 'meta' version 4.15 (https://github.com/guido-s/meta/).

Results

Literature search

13 studies published between 1997 and 2019 with a total of 7,036 patients were analyzed [10, 13-24]. **Figure 1** shows a flow diagram representing the process used to identify relevant studies. We identified 870 articles from 4 databases and by reviewing the references of relevant articles. Duplicates and articles not meeting the set inclusion criteria were screened out and excluded. The remaining 34 articles were

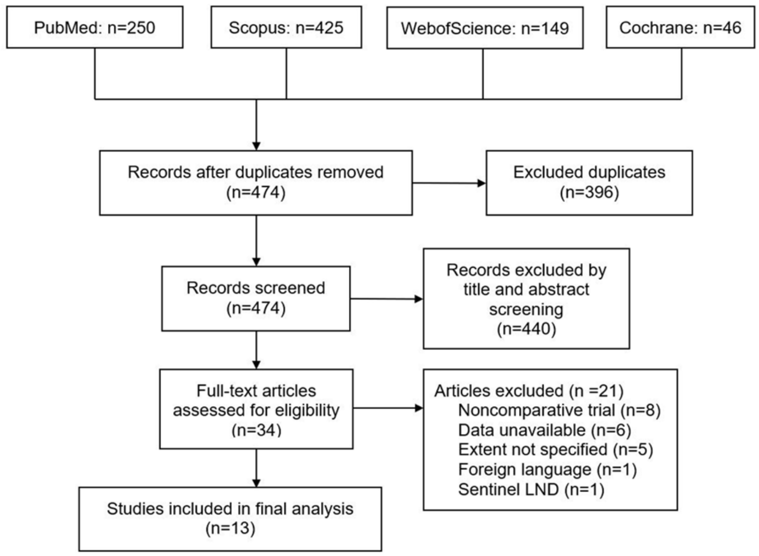

Figure 1. Flow diagram of the identification of relevant studies for final meta-analysis. Abbreviations: LND, Lymph node dissection.

reviewed, and 13 articles were included in the final analysis. The reasons for excluding the 21 articles from our final analysis were the article being noncomparative trial (n=8), data being unavailable (n=6), the article not specifying extent of PLND (n=5), the article being written in a foreign language (n=1), or the article studying sentinel LND instead of PLND (n=1).

Characteristics of included studies

Table 1 shows relevant characteristics of the 13 articles included in the final analysis and highlights their study designs. Of the studies included, 1 was a randomized clinical trial (RCT) [23] and the other 12 were observational studies (6 prospective studies, 5 retrospective studies, and one unspecified). Only studies with a comparative arm were included in this analysis. Some studies used the term 'limited PLND' in comparison to ePLND, but these templates corresponded to sPLND according to our criteria. Four studies used robot-assisted surgery [10, 13, 20, 24], four used laparoscopic surgery [14, 16, 17, 21], four used open surgery [15, 18, 19, 22], and one did not specify the surgical approach [23].

Table 2 shows clinical characteristics of the patient population in each study separated according to PLND template, including median PSA, Gleason score, clinical stage, risk stratification, number of lymph nodes retrieved, and lymph node positivity. Both the number of lymph nodes retrieved and percentage of patients with node positive disease are significantly higher in the extended group.

Table 3 shows rates of specific complications in each study separated according to PLND template, including symptomatic lymphocele, lymphedema, nerve injury, and thromboembolic events.

Extent of PLND and the risk of complications

Figure 2 shows the effect of sPLND vs ePLND on the risk of perioperative complications from our meta-analysis of 13 studies. Perioperative complications were reported in 351 out of 3,238 patients who underwent PLND (10.8%) and in 548 out of 3,798 patients who underwent ePLND (14.4%). The incidence of complications in sPLND was statistically significantly lower than in ePLND (P=0.04). There was significant heterogeneity among studies (I^2=77%; P<0.01), suggesting that a random-effects model would be appropriate. The funnel plot for assessing publication bias was symmetrical and the test for its asymmetry yielded a *p*-value of 0.188, suggesting no evidence of significant publication bias (**Figure 3**). The relative risk of complications in a random-effects model was lower in the sPLND group than the ePLND group (RR, 0.62; 95% CI 0.40-0.97). In most studies, overall complications were higher in ePLND, but some studies showed slightly higher complication rates in sPLND.

Subgroup analysis

Figure 4 shows the effect of sPLND vs ePLND on perioperative complications in a subgroup analysis comparing robotic vs open surgery. There was no significant heterogeneity among the studies in the robotic subgroup (P=0.760), suggesting clinically comparable patient populations and that a fixed-effects model would be appropriate. In the robotic surgery subgroup, there was no significant difference in complication rate between sPLND and ePLND according

Table 1. Characteristics of the 13 studies included for meta-analysis

Study	Year	Design	IPLND Population	ePLND Population	Surgical Method	Perioperative cx of IPLND vs ePLND, RR (95% CI)
Stone et al.	1997	Unknown	150	39	Open	0.06 (0.02-0.18)
Heidenreich et al.	2002	P	100	103	Open	1.03 (0.43-2.49)
Briganti et al.	2006	P	196	767	Open	0.41 (0.25-0.67)
Lindberg et al.	2009	R	64	108	Open	0.41 (0.20-0.83)
Arenas et al.	2010	R	381	163	Laparoscopic	0.88 (0.54-1.43)
Eden et al.	2010	P	311	121	Laparoscopic	0.35 (0.15-0.84)
Liss et al.	2013	R	231	54	Robotic	1.09 (0.57-2.10)
Rousseau et al.	2013	P	176	127	Laparoscopic	0.40 (0.26-0.62)
Yuh et al.	2013	P	204	202	Robotic	0.95 (0.66-1.36)
Eden et al.	2016	R	311	1000	Laparoscopic	0.61 (0.37-1.00)
Mistretta et al.	2017	R	75	109	Robotic	1.23 (0.76-1.99)
Altok et al.	2018	P	282	282	Robotic	0.82 (0.41-1.64)
Touijer et al.	2019	RCT	723	757	Unknown	1.10 (0.83-1.46)

Abbreviations: PLND, Standard pelvic lymph node dissection; ePLND, Extended pelvic lymph node dissection; cx, Complication; RR, Risk ratio; CI, Confidence interval; P, Prospective; R, Retrospective; RCT, Randomized clinical trial.

Table 2. Comparison of clinical characteristics of patient populations in each study separated according to PLND template

Study	PSA, median (range)	Gleason Score mean (range) or mode (%)**	Clinical stage, mode (%)	D'amico Risk Stratification	No. LNs Retrieved, median (IQR)	%pN1
Stone et al. (standard)	0-20 (74%)*	7-10 (43%)	T2-T3 (64%)	High	9.3 (1-31)	7.30%
Stone et al. (extended)	0-20 (74%)*	7-10 (66%)	T2-T3 (82%)	High	17.8 (2-51)	23.10%
Heidenreich et al. (standard)	14.9 (1.6-109)	5.2 (2.6-7.8)	T2 (65%)	Intermediate	11 (6-19)	12%
Heidenreich et al. (extended)	15.9 (1.2-129)	4.6 (2.3-6.9)	T2 (59%)	Intermediate	28 (21-42)	26.20%
Briganti et al. (standard)	8.8 (0.1-120)	≤6 (66.3)	cT1 (54%)	Low	17.7 (10-40)	3.60%
Briganti et al. (extended)	11.3 (0.02-240)	≤6 (61.1%)	cT1 (57.9%)	Intermediate	6.75 (1-9)	11.30%
Lindberg et al. (standard)	10 (2.3-26)	7 (48%)	T1-2 (97%)	Intermediate	7 (3-18)	6%
Lindberg et al. (extended)	10 (2.7-64)	7 (55%)	T1-2 (81%)	Intermediate	17 (5-40)	20%
Arenas et al. (standard)	22.5 (1.2-147)	6.8 (4-9)	cT2 (52%)	High	13.8 (6-51)	18.80%
Arenas et al. (extended)	17 (1.2-34.1)	7 (4-10)	cT1 (76.1%)	High	31.1 (5-78)	24.70%
Eden et al. (standard)	11.0 (2-20)	7 (4-10)	T2 (63%)	Intermediate	6.1 (2-8)	0.80%
Eden et al. (extended)	8.0 (1-15)	7 (6-10)	T2 (57%)	Intermediate	17.5 (2-23)	9.60%
Liss et al. (standard)	6.1 (4.4-9.2)	7 (60.2%)	T1 (58.9%)	Intermediate	18 (12-25)	3.90%
Liss et al. (extended)	8.5 (5.5-13.5)	≥8 (57.7%)	T2 (68.5%)	High	20 (16-28)	24.10%
Rousseau et al. (standard)	11.3 (2.01-47)	7 (53.6%)	T1 (60.9%)	Intermediate	6.7 (NA)	5.70%
Rousseau et al. (extended)	9 (1.45-66.4)	7 (59%)	T1 (60.5%)	Intermediate	15.6 (NA)	18.90%
Yuh et al. (standard)	5.9 (4.4-9.1)	3+4 (54.9%)	T1 (72.1%)	Intermediate	7 (5-9)	3.90%
Yuh et al. (extended)	5.5 (4.2-8.3)	3+4 (59.9%)	T1 (68.8%)	Intermediate	21.5 (17-27)	11.90%
Eden et al. (standard)	11.0 (10-14)	7 (6-7)	T2 (63%)	Intermediate	6 (5-7)	0.80%
Eden et al. (extended)	9.0 (6-13)	7 (7-7)	T2 (52.2%)	Intermediate	17 (12-22)	12.80%
Mistretta et al. (standard)	8.1 (4.9-12.9)	3+4 (37.6%)	T2 (50.5%)	Intermediate	11 (7-17)	12.80%
Mistretta et al. (extended)	9.4 (6.2-17.4)	3+4 (32%)	T2 (50.7%)	Intermediate	21 (16-29)	29.30%
Altok et al. (standard)	5.4 (4.2-7.5)	3+4 (56%)	cT1 (65%)	Intermediate	8 (6-12)	5%
Altok et al. (extended)	5.3 (4.1-8.1)	3+4 (58%)	cT1 (65%)	Intermediate	16 (11-21)	13%
Touijer et al. (standard)	NA	Unknown	Unknown	Unknown	12 (8-17)	11.20%
Touijer et al. (extended)	Unknown	Unknown	Unknown	Unknown	14 (10-20)	13.60%

*The Stone et al. study gave PSA data as a percentage of patients falling within a range rather than a median PSA. **While some studies gave a mean and range for patient Gleason scores, other studies only gave percentages of patients classified under a certain Gleason score. Abbreviations: PSA, Prostate-specific antigen; LN, Lymph node; IQR, Interquartile range; %pN1, Percent lymph node positive.

Table 3. Comparison of complication rates of specific complications in each study separated according to PLND template

Study	Symptomatic Lymphocele, %	Nerve injury, %	Lymphedema, %	Thromboembolic Events, %
Stone et al. (standard)	NA	0.70%	0%	NA
Stone et al. (extended)	NA	5.10%	10%	NA
Heidenreich et al. (standard)	9%	2%	NA	8%
Heidenreich et al. (extended)	10.60%	1.10%	NA	6.30%
Briganti et al. (standard)	4.60%	NA	NA	0.50%
Briganti et al. (extended)	10.30%	NA	NA	0.90%
Lindberg et al. (standard)	9%	NA	NA	3%
Lindberg et al. (extended)	18%	NA	NA	5.50%
Arenas et al. (standard)	1%	4.60%	NA	0.50%
Arenas et al. (extended)	1.20%	5.60%	NA	0.60%
Eden et al. (standard)	1.60%	0%	NA	0.30%
Eden et al. (extended)	0%	1.70%	NA	0.80%
Liss et al. (standard)	5.20%	NA	NA	NA
Liss et al. (extended)	5.20%	NA	NA	NA
Rousseau et al. (standard)	0.60%	NA	0.60%	0.60%
Rousseau et al. (extended)	6.4%	NA	15.70%	6.2%
Yuh et al. (standard)	2.90%	0.50%	0%	2.90%
Yuh et al. (extended)	2.50%	1.50%	0.10%	1.00%
Eden et al. (standard)	1%	0%	0%	0.30%
Eden et al. (extended)	0.03%	0.002%	0.012%	0.002%
Mistretta et al. (standard)	6.40%	NA	NA	NA
Mistretta et al. (extended)	9.30%	NA	NA	NA
Altok et al. (standard)	NA	NA	NA	NA
Altok et al. (extended)	NA	NA	NA	NA
Touijer et al. (standard)	NA	NA	NA	NA
Touijer et al. (extended)	NA	NA	NA	NA

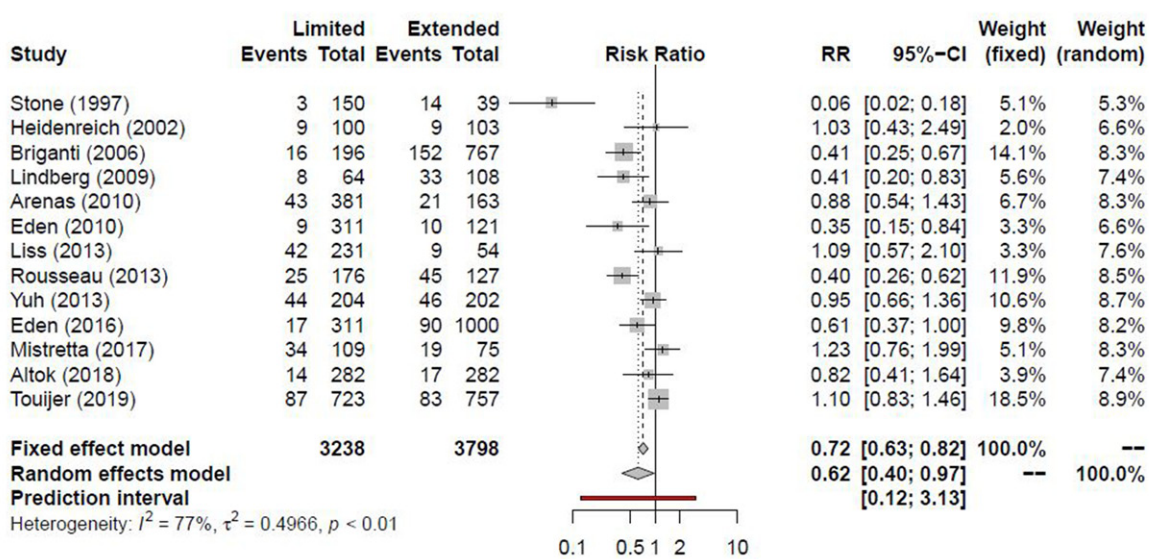

Figure 2. Forest plot showing perioperative complication in sPLND vs ePLND in a meta-analysis of 13 studies. Significant between study heterogeneity was detected (I-squared =77%, P≤0.01). Abbreviations: RR, Risk ratio.

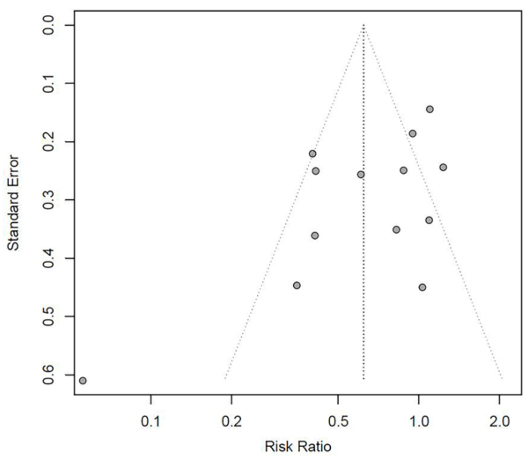

Figure 3. Funnel plot for assessing publication bias. The test for asymmetry yielded a *p*-value of 0.188.

to a fixed effects model (RR, 1.01; CI 95%, 0.79-1.30). Among the open surgery studies, there was significant between-study heterogeneity (I-squared =80%; P<0.01), suggesting that a random effects model would be appropriate. In the open surgery subgroup, there was no significant difference in complication rate between sPLND and ePLND (RR, 0.33; CI 95%, 0.05-2.16). Though the RR for complications in sPLND vs ePLND is 0.33, the confidence interval is too wide to declare statistical significance due to the small number of studies and significant between-study heterogeneity.

Discussion

Though PLND remains the gold standard for prostate cancer staging, the optimal extent of dissection is still unclear [1, 25]. In general, performing ePLND will result in detecting more patients diagnosed with nodal disease, but more extensive surgery can result in higher complication rate. We analyzed all identifiable studies comparing sPLND and ePLND that reported overall complication rates and sought to quantify the difference in complication risk between the two surgical templates.

Our analysis indicates that there is a significant difference in complications between sPLND and ePLND, in contradiction with previous reviews [1, 11]. The findings from our meta-analysis of 13 studies, including a total of 7,036 patients, show that sPLND has a lower risk of complications than ePLND (RR=0.62). This is consistent with the majority of studies in our analysis (9 out of 13) showing lower relative risk of complication in sPLND. These findings are in contrast to a previous meta-analysis conducted by Gao et al., which found no significant difference in complication rates between sPLND and ePLND [26]. However, our findings are consistent with a recent review and meta-analysis by Cacciamani et al. which found statistically significantly lower perioperative morbidity in sPLND compared to ePLND. A subgroup analysis was also conducted in this review and found no significant difference in complications between sPLND and ePLND in surgeries utilizing a robotic approach; our analysis also found no difference in complication rate in robotic surgeries [27].

We find these results consistent with the personal clinical experience of our authors who have completed PLNDs, particularly the results of the subgroup analysis suggesting that in robotic PLNDs, PLND template does not significantly affect complication rate. We note that in our experience, a robotic approach allows us to be more extensive in the dissection without risking more numerous or more severe complications. Therefore, in the case of a robotic PLND approach, we believe the findings from our analysis and the personal clinical experience of our authors suggest that in the majority of RP cases involving PLND, an ePLND template will yield greater diagnostic benefit without risking more frequent or more severe complications.

Since our meta-analysis includes studies of PLND from 1997 to 2019, multiple surgical methods of PLND were collectively analyzed, including traditional open surgery, laparoscopic surgery, and robotic surgery. Therefore, a subgroup analysis comparing sPLND and ePLND complications in open surgery vs robotic surgery was conducted in order to determine if surgical method affected the relative risk of complications in sPLND vs ePLND. Our subgroup meta-analysis shows that when performing robotic PLND, no significant difference in complications exists between sPLND and ePLND (RR=1.01). In our analysis comparing complications in the sPLND vs ePLND groups using open surgery, no significant difference was found, largely due to the small number of studies involved and significant between-study heterogeneity. Historically, some studies evaluating sPLND vs ePLND in open surgery have demonstrated a dramatically higher complication rate in ePLND [22]. Among studies compar-

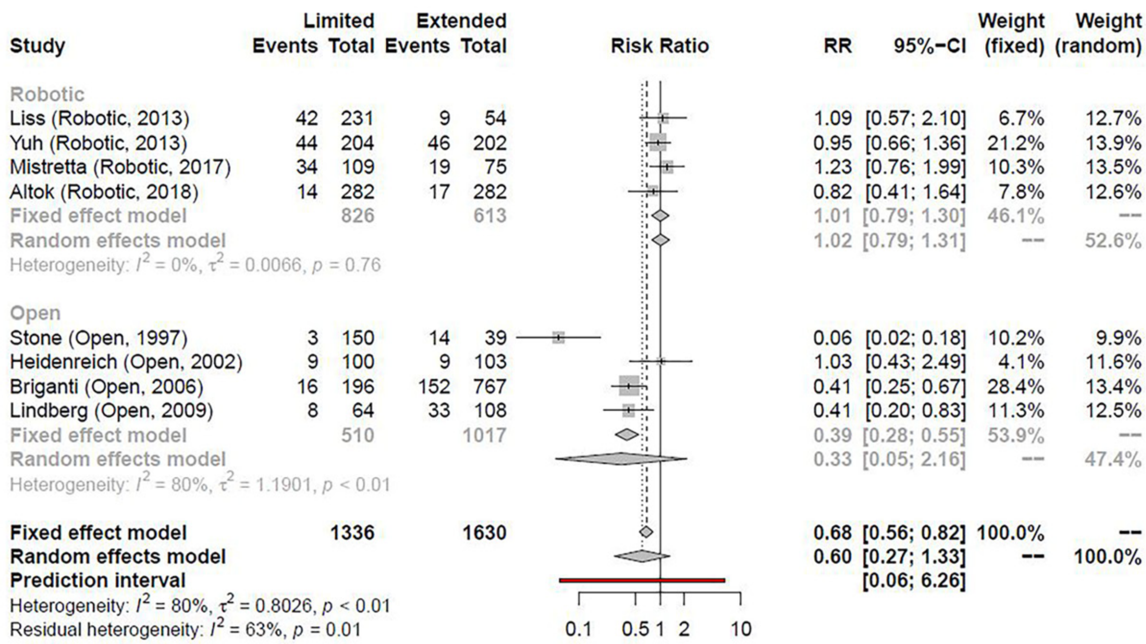

Figure 4. Forest plot showing perioperative complications in PLND vs ePLND in subgroup analysis by surgical method. No heterogeneity was detected in the Robotic subgroup (I-squared =0%, P=0.76). Significant between study heterogeneity was detected in the Open subgroup (I-squared =0%, P<0.01). Abbreviations: RR, Risk ratio.

ing the complication rates of different templates of PLND, the results are relatively inconsistent. Complication rates for standard PLND range from 2% to 30.6% [20, 22], while rates for extended PLND range from 6% to 35.9% [13, 22]. These conflicting results are even harder to interpret given the lack of randomized controlled clinical trials in this area.

A recent RCT found that ePLND provided better pathological staging than sPLND, but overall differences in oncological outcomes were not demonstrated [28]. The results of our meta-analysis indicate that the improved pathological staging of the extended template must be weighed against the greater risk of complications. However, our subgroup analysis showed no difference in complications for the standard vs extended templates of PLND in studies using the more modern robot-assisted approach. Therefore, for robot-assisted PLNDs, the extended template can potentially be used to better stage prostate cancer and determine lymph node metastasis without additional complication risk, although it remains to be determined if better staging has an impact on overall or cancer specific survival.

Our meta-analysis has limitations that should be addressed. First, the low number of articles limits the predictive power of our meta-analysis, and the analyzed studies only included 1 RCT while the other studies were all observational studies. Second, surgical methods and baseline patient characteristics varied across studies, indicating that allocation bias and other confounding factors may have biased our results. Third, differences in defining surgical extent and inconsistency in complication reporting further made reliable meta-analysis challenging. While some studies made a distinction between limited and standard PLND, we included all non-extended PLND into the sPLND group. Fourth, in our overall meta-analysis, the upper bound of the confidence interval from the random-effects model is very close to 1 (null) and the Stone et al. study is a significant outlier. If it was excluded from the analysis, it is likely the interval would cross the line of equal risk. Fifth, the heterogeneity statistic I-squared, which is a measure of variation in outcomes across studies, was 77% for our meta-analysis, suggesting that overall outcomes varied greatly between studies (P< 0.01). Similar issues of heterogeneity were also present in the open PLND subgroup. Lastly, we did not categorize complications according to type or complication grade. Reported data was insufficient to determine if SPLND and ePLND also differed significantly in either complication type and/or severity.

With these qualifying limitations, our meta-analysis demonstrates a significantly lower risk of complication in sPLND vs ePLND when considering all surgical modalities. However, our sub-group analysis shows that when a robotic surgical approach is utilized, there was no significant difference between sPLND and ePLND in the complication rate. It is unclear if this finding applies to open or laparoscopic PLND. Given that the robotic approach towards radical prostatectomies has become the most commonly used modality, the findings from our subgroup analysis may be more relevant in informing future treatment decisions. Studies specifically comparing the complication rates of sPLND and ePLND when utilizing the robotic approach should be conducted to explore and confirm our findings.

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Disclosure of conflict of interest

None.

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