Systematic Review and Meta-Analysis

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Comparison of clinical feasibility and oncological outcomes between video endoscopic and open inguinal lymphadenectomy for penile cancer

A systematic review and meta-analysis

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Abstract

Background: To compare the clinical feasibility and oncological outcomes of video endoscopic inguinal lymph node dissection (VE-ILND) and open inguinal lymph node dissection (O-ILND) in the management of penile cancer.

Methods: We searched published articles in the PubMed, Embase, Cochrane Library, Web of science, China National Knowledge Infrastructure, and Wanfang databases. Data were extracted by 2 independent authors, and meta-analysis was performed by using Review Manager software version 5.3.

Results: Ten studies were included. Compared with the O-ILND group, the VE-ILND group exhibited less intraoperative blood loss (standardized mean difference [SMD] = 3.12; 95% confidence intervals [95% CIs] [1.27, 4.98]; $P = .001$), shorter hospital stay (SMD = 1.77; 95% CIs [0.94, 2.60]; $P < .001$), shorter drainage time (SMD = 2.69; 95% CI [1.47, 3.91]; $P < .001$), reduced wound infection rate (odds ratio [OR] = 10.62; 95% CI [4.01, 28.10]; $P < .001$); reduced skin necrosis rate (OR = 7.48; 95% CI [2.79, 20.05]; $P < .001$), lower lymphedema rate (OR = 3.23; 95% CI [1.51, 6.88]; $P = .002$), equivalent lymphocele rate (OR = 0.83; 95% CI [0.31, 2.23]; $P = .720$), and parallel recurrence rate (OR = 1.54; 95% CI [0.41, 5.84]; $P = 0.530$). However, the number of dissected lymph nodes (OR = 0.25; 95% CI [0.03, 0.47]; $P = .030$) was slightly increased in the O-ILND group. GRADE recommendations of primary outcomes were shown in a summary of findings table.

Conclusions: For perioperative outcomes, VE-ILND is superior to O-ILND. For short-term oncological outcomes, VE-ILND is comparable to O-ILND. However, long-term oncological control still requires further verification.

Abbreviations: 95% CIs = 95% confidence intervals, LESS = laparoendoscopic single site, NA = not available, O-ILND = open inguinal lymph node dissection, OR = odds ratio, RCT = randomized controlled trial, SD = standard deviations, SMD = standardized mean difference, TFL = tensor fascia flap, VE-ILND = video endoscopic inguinal lymph node dissection.

Keywords: inguinal lymphadenectomy, meta-analysis, penile cancer

1. Introduction

Penile cancer is a rare malignant tumor caused by multiple factors, such as phimosis, poor genital hygiene, and human papillomavirus infection.[1] The estimated number of new cases in the United States was 2030 in 2016.[2] However, in developing countries, penile cancer represents up to 1% to 2% of malignancies in men.[3] Although the incidence is relatively low, penile cancer exhibits significant physiological and psychological impacts on patients.[4,5] The most common metastasis site for penile cancer is the inguinal lymph node and it indicates poor prognosis.[6,7] Therefore, after local treatment for primary lesion, inguinal lymph node dissection (ILND) is recommended if lymph node metastasis occurs or there is a high risk of developing lymph node metastasis.[8]

However, conventional open inguinal lymph node dissection (O-ILND) was associated with significant complications, such as wound infection, skin necrosis, lymphocele, and lymphedema, which limit clinical application of O-ILND.[9] To reduce the complication rates, clinicians have developed various technical modifications, such as preservation of saphenous vein, avoiding transposition of sartorius, dynamic sentinel-node biopsy, and reducing the dissection field.[10,11] In addition, several alternative management options, such as active surveillance, dynamic sentinel node biopsy, and modified lymphadenectomy, were recommended in the past decades. However, these modified techniques might miss micro-metastasis, which may cause a considerable false-negative rate and compromise oncologic control.[8,12]

Since 2003, the first report of video endoscopic inguinal lymph node dissection (VE-ILND) reported by Bishoff et al, great efforts

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had been made to develop VE-ILND and robotic-assisted inguinal lymph node dissection.[13,14] However, it is unclear whether VE-ILND is superior to conventional ILND. The best procedure of ILND remains controversial. Hence, we performed this meta-analysis on data extracted from available studies to compare the clinical feasibility and oncological outcome between VE-ILND and conventional O-ILND.

2. Methods

This study protocol was performed according to the preferred reporting items for systematic review and meta-analyses statement (PRISMA statement) and approved by the Institutional Review Board of our hospital before initiation.[15] An ethical standard statement was not required in this situation.

2.1. Search strategy

In accordance with the PRISMA statement, a systematic review of the literature was performed in January 2019 by searching PubMed, Embase, Cochrane Central Search Library, Web of science, China National Knowledge Infrastructure database, and Wanfang database. Search mesh terms included "penile cancer," "penile carcinoma," "inguinal lymph node dissection," "inguinal lymphadenectomy," and "ILND." For Pubmed database: the search strategy was ((((((Penile Neoplasms [MeSH Terms]) OR Penile Cancers [Title/Abstract]) OR Neoplasms, Penis [Title/Abstract]) OR Cancer of Penis [Title/Abstract]) OR Penis Cancers [Title/Abstract]) OR Penis Cancer [Title/Abstract])) AND (((complication) OR prognosis)) AND (((((inguinal lymph node dissection [Title/Abstract]) OR inguinal lymphadenectomy [Title/Abstract]) OR ILND [Title/Abstract])). For Embase database: the search strategy was ("penis tumor"/exp OR "penile cancers" OR "neoplasms, penis" OR "cancer of penis" OR "penis cancers" OR "penis cancer" OR "penile neoplasms") AND ("inguinal lymph node dissection" OR "inguinal lymphadenectomy" OR "ILND") AND ("complication" OR "prognosis"). We reviewed all abstracts and articles on those topics and manually searched references of original studies.

2.2. Inclusion and exclusion criteria

The population, intervention, comparison, outcome, and study design principle was adapted to define study eligibility. Randomized controlled trials (RCTs) or cohort studies (Study design) that compared clinical feasibility and oncological outcomes (Outcome) of penile cancer patients (Population) who underwent video endoscopic inguinal lymphadenectomy (Intervention) with patients who underwent open inguinal lymphadenectomy (Comparison) were considered relevant to this systematic review and meta-analysis. Eligible studies were selected based on the following detailed inclusion criteria:

(1) RCTs or cohort studies with controlled group;
(2) studies comparing perioperative parameters between conventional open ILND and VE-ILND;
(3) studies with sufficient data for the meta-analysis, including intraoperative outcomes, postoperative complications, and oncologic outcomes;
(4) studies providing sufficient information to estimate the odds ratio (OR) or standard mean difference (SMD) and their corresponding 95% confidence interval (95% CI);
(5) studies in English or Chinese language.

Exclusion criteria were as follows:

(1) study types including case report, review, case series, editorial, and letter;
(2) studies with insufficient data to estimate desirable effects; and
(3) nonhuman studies.

2.3. Data extraction and quality assessment

Data of included studies were extracted by 2 independent reviewers (JH and JC). Disagreement was resolved during a consensus meeting with a senior reviewer (XZ). Literature data and demographics, including study type, authors, publication date, sample size, survival analysis, follow-up period, and related outcomes, were extracted individually. The mean values and standard deviations (SD) are necessary for the pooled data to compare the risk of continuous variables. However, some published studies provided the continuous parameter with median and interquartile range. For these studies, we estimated the mean and SD from original data.[16] The quality of included studies were evaluated by using Cochrane risk of bias which includes 7 aspects: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. Each item was assessed with low risk, unclear risk, or high risk by 2 independent reviewers.

2.4. Outcome measurements and GRADE recommendations

Perioperative outcomes include the following: operation time, blood loss, hospital stay, duration of drainage, wound infection, skin necrosis, lymphedema, and lymphocele. Operation time was defined as the period elapsed from the beginning of skin incision to the completion of skin suture. Blood loss was measured during operation. Duration of drainage was defined as the period elapsed from the first day after surgery to the day the drainage tube was removed. However, the volume of drainage could not be analyzed due to insufficient data. Wound infection, skin necrosis, lymphedema, and lymphocele were diagnosed by visual inspection. All of these complications were graded according to the Clavien–Dindo system.[17] Clavien–Dindo I-II complications were defined as minor complications, and Clavien–Dindo III-IV complications were defined as major complications. Oncological outcomes included recurrence-free survival, progression-free survival, overall survival, number of dissected lymph nodes, and cancer-specific death. However, due to insufficient data, we only analyzed the number of dissected lymph nodes and recurrence rate. If the number of dissected lymph nodes was greater than 7, we thought the procedure achieved effective cancer control. We performed GRADE recommendations for primary outcomes of RCT and non-RCT subgroup, respectively. For the pooled results of RCT subgroup, the initial grade is high. In contrast, the initial grade of non-RCT subgroup is low. There are 5 factors that contribute to the downgrade, consisting of risk of bias, inconsistency, indirectness, imprecision, and publication bias. There are 3 factors that contribute to the upgrade, consisting of large effect, plausible residual confounding, and dose-response gradient.

2.5. Statistical analysis

Statistical heterogeneity among studies was measured using a formal Q-statistic and I^2.[18] I^2 value was used to describe the

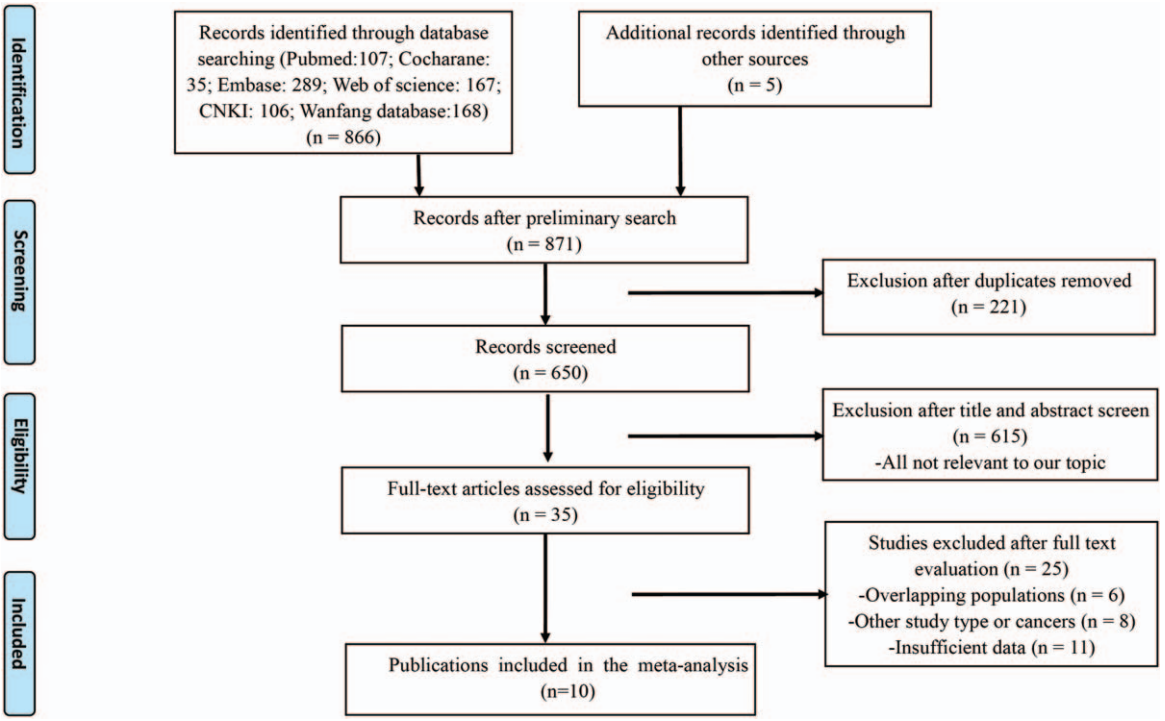

Figure 1. Flow chart of study selection.

degree of heterogeneity ($I^2 < 25\%$: no heterogeneity; $I^2 = 25\%$–50%: moderate heterogeneity; $I^2 > 50\%$: large heterogeneity). A random-effects model was used when heterogeneity was large. Otherwise, the fixed-effects model was used. The results of statistical analysis of dichotomous variables (wound infection, skin necrosis, lymphedema, lymphocele, minor complication, major complication, and recurrence) were expressed as OR and 95% CI. The results of continuous variables (operative time, blood loss, hospital stay, duration of the drainage, and number of lymph nodes) were expressed as SMD and 95% CI. $P < .05$ was considered to indicate a statistically significant difference. Then, we performed meta-analyses using Review Manager (RevMan) software version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen).

3. Results

3.1. Study selection and characteristics

A total of 866 references (598 English and 268 Chinese publications) were searched through databases (Fig. 1). Based on our selection criteria, 10 studies with a total of 307 patients were included in our meta-analysis.[19–28] These studies (8 cohort and 2 randomized control studies) were performed in the following geographical regions: Europe (n = 2), South America (n = 1), and Asia (n = 7). All of the studies were published between 2008 and 2017. The main characteristics of these included studies were summarized in Table 1. Detailed information of included studies was summarized in Table 2. Pooled results were summarized in Table 3. GRADE recommendations of primary

Table 1

Characteristics of publications included in the meta-analysis.

Author, yr	Study period	Country	Preservation of saphenous vein	Study design	Patients			Legs		Follow-up, mo	Reference
					Total	O-ILND	VE-ILND	O-ILND	VE-ILND		
Yadav (2017)	2013–2017	India	Yes	RCT	29	29	29	29	29	14	[29]
Tobias (2008)	2003–2006	Brazil	No	Cohort	15	5	10	10	20	31.93	[20]
Wang (2017)	2013–2015	China	No	Cohort	34	18	16	21	19	12	[23]
Kumar (2016)	2008–2015	UK	NA	Cohort	42	22	20	35	33	71 versus 16	[27]
Shi (2014)	2010–2014	China	No	Cohort	26	14	12	26	22	4–36	[21]
Qi (2013)	2007–2012	China	No	Cohort	23	13	10	26	20	22.4	[28]
Li (2014)	2010–2014	China	Yes	RCT	18	9	9	18	18	NA	[25]
Qiu (2016)	2013–2016	China	Yes	Cohort	28	15	13	30	26	22	[24]
Zhou (2017)	2009–2017	China	No	Cohort	50	23	27	33	37	60	[22]
Schwentner (2013)	NA	Germany	NA	Cohort	42	26	16	34	28	NA	[26]

NA = not available, O-ILND = open inguinal lymph node dissection, RCT = randomized controlled trial, VE-ILND = video endoscopic inguinal lymph node dissection.

Table 2

Summary of detailed surgical outcomes, postoperative complications, and oncologic outcomes of included studies.

		Surgical outcomes				Complications						Oncologic outcomes	
Author, yr	Treatment	Operative time, min	Blood loss, ml	Hospital stay, d	Drainage, d	Wound infection	Skin necrosis	Lymphedema	Lymphocele	Minor complication	Major complication	Number of lymph nodes	Recurrence
Yadav (2017)	O-ILND	92.04±48.89	NA	4.65±2.96	4±2.96	4	8	4	NA	8	2	NA	NA
	VE-ILND	155.2±46.67	NA	10.26±5.93	2±1.48	0	2	3	NA	18	0	NA	NA
Tobias (2008)	O-ILND	92±22.22	NA	NA	6.4±4.44	5	NA	2	NA	NA	NA	9.7±5.93	0
	VE-ILND	120±51.85	NA	NA	4.9±6.67	1	NA	2	NA	NA	NA	10.8±6.67	0
Wang (2017)	O-ILND	169.8±55.19	68.44±42.19	12.50±4.98	11.44±2.69	3	6	6	5	13	0	12.60±5.53	2
	VE-ILND	139.5±45.52	22.50±14.24	10.43±2.53	7.23±1.79	1	1	3	0	4	0	10.78±5.22	1
Kumar (2016)	O-ILND	94	NA	7.3±13.3	NA	24	NA	13	7	2	15	7.11	0
	VE-ILND	97	NA	2.5±10.37	NA	2	NA	1	9	1	1	9.36	0
Shi (2014)	O-ILND	156.6±33.1	81.6±42.5	15.8±5.5	NA	0	5	NA	0	NA	NA	NA	2
	VE-ILND	168.5±41.8	29. 2±15.3	24.3±10.8	NA	0	0	NA	2	NA	NA	NA	1
Qi (2013)	O-ILND	156.8±18.3	88.5±9.5	15.7±1.9	12.5±1.3	0	1	0	2	3	NA	10.3±1.5	0
	VE-ILND	103.6±15.2	56.5±6.8	8.5±1	5.8±0.8	0	0	0	0	0	NA	9.5±1.3	0
Li (2014)	O-ILND	127±18	21±17	8.0±0.5	6.8±1.71	NA	NA	NA	NA	NA	NA	19±6	NA
	VE-ILND	157±20	23±8	6.0±0.8	1.96±0.42	NA	NA	NA	NA	NA	NA	14±6	NA
Qiu (2016)	O-ILND	99.7±12.9	87.4±19.5	10.49±3.90	12.3±1.2	2	5	1	2	NA	NA	9.64±2.61	0
	VE-ILND	153.1±27.8	42.5±5.7	5.9±1.06	5.6±0.6	1	0	1	3	NA	NA	8.78±2.07	0
Zhou (2017)	O-ILND	53.1±2.2	50.7±2.7	19±2.0	8.1±2.2	4	4	2	2	NA	NA	11.1±2.3	2
	VE-ILND	80.2±4.3	27.3±1.5	13.4±1.0	4.7±1.1	0	0	0	2	NA	NA	11.6±2.9	2
Schwentner (2013)	O-ILND	101.7±40	NA	NA	NA	NA	NA	15	NA	NA	16	7.2±4.4	NA
	VE-ILND	136.3±27.7	NA	NA	NA	NA	NA	0	NA	NA	1	7.1±2.9	NA

NA = not available, O-ILND = open inguinal lymph node dissection, VE-ILND = video endoscopic inguinal lymph node dissection.

Table 3

Pooled results of perioperative parameters and oncological outcomes.

Parameters and outcomes	No. of studies	Pooled results [95% CI]	*P*	I^2 (%)	Effects model
Operation time	9	−1.21 [−2.40, −0.03]	.050	95	Random
Intraoperative blood loss	6	3.12 [1.27, 4.98]	.001	94	Random
Hospital stay	8	1.77 [0.94, 2.60]	<.001	89	Random
Drainage time	7	2.69 [1.47, 3.91]	<.001	91	Random
Wound infection	7	10.62 [4.01, 28.10]	<.001	22	Fixed
Skin necrosis	6	7.48 [2.79, 20.05]	<.001	0	Fixed
Lymphedema	6	3.23 [1.51, 6.88]	.002	1	Fixed
Lymphocele	6	0.83 [0.31, 2.23]	.720	21	Fixed
Clavien–Dindo I-II complications	4	4.58 [2.08, 10.11]	<.001	0	Fixed
Clavien–Dindo III-IV complications	4	18.75 [4.98, 70.54]	<.001	0	Fixed
Number of lymph nodes	7	0.25 [0.03, 0.47]	.030	0	Fixed
Recurrence	7	1.54 [0.41, 5.84]	.530	0	Fixed

CI = confidence interval.

outcomes were summarized in Table 4 and Supplementary Figure 1 to 3, http://links.lww.com/MD/D14.

3.2. Intraoperative outcomes and postoperative recovery

3.2.1. Operation time and intraoperative blood loss. Nine studies reported the operation time (minutes). The pooled SMD demonstrated that the O-ILND group exhibited a shorter operation time compared with the VE-ILND group (SMD = −1.21, 95% CI [−2.40, −0.03], $P = .050$) (Fig. 2A and B). Significant heterogeneity was detected between these studies ($I^2 = 95\%$; $P < .001$), so a random effects model was used. The heterogeneity may attribute to district and ethnicity differences. Accordingly, subgroup analysis stratified by different ethnicity indicated that the O-ILND group exhibited reduced operation time compared with the VE-ILND group among non-Asian studies (SMD = −0.86, 95% CI [−1.30, −0.42], $P < .001$). However, no significant difference was revealed among Asian studies (SMD = −1.35, 95% CI [−3.03, 0.32], $P = .110$). Six studies reported the blood loss (ml). The result demonstrated that the VE-ILND group experienced significantly reduced intraoperative blood loss compared with the O-ILND group (SMD = 3.12, 95% CI [1.27, 4.98], $P = .001$) (Fig. 2C). Significant heterogeneity existed among these studies ($I^2 = 94\%$, $P < .001$), so a random effects model was applied.

3.2.2. Hospital stay and drainage time. Eight studies reported the hospital stay (day). The pooled SMD demonstrated that the VE-ILND group exhibited a reduced hospital stay compared with the O-ILND group (SMD = 1.77, 95% CI [0.94, 2.60], $P < .001$) (Fig. 2D). Significant heterogeneity was noted between these studies ($I^2 = 89\%$, $P < .001$), so a random effects model was used. Heterogeneity may be caused by different study types. Accordingly, subgroup analysis stratified by study design was performed and revealed a similar trend compared with the overall analysis (prospective study: SMD = 1.32, 95% CI: [0.34, 2.31], $P = .008$; retrospective study: SMD = 2.06, 95% CI: [0.71, 3.40], $P = .003$) (Fig. 2D). Seven studies reported the drainage time. The pooled SMD demonstrated that the VE-ILND group had a shorter drainage time compared with the O-ILND group (SMD = 2.69, 95% CI [1.47, 3.91], $P < .001$) (Fig. 2E). A random-effects model was used given the significant heterogeneity.

3.3. Complications

3.3.1. Skin-related complications: wound infection and skin necrosis. Seven studies reported the wound infection and 6 studies recorded skin necrosis. The pooled OR demonstrated that the VE-ILND group exhibited reduced skin-related complications compared with the O-ILND group (wound infection: OR = 10.62, 95% CI [4.01, 28.10], $P < .001$, Fig. 3A; skin necrosis:

Table 4

Summary of findings table and GRADE recommendations.

	RCT subgroup		non-RCT subgroup	
Primary outcomes	Pooled results [95% CI]	GRADE recommendations	Pooled results [95% CI]	GRADE recommendations
Operation time	−1.40 [−1.90, −0.91]	Low	−1.17 [−2.75, 0.42]	Very low
Intraoperative blood loss	−0.14 [−1.07, 0.78]	Moderate	3.81 [1.76, 5.87]	Low
Hospital stay	1.89 [0.27, 3.51]	Low	1.76 [0.68, 2.85]	Very low
Drainage time	2.16 [−0.64, 4.97]	Low	3.01 [1.36, 4.67]	Low
Wound infection	10.41 [0.53, 202.83]	Low	10.65 [3.81, 29.77]	Low
Skin necrosis	5.14 [0.99, 26.81]	Moderate	8.88 [2.57, 30.70]	Moderate
Lymphedema	1.39 [0.28, 6.83]	Moderate	4.09 [1.70, 9.87]	Low
Lymphocele	NA	NA	0.93 [0.45, 1.93]	Low
Minor complications	4.30 [1.42, 13.00]	Moderate	4.87 [1.57, 15.11]	Low
Major complications	5.36 [0.25, 116.76]	Low	24.00 [5.42, 106.19]	Low
Number of lymph nodes	0.41 [−0.25, 1.07]	Moderate	0.23 [−0.01, 0.47]	Very low
Recurrence	NA	NA	1.54 [0.41, 5.84]	Very low

CI = confidence interval, NA = not available, RCT = randomized controlled trial.

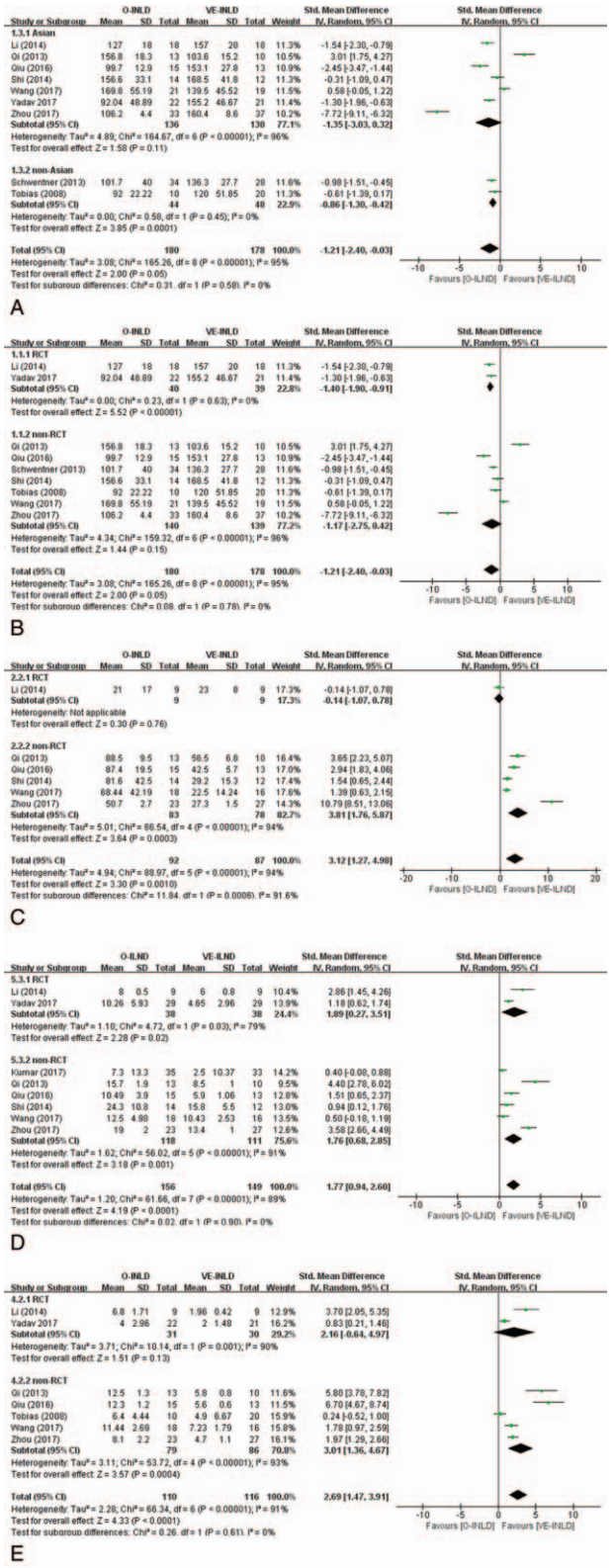

Figure 2. Forest plots for the comparison of intraoperative outcomes and postoperative recovery. (A) Operation time (Asian vs non-Asian); (B) operation time (RCT vs non-RCT); (C) intraoperative blood loss; (D) hospital stay; (E) drainage time. RCT = randomized controlled trial.

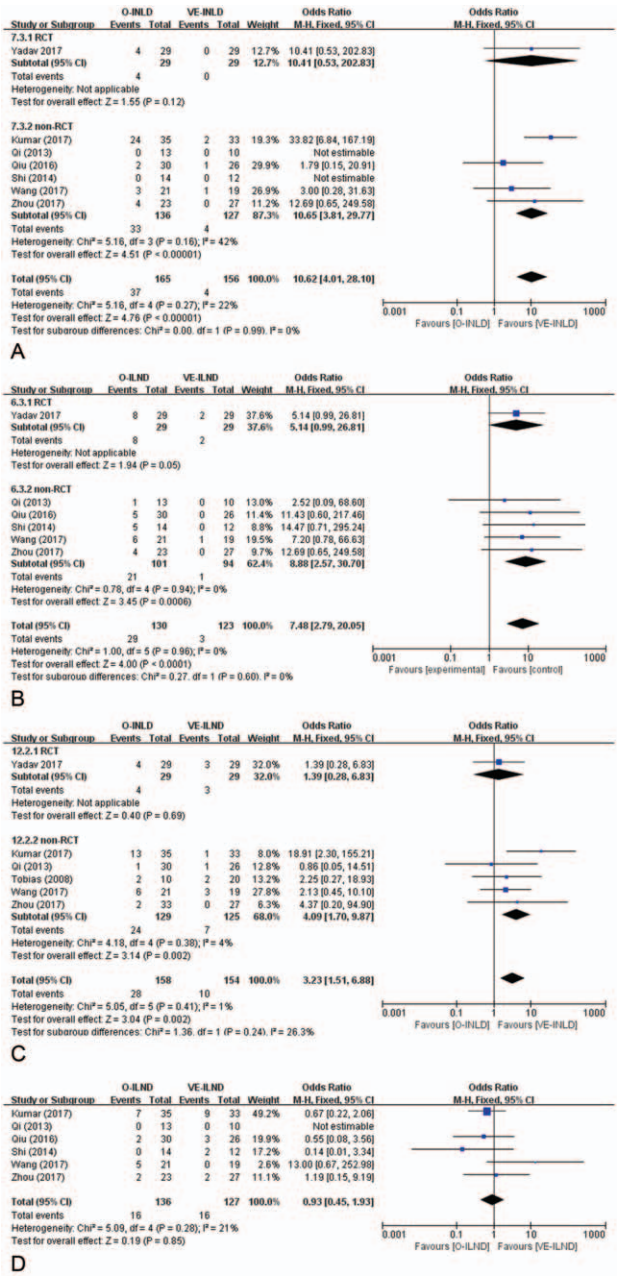

Figure 3. Forest plots for the comparison of complications. (A) Wound infection; (B) skin necrosis; (C) lymphedema; (D) lymphocele.

OR = 7.48, 95% CI [2.79, 20.05], $P < .001$, Fig. 3B). A random-effects model was used because of the acceptable heterogeneity (wound infection: $I^2 = 22\%$, $P = .27$; skin necrosis: $I^2 = 0\%$, $P = .960$).

3.3.2. Lymphatic complications: lymphedema and lymphocele. Six studies reported lymphedema and lymphocele. The pooled OR for lymphedema demonstrated that the VE-ILND group exhibited a reduced lymphedema rate compared with the O-ILND group (OR = 3.23, 95% CI [1.51, 6.88], $P = .002$) (Fig. 3C). A random-effects model was used with acceptable heterogeneity ($I^2 = 1\%$, $P = .41$). However, this beneficial effect of VE-ILND was not observed in terms of the lymphocele

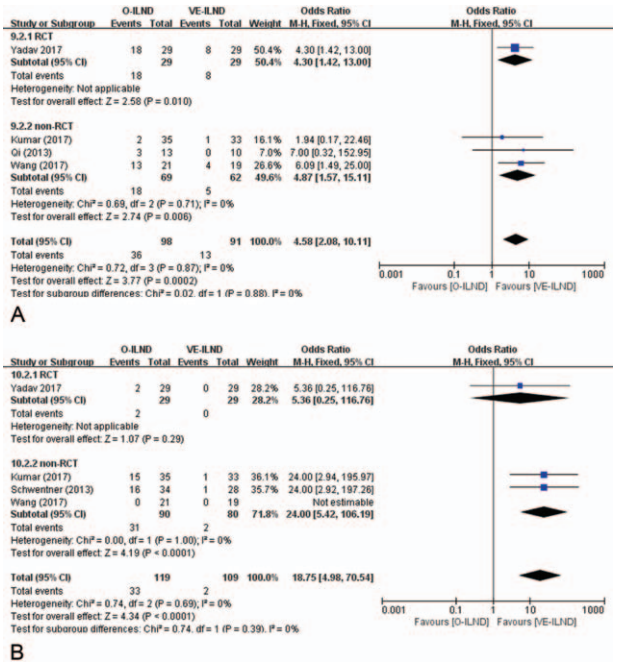

Figure 4. Forest plots for the comparison of overall complications: minor (Clavien–Dindo I-II) complications and major (Clavien–Dindo III-IV) complications. (A) Minor complications; (B) major complications.

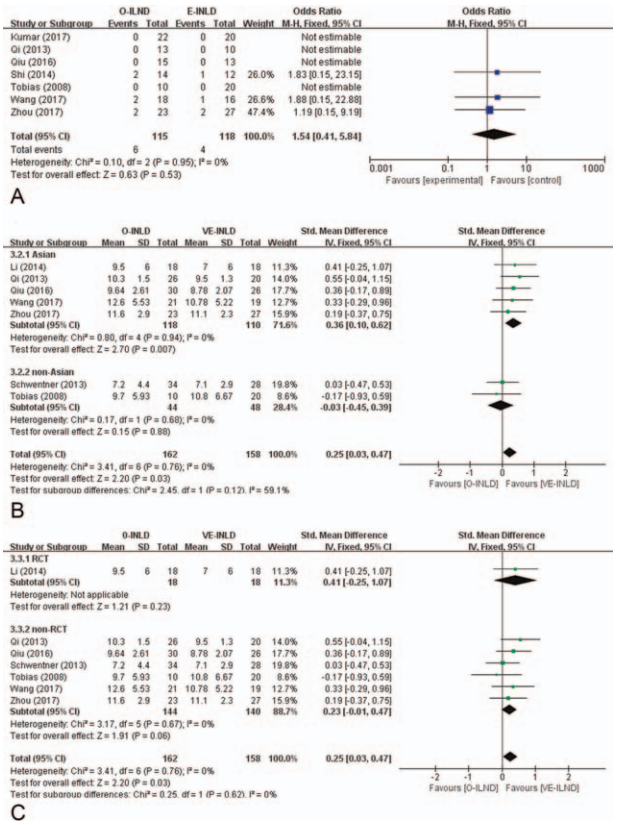

Figure 5. Forest plots for the comparison of oncologic outcomes. (A) Recurrence; (B) the number of dissected nodes (Asian vs non-Asian); (C) the number of dissected nodes (RCT vs non-RCT). RCT = randomized controlled trial.

(OR = 0.83, 95% CI [0.31, 2.23], $P = .720$) (Fig. 3D). A random-effects model was also used with acceptable heterogeneity ($I^2 = 21\%$, $P = .280$).

3.3.3. Overall complications: minor (Clavien–Dindo I-II) complications and major (Clavien–Dindo III-IV) complications. Four studies recorded minor or major complications. We graded the complications as minor or major based on the Clavien–Dindo classification of surgical complications. Pooled OR for minor complications indicated that the VE-ILND group exhibited a lower incidence rate compared with the O-ILND group (OR = 4.58, 95% CI [2.08, 10.11], $P < .001$) (Fig. 4A). A random-effects model was used with no heterogeneity ($I^2 = 0\%$, $P = .87$). Moreover, similar trends for major complications indicated a protective effect of VE-ILND (OR = 18.75, 95% CI [4.98, 70.54], $P < .001$) (Fig. 4B). A random-effects model was also used with acceptable heterogeneity ($I^2 = 0\%$, $P = .690$)

3.4. Oncological outcomes

3.4.1. Number of lymph nodes and recurrence. Seven studies reported the recurrence rate. However, only 3 studies among them contributed to the pooled estimation, and the other 4 studies did not observe any recurrence. The pooled OR for recurrence rate demonstrated no difference between O-ILND and VE-ILND groups (OR = 1.54, 95% CI [0.41, 5.84], $P = .530$) (Fig. 5A). A fixed effects model was used with no heterogeneity ($I^2 = 0\%$, $P = .950$). Seven studies reported the number of dissected lymph nodes. The pooled OR demonstrated that O-ILND group had more dissected lymph nodes compared with the VE-ILND group (SMD = 0.25, 95% CI [0.03, 0.47], $P = .030$) (Fig. 5B and C). Subgroup analysis stratified by different ethnicities indicated that the main differences existed among Asian studies (SMD = 0.36, 95% CI [0.10, 0.62], $P = .007$). No significant differences were observed between non-Asian studies (SMD = −0.03, 95% CI [−0.45, 0.39], $P = .880$).

3.4.2. Sensitivity analysis and bias of included studies. Sensitivity analysis of outcomes was performed using leave-one-out analysis to assess the stability of present meta-analysis results. We found that the pooled estimates did not change significantly when each individual study was sequentially omitted from pooled data. Given the rarity of penile cancer, it was difficult for current studies to achieve random allocation and blind analysis. The bias was presented in Figure 6. Funnel plots evaluating publication bias were presented in Figure 7.

4. Discussion

Radical ILND is recommended for patients with palpable inguinal lymph nodes, who have an approximately 85% risk of inguinal lymph node metastasis.[29,30] In addition, approximately 28% of patients with impalpable lymph nodes harbor micrometastatic disease.[30] For these patients, prophylactic ILND can achieve longer survival compared with other treatment options, such as inguinal radiotherapy and surveillance.[31] However, traditional ILND exhibits significant morbidity related to lymph drainage and wound healing despite the adaptation of many modifications. Therefore, minimally invasive surgery has gradually developed. Bishoff et al first reported endoscopic subcutaneous modified inguinal lymph node dissection.[13] Then, Tobias-Machado et al demonstrated that VE-ILND reduced

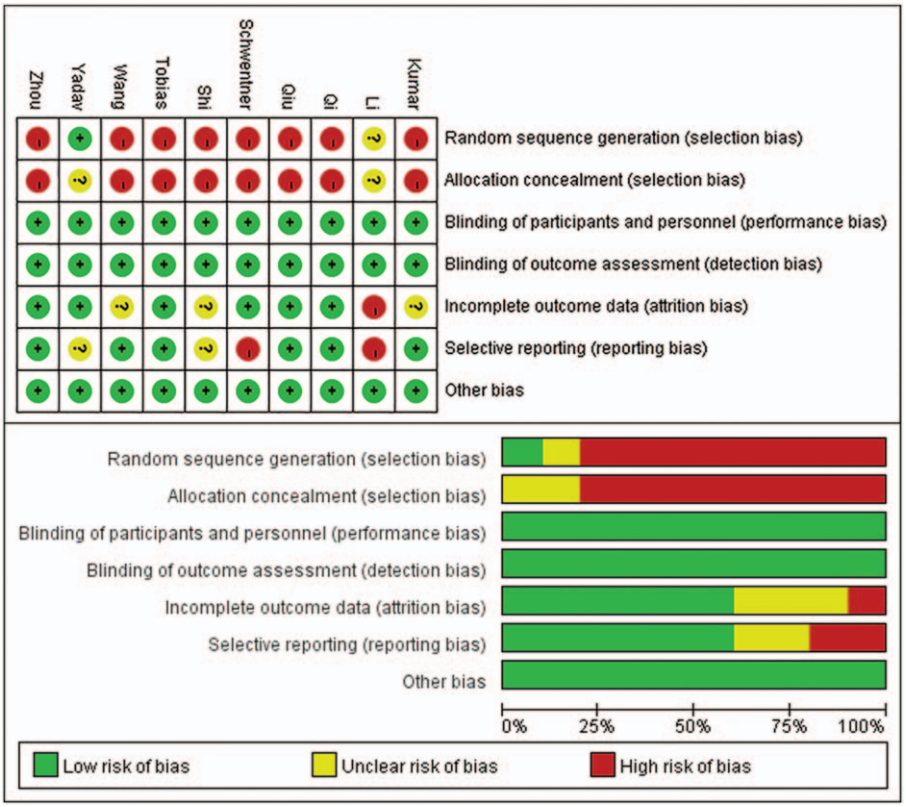

Figure 6. Bias assessment.

postoperative complications with comparable oncological control.[32] However, current evidence is inconsistent and it is difficult to prove whether VE-ILND is superior to conventional open ILND.

Results of the current meta-analysis demonstrated that VE-ILND prolonged the duration of surgery (VE-ILND: mean 134.82 minutes vs O-ILND: mean 116.53 minutes). This difference and corresponding heterogeneity might attribute to the learning curve for the VE-ILND procedure given the rarity of penile cancer. Clinicians typically lack surgical experience at their initial encounter of this rare disease. Accordingly, subgroup analysis results based on different regions revealed no difference between O-ILND and VE-ILND groups among studies from Asia, where the incidence of penile cancer was higher compared with developed countries. Intraoperative blood loss is another pivotal parameter to evaluate the safety of the 2 procedures. The pooled results demonstrated that VE-ILND was superior to O-ILND. This advantage benefits from the amplification effect of the surgical field in the VE-ILND group.

With regards to postoperative recovery, we found that the VE-ILND group exhibited reduced drainage time and hospital stay. Although cross-study heterogeneity existed, all studies revealed that VE-ILND could reduce the drainage time. This heterogeneity might be caused by different standards for removing the drainage tube. For example, Yadav et al removed the drainage tube when the daily output was less than 20 ml.[28] However, Wang et al removed the drainage tube when the daily output was less than 50 ml for 2 days.[22] Similarly, the length of hospital stay between studies was widely variable, ranging from 4 to 24.3 days in the O-ILND group and from 2.5 to 15.8 days in the VE-ILND group. However, pooled results suggested that patients in the VE-ILND group exhibited a reduced hospital stay.

Wound infection, skin necrosis, and lymphedema were the most common postoperative complications.[29] The skin necrosis rate ranged from approximately 16.7% to 36% in the O-ILND group and from 0% to 11.8% in the VE-ILND group. Accordingly, the pooled results demonstrated that VE-ILND was superior to O-ILND in reducing skin necrosis rates. Similarly, the rates of wound infection and lymphedema were also reduced in the VE-ILND group. However, no statistically significant difference in the lymphocele rate was noted between 2 groups, which might be due to the low incidence of lymphocele and the small sample size in the studies. Regarding the Clavien–Dindo complication system, our results demonstrated that VE-ILND could not only reduce the major complication rates but also reduced minor complication rates. For major complications, the pooled OR value reached 18.75.

Many modified techniques had been developed to reduce complications, such as preservation of saphenous vein, fascia lata preservation, use of myocutaneous flap, and avoiding transposition of sartorius.[33–36] Our team also made considerable efforts in this field. For example, we concluded that laparoendoscopic single site inguinal lymphadenectomy could provide better morphological results and comparable safety compared with 3-channel VE-ILND.[11] We demonstrated that saphenous vein preservation could reduce the overall complication rates.[37] In addition, we also demonstrated that video endoscopic inguinal lymphadenectomy via a hypogastric subcutaneous approach was safe and effective, and it could avoid the operation on both the

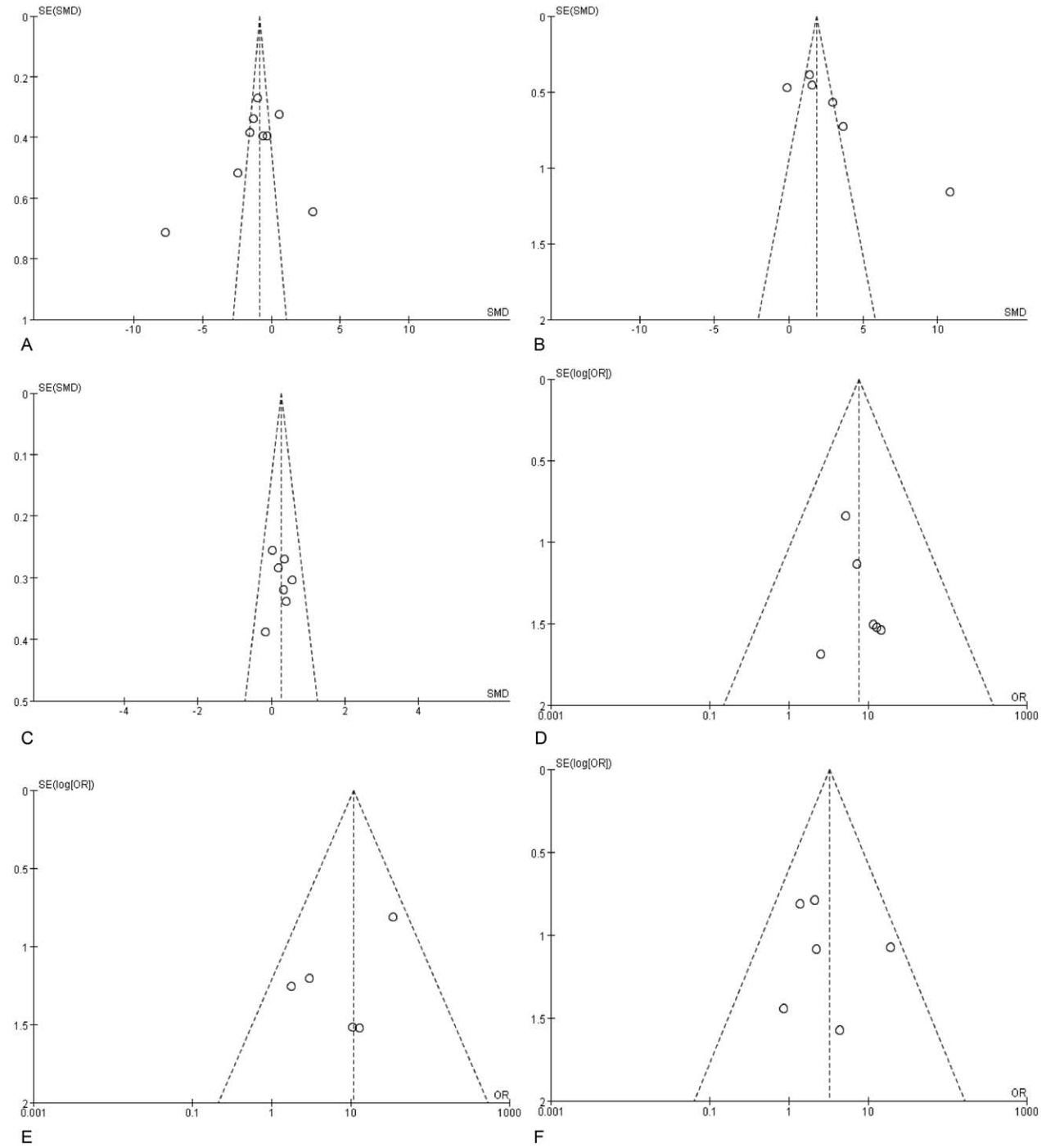

Figure 7. Funnel plots. (A) Operation time; (B) intraoperative blood loss; (C) the number of dissected nodes; (D) skin necrosis; (E) wound infection; (F) lymphedema.

limb and abdomen if simultaneous laparoscopic pelvic lymphadenectomy was required.[38]

Cancer control is decisive for long-term survival for penile cancer patients. Pooled results suggested no difference in the recurrence rate between the 2 groups. However, we can only conclude that there is no difference in tumor recurrence in the short term because of the short follow-up time of some studies. To achieve effective cancer control, the number of removed lymph nodes should be greater than 7.[39] Although the final pooled results revealed that the number of dissected lymph nodes in O-ILND group was slightly increased compared with the VE-ILND group, no significant difference was noted between the 2 groups in all individual studies. The number of dissected lymph nodes of the 2 groups in all included studies was greater than 7, which demonstrated that both groups achieved effective cancer control. Therefore, regarding the number of dissected lymph nodes, we can only conclude that there was no significant difference between the 2 groups according to current evidence. Furthermore, we could not

compare the overall survival or cancer-specific survival because the associated data were sporadic.

There are several limitations should be noted in our current meta-analysis. First, given the rarity of penile cancer, the number of included studies and subjects in our meta-analysis was small, and it is difficult to achieve random allocation or blind analysis, which may be the source of bias. Second, only 2 RCTs were included, and the others were cohort studies. Third, postoperative complications were not clearly defined, which could increase the reporting bias. Moreover, due to the regional differences in penile cancer, most of included studies were from Asia, which could increase the publication bias and heterogeneity.

5. Conclusions

VE-ILND can reduce hospital stay, drainage time, intraoperative blood loss, and postoperative complication rates compared with O-ILND. Two procedures can achieve comparable oncological control in the short term. However, the effects on long-term survival, such as overall survival and cancer-specific survival, require further verification. Due to some methodological limitations, the meta-analysis results must be carefully interpreted and require verification by multicentre, large sample size and prospective RCTs.

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