

OPEN

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

A systematic review and meta-analysis

Jiao Hu, MD^a, Huihuang Li, MD^a, Yu Cui, MD, PhD^a, Peihua Liu, MD, PhD^a, Xu Zhou, MD, PhD^b, Longfei Liu, MD, PhD^a, Hequn Chen, MD^a, Jinbo Chen, MD, PhD^{a,*}, Xiongbing Zu, PhD, MD^{a,*}

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

Editor: Giuseppe Lucarelli.

This work was supported by the National Natural Science Foundation of China (81572523, 81700665), the Hunan Province Funds for Distinguished Young Scientists of China (2016JJ1026), and the Fundamental Research Funds for the Central Universities of Central South University (2016zzts121).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

^a Department of Urology, ^b Reproductive Medicine Center, Xiangya Hospital, Central South University, Changsha, China.

* Correspondence: Xiongbing Zu, and Jinbo Chen, Department of Urology, Xiangya Hospital, Central South University, Changsha, China (e-mails: whzuxb@163.com, chenjinbo1989@yahoo.com).

Copyright © 2019 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2019) 98:22(e15862)

Received: 31 October 2018 / Received in final form: 13 March 2019 / Accepted: 4 May 2019

http://dx.doi.org/10.1097/MD.000000000015862

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.^[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

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

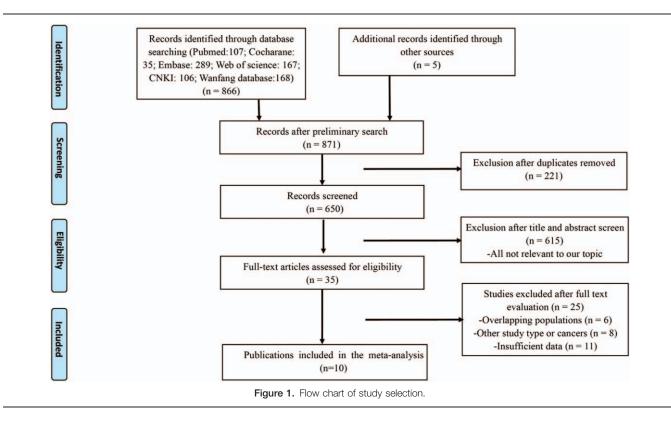
Data of included studies were extracted by 2 independent reviewers (JH and JC). Disagreement was resolved during a consensus meeting with a senior reviewer (XZ). Literature data and demographics, including study type, authors, publication date, sample size, survival analysis, follow-up period, and related 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



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

11-16

Characteristics of publications included in the meta-analysis.

						Patients	S	L	egs		
Author, yr	Study period	Country	Preservation of saphenous vein	Study design	Total	0-ILND	VE-ILND	0-ILND	VE-ILND	Follow-up, mo	Reference
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.

		• molification	ourgical outcomes				Cor	Complications			Oncologic outcomes	utcomes
	Operative ent 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
	92.04 ± 48.89	9 NA	4.65 ± 2.96	4 ± 2.96	4	8	4	NA	8	2	NA	NA
		7 NA	10.26 ± 5.93	2 ± 1.48	0	2	က	NA	18	0	NA	NA
IODIAS (2008) U-ILNU		2 NA	NA	6.4 ± 4.44	Ŋ	NA	2	NA	NA	NA	9.7 ± 5.93	0
VE-ILND	0 120 \pm 51.85	5 NA	NA	4.9 ± 6.67	-	NA	2	NA	NA	NA	10.8 ± 6.67	0
Wang (2017) 0-ILND	169.8 ± 55.19	9 68.44 ± 42.19	12.50 ± 4.98	11.44 ± 2.69	с	9	9	IJ	13	0	12.60 ± 5.53	2
NE-ILND	139.5 ± 45.52	$2 22.50 \pm 14.24$	10.43 ± 2.53	7.23 ± 1.79	-	-	က	0	4	0	10.78 ± 5.22	
Kumar (2016) 0-ILND		NA	7.3 ± 13.3	NA	24	NA	13	7	2	15	7.11	0
NE-ILND	26 C	NA	2.5 ± 10.37	NA	2	NA		6	-		9.36	0
Shi (2014) 0-ILND	156.6 ± 33.1	81.6 ± 42.5	15.8 ± 5.5	NA	0	2	NA	0	NA	NA	NA	2
-	,		24.3 ± 10.8	NA	0	0	NA	2	NA	NA	NA	
Qi (2013) 0-ILND	156.8 ± 18.3		15.7 ± 1.9	12.5 ± 1.3	0	-	0	2	с	NA	10.3 ± 1.5	0
VE-ILND	$0 103.6 \pm 15.2$	56.5 ± 6.8	8.5 ± 1	5.8 ± 0.8	0	0	0	0	0	NA	9.5 ± 1.3	0
Li (2014) 0-ILND	127 ± 18	21 ± 17	8.0 ± 0.5	6.8 ± 1.71	NA	NA	NA	NA	NA	NA	19 ± 6	NA
VE-ILND	0 157 \pm 20	23 ± 8	6.0 ± 0.8	1.96 ± 0.42	NA	NA	NA	NA	NA	NA	14 ± 6	NA
Qiu (2016) 0-ILND	99.7 ± 12.9	87.4 ± 19.5	10.49 ± 3.90	12.3±1.2	2	5		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	-	0		က	NA	NA	8.78 ± 2.07	0
Zhou (2017) 0-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	$0 80.2 \pm 4.3$	27.3 ± 1.5	13.4 ± 1.0	4.7 ± 1.1	0	0	0	2	NA	NA	11.6 ± 2.9	2
Schwentner 0-ILND (2013)	<pre>101.7 ± 40</pre>	NA	NA	NA	NA	NA	15	NA	NA	16	7.2±4.4	NA
VE-ILND	0 136.3±27.7	NA .	NA	NA	NA	NA	0	NA	NA	-	7.1 ± 2.9	NA

Medicine

Table 2

_	Fe 1 a	11-	

Parameters and outcomes	No. of studies	Pooled results [95% CI]	Р	<i>l</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 s	ubgroup	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

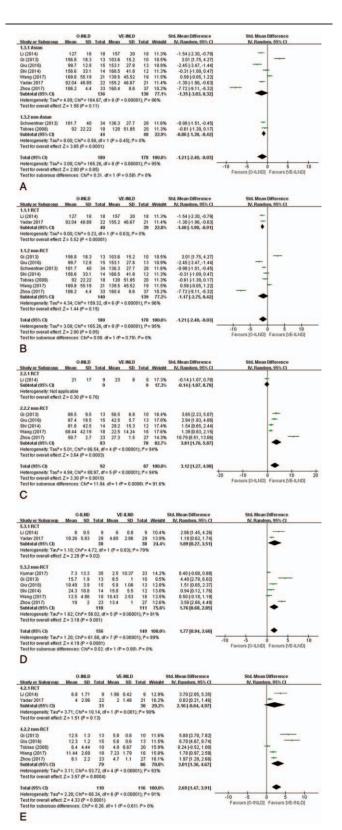


Figure 2. Forest plots for the comparison of intraoperative outcomes and postoperative recovery. (A) Operation time (Asian vs non-Asian); (B) operation time (RCT vs non-RCT); (C) intraoperative blood loss; (D) hospital stay; (E) drainage time. RCT=randomized controlled trial.

Study or Subgroup	0-INL Events		VE-INI Events		Weight	Odds Ratio M-H, Fixed, 95% Cl	Odds Ratio M-H, Fixed, 95% Cl
1.3.1 RCT (aday 2017	4	29	0	29			
adav 2017 Subtotal (95% CI)	4	29	0	29	12.7%	10.41 (0.53, 202.83) 10.41 [0.53, 202.83]	
otal events	4		0		10.11	10.41 [0.35, 202.05]	
leterogeneity: Not ap	oplicable						
est for overall effect	Z= 1.55 (P = 0.1	2)				
.3.2 non-RCT							
umar (2017)	24	35	2	33	19.3%	33.82 [6.84, 167.19]	
ii (2013)	0	13	0	10		Not estimable	
liu (2016)	2	30	1	26	29.9%	1.79 [0.15, 20.91]	
ihi (2014) Vang (2017)	03	14	0	12	26.9%	Not estimable 3.00 (0.28, 31,63)	
hou (2017)	4	23	0	27	11.2%	12.69 [0.65, 249.58]	
subtotal (95% CI)		136		127	87.3%	10.65 [3.81, 29.77]	•
otal events leterogeneity: Chi ^a = est for overall effect:	33 5.16, df = 7 = 4 51 (3 (P =	4 0.16); F=	42%			
otal (95% Cl)		165		156	100.0%	10.62 [4.01, 28.10]	-
otal events	37	100	4	100	10.010/0	and the strend of	
leterogeneity: Chi ^a = est for overall effect	Z= 4.76 (P < 0.0	0001)				0.001 0.1 1 10 100 Favours [0-INLD] Favours [VE-INLD]
est for subaroup diff	ferences:	Chr = I	J.UU. df =	1 (P=	0.99). (*=	0%	
4							
tudy or Subgroup	O-ILNI Events	D Total	VE-ILN Events	D Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% Cl
.3.1 RCT							
/adav 2017 Subtotal (95% CI)	8	29	2	29 29	37.6%	5.14 [0.99, 26.81] 5.14 [0.99, 26.81]	
Total events	8	29	2	29	31.07	2.14 [0.23, 20.81]	
Heterogeneity: Not ap Test for overall effect	plicable	P = 0.05					
.3.2 non-RCT							
0 (2013)	1	13	0	10	13.0%	2.52 [0.09, 68.60]	
Diu (2016)	5	30	0	26	11.4%	11.43 [0.60, 217.46]	
Shi (2014) Vang (2017)	5	14	0	12	8.8%	14.47 [0.71, 295.24] 7.20 [0.78, 66.63]	
thou (2017)	4	23	0	27	9.7%	12.69 10.65, 249.58	
Subtotal (95% CI)		101	-	94	62.4%	8.88 [2.57, 30.70]	-
Total events	21	a second	1				
Heterogeneity: Chi ² = Test for overall effect:	0.78, df = Z = 3.45 (F	4 (P = 0) P = 0.00	1.94); I*= 006)	0%			
fotal (95% CI)		130		123	100.0%	7.48 [2.79, 20.05]	-
Total events Heterogeneity: Chi ^a =	29	6 /P - *	3	0%			
Test for overall effect.	7 = 4.00 (8	< 0.00	001)	0.20		(0.001 0.1 1 10 100
				0-0	000 10-1		Favours [experimental] Favours [control]
Test for subaroup diffe	erences: C	hi ^z = 0	27. df = 1	(P=0	1.60). (*= (0%	Favours [experimental] Favours [control]
Test for subaroup diffe	erences: C	hi*= 0	.27. df = 1		1.60). I ^a = (Martin Control and Control of Control
Fest for subaroup diffe B Study or Subgroup	O-INL Events	.D	27. df = 1	ND		Odds Ratio	Odds Ratio
Test for subaroup difference of the subaroup subaroup subaroup 12.2.1 RCT	erences: C	D Total	27. df = 1 VE-ILI Events	ND Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Manager and the second state
Test for subaroup diff B Study or Subgroup 12.2.1 RCT Yaday 2017	erences: C	D Total 29	27. df = 1	ND Total 29	Weight 32.0%	Odds Ratio M-H, Fixed, 95% Cl 1.39 (0.28, 6.83)	Odds Ratio
Test for subgroup difference of subgroup diff	o-INL O-INL Events 4	D Total	27. df = 1 VE-ILI Events 3	ND Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio
Fest for subaroup diff B Study or Subgroup 12.2.1 RCT /aday 2017 Subtotal (95% CI) Fotal events teterogeneity: Not ap	O-INL Events 4 applicable	D Total 29 29	27. df = 1 VE-ILLI Events 3 3	ND Total 29	Weight 32.0%	Odds Ratio M-H, Fixed, 95% Cl 1.39 (0.28, 6.83)	Odds Ratio
Fest for subgroup diff Study or Subgroup 12.2.1 RCT (a day 2017 Subtotal (95% CI) Total events Heterogeneity: Not ag Fest for overall effect	O-INL Events 4 applicable	D Total 29 29	27. df = 1 VE-ILLI Events 3 3	ND Total 29	Weight 32.0%	Odds Ratio M-H, Fixed, 95% Cl 1.39 (0.28, 6.83)	Odds Ratio
Fest for subgroup diff B Study or Subgroup 12.2.1 RCT (aday 2017 Subtotal (95% CI) Total events -deterogeneity: Not ag Fest for overall effect: 12.2.2 non-RCT	O-INL Events 4 oplicable Z = 0.40 (D Total 29 29 29	27. df = 1 VE-ILI Events 3 3 99	ND Total 29 29	Weight 32.0% 32.0%	Odds Ratio M.H. Fixed, 95% CI 1.39 [0.28, 6.83] 1.39 [0.28, 6.83]	Odds Ratio
Fest for subarous diff Study or Subarous 12.2.1 RCT (aday 2017 Subtotal (95% CI) Total events Heterogeneity: Not ag Fest for overall effect: 12.2.2 non-RCT (umar (2017)	O-INL Events 4 applicable	D Total 29 29 29 29	27. df = 1 VE-ILLI Events 3 3	ND <u>Total</u> 29 29	Weight 32.0% 32.0% 8.0%	Odds Ratio M-H, Fixed, 95% CI 1.39 [0.28, 6.83] 1.39 [0.28, 6.83] 18.91 [2.30, 155.21] 0.66 [0.05, 14.51]	Odds Ratio
Fest for subarous diff B Study of Subgroup 12.2.1 RCT (aday 2017 Subtotal (95% CI) Total events releforgeneity. Not ap releforgeneity. Not ap	O-INL Events 4 4 oplicable 2 = 0.40 (13 1 2	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILLI <u>Events</u> 3 3 99)	ND Total 29 29 29 33 26 20	Weight 32.0% 32.0% 8.0% 12.8% 13.2%	Odds Ratio M-H. Fixed, 95% CI 1.39 [0.28, 6.83] 1.39 [0.28, 6.83] 18.91 [2.30, 155.21] 0.66 [0.05, 14.51] 2.25 [0.27, 18.93]	Odds Ratio
Feit for subaroue diff B Stuck or Subgroup 12.2.1 RCT fadav 2017 fadav 2017 fotal events telerogenetic. Not a fest for overall effect 12.2.2 non RCT cumar (2017) to (2013) fobias (2008) Nang (2017)	O-INL Events 4 4 oplicable Z = 0.40 (13 1 2 6	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL Events 3 3 99)	ND Total 29 29 33 26 20 19	Weight 32.0% 32.0% 8.0% 12.8% 13.2% 27.8%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 18,91 (2.30, 165 21) 0.86 (0.05, 14.51) 2.25 (0.27, 16.33) 2.13 (0.45, 10.10)	Odds Ratio
Fest for subarous diff B Study of Subarous 12.2.1 RCT (adar 2017 Subtotal (95% CI) Fotal events telerogeneity. Not ag fest for overall effect 12.2.2 non-RCT sumar (2017) bit (2013) fotals (2009) Wang (2017) hou (2017)	O-INL Events 4 4 oplicable 2 = 0.40 (13 1 2	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILLI <u>Events</u> 3 3 99)	ND Total 29 29 29 33 26 20	Weight 32.0% 32.0% 8.0% 12.8% 13.2%	Odds Ratio M-H, Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 18,91 (2.30, 155 21) 0.86 (0.05, 14.51) 2.25 (0.27, 18.33) 2.13 (0.45, 10.10) 4.37 (0.29, 04.90)	Odds Ratio
Feit for subarous diff B Study of Subarous 12.2.1 RCT (adar 2017 Subtotal (95% CI) Fotal events fest for overall effect 12.2.2 non-RCT sumar (2017) bit (2013) fotals (2008) Wang (2017) Subtotal (95% CI) Subtotal (95% CI) Subtotal (95% CI)	O-INL Events 4 4 oplicable Z = 0.40 (13 1 2 6 2 2 24	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL Events 3 3 99 1 1 2 3 0 7	ND Total 29 29 29 33 26 20 19 27 125	Weight 32.0% 32.0% 8.0% 12.8% 13.2% 27.8% 6.3%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 18,91 (2.30, 165 21) 0.86 (0.05, 14.51) 2.25 (0.27, 16.33) 2.13 (0.45, 10.10)	Odds Ratio
Feet for suberoue diff B Study of Subgroup 12,2,1 RCT 7 date 2017 Subtotal (95% C) Total events Heterogeneity, Not ap Feet for overall effect 12,2,2 non.RCT Kumar (2017) Totals (2008) Nang (2017) Total sc(2008) Nang (2017) Total events Heterogeneity, Chit ² =	0-INI Events 4 4 4 4 4 4 4 5 5 6 2 2 4 4.18, df=	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL Events 3 3 9) 1 1 2 3 0 7 0.38); P=	ND Total 29 29 29 33 26 20 19 27 125	Weight 32.0% 32.0% 8.0% 12.8% 13.2% 27.8% 6.3%	Odds Ratio M-H, Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 18,91 (2.30, 155 21) 0.86 (0.05, 14.51) 2.25 (0.27, 18.33) 2.13 (0.45, 10.10) 4.37 (0.29, 04.90)	Odds Ratio
Test for subarous diff B Study of Subarous 12.2.1 RCT radae 2017 Subotal (95% CI) folal events relation overall effect 12.2.2 Non-RCT (2017) Dir (2017) Dir (2017) Subtotal (95% CI) Subtotal (95% CI) Heterogeneity: Chif = Test for overall effect Total (95% CI)	O-INL Events 4 4 0plicable Z = 0.40 (13 1 2 6 2 2 4 4.18, df = Z = 3.14 (D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL Events 3 3 99 1 1 2 3 0 1 1 2 3 0 7 0.389; P*= 102)	ND Total 29 29 33 26 20 19 27 125 4%	Weight 32.0% 32.0% 8.0% 12.8% 13.2% 27.8% 6.3%	Odds Ratio M-H, Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 18,91 (2.30, 155 21) 0.86 (0.05, 14.51) 2.25 (0.27, 18.33) 2.13 (0.45, 10.10) 4.37 (0.29, 04.90)	Odds Ratio
Feel for subarous diff B Study of Subarous 12.2.1 RCT factor 2017 Subtrat (SS-G) Total events teterogenetic, Not ar Test for overall effect 12.2.2 non-RCT Kumar (2017) Totals (2013) Totals (2013) Totals (2013) Totals (2013) Totals (2017) Subtrat (SS-RC) Factor overall effect feel for overall effect Total events	C-INIL Events 4 4 opticable Z = 0.40 (13 1 2 6 2 2 4 4.18, df = Z = 3.14 (28	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL Events 3 3 9) 1 1 2 3 0 7 0.38); I* 10 2)	ND Total 29 29 33 26 20 19 27 125 4%	Weight 32.0% 32.0% 8.0% 12.8% 13.2% 6.3% 68.0%	Odds Ratio M.H. Fixed, 95%, CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.8, 91 (2.20, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.10) 4.37 (0.20, 94.50) 4.09 (1.70, 9.87)	Oddis Ratio
Feel for suberoue diff B Study of Subgroup 12.2 FRCT radias 2017 Subtrat (95% Ch) Total events Heterogeneity: Analy Aumar (2017) al (2013) Totals events Heterogeneity: Chi ² = Feel for overall effect Total events Heterogeneity: Chi ² = Feel for overall effect	C-INIL Events 4 4 4 4 4 0plicable Z = 0.40 (13 1 2 5 2 2 4 4.18, df Z = 3.14 (2 2 24 4.18, off Z = 3.14 (2 2 3.14 (2 2 3.14 (2 2 3.14 (2 3.14 (2 3.14 (2 3.14 (3 3.14 (3 3.14))) (1)) (1)) (1)) (1)) (1)) (1)) (1)) (D Total 29 29 P = 0.6 35 30 10 21 33 31 29 4 (P = P = 0.0 158 5 (P = P = 0.0	27. df= 1 VE-ILL Events. 3 3 3 99) 1 1 2 3 0 0 9) 1 1 2 3 0 0 0 1 0 1 0 1 0 0 0 0 1 0 1 0 0 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND <u>Total</u> 29 29 29 33 26 20 19 9 27 125 4% 154 154 154	Weight 32.0% 32.0% 12.8% 13.2% 27.8% 63.0% 100.0%	Odds Ratio M.H. Pixed, 95%, CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.39 (0.25, 14.51) 2.39 (0.25, 0.450) 4.09 (1.70, 9.87) 3.23 (1.51, 6.88)	Odds Ratio
réet for subarous diff B Study or Subarous 12.2.1 RCT rdate 2017 rdate 2017 real services fest for overall effect 12.2.2 mon.RCT sumar (2017) al (2013) robus (2008) wang (2017) robus (2008) robus (2008)	C-INIL Events 4 4 4 4 4 0plicable Z = 0.40 (13 1 2 5 2 2 4 4.18, df Z = 3.14 (2 2 24 4.18, off Z = 3.14 (2 2 3.14 (2 2 3.14 (2 2 3.14 (2 3.14 (2 3.14 (2 3.14 (3 3.14 (3 3.14))) (1)) (1)) (1)) (1)) (1)) (1)) (1)) (D Total 29 29 P = 0.6 35 30 10 21 33 31 29 4 (P = P = 0.0 158 5 (P = P = 0.0	27. df= 1 VE-ILL Events. 3 3 3 99) 1 1 2 3 0 0 9) 1 1 2 3 0 0 0 1 0 1 0 1 0 0 0 0 1 0 1 0 0 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND <u>Total</u> 29 29 29 33 26 20 19 9 27 125 4% 154 154 154	Weight 32.0% 32.0% 12.8% 13.2% 27.8% 63.0% 100.0%	Odds Ratio M.H. Pixed, 95%, CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.29 (0.27, 18.33) 2.39 (0.25, 14.51) 2.39 (0.25, 0.450) 4.09 (1.70, 9.87) 3.23 (1.51, 6.88)	Odds Platio MH, Fixed, 95% CI
eit for subarous diff B Links of Sabarous 2.2.1 RCT data 2017 data with density of the second density of th	O-INU Events. 4 4 4 4 4 9 9 13 1 2 2 4 4.18, d= 2 2 4 4.18, d= 2 2 4 4.18, d= 2 2 3.14 (2 8 5.05, d= 2 2.3.14 (2 8 5.2, d= 2.3.14 (2 8 5.2, d= 2.4,	D Total 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df= 1 VE-4LL Events 3 3 3 99) 1 1 2 3 0 0 7 7 0.38); P+ 1 0 0 0 1 0 0 1 0 3 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 1 2 3 0 0 1 1 1 2 3 0 0 1 1 1 2 1 2 1 3 0 0 1 1 1 2 1 3 0 0 1 1 1 1 1 2 1 3 0 0 1 1 1 1 2 1 3 0 0 1 1 1 1 2 3 0 0 1 1 1 2 1 1 1 2 1 3 0 1 1 1 2 1 3 0 1 1 1 2 1 3 0 1 1 1 1 2 1 3 0 1 1 1 1 2 1 3 0 1 1 1 1 2 1 3 0 1 1 1 1 1 1 2 1 3 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND Total 29 29 33 26 20 19 27 125 = 4% 154 = 1% 1 (P =	Weight 32.0% 32.0% 12.8% 13.2% 27.8% 63.0% 100.0%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 0.88 (0.05, 14, 51) 0.88 (0.05, 14, 51) 2.13 (0.45, 10, 15, 52, 11) 0.88 (0.05, 14, 51) 2.13 (0.45, 10, 15, 52, 12) 3.13 (0.45, 10, 15, 52, 12) 3.13 (0.45, 10, 15, 52, 12) 3.23 (1.51, 6.88) 3.23 (1.51, 6.88)	Oddis Ratio MH, Fixed 95% CI
réet for subaroue diff B Study of Subaroup 12.2.1 RCT radw 2017 Statewents telerogenetic (VSI) Gala events telerogenetic (VSI) ai (2013) constat (SSI) constat (SSI) constat (SSI) constat (SSI) telerogenetic (Chi* rest for overall effect feat for overall effect	C-INU Events: C 2	D Total 29 29 29 29 29 29 29 29 29 29	27. df= 1 VE-4LL Events 3 3 3 99) 1 1 2 3 0 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 0 1 1 1 2 1 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND Total 29 29 33 26 20 19 27 125 125 125 154 10P =	Weshiht 32.0% 32.0% 12.8% 52.2% 68.0% 100.0%	Odds Ratio M.H. Freed, 95% CT 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.80 (0.5, 14, 51) 2.13 (0.45, 0.15, 2.71) 0.88 (0.05, 14, 51) 2.13 (0.45, 10, 15, 2.71) 4.37 (0.20, 94.60) 4.37 (0.20, 94.60) 4.00 (1.70, 9.87) 3.23 (1.51, 6.88) 2.6, 3%	Odds Ratio M.H. Freed, 95% CI
réet for subaroue diff B Study of Saharosa 12,21 RCT (adas 2017 Suthotal (SS-G) Total events sterosares (SS-G) Total events sterosares (SS-G) Total events sterosares (SS-G) Total events telerogenetic, Chir sterosares (SS-G) Total events telerogenetic, Chir sterosares (SS-G) Total events telerogenetic, Chir sterosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares telerosares	O-INU Events. 4 4 4 4 4 9 9 13 1 2 2 4 4.18, d= 2 2 4 4.18, d= 2 2 4 4.18, d= 2 2 3.14 (2 8 5.05, d= 2 2.3.14 (2 8 5.2, d= 2.3.14 (2 8 5.2, d= 2.4,	hi*=0 D Total 29 29 P=0.6 35 30 10 21 33 129 P=0.0 158 5 (P= P=0.0 Chi*= D Total	27. df= 1 VE-ALL Prents 3 3 3 3 3 9 9 1 1 2 2 3 0 0 3 9 9 1 1 2 3 0 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 2 3 0 0 1 1 1 2 3 0 0 1 1 1 1 2 3 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND Total 29 29 33 26 20 19 27 125 = 4% 154 = 1% 1 (P = ND Total	Weight 32.0% 32.0% 12.8% 13.2% 63.0% 63.0% 63.0% 100.0% 0.24), P= Weight	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 16, 91 (2.20, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.55) 2.13 (0.45, 10.55) 2.13 (0.45, 10.55) 3.23 (1.51, 6.88) 3.23 (1.51, 6.88) 2.6, 3%	Odds Ratio MH, Fixed 95% CI
réet for subaroue diff B Study or Subaroue diff (22.2.1 RCT radar 2017) State vents feator overall effect (22.2.2 non-RCT (2017) State vents feator overall effect (22.2 non-RCT (2017) Subtotal (95% CD) Subtotal (95% CD) rotal events feator overall effect feator overall effect (22.2 march overall effect feator overall effect	C-INU Events: C 2	D Total 29 29 29 29 29 29 29 29 29 29	27. df= 1 VE-4LL Events 3 3 3 99) 1 1 2 3 0 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 1 1 2 3 0 0 0 0 1 1 1 2 1 0 0 0 0 0 1 1 1 1 1 1 1 1 1 1 1 1 1	ND Total 29 29 33 26 20 19 27 125 125 125 154 10P =	Weshiht 32.0% 32.0% 12.8% 52.2% 68.0% 100.0%	Odds Ratio M.H. Freed, 95% CT 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.80 (0.5, 14, 51) 2.13 (0.45, 0.15, 2.71) 0.88 (0.05, 14, 51) 2.13 (0.45, 10, 15, 2.71) 4.37 (0.20, 94.60) 4.37 (0.20, 94.60) 4.00 (1.70, 9.87) 3.23 (1.51, 6.88) 2.6, 3%	Odds Ratio M.H. Freed, 95% Cl
réet for subaroue diffi B Study of Subarcoun 12.2.1 RoCT (aday 2017 Subtoat (85% Ct) Total events deterogenetik, Not ag fest for overall effect 12.2.2 non RCT sumar (2017) at (2013) subtoat (85% Ct) Total events deterogenetik, Ctar ² fest for overall effect fest for overall effect fest for overall effect fest for subarcound aff C Study of Subarcound Sumar (2017) at (2013) Sumar (2017) at (2013) Sumar (2017) at (2013) at (2013) at (2013) at (2015)	O-IRIR Events 4 4 4 4 4 4 9 9 505, 12 2 2 2 2 4 4 13 1 1 2 6 2 2 2 2 2 2 2 2 4 505, 13 1 505, 13 2 2 2 2 2 2 2 2 3 14 1 2 2 5 5 5 15 1 5 15 15 15 15 15 15 15 15 15	hr#=0 D Total 29 29 29 29 29 29 29 29 29 29	VE-ALL Events. 3 3 3 99) 1 1 2 3 3 3 99) 1 1 2 3 3 0 0 7 1 0 0 0 1 1 2 3 3 0 0 0 0 1 1 2 3 3 3 3 99) 1 1 2 3 3 3 99) 1 1 2 3 3 0 0 0 0 1 1 2 3 3 0 0 0 0 1 1 2 3 3 0 0 0 0 1 1 2 3 3 0 0 0 0 1 1 1 2 3 3 0 0 0 0 1 1 1 2 3 1 0 0 0 0 1 1 1 2 3 1 0 0 0 0 1 1 1 2 3 1 0 0 0 0 1 1 1 2 3 1 0 0 0 0 1 1 1 2 3 1 0 0 0 1 1 1 2 3 1 0 0 0 0 1 1 1 1 2 3 1 0 0 0 1 1 1 1 2 3 1 0 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	ND <u>Total</u> 29 29 29 29 29 29 29 29 29 29	Weight 32.0% 32.0% 12.8% 8.0% 13.2% 8.3% 68.0% 100.0% 0.24). P= <u>Weight</u> 49.2% 19.9%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.89 (1.230, 165.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.23, 10.	Odds Platio MH, Freed, 95% Cl
réet for subaroue diff B Study of Subarous 122,3 / RCT (xise 2017 Subtrat (15% C)) Total events teterogeneity: Not ag fest for overall effect 122,2 non.RCT (umar (2017) al (2013) robais (2009) Nang (2017) Robu (2017) Subtrat (PS% C)) Fest for overall effect Fest for subarous diff C Study of Subarous diff C Study of Subarous diff C Study of Subarous diff C Study of Subarous diff Subarous	O.IRU Events 4 4 4 4 4 5 5 5 5 5 6 7 7 7 7 7 2 2 2 2 8 4 4 13 1 2 2 2 2 3 14 4 5 15 5 15 6 17 7 7 7 2 0 2 0 2 0 2 0 10 10 10 10 10 10 10 10 10 10 10 10 1	hr#=0 D Total 29 29 P=0.6 30 10 21 31 31 29 29 4 (P=0.0 5 (P=0.0 5 (P=0.0 5 (P=0.0 5 (P=0.0 5 30 10 21 129 9 9 9 9 9 9 9 9 9 9 9 9 9	27. df = 1 27. df = 1 2007 2007 2007 2007 2007 2007 2007 2007	ND <u>Total</u> 29 29 33 26 20 19 27 125 = 4% 154 1 (P = <u>Total</u> 33 10 26 20 19 27 125 = 4% 154 10 20 20 20 20 20 20 20 20 20 2	Weight 32.0% 32.0% 12.8% 68.0% 100.0% 0.24), P: Weight 49.2% 19.9%	Odds Ratio M.H. Freed, 95%, Cf 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 2.13 (0.45, 10.55, 21) 0.36 (0.05, 14.51) 2.13 (0.45, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10.15, 10	Odds Platio MH, Freed, 95% Cl
réet for subaroue diff B Study of Subarcoun 12.2.1 RoCT (adae 2017 Subtoat (8% c)) Total events deterogenetik, Not ag fest for overall effect 12.2.2 non RCT sumar (2017) at (2013) at (2013) at (2013) at (2013) subtoat (8% c)) Total events deterogenetik, Chir# fest for overall effect fest for subaroun diff C Subtoa (2015) at (2013) at (2014) Nang (2017)	O-IRM, Events Events 4 4 4 4 4 4 12 26 6 22 44.18, df= 28 25.05, df= 28 5.05, df= 7 0 20 0 5	hr#=0 D Total 29 29 29 29 29 29 29 29 29 29 29 20 20 21 33 30 10 21 33 31 29 4 (P = 0.6 6 21 33 31 29 29 29 29 29 29 29 29 29 29 29 29 29	VE-ILL 27. df = 1 VE-ILL 2007 1 1 2 2 3 3 3 3 3 3 3 3 3 3 3 3 3	ND <u>Total</u> 29 29 29 33 26 20 19 27 125 = 4% 154 = 1% 1 (P = ND <u>Total</u> 33 10 26 12 19 19 10 10 10 10 10 10 10 10 10 10	Weinht 32 0% 32.0% 32.0% 12.8% 12.8% 5.3% 68.0% 100.0% 0.24). P= 49.2% 19.9% 17.2% 2.6%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.99 (0.28, 6.83) 1.89 (0.28, 6.83) 18, 91 (2.30, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23) 1.13 (0.45, 0.25, 0.25) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 0.0445 Ratio M.H. Fixed, 95% CI Not estimate 0.55 (0.80, 3.56) 0.41 (0.01, 3.34) 0.55 (0.80, 3.56) 0.41 (0.01, 3.54) 0.55 (0.80, 3.56) 0.55 (0.80, 3.56	Odds Platio MH, Freed, 95% Cl
Test for subarous diff B Study of Shahprosen 12.2.1 RoCT (radae 2017 Suitotat (8% c)) Total events test for overall effect 12.2.2 mon.RCT Kumar (2017) 101 (2013) 101 (2013) 1	O.IRU Events 4 4 4 4 4 5 5 5 5 5 6 7 7 7 7 7 2 2 2 2 8 4 4 13 1 2 2 2 2 3 14 4 5 15 5 15 6 17 7 7 7 2 0 2 0 2 0 2 0 10 10 10 10 10 10 10 10 10 10 10 10 1	hi*=0 D Total 29 29 29 29 29 29 29 29 29 29 33 30 10 21 33 129 4 (P= P=0.0 158 5 (P= P=0.0 Chi*= 1 D Total 30 30 21 23	27. df = 1 27. df = 1 2007 2007 2007 2007 2007 2007 2007 2007	ND Total 29 29 29 29 29 29 27 125 125 154 154 1 (P = 154 1 (P = 154 1 (P = 154 1 (P = 154) 20 125 125 125 125 125 125 125 125 125 125	Weight 32.0% 32.0% 32.0% 12.2% 5.3% 68.0% 100.0% 0.24). P: 49.2% 49.2% 11.9% 11.1%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.89 (0.28, 6.83) 18, 91 (2.30, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23) 1.13 (0.45, 0.25, 0.25) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 0.45 (0.80, 3.56) 0.44 (0.01, 3.34) 0.57 (0.27, 22.99) Not estimated Not estimated 0.41 (0.01, 3.34) 0.41 (0.01, 3.54) 0.41 (0.01, 3.	Odds Ratio M.H. Freed, 95% Cl
réet for subaroue diff B 22.2 i RCT 12.2 Rom-RCT umar (2017) 10.1012 i RCT 12.2 Rom-RCT 12.2	erences: C O-IRM, Events: 4 4 4 4 4 4 4 4 4 4 4 4 4 4 8 6 6 2 2 4 4 4 8 6 6 2 2 4 4 4 8 6 6 2 2 4 4 4 8 6 6 2 2 4 4 4 8 5 5 6 6 7 7 7 7 7 0 8 8 7 7 8 9 7 8 9 7 8 7 8 7 7 7 8 7 7 8 7 7 7 7	hr#=0 D Total 29 29 29 29 29 29 29 29 29 29 29 20 20 21 33 30 10 21 33 31 29 4 (P = 0.6 6 21 33 31 29 29 29 29 29 29 29 29 29 29 29 29 29	27. df = 1 VE-ILL 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 2007 200	ND <u>Total</u> 29 29 29 33 26 20 19 27 125 = 4% 154 = 1% 1 (P = ND <u>Total</u> 33 10 26 12 19 19 10 10 10 10 10 10 10 10 10 10	Weight 32.0% 32.0% 32.0% 12.2% 5.3% 68.0% 100.0% 0.24). P: 49.2% 49.2% 11.9% 11.1%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.99 (0.28, 6.83) 1.89 (0.28, 6.83) 18, 91 (2.30, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23) 1.13 (0.45, 0.25, 0.25) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 0.0445 Ratio M.H. Fixed, 95% CI Not estimate 0.55 (0.80, 3.56) 0.41 (0.01, 3.34) 0.55 (0.80, 3.56) 0.41 (0.01, 3.54) 0.55 (0.80, 3.56) 0.55 (0.80, 3.56	Odds Platio MH, Freed, 95% Cl
réet for subaroue diff B Study of Subaroue 12,23 F6CT (adax 2017 Subtotal (5% Ch Total events teterogenetik, Not ag fest for overall effect 12,22 non.RCT sumar (2017) bit (2013) Totals (2008) Wang (2017) hou (2017) hou (2017) hou (2017) hou (2017) hou (2017) hou (2017) hou (2017) hou (2017) fest for overall effect fest for overall effect fest for subaroue diffect fest for subaroue diffect for (2017) hou (2017) hou (2017) hou (2017) for (2017) hou (2017) for (2017) hou (2017) for (2017) hou (201	erences: 0 0-3984 Events: 4 4 4 4 4 4 4 4 9 9 2 2 0 4 13 1 2 2 2 2 2 4 4 4 4 5 2 2 2 4 4 4 5 5 5 6 6 6 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7	Total 29 29 35 30 113 31 32 4 P=0.0 158 5 P=0.0 Chi#= 10 158 5 (P=0.0 Chi#= 10 133 30 136	27. df = 1 VE-ILL <u>Events</u> 3 3 3 9 9 1 1 1 2 3 3 3 9 9 1 1 1 2 3 3 3 9 9 1 1 1 2 3 3 0 0 1 1 1 2 3 3 0 9 9 1 1 1 2 3 3 0 0 1 1 1 2 3 3 0 0 0 1 1 1 2 3 0 0 0 1 1 1 2 3 0 0 0 1 1 1 2 3 0 0 0 1 1 1 2 3 0 0 0 1 1 1 2 3 0 0 0 1 1 1 1 2 3 0 0 0 1 1 1 1 2 3 0 0 0 1 1 1 1 2 3 0 0 0 1 1 1 1 2 3 0 0 0 1 1 1 1 2 3 0 0 0 1 1 1 1 1 2 3 0 0 0 1 1 1 1 1 2 1 1 1 1 1 1 1 1 1 1 1 1 1	ND Total 29 29 29 29 19 27 127 154 1 (P = ND 26 20 0 19 27 154 1 (P = ND 26 20 19 27 154 10 10 27 127 127 127 127 127 127 127	Weight 32.0% 32.0% 32.0% 12.2% 5.3% 68.0% 100.0% 0.24). P: 49.2% 49.2% 11.9% 11.1%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.89 (0.28, 6.83) 18, 91 (2.30, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23) 1.13 (0.45, 0.25, 0.25) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 0.45 (0.80, 3.56) 0.44 (0.01, 3.34) 0.57 (0.27, 22.99) Not estimated Not estimated 0.41 (0.01, 3.34) 0.41 (0.01, 3.54) 0.41 (0.01, 3.	Odds Ratio M.H. Exect, 95% CI 0.001 Favours [O-NLD] Favours [VE-NLD] Odds Ratio
réet for subaroue diff B 22.2 i RCT 12.2 Rom-RCT umar (2017) 10.1012 i RCT 12.2 Rom-RCT 12.2	erences: C O-iHui, Events: 4 4 4 4 4 4 4 4 4 4 4 4 4	Total D 29 29 29 29 29 30 10 21 33 129 4 (P = 0.0 158 5 (P = 0.0 ChiP = 0.0 158 5 (P = 0.0 ChiP = 0.0 158 5 (P = 0.0 ChiP = 0.0 136 136 4 (P = 1 136	27. df = 1 VE-ILL <u>Events</u> 3 3 3 9 9 1 1 2 3 3 0 0 0 2 3 0 0 0 2 1 0 0 0 1 1 2 3 0 0 0 0 1 1 2 3 3 0 0 0 0 1 1 2 3 3 0 0 0 0 1 1 2 3 3 0 0 0 0 0 1 0 1 0 1 0 0 0 0 1 0 1 0 0 0 0 0 0 1 0 1 0 0 0 0 0 0 0 0 0 0 0 0 0	ND Total 29 29 29 29 19 27 127 154 1 (P = ND 26 20 0 19 27 154 1 (P = ND 26 20 19 27 154 10 10 27 127 127 127 127 127 127 127	Weight 32.0% 32.0% 32.0% 12.2% 5.3% 68.0% 100.0% 0.24). P: 49.2% 49.2% 11.9% 11.1%	Odds Ratio M.H. Fixed, 95% CI 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.39 (0.28, 6.83) 1.89 (0.28, 6.83) 18, 91 (2.30, 155.21) 0.88 (0.05, 14.51) 2.13 (0.45, 10.23) 1.13 (0.45, 0.25, 0.25) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 3.23 (1.51, 6.89) 0.45 (0.80, 3.56) 0.44 (0.01, 3.34) 0.57 (0.27, 22.99) Not estimated Not estimated 0.41 (0.01, 3.34) 0.41 (0.01, 3.54) 0.41 (0.01, 3.	Odds Ratio MH, Fixed, 59% CI

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 randomeffects 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

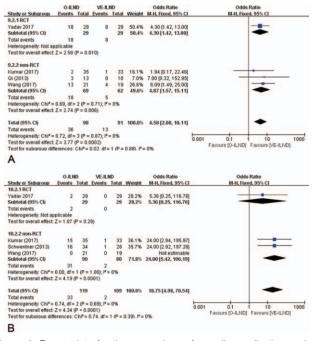


Figure 4. Forest plots for the comparison of overall complications: minor (Clavien–Dindo I-II) complications and major (Clavien–Dindo III-IV) complications. (A) Minor complications; (B) major complications.

(OR = 0.83, 95% CI [0.31, 2.23], P = .720) (Fig. 3D). A randomeffects 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

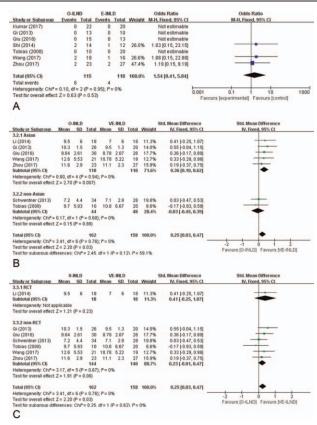


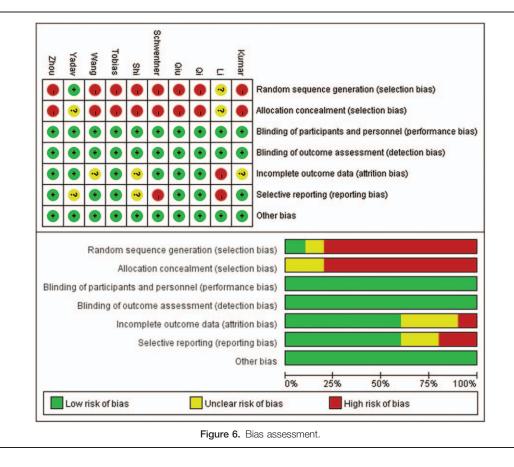
Figure 5. Forest plots for the comparison of oncologic outcomes. (A) Recurrence; (B) the number of dissected nodes (Asian vs non-Asian); (C) the number of dissected nodes (RCT vs non-RCT). RCT=randomized controlled trial.

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 leaveone-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



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.

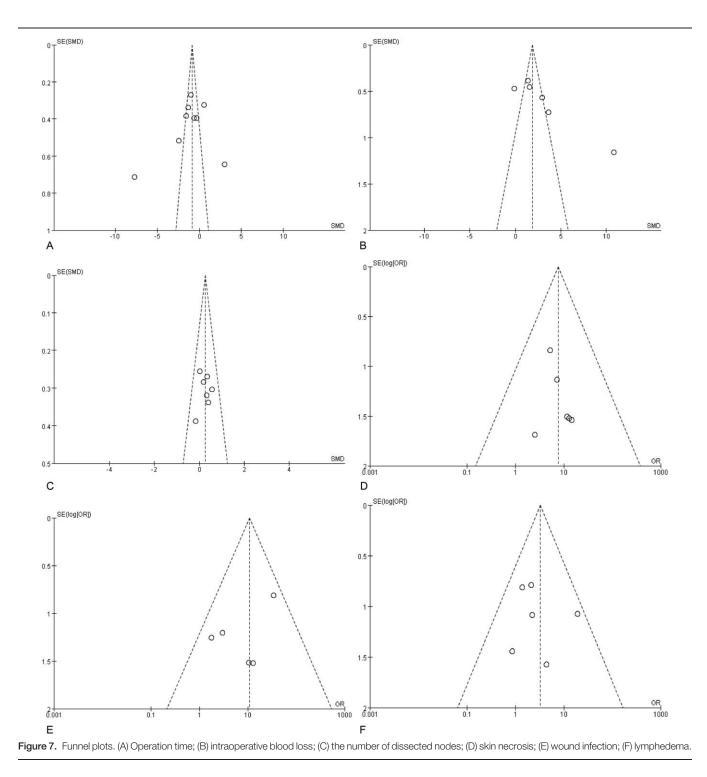
Results of the current meta-analysis demonstrated that VE-ILND prolonged the duration of surgery (VE-ILND: mean 134.82 minutes vs O-ILND: mean 116.53 minutes). This difference and corresponding heterogeneity might attribute to the learning curve for the VE-ILND procedure given the rarity of penile cancer. 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



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 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.

Acknowledgments

We sincerely thank Miss Wang Zong for editing the pictures.

Author contributions

Conceptualization: Jiao Hu.

- Investigation: Jiao Hu, Huihuang Li, Yu Cui, Peihua Liu, Xu Zhou, Jinbo Chen.
- Methodology: Jiao Hu, Huihuang Li, Yu Cui, Peihua Liu, Longfei Liu, Jinbo Chen, Xiongbing Zu.

Resources: Jiao Hu.

- Validation: Peihua Liu, Hegun Chen, Xiongbing Zu.
- Writing original draft: Jiao Hu.
- Writing review and editing: Jiao Hu, Xu Zhou, Longfei Liu, Hequn Chen, Jinbo Chen, Xiongbing Zu.

References

- [1] Daling JR, Madeleine MM, Johnson LG, et al. Penile cancer: importance of circumcision, human papillomavirus and smoking in in situ and invasive disease. Int J Cancer 2005;116:606–16.
- [2] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016;66:7–30.
- [3] Backes DM, Kurman RJ, Pimenta JM, et al. Systematic review of human papillomavirus prevalence in invasive penile cancer. Cancer Causes Control 2009;20:449–57.
- [4] Sansalone S, Silvani M, Leonardi R, et al. Sexual outcomes after partial penectomy for penile cancer: results from a multi-institutional study. Asian J Androl 2017;19:57–61.
- [5] Yu C, Hequn C, Longfei L, et al. Sexual function after partial penectomy: a prospectively study from China. Sci Rep 2016;6:21862.
- [6] Leijte JAP, Olmos RAV, Nieweg OE, et al. Anatomical mapping of lymphatic drainage in penile carcinoma with SPECT-CT: implications for the extent of inguinal lymph node dissection. Eur Urol 2008;54:885– 92.
- [7] Wen S, Ren W, Xue B, et al. Prognostic factors in patients with penile cancer after surgical management. World J Urol 2018;36:435–40.
- [8] Leijte JAP, Kirrander P, Antonini N, et al. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for follow-up based on a two-centre analysis of 700 patients. Eur Urol 2008;54:161–9.

- [9] Koifman L, Hampl D, Koifman N, et al. Radical open inguinal lymphadenectomy for penile carcinoma: surgical technique, early complications and late outcomes. J Urol 2013;190:2086–92.
- [10] Jacobellis U. Modified radical inguinal lymphadenectomy for carcinoma of the penis: technique and results. J Urol 2003;169:1349–52.
- [11] Yuan JB, Chen MF, Qi L, et al. Preservation of the saphenous vein during laparoendoscopic single-site inguinal lymphadenectomy: comparison with the conventional laparoscopic technique. BJU Int 2015;115:613–8.
- [12] Kirrander P, Andren O, Windahl T. Dynamic sentinel node biopsy in penile cancer: initial experiences at a Swedish referral centre. BJU Int 2013;111:E48–53.
- [13] Bishoff JT, Basler JW, Teichman JM, et al. Endoscopy subcutaneous modified inguinal lymph node dissection (ESMIL) for squamous cell carcinoma of the penis. J Urol 2003;169:178.
- [14] Josephson DY, Jacobsohn KM, Link BA, et al. Robotic-assisted endoscopic inguinal lymphadenectomy. Urology 2009;73:167–70.
- [15] Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010;8:336–41.
- [16] Higgins JP, White IR, Anzures-Cabrera J. Meta-analysis of skewed data: combining results reported on log-transformed or raw scales. Stat Med 2008;27:6072–92.
- [17] Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg 2009;250:187–96.
- [18] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
- [19] Tobias-Machado M, Tavares A, Silva MNR, et al. Can video endoscopic inguinal lymphadenectomy achieve a lower morbidity than open lymph node dissection in penile cancer patients? J Endourol 2008;22:1687–91.
- [20] Shi WQ, Wei JX, Zhang XP, et al. Clinical comparison and analysis of laparoscopic surgery and open surgery of inguinal lymphadenectomy. J Clin Urology 2014;29:1094–6.
- [21] Shangjun Z, Xuelu Z, Jianfeng Z, et al. Comparison and analysis of the effectiveness and safety of open and endoscopic inguinal lymph node dissection for long term follow-up. China Med Pharm 2017;7:16–20.
- [22] Wang S, Du P, Tang X, et al. Comparison of efficiency of video endoscopy and open inguinal lymph node dissection. Anticancer Res 2017;37:4623–8.
- [23] Xinkai1 Q, Dongliang Y, Yanhiu M, et al. Comparison of laparoscopic and open surgery for penile cancer inguinal lymph node dissection. Chin J Androl 2016;30:39–43.
- [24] Fujun L, Chaohui G, Yafei D, et al. Effect comparison of the ingurnal lymphadenectomy with laparoscope operation and open surgery for penile cancer. Chin J Exp Surg 2014;31:2905–7.
- [25] Schwentner C, Todenhöfer T, Seibold J, et al. Endoscopic inguinofemoral lymphadenectomy – extended follow-up. J Endourol 2013;27:497–503.
- [26] Kumar V, Sethia KK. Prospective study comparing video-endoscopic radical inguinal lymph node dissection (VEILND) with open radical ILND (OILND) for penile cancer over an 8-year period. BJU Int 2017;119:530–4.
- [27] Xiaolong Q, Zhangyue L, Feng L, et al. A retrospective analysis of laparoscopic and open inguinal lymphadenectomy for the treatment of the patients with penis carcinoma. Chin J Urol 2013;34:522–5.
- [28] Yadav SS, Tomar V, Bhattar R, et al. Video endoscopic inguinal lymphadenectomy vs open inguinal lymphadenectomy for carcinoma penis: expanding role and comparison of outcomes. Urology 2017;113:79–84.
- [29] Hakenberg OW, Comperat EM, Minhas S, et al. EAU guidelines on penile cancer: 2014 update. Eur Urol 2015;67:142–50.
- [30] Wang JY, Gao MZ, Yu DX, et al. Histological subtype is a significant predictor for inguinal lymph node metastasis in patients with penile squamous cell carcinoma. Asian J Androl 2018;20:265–9.
- [31] Leijte JA, Kirrander P, Antonini N, et al. Recurrence patterns of squamous cell carcinoma of the penis: recommendations for followup based on a two-centre analysis of 700 patients. Eur Urol 2008;54:161–8.
- [32] Tobias-Machado M, Tavares A, Ornellas AA, et al. Video endoscopic inguinal lymphadenectomy: a new minimally invasive procedure for radical management of inguinal nodes in patients with penile squamous cell carcinoma. J Urol 2007;177:953–7.
- [33] Catalona W. Modified inguinal lymphadenectomy for carcinoma of the penis with preservation of saphenous veins: technique and preliminary results. J Urol 1998;140:306–10.

- [34] Judson PL, Jonson AL, Paley PJ, et al. A prospective, randomized study analyzing sartorius transposition following inguinal-femoral lymphadenectomy. Gynecol Oncol 2004;95:226–30.
- [35] Nirmal TJ, Gupta AK, Kumar S, et al. Tensor fascia lata flap reconstruction following groin dissection: is it worthwhile? World J Urol 2011;29:555–9.
- [36] Yao K, Zou ZJ, Li ZS, et al. Fascia lata preservation during inguinal lymphadenectomy for penile cancer: rationale and outcome. Urology 2013;82:642–7.
- [37] Cui Y, Chen H, Liu L, et al. Saphenous vein sparing during laparoscopic bilateral inguinal lymphadenectomy for penile carcinoma patients. Int Urol Nephrol 2016;48:363–6.
- [38] Yuan P, Zhao C, Liu Z, et al. Comparative study of video endoscopic inguinal lymphadenectomy through a hypogastric vs leg subcutaneous approach for penile cancer. J Endourol 2018;32:66–72.
- [39] Spillane AJ, Cheung BL, Stretch JR, et al. Proposed quality standards for regional lymph node dissections in patients with melanoma. Ann Surg 2009;249:473–80.