Original Article

The association of tumor diameter with lymph node metastasis and recurrence in patients with endometrial cancer: a systematic review and meta-analysis

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Background: Tumor diameter (TD)/original lesion area has been reported to have a certain predictive effect on lymph node metastasis (LNM) and recurrence of endometrial cancer (EC) patients, but there is still controversy about their relationship. Therefore, we conducted a meta-analysis to provide reference for clinical management and follow-up studies of patients with EC.

Methods: The databases of PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang were searched, from inception to 27 October 2022, for studies regarding the association of TD with LNM risk and recurrence rate in EC. The search strategy was developed using a combination of free terms and medical subject headings (MeSH). Stata 15.0 was used to conduct the statistical analysis. Odds ratio (OR) with the 95% confidence interval (CI) were calculated to evaluate the association of TD and the risk of LNM and recurrence in EC patients. The OR value obtained from the multivariate analysis is first extracted; the results of univariate analysis were extracted for articles without the results of multivariate analysis. Newcastle-Ottawa Scale (NOS) assessed the quality of the included articles, publication bias was evaluated by Egger's test with funnel plots.

Results: There was a total of 69 studies 123,383 EC patients included. Meta-analysis showed higher LNM risk in EC patients with the TD >2 cm, which was 2.88 times higher than that in those with ≤2 cm, and the difference was statistically significant (OR =2.88; 95% CI: 2.12–3.89; P<0.001), publication bias had no effect on the results. The risk of recurrence in EC patients with a TD >2 cm was 2.45 times higher than that in those with ≤2 cm (OR =2.45; 95% CI: 1.73–3.48; P<0.001), publication bias exerted influence over the results.

Conclusions: TD is associated with LNM and recurrence in patients with EC. Therefore, TD should be considered in the scope of surgery and adjuvant therapy.

Keywords: Endometrial cancer (EC); lymph node metastasis (LNM); recurrence; tumor diameter (TD); meta-analysis

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Introduction

Endometrial cancer (EC) has been shown to be the most prevalent gynecological malignancy in developed countries, with a gradually increasing morbidity in developing countries. Abnormal uterine bleeding is one of the main clinical manifestations of EC, accounting for 75–90% of the cases, and the most prevalent risk factors include obesity, fat-rich diet, early menarche, type 2 diabetes, lynch syndrome, age over 55 years old, sterility and infertility, delayed menopause, concomitance with anovulatory diseases or functional ovarian tumor, and long-term medication history of single estrogen or tamoxifen (1-5). Pelvic and para-aortic lymph node dissection (LND) could be selectively added in the staging surgery for EC resting on the existence of high-risk factors for lymph node (LN) involvement (5,6). It is reported that the incidence of pelvic LN (PLN) or para-aortic LN (PALN) involvement ranges from 5% to 20% (7). Chemoradiotherapy could be considered based on the cancer stage of the patient. Lymph node metastasis (LNM) is the main spreading pattern of EC, and is closely related to patient prognosis. The recurrence rate of EC in LNM patients far exceeds that in non-LNM patients (48% *vs.* 8%) (8). Additionally, it is reported that the 5-year disease-free survival (DFS) is 90% in non-LNM patients, and 75% in those with pelvic LNM (PLNM). The occurrence of PLNM indicates poorer prognosis, with a 5-year DFS of only 38% (9,10). Therefore, the status of LNs has an important effect on the prognosis of EC patients.

It remains controversial whether LND should be performed during EC surgery, as well as the scope of dissection. Research by Bougherara *et al.* (11), has demonstrated that implementing LND could result in increased surgical time, perioperative bleeding, and injury to nerves, vessels, and ureter, as well as increased incidence of postoperative complications such as lymphedema, lymphocele, ileus, and lower limb vein thrombosis. Given this situation, some scholars have formulated different standards to assess the risk of LNM in EC patients. The Mayo clinic has developed an algorithm for EC treatment, that is, the "Mayo standard", which defines LNM low-risk EC patients as: endometrioid EC with the International Federation of Gynecology and Obstetrics (FIGO) grade 1 or 2, muscular infiltration (MI) <50%, and tumor diameter (TD) ≤2 cm. Other EC patients would be defined as high-risk. LND would be no longer considered for low-risk EC patients, whereas systematic LND up to the renal vein level should be performed for those with high risk (11). Though LN involvement accounts for approximately 15% of the endometrioid EC patients, 75% of the female patients need systematic LND when applying the Mayo standard (12). Therefore, Vargas *et al.* suggest that the definition of LNM low-risk EC patients in the Mayo standard could be modified as follows: endometrioid EC with pathological grade 1 and MI <50%, EC with pathological grade 2 and TD <3 cm, or EC with pathological grade 3 and without MI (13). A Gynecologic Oncology Group Study has proposed a Milwaukee model which defines the LNM low-risk patients as: TD ≤5 cm with MI ≤33% (10). It can be noticed that there is controversy among researchers over cut-off value of TD (whether should be 2, 3, or 5 cm). This controversy may be related to the small sample size included in the study, different ways of measuring TD, etc.

In addition, some scholars have developed different criteria for evaluating the prognosis of patients to formulate different treatment plans, in which the risk of recurrence is included. Characteristics of low-risk EC are defined, according to European Society for Medical Oncology (ESMO) guideline, as endometrioid carcinoma with MI ≤50% and FIGO grade I or II (14), which was modified by Bendifallah *et al.* in 2014 (15). The World Health Organization (WHO) has included lymphatic vascular space invasion (LVSI) in the model (ESMO-modified classification) (15). Keys *et al.* grade the risk in EC patients based on their age, histological classification, cancer grade, lymphatic invasion, and depth of basal invasion, so as to

Highlight box

Key findings

- The TD of EC patients is closely related to LNM and recurrence. TD >2 cm can be used as a reference index to predict LNM of EC patients.

What is known and what is new?

- As an easily available indicator, TD has been reported to have a certain predictive effect on LNM and recurrence of EC patients, but the relationship between TD and LNM and recurrence of EC is still controversial.
- This study resolves the controversy over the relationship between TD and LNM and recurrence in patients with EC.

What is the implication, and what should change now?

- TD is easily measured during surgery, so that clinicians using TD to determine a complete surgical staging could to some extent reduce unnecessary LND and avoid secondary surgery, while estimating the risk of recurrence based on TD can also lead to better treatment outcomes for the patient.

determine whether adjuvant treatment should be considered (GOG-99 standard) (16). The modified ESMO and GOG-99 were introduced for decision-making of adjuvant therapy in EC patients, yet TD remains unincluded, which might be due to that its effect is still under investigation (17). Some studies indicate an association between TD and LNM. Some researchers have proposed that TD might be associated with the recurrence of EC (18,19). TD is easily measured during surgery, so that clinicians using TD to determine a complete surgical staging could to some extent reduce unnecessary LND and avoid secondary surgery (20), while estimating the risk of recurrence based on TD can also lead to better treatment outcomes for the patient.

It can be gleaned from the studies mentioned above that TD is closely related to LNM and recurrence in EC patients, whereas the association of the TD with LNM and recurrence is still controversial. Therefore, this systematic review and meta-analysis aimed to evaluate the association of TD with LNM and recurrence in EC patients, so as to provide more evidence for clinical EC treatment. We present the following article in accordance with the MOOSE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2595/rc).

Methods

Literature search

The databases of PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure (CNKI), VIP, and Wanfang were searched, from inception to 27 October 2022, for studies regarding the association of EC diameter/original lesion area with the risk of LNM and recurrence. The search strategy and items were designed according to the Cochrane handbook and search rules of each database, with language restricted to Chinese and English.

Inclusion and exclusion criteria

Inclusion criteria

Patients who were diagnosed histologically with single EC before surgery; study that reported TD or data related to LNM and recurrence; outcome measures included LNM or recurrence; types of study: observational study (cohort study/case-control study).

Exclusion criteria

Animal study, study with data or full-text unavailable, literature review, meta-analysis, case report, monograph, ongoing clinical trial, and study with participants less than 20.

Data extraction

All retrieved articles were classified by two reviewers (Ruifang Fu and Xiaohan Yu) according to the data required. All the articles were divided into a LNM group and a recurrence group based on the following aspects:

(I) LNM: first author's surname, country of origin, year of publication, pathological grade, FIGO stage, type of study, number of patients (sample size), age, odds ratio (OR) and 95% confidence interval (CI) about the association of TD and the risk of LNM (the OR value obtained from the multivariate analysis is first extracted; the results of univariate analysis were extracted for articles without the results of multivariate analysis), LNM metastatic site and cut-off value (cm).

(II) Recurrence: first author's surname, country of origin, year of publication, pathological grade, FIGO stage, type of study, number of patients (sample size), age, OR and 95% CI about the association of TD and the risk of recurrence (the OR value obtained from the multivariate analysis is first extracted; the results of univariate analysis were extracted for articles without the results of multivariate analysis), and cut-off value (cm).

Quality assessment

Quality of included cohort studies were assessed using Newcastle-Ottawa Scale (NOS) (21). All studies included in this study were retrospective cohort studies, so all of them used NOS for quality assessment. The NOS contains 2 forms designed respectively for cohort study and case-control study. The form of cohort study involves 3 domains with 8 items: selection, comparability, and outcome. The form of case-control study also involves 3 domains with 8 items: selection, comparability, and exposure. It could be scored 1 point if meeting the requirements, with a total score for 9. The higher the score, the higher the quality of the study.

Statistical analysis

All data analyses were processed using Stata 15.0 software

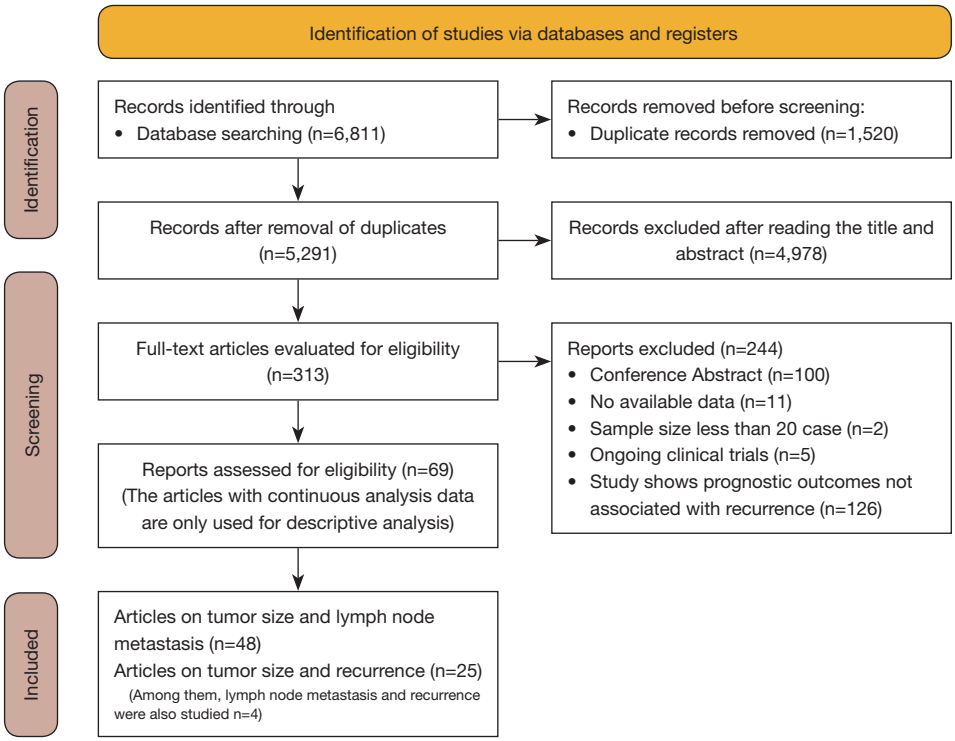

Figure 1 Flow chart of literature screening.

(StataCorp., College Station, TX, USA). OR and 95% CI were directly extracted from each publication to evaluate the association of TD and the risk of LNM and recurrence in EC patients. The OR value obtained from the multivariate analysis is first extracted from each study (all the multivariate analysis variables were statistically significant variables in the univariate analysis). The results of univariate analysis were extracted for articles without the results of multivariate analysis. The Cochran Q and I^2 statistical methods were applied to evaluate the heterogeneity among included studies. A $P \geq 0.1$ with an $I^2 < 50\%$ would indicate no significant heterogeneity among the studies, and fixed-effect model would be applied. Otherwise, $P < 0.1$ and $I^2 \geq 50\%$, significant heterogeneity would be considered, and random-effect model would be applied. Sensitivity analysis was carried out to assess the influence of each individual study on the pooled results by sequentially excluding each study and subgroup analysis would be performed to identify the source of heterogeneity. Potential publication bias was evaluated by Egger's test with funnel plots. Bilateral P value<0.05 was regarded statistically significant.

Results

Study selection

There were 6,811 articles identified, and 1,520 duplicated or ineligible articles were removed. Titles and abstracts of the remaining articles were browsed, in strict accordance with the inclusion and exclusion criteria, for initial screening. A total of 69 studies were finally included after reading the full-texts, in which 48 studies focused on LNM, 25 studies on recurrence, and 4 on the both. The study selection process is presented in *Figure 1*.

Characteristics of included studies

A total of 69 retrospective cohort studies were included. Detailed characteristics of included studies are presented in *Tables 1,2*.

Quality assessment of included studies

All included studies were retrospective and therapeutic

Table 1 Basic characteristics of included literature TD and LNM

Author	Year	Country/ region	Pathological grade	FIGO stage	Type of study	Sample size	Age (years)*	Univariate or multivariate	Metastatic site	Cut-off value (cm)
Li X (22)	2021	China	G1–G3	Not provided	RC	63,836	62.41±11.62	Multivariate	Full range	2, 5, 10
Meydanli MM (23)	2019	Turkey	G1–G3	I–IV	RC	966	58 [31–84]	Multivariate	Full range	4
Matsushita C (24)	2019	Japan	G1–G3	I–IV	RC	185	57 [33–78]	Multivariate	Full range	2
Dong Y (25)	2019	China	G1–G3	I–II	RC	1,427	60 [35–77]	Univariate	Full range	2
Nasioudis D (26)	2019	USA	G1–G3	IA, IB	RC	14,398	63.0	Univariate	Abdominal aorta	2
Günakan E (27)	2019	Turkey	Not provided	I–IV	RC	762	59.1	Univariate	Full range	2
Yildirim N (28)	2018	Turkey	G1–G4	I–IV	RC	278	60.1±9.8	Univariate	Full range	2
Toptaş T (29)	2017	Turkey	G1–G3	Not provided	RC	128	59.3±11.2	Multivariate	Full range	3
Sari ME (7)	2017	Turkey	G1–G4	I–IV	RC	641	59 [28–85]	Univariate	Abdominal aorta	2, 4
Lucic N (30)	2017	Serbia	G1–G3	Not provided	RC	221	60 [31–88]	Univariate	Full range	2
Boyraz G (31)	2017	Turkey	G1–G2	IA	RC	191	57.8	Univariate	Full range	2
Cox Bauer CM (32)	2016	USA	G1–G3	I–III	RC	737	62.8	Univariate	Full range	2, 3, 4, 5
Canlorbe G (33)	2016	France	G1–G3	I–II	RC	633	65.6 [58.0–72.3]	Univariate	Full range	2, 3.5
Bourgioti C (34)	2016	Hellenic	G1–G3	I–IV	RC	105	59.8±12.6	Univariate	Full range	4
Cetinkaya K (35)	2016	Turkey	G1–G3	I–III	RC	268	58.6 [27–80]	Univariate	Full range	2
Bendifallah S (36)	2015	France	G1–G3	I\IIIC	RC	523	64.9 [33–98]	Univariate	Full range	1
Bendifallah S (37)	2015	France	Not provided	I–III	RC	457	66.4 [31–98]	Univariate	Full range	1.5
Rathod PS (38)	2014	India	G1–G3	IA–IIIC2	RC	52	58.3 [31–76]	Univariate	Abdominal aorta and pelvic cavity	2
Mahdi H (39)	2015	USA	G1–G4	I	RC	19,692	62.1	Univariate	Full range	2, 5
Gilani S (40)	2014	USA	G1–G3	Not provided	RC	207	62.29±10.9	Univariate	Full range	2
AlHilli MM (41)	2013	USA	G1–G3	I–II	RC	883	63.9	Univariate	Full range	2
Shah C (20)	2005	USA	G1–G3	I–IV	RC	345	Not provided	Multivariate	Full range	1
Watanabe M (42)	2003	Japan	G1–G2	IA–IIIC	RC	107	54 [29–79]	Univariate	Full range	2
Cheng WF (43)	1998	China	G1–G3	Not provided	RC	42	52.3 [25–78]	Univariate	Full range	2.5
Wu SW (44)	2021	China	G1–G3	I–III	RC	1,346	60.0	Multivariate	Full range	2
Guo CM (45)	2021	China	Not provided	I–IV	RC	385	57±10	Univariate	Full range	2, 3, 4, 5
Chen SL (46)	2021	China	G1–G3	I–IV	RC	268	54.0	Univariate	Full range	2
Zang PP (47)	2020	China	G1–G3	Not provided	RC	84	55.3±7.4	Univariate	Pelvic cavity	2
Li YJ (48)	2020	China	G1–G3	I–IV	RC	393	56 [25–80]	Univariate	Pelvic cavity and abdominal aorta	3
Cheng F (49)	2020	China	G1–G3	I–IV	RC	520	55.3±8.4	Multivariate	Full range	2
Wang YL (50)	2019	China	G1–G3	Not provided	RC	192	Not provided	Multivariate	Full range	2
Li X (51)	2019	China	Not provided	Not provided	RC	653	52.53±8.49	Multivariate	Full range	2
Ji R (52)	2019	China	Not provided	I–III	RC	162	56.3	Univariate	Pelvic cavity and abdominal aorta	2

Table 1 (*continued*)

Table 1 (*continued*)

Author	Year	Country/ region	Pathological grade	FIGO stage	Type of study	Sample size	Age (years)*	Univariate or multivariate	Metastatic site	Cut-off value (cm)
Liu S (53)	2018	China	Not provided	I–III	RC	176	53.74±8.91	Univariate	Full range	2
Li Y (54)	2018	China	Not provided	Not provided	RC	1,724	55.20±8.72	Univariate	Full range	2
Li M (55)	2018	China	G1–G3	Not provided	RC	74	54.32±8.34	Univariate	Pelvic cavity	2
Zhang QH (56)	2017	China	G1–G3	I–IV	RC	136	53.46±7.8	Multivariate	Pelvic cavity	2
Liang DX (57)	2017	China	G1–G3	Not provided	RC	210	50.12±5.96	Univariate	Full range	2
Liu CY (58)	2017	China	G1–G3	I–IV	RC	366	53.734±7.900	Univariate	Full range	2
Zeng J (59)	2017	China	G1–G3	I–IV	RC	289	55 [23–78]	Multivariate	Full range	2
Zhang QH (60)	2016	China	G1–G3	I–IV	RC	136	53.46±7.84	Multivariate	Full range	2
Xu Z (61)	2014	China	G1–G3	I–IV	RC	358	50 [20–78]	Univariate	Full range	2
Yu ML (62)	2013	China	G1–G3	I–IV	RC	221	52.96±8.63	Multivariate	Full range	2
Huang J (63)	2011	China	G1–G3	IA–IIIC	RC	196	53.03±8. 9	Multivariate	Full range	2
Wang N (64)	2009	China	G1–G3	I–IV	RC	600	54.93±8.36	Univariate	Full range	2
Guo XX (65)	2005	China	G1–G3	I–IV	RC	128	55.3	Univariate	Full range	2
Cai HB (66)	2001	China	G1–G3	I–II	RC	156	55.2	Univariate	Full range	1.5
Khatib G (67)	2022	Turkey	G1–G3	I–IV	RC	213	56 [27–80]	Multivariate	Full range	2

*, data are presented as mean ± SD, median [range], or mean. TD, tumor diameter; LNM, lymph node metastasis; FIGO, International Federation of Gynecology and Obstetrics; RC, retrospective cohort study; SD, standard deviation.

research. Quality assessment was conducted for selection, comparability, and outcome/exposure using NOS (a "*" was scored 1 point, and the final score was the sum of all "*"), as shown in *Table 3*. We included articles with scores of >6 into this study. The higher the quality of the studies included in the meta-analysis, the higher the reliability of the meta-analysis results.

Association of TD with LNM

Results of meta-analysis for the association of TD with LNM

There were 48 studies that reported TD and LNM. Among them, 35 studies used TD =2 cm as the cut-off value. Heterogeneity among the studies was considered (I^2=77.5%; P=0.000), and the effects were pooled using random-effect model. The forest plot showed that LNM risk in EC patients with the TD >2 cm was 2.88 times higher than that in those with ≤2 cm (OR =2.88; 95% CI: 2.12–3.89; P<0.001) (*Figure 2*).

Subgroup analysis

An overview of the factors that might affect the results showed that participant's or the author's continents, the manifestation of the study results, and the pathological grades might be the source of heterogeneity. Subgroup analysis was performed based on these factors, and the heterogeneity results were provided. Inclusion of participants' continents, pathological grades, and FIGO stages yielded various heterogeneity, suggesting that those factors might be the source of heterogeneity (*Table 4*).

The association of different TD cut-off value with LNM

The summary of included studies showed that the selected cut-off value varied among different studies in discussing the influence of TD on LNM (1.5, 2, 2.5, 3, 3.5, and 5 cm, respectively). Subgroups were set based on different cut-off values to explore their association with LNM, as shown in *Table 5*.

Publication bias and sensitivity analysis

Egger's test was adopted to assess the publication bias, and the results showed no publication bias (P=0.07), which means our results are highly reliable, as shown in *Figure 3*.

Table 2 Basic information of included literature on TD and recurrence

Author	Year	Country/ region	Pathological grade	FIGO stage	Type of study	Sample size	Age (years)*	Univariate or multivariate	Cut-off value (cm)
Ocak B (68)	2021	Turkey	G1–G3	I	RC	284	60 [31–81]	Multivariate	Continuous
Ocak B (69)	2021	Turkey	G1–G3	I	RC	272	65.0	Multivariate	Continuous
Nwachukwu C (70)	2021	USA	G1	IA	RC	222	59.7±10.6	Multivariate	2
Eriksson LSE (71)	2021	Sweden	G1–G3	I –IV	RC	339	67 [60–72]	Multivariate	2
Liu CY (72)	2020	China	G1–G2	I–III	RC	238	60.0	Multivariate	2
Yildirim N (28)	2018	Turkey	G1–G4	I–IV	RC	278	60±9.8	Univariate	2
Sozzi G (73)	2018	Italy	G1–G3	I–III	RC	1,166	63.0	Multivariate	2.5
Güngördük K (74)	2018	Turkey	G1–G2	IA	RC	280	56.9	Multivariate	2
Senol T (19)	2015	Turkey	G1–G3	I –IV	RC	152	56.3	Univariate	2
Bendifallah S (75)	2014	France	G1–G3	I–III	RC	396	65.99 [31–86]	Multivariate	2
Chattopadhyay S (76)	2013	England	G1–G3	I	RC	216	66.0	Multivariate	Continuous
Misirlioglu S (77)	2012	Turkey	Not provided	I	RC	223	56 [55–80]	Univariate	2
Bandyopadhyay S (78)	2012	USA	Not provided	I–IV	RC	123	67.2	Univariate	2
Guo CM (45)	2021	China	Not provided	I–IV	RC	385	57±10	Univariate	2, 3, 4, 5
Ma HN (79)	2020	China	Not provided	I–II	RC	257	56.4±8.9	Multivariate	2
Guo DD (80)	2020	China	Not provided	I–II	RC	702	55.0	Univariate	2
Tao YZ (81)	2016	China	Not provided	I–II	RC	123	55.1±5.2	Multivariate	2
Zhong KN (82)	2015	China	G1–G3	I–II	RC	123	54.6±4.9	Multivariate	2
Wang L (83)	2015	China	G1–G3	I–II	RC	120	59.5±6.1	Multivariate	2
Li MZ (84)	2014	China	G1–G3	I–II	RC	398	57.0	Univariate	2
Doll KM (85)	2014	USA	G3	Not provided	RC	208	65.0	Multivariate	Continuous
Shah C (20)	2005	USA	G1–G3	I–IV	RC	345	65.0	Multivariate	Continuous
Zeng J (59)	2017	China	G1–G3	I–IV	RC	289	55 [23–78]	Univariate	2
Xing XR (86)	2022	China	G1–G3	I–III	RC	80	50.22±5.12	Univariate	2
Chen XL (87)	2022	China	G1–G3	I–IV	RC	94	58.24±9.33	Univariate	2

*, data are presented as mean ± SD, median [range], or mean. TD, tumor diameter; FIGO, International Federation of Gynecology and Obstetrics; RC, retrospective cohort study; SD, standard deviation.

After removal of any of the studies, the pooled effects of the rest of the studies were in the 95% CI range of the total effect, which suggested that the results were robust (*Figure 4*).

Association of TD with recurrence

Results of meta-analysis for the association of TD with recurrence

There were 25 studies that reported the association between TD and EC recurrence. Among them, there 18 studies used TD =2 cm as the cut-off value. Significant heterogeneity was considered among the studies (I^2=89.3%; P=0.000), and the effects were pooled using random-effect model. The recurrence risk in EC patients with TD >2 cm was 2.45 times higher than that in those with ≤2 cm (OR =2.45; 95% CI: 1.73–3.48; P<0.001) (*Figure 5*).

Subgroup analysis

A summary of the factors that might affect the results showed that participants' or the author's continents, the

Table 3 NOS quality evaluation included in the literature

Author	Year	Queue selection	Comparability	Result	Quality score
Li X	2021	****	*	***	8
Meydanli MM	2019	***	*	**	6
Matsushita C	2019	****	*	***	8
Dong Y	2019	****	*	**	7
Nasioudis D	2019	***	*	**	6
Günakan E	2019	***	*	***	7
Yildirim N	2018	****	*	***	8
Toptaş T	2017	****	*	***	8
Sari ME	2017	****	*	***	8
Lucic N	2017	***	*	**	6
Boyraz G	2017	*****	*	**	8
Cox Bauer CM	2016	*****	*	**	8
Canlorbe G	2016	****	*	**	7
Bourgioti C	2016	*****	*	***	9
Cetinkaya K	2016	***	*	**	6
Bendifallah S	2015	****	*	**	7
Rathod PS	2014	****	*	**	7
Mahdi H	2015	***	*	**	6
Gilani S	2014	***	*	**	6
AlHilli MM	2013	***	*	**	6
Shah C	2005	****	*	***	7
Watanabe M	2003	****	*	**	7
Cheng WF	1998	***	*	**	6
Wu SW	2021	****	*	**	7
Chen SL	2021	****	*	**	7
Zang PP	2020	****	*	**	7
Li YJ	2020	***	*	***	7
Cheng F	2020	***	*	**	6
Wang YL	2019	***	*	**	6
Li X	2019	***	*	**	6
Ji R	2019	***	*	**	6
Liu S	2018	***	*	***	7
Li Y	2018	***	*	**	6
Li M	2018	***	*	**	6
Zhang QH	2017	***	*	***	7

Table 3 (*continued*)

Table 3 (*continued*)

Author	Year	Queue selection	Comparability	Result	Quality score
Liang DX	2017	**	*	***	6
Liu CY	2017	***	*	**	6
Guo CM	2021	***	*	***	7
Xu Z	2014	***	*	***	7
Yu ML	2013	**	*	**	6
Huang J	2011	****	*	**	7
Wang N	2009	****	*	**	7
Guo XX	2005	**	*	***	6
Cai HB	2001	***	*	**	6
Ocak B	2021	*****	*	***	8
Ocak B	2021	*****	*	****	9
Nwachukwu C	2021	***	*	***	7
Eriksson LSE	2021	****	*	**	8
Liu CY	2020	***	*	**	6
Yildirim N	2018	***	*	**	6
Sozzi G	2018	****	*	**	6
Güngördük K	2018	***	*	***	7
Senol T	2015	***	*	**	6
Bendifallah S	2014	***	*	**	6
Chattopadhyay S	2013	***	*	**	6
Misirlioglu S	2012	****	*	**	7
Bandyopadhyay S	2012	***	*	**	6
Ma HN	2020	****	*	**	7
Guo DD	2020	***	*	**	6
Tao YZ	2016	***	*	**	6
Zhong KN	2015	***	*	***	7
Wang L	2015	****	*	**	7
Li MZ	2014	***	*	**	6
Doll KM	2014	****	*	**	7
Shah C	2005	***	*	**	6
Zeng J	2017	***	*	**	6
Khatib G	2022	**	**	**	6
Xing XR	2022	**	**	**	6
Chen XL	2022	***	**	**	7

A "*" was scored 1 point, and the final score was the sum of all "*". NOS, Newcastle-Ottawa Scale.

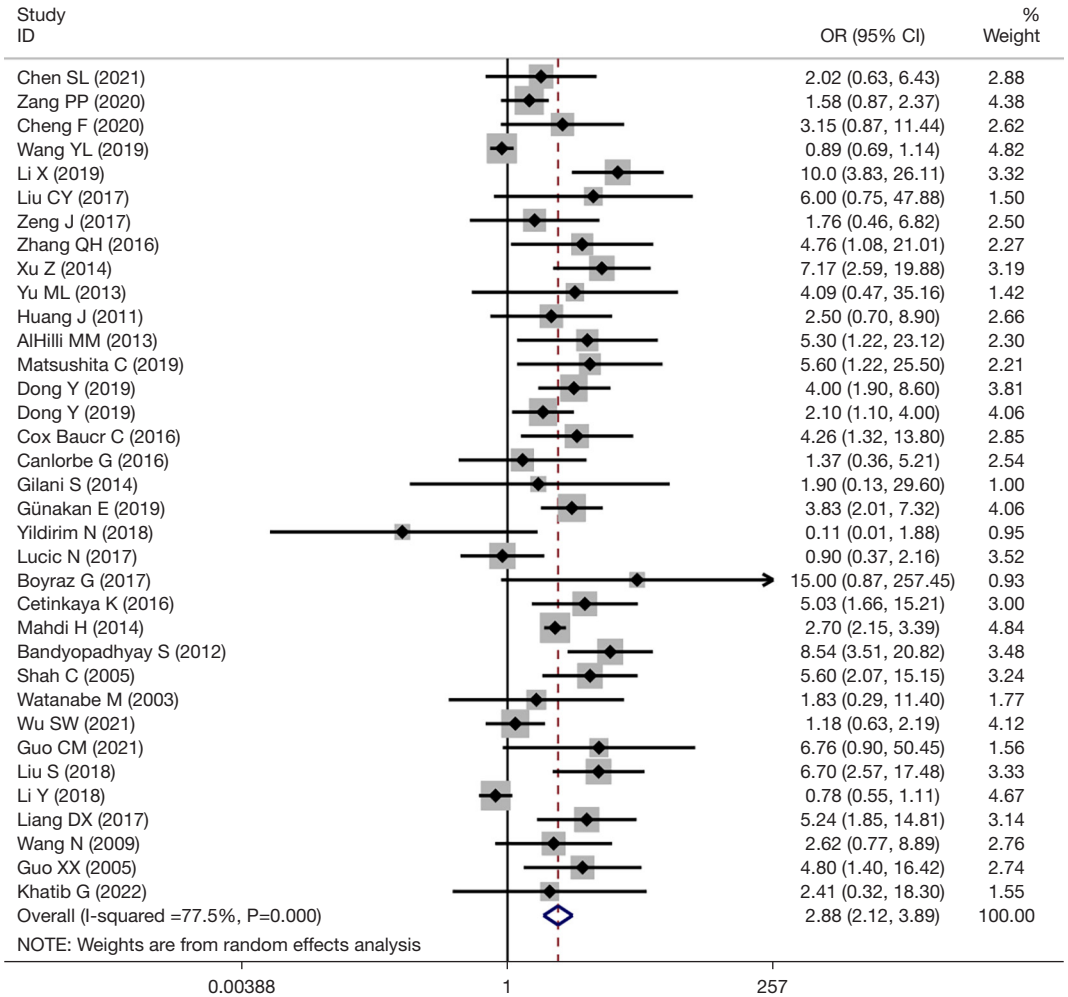

Figure 2 Forest plot of TD and LNM. OR, odds ratio; CI, confidence interval; TD, tumor diameter; LNM, lymph node metastasis.

manifestation of the study results, and the pathological grades might be the source of heterogeneity. Subgroup analysis was performed based on these factors, and the heterogeneity results were provided. Inclusion of participants' continents, pathological grades, and FIGO stages yielded various heterogeneity, suggesting that those factors might be the source of heterogeneity (*Table 6*).

Association of different TD cut-off value with EC recurrence

The summary of included studies showed that the selected cut-off value varied among different studies in discussing the influence of TD on EC recurrence (2, 2.5, and 3.75 cm, respectively). Subgroup analysis was performed and the results are shown in *Table 7*.

Publication bias and sensitivity analysis

Egger's test was adopted to assess the publication bias, and the result indicated the presence of significant publication bias (P=0.000), which means that our results are heavily influenced by publication bias and more research is needed, as shown in *Figure 6*. After removal of any of the studies, the pooled effects of the rest of the studies were in the 95% CI range of the total effect (*Figures 2,3*), which suggested that the results were robust (*Figure 7*).

Discussion

In this study, we extracted the data of included studies, and found that most of the studies followed the Mayo standard and the National Comprehensive Cancer Network

Table 4 Subgroup analysis of TD and LNM

Subgroup category	Number of documents included	OR	95% CI	P value	I^2	Q test P value
Continents						
Asia	27	2.83	1.97–4.07	<0.001	0.769	0.000
North America	6	4.18	2.54–6.89	0.124	0.422	0.124
Europe	2	1.02	0.49–2.12	0.606	0.000	0.606
Univariate or multivariate						
Univariate	26	2.85	2.06–3.95	<0.001	0.729	0.000
Multivariate	9	3.02	1.35–6.74	<0.001	0.785	0.000
Pathological grade						
G1–G3	25	2.67	1.90–3.74	<0.001	0.667	0.000
G1–G4	2	0.75	0.04–16.10	0.026	0.799	0.026
G1–G2	2	3.91	0.54–28.37	0.222	0.329	0.222
FIGO stage						
I–IV	16	4.14	3.06–5.62	<0.001	0.006	0.445
I–III	6	2.99	1.51–5.92	0.002	0.589	0.033
I–II	7	1.68	0.96–2.95	<0.001	0.124	0.331
IA	1	15	0.87–257.44	0.062	–	–
I	1	2.7	2.15–3.39	<0.001	–	–

TD, tumor diameter; LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

Table 5 Relationship between TD and LNM under different cut-off values

TD cut-off value (cm)	Number of documents included	OR	95% CI	P value	I^2	Q test P value
1.5	3	1.14	0.43–3.00	0.796	0.0	0.744
2	35	2.88	2.12–3.89	<0.001	0.782	0.000
2.5	1	12.571	1.437–110.009	0.022	–	–
3	3	3.27	1.91–5.79	<0.001	0.208	0.283
3.5	1	4.318	1.129–16.511	0.033	–	–
4	4	3.6	2.44–5.31	<0.001	0.375	0.187
5	3	3.46	1.81–6.61	<0.001	0.832	0.003

TD, tumor diameter; LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval.

(NCCN) guidelines. Both criteria considered TD less than 2 cm as a low risk factor for LNM in EC. We selected 2 cm as the cut-off value of TD. Participants with the TD <2 cm were assigned into LNM low-risk group. Yildirim *et al.* (28) conducted a study that involved 278 patients at I–IV stage. They found that TD was unassociated with LNM, and the positive rate of LN was 3/46 (6.5%) in EC patients with a TD <2 cm, and 10/232 (4.3%) in those with a TD ≥2 cm (P=0.457). LVSI and positive ascites cytology were considered crucial risk factors. Their findings were

inconsistent with our study, which might be caused by bias due to its retrospective-design. Additionally, LNM or recurrence had happened in few of the participants leading to too limited a sample size to perform the most robust statistical inference. An internal and external validation study by Dong *et al.* (25), constructed a nomogram based on 700 EC patients from Peking University People's Hospital, and validated the information of 727 EC patients from the cancer center of Fudan University. They found that in both of the populations, the LNM risk in EC patients with the TD ≥2 cm was 2.1 and 4.0 times higher, respectively, than that in those with the TD <2 cm [(OR =2.1; 95% CI: 1.1–4.0; P=0.019), (OR =4.0; 95% CI: 1.9–8.6; P≤0.001), respectively].

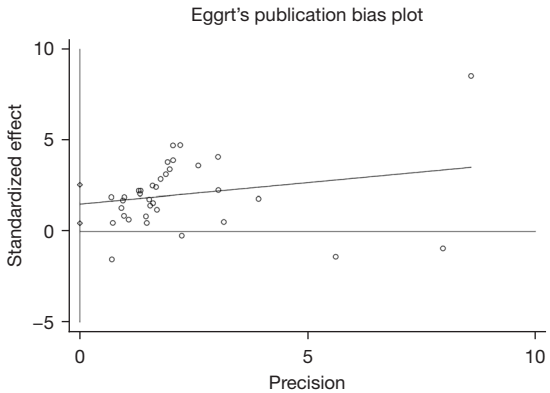

Figure 3 Egger diagram of TD and LNM. Small circle, included studies; X-axis, logarithm is 0; slash, regression line. TD, tumor diameter; LNM, lymph node metastasis.

In this study, 35 articles with a TD cut-off value of 2 cm were included and analyzed. The results showed that LNM risk in EC patients with the TD >2 cm was 2.88 times higher than that in those with the TD ≤2 cm, and the difference was statistically significant (OR =2.88; 95% CI: 2.12–3.89; P<0.001). Heterogeneity showed an I^2=77.5%, and Q test showed that P=0.000. Further heterogeneity analysis was performed due to the existing significant heterogeneity. We found that the origin of the participants, FIGO stages, and pathological grades affected the results. This also suggested that there was a certain association of TD with EC stages and pathological grades. Publication bias assessment showed that publication bias exerted no

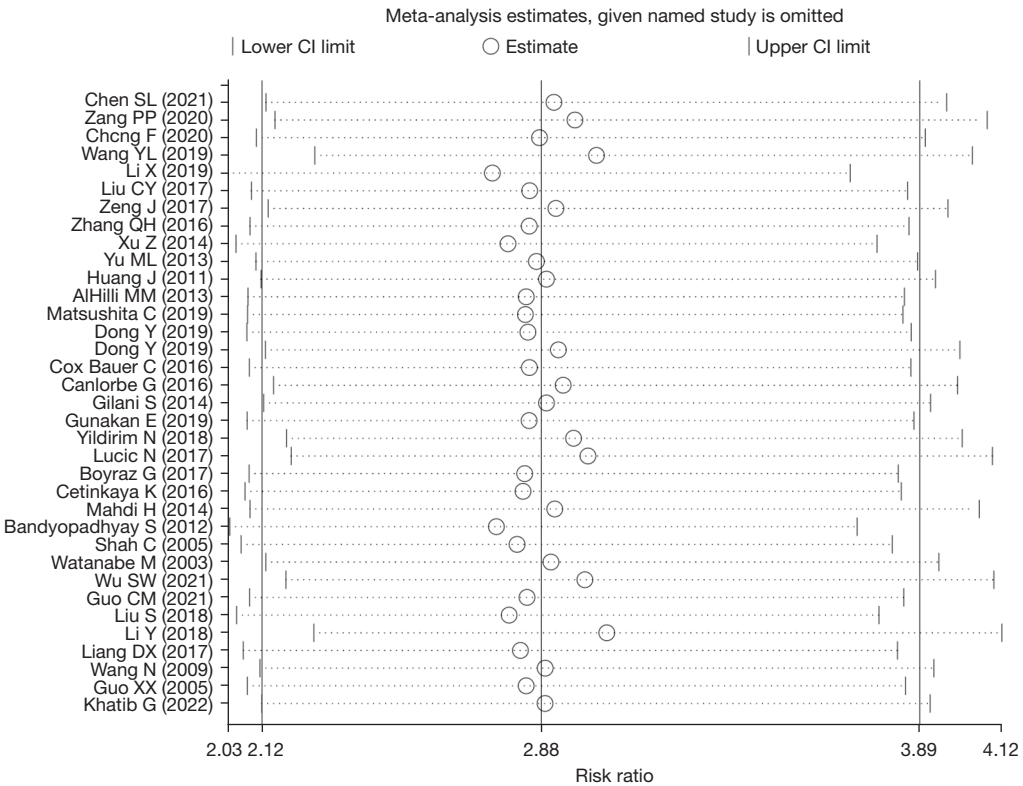

Figure 4 Sensitivity analysis of TD and LNM. CI, confidence interval; TD, tumor diameter; LNM, lymph node metastasis.

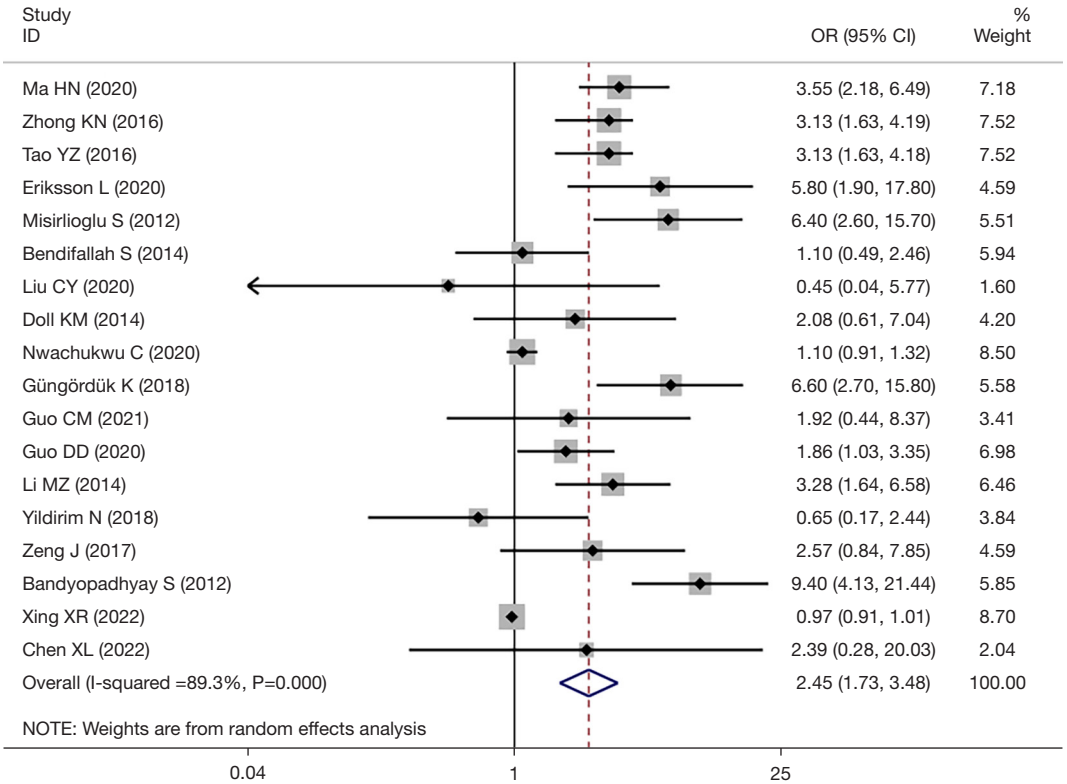

Figure 5 Forest plot of TD and recurrence. OR, odds ratio; CI, confidence interval; TD, tumor diameter.

influence on the results. Therefore, the high risk of LNM should be considered for EC patients with the TD >2 cm in clinical practice. TD is an important staging criterion for lung cancer and breast cancer, yet the mechanism of TD in EC staging and treatment remains elusive, which has been confirmed by our study.

LNM in EC patients represents a jumping process, which is different from the stepped process in cervical cancer patients. Even if there is no evidence of metastasis in PLN, cancer cells might migrate to PALN through the infundibulopelvic ligament. Therefore, some researchers have studied the association of TD with PLN and PALN, respectively. Five of included studies were divided into PLNM and para-aortic LNM (PALNM) according to the association of TD with LNM and the metastatic site. The risk of PLNM increased by 4.71 times in patients with the TD >2 cm (OR =4.71; 95% CI: 0.04–15.10; P=0.000), and the risk of PALN in patients with the TD >2 cm was 3.97 times higher than that in those with ≤2 cm (OR =3.97; 95% CI: 1.46–10.79; P=0.007). Stimulation was conducted using random-effect model and fixed-effect model, and the results were stable, which was in consistence with the results of studies mentioned above.

As a prognostic factor, TD is always associated with LNM, whereas the association of TD with EC recurrence is unclear (36,88,89). A study by Çakır *et al.* (90) revealed a 5-year DFS of 94% in EC patients with the TD <3.5 cm, and 89% in those with the TD >3.5 cm (P=0.128). TD failed to be a risk factor for post-LND recurrence in EC patients. Among the 17 studies that were finally included, most applied a TD cut-off value of 2 cm to assess the risk of recurrence. The results showed that the risk of recurrence in EC patients with the TD >2 cm was 2.45 times higher than that in those with the TD ≤2 cm (OR =2.45; 95% CI: 1.73–3.48; P<0.001). Significant heterogeneity existed among the studies (I^2=89.3%; P=0.000). The source of heterogeneity might be participants' continents, pathological grades, and FIGO stages. Publication bias assessment showed that publication bias exerted influence on the results. More RCT studies are needed to confirm the relationship between TD and recurrence It is worth noting that some studies have proposed that the risk of recurrence rise follows the increase of TD in EC patients, and the difference was statistically significant (76,83). There are also some studies (20,68,85)

Table 6 Subgroup analysis of TD and recurrence

Subgroup category	Number of documents included	OR	95% CI	P value	I^2	Q test P value
Continents						
Asia	13	2.44	1.45–4.10	0.001	0.090	0.000
North America	3	2.72	0.62–11.82	0.183	0.92	0.000
Europe	2	2.41	0.47–12.26	0.289	0.821	0.018
Univariate or multivariate						
Univariate	9	2.44	1.24–4.79	0.001	0.879	0.000
Multivariate	9	2.49	1.45–4.25	0.010	0.858	0.000
Pathological grade						
G1–G3	6	2.53	1.18–5.44	<0.001	0.896	0.000
G1–G4	1	0.65	0.17–2.44	0.520	–	–
G1–G2	1	6.6	2.70–15.80	<0.001	–	–
G1	1	1.1	0.91–1.32	0.351	–	–
G3	1	2.08	0.61–7.07	0.241	–	–
FIGO stage						
I–IV	6	3.01	1.31–6.94	0.010	0.629	0.019
I–III	3	0.97	0.92–1.02	0.217	0.00	0.794
I–II	5	2.96	2.33–3.76	<0.001	<0.001	0.554
IA	2	2.55	0.44–14.73	0.295	0.934	0.000
I	1	6.4	2.60–15.70	<0.001	–	–

TD, tumor diameter; OR, odds ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics.

Table 7 Relationship between TD and recurrence under different cut-off values

TD cut-off value (cm)	Number of documents included	OR	95% CI	P value	I^2	Q test P value
2	18	2.45	1.73–3.48	<0.001	0.893	0.000
2.5	1	18.7	2.4–140.3	<0.001	–	–
3.75	1	7.9	2.2–28.9	0.031	–	–

TD, tumor diameter; OR, odds ratio; CI, confidence interval.

which have presented the opposite attitude. This situation may be related to the FIGO stage and pathological grade of the participants. For example, study by Ocak *et al.* (68,69) recruited only FIGO stage-I patients, and the risk of early recurrence in these patients would be relatively low, so that it could not provide the best conclusion. If all the patients included had high pathological grade, the contribution of TD to recurrence might be masked due to the tendency of local and distant recurrence of highly malignant diseases (85).

Limitations

Our study also had some limitations. All extracted data were from published articles, and only part of the data contained patients' original information. All included studies were retrospectively designed so that the strength of evidence was lower that the evidence produced by prospective randomized controlled trials. There were few studies focusing on the association of TD with EC recurrence leading to bias in the

results. The inclusion and exclusion criteria varied among the studies leading to various dependent variables, which might induce bias in the results, even though the potential source of heterogeneity was analyzed. The lack of uniform standard for TD measurement might have affected the TD. TD measurement on hysterectomy specimens did not consider the effect of preoperative biopsy on TD.

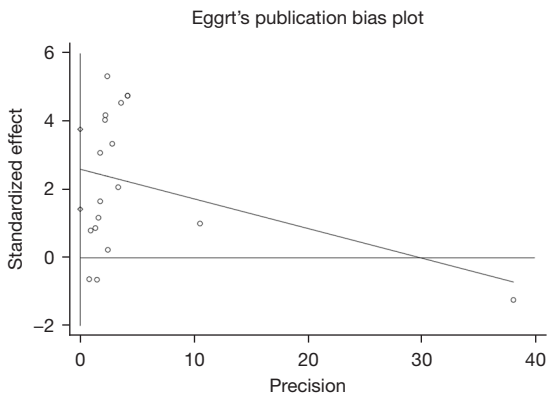

Figure 6 Egger diagram of TD and recurrence. Small circle, included studies; X-axis, logarithm is 0; slash, regression line. TD, tumor diameter.

Conclusions

EC patients with a TD >2 cm have a higher risk of LNM than those with a TD ≤2 cm. The risk of LNM and recurrence rises alongside the increase of TD in EC patients.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2595/rc

Conflicts of Interest: All authors have completed the ICMJE

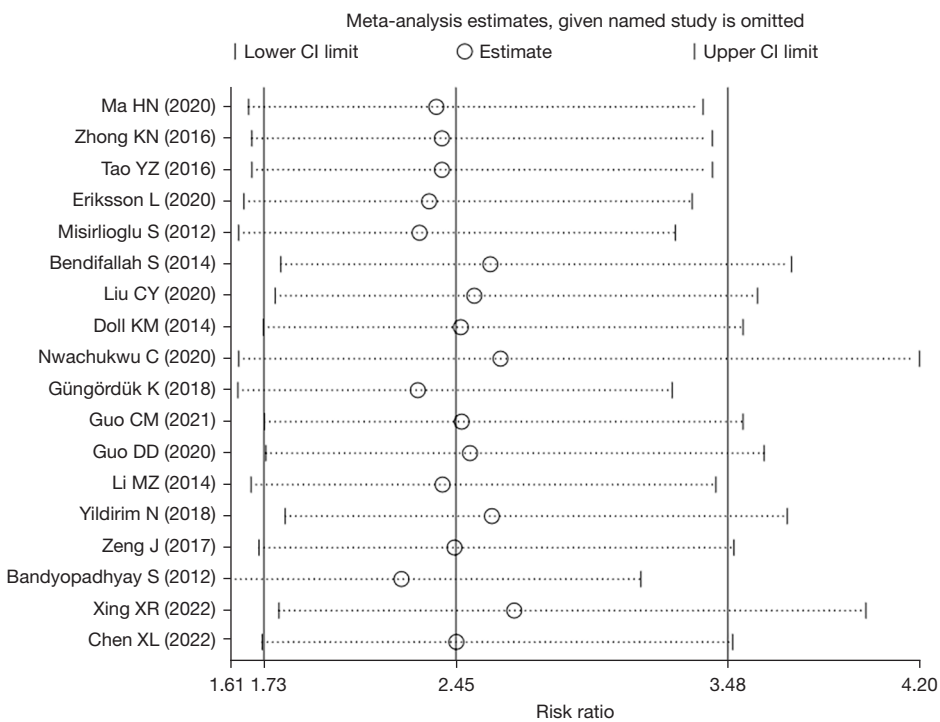

Figure 7 Sensitivity analysis of TD and recurrence. CI, confidence interval; TD, tumor diameter.

uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-2595/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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