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, fatty-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 LN (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 Bougerara 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 uninccluded, 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.amergroups.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
(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
| 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 | 221 | 60 [31–88] | Univariate | Abdominal aorta | 2, 4 |
| 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) | 2015 | Turkey | G1–G3 | I–III | RC | 268 | 58.6 [27–80] | Univariate | Full range | 2 |
| Bendifallah S (36) | 2014 | India | G1–G3 | I–IIIC | RC | 52 | 64.9 [33–98] | Univariate | Full range | 1.5 |
| Rathod PS (38) | 2014 | Turkey | G1–G2 | IA–IIIC2 | RC | 52 | 58.3 [31–76] | Univariate | Abdominal aorta and pelvic cavity | 2 |
| Mahdi H (39) | 2015 | Turkey | G1–G4 | I | RC | 19,692 | 62.1 | Univariate | Full range | 2, 5 |
| Giliani S (40) | 2014 | USA | G1–G3 | Not provided | RC | 207 | 62.29±10.9 | Univariate | Full range | 2 |
| Ali-Hilli MM (41) | 2013 | USA | G1–G3 | I–II | RC | 883 | 63.9 | Univariate | Full range | 2 |
| Shah C (42) | 2012 | USA | G1–G3 | I–IV | RC | 345 | Not provided | Multivariate | Full range | 1 |
| Watanabe M (43) | 2003 | Japan | G1–G2 | IA–IIIC | RC | 107 | 54 [29–79] | Univariate | Full range | 2 |
| Cheng WF (44) | 1998 | China | G1–G3 | Not provided | RC | 42 | 52.3 [25–78] | Univariate | Full range | 2.5 |
| Wu SW (45) | 2021 | China | G1–G3 | I–III | RC | 1,346 | 60.0 | Multivariate | Full range | 2 |
| Guo CM (46) | 2021 | China | Not provided | I–IV | RC | 385 | 57±10 | Univariate | Full range | 2, 3, 4, 5 |
| Chen SL (47) | 2021 | China | G1–G3 | I–IV | RC | 268 | 54.0 | Multivariate | Full range | 2 |
| Zang PP (48) | 2020 | China | G1–G3 | Not provided | RC | 84 | 55.3±7.4 | Univariate | Pelvic cavity | 2 |
| Li YJ (49) | 2020 | China | G1–G3 | I–IV | RC | 393 | 56 [25–80] | Univariate | Pelvic cavity and abdominal aorta | 3 |
| Cheng F (50) | 2020 | China | G1–G3 | I–IV | RC | 520 | 55.3±8.4 | Multivariate | Full range | 2 |
| Wang YL (51) | 2019 | China | G1–G3 | Not provided | RC | 192 | Not provided | 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)**
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.
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 (I²=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

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**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±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–II       | 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.
| 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             |
| Yıldırım 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)

| 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             |
| Gungördük 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.
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                           | 12.57| 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].

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 I²=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 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.

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

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

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**Table 6** Subgroup analysis of TD and recurrence

| Subgroup category       | Number of documents included | OR   | 95% CI       | P value | I²   | 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  | 0.91–3.12    | 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 | I²   | 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.
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.

**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

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

**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.

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