Predictive factors of sentinel lymph node failed mapping in endometrial carcinoma patients: a systematic review and meta-analysis

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ABSTRACT

Objective In endometrial carcinoma patients, sentinel lymph node bilateral mapping fails in 20–25% of cases, with several factors affecting the likelihood of detection. However, pooled data about predictive factors of failure are lacking. The aim of this systematic review and meta-analysis was to assess the predictive factors of sentinel lymph node failed mapping in endometrial cancer patients undergoing sentinel lymph node biopsy.

Methods A systematic review and a meta-analysis was performed searching all studies assessing predictive factors of sentinel lymph node failed mapping in apparent uterine-confined endometrial cancer patients undergoing sentinel lymph node biopsy through the cervical injection of indocyanine green. The associations between sentinel lymph node failed mapping and predictive factors of failure were assessed, calculating the odds ratio (OR) with 95% confidence intervals.

Results Six studies with a total of 1345 patients were included. Compared with patients with sentinel lymph node bilateral successful mapping, patients with sentinel lymph node failed mapping showed: OR 1.39 (p=0.41) for body mass index >30 kg/m^2; OR 1.72 (p=0.24) for menopausal status; OR 1.19 (p=0.74) for adenomyosis; OR 0.86 (p=0.55) for prior pelvic surgery; OR 2.38 (p=0.26) for prior cervical surgery; OR 0.96 (p=0.89) for prior Cesarean section; OR 1.39 (p=0.70) for lysis of adhesions during surgery before sentinel lymph node biopsy; OR 1.77 (p=0.02) for indocyanine green dose <3 mL; OR 1.28 (p=0.31) for deep myometrial invasion; OR 1.21 (p=0.42) for International Federation of Gynecology and Obstetrics (FIGO) grade 3; OR 1.89 (p=0.01) for FIGO stages III-IV; OR 1.62 (p=0.07) for non-endometrioid histotype; OR 1.29 (p=0.25) for lymph-vascular space invasion; OR 4.11 (p<0.0001) for enlarged lymph nodes; and OR 1.71 (p=0.022) for lymph node involvement.

Conclusion Indocyanine green dose <3 mL, FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement are predictive factors of sentinel lymph node failed mapping in endometrial cancer patients.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ In endometrial carcinoma patients, the rate of sentinel lymph node mapping failure ranges from 20–25%. Pooled data assessing predictive factors of sentinel lymph node mapping failure in endometrial cancer patients undergoing sentinel lymph node biopsy through the cervical injection of indocyanine green are lacking.

WHAT THIS STUDY ADDS

⇒ Indocyanine green dose <3 mL, advanced International Federation of Gynecology and Obstetrics (FIGO) stage, lymph node involvement, and bulky lymph nodes are predictive factors of sentinel lymph node mapping failure in endometrial cancer patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Injection of an indocyanine green dose >3 mL may be recommended, as well as the need for a re-injection in case of upfront sentinel lymph node mapping failure. The association between sentinel lymph node failed mapping and lymph node involvement supports the importance of adherence to the Memorial Sloan Kettering sentinel lymph node algorithm for surgical staging in endometrial cancer patients in avoiding understaging.

INTRODUCTION

Endometrial cancer is the most common gynecological malignancy in high-income countries, with an estimated number of new cases of 65 950 in the USA in 2022.[1] The standard surgical staging for apparent uterine-confined endometrial cancer includes total hysterectomy, bilateral salpingo-oophorectomy with pelvic and/or para-aortic lymphadenectomy, or sentinel lymph node mapping.[2] Two large randomized trials reported that lymph node staging in endometrial cancer patients does not have a therapeutic value, but it is crucial for adjuvant treatment decision-making.[3 4] In order to reduce the risk of post-operative morbidity and long-term complications associated with lymphadenectomy,[5] sentinel lymph node biopsy has been proposed for the staging of early-stage endometrial cancer. Several studies have shown that sentinel

lymph node biopsy has a high sensitivity and low false negative rate in patients with early-stage endometrial cancer.[6 7] Additionally, it may be associated with a more intensive pathologic assessment (ultrastaging), with the advantage of detecting low volume metastasis which could be missed by standard histological examinations.[8 9]

According to National Comprehensive Cancer Network guidelines,[10] sentinel lymph node biopsy through indocyanine green cervical injection can be considered for the surgical staging of apparent uterine-confined endometrial cancer. Such guidelines recommend adherence to the sentinel lymph node algorithm, which requires side-specific pelvic lymphadenectomy in case of failed mapping and debulking of any enlarged lymph nodes regardless of mapping. In fact, sentinel lymph node bilateral mapping fails in 20% to 25% of cases, with several factors affecting likelihood of detection.[7 11 12]

In order to obtain the highest rate of sentinel lymph node mapping and to minimize the number of side-specific lymphadenectomies performed, it is crucial to identify factors associated with sentinel lymph node mapping failure. Moreover, the identification of predictive factors of sentinel lymph node detection failure might help in pre-operative surgical planning. However, although several factors[7 11 13–19] have been reported to be associated with sentinel lymph node detection outcome, pooled data are lacking. The aim of this study was to assess predictive factors of sentinel lymph node failed mapping in early-stage endometrial cancer patients undergoing sentinel lymph node biopsy through indocyanine green cervical injection.

METHODS

Study Protocol

Each review step was independently conducted by two authors according to an *a priori* protocol. A third author was requested in case of disagreements. The study was reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist and guidelines.[20]

Search Strategy and Study Selection

MEDLINE, Scopus, Google Scholar, Web of Sciences, Cochrane Library, ClinicalTrial.gov, and Embase were searched from the inception of each database to October 2021, adopting a combination of the following text words: 'SLN'; 'sentinel lymph node'; 'biopsy'; 'SLND'; 'LND'; 'lymph node dissection'; 'lymphadenectomy'; 'lymph'; 'staging'; 'ultrastaging'; 'algorithm'; 'Indocyanine Green'; 'ICG'; 'dye'; 'endometr*'; 'mapping'; 'predictive factors'; 'prediction'; 'failure'; 'carcinoma'; 'cancer'; 'tumor'; 'neoplasia'; 'malignancy'; 'uter*'. Reference lists from eligible studies were also screened.

Peer reviewed studies assessing predictive factors of sentinel lymph node failed mapping in early-stage endometrial cancer patients undergoing sentinel lymph node biopsy through indocyanine green cervical injection were included. *A priori* exclusion criteria were: reviews articles; case reports; studies adopting dye different from indocyanine green; and studies adopting indocyanine green injection site different from cervix.

Risk of Bias Within Studies

Risk of bias within the studies was assessed according to the Methodological Index for Non-Randomized Studies (MINORS).[21] Five applicable domains were assessed: (1) Aim (if studies had a clearly stated aim); (2) Consecutive patients (if all patients potentially fit for inclusion were included during the study period); (3) Prospective data collection (if data were collected according to a protocol established before the beginning of the study); (4) Endpoints appropriate to the aim of the study (if the most relevant predictive factors of sentinel lymph node failed mapping were assessed); (5) Unbiased assessment of endpoints (if absolute number of patients with sentinel lymph node failed mapping were reported; if a minimally-invasive approach was adopted). Each domain for each included study was judged at 'low', 'unclear', or 'high risk' of bias based on data that were 'reported and adequate', 'not reported' or 'reported but inadequate', respectively.

Data Extraction

The PICO (Population, Intervention, Comparator, Outcomes) items[20] were used for data extraction. 'Population' was early-stage endometrial cancer patients undergoing sentinel lymph node biopsy through indocyanine green cervical injection. 'Intervention' was sentinel lymph node failed mapping, including both bilateral and unilateral failed mapping. 'Comparator' was sentinel lymph node successful mapping, defined as mapping of at least one sentinel lymph node in each hemipelvis. 'Outcomes' were the associations between sentinel lymph node failed mapping and the presence of predictive factors of failure.

For each included study, two by two contingency tables were built considering two qualitative variables:

- sentinel lymph node mapping, dichotomized as 'failed' and 'successful'
- predictive factors of failure, dichotomized as 'present' and 'absent'.

Data Analysis

The associations between sentinel lymph node failed mapping and predictive factors of failure were assessed by calculating the odds ratio (OR) with 95% confidence interval (95% CI) for individual studies and as pooled estimates. In case of impossibility to calculate OR because of non-extractable data (absolute number of patients with sentinel lymph node failed and successful mapping not reported for each comparison), pooled analyses were based directly on OR. Results were reported graphically on forest plots.

All analyses were performed adopting the random effect model of DerSimonian and Laird[22] and assessing the statistical heterogeneity among studies by the inconsistency index (I^2). In detail, heterogeneity was judged as null in case of $I^2=0\%$, very low in case of $0\%<I^2\leq25\%$, low in case of $25\%<I^2\leq50\%$, moderate in case of $50\%<I^2<75\%$, and high in case of $I^2\geq75\%$.

Review Manager version 5.4 (Copenhagen: The Nordic Cochrane Centre, Cochrane Collaboration, 2014) and Meta-DiSc version1.4 (Clinical Biostatistics Unit, Ramon y Cajal Hospital, Madrid, Spain) were used as software.

Table 1 Summary of associations between sentinel lymph node failed mapping and predictive factors of failure

Predictive factor of failure	OR (95% CI)	P value
BMI >30 kg/m^2	1.39 (0.63 to 3.07)	0.41
Menopausal status	1.72 (0.69 to 4.31)	0.24
Adenomyosis	1.19 (0.43 to 3.30)	0.74
Prior pelvic surgery	0.86 (0.52 to 1.43)	0.55
Prior cervical surgery	2.38 (0.53 to 10.77)	0.26
Prior Cesarean section	0.96 (0.49 to 1.88)	0.89
Lysis of adhesions	1.39 (0.27 to 7.23)	0.70
Indocyanine green dose <3 mL	**1.77 (1.11 to 2.83)**	**0.02**
Deep myometrial invasion	1.28 (0.80 to 2.03)	0.31
FIGO grade 3	1.21 (0.76 to 1.92)	0.42
FIGO stages III-IV	**1.89 (1.16 to 3.09)**	**0.01**
Non-endometrioid histotype	1.62 (0.96 to 2.74)	0.07
Lymph-vascular space invasion	1.29 (0.84 to 1.99)	0.25
Enlarged lymph nodes	**4.11 (2.30 to 7.35)**	**<0.0001**
Lymph node involvement	**1.71 (1.08 to 2.72)**	**0.02**

BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics.

RESULTS

Studies Selection

The electronic searches resulted in 9120 studies. Of these, 4997 studies remained after duplicate removal, 193 studies remained after title screening, and nine studies remained after abstract screening. Lastly, six studies with a total of 1345 patients were included in the qualitative and quantitative analyses after full-text evaluation[11 14–17 19] (online supplemental figure S1).

Study and Patient Details

All included studies were observational cohort studies: two were prospective[11 16] and four were retrospective[14 15 17 19] (online supplemental table S1). Patients' age and body mass index (BMI) ranged from 26 to 91 years and 17–65.3 kg/m^2, respectively. From studies with available data, 89.7% of women had a menopausal status, 15.8% adenomyosis, 35.7% prior pelvic surgery, 1.6% prior cervical surgery, 12.1% prior Cesarean section, and 13.7% required lysis of adhesions during surgery (online supplemental table S2).

Endometrial cancer had deep myometrial invasion in 27.1% of cases, International Federation of Gynecology and Obstetrics (FIGO) grade 3 in 21.8%, FIGO stage III-IV in 13.7%, non-endometrioid histotype in 14.7%, lymph-vascular space invasion in 23.4%, enlarged lymph nodes in 7.4%, and lymph node involvement in 10.4% (online supplemental table S2).

The surgical approach was robotic and/or laparoscopic in three studies,[14 16 19] and mixed (laparoscopic, robotic, open, and vaginal) in three studies[11 15 17] (online supplemental table S3). In all included studies, the injection was performed into the cervix at the 3 o'clock and 9 o'clock positions. Indocyanine green concentration was 1.25 mg/mL in five studies[11 14 16 17 19] and 2.5 mg/mL in one study.[15] The indocyanine green dose ranged from 2–4 mL. All included studies adopted an indocyanine green superficial and deep injection, with the exception of one study[19] which only adopted a superficial injection (online supplemental table S3).

The rate of sentinel lymph node failed mapping was 21.7% (online supplemental table S3). Predictive factors of sentinel lymph node failed mapping suitable for quantitative analysis from the included studies were: BMI >30 kg/m^2, menopausal status, adenomyosis, prior pelvic surgery, prior cervical surgery, prior Cesarean section, lysis of adhesions, indocyanine green dose <3 mL, deep myometrial invasion, FIGO grade 3, FIGO stage III-IV, non-endometrioid histotype, lymph-vascular space invasion, enlarged lymph nodes, and lymph node involvement.

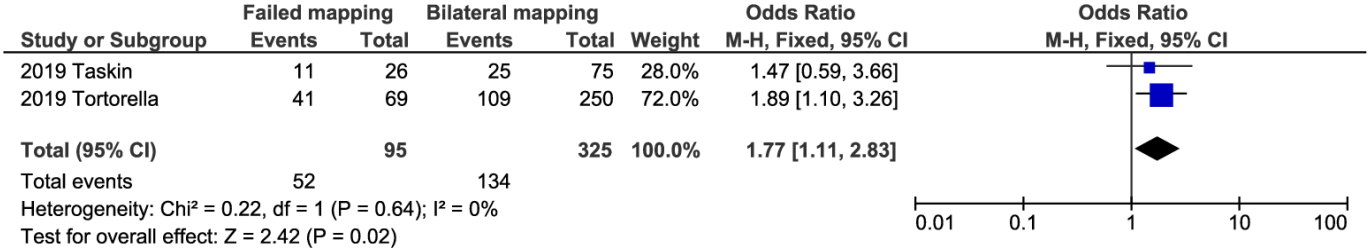

Figure 1 Forest plot of individual studies and pooled odds ratios with 95% confidence intervals assessing the associations between sentinel lymph node failed mapping and indocyanine green dose <3 mL.

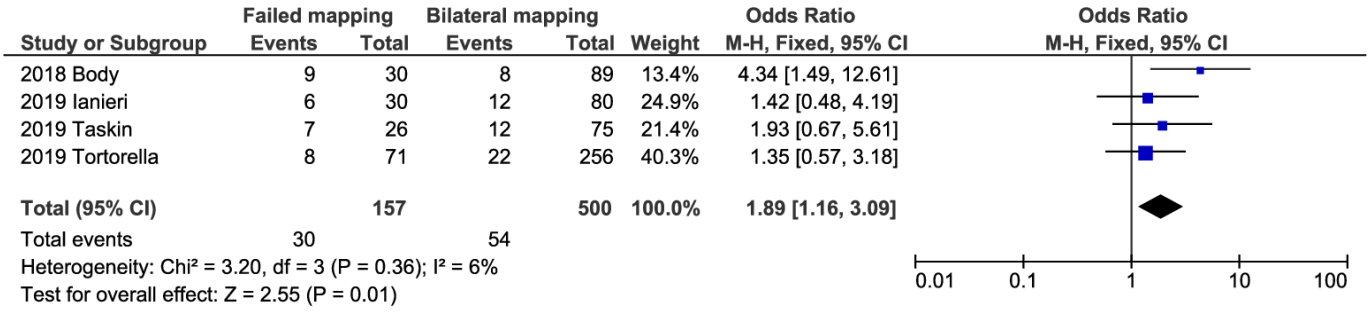

Figure 2 Forest plot of individual studies and pooled odds ratios with 95% confidence intervals assessing the associations between sentinel lymph node failed mapping and FIGO stages III-IV. FIGO, International Federation of Gynecology and Obstetrics.

Risk of Bias Within Studies

All included studies were considered at low risk of bias in the 'Aim' and 'Prospective data collection' domains. In the 'Consecutive patients' domain, two studies[11 16] were considered at unclear risk of bias because they did not report if all patients potentially fit for inclusion were included in the study during the study period. In the 'Endpoints appropriate to the aim of the study' domain, one study[14] was considered at unclear risk of bias because it only assessed obesity as the predictive factor of sentinel lymph node failed mapping. In the 'Unbiased assessment of endpoints' domain, three studies were considered at unclear risk of bias: one study[19] because it did not report the absolute number of patients with sentinel lymph node failed and successful mapping for each comparison, only reporting ORs; the other three studies[11 15 17] because they did not exclusively adopt a minimally-invasive approach to assess predictive factors of sentinel lymph node failed mapping.

Risk of bias within studies assessment is graphically shown in online supplemental figure S2.

Predictive Factors

Out of six included studies: three studies were eligible for assessing BMI >30 kg/m^2 [14 16 17]; three for menopausal status[11 15 16]; two for adenomyosis[17 19]; two for prior pelvic surgery[16 17]; two for prior cervical surgery[16 17]; three for prior Cesarean section[15–17]; two for lysis of adhesions during surgery before sentinel lymph node biopsy[17 19]; two for indocyanine green dose <3 mL[11 17]; three for deep myometrial invasion[11 16 17]; three for FIGO grade 3[11 15 17]; four for FIGO stages III-IV[11 15–17]; three for non-endometrioid histotype[11 15 17]; four for lymph-vascular space invasion[11 15–17]; two for enlarged lymph nodes[17 19]; and two for lymph node involvement.[17 19]

A summary of pooled ORs with 95% CIs assessing the associations between sentinel lymph node failed mapping and predictive factors of failure is reported in Table 1.

Forest plots of individual studies and pooled ORs with 95% CIs assessing the associations between sentinel lymph node failed mapping and each predictive factor of failure are available on Figures 1–4 and online supplemental figures S3-S13).

DISCUSSION

Main Results

This study shows that indocyanine green dose <3 mL, FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement are predictive factors of sentinel lymph node failed mapping in endometrial cancer patients. However, BMI >30 kg/m^2, menopausal status, adenomyosis, prior pelvic or cervical surgery or Cesarean sections, lysis of adhesions at the beginning of surgery, deep myometrial invasion, FIGO grade 3, non-endometrioid histotype, and lymph-vascular space invasion were not significantly associated with sentinel lymph node mapping detection outcome.

Results in the Context of Published Literature

Sentinel lymph node biopsy, instead of systematic pelvic and paraaortic lymphadenectomy, can be routinely adopted for surgical staging of early-stage endometrial cancer.[10 23] Although the use of indocyanine green and the standardization of the injection technique improved the overall sentinel lymph node detection rate,[24] sentinel lymph node bilateral mapping failed in 20% to 25% of cases.[7 11 12] Unfortunately, to date, pooled estimates regarding

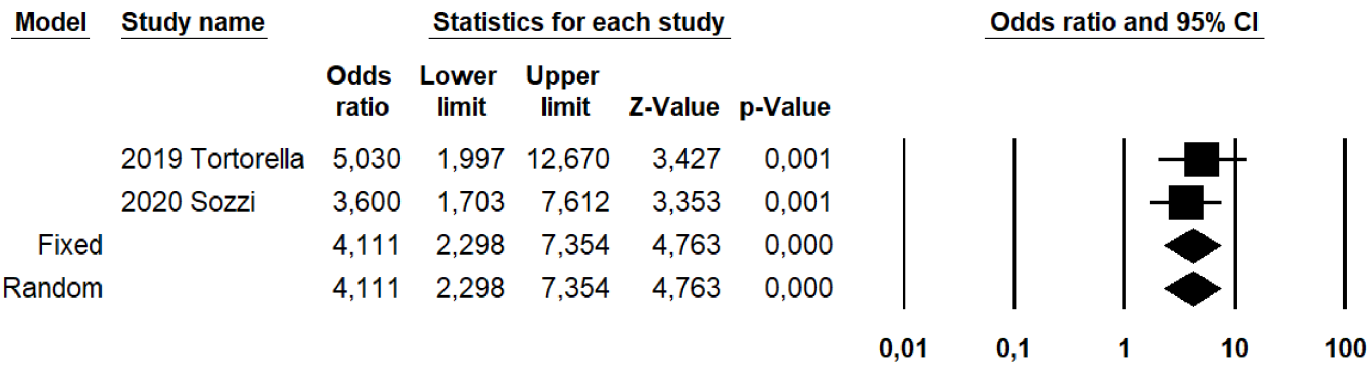

Figure 3 Forest plot of individual studies and pooled odds ratios with 95% confidence intervals assessing the associations between sentinel lymph node failed mapping and enlarged lymph nodes.

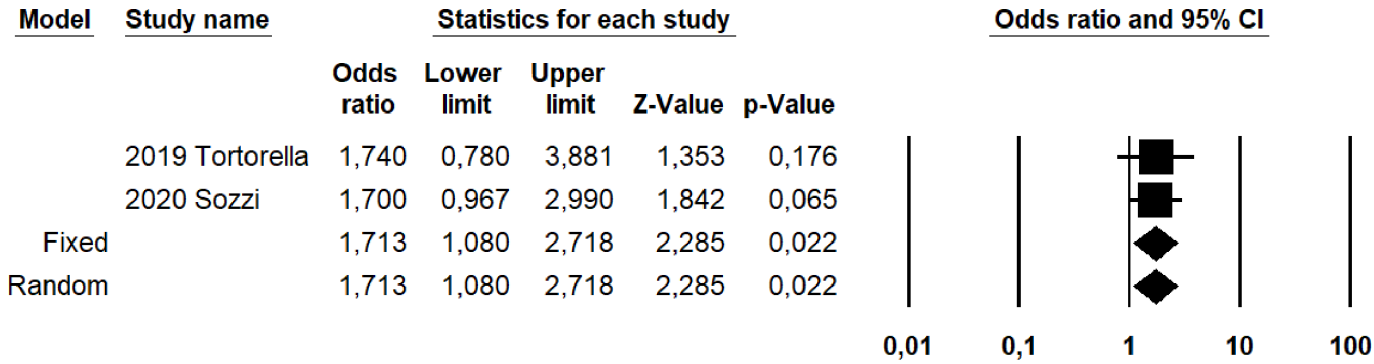

Figure 4 Forest plot of individual studies and pooled odds ratios with 95% confidence intervals assessing the associations between sentinel lymph node failed mapping and lymph node involvement.

predictive factors of sentinel lymph node detection failure are not yet available.

Regarding clinical features, we found that obesity, menopausal status, and adenomyosis were not significantly associated with sentinel lymph node mapping failure. The association between obesity and sentinel lymph node mapping failure was previously reported by Tanner et al,[13] who showed that obese patients had a lower bilateral sentinel lymph node detection rate using blue dye or indocyanine green. However, comparing the two dyes, they showed that indocyanine green had a higher bilateral detection rate than blue dye when used in patients with BMI >30 kg/m^2, in accordance with data from a meta-analysis by Smith et al.[7] Our pooled data suggest that obesity has a non-significant detrimental effect on sentinel lymph node mapping detection when the indocyanine green was adopted as a dye. Concerning menopausal status, although it has been associated with a worsening of the lymphatic flow due to increased vascular permeability,[16] such an effect did not impact sentinel lymph node mapping detection in our analysis.

Surgical history was not significantly associated with sentinel lymph node mapping failure. Unfortunately, a sub-group analysis based on the type of previous surgery was not feasible. In fact, some types of surgery, such as retroperitoneal surgery, show a higher risk of lymphatic damage, possibly affecting lymphatic flow more.[16] We did not find a significant association also assessing the need of lysis of adhesions at the beginning of surgery, which was instead reported to be correlated with sentinel lymph node mapping failure.[17] When lysis of adhesions is required, this must be done before the indocyanine green cervical injection, thus reducing the risk of lymphatic damage.[19]

Regarding the indocyanine green dose, it appeared as a significant predictive factor of sentinel lymph node mapping failure if <3 mL. Our pooled analysis appeared to overcome the lack of statistical significance reported in the individual studies. In detail, although the sentinel lymph node mapping success rate was higher in patients undergoing indocyanine green dose >3 mL in both individual studies included in our analysis,[11 17] they failed to demonstrate a statistically significant association between an indocyanine green dose <3 mL and lymph node mapping failure because of insufficient statistical power. Our finding would support an injection of an indocyanine green dose >3 mL and the need for a re-injection in case of upfront sentinel lymph node mapping failure as a failed detection appeared to be associated with a lower indocyanine green dose.

Among tumor characteristics, deep myometrial invasion, FIGO grade 3, non-endometrioid histotype, and lymph-vascular space invasion were not associated with sentinel lymph node mapping outcome. These findings were similar to those reported for sentinel lymph node biopsy in breast cancer,[25–27] and would further support the use of sentinel lymph node biopsy for surgical staging even in high risk endometrial cancer patients.[28–33] On the other hand, FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement appeared as predictive factors of sentinel lymph node failed mapping in endometrial cancer patients. These findings would be explained by the hypothesis that the presence of high volume lymphatic metastasis would lead to a blockage of the physiological lymphatic drainage by the presence of tumoral thrombi.[11 13 17 19] Based on these results, pre-operative imaging appears to be crucial in identifying patients with bulky lymph nodes or metastatic disease, who may be at higher risk of unsuccessful sentinel lymph node mapping. This could help surgery planning. Moreover, our findings support the importance of adherence to the Memorial Sloan Kettering sentinel lymph node algorithm for surgical staging in endometrial cancer patients.[34] In fact, this algorithm includes retroperitoneal evaluation with excision of any suspicious enlarged nodes regardless of mapping and side-specific pelvic and para-aortic lymphadenectomy in the case of unmapped hemi-pelvis.[10 23] This management appears crucial to avoid understaging as sentinel lymph node failed mapping appeared to be associated with FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement.

Strengths and Weaknesses

To the best of our knowledge, this study is the first systematic review and meta-analysis to investigate predictive factors of sentinel lymph node failed mapping in early-stage endometrial cancer patients undergoing sentinel lymph node biopsy through indocyanine green cervical injection.

Our findings are supported by an overall good quality of the included studies, as shown in the risk of bias within studies evaluation. However, our study has a number of limitations. First, not all included studies assessed each evaluable predictive factor. Moreover, one study did not report the absolute number of patients with sentinel lymph node failed and successful mapping by predictive factor,[19] not allowing us to pool its data with those from other included studies. However, such study reported odds ratios for each predictive factor, and was considered in case of lack of at least two included studies which reported absolute numbers. Second, among

possible predictive factors of sentinel lymph node failed mapping in endometrial cancer, we were unable to assess surgeon expertise as it was differently defined in each included study. In fact, according to Ianieri et al,[16] the only factor which showed significant association with sentinel lymph node successful mapping was the experience of the surgeon. Third, another limitation of our study may be the impossibility to assess the presence of adipose-only sentinel lymph node among the detected sentinel lymph nodes in the included studies. In fact, adipose-only sentinel lymph node consists of the excision of a suspected mapped lymph node which reveals to be only fat tissue without nodal tissue on final pathology. Therefore, it can falsely increase the rate of successful sentinel lymph node mapping.[35] However, the adipose-only sentinel lymph node rate is expected to be low (<15%).[35]

Implications for Practice and Future Research

As failed sentinel lymph node detection appears to be associated with a lower indocyanine green dose, an injection of an indocyanine green dose >3 mL may be recommended, as well as the need for a re-injection in case of upfront sentinel lymph node mapping failure. On the other hand, the association between sentinel lymph node failed mapping and FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement supports the importance of (1) preoperative imaging for better surgery planning (identifying patients with bulky lymph nodes or metastatic disease, and thus at higher risk of unsuccessful sentinel lymph node mapping); and (2) adherence to the Memorial Sloan Kettering sentinel lymph node algorithm for surgical staging in endometrial cancer patients for avoiding understaging. Additional studies are encouraged to validate and further investigate these findings.

Conclusions

Indocyanine green dose <3 mL, FIGO stage III-IV, enlarged lymph nodes, and lymph node involvement are predictive factors of sentinel lymph node failed mapping in endometrial cancer patients.

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