



# Diagnosis and Surgical Management of Uterine Cancer: A Comprehensive Systematic Review of Minimally Invasive Techniques, Molecular Staging, and Oncological Outcomes

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## ABSTRACT

### Introduction

Uterine cancer, overwhelmingly represented by endometrial carcinoma (EC), is the most frequently diagnosed gynecologic malignancy in developed nations, with incidence rates steadily rising. Definitive surgical staging—historically involving hysterectomy, bilateral salpingo-oophorectomy, and comprehensive lymphadenectomy—is the cornerstone of management, dictating prognosis and the requirement for adjuvant therapy. This review systematically synthesizes high-level evidence on comparative diagnostic accuracy, the oncological safety of minimally invasive surgery (MIS) versus open surgery (OS), and the non-inferiority of Sentinel Lymph Node Biopsy (SLNB) in the context of emerging molecular risk stratification frameworks, notably the 2023 International Federation of Gynecology and Obstetrics (FIGO) staging system.

## Methods

A rigorous systematic search was executed across major medical literature databases (PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library) for comparative studies, systematic reviews, and meta-analyses published since 2017. Inclusion was restricted to studies comparing diagnostic modalities (Transvaginal Ultrasound vs. Hysteroscopy) and surgical interventions (Minimally Invasive Surgery vs. Open Surgery; SLNB vs. comprehensive Lymphadenectomy) in EC patients. Data extraction focused on 15 specific outcomes encompassing long-term survival endpoints (Overall Survival, Disease-Free Survival), perioperative morbidity (blood loss, lymphedema), and staging accuracy. Given the observational nature of most surgical comparisons, the Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I) tool was employed for quality assessment (Cochrane Methods Bias, 2024).

## Results

The synthesis incorporated evidence from 16 high-quality publications, integrating data from meta-analyses pooling over 10,000 patients. Diagnostic accuracy studies confirmed the superior performance of hysteroscopy, achieving an overall accuracy of 93.3% versus 83.5% for TVUS (Huang et al., 2023). For surgical safety, the comparison of MIS versus OS confirmed oncological non-inferiority, even in high-risk EC, with comparable 5-year Disease-Free Survival (DFS) (Relative Risk 0.93, 95% CI 0.82–1.05) and Overall Survival (OS) (RR 0.92, 95% CI 0.77–1.11) (Mariani et al., 2023). Nodal management data decisively favored SLNB, which demonstrated significantly reduced operative blood loss (Mean Difference -54.40) and minimized the

long-term risk of debilitating lymphedema (RR 0.25) (Chen et al., 2020; SGO/Mayo Clinic, 2021). Furthermore, SLNB proved superior in detecting positive pelvic nodes (Odds Ratio 1.35) due to mandatory ultra-staging protocols (Toro et al., 2019).

### **Discussion**

The collective, high-level evidence mandates a unified standard of care for EC: an approach that is minimally invasive, highly selective in nodal staging via SLNB, and precisely guided by molecular risk stratification (FIGO 2023). The established safety of MIS across all risk strata ensures rapid recovery, while the high fidelity of SLNB staging provides the necessary prognostic information. The integration of molecular markers (e.g., POLE status) into FIGO 2023 staging allows for safe treatment de-escalation, potentially sparing approximately 16% of early-stage patients from unnecessary adjuvant therapy (Tureanu et al., 2023).

### **Conclusion**

Minimally Invasive Surgery and Sentinel Lymph Node Biopsy are decisively endorsed as the standard surgical approach for EC, providing equivalent oncological outcomes to traditional methods while significantly improving surgical safety and quality of life metrics. Future research should prioritize de-escalating surgical and adjuvant therapy for patients with ultra-favorable molecular profiles.

### **Keywords**

Endometrial Cancer; Uterine Cancer; Minimally Invasive Surgery; Sentinel Lymph Node Biopsy; Lymphadenectomy; FIGO 2023; Molecular Classification; Systematic Review; Oncological Outcomes.

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## INTRODUCTION

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### Background and Epidemiology of Endometrial Cancer (EC)

Endometrial cancer stands as the most common gynecological malignancy in affluent nations, presenting a rising global health burden marked by increasing incidence and associated mortality (Stefanova et al., 2024; Papatheodorou et al., 2023). The foundation of effective EC management rests upon accurate surgical staging, which involves the removal of the uterus, tubes, and ovaries, coupled with a thorough assessment of regional lymph nodes (Zang et al., 2021). The staging outcome is the primary determinant for patient prognosis and the necessity for adjuvant treatments, such as radiation or chemotherapy.

### The Molecular Paradigm Shift (FIGO 2023)

Traditional EC classification, dividing tumors into Type I (estrogen-driven, low-grade) and Type II (aggressive, non-estrogen related), has been largely superseded by molecular classification derived from The Cancer Genome Atlas (TCGA) (Zang et al., 2021). This refined system categorizes EC into four prognostic groups based on key molecular alterations: POLE hypermutated, Mismatch Repair Deficient (MMRD), Non-Specific Molecular Profile (NSMP), and TP53 abnormal (p53abn) (Tureanu et al., 2023).

The International Federation of Gynecology and Obstetrics (FIGO) formally integrated these molecular markers into the updated **FIGO 2023 staging system**, marking a profound shift toward precision oncology (Soliman et al., 2024; Stefanova et al., 2024). This revision provides more precise prognostic definitions, distinguishing between early-stage tumors that may safely forgo adjuvant therapy (e.g., POLE ultra-mutated) and those requiring aggressive systemic management (e.g., p53abn) (Tureanu et al., 2023). Furthermore, FIGO 2023 now mandates distinguishing between micrometastases (IIIC1i) and macrometastases (IIIC1ii) in lymph nodes, underscoring the necessity for high-fidelity nodal assessment (Soliman et al., 2024).

## Objectives of the Systematic Review

This systematic review aims to synthesize the most robust, contemporary clinical evidence across the EC care continuum, addressing three critical domains:

1. To quantitatively compare the diagnostic performance (sensitivity and accuracy) of hysteroscopy versus transvaginal ultrasound (TVUS) in women presenting with abnormal uterine bleeding (AUB).
2. To establish the oncological equivalence of Minimally Invasive Surgery (MIS) compared to Open Surgery (OS), particularly in historically under-studied, high-risk EC populations.
3. To comprehensively assess the operative, safety, and oncological outcomes of Sentinel Lymph Node Biopsy (SLNB) against comprehensive Lymphadenectomy (LND), validating SLNB as the preferred staging method in the molecular era.

## Research Gap and Novelty

A significant gap in the literature concerned the confidence to recommend MIS for patients with aggressive, high-risk EC subtypes (e.g., serous, clear cell, Grade 3 endometrioid) due to historical concerns about adequate staging or tumor spill (Mariani et al., 2023; Papatheodorou et al., 2023). Previous large-scale randomized trials primarily focused on low- and intermediate-risk cohorts.

The novelty of this review lies in its synthesis of the latest high-volume meta-analyses that specifically address this high-risk population, definitively establishing MIS as oncologically equivalent (Mariani et al., 2023; Papatheodorou et al., 2023). Furthermore, this review explicitly connects the adoption of low-morbidity surgical techniques (MIS + SLNB) with the enhanced prognostic power of the new FIGO 2023 molecular staging, demonstrating how surgical precision and biological risk stratification work synergistically to personalize treatment and safely de-escalate adjuvant therapy (Tureanu et al., 2023).

## Hypotheses

H1: Minimally Invasive Surgery (MIS) achieves equivalent long-term Disease-Free Survival (DFS) and Overall Survival (OS) compared to Open Surgery (OS) in high-risk endometrial cancer.

H2: Sentinel Lymph Node Biopsy (SLNB) significantly reduces perioperative and long-term morbidity (e.g., lymphedema) compared to Lymphadenectomy (LND) while maintaining non-inferior survival outcomes.

H3: Hysteroscopy exhibits superior diagnostic accuracy and sensitivity compared to Transvaginal Ultrasound (TVUS) for endometrial pathology.

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## METHODS

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### Search Strategy and Data Sources

The literature search utilized the following search terms and Boolean operators: ("Endometrial Cancer" OR "Uterine Cancer") AND ("Minimally Invasive Surgery" OR "Robotic Surgery" OR "Laparoscopy") AND ("Sentinel Lymph Node" OR "Lymphadenectomy") AND ("FIGO 2023" OR "Molecular Classification" OR "Survival"). Databases included PubMed, Google Scholar, Semantic Scholar, Springer, Wiley Online Library. The search focused on publications from January 2017 to the present to capture contemporary surgical and molecular staging data.

### Eligibility and Study Selection

Inclusion criteria targeted high-level evidence: systematic reviews, meta-analyses, and high-quality comparative cohort studies (retrospective and prospective). Studies were included if they provided quantifiable comparisons between the designated interventions (MIS vs. OS, SLNB vs. LND, Hysteroscopy vs. TVUS) and reported on at least one of the 15 pre-specified outcomes (see Section 2.3). A minimum of 16 key publications were synthesized, which incorporated pooled data from dozens of underlying primary studies.

### Data Extraction and Outcomes Analyzed

Data extraction was performed independently by reviewers to mitigate bias. Fifteen critical

outcomes were extracted across three domains:

| Domain                            | Key Outcomes Analyzed (Total = 15)                                                                                                                                                                                     |
|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Diagnosis (Hysteroscopy vs. TVUS) | Hysteroscopy Accuracy, TVUS Accuracy, Hysteroscopy Sensitivity.                                                                                                                                                        |
| Surgical Approach (MIS vs. OS)    | Disease-Free Survival (DFS), Overall Survival (OS), Local Recurrence Rate, Total Complication Rate (Clavien-Dindo \ge III).                                                                                            |
| Nodal Staging (SLNB vs. LND)      | Intraoperative Blood Loss, Positive Pelvic Node Detection Rate, Para-aortic LN Detection Rate, Total Nodal Yield, Overall Recurrence Rate, Progression-Free Survival (PFS), Overall Survival (OS), Risk of Lymphedema. |

### Quality Assessment and Risk of Bias (RoB)

Given the scarcity of large, dedicated Randomized Controlled Trials (RCTs) for surgical comparisons in high-risk EC, the majority of evidence synthesized was derived from observational studies and their subsequent meta-analyses (Mariani et al., 2023; Chen et al., 2020). Therefore, the **ROBINS-I (Risk of Bias in Non-randomized Studies – of Interventions)** tool was used to assess methodological quality (Cochrane Methods Bias, 2024).

The assessment highlighted that studies comparing MIS vs. OS and SLNB vs. LND

consistently carry a "Serious" risk of bias, particularly in the domains of confounding and selection of participants (Table 1). This is a well-recognized limitation, as patients selected for less invasive procedures often possess more favorable underlying prognostic factors (e.g., lower BMI, smaller tumor burden), necessitating caution when interpreting non-inferiority results (Chen et al., 2020).

**Table 1: Risk of Bias Assessment (ROBINS-I) for Key Comparative Analyses**

| Comparative Analysis   | Author, Year          | Bias due to Confounding | Bias in Selection of Participants | Bias due to Deviations (Treatment ) | Overall Risk of Bias |
|------------------------|-----------------------|-------------------------|-----------------------------------|-------------------------------------|----------------------|
| MIS vs. OS (High-Risk) | Mariani et al. (2023) | Serious                 | Serious                           | Low                                 | Serious              |
| SLNB vs. LND           | Chen et al. (2020)    | Serious                 | Serious                           | Low                                 | Serious              |
| SLNB vs. LND           | Toro et al. (2019)    | Serious                 | Serious                           | Low                                 | Serious              |
| Hysteroscopy vs. TVUS  | Huang et al. (2023)   | Low                     | Low                               | N/A                                 | Low                  |

### Data Synthesis and Statistical Analysis

Quantitative synthesis relied on extracting pooled effect measures (Relative Risks, Odds

Ratios, Mean Differences) and their 95% Confidence Intervals (CI) from the meta-analyses. Heterogeneity ( $I^2$ ) was critically evaluated; high  $I^2$  values indicated significant variability across pooled studies, prompting the use of random-effects models in the original source analyses to account for differences in surgical technique and patient cohorts (Chen et al., 2020).

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## RESULTS

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### Overview of Synthesized Evidence Base

The systematic review focused on three primary areas, supported by the following high-impact meta-analyses and systematic reviews:

1. **MIS vs. OS in High-Risk EC:** Mariani et al. (2023) synthesized data from 14 cohorts (N=2,874).
2. **SLNB vs. LND Outcomes:** Chen et al. (2020) pooled 15 studies (N=5,820) and Toro et al. (2019) provided focused data on detection rates.
3. **Diagnostic Accuracy:** Huang et al. (2023) synthesized data comparing Hysteroscopy and TVUS.

Table 2 details the characteristics of the primary meta-analyses that constitute the evidence base of this review.

**Table 2: Characteristics of Synthesized Evidence for Uterine Cancer Management**

| Author,<br>Year (Ref) | Study<br>Design | Patient<br>Population<br>(N) | Intervention<br>Comparison | FIGO<br>Stage<br>Focus | Key<br>Outcomes<br>Reported |
|-----------------------|-----------------|------------------------------|----------------------------|------------------------|-----------------------------|
|                       |                 |                              |                            |                        |                             |

|                       |                               |                               |                                                 |                                 |                                                   |
|-----------------------|-------------------------------|-------------------------------|-------------------------------------------------|---------------------------------|---------------------------------------------------|
| Mariani et al. (2023) | SR/Meta-analysis (14 cohorts) | 2,874                         | MIS vs. Open Surgery (OS)                       | Mixed, but focused on High-Risk | DFS, OS, Complication Rate                        |
| Chen et al. (2020)    | SR/Meta-analysis (15 studies) | 5,820                         | SLNB vs. Lymphadenectomy (LND)                  | I-III (Predominantly Early)     | Blood Loss, Nodal Detection, Recurrence, Survival |
| Toro et al. (2019)    | SR/Meta-analysis              | >10 primary studies           | SLNB vs. LND                                    | I-III                           | Nodal detection and Recurrence Rates              |
| Huang et al. (2023)   | Diagnostic Accuracy Review    | 150 (Primary cohort reviewed) | Hysteroscopy vs. Transvaginal Ultrasound (TVUS) | Diagnosis                       | Sensitivity, Accuracy, NPV                        |
| Tureanu et al. (2023) | Impact Analysis               | 211                           | FIGO 2023 vs. FIGO 2009                         | I-II                            | Adjuvant Treatment Risk                           |

|  |  |  |         |  |           |
|--|--|--|---------|--|-----------|
|  |  |  | Staging |  | Reduction |
|--|--|--|---------|--|-----------|

### Diagnostic Modality Outcomes

Accurate initial diagnosis is paramount, especially as molecular subtyping requires high-quality tissue (Zang et al., 2021). Comparative analysis demonstrated the significant superiority of hysteroscopy in primary EC detection (Huang et al., 2023).

**Table 3: Comparative Diagnostic Accuracy (Hysteroscopy vs. TVUS)**

| Outcome                                     | Modality     | Pooled Estimate | 95% Confidence Interval | P-value | Significance |
|---------------------------------------------|--------------|-----------------|-------------------------|---------|--------------|
| <b>Hysteroscopy Accuracy</b><br>(Outcome 1) | Hysteroscopy | 93.3%           | N/A                     | N/A     | Superior     |
| <b>TVUS Accuracy</b><br>(Outcome 2)         | TVUS         | 83.5%           | N/A                     | N/A     | Lower        |
| <b>Hysteroscopy Accuracy</b>                | Hysteroscopy | 94.9%           | N/A                     | N/A     | High         |

|                                     |  |  |  |  |  |
|-------------------------------------|--|--|--|--|--|
| py<br>Sensitivity<br>(Outcome<br>3) |  |  |  |  |  |
|-------------------------------------|--|--|--|--|--|

Hysteroscopy, often performed with directed endometrial biopsy, achieved a high sensitivity of 94.9% and an overall accuracy of 93.3% (Huang et al., 2023). This higher accuracy is essential because blind sampling methods risk missing focal lesions or failing to yield sufficient tumor volume for comprehensive molecular analysis (Zang et al., 2021). The findings mandate that hysteroscopy-guided sampling is the definitive diagnostic method, enabling the crucial first step of molecular profiling.

Surgical Approach Comparison: MIS vs. Open Surgery in High-Risk EC

The synthesis directly addressed the critical research gap concerning the use of MIS in aggressive, high-risk EC, encompassing Grade 3 endometrioid, serous, clear cell, and carcinosarcoma histologies (Mariani et al., 2023). The combined data confirmed that MIS is oncologically non-inferior to traditional OS.

Table 4: Oncological and Morbidity Outcomes (MIS vs. Open Surgery in High-Risk EC)

| Outcome      | Comparison | Effect Measure | Pooled Estimate (95% CI) | I <sup>2</sup> Heterogeneity (%) | P-value | Significance   |
|--------------|------------|----------------|--------------------------|----------------------------------|---------|----------------|
| Disease-Free | MIS vs. OS | Relative Risk  | 0.93 (0.82–              | 20%                              | 0.23    | Non-Inferiorit |

|                                             |               |                          |                         |     |      |                                                                            |
|---------------------------------------------|---------------|--------------------------|-------------------------|-----|------|----------------------------------------------------------------------------|
| <b>Survival (DFS)</b><br>(Outcome 4)        |               | (RR)                     | 1.05)                   |     |      | y<br>Establish<br>ed<br>(Mariani<br>et al.,<br>2023)                       |
| <b>Overall Survival (OS)</b><br>(Outcome 5) | MIS vs.<br>OS | Relative<br>Risk<br>(RR) | 0.92<br>(0.77–<br>1.11) | 31% | 0.12 | Non-<br>Inferiorit<br>y<br>Establish<br>ed<br>(Mariani<br>et al.,<br>2023) |
| <b>Local Recurrence Rate</b><br>(Outcome 6) | MIS vs.<br>OS | Relative<br>Risk<br>(RR) | 1.05<br>(0.95–<br>1.16) | 15% | 0.35 | Non-<br>Significa<br>nt<br>Differenc<br>e                                  |
| <b>Total Complication Rate</b>              | MIS vs.<br>OS | Relative<br>Risk<br>(RR) | 0.85<br>(0.75–<br>0.96) | 55% | 0.01 | Significa<br>nt<br>(Favors<br>MIS)                                         |

|                                        |  |  |  |  |  |  |
|----------------------------------------|--|--|--|--|--|--|
| (Clavien-Dindo \ge III)<br>(Outcome 7) |  |  |  |  |  |  |
|----------------------------------------|--|--|--|--|--|--|

The primary survival endpoints—DFS (RR 0.93) and OS (RR 0.92)—demonstrated confidence intervals that comfortably included unity, confirming statistically similar long-term oncological safety for MIS across the high-risk spectrum (Mariani et al., 2023; Papatheodorou et al., 2023). Importantly, MIS showed a statistically significant reduction in severe postoperative complications (Outcome 7), leading to quicker recovery and the potential for earlier commencement of adjuvant therapy, if needed (Mariani et al., 2023). The low heterogeneity for DFS ( $I^2$  20%) further reinforces the consistency of this finding across international cohorts.

**Lymph Node Management Comparison: SLNB vs. LND**

SLNB has rapidly replaced systematic LND as the staging procedure of choice (Papatheodorou et al., 2023). The synthesis of multiple large meta-analyses decisively supports this shift based on reduced morbidity and superior detection quality.

**Table 5: Morbidity and Nodal Efficacy Outcomes (SLNB vs. LND)**

| Outcome     | Comparison | Effect Measure | Pooled Estimate (95% CI) | $I^2$ Heterogeneity (%) | Significance |
|-------------|------------|----------------|--------------------------|-------------------------|--------------|
| Intraoperat | SLNB vs.   | Mean           | -54.40 (-                | 74%                     | Significant  |

|                                                           |              |                    |                  |     |                                                                     |
|-----------------------------------------------------------|--------------|--------------------|------------------|-----|---------------------------------------------------------------------|
| <b>ive Blood Loss (mL)</b><br>(Outcome 8)                 | LND          | Difference (MD)    | 85.36 to -23.45) |     | (Favors SLNB)<br>(Chen et al., 2020)                                |
| <b>Risk of Lymphedema</b><br>(Outcome 15)                 | SLNB vs. LND | Relative Risk (RR) | 0.25 (0.10–0.45) | 10% | Significant (Favors SLNB)<br>(SGO/Mayo Clinic, 2021)                |
| <b>Positive Pelvic Node Detection Rate</b><br>(Outcome 9) | SLNB vs. LND | Odds Ratio (OR)    | 1.35 (1.15–1.58) | 36% | Significant (Favors SLNB)<br>(Chen et al., 2020; Toro et al., 2019) |
| <b>Para-aortic LN Detection Rate</b><br>(Outcome 10)      | SLNB vs. LND | Odds Ratio (OR)    | 1.05 (0.90–1.22) | 50% | Non-Significant (Equivalence ) (Toro et al., 2019)                  |

|                                                  |              |                      |                       |     |                                                            |
|--------------------------------------------------|--------------|----------------------|-----------------------|-----|------------------------------------------------------------|
| <b>Total Nodal Yield (Count)</b><br>(Outcome 11) | SLNB vs. LND | Mean Difference (MD) | -12.5 (-15.5 to -9.5) | 99% | Non-Significant (Lower count for SLNB) (Chen et al., 2020) |
|--------------------------------------------------|--------------|----------------------|-----------------------|-----|------------------------------------------------------------|

The morbidity data strongly supports SLNB. The procedure resulted in a significant reduction in mean blood loss (MD -54.40) (Chen et al., 2020). Most importantly, SLNB resulted in a highly significant, 75% reduction in the incidence of debilitating long-term lymphedema (RR 0.25), a major complication associated with comprehensive LND (SGO/Mayo Clinic, 2021; Papatheodorou et al., 2023).

Despite harvesting a far lower total nodal count (Outcome 11), SLNB demonstrated **superiority** in detecting positive pelvic nodes (Outcome 9) (Toro et al., 2019). This is attributed to the mandatory ultra-staging protocol applied to the limited number of sentinel nodes, which increases the detection of small-volume disease, such as micrometastases, that would be missed by routine LND specimen processing (Chen et al., 2020). Crucially, SLNB achieved non-inferiority in detecting para-aortic nodal disease compared to LND (Outcome 10) (Toro et al., 2019).

### **Oncological Equivalence of Nodal Assessment**

The primary concern regarding SLNB was whether reduced nodal removal compromises long-term oncological control. The pooled survival data confirmed non-detrimental outcomes (Chen et al., 2020).

**Table 6: Oncological Equivalence Outcomes (SLNB vs. LND)**

| Outcome                                                | Comparison   | Effect Measure     | Pooled Estimate (95% CI) | I <sup>2</sup> Heterogeneity (%) | P-value | Significance                                            |
|--------------------------------------------------------|--------------|--------------------|--------------------------|----------------------------------|---------|---------------------------------------------------------|
| <b>Overall Recurrence Rate</b><br>(Outcome 12)         | SLNB vs. LND | Relative Risk (RR) | 1.01<br>(0.87–1.18)      | 75%                              | 0.41    | Non-Significant<br>(Equivalence)<br>(Chen et al., 2020) |
| <b>Progression-Free Survival (PFS)</b><br>(Outcome 13) | SLNB vs. LND | Hazard Ratio (HR)  | 1.03<br>(0.91–1.17)      | 52%                              | 0.31    | Non-Significant<br>(Equivalence)<br>(Chen et al., 2020) |
| <b>Overall Survival (OS)</b><br>(Outcome 14)           | SLNB vs. LND | Hazard Ratio (HR)  | 0.99<br>(0.85–1.15)      | 79%                              | 0.94    | Non-Significant<br>(Equivalence)                        |

|     |  |  |  |  |  |                     |
|-----|--|--|--|--|--|---------------------|
| 14) |  |  |  |  |  | (Chen et al., 2020) |
|-----|--|--|--|--|--|---------------------|

The pooled estimates for Overall Recurrence Rate (RR 1.01), PFS (HR 1.03), and OS (HR 0.99) all strongly indicated non-inferiority of SLNB compared to LND (Chen et al., 2020). Although heterogeneity was high for some survival outcomes, likely due to variations in patient population risk profiles and follow-up duration, the statistical equivalence across all major survival metrics confirms that the biological prognostic information derived from SLNB ultra-staging is more important than the gross number of nodes removed.

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## DISCUSSION

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### **The Role of Minimally Invasive Surgery in the Modern EC Pathway**

The findings of this systematic review solidify the recommendation for MIS—either laparoscopic or robotic—as the standard surgical approach for all EC patients, irrespective of traditional risk status (Mariani et al., 2023; Papatheodorou et al., 2023). The established oncological equivalence (Table 4) is critical, as it eliminates the safety concerns previously associated with using MIS in high-risk tumors (Mariani et al., 2023). The inherent benefits of MIS, including reduced blood loss and shorter hospital stays, are now extended across the entire EC population, directly leading to lower severe morbidity rates (Outcome 7) and facilitating earlier entry into adjuvant treatment pathways when necessary (Papatheodorou et al., 2023).

### **Precision Staging via SLNB and the Avoidance of Overtreatment**

The debate over nodal staging has concluded; SLNB is the preferred method. Systematic LND is inherently aggressive (Papatheodorou et al., 2023), causing long-term disability, most notably lymphedema (Outcome 15) (SGO/Mayo Clinic, 2021). SLNB circumvents this morbidity without compromising staging quality (Chen et al., 2020). Its superior detection of positive pelvic

nodes (OR 1.35, Outcome 9) results from the meticulous ultra-staging applied to the few nodes harvested (Toro et al., 2019). This high-fidelity staging is essential because the FIGO 2023 system differentiates small-volume disease (micrometastasis) from larger spread (macrometastasis), which is crucial for determining the extent of adjuvant radiation (Soliman et al., 2024).

**Impact of Molecular Classification on Adjuvant Therapy**

The molecular era, underpinned by the FIGO 2023 update, transforms prognosis from a purely clinicopathological estimate to a biologically driven risk assessment (Tureanu et al., 2023). The prognostic spectrum defined by the molecular subgroups dictates the need for and the intensity of post-operative therapy (Zang et al., 2021).

**Table 7: Prognostic and Therapeutic Implications of FIGO 2023 Molecular Subgroups**

| Molecular Subgroup | Underlying Alteration                                  | Prognosis/Recurrence Risk               | Adjuvant Therapy Recommendation                            | Key Implication                                                             |
|--------------------|--------------------------------------------------------|-----------------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------|
| POLE Ultramutated  | DNA Polymerase $\epsilon$ exonuclease domain mutations | Exceptionally Favorable (Very Low Risk) | Adjuvant therapy often omitted, even with adverse factors. | Maximize de-escalation; potential for no nodal staging (Zang et al., 2021). |
| MMR Deficient      | Loss of Mismatch                                       | Intermediate/High Risk                  | Post-operative radiation (often                            | Guide to immunotherap                                                       |

|                                              |                                          |                                  |                                                                                                  |                                                                     |
|----------------------------------------------|------------------------------------------|----------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| <b>(MMRD)</b>                                | Repair protein expression                |                                  | vaginal brachytherapy) ; high sensitivity to immunotherapy in advanced disease (PSGO, 2025).     | y for recurrence.                                                   |
| <b>Non-Specific Molecular Profile (NSMP)</b> | No specific alteration (Low Copy Number) | Intermediate Risk                | Risk is determined primarily by classic clinicopathology (LVSI, grade).                          | Managed by standard ESGO/ESTRO /ESP guidelines (Zang et al., 2021). |
| <b>TP53 Abnormal (p53abn)</b>                | Mutation in TP53                         | Poor/Aggressive (Very High Risk) | Requires aggressive systemic therapy (chemotherapy and/or external beam radiation) (PSGO, 2025). | Need for systemic treatment intensification.                        |

The clinical benefit of this molecular integration is profound: the re-staging of early-stage EC patients according to FIGO 2023 results in a decreased relative risk (RR 0.84) for requiring any type of adjuvant treatment (Tureanu et al., 2023). This ability to safely spare approximately 16% of patients from potentially toxic systemic therapies underscores the clinical utility of integrating molecular diagnostics (POLE, MMR, p53 status) with the high-quality staging provided by SLNB.

### **Methodological Strengths and Future Research**

The primary strength of this review lies in its comprehensive integration of large-scale meta-analyses, pooling thousands of patients across key outcomes, confirming the robust nature of the conclusions (Mariani et al., 2023; Chen et al., 2020). However, the acknowledged "Serious" risk of bias in surgical comparisons (Table 1) necessitates continued vigilance.

Future research must focus on prospective trials or model-based analyses (Zuo et al., 2023) to fully define the cost-effectiveness of this new pathway and to address remaining de-escalation questions, such as: Can POLE-mutated tumors entirely bypass nodal assessment? Are there racial or socioeconomic disparities in access to and utilization of the guideline-concordant molecular testing and minimally invasive surgery (Smith, 2024)? Answering these questions will be essential to truly realize the potential of personalized EC care.

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## **CONCLUSION AND RECOMMENDATIONS**

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### **Summary of Conclusions**

This systematic review confirms the culmination of advancements in uterine cancer management, culminating in a highly personalized, low-morbidity standard of care. Minimally Invasive Surgery provides non-inferior oncological control compared to open surgery across all risk groups (Mariani et al., 2023). Sentinel Lymph Node Biopsy is superior to Lymphadenectomy, significantly reducing lymphedema (RR 0.25) while enhancing staging accuracy through ultra-staging (Toro et al., 2019; SGO/Mayo Clinic, 2021). This combined surgical approach, guided by the precise prognostic power of the FIGO 2023 molecular classification, defines the optimal clinical

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pathway for endometrial cancer staging and management.

### Clinical Recommendations and Suggestions

1. **Diagnostic Standard:** Utilize hysteroscopy-guided biopsy as the primary diagnostic tool to ensure sufficient high-quality tissue is obtained for mandatory molecular subtyping (POLE, MMR, p53 status) (Huang et al., 2023).
2. **Surgical Access:** Minimally Invasive Surgery (laparoscopic or robotic) should be universally adopted for EC staging hysterectomy, including in patients with high-risk histologies, due to its comparable survival outcomes and enhanced safety profile (Mariani et al., 2023).
3. **Nodal Staging:** SLNB must be the standard for nodal assessment in clinically early-stage EC. Systematic Lymphadenectomy is reserved only for failed SLN mapping or for situations where bulky nodal disease is macroscopically evident (Papatheodorou et al., 2023).
4. **Adjuvant Therapy:** Treatment planning should explicitly incorporate the FIGO 2023 molecular classification, particularly for POLE-mutated and p53-abnormal tumors, to safely de-escalate or intensify adjuvant therapy, respectively (Tureanu et al., 2023).

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