Submitted: 29 May, 2025 Accepted: 13 August, 2025 Published: 15 November, 2025 DOI:10.22514/ejgo.2025.134

SYSTEMATIC REVIEW

European Journal of Gynaecological Oncology

Total mesometrial resection for cervical cancer: a systematic review of oncological outcomes and comparative analysis with radical hysterectomy

Carlo Ronsini[1,*], Giuseppe Cucinella[1], Maria Cristina Solazzo[1], Mariano Catello Di Donna[1], Cono Scaffa[1], Stefano Restaino[2], Giuseppe Vizzielli[2], Vito Chiantera[1]

[1]Unit of Gynecologic Oncology, National Cancer Institute, IRCCS, Fondazione "G. Pascale", 80131 Naples, Italy
[2]Unit of Obstetrics and Gynecology, "Santa Maria della Misericordia" University Hospital, Azienda Sanitaria Universitaria Friuli Centrale, 33100 Udine, Italy

***Correspondence**
carlo.ronsini@unicampania.it
(Carlo Ronsini)

Abstract

Background: This systematic review aims to assess the oncologic efficacy and safety of Total Mesometrial Resection (TMMR) in cervical cancer, focusing on 3-year disease-free survival (DFS) and overall survival (OS). Additionally, TMMR outcomes are compared with open radical hysterectomy, the current standard of care, as reported in the Locally Advanced Cervical Cancer (LACC) trial. **Methods**: A systematic search was conducted in PubMed and Scopus following Preferred Reported Instruments for Systematic Review and Meta-analysis (PRISMA) guidelines. Studies evaluating TMMR in cervical cancer were included if they reported DFS, OS, recurrence patterns, and perioperative complications. Newcastle-Ottawa Scale (NOS) was used for quality assessment, and hazard ratios (HR) were computed for comparative analysis. **Results**: Seven studies met the inclusion criteria, including 1071 patients treated with TMMR. The 3-year DFS ranged from 85% to 97.1%, and OS from 87.9% to 100%. TMMR showed a higher recurrence risk compared to open radical hysterectomy (HR 4.89, 95% CI: 2.42–9.88, $p < 0.001$) and a significantly increased mortality risk (HR 16.48, 95% CI: 4.08–65.99, $p < 0.001$). However, in a subgroup analysis restricted to patients with disease stages below IB3 (n = 447), the HR for recurrence was 1.32 (95% CI: 0.57–3.07, $p = 0.57$), for local recurrence 2.31 (95% CI: 0.76–7.01, $p = 0.14$), and for OS 0.70 (95% CI: 0.10–4.92, $p = 0.72$), suggesting no statistically significant difference compared to standard radical hysterectomy. **Conclusions**: While TMMR demonstrates favorable survival rates, its higher recurrence and mortality risks compared to standard radical hysterectomy raise concerns. Further prospective multicenter studies are needed to determine its role in clinical practice. **The PROSPERO Registration**: CRD420251125129.

Keywords

TMMR; Cervical cancer; Disease-free survival; Overall survival; Radical hysterectomy; Recurrence; Adjuvant therapy

1. Introduction

Cervical cancer remains a significant global health concern, particularly in low-resource settings, despite advances in prevention and treatment strategies [1]. The standard surgical approach for early-stage cervical cancer (FIGO (International Federation of Gynecology and Obstetrics) IB–IIA) consists of radical hysterectomy with pelvic lymphadenectomy, often followed by adjuvant radiotherapy and/or chemotherapy in high-risk cases [2, 3]. While this multimodal strategy has proven effective in improving oncological outcomes, it is also associated with substantial morbidity, including bladder and bowel dysfunction, lymphedema, and reduced quality of life [4, 5].

Total Mesometrial Resection (TMMR) has emerged as a novel surgical concept that aims to improve oncological control while minimizing the need for adjuvant therapy [6]. Based on ontogenetic compartment theory, TMMR involves precisely removing embryologically defined mesometrial compartments, preserving autonomic pelvic nerves and potentially reducing treatment-related morbidity, avoiding any adjuvant treatment. Unicentric studies have demonstrated excellent local control rates with TMMR alone, suggesting that it may offer an alternative to standard radical hysterectomy in selected patients [6, 7]. However, TMMR has not yet been widely adopted as a standard approach due to limited multicenter prospective data and concerns regarding reproducibility across different surgical teams and institutions.

This is an open access article under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/).

2. Objectives

Given the promising oncological outcomes reported in single-center studies and the lack of large-scale evidence supporting TMMR as a standard treatment, we conducted a systematic review to evaluate its efficacy and safety. The primary outcome of interest is 3-year disease-free survival (DFS), while secondary outcomes include overall survival (OS), recurrence patterns (loco-regional, distant), and the incidence of perioperative and postoperative complications. In addition to analyzing oncological outcomes, this study also aims to contextualize the clinical significance of TMMR by comparing its outcomes with the open surgery arm of the LACC trial (Ramirez *et al.* [8]), which represents the current standard of care for early-stage cervical cancer. Specifically, we will compare overall recurrence risk, locoregional recurrence risk, and overall survival rates between TMMR and radical abdominal hysterectomy, assessing statistical differences using hazard ratios (HR) and 95% confidence intervals (CI). This comparative approach will provide a broader perspective on the potential role of TMMR in clinical practice. By synthesizing the current evidence on TMMR, we aim to clarify its role in managing early-stage cervical cancer and provide insights into its potential advantages and limitations compared to conventional radical hysterectomy.

3. Material and methods

The methods for this study were specified a priori based on the recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [9]. We registered the Review to the International Prospective Register of Systematic Reviews (PROSPERO) site for systematic review and meta-analysis with protocol number CRD1125129.

3.1 Search method

A systematic literature search was conducted to identify studies evaluating Total Mesometrial Resection (TMMR) for cervical cancer. The search was performed in PubMed and Scopus databases in January 2025. We included all studies published up to the search date, with no restrictions on publication year or country of origin. Only studies entirely published in English were considered for inclusion.

To ensure comprehensive coverage, the search strategy included the following Medical Subject Headings (MeSH) and free-text terms: “Hysterectomy” AND “Uterine Cervical Neoplasms”. The search was adapted to each database according to its specific syntax and indexing system.

3.2 Study selection

Study selection was made independently by GC and MCS. In case of discrepancy, CR decided on inclusion or exclusion. Inclusion criteria were: (1) studies that included patients with Early-stage cervical cancer or stage IB3 or IIB according to FIGO [10]; (2) studies that reported at least one outcome of interest (DFS, OS); (3) peer-reviewed articles published originally. We excluded non-original studies, preclinical trials, animal trials, abstract-only publications, and articles in languages other than English. If possible, the authors of studies that were only published as congress abstracts were contacted via email and asked to provide their data. We mentioned the studies selected and all reasons for exclusion in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Fig. 1). We assessed all included studies regarding potential conflicts of interest. A PRISMA checklist is included in **Supplementary material**.

3.3 Outcome measures and data extraction

The primary outcome of this systematic review was 3-year disease-free survival (DFS), defined as the percentage of patients free from disease 36 months after undergoing TMMR. The secondary outcome was 3-year overall survival (OS), calculated as the proportion of patients alive at 36 months post-TMMR. Additionally, we assessed the recurrence rate (RR), which is defined as the proportion of patients experiencing disease recurrence during the study’s follow-up period. Recurrence was determined based on clinical and/or imaging findings, as reported in the individual studies included in the systematic review.

Recurrences were categorized as follows: Local recurrence: Tumor recurrence confined to the pelvis; Distant recurrence: Disease spread beyond the pelvis and/or parenchymal metastases.

Patients presenting both local and distant recurrences were counted under each recurrence type but only once in the overall recurrence rate (RR).

For each included study, the following data were extracted: Study design, Number of enrolled patients, Country of study conduction, Patient enrollment period, Follow-up duration expressed in months, FIGO staging, classified according to the 2018 International Federation of Gynecology and Obstetrics (FIGO) criteria for cervical cancer.

Postoperative complications were defined as any adverse event occurring within the first 30 days post-surgery and were classified according to the Clavien-Dindo system [11]. Only complications classified as Grade III or higher were included in the analysis. The number of patients experiencing at least one complication was reported as absolute values and percentages.

3.4 Surgical technique

Radical hysterectomy, as classically defined by the Piver-Rutledge classification (Type II–III) and adopted in most clinical guidelines, involves the en bloc removal of the uterus, upper vaginal cuff, parametria, and uterosacral ligaments, often sacrificing pelvic autonomic nerves. This procedure aims to ensure wide surgical margins and local tumor control. In contrast, TMMR is based on the ontogenetic cancer field theory and focuses on the precise removal of the Müllerian compartment as defined during embryonic development, preserving autonomic nerves and minimizing collateral damage [6]. Key anatomical differences include the boundaries of resection: while radical hysterectomy extends laterally to include parametria, TMMR targets the mesometrial tissue with embryologic precision. Technically, TMMR avoids direct tumor manipulation and aims for complete resection of at-risk

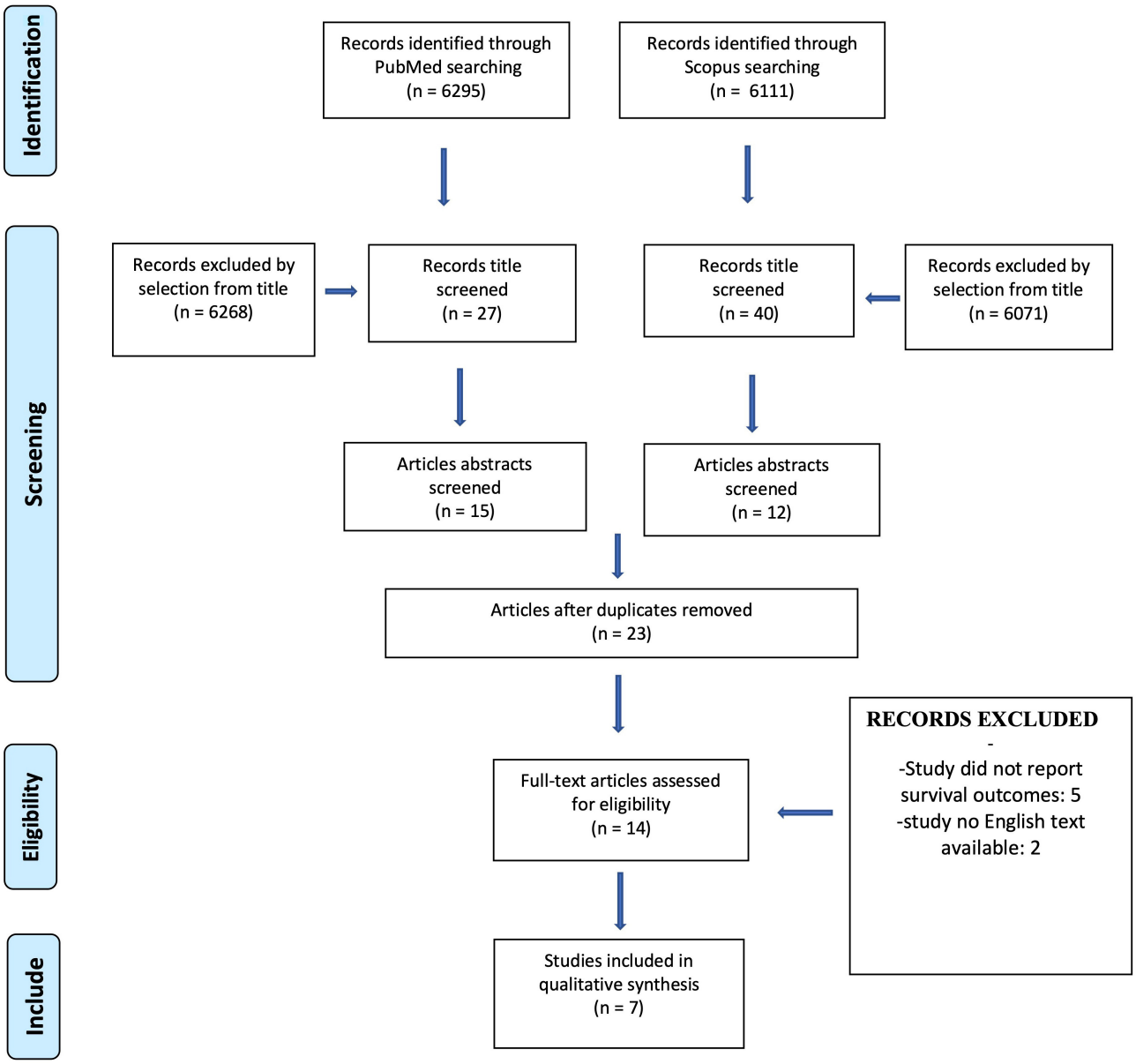

FIGURE 1. PRISMA flow diagram.

compartments with preservation of nerve structures. These differences may account for the variations in recurrence patterns and functional outcomes observed between the two techniques. TMMR was defined in accordance with the technique described initially by Höckel *et al.* [6] in 2003, which is based on the ontogenetic cancer field theory. This approach involves the en bloc resectioning of the embryologically defined Müllerian compartment while preserving the autonomic pelvic nerves. This systematic review considered both open (laparotomic) TMMR and minimally invasive TMMR (laparoscopic and robotic-assisted approaches).

The procedure consists of the following standardized surgical steps:

1. Identification of the Müllerian compartment: The uterus, mesometria, upper two-thirds of the vagina, and paracervical lymphatic drainage pathways are resected in continuity.

2. Dissection of the vascular mesometrium: The uterine artery is ligated at its origin, and all mesometrial lymphatic structures are removed.

3. Resection of the ligamentous mesometrium: The paracolpium and the sacrouterine and rectovaginal ligaments are dissected to their embryological boundaries.

4. Nerve-sparing approach: The hypogastric plexus and visceral pelvic nerves are carefully preserved.

5. Lymphadenectomy: A systematic pelvic lymph node dissection includes the paravisceral, external iliac, common iliac, and presacral nodes. Para-aortic lymphadenectomy is performed selectively based on tumor staging and intraoperative findings.

For laparoscopic and robotic-assisted TMMR, the exact anatomical principles were applied, with modifications to accommodate minimally invasive instrumentation. The main differences include Pneumoperitoneum establishment and trocar placement for optimal access; Endoscopic suturing techniques for vaginal cuff closure and lymphatic sealing.

This definition of TMMR was consistently applied across the included studies to maintain the comparability of oncological and perioperative outcomes.

3.5 Statistical analysis

Descriptive statistics were used to summarize patient characteristics, surgical variables, and oncological outcomes. Continuous variables (*e.g.*, follow-up duration, age, operative time) were reported as means. Categorical variables (*e.g.*, recurrence type, complication rates) were presented as absolute numbers and percentages.

Pooled estimates were calculated when feasible for the primary outcome, 3-year disease-free survival (DFS), and the secondary outcome, 3-year overall survival (OS). Recurrence rates (local and distant) were analyzed separately. In cases of concurrent recurrences, patients were counted in each respective category but only once in the total recurrence rate.

Additionally, to improve clinical contextualization, a comparative analysis was conducted between the pooled TMMR data and the open surgery arm of the LACC trial (Ramirez *et al.* [8]), which serves as the current standard of care for early-stage cervical cancer. Hazard ratios for overall recurrence, locoregional recurrence, and overall survival were calculated using Cox proportional hazards regression models, with statistical significance assessed using log-rank tests. A Fisher's exact test was used for categorical variables when event counts were low.

All statistical analyses were performed using R software (meta-package), following PRISMA guidelines [9]. A p-value < 0.05 was considered statistically significant.

3.6 Quality assessment

The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) [12]. This tool assesses study quality based on three main domains: selection of study participants, comparability of cohorts, and assessment of outcomes (for cohort studies) or exposure (for case-control studies). The NOS assigns scores ranging from 0 (lowest quality) to 9 (highest quality), with higher scores indicating a lower risk of bias.

Two independent reviewers (CS and MCDD) conducted the quality assessment. In case of discrepancies, consensus was reached through discussion, and if needed, a third reviewer (VC) was consulted to make the final decision.

The detailed Newcastle-Ottawa Scale scoring for each included study is provided in the **Supplementary material**.

4. Results

4.1 Studies' characteristics

Following the database search, 67 articles met the initial search criteria. After removing duplicates, records without full-text availability, and studies with ineligible designs (*e.g.*, reviews, meta-analyses), 14 studies remained for full-text screening. Of these, 7 studies met the inclusion criteria and were included in the systematic review. 6 studies were non-comparative, single-arm investigations evaluating only TMMR, one study compared TMMR to radical hysterectomy. Study quality was assessed using the Newcastle-Ottawa Scale (NOS), as detailed in the **Supplementary Table 1**. The included studies were published between 1998 and 2024, encompassing patients diagnosed with FIGO 2009 stage IA–IIB cervical cancer who underwent TMMR [13]. 2 studies by Falconer and Hockel, included patients with positive node at the imaging. The mean follow-up period ranged from 18 to 62 months. A summary of the study characteristics, including publication year, study design, FIGO stage, number of participants, and country of origin, is presented in Table 1 (Ref. [14–20]).

TABLE 1. Characteristics of studies included.

Study	Country	Study type	Year	No. of patients	FIGO stage	FUP (mon)
Buderath P. 2022 [14]	Germany	Multicentric prospective, observational study	2013–2022	116	IB1 IIA	61.8
Chiantera V. 2015 [15]	Italy	Monocentric prospective, observational, cohort study	2013–2014	104	IA2–IB1	18
Falconer H. 2024 [16]	Sweden	Monocentric Retrospective Observational cohort study	2011–2020	274*	IB1–IIB	60
Hockel M. 2019 [17]	Germany	Monocentric retrospective, observational, cohort study	1999–2017	454	IB1 - IIB	62
Kimming R. 2013 [18]	Germany	Monocentric prospective, observational, cohort study	2006–2010	26	IA IIB	18
Nasser S. 2016 [19]	Germany	Monocentric prospective, observational, cohort study	2012–2016	34	IB IIA IIB	26
Vizzelli G. 2016 [20]	Italy	Monocentric Retrospective Observational study	2013–2015	63	IA2 IB1	22

**Sub-analysis group. FIGO: International Federation of Gynecology and Obstetrics; FUP: Follow-Up.*

4.2 Outcomes

A total of 1071 patients were included in the review. All the 7 selected studies presented DFS data and OS data.

The main outcome was DFS at 3 years. In the included studies, the series described by Falconer *et al.* [16] had the lowest DFS (85%), while the highest was published by Chiantera *et al.* [15] (97.1%). Regarding the 3-year OS, the reported values ranged from 87.9% to 100%. Those results are summarized in Table 2 (Ref. [14–20]).

The RR ranged from 0.3% to 14.3%, with 2/7 studies having results below 1%. Regarding the recurrence pattern, only the Hockel [17], Falconer [16], and Buderath [14] studies reported extrapelvic (Distant) recurrences. Conversely, all reported studies reported at least 1 pelvic recurrence. These results are summarized in Table 3 (Ref. [14–20]).

Only 6 studies reported complication rates in the first 30 days post-treatment. Buderath's study [14] is the only one that reported an event rate above 5% (17.4%). The remaining studies reported case histories between 1 and 4%. The rates of the individual studies are shown in Table 4 (Ref. [14, 15, 17–20]).

4.3 Comparison with LACC trial

To enhance the clinical relevance of the findings, we reanalyzed the reported cases by comparing them with the open surgery arm of the LACC trial (Ramirez *et al.* [8]), which currently represents the standard of care for the surgical treatment of early-stage cervical cancer.

4.4 Recurrence analysis

Among patients undergoing TMMR, a total of 122 recurrences out of 1071 patients were reported, compared to 8 recurrences

TABLE 2. TMMR oncological outcomes.

Name	3Y DFS (%)	3Y OS (%)
Buderath P. 2022 [14]	92.2%	98.2%
Chiantera V. 2015 [15]	97.1%	100%
Falconer H. 2024 [16]	85%	92.3%
Hockel M. 2019 [17]	85.5%	87.9%
Kimming R. 2013 [18]	96.1%	96.1%
Nasser S. 2016 [19]	94.1%	100%
Vizzelli G. 2016 [20]	95.2%	100%

DFS: disease-free survival; OS: Overall survival.

TABLE 3. Type of recurrence.

Name	Recurrence (%)	Loco-regional Recurrence Rate (%)	Distant Recurrence Rate (%)
Buderath P. 2022 [14]	9 (7.8%)	7 (6%)	2 (1.8%)
Chiantera V. 2015 [15]	2 (2%)	2 (2%)	0
Falconer H. 2024 [16]	41 (14.3%)	14 (5.1%)	27 (9.8%)
Hockel M. 2019 [17]	66 (14.3%)	34 (7.5%)	27 (5.9%)
Kimming R. 2013 [18]	1 (0.2%)	1 (0.2%)	0
Nasser S. 2016 [19]	1 (0.3%)	1 (0.3%)	0
Vizzelli G. 2016 [20]	2 (1.2%)	2 (1.2%)	0

TABLE 4. Postoperative complications.

Name	Complications Rate*
Buderath P. 2022 [14]	15 (17.4%)
Chiantera V. 2015 [15]	3 (4%)
Hockel M. 2019 [17]	15 (3%)
Kimming R. 2013 [18]	5 (1.3%)
Nasser S. 2016 [19]	3 (1%)
Vizzelli G. 2016 [20]	2 (1.2%)

**Clavien-Dindo grades III or higher.*

out of 312 patients in the open surgery arm of the LACC trial. This resulted in a Hazard Ratio (HR) of 4.89 (95% CI: 2.42–9.88, $p < 0.001$) for overall recurrence risk, indicating a statistically significant difference between the two surgical approaches.

For locoregional recurrences, patients treated with TMMR had an HR of 4.65 (95% CI: 1.70–12.69, $p = 0.001$) compared to those who underwent radical abdominal hysterectomy, suggesting a higher but significant risk of local recurrence.

4.5 Survival analysis

Regarding overall survival (OS), the estimated risk of death among TMMR patients was HR 16.48 (95% CI: 4.08–65.99, $p < 0.001$) compared to the LACC trial's open surgery arm, further indicating a statistically significant difference in mortality between the two approaches.

These comparative results are summarized in Table 5.

4.6 Comparison for patients with early-stage cervical cancer

To refine our analysis further, we conducted a pooled subgroup analysis restricted to patients with disease stages below IB3 (447). In this subgroup, the Hazard Ratio (HR) for recurrence associated with TMMR was 1.32 (95% CI: 0.57–3.07, $p = 0.57$), indicating a no statistically significant difference compared to the control group. Regarding local recurrence, the HR was 2.31 (95% CI: 0.76–7.01, $p = 0.14$), failing to reach statistical significance. Similarly, for OS, the HR was 0.70 (95% CI: 0.10–4.92, $p = 0.72$), suggesting no meaningful survival difference between the two groups. These results are summarized in Table 6.

5. Discussion

5.1 Interpretation of results

This systematic review evaluates the oncological and safety performance of TMMR in the surgical management of early-stage cervical cancer. The findings indicate high oncological effectiveness, with all studies reporting 3-year DFS and OS above 85%. The safety profile of TMMR also appears acceptable, with a complication rate below 5% in five out of six studies. However, one study (Buderath *et al.* [14]) deviates from this trend, reporting a threefold higher complication rate than other studies included in this systematic review. Notably, this study is the only multicenter investigation involving 15 different centers. Despite its multicentric design, the study included only 116 patients, suggesting that several centers performed fewer than 10 procedures over 9 years. This low-volume bias may have influenced the observed higher complication rate and lower oncological performance.

A key finding is the higher recurrence risk associated with TMMR compared to the open surgery arm of the LACC trial. Our pooled analysis found a statistically significant increase in overall and locoregional recurrence risk in patients undergoing TMMR. These results suggest that TMMR may be associated with a higher rate of tumor persistence or local failure, potentially due to technical inconsistencies or patient selection bias. However, it is important to note that TMMR was also performed in patients with higher-stage disease (IB3/IIB). In contrast, LACC [8] strictly excluded such cases, possibly overestimating recurrence risk in the TMMR cohort. Furthermore, it is important to acknowledge that the LACC trial itself has been the subject of significant debate in the literature. Since its publication, several studies have raised concerns about methodological limitations, including heterogeneous patient selection, lack of central pathology review, variability in surgical technique across centers, and the limited experience of some participating surgeons with minimally invasive approaches. These flaws may have influenced the trial's outcomes and limit its utility as a definitive benchmark. As such, while LACC remains a widely cited reference, caution should be exercised when using it as the sole comparator for assessing alternative surgical strategies such as TMMR. Survival outcomes showed an even greater difference, with a 16-fold increased mortality risk in TMMR patients compared to the LACC trial's open surgery arm [8]. While this finding is statistically significant, it should be interpreted with caution, as differences may influence it in baseline patient characteristics, adjuvant treatment administration, and disease burden. Fur-

TABLE 5. Comparison with open radical hysterectomy.

Outcome	TMMR no. of events/no. of patients	Open Surgery no. of events/no. of patients	Hazard Ratio (95% CI)	*p*-Value
Recurrence	122/1071	8/312	4.89 (2.42–9.88)	<0.001
Locoregional Recurrence	61/1071	4/312	4.65 (1.70–12.69)	0.001
Death by disease	113/1071	2/312	16.48 (4.08–65.99)	<0.001

TMMR: total mesometrial resection; CI: Confidence Interval.

TABLE 6. Comparison with LACC trial for early-stage cervical cancer.

Outcome	TMMR no. of events/no. of patients	Open Surgery no. of events/no. of patients	Hazard Ratio (95% CI)	*p*-Value
Recurrence	15/447	8/312	1.32 (0.57–3.07)	0.57
Locoregional Recurrence	13/447	4/312	2.31 (0.76–7.01)	0.14
Death by disease	2/447	2/312	0.70 (0.10–4.92)	0.72

TMMR: total mesometrial resection; CI: Confidence Interval.

thermore, including higher-stage cases in the TMMR studies may have introduced a survival disadvantage that is not directly attributable to the surgical approach itself. For example, the study that showed the worst oncological outcomes is also the study with the highest percentage of locally advanced tumors (38%). In addition, the studies by Falconer [16] and Hockel [17] enrolled patients with diagnosed lymph node positivity, including patients with a loss of local disease control, who would likely benefit from adjuvant treatment. Not surprisingly, these his studies showed the highest reported rate of recurrence and mortality. Therefore, a subanalysis limited to early-stage cervical cancer was conducted. These findings indicate that when excluding higher-stage cases (IB3 or above), TMMR does not appear to confer a higher risk of recurrence or mortality compared to standard radical hysterectomy. However, given the wide confidence intervals and the non-significant *p*-values, these results should be interpreted with caution and warrant further prospective validation.

Another important consideration is the local recurrence rate. While TMMR is conceptually designed to remove all tissues ontogenetically susceptible to tumor spread, thus theoretically minimizing the risk of locoregional recurrence, this principle should not be interpreted as implying that recurrence risk is null or that adjuvant oncological treatment is unnecessary. Contemporary cancer management emphasizes a multidisciplinary approach, and the decision to omit adjuvant therapy must be based on a rigorous assessment of individual risk factors such as tumor size, lymphovascular space invasion, nodal involvement, and surgical margins. Although TMMR may reduce the need for additional treatment in selected early-stage cases, the benefits of systemic therapy and radiotherapy remain well-established, particularly in higher-risk patients. Therefore, any suggestion that TMMR can fully replace oncological treatment must be approached with caution and supported by prospective validation. While most studies report low local recurrence rates ($<1\%$), complete local control was observed in Höckel's original study [7], which first described the technique. The presence of locoregional recurrences in other studies suggests that technical execution variability and surgical expertise play a crucial role in determining oncological outcomes. This finding emphasizes the need for standardization and surgeon training to ensure optimal application of TMMR in clinical practice. Furthermore, the worst oncologic results were in the larger series, which also suggested greater variability of surgeons. This observation aligns with one of the major criticisms of the LACC trial, where significant variability in surgeon experience and a lack of standardized credentialing processes were identified as major limitations. Specifically, post-publication commentaries highlighted that participating surgeons had to perform only a minimal number of minimally invasive radical hysterectomies (as few as 10 cases) to be eligible, which may not be sufficient for overcoming the steep learning curve associated with such procedures. These factors may have contributed to the unexpectedly high recurrence rates observed in the minimally invasive arm. Similarly, the wide variability in TMMR outcomes across studies in our review may reflect differences in institutional expertise and the centralization of complex surgery in high-volume centers. This reinforces the necessity of standardizing training pathways and considering volume thresholds for surgeons performing TMMR in future prospective trials. This might testify that the technique requires very high expertise and experience, and single-center series at smaller volumes might have benefited from the performance of a single surgeon.

5.2 Clinical implication

The findings of this systematic review provide valuable insights into the oncological and safety profile of TMMR, reinforcing its potential role in the surgical management of early-stage cervical cancer in highly selected patients and experienced centers. Despite not being widely adopted as a standard approach, TMMR demonstrates a vast difference in DFS and OS rates, with reports comparable to those reported for radical hysterectomy, with the additional advantage of potentially reducing the need for adjuvant therapy. This could be particularly relevant for patients who wish to avoid radiotherapy-related morbidity, preserving quality of life while maintaining effective oncological control. In addition to its theoretical oncological advantages, TMMR may also offer short-term clinical benefits compared to traditional radical hysterectomy. These advantages are likely due to the more anatomically tailored dissection and preservation of autonomic nerves.

However, the variability in local recurrence rates across studies highlights the critical importance of technical standardization. Since TMMR is designed to remove all ontogenetically susceptible tissues, any local recurrence could suggest inconsistencies in surgical execution. This underscores the need for centralized surgical training programs and strict adherence to standardized TMMR protocols to ensure optimal oncological outcomes. This is also evidenced by how only two studies differed significantly from the rates of the other five, raising the possibility that the biases are related to applying the technique.

The comparison with the LACC trial [8] also discourages TMMR as an alternative to open radical hysterectomy. The observed data indicate a higher recurrence risk and death risk. Finally, TMMR represents a conceptually unique surgical approach based on the ontogenetic cancer field theory. If validated through additional research, it could pave the way for a paradigm shift in gynecologic oncology surgery, promoting a more tailored and compartmentalized approach to cervical cancer treatment.

5.3 Comparison with literature

With the publication of the LACC trial [8], huge reevaluations have occurred on the appropriateness of surgical treatment for cervix carcinomas. This may be related to the need to adhere to well-established surgical principles since their description by Shauta in 1908 [21] and Wertheim in 1911 [22]. TMMR should combine the principles of no direct exposure of the tumor with removing all tissue ontogenetically susceptible to disease, adding a level of oncologic safety. The impression is that where surgery adheres to these principles, DFS and OS rates are extremely high regardless of technique.

However, our analysis also highlights discrepancies in recurrence rates across studies, particularly regarding local control. This mirrors observations from studies on laparo-assisted vagi-

nal radical hysterectomy (LAVRH) [23, 24], where differences in local recurrence patterns were attributed to variations in surgical technique and experience levels among operators. This suggests technical variability, learning curve effects, and deviations from the original technique may account for isolated failures.

A key point of discussion is the role of adjuvant therapy. Unlike the open surgery arm of the LACC trial [8], where adjuvant treatment was administered according to Sedlis criteria [25], TMMR is designed as a standalone surgical approach [7]. This fundamental difference may account for the observed recurrence disparities and highlights the need for long-term follow-up studies directly comparing TMMR with and without adjuvant therapy. An additional consideration is that the TMMR series has included patients with IB3 and IIB cervical cancer, stages that, according to major clinical guidelines, would typically require definitive chemoradiotherapy (CCRT) rather than primary surgery [2, 3]. However, recent studies have suggested that post-neoadjuvant surgery may have a role in the management of these tumors, challenging the traditional paradigm of exclusive CCRT [26]. In contrast, TMMR is based on the opposite principle, proposing surgery as the primary and sole treatment for these patients. Given this conceptual divergence, a subgroup analysis focusing on patients with IB3 and IIB disease is essential to clarify whether TMMR offers comparable or superior oncological outcomes compared to standard multimodal treatment. Although we cannot perform this subanalysis in the reported studies, it should be noted that the worst oncological performance was reported in the study with the highest percentage of locally advanced carcinomas or including lymph node positive patients [16, 17]. This finding would also seem to be supported by the fact that the subanalysis devoted to the early stage cervical cancer groups showed no statistically significant differences with the standard of care, suggesting that adjuvant therapy played a large role in determining cancer outcomes in at-risk patients.

5.4 Strength and limitation

One of the main strengths of this study is the rigorous methodology, following PRISMA guidelines [9], which ensures a transparent and systematic analysis of the available literature. By evaluating DFS, OS, recurrence patterns, and perioperative complications, this review comprehensively assesses TMMR's clinical impact, addressing its effectiveness, feasibility, and potential risks. A key strength is the comparative evaluation with the LACC trial [8], which serves as the gold standard for open radical hysterectomy. This comparison allows for a clinically relevant contextualization of TMMR outcomes, helping to clarify whether this approach can be considered comparable to standard radical surgery.

Despite these strengths, several limitations must be acknowledged. First, the heterogeneity of the included studies is a major challenge, as they differ in sample size, surgical execution, patient selection criteria, and follow-up duration, making direct comparisons difficult. Additionally, most studies are single-center and retrospective, meaning that results may be influenced by institutional expertise and selection biases, limiting the generalizability of the findings.

A particularly relevant limitation is that all available studies on TMMR have been conducted in only three countries: Italy, Sweden, and Germany. This clearly indicates that TMMR remains a highly niche technique with limited international adoption. The lack of multicentric, multinational trials raises concerns about whether TMMR outcomes are reproducible across different clinical settings or whether its success is highly dependent on a few experienced centers. Another critical issue is the potential learning curve effect. The fact that recurrence rates vary significantly across studies suggests that surgeon experience and case volume play a significant role in oncological success. In particular, the multicentric study by Buderath *et al.* [14], which included multiple centers with low case volumes, showed higher complication rates and poorer oncological outcomes, reinforcing the idea that TMMR requires significant expertise to achieve optimal results.

Additionally, this review underscores the lack of randomized controlled trials (RCTs) directly comparing TMMR to standard radical hysterectomy. Without such data, it remains difficult to determine whether TMMR truly represents an alternative in terms of long-term oncological control. Finally, an unresolved issue concerns the role of adjuvant therapy in TMMR. While this technique is designed to eliminate the need for additional treatments, no study has directly compared patients undergoing TMMR with and without adjuvant therapy, leaving open questions regarding its optimal application in clinical practice.

One of the significant limitations of the included studies is the lack of analyses assessing the correlation between oncologic outcomes and tumor-intrinsic factors. The significant variability in patient enrollment, particularly regarding tumor size and extracervical dissemination, may obscure the true efficacy of TMMR. This is especially relevant because TMMR has often been applied to very high-risk patients, who would not typically be considered for surgical treatment under current standards of care. Future studies with more rigorous patient selection criteria will be necessary to clarify these uncertainties.

6. Conclusions

Although this systematic review supports the potential role of TMMR in cervical cancer surgery in highly selected cases and centers, it also highlights critical gaps that must be addressed before it can be widely adopted. This systematic review supports the potential role of TMMR as an effective and anatomically grounded surgical approach for early-stage cervical cancer. When performed in expert centers with standardized techniques and careful patient selection, TMMR demonstrates oncological outcomes comparable to standard radical hysterectomy, with the added advantage of possibly reducing the need for adjuvant therapy. While it is not yet ready for universal adoption due to the lack of large prospective trials, current evidence positions TMMR as a promising and innovative alternative that warrants further multicentric validation. Further prospective multicenter studies involving a more diverse range of institutions and patient populations are essential to establish TMMR's true oncological value. Additionally, standardization of surgical technique, better definition of patient selection criteria, and long-term survival analyses

will be necessary to confirm whether TMMR can truly stand as a reliable alternative to radical hysterectomy in broader clinical practice.

ABBREVIATIONS

CCRT, Concurrent Chemoradiotherapy; CI, Confidence Interval; DFS, Disease-Free Survival; FIGO, International Federation of Gynecology and Obstetrics; FUP, Follow-Up; HR, Hazard Ratio; LACC, Laparoscopic Approach to Cervical Cancer; NCCN, National Comprehensive Cancer Network; NOS, Newcastle-Ottawa Scale; OS, Overall Survival; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, Randomized Controlled Trial; RR, Recurrence Rate; TMMR, Total Mesometrial Resection; PROSPERO, International Prospective Register of Systematic Reviews; MeSH, Medical Subject Headings; NOS, Newcastle Ottawa Scale.

AVAILABILITY OF DATA AND MATERIALS

All data and the methodological process for their calculation can be supplied under explicit request to the corresponding author and provided as an ".R" file.

AUTHOR CONTRIBUTIONS

CR—Conceptualization, Data curation; Investigation; Project administration; Software; Writing–Original Draft; Writing–review & editing. GC—Data curation; Investigation. MCS—Data Curation; Investigation. MCDD—Visualization. CS—Data curation. SR—Data curation. GV—Validation. VC—Supervision; Validation. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

ACKNOWLEDGMENT

Not applicable.

FUNDING

This research received no external funding.

CONFLICT OF INTEREST

The authors declare no conflict of interest. Carlo Ronsini and Stefano Restaino are serving as the Editorial Board members of this journal. We declare that Carlo Ronsini and Stefano Restaino had no involvement in the peer review of this article and had no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to EH.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.ejgo.net/files/article/1989223442400854016/attachment/Supplementary%20material.docx.

REFERENCES

[1] Arbyn M, Weiderpass E, Bruni L, de Sanjosé S, Saraiya M, Ferlay J, *et al*. Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis. The Lancet Global Health. 2020; 8: e191–e203.

[2] European Society of Gynaecological Oncology (ESGO), European Society for Radiotherapy and Oncology (ESTRO), & European Society of Pathology (ESP). ESGO/ESTRO/ESP Guidelines for the management of patients with cervical cancer. 2023. Available at: https://www.esgo.org (Accessed: 18 October 2025).

[3] National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology: cervical cancer (Version 4). 2019. Available at: https://www.nccn.org/guidelines (Accessed: 17 October 2025).

[4] Restaino S, Pellecchia G, Arcieri M, Bogani G, Taliento C, Greco P, *et al*.; Gynecologic Oncology Group. Management for cervical cancer patients: a comparison of the guidelines from the international scientific societies (ESGO-NCCN-ASCO-AIOM-FIGO-BGCS-SEOM-ESMO-JSGO). Cancers. 2024; 16: 2541.

[5] Maggino T, Landoni F, Sartori E, Zola P, Zanagnolo V, Pasinetti B, *et al*. Patterns of local and distant failure in cervical cancer patients treated with radical surgery. Cancer. 2006; 106: 927–933.

[6] Höckel M, Horn LC, Hentschel B, Höckel S, Naumann G. Total mesometrial resection: high resolution nerve-sparing radical hysterectomy based on developmentally defined surgical anatomy. International Journal of Gynecological Cancer. 2003; 13: 791–803.

[7] Höckel M, Horn LC, Manthey N, Braumann UD, Wolf U, Teichmann G, *et al*. Resection of the embryologically defined uterovaginal (Müllerian) compartment and pelvic control in patients with cervical cancer: a prospective analysis. The Lancet Oncology. 2009; 10: 683–692.

[8] Ramirez PT, Frumovitz M, Pareja R, Lopez A, Vieira M, Ribeiro R, *et al*. Minimally invasive versus abdominal radical hysterectomy for cervical cancer. The New England Journal of Medicine. 2018; 379: 1895–1904.

[9] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine. 2009; 151: 264.

[10] Bhatla N, Berek JS, Cuello Fredes M, Denny LA, Grenman S, Karunaratne K, *et al*. Revised FIGO staging for carcinoma of the cervix uteri. International Journal of Gynaecology and Obstetrics. 2019; 145: 129–135.

[11] Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Annals of Surgery. 2004; 240: 205–213.

[12] Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M, *et al*. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Accessed: 17 October 2025).

[13] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. International Journal of Gynaecology and Obstetrics. 2009; 105: 103–104.

[14] Buderath P, Stukan M, Ruhwedel W, Strutas D, Feisel-Schwickardi G, Wimberger P, *et al*. Total mesometrial resection (TMMR) for cervical cancer FIGO IB–IIA: first results from the multicentric TMMR register study. Journal of Gynecologic Oncology. 2022; 33: e9.

[15] Chiantera V, Vizzielli G, Lucidi A, Gallotta V, Petrillo M, Legge F, *et al*. Laparoscopic radical hysterectomy in cervical cancer as total mesometrial resection (L-TMMR): a multicentric experience. Gynecologic Oncology. 2015; 139: 47–51.

[16] Falconer H, Norberg-Hardie A, Salehi S, Alfonzo E, Weydandt L, Dornhöfer N, *et al*. Oncologic outcomes after total mesometrial resection

(TMMR) or treatment according to current international guidelines in FIGO (2009) stages IB1–IIB cervical cancer: an observational cohort study. EClinicalMedicine. 2024; 73: 102696.

[17] Höckel M, Wolf B, Schmidt K, Mende M, Aktas B, Kimmig R, *et al*. Surgical resection based on ontogenetic cancer field theory for cervical cancer: mature results from a single-centre, prospective, observational, cohort study. The Lancet Oncology. 2019; 20: 1316–1326.

[18] Kimmig R, Wimberger P, Buderath P, Aktas B, Iannaccone A, Heubner M. Definition of compartment-based radical surgery in uterine cancer: radical hysterectomy in cervical cancer as 'total mesometrial resection (TMMR)' by M Höckel translated to robotic surgery (rTMMR). World Journal of Surgical Oncology. 2013; 11: 211.

[19] Nasser S, Almuheimid J, Plett H, Sehouli J, Muallem MZ. Feasibility and safety of laparoscopic total mesometrial resection in early-stage cervical cancer. Anticancer Research. 2016; 36: 4903–4907.

[20] Vizzielli G, Lucidi A, Gallotta V, Petrillo M, Dessole M, Fagotti A, *et al*. Robotic total mesometrial resection versus laparoscopic total mesometrial resection in early cervical cancer: a case-control study. Journal of Minimally Invasive Gynecology. 2016; 23: 804–809.

[21] Schauta F. Extended Vaginal Total Hysterectomy for Cervical Cancer. Josef Safár: Wien; Leipzig. 1908.

[22] Wertheim E. The Extended Abdominal Operation for Carcinoma of the Cervix Uteri (Based on 500 Cases). Wien: Berlin. 1911.

[23] Ronsini C, Köhler C, De Franciscis P, La Verde M, Mosca L, Solazzo MC, *et al*. Laparo-assisted vaginal radical hysterectomy as a safe option for minimal invasive surgery in early stage cervical cancer: a systematic review and meta-analysis. Gynecologic Oncology. 2022; 166: 188–195.

[24] Kwon BS, Roh HJ, Lee S, Yang J, Song YJ, Lee SH, *et al*. Comparison of long-term survival of total abdominal radical hysterectomy and laparoscopy-assisted radical vaginal hysterectomy in patients with early cervical cancer: Korean multicenter, retrospective analysis. Gynecologic Oncology. 2020; 159: 642–648.

[25] Sedlis A, Bundy BN, Rotman MZ, Lentz SS, Muderspach LI, Zaino RJ. A randomized trial of pelvic radiation therapy versus no further therapy in selected patients with stage IB carcinoma of the cervix after radical hysterectomy and pelvic lymphadenectomy: a Gynecologic Oncology Group study. Gynecologic Oncology. 1999; 73: 177–183.

[26] Ronsini C, Solazzo MC, Braca E, Andreoli G, Vastarella MG, Cianci S, *et al*. Locally advanced cervical cancer: neoadjuvant treatment versus standard radio-chemotherapy—an updated meta-analysis. Cancers. 2024; 16: 2542.

How to cite this article: Carlo Ronsini, Giuseppe Cucinella, Maria Cristina Solazzo, Catello Di Donna, Cono Scaffa, Stefano Restaino, *et al.* Total mesometrial resection for cervical cancer: a systematic review of oncological outcomes and comparative analysis with radical hysterectomy. European Journal of Gynaecological Oncology. 2025; 46(11): 11-20. doi: 10.22514/ejgo.2025.134.