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Back to Beginning: Peritoneal Wash Cytology in Endometrial Cancer

—A Review of the Literature

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Abstract

Background: The role of peritoneal wash cytology (PWC) in endometrial cancer has fluctuated over five decades. It was introduced into FIGO endometrial cancer staging in 1988 as Stage IIIA but was removed in 2009 when evidence showed that cytology alone lacked independent prognostic value. In the molecular era, its relevance is being reconsidered. **Methods:** A systematic search of PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library (inception—30 August 2025) identified studies assessing PWC in endometrial cancer. Eligible designs included cohort, case-control, randomized trials, meta-analyses, guidelines reporting recurrence and survival outcomes, and treatment recommendations. **Results:** Eighteen studies were included. Classic cohorts demonstrated no survival disadvantage with cytology-only positivity, supporting its removal from FIGO staging. However, national databases and meta-analyses suggested adverse prognostic associations, particularly in high-risk disease. Recent molecular-era studies highlight that PWC's prognostic impact is subtype-specific: adverse in p53-abnormal and No Specific Molecular Profile (NSMP) tumors, but not in POLE-mutated or Mismatch Repair deficient (MMRd) cancers. Current National Comprehensive Cancer Network (NCCN) guidelines still incorporate PWC in treatment decisions for high-risk histology such as serous and clear cell carcinoma. Concerns remain regarding the iatrogenic consequences of surgical factors (e.g., hysteroscopy, distension media) influencing cytology results. **Conclusion:** PWC no longer defines stage but retains prognostic and therapeutic relevance in high-risk early-stage uterine cancers. Its value may be best realized when integrated with molecular classification. Future prospective, molecular-stratified studies are essential to determine its role in precision oncology.

Keywords

Endometrial Cancer, Cytology, Peritoneal Wash

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in developed countries, and its management has undergone a remarkable transformation over the past five decades. Among the many questions that have shaped this evolution is the role of peritoneal wash cytology (PWC)—once considered central to staging, later dismissed, and now resurfacing as a potential prognostic marker in selected contexts.

The journey of PWC reflects how gynecologic oncology as a field responds to evidence, adapts staging systems, and occasionally circles back to questions once thought resolved. When the International Federation of Gynecology and Obstetrics (FIGO) introduced its first surgical staging system for endometrial carcinoma in 1971, peritoneal cytology was not incorporated [1]. However, by the late 1970s and 1980s, studies by Kashimura *et al.* suggested that positive cytology was associated with increased risk of recurrence and reduced survival [2]. These observations led FIGO in 1988 to formally include positive peritoneal cytology as a staging criterion, designating it as Stage IIIA1 disease—equating cytology-only positivity with histologically proven extrauterine spread [3].

Over the following decades, however, larger and more rigorously designed studies challenged this assumption. Tebeu *et al.* (2004) demonstrated that women with cytology-only Stage IIIA disease had outcomes comparable to Stage I patients, while those with histologic Stage IIIA had markedly worse survival [4]. Similarly, Wethington and colleagues (2009) reported that the prognostic significance of positive cytology was not uniform; while low-risk patients with positive cytology had minimal recurrence risk, those with high-risk features faced a recurrence rate exceeding 30% [5] [6]. Collectively, these data showed that PWC lacked independent prognostic value when adjusted for established risk factors such as myometrial invasion, tumor grade, and histology. As a result, the 2009 FIGO staging revision removed peritoneal cytology from the staging algorithm, redefining Stage IIIA as serosal or adnexal invasion only [7].

Yet, the story did not end there. While cytology no longer determines stage, research continues to explore whether it retains prognostic significance, particularly in the framework of modern molecular classification systems. In addition, it is still included in the National Comprehensive Cancer Network (NCCN) and American Joint Committee on Cancer (AJCC) guidelines and impacts the management recommendations [8]. AJCC guidelines include peritoneal cytology as a factor that can influence risk stratification, even though it does not alter the surgical stage.

This review traces the trajectory of peritoneal wash cytology in endometrial

cancer—from its introduction and removal in FIGO staging to the renewed interest in its relevance today. By synthesizing historical evidence, contemporary studies, and emerging molecular insights, we aim to clarify whether PWC is merely a relic of the past or a tool worth reconsidering in the precision oncology era.

2. Methodology

PubMed/MEDLINE, Embase, Web of Science, and the Cochrane Library were searched from inception to 30 August 2025 for studies evaluating peritoneal wash cytology in endometrial cancer, including i) prognostic impact overall and/or by molecular subtype and ii) potential procedure-related influences (e.g., hysteroscopy). Table 1 lists the search strategy of combined controlled vocabulary and free-text terms. Backward and forward citation searching was performed for all eligible articles to capture additional studies relevant to the objectives. Where interim reports were identified, results and references were updated when full publications became available.

Table 1. Search Strategy terms.

Category	Term
Pathophysiology	Endometrial cancer, Endometrial neoplasms, Peritoneal cytology, Peritoneal washing, Peritoneal lavage, Peritoneal fluid cytology, Washings
Procedure	Hysteroscopy, Dilation and curettage, Pipelle, Saline, Intrauterine pressure
Outcomes	Prognosis, Recurrence, Survival
Molecular	POLE, Mismatch repair deficiency, MMRd, p53, Abnormal/TP53, NSMP
Guideline	FIGO, NCCN

Eligibility and selection: We included randomized/controlled studies, cohort and case-control studies, meta-analyses, and guideline/consensus statements that reported PWC status and at least one outcome of interest (cytology positivity, upstaging, recurrence-free/disease-free survival, overall survival, or treatment recommendations). We excluded case reports/series without comparators, non-uterine primaries, animal studies, and conference abstracts without full data. Titles/abstracts and full texts were screened, and data were extracted on study design, population, staging/histology, molecular class (when available), PWC collection/processing details, adjuvant therapy, and adjusted effect estimates. Risk of bias assessment was performed using the RoB 2 tool [9].

Figure 1 shows the study selection and exclusion process outlined in the PRISMA diagram [10].

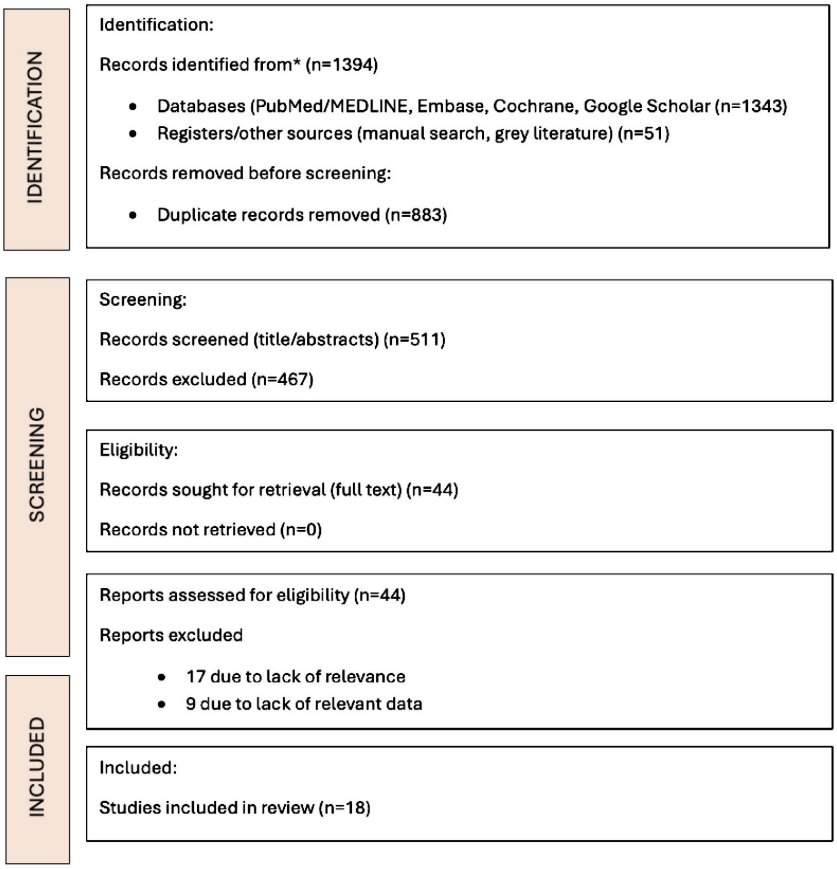

Figure 1. PRISMA 2020 flow of study selection for peritoneal wash cytology in Endometrial Cancer.

3. Results

Eighteen studies fitting the inclusion criteria were identified. The risk of bias was low for all studies. **Table 2** summarizes studies from the pre-molecular era of 1983 through 1997 [2] [11]-[14]. These retrospective studies with a combined total of 1,258 patients establish the higher risk of recurrence and distant disease with malignant PWC but also show an association of PWC findings with other factors such as high-risk histology, lymph vascular invasion (LVSI), and deep myometrial invasion.

Table 2. Comparative evidence on prognostic role of peritoneal wash cytology in Endometrial Cancer 1983-1997: Pre-molecular era.

No. Year	Author	N (Design)	Inclusion	Findings	Notes
1. 1983	Yazigi [11]	93 (retrospective)	Stage I EC	Malignant PWC is associated with inferior outcomes in early-stage disease.	Early evidence suggesting the prognostic role of PWC.
2. 1988	Mazurka [12]	280 (retrospective)	Mixed stages	PWC correlated with adverse histopathology and worse survival.	PWC correlated with adverse histopathology and worse survival.

Continued

3. 1990	Grimshaw [13]	381 (retrospective)	Stage I-IV	PWC is not independently prognostic when controlling for extrauterine disease.	Highlights stage confounding.
4. 1997	Kashimura [2]	303 (retrospective)	Stage I-IV EC	Positive PWC in 15%; associated with deep myometrial invasion and lymph node metastasis.	Suggested a biological link between invasion depth and PWC positivity.
5. 1997	Deschamps [14]	201 (retrospective)	Stage I-II clinical	PWC+ is linked to a higher risk of distant relapse.	Radiation-era study emphasizing distant failures.

Table 3 summarizes studies from 2001 through 2012 [4] [5] [15]-[20]. These retrospective studies with a combined total of 2,662 patients confirmed the earlier observations that positive cytology was associated with a higher recurrence rate and reduced survival.

Table 3. Comparative evidence on prognostic role of peritoneal wash cytology in Endometrial Cancer from 2001 through 2012: Pre-molecular era.

No. Year	Author	N (Design)	Inclusion	Findings	Notes
6. 2001	Obermair [15]	369 (retrospective)	Stage I, node negative	PWC independently associated with shorter DFS.	Validated prognostic value even in surgically staged cohorts.
7. 2001	Takeshima [16]	543 (retrospective)	Stage I-IV (subset analysis)	Positive cytology is linked to poorer survival; it is strongest in early stages.	Consistent trend across subgroups.
8. 2002	Preyer [17]	186 (retrospective)	FIGO IIIA	PWC positivity contributed to worse outcomes in IIIA, defined by cytology.	Clarified heterogeneity within 1988 FIGO IIIA.
9. 2003	Tebeu [4]	295 (retrospective)	Stage I-III	Positive PWC predictive of reduced survival.	Supported FIGO 1988 inclusion of PWC in staging.
10. 2003	Kasamatsu [5]	280 (retrospective)	Uterus confined Endometrial cancer	PWC alone is not independently prognostic after adjusting for LVSI and Myometrial invasion.	Emphasized multivariable context.
11. 2004	Tebeu [18]	331 (retrospective)	Stage I-III	Positive cytology retained prognostic effect for recurrence.	Strengthened prognostic consistency.
12. 2006	Saga [19]	307 (retrospective)	Uterus confined Endometrial cancer	Positive cytology worsened 5-year DFS.	Reinforced role even in uterus-confined tumors.
13. 2012	Gultekin [20]	351 (retrospective)	All stages	Despite the removal of PWC from FIGO 2009, survival differences.	Highlighted ongoing prognostic relevance.

Table 4 summarizes studies from the modern era, 2013 to 2025 [21]-[25]. This set of studies includes large population-based data, which confirms the poorer outcomes related to positive cytology. In addition, smaller prospective studies have started to subset out PWC positive risk with poor prognosis molecular markers such as p53 mutant subtype [24].

Table 4. Comparative evidence on prognostic role of peritoneal wash cytology in Endometrial Cancer from 2013 through 2025: Molecular era.

No. Year	Author	N (Design)	Inclusion	Findings	Notes
14. 2013	Garg [21]	14,704 (SEER)	Stage I-II	PWC+ is independently associated with decreased OS and DSS.	Population-level confirmation of risk.
15. 2014	Shiozaki [22]	265 (retrospective)	Stage I	PWC effect is limited to high-grade or deep myometrial invasion cases.	Suggested interaction with risk factors.
16. 2018	Seagle [22]	24,800+ (NCDB)	Early endometrial cancer	PWC+ predicted worse survival; adjuvant chemotherapy improved outcomes.	Supported individualized adjuvant approach for PWC+.
17. 2024	Villiger [24]	250 (prospective)	TCGA/ ProMisE-typed	PWC+ independently adverse in p53-abnormal subtype; not in MMRd/POLE.	Connected molecular phenotype with peritoneal spread.
18. 2025	Sakai [25]	39,000+ (JSOG registry)	All stages	PWC+ is associated with poorer outcomes nationwide; prognostic independent of other variables.	Strongest population-based confirmation in the modern era.

4. Discussion

Figure 2 illustrates the historical timeline of including peritoneal cytology data into staging for endometrial cancer. In the 1988 FIGO staging system, positive peritoneal cytology (PWC) was grouped with adnexal and serosal involvement as Stage IIIA disease, even in the absence of visible spread. This decision reflected early single-institution series suggesting that malignant washings were associated with worse prognosis [3].

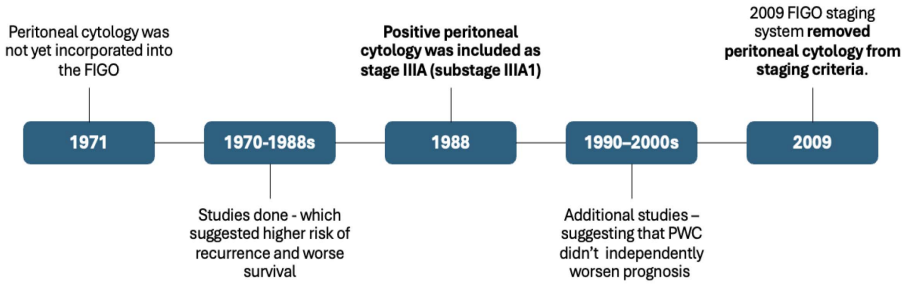

Figure 2. Historical evolution of PWC in FIGO staging in Endometrial Cancer.

However, landmark population-based work by Tebeu *et al.* (2004) challenged this paradigm [18]. Using Geneva registry data, they demonstrated that patients with cytology-only Stage IIIA disease had 5-year disease-specific survival similar to Stage I (91% vs 92%), while those with histological IIIA disease fared far worse (50%). Adjusted analyses confirmed that cytology alone did not increase mortality risk (HR 0.7), whereas histologic spread increased mortality four-fold (HR 4.2) [4].

Other retrospective cohorts echoed this. Kasamatsu *et al.* (2003) analyzed 280 surgically staged patients confined to the uterus and found no independent prognostic role of cytology [5]. Instead, histologic grade emerged as the strongest predictor of survival. Similarly, Wang *et al.* (2020) reported on 1,284 women with stage IA endometrioid carcinoma: only 2.9% had positive cytology, and no one experienced recurrence or death. PWC had no effect on DFS, OS, or cancer-specific survival, even with adjuvant therapy [26].

These findings, together with the heterogeneity in results from smaller institutional series, ultimately led FIGO in 2009 to remove cytology from staging [7].

Yet some evidence suggested a difference in outcomes by cytologic presence of free-floating endometrial cancer cells. A 2024 systematic review and meta-analysis by Pergialiotis *et al.* synthesized 15 studies including >19,000 women with early-stage EC [27]. The pooled results suggested that positive cytology is associated with significantly lower recurrence-free survival (HR 0.26) and reduced overall survival (HR 0.50). Despite limitations, this analysis concluded that PWC may be a negative prognostic factor in early disease, reigniting debate over its dismissal from FIGO staging.

In the post-2009 era, large database studies have provided further nuance, suggesting a prognostic role of cytology beyond staging. Seagle *et al.* (NCDB, 2010-2013) reported that positive cytology was independently associated with worse survival in stage I-II EC (HR 1.85) [23]. Similarly, the Mayo Clinic cohort (1999-2021) showed that in patients defined as "low-risk" by NCCN or ESGO criteria, overall survival was unaffected, but recurrence-free survival was significantly worse with positive cytology (HR 2.6, NCCN; HR 2.34, ESGO) [28].

In the current molecular era, recent work has integrated cytology into the TCGA molecular framework. A Swiss Bern cohort study (Villiger *et al.*, 2024) found cytology positivity rates varied by molecular subtype: 41% in p53-abnormal, 24% in NSMP, 25% in POLE, and 16% in MMRd tumors [24]. Prognostic impact was restricted to p53-abnormal and NSMP subgroups, where positive cytology independently predicted recurrence ($p = 0.033$) and death ($p = 0.008$). From studies to date, PWC behaves differently in POLE/MMRd vs p53/NSMP subtypes. This may link to biological mechanisms of dissemination or the immune microenvironment. This aligns with the emerging consensus that PWC's meaning is biologically contextual. Current information has led to considerations of new clinical practice guidelines. Although no longer part of FIGO staging, PWC continues to influence management. NCCN guidelines (2025) recommend systemic therapy plus brachytherapy (±EBRT) for patients with serous and clear cell histology when washings are positive in endometrium-confined disease, while observation may be reason-

able if cytology is negative [8]. Thus, PWC still plays a role in adjuvant treatment decisions, even if not in staging.

4.1. Procedure-Related Considerations: The Hysteroscopy Debate

A related concern is whether diagnostic hysteroscopy contributes to positive cytology and whether this can iatrogenically lead to worse outcomes. A multi-center study of >1700 patients showed no difference in outcomes between hysteroscopy and Pipelle sampling, affirming hysteroscopy's safety [29]. Conversely, a 2009 meta-analysis (Polyzos *et al.*) reported a higher rate of malignant cytology with hysteroscopy, especially when saline distension was used (OR 2.89) [30]. More recent series, however, using low-pressure saline, found no increase in positive cytology or microscopic spread [31]. This inconsistency underscores that surgical technique and intrauterine pressure may confound cytology interpretation, particularly in low-risk disease [30]. Given a potential risk of tumor cell dissemination, low-pressure saline use and limited manipulation should be practiced.

The trajectory of PWC illustrates how oncology continuously revisits old questions with new tools. Once upstaging thousands of women as Stage IIIA, it was later deemed non-prognostic and removed. Today, molecularly stratified data show that while cytology is irrelevant in POLE and MMRd tumors, it is highly prognostic in p53-abnormal and NSMP cancers and continues to guide therapy in aggressive histologies per NCCN [8].

4.2. Gaps and Future Research

Despite decades of research, the role of peritoneal wash cytology (PWC) in endometrial cancer remains unresolved. Its historical trajectory—from initial omission in FIGO staging, to inclusion as Stage IIIA1, and later removal in 2009 reflects both its potential relevance and the inconsistency of evidence supporting it. Several key gaps are summarized in **Table 5**.

Table 5. Summary of potential concerns about peritoneal cytology in Endometrial Cancer.

General Category	Continued Questions
Heterogeneity of Prognostic Value	1) Studies show conflicting results: while early reports suggested poor outcomes with positive cytology, larger series later demonstrated no independent prognostic effect when adjusted for grade, myometrial invasion, and adjuvant therapy. 2) More recent data suggest that its significance is not universal, but context-dependent, particularly relevant in p53-abnormal and NSMP molecular subgroups, as well as in aggressive histologies like serous and clear cell carcinomas.
Influence of Surgical and Technical Factors	1) The accuracy of cytology may be influenced by hysteroscopy, uterine manipulation, or the distension medium, raising concerns about false positives. 2) Standardization of sampling and interpretation remains lacking across centers, making cross-study comparisons difficult.

Continued

Absence in Current Staging, yet Persistence in Guidelines	While PWC has been excluded from FIGO staging since 2009, it is still included in NCCN guidelines for treatment decision-making in high-risk histologies. This creates a paradox: it is not considered prognostic enough for staging but still influences management in select situations.
Cost-Effectiveness and Overtreatment Concerns	1) Although individually inexpensive, routine use in all patients adds to cumulative healthcare costs and pathology workload. 2) Positive results in otherwise low-risk patients may prompt unnecessary escalation of treatment, contributing to overtreatment.

To truly clarify the role of PWC, future research should focus on:

- Molecularly integrated analyses: Large prospective cohorts incorporating TCGA-based molecular classification (POLE, MMRd, p53-abn, NSMP) are needed to define in which subgroups cytology meaningfully alters prognosis.
- Histology-specific studies: Dedicated analyses in serous, clear cell, and carcinosarcoma subtypes, where extrauterine spread risk is intrinsically higher.
- Standardization of technique: Consensus on timing, sampling, and cytological interpretation to minimize variability introduced by surgical factors.
- Clinical utility endpoints: Trials designed to assess whether incorporating cytology into adjuvant therapy algorithms improves outcomes compared to relying solely on histopathologic and molecular factors.
- Health economics perspective: Evaluating whether selective rather than universal use of cytology offers an optimal balance between cost, workload, and prognostic yield.

5. Conclusions

Peritoneal wash cytology (PWC) has had a fluctuating role in endometrial cancer. Its complete dismissal as a prognostic indicator has proven premature. Emerging evidence in the molecular era highlights that PWC may still hold prognostic significance in specific subgroups, particularly in p53-abnormal and NSMP tumors, as well as in high-risk histology such as serous and clear cell carcinomas.

Today, PWC no longer determines stage, but it remains referenced in NCCN guidelines and continues to inform treatment strategies in selected high-risk cases. Its value lies not in universal application but in nuanced, context-dependent interpretation [8].

As endometrial cancer care shifts toward precision oncology, the future role of PWC will depend on whether it can be meaningfully integrated with molecular classification systems, histologic risk groups, and treatment algorithms [27]. Rather than asking whether cytology should be discarded or reinstated in staging, the more relevant question is—in whom does it matter, and how can it refine care?

Thus, peritoneal cytology may best be viewed not as a relic of past staging systems, but as an unanswered research question—a simple, low-cost tool whose true value will be defined only through modern, molecularly stratified research.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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