

Modern Management of Endometrial Cancer: Molecular Classification, Surgery, Immunotherapy, and Regional Challenges

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Abstract

Background: The management of endometrial cancer has evolved with the integration of molecular classification, minimally invasive surgery, sentinel lymph node mapping, and immune checkpoint inhibitors. These advances have improved risk stratification and expanded treatment options across early-stage and advanced disease.

Methods: This narrative review evaluated clinical guidelines, randomized trials, systematic reviews, major prospective studies, and large relevant cohorts published between 2013 and 2026 using PubMed/MEDLINE, Scopus, and Web of Science. Evidence was selected according to clinical relevance and methodological strength, with emphasis on molecular classification, surgical staging, immunotherapy, and regional implementation. No formal PRISMA-based screening or systematic evidence synthesis was performed.

Main Findings: Molecular classification complements conventional risk assessment through POLEmut, MMRd, p53abn, and NSMP subgroups. Minimally invasive surgery and sentinel lymph node mapping offer less morbid staging approaches in selected patients. In advanced and recurrent disease, phase III trials including RUBY, NRG-GY018, DUO-E, and AtTend have demonstrated clinically relevant benefits from immune checkpoint inhibitor-based strategies, with the greatest effects generally observed in MMRd/dMMR tumors.

Conclusion: Endometrial cancer management is increasingly guided by molecular and biomarker-based approaches alongside conventional histopathology and staging. The extent of implementation of these strategies in Azerbaijan and the Caucasus remains insufficiently documented. Regional registries, assessment of molecular testing capacity, and multicenter clinical data collection may help define current practice and support future development.

Keywords: endometrial cancer; molecular classification; sentinel lymph node; immunotherapy; MMRd; POLEmut; Caucasus.



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1 | Introduction

Endometrial cancer is one of the most common malignant tumors of the female reproductive system. Because a large proportion of patients are diagnosed at an early stage, the overall prognosis is often favorable. Nevertheless, recurrence and disease-related mortality remain clinical concerns in high-risk, locally advanced, and metastatic disease [1].

For many years, treatment decisions were based mainly on FIGO stage, histological type, tumor grade, myometrial invasion, and lymphovascular invasion. Although this approach has been useful in clinical practice, the different clinical courses observed among patients with similar morphological characteristics have highlighted the need for a broader understanding of tumor biology [2].

In 2013, the genomic classification introduced by The Cancer Genome Atlas provided a clearer picture of the molecular heterogeneity of endometrial cancer. The disease was divided into POLE-ultramutated, microsatellite instability-hypermutated, copy-number low, and copy-number high groups, and these groups were shown to have distinct clinical characteristics [3].

Subsequent studies adapted this approach into a more practical clinical framework and expanded the use of the POLE-mutated (POLEmut), mismatch repair-deficient (MMRd), p53-abnormal (p53abn), and no specific molecular profile (NSMP) groups [4].

The 2023 revision of FIGO staging also gave greater consideration to histological and molecular information than previous systems [5]. The ESGO–ESTRO–ESP guideline published in 2025 further linked these developments with risk assessment, surgical management, adjuvant therapy, and the management of metastatic or recurrent disease [6].

Surgical management has also gradually moved toward less invasive approaches. Minimally invasive hysterectomy is widely used in appropriate patients with early-stage disease, while sentinel lymph node mapping is accepted as a less morbid staging approach compared with systematic lymphadenectomy [7].

The aim of this review is to summarize contemporary molecular, surgical, and systemic treatment approaches in endometrial cancer, discuss their role in clinical practice, and highlight current evidence gaps related to the implementation of these strategies in Azerbaijan and the Caucasus region.

2 | Materials and Methods

This work was prepared as a narrative review combining current clinical evidence with a regional implementation perspective rather than as a systematic review. The structure and reporting of the manuscript were informed by the SANRA principles developed for the quality assessment of narrative review articles [8].



The literature search was conducted using PubMed/MEDLINE, Scopus, and Web of Science. Search terms included “endometrial cancer,” “molecular classification,” “POLE,” “POLEmut,” “mismatch repair,” “MMRd,” “p53,” “p53abn,” “NSMP,” “FIGO staging,” “sentinel lymph node,” “indocyanine green,” “minimally invasive surgery,” “immunotherapy,” “dostarlimab,” “pembrolizumab,” “durvalumab,” “atezolizumab,” “Azerbaijan,” and “Caucasus,” as well as appropriate combinations of these terms.

The review focused mainly on international clinical guidelines, randomized phase III trials, systematic reviews, prospective studies, and large clinically relevant cohorts published between 2013 and 2026. Publications were prioritized according to their clinical relevance, methodological quality, study size, and contribution to current management. Larger and methodologically stronger main search period were retained when necessary to provide historical or clinical context.

Because this was a narrative rather than a systematic review, study selection was based on relevance to the predefined clinical themes rather than a formal PRISMA-based screening algorithm. Formal duplicate screening, risk-of-bias assessment, and quantitative evidence synthesis were therefore not performed.

For the section addressing Azerbaijan and the Caucasus, only publicly available and verifiable information was considered. Where reliable regional data were unavailable, this was presented as an evidence gap rather than as evidence of inadequate clinical practice or service provision.

Molecular Classification and Risk-Adapted Treatment

After molecular classification entered clinical practice, it did not replace conventional histopathological assessment but instead became an additional source of information that complements it. Validation studies have shown that the molecular groups are associated with different prognostic characteristics [9].

Table 1. Main Molecular Groups of Endometrial Cancer

Molecular group	Main feature	General prognostic profile	Clinical application
POLEmut	POLE exonuclease-domain mutation	Usually favorable	De-escalation of treatment intensity is being investigated in selected patients
MMRd	Loss of MMR proteins and/or MSI-H	Heterogeneous	Evaluation for Lynch syndrome and selection for immunotherapy



NSMP	Absence of the other three molecular features	Heterogeneous	Assessed together with histology and additional biomarkers
p53abn	Aberrant alterations	p53/TP53 Higher risk in most cases	May support consideration of more intensive treatment strategies

studies were generally prioritized over smaller series reporting similar findings. Landmark studies published outside the

Despite their high mutational burden, POLEmut tumors often have a favorable clinical course, which has led to investigation of whether adjuvant treatment intensity may be reduced in selected patients [10]. Treatment de-escalation in this setting remains an area of ongoing clinical investigation rather than a universal standard applicable to all patients with POLEmut tumors.

p53abn tumors, in contrast, are generally associated with a higher risk of recurrence. Molecular analyses in high-risk endometrial cancer have suggested that this group may derive greater benefit from combined adjuvant treatment in selected clinical settings [11].

MMRd tumors have practical value both for identifying patients who may require evaluation for Lynch syndrome and as biomarkers relevant to immunotherapy. Assessment of MMR status can therefore be useful not only for prognostic characterization but also for hereditary risk

evaluation and systemic treatment selection [12].

NSMP remains a biologically and clinically heterogeneous category. Risk assessment within this group continues to depend on integration of molecular findings with histopathological characteristics and additional biomarkers.

Surgical Management and Sentinel Lymph Node Assessment

Total hysterectomy with bilateral salpingo-oophorectomy remains the basis of surgical treatment for early-stage endometrial cancer. In appropriately selected patients, minimally invasive surgery is associated with less blood loss, shorter hospitalization, and faster recovery.

Long-term results from the LAP2 trial showed satisfactory oncologic outcomes with laparoscopic surgery compared with open surgery and supported the broader adoption of minimally invasive approaches [13].

Sentinel lymph node mapping has also become more widely used for nodal assessment in recent years. Although systematic lymphadenectomy provides information for nodal staging, it may be



associated with complications such as lymphedema and lymphocele formation [14].

The FIRES trial demonstrated high diagnostic accuracy of sentinel lymph node mapping for detecting nodal metastases [15]. The SENTOR study, which also included higher-risk histological groups, further supported the practical value of this approach when an appropriate mapping algorithm and pathological ultrastaging are used [16].

Indocyanine green-based near-infrared imaging is currently one of the commonly used mapping techniques. However, outcomes depend not only on technical equipment but also on surgeon experience, adherence to a standardized sentinel lymph node algorithm, and access to pathological ultrastaging.

Systemic Therapy and Immunotherapy

Carboplatin and paclitaxel have long been among the main systemic treatment regimens for advanced and recurrent endometrial cancer. In recent years, immune checkpoint inhibitors used in combination with chemotherapy have expanded available treatment options.

In the RUBY trial, the addition of dostarlimab to carboplatin–paclitaxel improved progression-free survival, with a particularly pronounced benefit in the dMMR/MSI-H population [17]. The magnitude and interpretation of benefit should therefore be considered in the context of the molecular subgroup and population evaluated in the trial.

In NRG-GY018, pembrolizumab in combination with chemotherapy was evaluated separately in dMMR and pMMR cohorts. A progression-free survival benefit was demonstrated in both cohorts, although the relative benefit was substantially greater in patients with dMMR disease [18].

The DUO-E trial evaluated durvalumab in combination with chemotherapy followed by maintenance durvalumab, with or without olaparib. The study provided additional evidence supporting immunotherapy-based maintenance strategies in advanced endometrial cancer, while the role of specific combinations and patient-selection biomarkers continues to evolve [19].

In the AtTend trial, the addition of atezolizumab to platinum-based chemotherapy demonstrated clinical benefit in the overall study population, with particularly prominent effects observed in the dMMR subgroup [20].



Table 2. Major Phase III Immunotherapy Trials in Advanced and Recurrent Endometrial Cancer

Study	Treatment approach	Overall finding
RUBY	Dostarlimab + carboplatin/paclitaxel	Clinical benefit, with particularly pronounced benefit in the dMMR/MSI-H group
NRG-GY018	Pembrolizumab carboplatin/paclitaxel	+ PFS benefit demonstrated in both dMMR and pMMR cohorts, with greater relative benefit in dMMR disease
DUO-E	Durvalumab + chemotherapy durvalumab ± olaparib	→ Supported further development of immunotherapy-based maintenance strategies
AtTend	Atezolizumab carboplatin/paclitaxel	+ Clinical benefit with particularly prominent effects in the dMMR population

These results demonstrate that the magnitude of benefit from immunotherapy is not uniform across all patients and highlight the increasing clinical importance of molecular characteristics when systemic treatment is selected.

In recurrent disease, the combination of pembrolizumab and lenvatinib has also provided an additional systemic treatment option following previous platinum-based therapy, particularly in patients with pMMR disease [21].

Regional Implementation Challenges

The integration of contemporary endometrial cancer management into clinical practice is not determined solely by the availability of international guidelines. Molecular pathology capacity, pathology quality, surgical expertise, technical equipment, drug availability, reimbursement models, and multidisciplinary infrastructure may also influence implementation. In Azerbaijan and

the wider Caucasus region, broad multicenter data describing the frequency and distribution of molecular testing, sentinel lymph node programs, and use of newer systemic therapies remain limited.

This lack of published regional data should not be interpreted as evidence that these approaches are unavailable or inadequately implemented. Rather, it represents an evidence gap regarding the extent, consistency, and outcomes of implementation across different institutions.

For this reason, rather than making broad assumptions about regional practice, assessment through prospective registries, institutional audits, and multicenter data collection would provide a more reliable description of current practice.

IARC data allow estimation of the overall cancer burden in Azerbaijan but do not provide detailed clinical information



regarding molecular subtypes of endometrial cancer, treatment patterns, use of sentinel

lymph node mapping, or center-specific outcomes [22].

Table 3. Main Areas for Assessing Regional Implementation

Area	Contemporary approach	Potential issue to assess at the regional level
Molecular pathology	MMR, p53, and POLE testing when appropriate	Actual frequency and availability of testing
Surgical staging	Minimally invasive surgery and SLN mapping	Availability of ICG/NIR, standardized mapping algorithms, and ultrastaging
Systemic therapy	Biomarker-based chemo-immunotherapy	Real-world access to contemporary treatments
Multidisciplinary care	MDT and integration of molecular information	Use of molecular results in treatment decisions
Data infrastructure	Registries and outcome monitoring	Systematic collection of treatment and survival outcomes

In countries with different levels of healthcare resources, gradual implementation of new oncology technologies and adaptation to local capacity may represent a practical approach [23].

3 | Limitations and Future Directions

This review has several limitations. Because it was prepared as a narrative review, a formal PRISMA screening process, systematic study-selection procedure, and risk-of-bias assessment were not performed.

In addition, systemic treatment of endometrial cancer is a rapidly evolving field, and long-term overall survival results

from some immunotherapy trials continue to mature.

Heterogeneity also remains within the currently recognized molecular groups. In particular, NSMP represents a heterogeneous category that may eventually be subdivided using additional molecular and clinicopathological biomarkers.

The main limitation of the regional section is the lack of broad, contemporary patient-level data from Azerbaijan and the Caucasus. Therefore, rather than providing definitive conclusions regarding regional practice, this



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review primarily identifies areas in which further data collection may be useful.

The RAINBO program, which evaluates molecularly directed adjuvant treatment strategies, represents an important example of ongoing research designed to refine treatment according to molecular characteristics [24].

Several additional approaches are also under investigation. These include circulating tumor DNA and molecular residual disease (ctDNA/MRD) monitoring, HER2-directed and other biomarker-based targeted therapies, novel immunotherapy combinations, and digital or computational pathology.

At present, these emerging strategies should be regarded as areas of ongoing research or evolving clinical application rather than universally established components of routine management. Further prospective validation and integration into treatment algorithms will be required before their role can be defined more precisely.

6 | Conclusion

Contemporary endometrial cancer management increasingly integrates molecular classification with established histopathological and anatomical assessment. POLEmut, MMRd, NSMP, and p53abn subgroups may refine prognostic assessment and treatment selection, while minimally invasive surgery and sentinel lymph node mapping can reduce surgical morbidity in selected patients. Immune checkpoint

inhibitor-based strategies have expanded treatment options in advanced and recurrent disease, although benefit varies across molecular subgroups and trial populations. In Azerbaijan and the Caucasus, multicenter data on molecular testing, sentinel lymph node programs, access to modern therapies, and patient outcomes are needed to better characterize implementation and guide future clinical development.

Declarations

Ethics Approval

Not applicable. This article is a narrative review based exclusively on previously published literature and did not involve human participants, patient-level data, or animal experiments.

Consent to Participate

Not applicable.

Consent for Publication

Not applicable.

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Conflict of Interest

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Data Availability



No new datasets were generated or analyzed in this study. All information discussed in this review was obtained from previously published and publicly available sources cited in the manuscript.

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