


A NARRATIVE REVIEW OF THERAPEUTIC OPTIONS IN ADVANCED ENDOMETRIAL CANCER

Michał Stermach¹  , **Nina Kubikowska**¹ ,
Iga Poprawa¹ , **Artur Marcysiak**¹ ,
Agata Leszek² , **Zuzanna Lecyk**² ,
Przemysław Krukowski³ , **Zuzanna Gąsior**³ ,
Paweł Mikołajczak⁴ , **Dominik Koryciński**⁵ 

¹ Medical University of Warsaw, Poland

² 4th Military Clinical Hospital in Wrocław, Poland

³ Tytus Chałubiński District Hospital in Zakopane, Poland

⁴ National Medical Institute of the Ministry of the Interior and Administration, Warsaw, Poland

⁵ Łazarski University, Warsaw, Poland



[download article \(pdf\)](#)

 michal.stermach@icloud.com

ABSTRACT

BACKGROUND

Advanced and recurrent endometrial cancer is associated with limited survival and marked clinical heterogeneity. Treatment outcomes vary according to disease extent, resectability, molecular characteristics, and patient related factors. Despite the introduction of immunotherapy and targeted approaches, uncertainty remains regarding the comparative effectiveness and clinical positioning of available treatment modalities.

AIMS

To analyze the roles, effectiveness, and limitations of surgery, chemotherapy, radiotherapy, and immunotherapy in advanced and recurrent endometrial cancer, and to evaluate how treatment selection is determined by clinical and molecular factors.

METHODS

This narrative review was conducted using a structured literature search in PubMed, PubMed Central, Google Scholar, Directory of Open Access Journals, and Cochrane Library. Studies published between 2010 and 2025 were considered. Eligible sources included randomized and nonrandomized clinical trials, observational studies, meta-analyses, and clinical guidelines addressing therapeutic strategies in advanced or recurrent disease. Selection was based on clinical relevance and reporting of outcomes such as overall survival, progression free survival, response rates, and treatment related toxicity.

RESULTS

The available evidence demonstrates that treatment modalities are not interchangeable and provide benefit in specific clinical contexts. Cytoreductive surgery is associated with improved outcomes only when complete macroscopic resection is achievable. In unresectable or disseminated disease, systemic therapy represents the principal treatment approach. Carboplatin and paclitaxel remain the reference first line regimen due to consistent efficacy and predictable toxicity. Radiotherapy contributes to local control and symptom management but does not demonstrate consistent survival benefit in advanced disease. Immunotherapy shows substantial and durable responses in MSI H and dMMR tumors, whereas its activity in mismatch repair proficient disease is limited. Combination therapy with pembrolizumab and lenvatinib extends treatment activity to broader populations but is associated with increased toxicity.

CONCLUSIONS

The management of advanced endometrial cancer requires a stratified approach based on resectability, molecular profile, and patient related factors. Chemotherapy remains the central systemic component in unselected populations, while immunotherapy provides clinically meaningful benefit in molecularly defined subgroups. No single therapeutic strategy demonstrates consistent superiority across all patients. Interpretation of available data is limited by heterogeneity of study designs and incomplete representation of real world populations. Optimal sequencing and integration of treatment modalities remain insufficiently defined and require further investigation in prospective studies with molecular stratification.

Keywords: advanced endometrial cancer, chemotherapy, radiotherapy, immunotherapy, carboplatin, paclitaxel, MSI H, dMMR.

INTRODUCTION

Advanced endometrial cancer remains associated with poor prognosis and limited therapeutic options in advanced and recurrent settings. Despite favorable outcomes in early stage disease, patients with stage III to IV or recurrent cancer demonstrate substantially reduced survival, reflecting a persistent unmet clinical need. In Poland, endometrial cancer is the most common gynecologic malignancy, with more than 6,000 new cases diagnosed annually and a steadily increasing incidence, particularly in aging populations [2],[44].

Over the past decade, the therapeutic landscape has undergone significant changes driven by advances in molecular classification and the introduction of targeted and immune based therapies. Identification of mismatch repair deficiency and microsatellite instability has enabled the use of immune checkpoint inhibitors, which have demonstrated clinically relevant activity in selected patient populations [27],[29],[33]. At the same time, combination strategies such as pembrolizumab with lenvatinib have extended treatment options to patients without these molecular features [34],[35]. However, these advances have not resolved key clinical uncertainties.

At present, treatment of advanced endometrial cancer is based on a multimodal approach, but there is no consistently defined framework for selecting and sequencing therapeutic strategies across clinical scenarios. The relative roles of primary cytoreductive surgery and neoadjuvant chemotherapy remain insufficiently defined in stage III to IV disease [10],[14]. The optimal positioning of immunotherapy within treatment lines is unclear, particularly in relation to platinum based regimens and molecular subtypes [3],[19],[42]. In addition, available evidence is heterogeneous, with variability in study design, patient populations and reported outcomes, which limits direct comparison of therapeutic approaches and complicates clinical decision making.

Thus, the key scientific problem is the lack of a clinically oriented synthesis that integrates surgical, systemic and radiotherapeutic approaches with molecular stratification and defines their practical roles, limitations and indications in advanced disease.

RELEVANCE AND NOVELTY

Although multiple studies and reviews have examined individual treatment modalities, including chemotherapy, immunotherapy and targeted therapies [19],[30],[39], available evidence remains fragmented with respect to their combined use in real clinical settings. Existing analyses often focus on single therapeutic strategies without addressing their interaction within multimodal treatment.

The present review is focused on the integrated evaluation of major treatment approaches across clinically relevant scenarios, including differences related to disease extent, treatment line and molecular profile. Particular attention is given to limitations of available evidence, inconsistencies in reported outcomes and areas where data do not allow clear clinical interpretation.

Such an approach is intended to provide a clinically applicable synthesis that reflects the complexity of therapeutic decision making and highlights specific areas where current evidence remains insufficient.

OBJECTIVES AND RESEARCH TASKS

The objective of this narrative review is to analyze current and emerging therapeutic strategies in advanced endometrial cancer with emphasis on their clinical applicability and limitations within multimodal management.

The review addresses the following research tasks.

1. To analyze the roles and outcomes of surgery, chemotherapy and radiotherapy in advanced and recurrent endometrial cancer, taking into account disease extent and patient related factors [10],[14],[20],[21].
2. To evaluate the effectiveness and limitations of systemic therapy, including platinum based chemotherapy, immunotherapy and combination treatment strategies, with consideration of molecular subtypes [9],[27],[34].
3. To examine current approaches to treatment selection and sequencing, including the positioning of surgery, systemic therapy and immunotherapy at different stages of disease [3],[19],[42].
4. To assess limitations of available evidence, including heterogeneity of study design, patient populations and reported outcomes, and their impact on interpretation of results.
5. To identify key gaps in current knowledge that limit evidence based clinical decision making and define priorities for further research.

Such formulation is consistent with the narrative design of the review and reflects the actual level of available evidence.

METHODOLOGY

This study was conducted as a narrative review with a structured literature search aimed at identifying and synthesizing clinically relevant evidence on therapeutic strategies in advanced and recurrent endometrial cancer.

A literature search was performed in January 2026 using the following freely accessible databases: PubMed, PubMed Central, Google Scholar, Directory of Open Access Journals, and Cochrane Library. The search covered studies published between 2010 and 2025 in order to reflect contemporary therapeutic approaches, including the role of molecular classification and immunotherapy. Reference lists of selected publications were also screened to identify additional relevant sources.

The search strategy combined controlled vocabulary and free text terms related to disease stage and treatment modalities. Core concepts included endometrial cancer, advanced or recurrent disease, and therapeutic approaches such as surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy. In PubMed, both MeSH terms and free text terms were applied with filters for human studies and English language publications. In other databases, analogous keyword combinations were used, with adaptations appropriate to each platform.

A total of 85 records were identified. Publications not relevant to advanced or recurrent disease, lacking clinically meaningful outcomes, or not meeting inclusion criteria were excluded. Overall, 44 studies were included in the final analysis. For transparency of the selection process, reasons for exclusion at the full text stage were documented and categorized as lack of relevance to advanced or recurrent disease, absence of clinically meaningful outcomes, inappropriate study design, or duplication of previously included data.

Eligible sources included randomized and nonrandomized clinical trials, observational studies, systematic reviews, meta analyses, and international clinical guidelines addressing therapeutic interventions in advanced, recurrent, or metastatic endometrial cancer. Only studies reporting clinically relevant outcomes such as overall survival, progression free survival, response rates, treatment related toxicity, or quality of life were considered.

Studies focused exclusively on early stage disease, non epithelial histological subtypes, or preclinical research without clinical endpoints were excluded. Editorials, letters, and conference abstracts were not included due to limited methodological reliability.

Study selection and evaluation were performed by two reviewers with resolution of discrepancies through discussion. In cases of overlapping data, preference was given to studies with larger sample size, more recent publication, and higher methodological rigor.

The evidence was analyzed qualitatively and organized according to treatment modality, including surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy. Particular attention was given to differences in

clinical outcomes and to molecular subgroups, including mismatch repair status.

Given the narrative design, no quantitative synthesis or formal risk of bias assessment was performed. Methodological quality was considered descriptively based on study design, sample size, and consistency of findings, and this was taken into account in the interpretation of results.

Limitations of the approach include restriction to selected databases, potential selection bias, and the absence of standardized quantitative synthesis.

RESULTS

Current primary treatment methods – surgery, chemotherapy and radiotherapy

The current management of advanced endometrial cancer is based on a multimodal approach combining systemic chemotherapy, maximal cytoreductive surgery, and radiotherapy. Treatment decisions depend on disease extent, prior therapy, comorbidities, and increasingly on molecular classification [7], [8], [9].

SURGICAL TREATMENT

Surgery remains a key component when resection is technically feasible and the patient is an appropriate candidate. Contemporary studies and meta-analyses demonstrate that maximal cytoreductive surgery in stage III–IV disease is associated with improved overall survival, particularly when followed by adjuvant treatment [10]. However, surgery alone is insufficient in advanced cases [11]. Achieving complete macroscopic resection is consistently associated with better outcomes, although the definition and prognostic impact of “optimal” versus “suboptimal” debulking remain heterogeneous across studies [12], [13]. Therefore, upfront cytoreduction is preferred when complete or near-complete resection is achievable [10].

In patients with unresectable disease or high surgical risk, neoadjuvant chemotherapy followed by interval debulking has emerged as an alternative strategy. Retrospective and cohort studies suggest that this approach may increase rates of optimal cytoreduction and reduce perioperative morbidity, although robust long-term survival data remain limited [14], [8]. In recurrent or oligometastatic disease, selected patients may benefit from metastasectomy or salvage surgery; however, the available evidence is largely retrospective, highlighting the importance of careful multidisciplinary selection and integration with radiotherapy or systemic treatment [15], [16].

SYSTEMIC CHEMOTHERAPY

Systemic chemotherapy remains the cornerstone of treatment for inoperable stage III–IV disease and disseminated recurrence [5]. Historically, doxorubicin-based regimens and the triplet paclitaxel–doxorubicin–cisplatin (TAP) demonstrated higher response rates but were associated with substantial neurotoxicity and cardiotoxicity. The GOG 0209 trial established carboplatin plus paclitaxel (CP) as the preferred first-line regimen, showing comparable overall and progression-free survival with significantly improved tolerability and reduced toxicity [9], [8], [17], [12]. As a result, CP is currently the standard of care in advanced and recurrent chemotherapy-naïve disease, while alternative regimens are generally reserved for selected or later-line settings [18], [19], [16].

CHEMORADIOOTHERAPY

Chemoradiotherapy represents an important strategy at the interface of locoregional and advanced disease. Phase III trials, including PORTEC-3 and GOG 258, have demonstrated that combined modality treatment improves failure-free survival and reduces pelvic and distant recurrence compared with radiotherapy alone, although the overall survival benefit remains limited and varies according to tumor characteristics [20], [21], [22], [23], [24]. Consequently, adjuvant or consolidative chemoradiotherapy (typically CP combined with external beam radiotherapy ± brachytherapy) is widely used in high-risk patients, particularly those with high-grade, deeply invasive, lymphovascular space invasion–positive, or node–positive disease [25], [12], [15].

RADIOOTHERAPY

Radiotherapy alone continues to play a critical role in selected clinical scenarios, particularly in patients who are not candidates for surgery or in the setting of localized recurrence. Modern external beam techniques and brachytherapy provide effective local control with acceptable toxicity profiles [16], [15], [26], [22]. In previously unirradiated patients with pelvic or vaginal relapse, definitive radiotherapy, with or without concurrent chemotherapy, may achieve durable disease control [16], [26]. In contrast, in patients with disseminated or symptomatic disease, palliative radiotherapy is commonly used to alleviate symptoms such as pain, bleeding, or neurologic complications, with advanced techniques enabling precise targeting while minimizing toxicity [15].

Overall, current evidence supports a multimodal, individualized approach in which surgery, chemotherapy, and radiotherapy are integrated based on disease characteristics and patient factors. While complete cytoreduction followed by platinum-based chemotherapy remains the preferred strategy when feasible, alternative approaches such as neoadjuvant chemotherapy or radiotherapy-based strategies are appropriate in selected patient populations.

Across these modalities, current reviews highlight that the management of advanced endometrial cancer is becoming more personalized. Surgical decisions must weigh the survival benefits of aggressive cytoreduction versus morbidity. Chemotherapy now uses CP almost universally as a basis for treatment, often as part of blended programs. Radiotherapy follows the criteria of dose, volume and purpose (curative vs. palliative) for existing therapies used in the past and the distribution of disease. Thus, the three modalities are most effectively combined through multidisciplinary dialogue in established settings in order to maximize outcomes in this high-risk group [25], [12], [19], [13]. The table below presents examples of studies comparing the previously described treatment methods along with the results.

Table 1. Comparative outcomes of primary treatment strategies in advanced endometrial cancer

Author, year	Study design	Sample size	Therapy	Results
Ann H Klopp et al. 2024[26]	Randomized clinical trial	165	Radiotherapy vs chemoradiotherapy	No improvement in outcomes with addition of chemotherapy; increased toxicity in combined group.
Hariyono Winarto et al. 2022[23]	Meta-analysis	17 studies; n ₁ = 23,975; n ₂ = 50,502	CRT vs RT vs CT	Adjuvant chemoradiotherapy was associated with improved overall survival compared with radiotherapy or chemotherapy alone, and with improved disease-free survival compared with chemotherapy alone.
Benjamin B. Albright et al. 2021 [11]	Meta-analysis	34 studies; (n≤2343)	Cytoreductive surgery	Significant number of patients with advanced stage cancer undergo suboptimal debulking. Thus, that group exhibits higher recurrence and mortality.
Daniela Matei et al. 2024 [24]	Randomized phase III trial	813	Chemoradiotherapy avs chemotherapy	Chemoradiotherapy reduces risk of local recurrence compared to chemotherapy alone. Overall survival remains similar in both cases.

Abbreviations: CRT – chemoradiotherapy; RT – radiotherapy; CT – chemotherapy; n – number of patients

ANTI-PD-1 MONOTHERAPY IN ADVANCED ENDOMETRIAL CANCER

Anti-PD-1 monotherapy plays an important role in the treatment of advanced endometrial cancer, especially in patients with specific molecular features such as mismatch repair deficiency (dMMR) or high microsatellite instability (MSI-H) [27],[28]. These tumors are characterized by a high mutational burden, which makes them more sensitive to immune checkpoint inhibition [29],[30]. Pembrolizumab is a monoclonal antibody targeting the PD-1 receptor on T cells, restoring antitumor immune response and promoting tumor cell destruction [28],[29].

Clinical evidence supporting pembrolizumab monotherapy is primarily derived from the KEYNOTE-158 study, which demonstrated clinically meaningful and durable responses in previously treated patients with MSI-H/dMMR advanced endometrial cancer [27]. The objective response rate in this subgroup was substantial with many responses being long-lasting, indicating the potential for durable disease control [27],[31]. Notably, treatment responses were observed regardless of prior lines of therapy, suggesting activity even in heavily pretreated populations [31], [19]. Based on these findings, pembrolizumab received regulatory approval for MSI-H/dMMR advanced endometrial cancer after progression on prior systemic therapy [28],[32].

Dostarlimab is another anti-PD-1 antibody that has demonstrated comparable efficacy in a similar patient population [29],[33]. In the GARNET trial, dostarlimab achieved clinically meaningful objective response rate in patients with recurrent or advanced dMMR endometrial cancer with durable responses and acceptable safety profile [33],[19]. The majority of adverse events associated with anti-PD-1 monotherapy are immune-related but generally manageable with appropriate monitoring and corticosteroid treatment when necessary [32],[30]. The most frequent side effects include fatigue, rash, diarrhea, and thyroid dysfunction [32].

Importantly, the efficacy of anti-PD-1 monotherapy is strongly dependent on molecular characteristics. While patients with MSI-H/dMMR tumors derive substantial benefit, response rates in mismatch repair-proficient disease remain significantly lower [29],[31]. Therefore molecular testing for MMR or MSI status is essential for appropriate patient selection [28], [30]. Current international guidelines recommend pembrolizumab or dostarlimab as preferred treatment options in patients with advanced or recurrent MSI-H/dMMR endometrial cancer after failure of platinum-based chemotherapy [28],[19].

Overall, anti-PD-1 monotherapy represents an effective and biologically targeted treatment strategy in a defined subgroup of patients, offering durable responses with a manageable toxicity profile, but with limited applicability in molecularly unselected populations [27], [29].

Pembrolizumab Plus Lenvatinib as a Therapeutic Option in Advanced Endometrial Cancer

Combination therapy with pembrolizumab and lenvatinib has emerged as an important treatment option for patients with advanced endometrial cancer, particularly those who are not candidates for further chemotherapy. This approach targets both immune checkpoints and tumor angiogenesis, potentially enhancing antitumor activity compared with monotherapy [4]. Clinical trials have demonstrated that addition of lenvatinib to pembrolizumab results in higher response rates in patients with advanced or recurrent disease [34].

In a pivotal phase II study, the combination achieved an objective response rate of approximately 38% in patients with advanced endometrial cancer previously treated with systemic chemotherapy, suggesting a clinically meaningful benefit. [35]. Median progression-free survival in these patients was approximately 7.4 months, representing an improvement compared with historical outcomes observed with single-agent monotherapy [35]. Importantly, unlike anti-PD-1 monotherapy, the efficacy of this combination appears to be independent of mismatch repair status, thereby extending therapeutic benefit to patients with mismatch repair-proficient disease [34], [35].

However, this increased efficacy is associated with a higher incidence of treatment-related adverse events, including hypertension, fatigue, and gastrointestinal toxicity, which often require dose modifications or supportive management, although the overall safety profile remains manageable in appropriately selected patients [36].

Current clinical guidelines increasingly recognize pembrolizumab plus lenvatinib as a recommended treatment option after progression on prior systemic therapy [36]. Ongoing studies aim to optimize dosing strategies and identify predictive biomarkers to better define patients populations most likely to benefit from this regimen [4],[36]. Early phase studies also confirmed encouraging antitumor activity and an acceptable safety profile at recommended dosing schedules [37]. Real-world data further suggest that treatment outcomes may be influenced by patient performance status and lenvatinib dose intensity [38].

Overall, the combination of pembrolizumab and lenvatinib represents a significant advancement in the management of advanced endometrial cancer, particularly for patients with mismatch repair-proficient tumors, although this benefit must be balanced against increased toxicity compared with monotherapy. The outcomes of previously discussed immunotherapy methods in the treatment of endometrial cancer are presented below, in the form of a table.

Table 2. Comparative outcomes of immunotherapy strategies in advanced endometrial cancer.

Author, year	Study design	Sample size	Therapy	Results
--------------	--------------	-------------	---------	---------

Alixé Salmon et al. 2024 [39]	Systematic review	98 studies	Anti-PD-1 monotherapy; pembrolizumab + lenvatinib	Anti-PD-1 monotherapy showed higher response rates in dMMR/MSI-H tumors than in pMMR disease, while pembrolizumab plus lenvatinib extended benefit to pMMR populations at the cost of increased toxicity.
Powell MA et al. 2024[40]	Randomized clinical trial	494	Dostarlimab + carboplatin-paclitaxel vs chemotherapy	Improved OS vs chemotherapy alone (HR 0.69); greater benefit in dMMR/MSI-H (HR 0.32) and limited benefit in pMMR (HR 0.79)
Mamat Yusof, M. M. et al. 2023 [41]	Meta-analysis	5 studies; (n = 480)	PD-1/PD-L1 monotherapy	ORR 26% overall; 44% in dMMR vs 8% in pMMR; DCR 41%; grade ≥3 AEs 16%

Abbreviations: ORR – objective response rate; DCR – disease control rate; AEs – adverse events; OS – overall survival; dMMR – mismatch repair deficiency; pMMR – mismatch repair proficient.

Immunotherapy demonstrates the greatest efficacy in patients with dMMR/MSI-H tumors, while combination strategies extend clinical benefit to a broader population at the cost of increased toxicity.

Immune checkpoint inhibition represents an important therapeutic strategy in advanced and recurrent endometrial cancer, particularly in tumors with mismatch repair deficiency (dMMR/MSI-H). Clinical trials and meta-analyses demonstrate substantially higher response rates in dMMR populations (approximately 40–50%) compared with mismatch repair-proficient tumors (approximately 5–10%) [41], [39]. In unselected populations, overall efficacy remains more modest, with an objective response rate of approximately 26% [41]. These findings indicate that the benefit of immunotherapy is strongly dependent on molecular characteristics, particularly MMR status and tumor mutational burden [39]. While the addition of immune checkpoint inhibitors to chemotherapy improves progression-free survival, particularly in dMMR/MSI-H tumors [42],[39],[43], combination strategies such as pembrolizumab with lenvatinib further extend therapeutic options in mismatch repair-proficient disease, albeit with increased toxicity[42], [39].

DISCUSSION

The results of this review indicate that the management of advanced endometrial cancer is based on a multimodal approach integrating surgery, chemotherapy, and radiotherapy, with treatment selection determined by disease extent, prior treatment, comorbidities, and molecular characteristics. These modalities are not interchangeable and demonstrate benefit in different clinical contexts.

Cytoreductive surgery is associated with improved overall survival in patients with advanced disease when complete macroscopic resection is achieved [10],[11]. This effect is restricted to selected patients with resectable tumors. In patients with unresectable disease or poor performance status, surgery does not provide comparable benefit. In such cases, neoadjuvant chemotherapy followed by interval debulking may increase the likelihood of optimal cytoreduction, although evidence remains limited and heterogeneous [8],[14].

Systemic chemotherapy remains the central treatment component in advanced and recurrent disease. The combination of carboplatin and paclitaxel is supported by randomized evidence demonstrating comparable survival outcomes to anthracycline based regimens with improved tolerability, which justifies its use as the standard first line regimen [9],[17]. Other regimens are less consistently supported and are generally reserved for specific clinical situations or subsequent lines of therapy [18],[19].

Radiotherapy has a defined but limited role. In recurrent disease, it contributes to local control, while in disseminated disease its function is predominantly palliative [16],[26]. Evidence from comparative studies is inconsistent. Adjuvant chemoradiotherapy has been associated with improved survival outcomes in some analyses [23], whereas randomized trials have not consistently demonstrated a benefit in relapse free survival when radiotherapy is added to chemotherapy [24]. These findings indicate that the benefit of radiotherapy is context dependent and cannot be generalized across all patient groups.

Systemic treatment outcomes differ substantially according to molecular subtype. Anti PD 1 monotherapy demonstrates clinically meaningful and durable responses in MSI H and dMMR tumors [27],[33]. In contrast, response rates in mismatch repair proficient disease remain low, indicating limited efficacy of monotherapy in this population [29],[31],[41]. Quantitative data confirm this difference, with markedly higher response rates observed in dMMR compared with pMMR tumors [41]. These findings support the use of immunotherapy primarily in molecularly defined subgroups.

Combination therapy with pembrolizumab and lenvatinib extends treatment activity to patients without mismatch repair deficiency [34],[35]. This approach is associated with improved response rates and progression free survival compared with historical chemotherapy outcomes [35]. However, increased efficacy is accompanied by higher toxicity, including hypertension and gastrointestinal adverse events, which may require dose modification and limit treatment applicability [35],[36]. The balance between efficacy and tolerability is therefore a critical determinant of treatment selection.

Randomized data further demonstrate that the magnitude of benefit of immunotherapy based strategies varies according to molecular profile. In the RUBY trial, the addition of dostarlimab to carboplatin and paclitaxel improved overall survival, with a greater effect observed in dMMR or MSI H tumors compared with pMMR disease [40]. These findings confirm that treatment effect is not uniform and is strongly influenced by tumor biology.

Across all treatment modalities, the available evidence indicates that outcomes are determined by the interaction of resectability, molecular characteristics, and patient related factors. No single therapeutic strategy demonstrates consistent superiority across unselected populations.

Interpretation of these findings is limited by the structure of the available evidence. The included studies are heterogeneous with respect to design, patient populations, endpoints, and treatment protocols, which restricts direct comparison [23],[39]. A substantial proportion of data is derived from nonrandomized studies and single arm trials, while randomized evidence is limited to selected interventions [24],[40]. In addition, clinical trial populations do not adequately represent real world patients, particularly elderly individuals and those with comorbidities [19],[39].

The narrative design of this review further limits the strength of conclusions. No formal assessment of risk of bias was performed, and heterogeneous study types were analyzed without hierarchical weighting. These factors reduce the reliability of comparative interpretation.

Overall, the evidence supports a stratified approach to advanced endometrial cancer. Carboplatin and paclitaxel remain the standard first line systemic treatment. Immunotherapy provides clinically relevant benefit in MSI H and dMMR tumors, while combination regimens extend activity to broader populations at the cost of increased toxicity. Optimal sequencing of therapies and integration of available treatment options remain insufficiently defined and require further investigation in prospective studies with standardized endpoints and appropriate molecular stratification.

CONCLUSIONS

Therapeutic strategies in advanced endometrial cancer differ in effectiveness, safety, and clinical applicability and cannot be considered interchangeable. Maximal cytoreductive surgery improves outcomes only when complete macroscopic resection is achievable and is therefore limited to selected patients. In unresectable or disseminated disease, systemic therapy represents the principal treatment approach.

Carboplatin plus paclitaxel remains the reference first line regimen due to consistent survival outcomes and a well characterized toxicity profile. Other regimens are supported by less consistent evidence and are used mainly in selected settings or later lines.

The effectiveness of immunotherapy is determined by mismatch repair status. Anti PD 1 monotherapy provides durable benefit in MSI H and dMMR tumors, while its activity in mismatch repair proficient disease is limited. Combination therapy with pembrolizumab and lenvatinib extends treatment options to this population but is associated with increased toxicity.

Treatment selection is driven by the interaction of clinical factors and molecular characteristics rather than by the superiority of a single modality. Interpretation of available evidence is limited by heterogeneity of study designs, reliance on nonrandomized data, and limited representation of real-world populations.

A stratified approach based on resectability, molecular profile, and treatment tolerance is required. Optimal sequencing and integration of therapies remain insufficiently defined and require further prospective investigation.

DISCLOSURE

AUTHORS' CONTRIBUTIONS

USE OF ARTIFICIAL INTELLIGENCE:

The authors declare that no artificial intelligence tools were used in the generation, writing, editing, or revision of this manuscript. All content was created solely by the authors.

FUNDING:

The article did not receive any funding.

Conflict of Interest:

Authors declare no conflicts of interest.

REFERENCES

1. Gzowska D, Szablewska AW. Holistic gynecological care of the patient after hysterectomy for malignant endometrial cancer. *Problemy Pielęgniarstwa*. 2025;33(2):92-7. DOI: <https://doi.org/10.5114/ppiel.2025.152389>
2. Misiek M, Witczak G, Picheta A, Skuza M, Misiek A, Kluz T, et al. Trends in Endometrial Cancer in Poland: Shifts in Clinical Features and Survival Outcomes over 18 Years. *J Clin Med*. 2025;14(2). DOI: <https://doi.org/10.3390/jcm14020566>
3. Bogani G, Monk BJ, Powell MA, Westin SN, Slomovitz B, Moore KN, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. *Annals of Oncology*. 2024;35(5):414-28. DOI: <https://doi.org/10.1016/j.annonc.2024.02.006>
4. Makker V, Taylor MH, Aghajanian C, Oaknin A, Mier J, Cohn AL, et al. Lenvatinib Plus Pembrolizumab in Patients With Advanced Endometrial Cancer. *J Clin Oncol*. 2020;38(26):2981-92. DOI: <https://doi.org/10.1200/JCO.19.02627>
5. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA. Adjuvant chemotherapy for advanced endometrial cancer. *Cochrane Database Syst Rev*. 2014;2014(5):CD010681. DOI: <https://doi.org/10.1002/14651858.CD010681.pub2>
6. Arend RC, Jones BA, Martinez A, Goodfellow P. Endometrial cancer: Molecular markers and management of advanced stage disease. *Gynecologic Oncology*. 2018;150(3):569-80. DOI: <https://doi.org/10.1016/j.ygyno.2018.05.015>
7. Dizon D. Treatment options for advanced endometrial carcinoma. *Gynecologic oncology*. 2010. DOI: <https://doi.org/10.1016/j.ygyno.2010.02.007>
8. Bestvina CM, Fleming GF. Chemotherapy for Endometrial Cancer in Adjuvant and Advanced Disease Settings. *Oncologist*. 2016;21(10):1250-9. DOI: <https://doi.org/10.1634/theoncologist.2016-0062>
9. Miller DS, Filiaci VL, Mannel RS, Cohn DE, Matsumoto T, Tewari KS, et al. Carboplatin and Paclitaxel for Advanced Endometrial Cancer: Final Overall Survival and Adverse Event Analysis of a Phase III Trial (NRG Oncology/GOG0209). *J Clin Oncol*. 2020;38(33):3841-50. DOI: <https://doi.org/10.1200/JCO.20.01076>
10. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. *Gynecol Oncol*. 2010;118(1):14-8. DOI: <https://doi.org/10.1016/j.ygyno.2010.04.005>
11. Albright BB, Monuszko KA, Kaplan SJ, Davidson BA, Moss HA, Huang AB, et al. Primary cytoreductive surgery for advanced stage endometrial cancer: a systematic review and meta-analysis. *Am J Obstet Gynecol*. 2021;225(3):237 e1- e24. DOI: <https://doi.org/10.1016/j.ajog.2021.04.254>
12. Corr BE, Barber E, Fisher C, Slomovitz B. Advances in the management of endometrial cancer. *BMJ Open*. 2025. DOI: <https://doi.org/10.1136/bmj-2024-080978>
13. Baker-Rand H, Kitson SJ. Recent Advances in Endometrial Cancer Prevention, Early Diagnosis and Treatment. *Cancers*. 2024;16(5). DOI: <https://doi.org/10.3390/cancers16051028>
14. Mantovani G, Coada CA, Di Costanzo S, Mezzapesa F, Genovesi L, Bogani G, et al. Primary or Interval Debulking Surgery for Advanced Endometrial Cancer with Carcinosis: A Systematic Review and Individual Patient Data Meta-Analysis of Survival Outcomes. *Cancers (Basel)*. 2025;17(6). DOI: <https://doi.org/10.3390/cancers17061026>
15. Bostan I-S, Mihaila M, Roman V, Radu N, Neagu MT, Bostan M, et al. Landscape of Endometrial Cancer:

- Molecular Mechanisms, Biomarkers, and Target Therapy. *Cancers*. 2024;16(11). DOI: <https://doi.org/10.3390/cancers16112027>
16. Rutten H, Verhoef C, van Weelden WJ, Smits A, Dhanis J, Ottevanger N, et al. Recurrent Endometrial Cancer: Local and Systemic Treatment Options. *Cancers (Basel)*. 2021;13(24). DOI: <https://doi.org/10.3390/cancers13246275>
 17. Rubinstein M, Shen S, Monk BJ, Tan DSP, Nogueira-Rodrigues A, Aoki D, et al. Looking beyond carboplatin and paclitaxel for the treatment of advanced/recurrent endometrial cancer. *Gynecologic Oncology*. 2022;167(3):540-6. DOI: <https://doi.org/10.1016/j.ygyno.2022.10.012>
 18. Wilson EM, Eskander RN, Binder PS. Recent Therapeutic Advances in Gynecologic Oncology: A Review. *Cancers*. 2024;16(4). DOI: <https://doi.org/10.3390/cancers16040770>
 19. Gordhandas S, Zammarrelli WA, Rios-Doria EV, Green AK, Makker V. Current Evidence-Based Systemic Therapy for Advanced and Recurrent Endometrial Cancer. *J Natl Compr Canc Netw*. 2023;21(2):217-26. DOI: <https://doi.org/10.6004/jnccn.2022.7254>
 20. van den Heerik A, Horeweg N, de Boer SM, Bosse T, Creutzberg CL. Adjuvant therapy for endometrial cancer in the era of molecular classification: radiotherapy, chemoradiation and novel targets for therapy. *Int J Gynecol Cancer*. 2021;31(4):594-604. DOI: <https://doi.org/10.1136/ijgc-2020-001822>
 21. de Boer SM, Powell ME, Mileshkin L, Katsaros D, Bessette P, Haie-Meder C, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol*. 2018;19(3):295-309. DOI: [https://doi.org/10.1016/S1470-2045\(18\)30079-2](https://doi.org/10.1016/S1470-2045(18)30079-2)
 22. Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. *Lancet*. 2010;375(9717):816-23. DOI: [https://doi.org/10.1016/S0140-6736\(09\)62163-2](https://doi.org/10.1016/S0140-6736(09)62163-2)
 23. Winarto H, Ibrahim NAA, Putri YM, Adnan F, Safitri ED. Adjuvant chemoradiotherapy versus chemotherapy or radiotherapy in advanced endometrial cancer: a systematic review and meta-analysis. *PeerJ*. 2022;10:e14420. DOI: <https://doi.org/10.7717/peerj.14420>
 24. Matei DE, Enserro DM, Randall ME, Mutch D, Small W, DiSilvestro PA, et al. Long-Term Follow-Up and Overall Survival in NRG258, a Randomized Phase III Trial of Chemoradiation Versus Chemotherapy for Locally Advanced Endometrial Carcinoma. *J Clin Oncol*. 2025;43(9):1055-60. DOI: <https://doi.org/10.1200/JCO.24.01121>
 25. Brooks RA, Fleming GF, Lastra RR, Lee NK, Moroney JW, Son CH, et al. Current recommendations and recent progress in endometrial cancer. *CA Cancer J Clin*. 2019;69(4):258-79. DOI: <https://doi.org/10.3322/caac.21561>
 26. Klopp AH, Enserro D, Powell M, Randall M, Schink JC, Mannel RS, et al. Radiation Therapy With or Without Cisplatin for Local Recurrences of Endometrial Cancer: Results From an NRG Oncology/GOG Prospective Randomized Multicenter Clinical Trial. *J Clin Oncol*. 2024;42(20):2425-35. DOI: <https://doi.org/10.1200/JCO.23.01279>
 27. O'Malley DM, Bariani GM, Cassier PA, Marabelle A, Hansen AR, De Jesus Acosta A, et al. Pembrolizumab in Patients With Microsatellite Instability-High Advanced Endometrial Cancer: Results From the KEYNOTE-158 Study. *J Clin Oncol*. 2022;40(7):752-61. DOI: <https://doi.org/10.1200/JCO.21.01874>
 28. Green AK, Feinberg J, Makker V. A Review of Immune Checkpoint Blockade Therapy in Endometrial Cancer. *Am Soc Clin Oncol Educ Book*. 2020;40:1-7. DOI: https://doi.org/10.1200/EDBK_280503
 29. Johnson RL, Ganesan S, Thangavelu A, Theophilou G, de Jong D, Hutson R, et al. Immune Checkpoint Inhibitors Targeting the PD-1/PD-L1 Pathway in Advanced, Recurrent Endometrial Cancer: A Scoping Review with SWOT Analysis. *Cancers (Basel)*. 2023;15(18). DOI: <https://doi.org/10.3390/cancers15184632>
 30. Tuninetti V, Farolfi A, Rognone C, Montanari D, De Giorgi U, Valabrega G. Treatment Strategies for Advanced Endometrial Cancer According to Molecular Classification. *Int J Mol Sci*. 2024;25(21). DOI: <https://doi.org/10.3390/ijms252111448>
 31. Pinheiro LP, Morel Alineri TP, de Mauro HA, Rochetti Bezerra TA, Martins Malaquias DT, Ferreira da Silva JC, et al. Treatment Of Advanced Endometrial Cancer: A Systematic Review Of Efficacy And Safety In Clinical Trials, Molecular-Targeted Therapies And Immunotherapy. *Journal of Clinical Obstetrics and Gynecology Research*. 2025;12(1):1-7. DOI: <https://doi.org/10.52338/jocogr.2025.4937>
 32. Bujnak AC, File B, Tewari KS. Clinical Use of Dostarlimab in Advanced Stage and Recurrent Endometrial Cancer: Patient Selection and Perspectives. *Cancer Manag Res*. 2025;17:161-70. DOI: <https://doi.org/10.2147/CMAR.S341469>

33. Kokori E, Olatunji G, Abdulbasit M, Aderinto N. The efficacy and safety of pembrolizumab and dostarlimab in advanced endometrial carcinoma: a systematic review. *Discover Medicine*. 2024;1(1). DOI: <https://doi.org/10.1007/s44337-024-00062-2>
34. Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol*. 2019;20(5):711-8. DOI: [https://doi.org/10.1016/S1470-2045\(19\)30020-8](https://doi.org/10.1016/S1470-2045(19)30020-8)
35. Makker V, Colombo N, Casado Herraes A, Santin AD, Colomba E, Miller DS, et al. Lenvatinib plus Pembrolizumab for Advanced Endometrial Cancer. *N Engl J Med*. 2022;386(5):437-48. DOI: <https://doi.org/10.1056/NEJMoa2108330>
36. Tinker AV, Dhani NC, Ghatage P, McLeod D, Samouelian V, Welch SA, et al. A rapidly evolving landscape: immune checkpoint inhibitors in pretreated metastatic endometrial cancer. *Ther Adv Med Oncol*. 2023;15:17588359231157633. DOI: <https://doi.org/10.1177/17588359231157633>
37. Taylor MH, Lee CH, Makker V, Rasco D, Dutcus CE, Wu J, et al. Phase IB/II Trial of Lenvatinib Plus Pembrolizumab in Patients With Advanced Renal Cell Carcinoma, Endometrial Cancer, and Other Selected Advanced Solid Tumors. *J Clin Oncol*. 2020;38(11):1154-63. DOI: <https://doi.org/10.1200/JCO.19.01598>
38. Nagase Y, Nakagawa S, Kobayashi M, Kurahashi H, Ogimoto H, Tanaka A, et al. Prognostic factors of lenvatinib plus pembrolizumab therapy for advanced or recurrent endometrial cancer: analysis of a multicenter cohort study in Japan. *Int J Clin Oncol*. 2025;30(11):2342-51. DOI: <https://doi.org/10.1007/s10147-025-02842-x>
39. Salmon A, Lebeau A, Strel S, Dheur A, Schoenen S, Goffin F, et al. Locally advanced and metastatic endometrial cancer: Current and emerging therapies. *Cancer Treat Rev*. 2024;129:102790. DOI: <https://doi.org/10.1016/j.ctrv.2024.102790>
40. Powell MA, Bjorge L, Willmott L, Novak Z, Black D, Gilbert L, et al. Overall survival in patients with endometrial cancer treated with dostarlimab plus carboplatin-paclitaxel in the randomized ENGOT-EN6/GOG-3031/RUBY trial. *Ann Oncol*. 2024;35(8):728-38. DOI: <https://doi.org/10.1016/j.annonc.2024.05.546>
41. Mamat Yusof MN, Chew KT, Hafizz A, Abd Azman SH, Ab Razak WS, Hamizan MR, et al. Efficacy and Safety of PD-1/PD-L1 Inhibitor as Single-Agent Immunotherapy in Endometrial Cancer: A Systematic Review and Meta-Analysis. *Cancers (Basel)*. 2023;15(16). DOI: <https://doi.org/10.3390/cancers15164032>
42. Bartoletti M, Montico M, Lorusso D, Mazzeo R, Oaknin A, Musacchio L, et al. Incorporation of anti-PD1 or anti PD-L1 agents to platinum-based chemotherapy for the primary treatment of advanced or recurrent endometrial cancer. A meta-analysis. *Cancer Treat Rev*. 2024;125:102701. DOI: <https://doi.org/10.1016/j.ctrv.2024.102701>
43. Eskander RN, Sill MW, Beffa L, Moore RG, Hope JM, Musa FB, et al. Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer. *N Engl J Med*. 2023;388(23):2159-70. DOI: <https://doi.org/10.1056/NEJMoa2302312>
44. Choręza P, Owczarek AJ, Chudek J. Have Polish women started getting tested? Epidemiology of gynaecological cancers in Poland in 2015–2021. *Journal of Public Health*. 2025. DOI: <https://doi.org/10.1007/s10389-025-02524-y>

[back](#)