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Original Article

Adjuvant therapy guided by molecular classification in endometrial cancer: survival benefit and safety profile

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Abstract: Objectives: To evaluate the effect of molecular classification-based postoperative adjuvant therapy on survival outcomes and treatment safety in patients with endometrial cancer. Methods: This retrospective study included 208 endometrial cancer patients treated between January 2022 and January 2025. Patients were divided into a control group (n = 102), receiving conventional adjuvant therapy, and an observation group (n = 106), receiving molecular classification-based personalized regimens. The primary endpoints were disease-free survival (DFS) and overall survival (OS). Secondary measures included objective response, treatment-related toxicity, treatment delivery factors, patient-reported outcomes, and next-generation sequencing of circulating tumor DNA (ctDNA). Multivariate Cox regression was used to explore molecular subtypes and clinicopathologic predictors of 5-year DFS. Results: In the observation group, immune therapy was exclusively administered, and treatment regimens significantly differed from the control group, which received chemoradiotherapy. The observation group showed significantly better DFS (HR = 0.52, 95% CI 0.30-0.89, P = 0.01) and OS (HR = 0.45, 95% CI 0.21-0.95, P = 0.03). Molecular subtype analysis indicated better prognosis for POLE-ultramutated tumors and poorer prognosis for p53-abnormal tumors. The observation group had fewer adverse events (grade ≥ 2: 38.7% vs. 63.7%, P = 0.001) and higher objective response rates (65.1% vs. 43.1%, P = 0.001). Conclusions: Molecular classification-based adjuvant therapy improved survival, response rates, and ctDNA clearance with fewer toxicities. These findings support incorporating molecular classification into postoperative treatment to enhance outcomes in endometrial cancer.

Keywords: Endometrial cancer, molecular classification, adjuvant therapy, postoperative treatment, precision medicine

Introduction

Endometrial cancer (EC) is the leading gynecologic cancer in industrialized nations, with its incidence steadily rising globally due to aging populations and increasing obesity rates [1]. While most patients are diagnosed at an early stage and experience good outcomes post-surgery, a significant proportion face disease recurrence and poor prognosis [2]. Optimizing postoperative adjuvant therapy is crucial, as individual outcomes cannot be accurately predicted solely by traditional risk models based on clinicopathologic factors.

Recent advances in molecular classification have revolutionized our understanding of EC biology [3-5]. The Cancer Genome Atlas (TCGA) project identified four distinct molecular subtypes: POLE ultramutated, microsatellite instability-high (MSI-H), copy-number-low, and copy-number-high (p53 abnormal), each associated with distinct prognostic and treatment implications [6, 7]. These classifications have been integrated into clinical practice with simplified surrogate markers, allowing molecular stratification for standard clinical settings. Notably, molecular classification has demonstrated superior prognostic accuracy compared to conventional clinicopathologic factors, suggesting that it can guide more precise adjuvant treatment decisions [8-10].

Personalizing adjuvant therapy based on molecular subtypes may improve oncologic outcomes while minimizing overtreatment [11-13]. For instance, patients with POLE-mutated tumors generally have an excellent prognosis and

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may not require intensive adjuvant therapy [14], whereas patients with p53-abnormal tumors exhibit more aggressive disease and may benefit from integrated chemoradiation approaches [15, 16]. However, most existing studies are qualitative, heterogeneous, or based on small sample sizes, leaving significant gaps in the literature regarding the actual effectiveness of molecular classification-based adjuvant therapy.

Given the need for high-quality evidence, this study aims to assess the effectiveness of molecular classification-based postoperative adjuvant therapy in EC patients. Through a systematic review of clinical outcomes by molecular subtype, we sought to determine whether precision treatment strategies can improve survival, reduce recurrence rates, and provide a robust approach to individualized patient care.

Materials and methods

Case section

This retrospective study involved 208 patients diagnosed with EC, treated at Luxi County People's Hospital between January 2022 and January 2025. Based on the actual adjuvant treatment regimens recorded in clinical practice, patients were categorized into a control group (n = 102) that received conventional clinicopathology-guided postoperative adjuvant therapy, and an observation group (n = 106) that received personalized regimens guided by molecular classification. The control group received conventional adjuvant therapy based on clinical and pathologic characteristics, including tumor stage, histology, and lymph node metastasis. In contrast, the observation group received individual adjuvant therapy based on molecular classification, with treatment modifications based on specific molecular markers observed in their tumors. The molecular classification-guided therapy choices are detailed in Supplementary Table 1. Strict inclusion and exclusion criteria were applied to ensure reliable retrospective analysis. Inclusion criteria: (1) adult patients (≥ 18 years); (2) primary surgery (hysterectomy and/or lymphadenectomy) for EC [17]; (3) availability of sufficient tissue for molecular testing; (4) follow-up duration ≥ 12 months. Exclusion criteria: (1) patients with non-endometrial malignancies or combined malignancies; (2) incomplete medical records or absent follow-up data; (3) patients who received neoadjuvant treatment followed by surgery; (4) patients with recurrent or metastatic disease at diagnosis; (5) patients who refused molecular classification analysis or adjuvant therapy.

Data extraction

Two independent investigators (Lu Liu and Jian Ouyang) retrieved comprehensive data from institutional electronic medical records and pathology archives following a predefined protocol to ensure consistent data retrieval and minimize bias. Baseline demographic and clinical variables included age, body mass index (BMI), menopausal status, and comorbidities such as hypertension, diabetes, and cardiovascular disease. Surgical and histopathologic reports provided tumor-related characteristics, including FIGO stage (2018 classification), histological subtype, tumor grade, lymph node status, depth of myometrial invasion, and the presence of lymphovascular space invasion (LVSI). Molecular classification data were obtained using standardized testing based on the TCGA framework, with classifications into POLE ultramutated, MSI-H or dMMR, p53-abnormal (p53abn), and no specific molecular profile (NSMP) subtypes. Treatment records included information on postoperative adjuvant therapies (chemotherapy, radiotherapy, chemoradiotherapy, hormonal therapy, targeted therapy, and immunotherapy), their intensity (doses, cycles, and relative dose intensity [RDI]). Clinical notes and follow-up data were used to validate survival outcomes (surgery date, recurrence, last follow-up, and death), allowing the calculation of disease-free survival (DFS) and overall survival (OS). Tumor response was evaluated radiologically according to RECIST version 1.1. Adverse events were recorded based on clinical documentation and graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Patient-reported outcomes, such as sexual function, were captured using standardized questionnaires during follow-up visits. Circulating tumor DNA (ctDNA) changes were monitored at baseline (pre-surgery), one month, and six months post-surgery, marking the cutoff for adjuvant therapy.

Outcome measures

The primary outcomes were oOS and DFS. DFS was defined as the interval between surgery

and the first occurrence of disease recurrence, progression, or death from any cause; patients without such events were censored at the last follow-up date [17]. OS was measured as the number of days from surgery to death, irrespective of cause; surviving patients were censored at the last follow-up [18]. Secondary outcomes included efficacy, safety, and translational parameters. Radiologically measured objective tumor response was evaluated 3-6 months post-surgery using RECIST version 1.1, classified as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD), and the objective response rate (ORR) was computed as CR + PR [19]. Treatment-related toxicity was graded per cycle using CTCAE version 5.0, and both hematologic and non-hematologic adverse events were systematically recorded. Treatment delivery factors, including chemotherapy cycles, cumulative doses, radiotherapy dose, and RDI (ratio of delivered to planned dose), were also assessed. ctDNA was analyzed at baseline, one month, and upon completion of adjuvant therapy using a validated next-generation sequencing (NGS) platform (Illumina NovaSeq 6000) with a custom 500-gene panel targeting common cancer-related mutations. ctDNA positivity was defined with a variant allele frequency (VAF) cutoff of 0.5%, with the assay demonstrating 95% sensitivity and 99% specificity. The overlap between ctDNA positivity and radiological evidence of relapse was used to define recurrence detection lead time. Exploratory analyses examined the prognostic value of molecular subtypes (POLE, MSI-H/dMMR, p53-abnormal, NSMP) and clinicopathologic variables on 5-year DFS, with multivariate Cox regression used to assess independent predictors.

Statistical analysis

Statistical analyses were performed using SPSS (version 23.0) and R (version 4.4.1). Continuous variables, expressed as mean ± standard deviation (SD), were compared using the independent-samples t test, and categorical variables expressed as counts and rates using chi-square or Fisher's exact test. The median follow-up time was estimated using the reverse Kaplan-Meier method. Survival outcomes were estimated by the Kaplan-Meier method and compared using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were derived from Cox proportional hazards models. Variables with $P < 0.10$ in univariate analysis were entered into multivariate models. ORRs were assessed per RECIST v1.1, and adverse events were graded per CTCAE v5.0. ctDNA positivity rates were compared using chi-square tests, and lead time to recurrence detection was assessed by paired t test. RDI for chemotherapy and radiotherapy was calculated as the ratio of delivered to planned dose and compared using the Mann-Whitney U test. All tests were two-sided, with $P < 0.05$ considered significant. Multiple comparisons were adjusted using the Benjamini-Hochberg procedure.

Results

Comparison of demographic and baseline clinical characteristics

Most patients were postmenopausal, and the prevalence of comorbidities such as hypertension, diabetes, and cardiovascular disease was similar between the two groups (all $P > 0.05$). FIGO stage distribution was predominantly stage I disease (56.9% vs. 56.6%), followed by stage III (22.5% vs. 22.6%), with few patients in stage IV. Histologic type was mainly endometrioid carcinoma (> 80% in both groups), with approximately one-quarter of tumors being grade 3. The rates of lymph node metastasis, LVSI, and deep myometrial invasion were comparable. Molecular classification revealed balanced proportions of POLE ultramutated, MSI-H, p53-abnormal, and NSMP subtypes in both groups (all $P > 0.05$, **Table 1**).

Comparison of distribution of postoperative adjuvant therapy regimens

Chemotherapy was the most common treatment method, with similar percentages in the control (44.1%) and observation (35.8%) groups ($P = 0.223$). A trend toward less radiotherapy was observed in the observation group (9.4%) compared to the control group (17.6%) ($P = 0.083$). Chemoradiotherapy was significantly more common in the control group (30.4%) than in the observation group (17.0%) ($P = 0.023$). The use of selected therapies, including mTOR/VEGF inhibitors, was low in

Table 1. Demographic and baseline clinical characteristics in the two groups

Characteristic	Control group (n = 102)	Observation group (n = 106)	χ^2/t	*P* value
Age, years (mean ± SD)	58.7 ± 9.3	59.2 ± 8.7	0.084	0.933
BMI, kg/m^2 (mean ± SD)	27.3 ± 4.1	27.0 ± 4.5	1.343	0.181
Menopausal status, n (%)			0.019	0.891
Premenopausal	28 (27.5)	30 (28.3)		
Postmenopausal	74 (72.5)	76 (71.7)		
Comorbidities, n (%)				
Hypertension	35 (34.3)	37 (34.9)	0.008	0.929
Diabetes mellitus	18 (17.6)	19 (17.9)	0.003	0.958
Cardiovascular disease	9 (8.8)	11 (10.4)	0.144	0.704
FIGO Stage, n (%)			2.073	0.557
I	58 (56.9)	60 (56.6)		
II	16 (15.7)	17 (16.0)		
III	23 (22.5)	24 (22.6)		
IV	5 (4.9)	5 (4.7)		
Histological type, n (%)			0.098	0.992
Endometrioid	84 (82.4)	86 (81.1)		
Serous	12 (11.8)	13 (12.3)		
Clear cell	4 (3.9)	5 (4.7)		
Mixed/other	2 (2.0)	2 (1.9)		
Histological grade, n (%)			0.031	0.985
G1	29 (28.4)	30 (28.3)		
G2	48 (47.1)	51 (48.1)		
G3	25 (24.5)	25 (23.6)		
Lymph node metastasis, n (%)	19 (18.6)	20 (18.9)	0.002	0.965
LVSI (lymphovascular space invasion), n (%)	15 (14.7)	16 (15.1)	0.006	0.937
Myometrial invasion, n (%)			0.007	0.933
< 50%	61 (59.8)	64 (60.4)		
≥ 50%	41 (40.2)	42 (39.6)		
Molecular classification, n (%)			0.117	0.990
POLE ultramutated	7 (6.9)	8 (7.5)		
MSI-H	18 (17.6)	20 (18.9)		
p53 abnormal	22 (21.6)	23 (21.7)		
NSMP	55 (53.9)	55 (51.9)		
Median follow-up time (months)	18.2 (range: 12-36)	17.9 (range: 12-35)	-	-

both groups but showed a non-significant trend toward higher prevalence in the observation group (6.6% vs. 2.0%, P = 0.100). Notably, PD-1/PD-L1 inhibitors were administered exclusively in the observation group (7.5% vs. 0.0%, P = 0.005). Hormonal therapy was rarely used in both groups (5.9% vs. 4.7%, P = 0.707) (**Table 2**). These findings highlight significant differences in the adoption of chemoradiotherapy and immunotherapy approaches, with other treatment modalities showing similar distributions.

Kaplan-Meier survival curves for DFS and OS

As shown in **Figure 1A**, the observation group exhibited a longer DFS compared to the control group (HR = 0.52, 95% CI: 0.30-0.89, P = 0.01). Similarly, OS was significantly prolonged in the observation group (HR = 0.45, 95% CI: 0.21-0.95, P = 0.03; **Figure 1B**). These findings suggest that the intervention was associated with a substantial reduction in recurrence and mortality, providing a survival benefit over standard management.

Table 2. Distribution of postoperative adjuvant therapy regimens

Therapy modality	Control group (n = 102)	Observation group (n = 106)	χ^2	*P* value
Chemotherapy alone	45 (44.1)	38 (35.8)	1.482	0.223
Radiotherapy alone	18 (17.6)	10 (9.4)	3.010	0.083
Chemoradiotherapy	31 (30.4)	18 (17.0)	5.192	0.023
Targeted therapy (e.g., mTOR/VEGF inhibitors)	2 (2.0)	7 (6.6)	2.707	0.100
Immunotherapy (PD-1/PD-L1 inhibitors)	0 (0.0)	8 (7.5)	8.006	0.005
Hormonal therapy	6 (5.9)	5 (4.7)	0.141	0.707

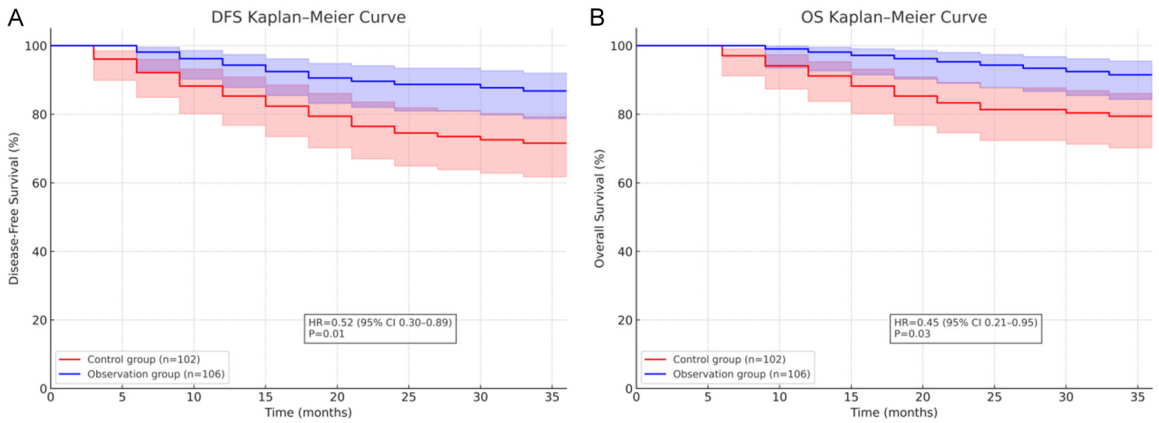

Figure 1. Kaplan-Meier survival curves for disease-free survival (DFS) and Overall Survival (OS) between the two groups. (A) Disease-Free Survival, (B) Overall Survival (OS).

Association of molecular subtypes with DFS and OS

Patients with POLE ultramutated tumors exhibited significantly better prognosis, with a reduced risk of recurrence and death compared to other subtypes (DFS: HR < 1, P = 0.020; OS: HR < 1, P = 0.015). In contrast, the p53abn group was associated with worse outcomes, showing more than a twofold increase in the hazard for both recurrence and mortality (DFS: HR > 2, P = 0.001; OS: HR > 2, P = 0.001). The dMMR subtype showed a trend toward a modest, non-significant reduction in DFS (HR ≈ 0.85, P = 0.120) and no significant association with OS (HR ≈ 0.95, P = 0.650). NSMP patients had outcomes similar to the overall cohort, with no significant differences in DFS (HR ≈ 1.10, P = 0.450) or OS (HR ≈ 1.20, P = 0.300) (**Figure 2**). These findings underline the prognostic heterogeneity among molecular subtypes, emphasizing the clinical relevance of molecular classification for predicting recurrence and survival outcomes.

Comparison of adverse events

The observation group had lower rates of neutropenia (15.1% vs. 27.5%, P = 0.029), anemia (13.2% vs. 24.5%, P = 0.022), nausea/vomiting (18.0% vs. 31.4%, P = 0.015), and diarrhea (8.5% vs. 20.6%, P = 0.013) compared to the control group. However, the incidence of thyroid dysfunction was higher in the observation group (6.6%) than in the control group (1.0%, P = 0.035). The overall cumulative rate of grade 2 or higher adverse events was significantly lower in the observation group (38.7%) compared to the control group (63.7%, P < 0.001) (**Table 3**). These results suggest that the observation regimen had a more favorable safety profile, with fewer hematologic and non-hematologic toxicities, except for an increased risk of thyroid dysfunction.

Comparison of circulating ctDNA

At baseline, pre-surgical ctDNA positivity was comparable between the two groups (38.2% vs. 39.6%, P = 0.837). One month post-surgery,

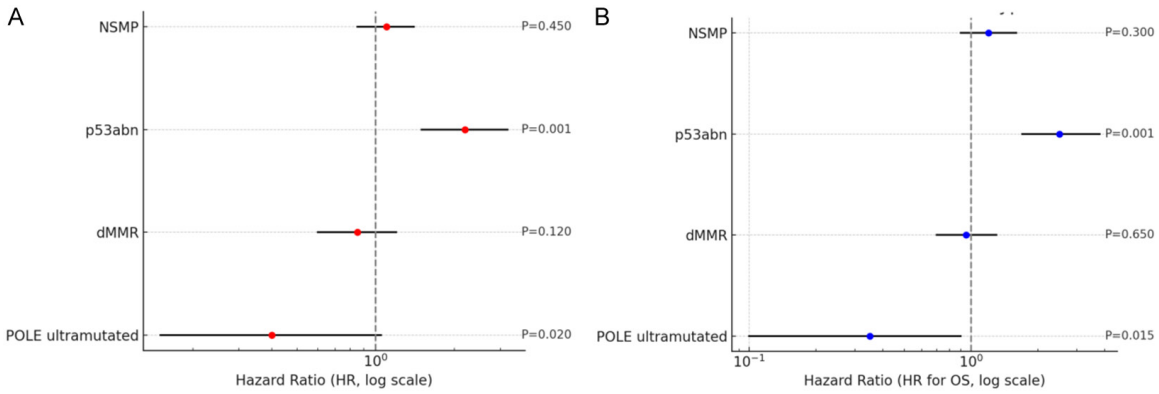

Figure 2. Association of molecular subtypes with disease-free survival (DFS) and overall survival (OS). (A) Molecular Subtypes with DFS, (B) Molecular Subtypes with OS.

Table 3. Comparison of adverse events between the two groups

Adverse Event (≥ Grade 2)	Control group (n = 102), n (%)	Observation group (n = 106), n (%)	χ^2	*P*-value
Neutropenia	28 (27.5)	16 (15.1)	4.759	0.029
Anemia	25 (24.5)	13 (12.3)	5.220	0.022
Nausea/Vomiting	32 (31.4)	18 (17.0)	5.896	0.015
Diarrhea	21 (20.6)	9 (8.5)	6.164	0.013
Peripheral neuropathy	19 (18.6)	9 (8.5)	4.585	0.032
Thyroid dysfunction	1 (1.0)	7 (6.6)	4.445	0.035
Severe fatigue	23 (22.5)	11 (10.4)	5.632	0.018
Sexual dysfunction (patient-reported)	21 (20.6)	9 (8.5)	6.164	0.013
Overall AE rate (≥ Grade 2)	65 (63.7)	41 (38.7)	13.048	< 0.001

ctDNA positivity declined in both groups, with a greater reduction observed in the observation group (19.8% vs. 28.4%), though this difference was not significant (P = 0.146). Six months after completing adjuvant therapy, ctDNA positivity was significantly lower in the observation group compared to the control group (8.5% vs. 21.6%, P = 0.008), indicating improved clearance of minimal residual disease. Moreover, ctDNA-based recurrence detection showed a significantly longer lead time compared to radiological imaging in the observation group (4.6 vs. 1.2 months, P = 0.011) (**Table 4**), highlighting ctDNA's superior sensitivity for early relapse detection.

Comparison of radiotherapy/chemotherapy dose intensity

The observation group received significantly higher radiotherapy doses than the control group. The planned total dose was 65.67 ± 5.26 Gy in the observation group compared to 58.35 ± 4.95 Gy in the control group (P < 0.001). The actual delivered dose was 52.95 ± 7.90 Gy in the observation group versus 54.46 ± 7.64 Gy in the control group (P < 0.001). The observation group also had a higher treatment completion rate (92.5% vs. 80.3%, P = 0.011), fewer treatment delays (10.3% vs. 21.6%, P = 0.027), and a lower dose reduction due to toxicity (9.4% vs. 19.6%, P = 0.037). In chemotherapy, the observation group had a higher RDI (97.52 ± 10.00% vs. 89.35 ± 12.73%, P < 0.001), more completed cycles (6.00 ± 1.32 vs. 5.00 ± 1.65, P < 0.001), and greater actual cumulative doses (2341.20 ± 322.07 mg/m^2 vs. 2115.28 ± 327.71 mg/m^2, P < 0.001). The chemotherapy RDI in the observation group was also higher (91.94 ± 12.42% vs. 83.43 ± 12.85%, P < 0.001) (**Table 5**).

Comparison of ORR between the two groups

The observation group had a higher CR rate compared to the control group (25.5% vs.

Table 4. Comparison of circulating ctDNA dynamics between groups

Timepoint	ctDNA positivity (Control group, %)	ctDNA positivity (Observation group, %)	χ^2	*P*-value
Pre-surgery	38.2	39.6	0.042	0.837
Post-surgery (1 month)	28.4	19.8	2.115	0.146
Post-adjuvant therapy (6 months)	21.6	8.5	7.010	0.008
Recurrence detection (median lead time vs imaging, months)	1.2	8.5	6.406	0.011

Table 5. Comparison of radiotherapy/chemotherapy dose intensity between the two groups

Factor	Control group (n = 102)	Observation group (n = 106)	χ^2/t	*p* value
Radiotherapy				
Planned total dose (Gy), mean ± SD	58.35 ± 4.95	65.67 ± 5.26	10.329	< 0.001
Actual delivered dose (Gy), median (range)	54.46 ±7.64	62.95 ± 7.90	7.871	< 0.001
Fraction dose (Gy), mean ± SD	1.95 ± 0.03	1.94 ± 0.14	1.161	0.247
Treatment completion rate (%)	80.3%	92.5%	6.491	0.011
Treatment delay > 7 days (%)	21.6%	10.3%	4.877	0.027
Dose reduction due to toxicity (%)	19.6%	9.4%	4.359	0.037
Relative dose intensity (RDI, %), mean ± SD	89.35 ± 12.73	97.52 ± 10.00	5.158	< 0.001
Grade ≥ 3 radiation toxicity (%)	14.7%	10.4%	0.890	0.345
Actual completed cycles, mean ± SD	5.00 ± 1.65	6.00 ± 1.32	4.844	< 0.001
Planned cumulative dose (mg/m^2), mean ± SD	2399.77± 281.35	2405.93 ± 300.69	0.153	0.879
Actual delivered cumulative dose (mg/m^2), mean ± SD	2115.28 ± 327.71	2341.20 ± 322.07	5.014	< 0.001
Relative dose intensity (RDI, %), mean ± SD	83.43 ± 12.85	91.94 ± 12.02	4.936	< 0.001

14.7%, P = 0.042). The PR rate also increased significantly in the observation group (39.6% vs. 28.4%, P = 0.048). The proportion of patients with SD was slightly lower in the observation group (24.5% vs. 35.3%), though not statistically significant (P = 0.067). Notably, the incidence of PD was significantly lower in the observation group (10.4% vs. 21.6%, P = 0.029). The overall response rate (ORR, CR + PR) was also significantly higher in the observation group (65.1% vs. 43.1%, P = 0.001) (**Figure 3**). These findings suggest that the intervention in the observation group resulted in better tumor responses than in the control group.

Multivariate cox regression analysis (predictors of 5-year DFS)

Advanced FIGO stage (III-IV) was strongly associated with a higher risk of recurrence (HR 2.46, 95% CI 1.61-3.77, P < 0.001). Tumors with a p53-abnormal subtype showed significantly worse DFS compared to other molecular subtypes (HR 1.87, 95% CI 1.22-2.88, P = 0.004). Lymph node metastasis was also an unfavorable prognostic factor (HR 1.65, 95% CI 1.07-2.55, P = 0.024). In contrast, molecular classification-guided therapy was associated with a reduced risk of recurrence (HR 0.52, 95% CI 0.33-0.81, P = 0.004). Age ≥ 60 years did not significantly affect DFS (HR 1.22, 95% CI 0.88-1.71, P = 0.23) (**Figure 4**).

Discussion

The current research provides credible evidence that adjuvant therapy guided by molecular classification offers significant survival advantages and a positive toxicity profile over conventional management in patients diagnosed with EC. Notably, patients in the observation group, who received individualized therapy based on molecular subtypes and ctDNA dynamics, exhibited significantly betterDFS, OS, adherence to therapy, and tumor response rates. Additionally, hematologic and non-hematologic toxicities were less common in the observation group, except for a statistically insignificant increase in thyroid dysfunction,

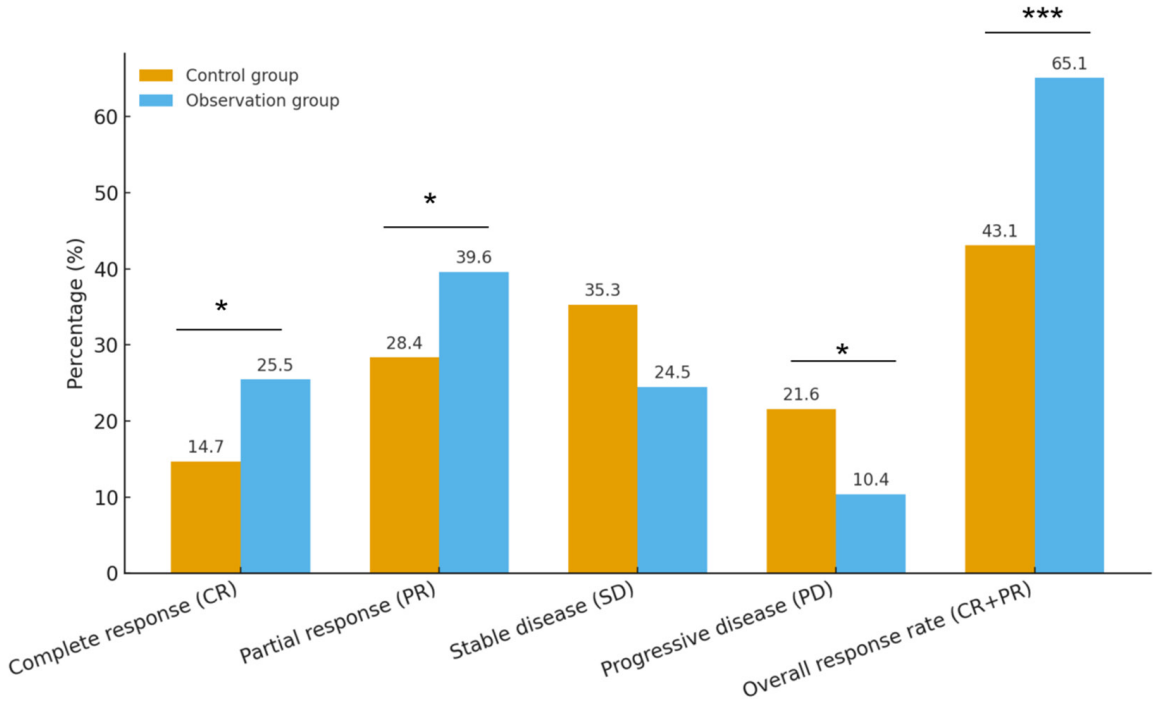

Figure 3. Comparison of objective response rate (ORR) between the two groups. Compared to the control group, *P < 0.05, ***P < 0.001.

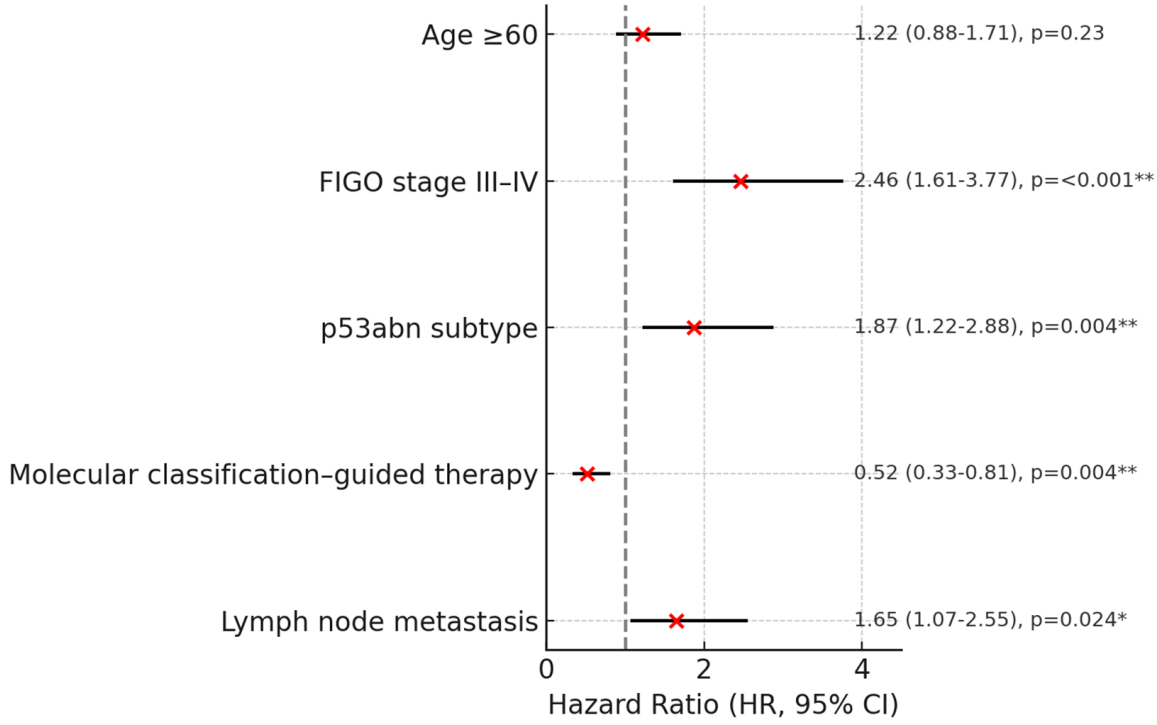

Figure 4. Multivariate Cox regression analysis (Predictors of 5-year DFS).

which highlights the clinical feasibility and safety of this precision medicine approach. This study marks a paradigm shift by incorporating molecular profiling and ctDNA tracking into

postoperative care, moving towards personalized therapy.

We identified prognostic heterogeneity across molecular subtypes and emphasized the clinical utility of genomic stratification. In line with the TCGA classification and prior research [20, 21], POLE-ultramutated tumors were associated with the best prognosis, while the p53abn subtype showed a significantly poorer outcome. Biologically, POLE mutations induce hypermutability and immunogenicity, enabling effective anti-tumor immune responses, whereas p53abn tumors tend to exhibit chromosomal instability and resistance to DNA-damaging treatments. In contrast, dMMR and NSMP subtypes showed intermediate or neutral prognostic implications, consistent with previous meta-analyses [22]. These findings underscore the urgent need to integrate molecular classification into therapeutic decision-making, rather than relying solely on traditional clinicopathologic risk factors.

The improved survival outcomes observed in the observation group may be attributed to the early detection and clearance of minimal residual disease through ctDNA-led monitoring. Our study showed that ctDNA positivity at the completion of adjuvant therapy was significantly lower in the observation group, and ctDNA recurrence detection occurred more than three months earlier than radiological recurrence on average. This lead time benefit aligns with findings from recent clinical trials in colorectal and breast cancer [23-26], where ctDNA was a highly predictive indicator of recurrence. Mechanistically, ctDNA enables real-time molecular surveillance, facilitating timely therapeutic adjustments, which may underlie the enhanced DFS observed.

A second key result is that, compared to conventional therapy, precision-guided therapy improved both the extent and completion rate of treatment without increasing severe toxicity. The observation group received higher doses of radiotherapy and chemotherapy, with a higher RDI, even though fewer patients experienced grade ≥ 2 toxicities. Clinically, this is significant as suboptimal dose intensity is a known predictor of treatment failure [27]. This likely results from customized regimens reducing overtreatment and cumulative toxicity, while maximizing compliance. Furthermore, targeted application of immunotherapy and other biologically relevant agents, such as PD-1 inhibitors in dMMR tumors, likely contributed to the higher overall response rates and reduced exposure to ineffective treatments.

Immunotherapy was used exclusively in the observation group and was associated with better clinical outcomes, consistent with previous phase III studies demonstrating the utility of PD-1 blockade in dMMR EC [28]. The selective application of VEGF/mTOR inhibitors in high-risk subgroups further supports the shift towards integrating biologically targeted agents into treatment regimens. These agents are likely complementary to conventional chemotherapy and radiotherapy by modulating the tumor microenvironment and reducing angiogenesis. However, their effects on survival and quality of life need to be confirmed in larger randomized trials.

In our study, patients with the p53-abnormal subtype showed persistently poor prognosis despite receiving combined chemoradiotherapy, highlighting the need for a better understanding of the mechanisms underlying treatment resistance in this subgroup. p53-abnormal tumors are characterized by high chromosomal instability, impaired DNA repair, and aggressive progression, all of which contribute to diminished sensitivity to DNA-damaging therapies. Preclinical evidence suggests that loss of p53 function disrupts cell-cycle checkpoints and apoptotic pathways, fosters tumor heterogeneity, and promotes clonal evolution, enabling resistance to conventional cytotoxic therapies. Potential strategies to overcome this resistance may include integrating novel targeted approaches, such as PARP inhibitors, which exploit synthetic lethality in defective DNA repair backgrounds, or agents that restore therapeutic vulnerability by modulating cell-cycle checkpoints (e.g., WEE1 or ATR inhibitors). Given the emerging role of immune evasion and the tumor microenvironment in p53-abnormal cancers, combining immunotherapy or anti-angiogenic agents may further enhance therapeutic efficacy. Future translational research should prioritize investigating the molecular mechanisms of p53-abnormal tumors and designing biomarker-driven clinical trials to validate these strategies and improve outcomes for this high-risk population.

Regarding safety, our research confirms that personalized therapy is less toxic systemically and introduces new considerations for endocrine monitoring. The incidences of hematologic adverse events, gastrointestinal toxicities, and neuropathy were significantly lower in the observation group, supporting the efficacy of optimized regimens in reducing treatment-related morbidity. The mild increase in thyroid dysfunction observed may be linked to immune-induced adverse events associated with checkpoint inhibitors [29]. This highlights the importance of active endocrine follow-up and multidisciplinary interventions when immunotherapy is used as an adjuvant therapy. In general, the good tolerability of precision-guided therapy makes it a more patient-centered approach.

While these findings are promising, there were several limitations to our study. First, the observational design may introduce selection bias, although multivariate adjustment and subgroup analyses were conducted to minimize confounding. Second, the statistical power may be limited due to the sample size, which was sufficient to measure primary endpoints but may not fully capture rare events or subgroups. Third, although the follow-up period was adequate to identify early recurrences, it may not be long enough to track long-term survival or chronic late toxicities. Finally, before ctDNA-guided management becomes mainstream, considerations related to assay standardization, cost-effectiveness, and availability need to be addressed.

In conclusion, our findings suggest that molecular classification-based adjuvant treatment, guided by ctDNA monitoring, leads to better survival, increased treatment compliance, and reduced toxicity in patients with EC. These results support the paradigm shift from traditional risk-based interventions to precision oncology approaches that integrate genomic profiling and liquid biopsy.

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Disclosure of conflict of interest

None.

Abbreviations

EC, Endometrial cancer; MSI-H, Microsatellite instability high; POLE, DNA polymerase epsilon; p53abn, p53 abnormal; dMMR, Deficient mismatch repair; NSMP, No specific molecular profile; RDI, Relative dose intensity; DFS, Disease-free survival; OS, Overall survival; HR, Hazard ratio; CTCAE, Common Terminology Criteria for Adverse Events; CR, Complete response; PR, Partial response; SD, Stable disease; PD, Progressive disease; ORR, Objective response rate; ctDNA, Circulating tumor DNA; mTOR, Mechanistic target of rapamycin; VEGF, Vascular endothelial growth factor; PD-1, Programmed cell death 1; PD-L1, Programmed cell death ligand 1; NGS, Next-generation sequencing; FIGO, International Federation of Gynecology and Obstetrics.

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Supplementary Table 1. Decision algorithm: molecular classification-guided therapy choices

Molecular Subtype	Therapy Choice	Rationale/Notes
POLE ultramutated	Observation only (no adjuvant therapy)	Excellent prognosis; adjuvant therapy generally not required due to high immunogenicity and low recurrence risk.
MSI-H/dMMR	Immunotherapy (PD-1/PD-L1 inhibitors ± limited chemotherapy)	High mutational burden and responsiveness to checkpoint inhibitors; reduced exposure to cytotoxic therapy to minimize toxicity.
p53-abnormal	Combined chemoradiotherapy (platinum-based chemotherapy + pelvic radiotherapy)	Aggressive biology with high chromosomal instability; integrated chemoradiation shown to improve local control and survival.
NSMP	Conventional clinicopathology-guided adjuvant therapy (chemotherapy ± radiotherapy)	Intermediate risk profile; treated per standard clinicopathologic risk assessment.
Targeted therapy (VEGF/mTOR inhibitors)	Reserved for selected high-risk patients across subtypes	Applied when biologically reasonable based on molecular features or poor response to standard regimens.
Hormonal therapy	Rarely used (e.g., low-grade, hormone-receptor-positive tumors)	Considered for selected patients intolerant of cytotoxic regimens or with indolent disease behavior.