

Original Article

Effect of adjuvant concurrent chemoradiotherapy on survival outcomes in patients with advanced-stage, high-risk endometrial cancer: a single-center retrospective cohort study

Wei Shan¹, Hongliang Mao²

¹Department of Gynaecology and Obstetrics, Shanghai First People's Hospital Jiuquan Hospital (Jiuquan People's Hospital), Jiuquan 735000, Gansu, China; ²Department of Oncology, Shanghai First People's Hospital Jiuquan Hospital (Jiuquan People's Hospital), Jiuquan 735000, Gansu, China

Received June 28, 2026; Accepted September 19, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: To evaluate whether adjuvant concurrent chemoradiotherapy (CCRT) improves overall survival (OS) and recurrence-free survival (RFS) compared with radiotherapy alone in patients with advanced-stage, high-risk endometrial cancer. This single-center retrospective cohort study included 218 patients (97 radiotherapy alone, 121 CCRT). Demographic, clinicopathological, and molecular data were collected. Baseline serum CA125 levels were measured. Treatment completion, adverse events (CTCAE v5.0), recurrence patterns, OS, and RFS were evaluated. Multivariate Cox regression was performed to identify independent prognostic factors. Locoregional recurrence was significantly lower in the CCRT group (8.26% vs. 17.53%, $P=0.039$), but the overall recurrence rate did not differ significantly between groups (21.49% vs. 26.8%, $P=0.360$). Grade ≥ 3 adverse events (52.89% vs. 36.08%, $P=0.013$) and neutropenia (26.45% vs. 7.22%, $P<0.001$) were more common in the CCRT group. Kaplan-Meier analysis with log-rank test showed that the CCRT group had significantly better OS than the radiotherapy-alone group ($P=0.010$) and significantly better RFS ($P=0.009$). Multivariate analysis identified CCRT as an independent protective factor for OS (HR=0.71, 95% CI 0.53-0.95, $P=0.021$), while FIGO stage IIIC (HR=2.12), non-endometrioid histology (HR=1.92), grade 3 tumors (HR=1.78), and abnormal p53 expression (HR=4.34) were independent adverse prognostic factors (all $P<0.05$). Adjuvant CCRT was significantly associated with improved 5-year OS and RFS compared with radiotherapy alone, albeit with higher toxicity.

Keywords: Endometrial cancer, concurrent chemoradiotherapy, radiotherapy, overall survival, recurrence-free survival

Introduction

Endometrial cancer is one of the most common gynecologic malignancies, with its incidence rising globally. Advanced-stage, high-risk endometrial cancer, characterized by higher stages and more aggressive histological subtypes, poses significant treatment challenges and worsens patient outcomes [1-3]. Despite advancements in surgical techniques and adjuvant therapies, the prognosis for these patients remains poor, necessitating a deeper exploration of effective treatment modalities [4, 5].

Radiotherapy has long been a cornerstone of endometrial cancer management, particularly

for those at high risk of recurrence. External-beam radiotherapy (EBRT) targets the tumor bed and regional lymph nodes to eradicate residual microscopic disease and reduce locoregional recurrence risk. Vaginal brachytherapy (VBT) is often added to improve local control by delivering high radiation doses directly to the vaginal cuff, the most common site of recurrence [6, 7]. While EBRT and VBT have demonstrated effectiveness in controlling local disease, their impact on distant metastasis and overall survival remains limited. Radiotherapy alone may not adequately address systemic spread, potentially leading to distant metastases and poorer long-term outcomes [8, 9].

Therefore, there is a need for more comprehensive treatment strategies that combine local and systemic therapies to improve patient survival and quality of life.

CCRT is an innovative approach that combines chemotherapy with radiotherapy to enhance therapeutic efficacy both locally and systemically. In CCRT, cisplatin-based chemotherapy is administered concurrently with EBRT, followed by adjuvant carboplatin-paclitaxel chemotherapy. This combination is based on the synergistic effects of chemotherapy and radiation. Chemotherapeutic agents such as cisplatin act as radiosensitizers, increasing the vulnerability of cancer cells to radiation-induced damage. This dual action aims to achieve better eradication of residual microscopic disease within the pelvic region while also targeting potential distant metastatic sites through systemic chemotherapy [10-12]. Combining chemotherapy with radiotherapy may also stimulate an anti-tumor immune response, potentially improving long-term outcomes. Although CCRT is promising, it is associated with increased toxicity compared with radiotherapy alone, necessitating careful patient selection and effective supportive care [13, 14].

The choice between radiotherapy alone and CCRT depends on multiple factors, including patient performance status, comorbidity profile, and physician discretion. In real-world clinical practice, treatment decisions are typically made by a multidisciplinary team of gynecologic, radiation, and medical oncologists to tailor treatment plans to individual needs. However, the optimal adjuvant treatment strategy for advanced high-risk endometrial cancer remains controversial due to the lack of definitive evidence from large-scale randomized controlled trials. This study aims to add to the existing evidence by comparing CCRT versus radiotherapy alone on survival outcomes in a single-center retrospective cohort. This study focuses on evaluating the impact of two primary adjuvant treatment approaches - radiotherapy alone and CCRT - on overall survival and recurrence-free survival in patients with advanced high-risk endometrial cancer.

Methods

Ethical approval and study protocol

This single-center retrospective cohort study was conducted at Shanghai First People's

Hospital Jiuquan Hospital (Jiuquan People's Hospital), after approval by the Medical Ethics Committee of Shanghai First People's Hospital Jiuquan Hospital (Jiuquan People's Hospital) (Approval Number: 20260706038). All procedures were performed in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments. Given the retrospective nature of the study and the use of anonymized clinical data, the requirement for written informed consent from individual patients was waived by the IRB. Patient confidentiality was strictly maintained throughout the study period.

Patient selection and eligibility criteria

All consecutive patients with histologically confirmed endometrial cancer who underwent comprehensive surgical staging at our institution between January 2014 and December 2020 were screened for inclusion. Surgical staging included total hysterectomy, bilateral salpingo-oophorectomy, and systematic pelvic and para-aortic lymphadenectomy, performed by experienced gynecologic oncologists.

Inclusion criteria: (1) histologically confirmed endometrial cancer with International Federation of Gynecology and Obstetrics (FIGO) 2009 [15] stage III or IVA disease; (2) high-risk features according to the European Society of Gynecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology (ESGO-ESTRO-ESP) consensus guidelines [16], including deep myometrial invasion ($\geq 50\%$), lymphovascular space invasion (LVSI), grade 3 endometrioid histology, or non-endometrioid histotypes (serous, clear cell, carcinosarcoma); (3) receipt of adjuvant therapy at our institution; and (4) availability of complete clinical and pathological records and 5-year follow-up data.

Exclusion criteria: (1) prior pelvic or abdominal radiotherapy for any malignancy; (2) presence of synchronous or metachronous other malignancies (except non-melanoma skin cancer or carcinoma in situ of the cervix); (3) incomplete medical records or loss to follow-up within the first 12 months after surgery; (4) receipt of neoadjuvant chemotherapy or radiotherapy before surgical staging; (5) FIGO stage IVB disease or distant metastases at presentation; and (6) receipt of adjuvant hormonal therapy alone without chemotherapy or radiotherapy.

Adjuvant treatment regimens

Patients were categorized into two groups according to the adjuvant treatment received after complete surgical staging. Treatment assignment was not randomized and was based on patient preference, physician discretion, performance status, and comorbidity profile, consistent with real-world clinical practice in a retrospective cohort design. All treatment decisions were made by a multidisciplinary tumor board that included gynecologic oncologists, radiation oncologists, and medical oncologists.

Radiotherapy-alone group: Patients who received pelvic EBRT with or without VBT and no systemic chemotherapy were assigned to the radiotherapy-alone group. EBRT was delivered using a linear accelerator (Synergy®, Elekta AB, Stockholm, Sweden) with computed tomography (CT)-based three-dimensional conformal radiotherapy or intensity-modulated radiotherapy (IMRT). The planning target volume included the vaginal cuff, parametria, presacral region, and pelvic lymph node regions (external and internal iliac, obturator, and common iliac nodes). For patients with histologically confirmed common iliac or para-aortic lymph node involvement, the radiation field was extended to cover the para-aortic region up to the renal vessels. The prescribed total dose was 45 Gy in 1.8-Gy fractions, delivered once daily, five days per week, for 5-6 weeks. For patients with close (<5 mm) or involved surgical margins, a sequential EBRT boost of 5.4 Gy in three fractions was delivered to the vaginal cuff. VBT was delivered at the discretion of the treating radiation oncologist, typically for patients with cervical stromal invasion, deep myometrial invasion, or high-grade histology. VBT was administered using a high-dose-rate remote afterloading system (MicroSelectron HDR, Nucletron B.V., Veenendaal, the Netherlands), with a dose of 7 Gy prescribed to 5 mm depth of the vaginal cuff, delivered in three fractions at weekly intervals. No patient in this group received any cycles of systemic chemotherapy.

Concurrent chemoradiotherapy group: Patients who received cisplatin-based CCRT followed by adjuvant carboplatin-paclitaxel chemotherapy were assigned to the CCRT group. The concurrent phase comprised two cycles of intravenous cisplatin (50 mg/m²) on days 1 and 29 of

radiotherapy. Each cisplatin dose was preceded and followed by adequate intravenous hydration (≥1 L of normal saline with 20 mEq of KCl and 2 g of gSO₄) and prophylactic antiemetics (5-HT₃ antagonist and dexamethasone). Radiotherapy was delivered concurrently using the same protocol as in the radiotherapy-alone group, with the same total dose and fractionation schedule (45 Gy in 1.8 Gy fractions). For patients with cervical stromal invasion or involved surgical margins, the same EBRT boost or VBT was added at the discretion of the treating radiation oncologist.

After completion of concurrent chemoradiotherapy, patients proceeded to the adjuvant chemotherapy phase, which consisted of four to six cycles of carboplatin and paclitaxel administered intravenously every three weeks. Each cycle of chemotherapy was delivered as follows: paclitaxel 175 mg/m² was infused over three hours, followed by carboplatin with an area under the curve (AUC) of 5 to 6 (calculated using the Calvert formula with a target AUC of 5 for patients with a glomerular filtration rate <60 mL/min or AUC of 6 for patients with normal renal function) infused over 30 to 60 minutes. Premedication for paclitaxel included dexamethasone (20 mg intravenously), diphenhydramine (50 mg intravenously), and an H₂-receptor antagonist (ranitidine 50 mg intravenously) administered 30 to 60 minutes before paclitaxel infusion. Filgrastim (granulocyte colony-stimulating factor, 5 µg/kg once daily for five days) was administered at the discretion of the treating medical oncologist for patients with documented neutropenia or at high risk of febrile neutropenia. Chemotherapy cycles were delayed for up to two weeks if recovery from adverse events was incomplete; dose reductions were performed according to standard protocols for grade 3 or higher hematologic or non-hematologic toxicities.

Data collection and clinicopathological variables

Demographic and clinicopathological data were extracted from electronic medical records. Tumor characteristics were obtained from pathology reports following surgical staging. Tumor grade according to the International Federation of Gynecology and Obstetrics grading system for endometrioid tumors; non-endometrioid histotypes were classified as grade 3 for analy-

sis. Depth of myometrial invasion was categorized as <50% or ≥50% of the myometrial thickness. Adnexal involvement was defined as tumor involvement of the fallopian tube or ovary. Blood samples were collected within one week prior to surgery (baseline). Serum CA125 levels were measured using a chemiluminescent immunoassay (CLIA) on an automated analyzer (Architect i2000SR, Abbott Diagnostics, Abbott Park, IL, USA) with a commercial kit (Abbott Diagnostics).

Immunohistochemical analysis of p53 and mismatch repair proteins

Formalin-fixed, paraffin-embedded (FFPE) tumor tissue sections from the primary tumor were retrieved for all patients. Immunohistochemistry (IHC) was performed to assess p53 expression and mismatch repair (MMR) protein status (MLH1, PMS2, MSH2, and MSH6) using standard automated IHC systems in the Department of Pathology. A mouse monoclonal anti-p53 antibody (clone DO-7, DakoCytomation, Glostrup, Denmark) was used. MMR protein expression was assessed using mouse monoclonal antibodies against MLH1 (clone ES05, Dako), PMS2 (clone EP51, Dako), MSH2 (clone FE11, Dako), and MSH6 (clone EP49, Dako). p53 expression was classified as wild-type (normal) if <10% of tumor cell nuclei showed weak-to-moderate staining, or as abnormal (overexpression or null) if >70% showed intense uniform staining or complete absence of nuclear staining with positive internal controls. MMR proficiency (pMMR) was defined as preserved nuclear staining for all four MMR proteins, while MMR deficiency (dMMR) was defined as complete loss of nuclear staining for at least one MMR protein, confirmed by the presence of positive internal controls (stromal cells and lymphocytes) within the same section. All IHC slides were evaluated independently by two dedicated gynecologic pathologists blinded to clinical outcome data, and discordant cases were resolved by consensus review.

Treatment completion and toxicity assessment

Treatment completion was defined per the planned treatment regimen. For the radiotherapy-alone group, completion of prescribed radiotherapy fractions was recorded as the percentage of patients who received the full pre-

scribed 45-Gy dose with all fractions delivered. For the CCRT group, completion was recorded as the number and percentage of patients who received all six planned carboplatin-paclitaxel cycles without permanent discontinuation. Reasons for discontinuation of chemotherapy, including toxicity, patient refusal, disease progression, or other clinical reasons, were recorded from medical notes.

Acute treatment-related adverse events were documented from clinical records during treatment and up to 30 days after adjuvant therapy completion. Toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Hematologic toxicities assessed included neutropenia (absolute neutrophil count $<1.0 \times 10^9/L$ for grade 3, $<0.5 \times 10^9/L$ for grade 4), thrombocytopenia (platelet count $<50.0 \times 10^9/L$ for grade 3, $<25.0 \times 10^9/L$ for grade 4), and anemia (hemoglobin <80 g/L for grade 3, <65 g/L for grade 4). Complete blood counts were obtained at baseline before each chemotherapy cycle and repeated weekly or as clinically indicated. Non-hematologic toxicities assessed included gastrointestinal toxicity (nausea, vomiting, diarrhea rated according to CTCAE grade ≥3 criteria, defined as requiring hospitalization for management of symptoms, severe impairment of oral intake or hydration, or more than seven episodes of diarrhea per day above baseline), neuropathy (sensory or motor neuropathy grade ≥3, defined as severe symptoms limiting self-care activities of daily living), and fatigue (grade ≥3, defined as severe fatigue limiting self-care activities of daily living). All adverse events were recorded as the highest grade observed during the treatment period for each patient.

Follow-up and outcome assessment

The primary endpoints were overall survival (OS) and recurrence-free survival (RFS). OS was defined as the interval from the date of surgery to death of any cause or last known follow-up. RFS was defined as the interval from surgery to first documented disease recurrence (locoregional or distant) or death from any cause, whichever occurred first. The interval from surgery to the start of adjuvant treatment was calculated for each patient and compared between the two groups. Patients who were alive and free of recurrence at the end of the study period were censored on the date of their last follow-up.

Follow-up data were obtained from outpatient clinic records, imaging reports, and telephone interviews. After completion of adjuvant therapy, all patients were scheduled for routine follow-up examinations according to institutional guidelines. Follow-up visits were scheduled every three months for the first two years, every six months for years three to five. At each follow-up visit, patients underwent a complete physical examination including pelvic examination. Imaging studies included pelvic ultrasound or computed tomography (CT) of the chest, abdomen, and pelvis performed every six months for the first two years and annually thereafter, or as clinically indicated based on symptoms or physical examination findings. Suspected disease recurrence was confirmed by imaging (CT, magnetic resonance imaging [MRI], or positron emission tomography [PET]-CT) and, when feasible, by histopathological biopsy of the suspected lesion. Disease recurrence was classified as locoregional (vaginal recurrence, pelvic recurrence including central pelvis and pelvic sidewall, or para-aortic lymph node recurrence) or distant metastasis (intra-abdominal spread outside the pelvis, lung, liver, bone, brain, or other extra-abdominal sites). Patients with both locoregional and distant recurrence were recorded in both categories for pattern of recurrence analysis. Any recurrence was defined as the first documented recurrence event; patients who developed simultaneous locoregional and distant recurrence at the time of first recurrence were recorded as a separate “simultaneous recurrence” category.

Statistical analysis

All statistical analyses were performed using SPSS version 29.0 (IBM Corp., Armonk, NY, USA). Continuous variables were tested for normality using the Shapiro-Wilk test. All continuous variables were normally distributed and are expressed as mean $\pm$ standard deviation (SD); between-group comparisons were performed using the independent-samples t-test. Categorical variables are expressed as frequencies and percentages and were compared between the two groups using the chi-square (χ^2) test or Fisher's exact test, as appropriate (Fisher's exact test was applied when any expected cell frequency was less than 5). All statistical tests were two-tailed, and a *P* value <0.05 was considered statistically significant. No adjustment for multiple comparisons was performed, as

the analyses were primarily descriptive and confirmatory.

Kaplan-Meier curves were constructed to estimate OS and RFS distributions for the two treatment groups, and differences in survival distributions were compared using the two-sided log-rank test. Median follow-up duration was calculated using the reverse Kaplan-Meier method. Multivariate Cox proportional hazards regression analysis was performed to identify independent prognostic factors for OS. Variables with $P < 0.10$ in univariate analysis were entered into the multivariate model using a forward stepwise selection method. The proportional hazards assumption was verified by testing the scaled Schoenfeld residuals, and no violation was detected. Hazard ratios (HRs) with 95% confidence intervals (CIs) were reported for each variable.

Results

Patient characteristics

No significant between-group differences were observed for any baseline demographic or clinical variables (all $P > 0.05$; **Table 1**). The two groups were well balanced with respect to age, body mass index, menopausal status, smoking history, hypertension, diabetes mellitus, prior abdominal surgery history, and baseline CA125 level.

Tumor characteristics

All tumor characteristics and pathologic parameters were comparable between the two groups, with no statistically significant differences in FIGO stage, histological type, tumor grade, depth of myometrial invasion, lymphovascular space invasion, cervical stromal invasion, adnexal involvement, or number of positive lymph nodes (all $P > 0.05$, **Table 2**).

Molecular classification

The distribution of p53 expression and mismatch repair protein status did not differ significantly between the radiotherapy-alone group and the concurrent chemoradiotherapy group ($P > 0.05$ for both comparisons, **Table 3**).

Treatment-related variables

Completion rates of prescribed radiotherapy were similarly high in both groups (96.91% vs.

Progression-free and overall survival analysis

Table 1. Baseline demographic and clinical characteristics

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	t/ χ^2	P
Age (years)	57.98 ± 10.45	58.43 ± 9.92	0.323	0.747
BMI (kg/m ²)	26.52 ± 3.28	26.78 ± 3.41	0.567	0.571
Menopausal status (Premenopausal/Postmenopausal), n (%)	18 (18.56%)/79 (81.44%)	20 (16.53%)/101 (83.47%)	0.154	0.695
Smoking history (Ever smoker/Never smoker), n (%)	10 (10.31%)/87 (89.69%)	11 (9.09%)/110 (90.91%)	0.092	0.762
Hypertension (Yes/No), n (%)	39 (40.21%)/58 (59.79%)	45 (37.19%)/76 (62.81%)	0.207	0.649
Diabetes mellitus (Yes/No), n (%)	26 (26.8%)/71 (73.2%)	29 (23.97%)/92 (76.03%)	0.230	0.632
Prior abdominal surgery history (Yes/No), n (%)	29 (29.9%)/68 (70.1%)	31 (25.62%)/90 (74.38%)	0.494	0.482
Baseline CA125 (U/mL)	38.26 ± 18.43	36.91 ± 17.05	0.560	0.576

BMI, body mass index; CA125, cancer antigen 125.

Table 2. Tumor characteristics and pathologic parameters

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	χ^2	P
FIGO stage, n (%)			0.229	0.892
IIIA	22 (22.68%)	30 (24.79%)		
IIIB	15 (15.46%)	20 (16.53%)		
IIIC	60 (61.86%)	71 (58.68%)		
Histological type, n (%)			0.334	0.953
Endometrioid	56 (57.73%)	73 (60.33%)		
Serous	23 (23.71%)	29 (23.97%)		
Clear cell	12 (12.37%)	13 (10.74%)		
Carcinosarcoma	6 (6.19%)	6 (4.96%)		
Tumor grade, n (%)			0.120	0.942
Grade 1	6 (6.19%)	8 (6.61%)		
Grade 2	26 (26.8%)	30 (24.79%)		
Grade 3	65 (67.01%)	83 (68.6%)		
Depth of myometrial invasion (<50%/≥50%), n (%)	27 (27.84%)/70 (72.16%)	33 (27.27%)/88 (72.73%)	0.009	0.926
LVSI (Absent/Present), n (%)	39 (40.21%)/58 (59.79%)	54 (44.63%)/67 (55.37%)	0.430	0.512
Cervical stromal invasion (Yes/No), n (%)	36 (37.11%)/61 (62.89%)	41 (33.88%)/80 (66.12%)	0.246	0.620
Adnexal involvement (Yes/No), n (%)	26 (26.8%)/71 (73.2%)	29 (23.97%)/92 (76.03%)	0.230	0.632
Number of positive lymph nodes, n (%)			0.308	0.857
0	31 (31.96%)	42 (34.71%)		
1-2	45 (46.39%)	56 (46.28%)		
≥3	21 (21.65%)	23 (19.01%)		

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion.

95.87%, $P=0.966$), and the proportion of patients receiving vaginal brachytherapy did not differ significantly (37.11% vs. 32.23%, $P=0.451$; **Table 4**). In the CCRT group, 86 patients (71.07%) completed all six prescribed chemotherapy cycles. The remaining 35 patients (28.93%) discontinued prematurely due to toxicity ($n=16$, 13.22%), disease progression ($n=8$, 6.61%), patient refusal ($n=7$, 5.79%), or other clinical reasons ($n=4$, 3.31%). The 5-year OS rate was 86.05% for completers versus 71.43% for non-completers ($P=0.068$); the corresponding 5-year RFS rates were 83.72% and 65.71% ($P=0.041$).

The median interval from surgery to the start of adjuvant treatment was 5.2 weeks (IQR: 4.1-6.3 weeks) in the radiotherapy-alone group and 5.4 weeks (IQR: 4.3-6.5 weeks) in the CCRT group, with no significant difference between the two groups ($P=0.412$).

Five-year survival outcomes

Kaplan-Meier analysis with the log-rank test showed that the CCRT group had significantly better OS ($P=0.010$) and RFS ($P=0.009$) than the radiotherapy-alone group (**Figure 1**). The median follow-up duration for the entire cohort was 60.2 months: 59.8 months for the radio-

Table 3. Molecular classification by immunohistochemistry

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	χ^2	P
p53 expression, n (%)			0.288	0.866
Wild-type (normal)	57 (58.76%)	75 (61.98%)		
Abnormal (overexpression/null)	19 (19.59%)	23 (19.01%)		
Not tested/indeterminate	21 (21.65%)	23 (19.01%)		
MMR status, n (%)			0.233	0.890
Proficient (pMMR)	55 (56.7%)	71 (58.68%)		
Deficient (dMMR)	21 (21.65%)	23 (19.01%)		
Not tested/indeterminate	21 (21.65%)	27 (22.31%)		

MMR, mismatch repair; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

Table 4. Treatment details and completion rates

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	χ^2	P
Radiotherapy completion (Yes/No), n (%)	94 (96.91%)/3 (3.09%)	116 (95.87%)/5 (4.13%)	0.002	0.966
Vaginal brachytherapy (Yes/No), n (%)	36 (37.11%)/61 (62.89%)	39 (32.23%)/82 (67.77%)	0.569	0.451
Completion of all six prescribed chemotherapy cycles, n (%)	/	86 (71.07%)	/	/

therapy-alone group and 60.5 months for the CCRT group. This is consistent with the study's inclusion criterion requiring at least 5 years of follow-up data for all patients.

Patterns of recurrence

Although the overall recurrence rate did not differ significantly between groups ($P=0.360$), locoregional recurrence was significantly less frequent in the CCRT group (8.26% vs. 17.53%, $\chi^2=4.256$, $P=0.039$; **Table 5**). Distant metastasis rates were similar between the groups (24.74% vs. 21.49%, $P=0.570$). The sum of locoregional and distant recurrence rates exceeds the "any recurrence" rate because 15 patients (15.46%) in the radiotherapy-alone group and 10 (8.26%) in the CCRT group had simultaneous locoregional and distant recurrence at first documented recurrence.

Treatment-related toxicity

Patients in the CCRT group had a significantly higher incidence of grade ≥ 3 adverse event than those in the radiotherapy-alone group (52.89% vs. 36.08%, $\chi^2=6.137$, $P=0.013$; **Table 6**). Neutropenia (grade 3-4) was markedly more common in the CCRT group (26.45% vs. 7.22%, $\chi^2=13.553$, $P<0.001$). No significant differences were observed for thrombocytopenia, anemia, gastrointestinal toxicity, neuropathy, or fatigue (all $P>0.05$).

Of the 35 patients in the CCRT group who did not complete all six planned chemotherapy cycles, 16 patients (13.22% of the CCRT group) discontinued specifically because of treatment-related toxicity. The most common toxicity leading to discontinuation was grade 4 neutropenia ($n=7$), followed by persistent grade 3 gastrointestinal toxicity ($n=5$) and grade 3 neuropathy ($n=4$).

Multivariate Cox regression analysis

For multivariate Cox regression analysis, variables were selected based on statistical criteria and clinical importance. Variables meeting the prespecified entry criterion ($P<0.10$) in univariate analysis and entered into the final multivariate model included: treatment group (CCRT vs. radiotherapy alone), FIGO stage (IIIB and IIIC vs. IIIA), histological type (non-endometrioid vs. endometrioid), tumor grade (grade 3 vs. grade 1-2), and p53 status (abnormal vs. wild-type). In addition, clinically well-established prognostic factors - including age (>60 vs. ≤ 60 years), LVSI status (present vs. absent), and MMR status (dMMR vs. pMMR) - were forced into the model a priori to adjust for potential confounding, regardless of their univariate P values. Baseline serum CA125 level (as a continuous variable) did not meet the univariate entry criterion and was not entered into the multivariate model.

Progression-free and overall survival analysis

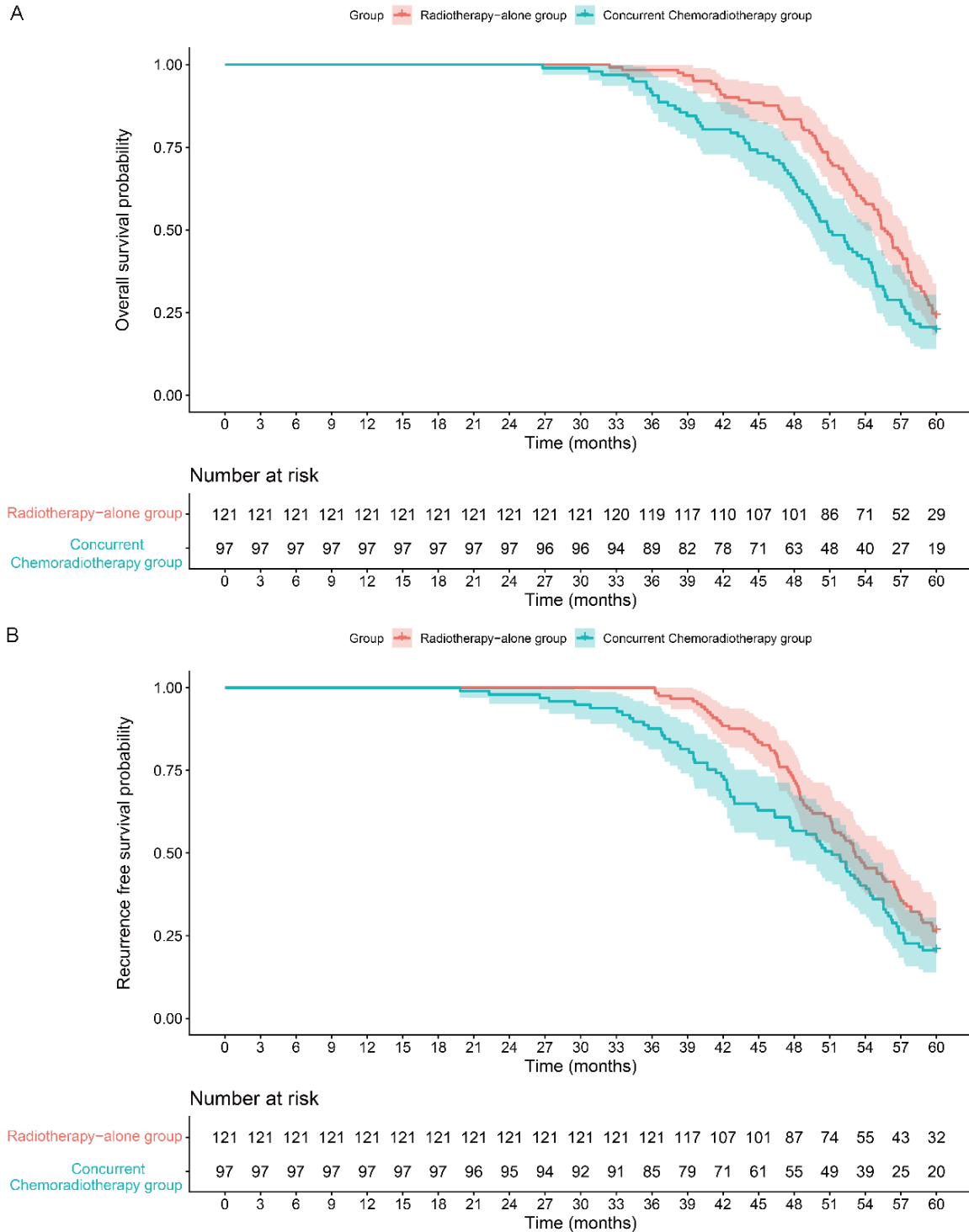


Figure 1. Kaplan-Meier curves for overall survival (A) and recurrence-free survival (B), stratified by radiotherapy alone versus concurrent chemoradiotherapy. *P* values were from two-sided log-rank tests (OS: *P*=0.010; RFS: *P*=0.009).

Multivariate Cox regression analysis identified concurrent chemoradiotherapy as an independent protective factor for overall survival compared with radiotherapy alone (HR=0.71, 95% CI 0.53-0.95, *P*=0.021, **Table 7**). Compared

with FIGO stage IIIA, stage IIIC was independently associated with worse OS (HR=2.27, 95% CI 1.35-3.81, *P*=0.002), while stage IIIB did not show a statistically significant difference (HR=1.51, 95% CI 0.72-3.16, *P*=0.274).

Progression-free and overall survival analysis

Table 5. Patterns of disease recurrence

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	χ^2	P
Any recurrence, n (%)	26 (26.8%)	26 (21.49%)	0.838	0.360
Locoregional recurrence, n (%)	17 (17.53%)	10 (8.26%)	4.256	0.039
Pelvic recurrence	11	6		
Vaginal recurrence	6	4		
Distant metastasis, n (%)	24 (24.74%)	26 (21.49%)	0.323	0.570

Table 6. Grade 3 or higher treatment-related adverse events

Parameter	Radiotherapy-alone Group (n=97)	Concurrent Chemoradiotherapy Group (n=121)	χ^2	P
Any grade ≥ 3 adverse event, n (%)	35 (36.08%)	64 (52.89%)	6.137	0.013
Neutropenia (grade 3-4), n (%)	7 (7.22%)	32 (26.45%)	13.553	<0.001
Thrombocytopenia (grade 3-4), n (%)	3 (3.09%)	11 (9.09%)	3.223	0.073
Anemia (grade 3-4), n (%)	5 (5.15%)	10 (8.26%)	0.813	0.367
Gastrointestinal toxicity (grade ≥ 3), n (%)	11 (11.34%)	24 (19.83%)	2.883	0.090
Neuropathy (grade ≥ 3), n (%)	2 (2.06%)	6 (4.96%)	0.590	0.442
Fatigue (grade ≥ 3), n (%)	5 (5.15%)	13 (10.74%)	2.220	0.136

Table 7. Multivariate Cox regression analysis of factors associated with overall survival

Parameter	Category	HR (95% CI)	P
Treatment group	Concurrent chemoradiotherapy vs. radiotherapy alone	0.71 (0.53-0.95)	0.021
FIGO stage	IIIB vs. IIIA	1.51 (0.72-3.16)	0.274
	IIIC vs. IIIA	2.27 (1.35-3.81)	0.002
Histological type	Non-endometrioid vs. endometrioid	1.92 (1.15-3.21)	0.013
Tumor grade	Grade 3 vs. Grade 1-2	1.78 (1.03-3.08)	0.040
p53 status	Abnormal vs. wild-type	4.34 (2.85-6.62)	<0.001
MMR status	dMMR vs. pMMR	1.45 (0.91-2.31)	0.119
Age	>60 vs. ≤ 60 years	1.35 (0.84-2.17)	0.213
LVSI	Present vs. absent	1.44 (0.91-2.28)	0.122

HR, hazard ratio; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; MMR, mismatch repair.

Non-endometrioid histology (HR=1.92, 95% CI 1.15-3.21, P=0.013), grade 3 tumors (HR=1.78, 95% CI 1.03-3.08, P=0.040), and abnormal p53 expression (HR=4.34, 95% CI 2.85-6.62, P<0.001) were independently associated with worse overall survival. MMR status, age, and LVSI showed no independent prognostic value (all P>0.05). In the univariate Cox regression analysis, baseline serum CA125 level (as a continuous variable) did not meet the prespecified entry criterion (P<0.10) and was therefore not entered into the multivariate model.

Discussion

Advanced-stage, high-risk endometrial cancer poses significant challenges in terms of treat-

ment and survival outcomes. This study aimed to evaluate the impact of adjuvant CCRT compared to radiotherapy alone on overall survival and recurrence-free survival in patients with advanced-stage endometrial cancer. The findings indicate a positive association between CCRT and improved long-term outcomes in this patient cohort, although it is associated with higher rates of adverse events.

Baseline characteristics were well balanced between the groups, ensuring comparability. This balance suggests that observed differences are likely attributable to the treatment rather than to pre-existing patient factors. Both groups had similar demographic and clinical profiles, including age, BMI, menopausal status, smok-

ing history, and comorbidities. Similarly, tumor characteristics such as FIGO stage, histological type, tumor grade, depth of myometrial invasion, and lymphovascular space invasion did not differ significantly between the two groups. These similarities provide a strong foundation for comparing the effectiveness of the two treatment approaches.

The 5-year OS and PFS were higher in the CCRT group compared to the radiotherapy-alone group. Several mechanisms may explain these differences. First, adding chemotherapy to radiotherapy enhances eradication of residual microscopic disease, reducing local recurrence risk. Chemotherapy agents such as cisplatin have radiosensitizing properties that increase radiation effectiveness by making cancer cells more susceptible to radiation-induced damage. This combination allows more effective targeting of primary tumors and microscopic metastases, thereby improving local control and preventing recurrence. Additionally, systemic chemotherapy targets distant metastatic sites, preventing cancer spread beyond the primary tumor. The dual action of local and systemic therapies provided by CCRT may account for the observed improvement in survival outcomes [17-19].

Although the subgroup analysis suggested a potential survival benefit for completing all six chemotherapy cycles, this comparison should be interpreted with caution. The observed difference is susceptible to confounding by prognosis-related factors, as patients who complete the full regimen likely have better baseline performance status and fewer comorbidities, which may independently influence outcomes.

Locoregional recurrence was less frequent in the CCRT group, indicating that the combined treatment effectively controls local disease. This reduction may be attributed to the synergistic effects of chemotherapy and radiotherapy. Radiation damages cancer cell DNA, while chemotherapeutic agents disrupt cell division and repair processes. Together, they create a more potent anti-tumor effect, leading to better local control. In contrast, distant metastasis rates were similar between the groups, suggesting that while CCRT improves local control, its impact on preventing distant metastases may be limited. Further research is needed to

explore whether additional systemic therapies could further reduce the risk of distant metastases [20-22].

Treatment-related toxicity was higher in the CCRT group, particularly hematologic adverse events such as neutropenia. The higher incidence of severe adverse events highlights the need for careful monitoring and supportive care during CCRT. Neutropenia, a common chemotherapy side effect, increases infection risk and other complications [23-25]. Strategies to mitigate these risks, such as prophylactic antibiotics or growth factor support, should be considered to ensure patient safety. Specifically, routine use of prophylactic granulocyte colony-stimulating factor (G-CSF) during adjuvant chemotherapy and protocol-driven dose modifications for grade ≥ 3 hematologic toxicities are practical measures to improve treatment tolerability and completion rates. Despite these challenges, the potential survival benefits of CCRT must be weighed against the increased risk of adverse events [26, 27].

Multivariate Cox regression analysis identified several independent predictors of worse OS, including FIGO stage IIIC, non-endometrioid histology, grade 3 tumors, and abnormal p53 expression. These factors highlight the importance of considering tumor biology and staging when making treatment decisions. Patients with these high-risk features may benefit most from aggressive strategies such as CCRT. For instance, abnormal p53 expression is associated with poorer prognosis due to its role in regulating cell cycle progression and apoptosis. Targeting this pathway with combined-modality treatments may help overcome resistance and improve response rates [28-30]. The particularly strong adverse prognostic impact of abnormal p53 expression warrants emphasis. This finding underscores the aggressive biology of p53-abnormal tumors, which often have high genomic instability and rapid disease progression. Moreover, the overrepresentation of such molecular alterations in advanced-stage disease in this cohort may have contributed to the effect magnitude. Similarly, non-endometrioid histologies tend to have more aggressive behavior, and thus, more intensive treatment approaches like CCRT may be necessary to achieve optimal outcomes. The analysis confirmed that CCRT is an independent protective factor for overall survival, reinforcing the poten-

tial benefits of this approach in selected populations. Identifying specific patient subgroups that derive the most benefit from CCRT can help personalize treatment plans and improve overall survival.

Despite the promising findings, this study has several limitations. We acknowledge that the retrospective design carries an inherent risk of selection bias. Although we used multivariate Cox regression to adjust for measured confounders, we did not perform propensity score matching (PSM). Given the relatively limited sample size (97 in the radiotherapy group and 121 in the CCRT group), 1:1 PSM would have substantially reduced effective sample size and statistical power, potentially introducing new biases. Therefore, residual confounding by unmeasured variables (e.g., performance status, detailed comorbidity burden) cannot be excluded, and our findings should be interpreted as associations rather than causal effects. The retrospective design introduces inherent bias, and selection bias cannot be entirely ruled out because of non-randomized treatment allocation. The single-center design and limited sample size may restrict the generalizability of our findings.

Upon re-adjudication, we confirmed that all 22 deaths in the CCRT group occurred in patients with documented disease recurrence. Although this observation may initially appear unusual, it is plausibly explained by the inclusion criterion requiring complete 5-year follow-up data. This criterion may have systematically excluded patients who died early from treatment-related toxicity or intercurrent illness, as they would lack complete follow-up records. Consequently, the cohort may have been enriched for patients who either remained recurrence-free or survived long enough to recur before death, introducing survivorship bias. This limitation should be considered when interpreting the absolute survival rates, and caution is warranted in generalizing these findings to unselected real-world populations with less stringent follow-up requirements.

Future prospective randomized controlled trials are needed to validate these preliminary findings and explore the broader implications of CCRT in advanced-stage, high-risk endometrial cancer. Larger sample sizes and longer follow-up periods would provide more robust evidence

on the long-term efficacy and safety of CCRT. Further research should also aim to identify patient subgroups most likely to benefit and to assess the cost-effectiveness of CCRT in routine clinical practice. By addressing current limitations and expanding future research scope, we aim to refine CCRT application and ultimately improve care for patient with advanced-stage, high-risk endometrial cancer. Enhancing patient-centered care through evidence-based practices remains a priority for improving the experience and outcomes of those undergoing treatment for this challenging disease.

Conclusion

In this retrospective cohort, adjuvant CCRT was associated with improved OS and RFS compared with radiotherapy alone in patients with advanced-stage, high-risk endometrial cancer. The findings indicate that CCRT may enhance local control and reduce locoregional recurrence risk. However, CCRT is associated with a higher incidence of adverse events, particularly hematologic toxicities, necessitating careful monitoring and supportive care. Although these results are promising, further prospective studies are needed to validate these observations and identify patient subgroups most likely to benefit. Overall, CCRT holds promise for improving outcomes in this challenging patient population, but further research is warranted to fully establish its efficacy and safety.

Disclosure of conflict of interest

None.

Address correspondence to: Hongliang Mao, Department of Oncology, Shanghai First People's Hospital Jiuquan Hospital (Jiuquan People's Hospital), Jiuquan 735000, Gansu, China. E-mail: nihao667652@163.com

References

- [1] Volinsky-Fremont S, Horeweg N, Andani S, Barkey Wolf J, Lafarge MW, de Kroon CD, Ørtoft G, Høgdaal E, Dijkstra J, Jobsen JJ, Lutgens LCHW, Powell ME, Mileshekin LR, Mackay H, Leary A, Katsaros D, Nijman HW, de Boer SM, Nout RA, de Bruyn M, Church D, Smit VTHBM, Creutzberg CL, Koelzer VH and Bosse T. Prediction of recurrence risk in endometrial cancer with

- multimodal deep learning. *Nat Med* 2024; 30: 1962-1973.
- [2] Collins A, Jacob A and Moss E. Robotic-assisted surgery in high-risk surgical patients with endometrial cancer. *Best Pract Res Clin Obstet Gynaecol* 2024; 92: 102421.
- [3] Baker-Rand H and Kitson SJ. Recent advances in endometrial cancer prevention, early diagnosis and treatment. *Cancers (Basel)* 2024; 16: 1028.
- [4] Sun Y, Lin S, Wu W, Nie F, Liu Y, Wen J, Cheng X, Liu Q, Wang Y and Ren F. Whether surgical procedure can improve the prognosis of endometrial cancer arising in adenomyosis (EC-AIA)? A systematic review and meta-analysis. *Int J Surg* 2024; 110: 3072-3080.
- [5] Galant N, Krawczyk P, Monist M, Obara A, Gajek Ł, Grenda A, Nicos M, Kalinka E and Milanowski J. Molecular classification of endometrial cancer and its impact on therapy selection. *Int J Mol Sci* 2024; 25: 5893.
- [6] Sibarani CNR, Salima S and Adrianto N. Comparative efficacy and safety of vaginal brachytherapy versus combined pelvic external beam radiotherapy and vaginal brachytherapy in managing intermediate to high-risk endometrial cancer: a systematic review and meta-analysis. *J Egypt Natl Canc Inst* 2025; 37: 45.
- [7] Guo T, Zhao Y, Zeng J, Tang E, Zhang Y and Wu L. Effect of prior adjuvant radiotherapy on immunotherapy outcomes in recurrent endometrial cancer. *Int J Gynecol Cancer* 2025; 35: 101937.
- [8] Ferioli M, Macchia G, Cilla S, Malizia C, Perrone AM, Tagliaferri L, Buwenge M, Deodato F, Galletta E, Donati CM, Zamfir AA, Strigari L, Cammelli S, Iaco P and Morganti AG. Evaluating the feasibility of modern external beam radiotherapy as an alternative approach to brachytherapy in endometrial cancer treatment: a systematic review. *J Contemp Brachytherapy* 2024; 16: 383-389.
- [9] Autorino R, Cusumano D, Rinaldi RM, Giannini R, De Luca V, Campitelli M, Lancellotta V, Di Franco S, Macchia G, Ferrandina G and Gambacorta MA. Correlation between radiation dose to bone marrow subregions and acute hematologic toxicity in endometrial cancer treated with external beam radiotherapy. *Clin Transl Radiat Oncol* 2025; 52: 100942.
- [10] Xue Y, Li G, Xie T, Xu H, Xu T, Li Z, Zhu L, Li X, Li Z and Xiong W. Concurrent chemoradiotherapy versus radiotherapy alone for stage II nasopharyngeal carcinoma in the era of intensity-modulated radiotherapy. *Eur Arch Otorhinolaryngol* 2023; 280: 3097-3106.
- [11] Xin W, Rixin S, Linrui L, Zhihui Q, Long L and Yu Z. Machine learning-based radiomics for predicting outcomes in cervical cancer patients undergoing concurrent chemoradiotherapy. *Comput Biol Med* 2024; 177: 108593.
- [12] Sibarani CNR, Salima S, Suardi D, Adrianto N and Mangkuliguna G. Efficacy and safety of neoadjuvant chemotherapy plus concurrent chemoradiotherapy compared to concurrent chemoradiotherapy alone in locally advanced cervical cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev* 2025; 26: 2793-2802.
- [13] Dai D, Pei Y, Zhu B, Wang D, Pei S, Huang H, Zhu Q, Deng X, Ye J, Xu J, Chen X, Huang M and Xiao Y. Chemoradiotherapy-induced ACKR2(+) tumor cells drive CD8(+) T cell senescence and cervical cancer recurrence. *Cell Rep Med* 2024; 5: 101550.
- [14] Agustí N, Viveros-Carreño D, Wu CF, Wilke RN, Kanbergs A, Barajas K, Zamorano AS, Pareja R, Melamed A and Rauh-Hain JA. Adjuvant chemoradiotherapy vs radiotherapy alone for patients with intermediate-risk cervical cancer. *JAMA Oncol* 2025; 11: 511-518.
- [15] Rios-Doria E, Abu-Rustum NR, Glaser G, McGree M, Eriksson AG, Pham M, Soliman P, Ataseven B, Alektiar K, Zamarin D, Leitao ML Jr and Mueller J. 2009 International Federation of Gynecology and Obstetrics (FIGO) stage IIIA endometrial cancer: oncologic outcomes based on involvement of adnexa, serosa, or both. *Int J Gynecol Cancer* 2024; 34: 1580-1587.
- [16] Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, Ledermann J, Bosse T, Chargari C, Fagotti A, Fotopoulou C, Gonzalez Martin A, Lax S, Lorusso D, Marth C, Morice P, Nout RA, O'Donnell D, Querleu D, Raspollini MR, Sehouli J, Sturdza A, Taylor A, Westermann A, Wimberger P, Colombo N, Planchamp F and Creutzberg CL. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer* 2021; 31: 12-39.
- [17] Printz C. PORTEC-3 trial finds that adjuvant chemoradiotherapy significantly improves 10-year survival for patients with high-risk endometrial cancer. *CA Cancer J Clin* 2026; 76: e70063.
- [18] Lee SS, Weil CR, Boyd LR, DeCesaris C, Gaffney D and Suneja G. Trends in use of radiation therapy, chemotherapy, and combination chemoradiotherapy in advanced uterine cancer before, during, and after GOG 258. *Int J Gynecol Cancer* 2023; 33: 1408-1418.
- [19] Fan M, Zhang W, Zhou Y, Li M, Wang D, Qiu K, Li M, Guo H and Yan L. A retrospective study on the analysis of influencing factors of neutropenia in endometrial cancer with adjuvant chemoradiotherapy. *Radiat Oncol* 2024; 19: 76.

- [20] Post CCB, de Boer SM, Powell ME, Mileskin L, Katsaros D, Bessette P, Leary A, Ottevanger PB, McCormack M, Khaw P, D'Amico R, Fyles A, Chargari C, Kitchener HC, Do V, Lissoni A, Provencher D, Genestie C, Nijman HW, Whitmarsh K, Jürgenliemk-Schulz IM, Feeney A, Lutgens LCHW, Bouma J, Leon-Castillo A, Nout RA, Putter H, Bosse T and Creutzberg CL. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): 10-year clinical outcomes and post-hoc analysis by molecular classification from a randomised phase 3 trial. *Lancet Oncol* 2025; 26: 1370-1381.
- [21] Kim HJ, Lee J, Lee KB, Sung K, Kim YB and Kim YS. Choosing the right adjuvant therapy for stage III-IVA endometrial cancer: a comparative analysis of chemoradiotherapy and chemotherapy. *Gynecol Oncol* 2024; 182: 39-44.
- [22] Cao SY, Fan Y, Zhang YF, Ruan JY, Mu Y and Li JK. Recurrence and survival of patients with stage III endometrial cancer after radical surgery followed by adjuvant chemo- or chemoradiotherapy: a systematic review and meta-analysis. *BMC Cancer* 2023; 23: 31.
- [23] Zhang BZ, Li Y, Xu LM, Chai YL, Qu C, Cao YJ, Wang J, Hou HL and Zhang J. The relationship between the radiation dose of pelvic-bone marrow and lymphocytic toxicity in concurrent chemoradiotherapy for cervical cancer. *Radiat Oncol* 2023; 18: 12.
- [24] Xie WH, Xiao WW, Chang H, Xu MJ, Hu YH, Zhou TC, Zhong Q, Chen CY, Lu LX, Wang QX, Zhu YJ, Yang J, Shi XY, Kang HL, Wei JW, Huang R, Peng HH, Yuan Y, Wu SH, Jiang XH, Liu YJ, Wen BX and Gao YH. Four cycles of docetaxel plus cisplatin as neoadjuvant chemotherapy followed by concurrent chemoradiotherapy in stage N2-3 nasopharyngeal carcinoma: phase 3 multicentre randomised controlled trial. *BMJ* 2025; 389: e081557.
- [25] Saito M, Tanabe H, Yamauchi K, Kuroda T, Takano H, Yamada K and Okamoto A. Evaluation of non-hematologic toxicity in patients with cervical cancer after Type 3 radical hysterectomy followed by concurrent chemoradiotherapy: a retrospective study. *Jpn J Clin Oncol* 2023; 53: 393-400.
- [26] Heinzerling JH, Mileham KF, Robinson MM, Symanowski JT, Induru RR, Brouse GM, Corso CD, Prabhu RS, Haggstrom DE, Moeller BJ, Bobo WE, Fasola CE, Thakkar VV, Pal SE, Gregory JM, Norek SL, Begic XJ, Kesarwala AH, Burri SH and Simone CB 2nd. Primary lung tumour stereotactic body radiotherapy followed by concurrent mediastinal chemoradiotherapy and adjuvant immunotherapy for locally advanced non-small-cell lung cancer: a multicentre, single-arm, phase 2 trial. *Lancet Oncol* 2025; 26: 85-97.
- [27] Chen M, Wang D, Bao Z, Yi Z, Mei Z, Sun S, Xiang Q, Yang C, Yang H, Qiu H and Xie C. The impact of bone marrow irradiation dose on acute haematologic toxicity in cervical cancer patients treated with concurrent chemoradiotherapy. *Radiat Oncol* 2023; 18: 66.
- [28] Zouzoulas D, Tsolakidis D, Sofianou I, Tzitzis P, Pervana S, Topalidou M, Timotheadou E and Grimbizis G. Molecular classification of endometrial cancer: impact on adjuvant treatment planning. *Cytojournal* 2024; 21: 47.
- [29] Ronchi S, Di Lauro E, Facco C, Raffone A, Fulgione C, Casarin J, Santoro A, Arciuolo D, Angelico G, Zannoni GF, La Rosa S and Travaglino A. Low-grade endometrial endometrioid carcinoma of the p53-abnormal group: case presentation and diagnostic issues. *Pathologica* 2024; 116: 320-323.
- [30] Clements A, Enserro D, Strickland KC, Previs R, Matei D, Mutch D, Powell M, Klopp A, Miller DS, Small W Jr, DiSilvestro P, Spirtos N, Cosgrove C, Sfakianos G, Liu JR, Vargas R, Shahin M, Corr B, Dessources K, Ueland F, Warshal D, Gillen J and Secord AA. Molecular classification of endometrial cancers (EC) and association with relapse-free survival (RFS) and overall survival (OS) outcomes: ancillary analysis of GOG-0258. *Gynecol Oncol* 2025; 193: 119-129.