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ORIGINAL RESEARCH

# Analysis of Prognostic Factors and Cancer-Specific Survival in Patients with Undifferentiated and Dedifferentiated Endometrial Carcinoma Undergoing Various Postoperative Adjuvant Therapies

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**Purpose:** To investigate prognostic factors affecting cancer-specific survival (CSS) and to analyze the survival outcomes of patients with undifferentiated and dedifferentiated endometrial carcinoma (UDEC) who underwent various postoperative adjuvant therapies.

**Methods:** The independent risk factors affecting CSS were studied using univariate and multivariate Cox regression analysis, and CSS in the presence of various postoperative treatments was evaluated using Kaplan-Meier method based on the cohort with pathologically confirmed UDEC from the Surveillance, Epidemiology, and End Results (SEER) database. Meanwhile, the study included 18 cases with UDEC in our center and explored their molecular characteristics and prognosis.

**Results:** Between 2000 and 2019, a total of 443 patients were included from the SEER database. The median CSS duration was 14 months, with corresponding 3- and 5-year CSS rates of 45.9% and 44.0%, respectively. Factors such as pTNM stage, surgical resection of primary lesion, and chemoradiation independently influenced CSS. Postoperative chemotherapy alone improved CSS in patients with initial tumor spread beyond the uterus (pT3 and pT4), or lymph node (LN) invasion, or distant metastases. Additionally, postoperative radiotherapy enhanced CSS in patients who had undergone postoperative chemotherapy, those with primary tumors progressing to stage pT3, and those with LN involvement but without distant metastases. Of the 18 patients diagnosed at our center, with a median follow-up of 15.5 months, one experienced relapse and two succumbed to UDEC, who exhibited aberrant p53 expression in immunohistochemical staining.

**Conclusion:** Postoperative chemotherapy and radiotherapy are beneficial for UDEC patients with tumors extending beyond the uterus or involving lymph nodes.

**Keywords:** undifferentiated and dedifferentiated endometrial carcinoma, cancer-specific survival, prognostic factors, postoperative adjuvant therapy

## Introduction

Endometrial carcinoma (EC), the second most common gynecologic malignancy, accounts for approximately 4.5% of all newly diagnosed cancers in women, with 417,367 new cases and 97,370 deaths worldwide in 2020.[1] Undifferentiated and dedifferentiated endometrial carcinoma (UDEC), representing approximately 1–9% in endometrial cancers, is described as a rare subtype of EC according to the WHO classification.[2–4] Undifferentiated endometrial carcinoma (UEC) is an endometrial neoplasm epithelial malignancy that histologically lacks any differentiating features and cannot be classified into any other histologic type, according to the 5th edition World Health Organization (WHO) classification of female genital tumors.[4] Dedifferentiated endometrial carcinoma (DEC) is a mixed carcinoma with undifferentiated components and well-differentiated carcinoma.[4]

UDEC is characterized by high aggressiveness and poor prognosis, with approximately 54% of patients being diagnosed with advanced-stage disease, and its 5-year overall survival (OS) rate ranging from 11% to 44%.[3,5–7] The



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deep location of UDEC in endometrium makes it difficult to be diagnosed by endometrial biopsy.[8] In addition, UDEC lacks specific pathologic features and immunohistochemical markers, making it more likely to be misdiagnosed as high-grade endometrioid adenocarcinoma, uterine endometrial stromal sarcoma (UESS), uterine neuroendocrine carcinoma (UNEC), or uterine carcinosarcoma (UCS).[2,9,10]

Currently, there is a lack of large-sample multicenter prospective studies on UDEC due to its rarity. The National Comprehensive Cancer Network (NCCN) guidelines recommend that the treatment of UDEC should refer to the treatment strategies for intermediate- and high-risk endometrioid adenocarcinoma.[5] However, the biological behavior and clinicopathological features of UDEC are quite different from those of endometrioid adenocarcinoma.[5,6,11] Consequently, no consensus has been reached on the treatment of UDEC, especially on postoperative adjuvant therapies, such as chemotherapy (ChT) and radiotherapy (RT).

The present study was to investigate the prognostic factors affecting cancer-specific survival (CSS) in UDEC and analyze survival outcomes for patients on different adjuvant therapies following surgery based on the Surveillance, Epidemiology, and End Results (SEER) database. Meanwhile, 18 patients with UDEC in our center were included in this study to analyze the clinical and immunohistochemical features of UDEC and to explore their potential roles in guiding treatment and determining prognosis.

# Methods

## Study Design and Data Extraction

The data used in the present study were retrieved from the SEER database (Incidence-SEER Research Plus Data, 17 Registries, Nov. 2021 Sub (2000–2019)), which covers approximately 35% of the US population, using SEER*Stat software (Version 8.4.1, www.seer.cancer.gov). The histology/behavior codes were 8020/3 and site codes were: C54.0-C54.3, C54.8-C54.9 and C55.9 according to the International Classification of Diseases of Oncology, Third Edition (ICD-O-3). Patients with newly histologically confirmed UDEC as the first primary tumor between January 2000 and December 2019, known survival months and cause of death were eligible. The patients diagnosed through autopsy or death certificates were excluded, along with those with non-UDEC causes of death or unknown causes of death, unknown American Joint Committee on Cancer (AJCC) stage, or survival time less than one month. Ultimately, a total of 443 women with UDEC were enrolled in this study. The data processing is shown in Figure 1.

The study was conducted in accordance with the Declaration of Helsinki (revised, 2013). The SEER database is publicly available, and review is not required by the Institutional Ethics Committee. The acquisition of the data for research purposes from the SEER program was approved by National Cancer Institute (reference number: 12,971-Nov 2022). The following variables were retrieved: patient's age, race, marital status, sequence number of multi-primary tumors, pathological tumor, node, metastasis (pTNM) stage, AJCC stage, tumor size, surgery of primary site, surgery of regional lymph nodes (LN), surgery of distant metastasis, chemotherapy, radiation, survival time, vital status, and cause of death. To control for bias and to reach valid conclusions, we did not incorporate variables with missing values in more than 20% patients, such as peritoneal cytology and tumor size, for which data were missing in 254 (57.3%) and 102 (23.1%) patients, respectively.

Meanwhile, the present study included 18 cases with pathologically confirmed UDEC at the First Affiliated Hospital with Nanjing Medical University from January 2018 to August 2023. The study was approved by the Ethical Committees of The First Affiliated Hospital with Nanjing Medical University (Nanjing, China) (approval number:2021-SR-239). Written informed consent was obtained from the patients involved in the study. The clinicopathological characteristics, treatment, and outcomes were extracted from the medical records. The immunohistochemical (IHC) results of estrogen receptor (ER), progesterone receptor (PR), Ki-67, p53, mismatch repair (MMR) proteins (MLH1, MSH2, MSH6, and PMS2) were also obtained. All tissue sections with IHC staining were reviewed by two senior pathologists. ER, PR, Ki-67, p53 expression was deemed positive if significant nuclear staining was seen. According to the Allred scoring system, the expression of ER and PR was defined as positive when the sum score of staining intensity of tumor cells and proportion of positive cells reached 3 or more, otherwise it was negative.[12] Ki-67 expression was depicted as the percentage of positive neoplastic cells out of total neoplastic cells.[13] The p53 expression was assessed as abnormal (p53abn) in the presence of intense and diffuse nuclear staining of 80–100% neoplastic cells, or a complete loss of

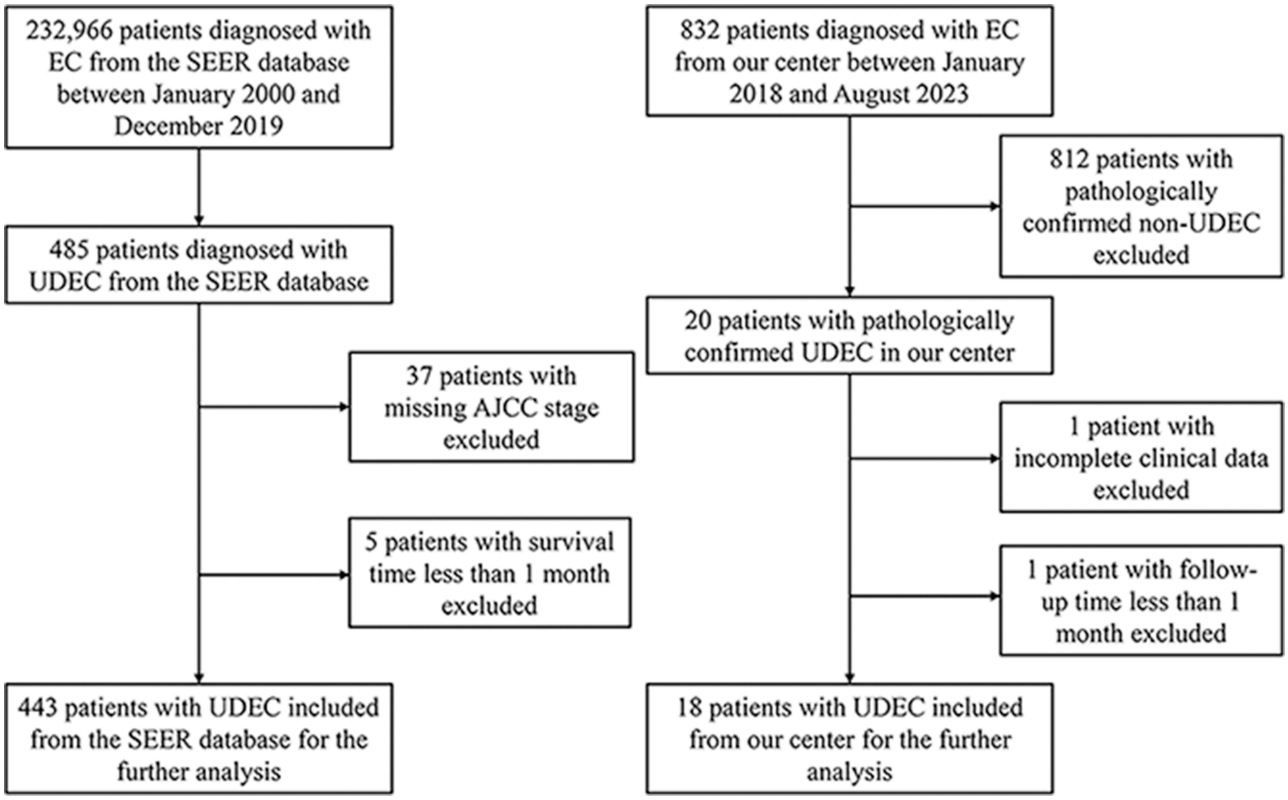


**Figure 1** Flowchart of data processing for this study.
**Abbreviations**: EC, endometrial carcinoma; UDEC, undifferentiated and dedifferentiated endometrial carcinoma; SEER, Surveillance, Epidemiology, and End Results; AJCC, American Joint Committee on Cancer.

nuclear staining, otherwise, it was defined normal (p53wt).[14] Mismatch repair proteins (MLH1, PMS2, MSH2, and MSH6) were considered negative when complete loss of nuclear staining presented or percentage of positive neoplastic cells was less than 1%. Negative expression for any of the four proteins was defined as MMR-deficient (MMRd), and all the other cases were considered as MMR-proficient (MMRp).[13,15]

## Statistical Analyses

Statistical analyses were performed with Statistical Product and Service Solutions (SPSS) Statistics Version 22.0 (IBM Corps., Armonk, NY, USA) and R software (https://www.r-project.org/, version 4.1.3). The R packages "survival" (version 3.5.0; https://CRAN.R-project.org/package=survival), "survminer" (version 0.4.8; https://CRAN.R-project.org/package=survminer), were employed for the analyses.[16,17] Quantitative variables were described by means ± standard deviations (SD) or medians with interquartile range (IQR). Discrete variables were depicted with frequencies and percentages. Missing data were specified. The prognostic factors affecting CSS were analyzed using univariate and multivariate Cox regression analysis. The survival analysis among different adjuvant treatments was performed by using the Kaplan-Meier method and Log rank test. Furthermore, we performed analyses on subgroups stratified by adjuvant RT, ChT, chemo-radiotherapy (CRT) or no adjuvant treatment (NAT) after surgery in combination with pTNM staging, to investigate the effect of adjuvant treatment on CSS for patients with different disease stages. Statistical differences were considered significant when two-sided P value was less than 0.05.

# Results

## Characteristics of Patients

A total of 485 UDEC patients diagnosed between January 2000 and December 2019 were initially included in this study from the SEER database. After excluding 37 cases with missing AJCC staging and 5 with survival time of less than 1

month, 443 UDEC patients were finally recruited. The baseline characteristics of the cohort are shown in Table 1. The median age at the time of diagnosis was 63 (IQR 57–72) years. And 288 (65.0%) patients were at an advanced stage when initially diagnosed: 145 (32.7%) at stage III and 143 (32.3%) at stage IV, compared with 155 (35.0%) at earlier

**Table 1** Demographic, Clinical and Treatment Features of the 443 Patients with UDEC

| Variable | n (%) (n=443) |
|---|---|
| **Year of diagnosis** | |
| 2000–2010 | 90 (20%) |
| 2010–2020 | 353 (80%) |
| **Age (years)[#]** | |
| Median [IQR] | 63 [57, 72] |
| **Race** | |
| White | 340 (77%) |
| Black | 49 (11%) |
| Other | 54 (12%) |
| **Multi-primary tumors** | |
| One primary only | 352 (79%) |
| 1st of 2 or more primaries | 91 (21%) |
| **Summary stage** | |
| Localized | 122 (28%) |
| Regional | 182 (41%) |
| Distant | 139 (31%) |
| **Stage T** | |
| T1 | 172 (39%) |
| T2 | 50 (11%) |
| T3 | 181 (41%) |
| T4 | 40 (9.0%) |
| **Stage N** | |
| N0 | 264 (60%) |
| N1 | 179 (40%) |
| **Stage M** | |
| M0 | 318 (72%) |
| M1 | 125 (28%) |
| **AJCC stage** | |
| I | 127 (29%) |
| II | 28 (6.3%) |

(*Continued*)

**Table 1** (Continued).

| Variable | n (%) (n=443) |
|---|---|
| III | 145 (33%) |
| IV | 143 (32%) |
| **Surgery of primary site** | |
| Yes | 390 (88%) |
| No | 53 (12%) |
| **Surgery of LNs** | |
| Yes | 303 (68%) |
| No | 140 (32%) |
| **Surgery of distant metastasis** | |
| Yes | 73 (16%) |
| No | 370 (84%) |
| **Treatment** | |
| NAT | 103 (23%) |
| CHT | 130 (29%) |
| RT | 65 (15%) |
| CRT | 145 (33%) |
| **Radiotherapy** | |
| Yes | 210 (47%) |
| No | 233 (53%) |
| **Chemotherapy** | |
| Yes | 275 (62%) |
| No | 168 (38%) |
| **Number of LNs examined#** | |
| Median [IQR] | 5 [0, 16] |
| **Number of positive LNs#** | |
| Median [IQR] | 0 [0, 1] |
| Missing | 69 (16%) |
| **Peritoneal cytology** | |
| Positive | 46 (10.4%) |
| Negative | 143 (32.3%) |
| Missing | 254 (57.3%) |
| **Tumor size (mm)#** | |
| Median [IQR] | 65 [40, 100] |
| Missing | 102 (23%) |

(*Continued*)

**Table 1** (Continued).

| Variable | n (%) (n=443) |
|---|---|
| **OS** | |
| Alive | 191 (43%) |
| Dead | 252 (57%) |
| **CSS** | |
| Alive | 223 (50%) |
| Cancer specific death | 220 (50%) |
| **Survival months (months)[#]** | |
| Median [IQR] | 14 [5, 51] |

**Notes**: [#]The variables were non-normally distributed.
**Abbreviations**: IQR, interquartile range; UDEC, undifferentiated and dedifferentiated endometrial carcinoma; Stage T, stage of primary tumor; Stage N, stage of lymph nodes; Stage M, stage of metastasis; AJCC, American Joint Committee on Cancer; LNs, lymph nodes; NAT, no adjuvant treatment; ChT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy; OS, overall survival; CSS, cancer-specific survival.

stages: 127 (28.7%) at stage I and 28 (6.3%) at stage II. Of all the 443 patients, 53 (12.0%) did not receive surgery, and 390 (88.0%) underwent surgery that comprised at least hysterectomy. Information on distant metastases was included for 353 patients diagnosed after 2010, with lung metastasis being the most common site (34/353), followed by metastases to the bone (16/353), liver (14/353) and brain (7/353). The median follow-up time was 14 (range: 1–249) months, and 220 (49.7%) individuals died because of UDEC. The median CSS time for the entire cohort was 14 months (IQR 5–51), with the 3- and 5-year CSS rates of 45.9% and 44.0%, respectively (Figure S1A).

## Prognostic Factors Affecting CSS in UDEC Patients

The prognostic factors affecting CSS in UDEC patients were explored using univariate and multivariate Cox regression analysis in the whole population (Table S1). Univariate Cox regression analysis revealed that a higher pTNM stage was associated with poorer CSS, while surgical resection of the primary lesion, surgical excision of lymph nodes, chemoradiation, and the presence of multiple primary malignancies other than UDEC improved CSS ($P < 0.05$). The above factors were further incorporated into multivariate Cox regression analysis, which showed that pTNM stage, surgical resection of the primary lesion, and CRT were independent prognostic factors affecting CSS in UDEC patients. Patients with greater TNM staging (hazard ratio [HR] = 2.43 for pT2, HR = 3.5 for pT3, and HR = 3.43 for pT4 vs pT1), pN1 (HR = 1.56 vs pN0), and pM1 (HR = 1.90 vs pM0) had a higher risk of cancer-specific death. Patients who underwent initial tumor excision or CRT had better CSS than those who did not, with HRs of 0.53 and 0.47, respectively. The independent predictors affecting CSS in patients with UDEC, and their HRs are visualized in a forest plot (Figure 2).

## CSS in the Presence of Various Adjuvant Treatments for UDEC Patients

The above findings showed that patients with UDEC had a significantly better prognosis if they had received surgical treatment (at least hysterectomy) and CRT. To further explore the potential survival benefits associated with the postoperative adjuvant therapy for patients with UDEC, the 390 individuals who had undergone at least hysterectomy were divided into the following groups based on the postoperative adjuvant treatment they received: NAT group (86 cases, 22.1%), ChT group (116 cases, 29.7%), RT group (58 cases, 6.4%), and CRT group (130 cases, 33.3%). The baseline characteristics of the four groups are shown in Table S2. The data were analyzed using the Kaplan-Meier curve and the Log rank test, which demonstrated significant variations in CSS across the four groups ($P < 0.001$). The further two-by-two comparisons revealed that postoperative adjuvant chemotherapy was associated with a decreased CSS,

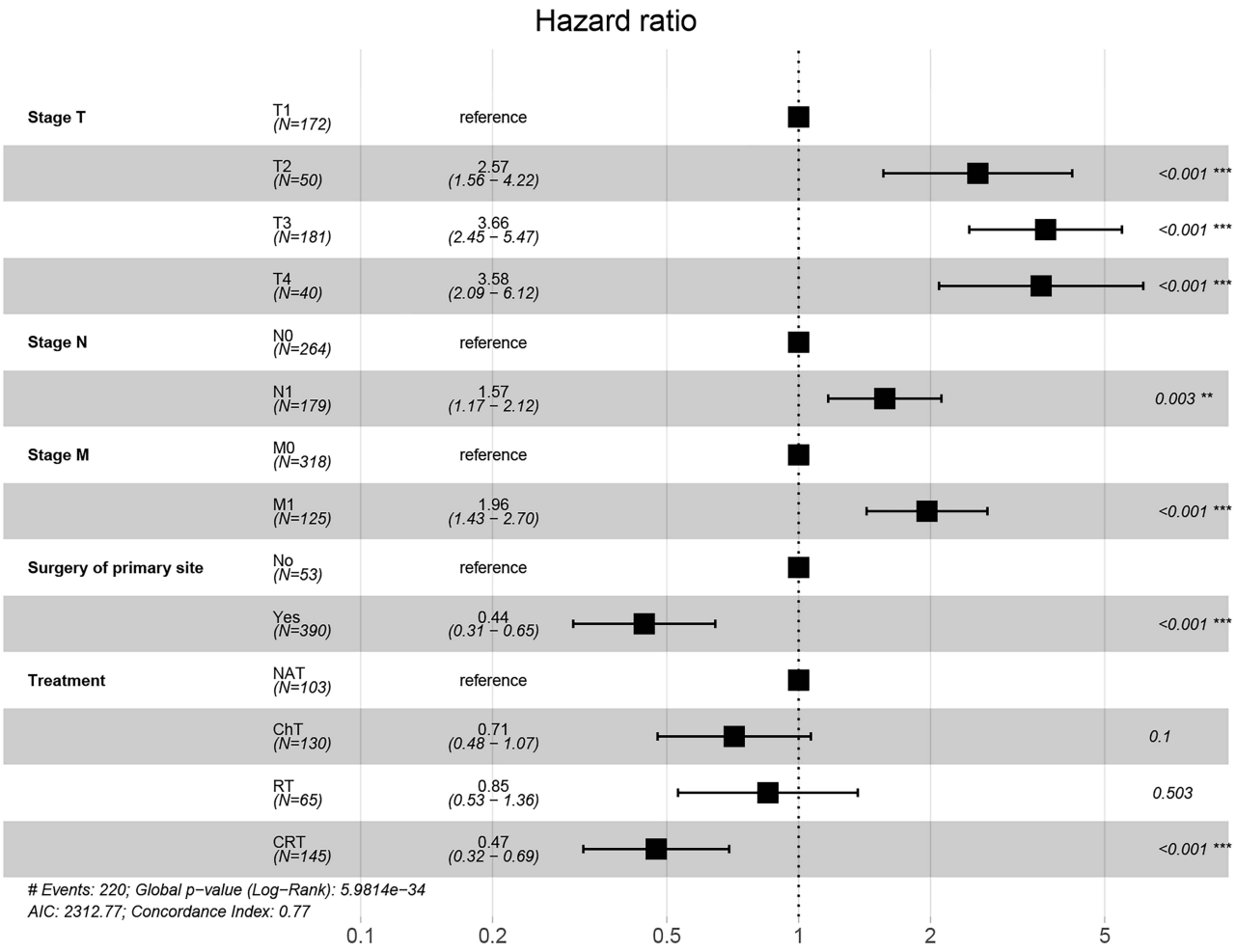


**Figure 2** Forest plot demonstrating independent factors for predicting CSS in UDEC patients with multivariate Cox regression analysis. **, P values < 0.01; ***, P values < 0.001. **Abbreviations**: CSS, cancer specific survival; UDEC, undifferentiated and dedifferentiated endometrial carcinoma; stage T, pathologic stage of primary tumor; stage N, pathologic stage of lymph nodes; stage M, pathologic stage of metastasis; NAT, no adjuvant treatment; ChT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

whereas postoperative RT and CRT improved CSS (Figure S1B). Subgroup analyses based on different AJCC stages were then performed to investigate whether the same effects of postoperative adjuvant treatment could be achieved in all patients. Due to the small number of patients at AJCC stages II and IV, the UDEC patients undergoing surgery were classified into the early-stage (AJCC stages I and II) group and the advanced-stage (AJCC stages III and IV) group. There was no difference in CSS among those with early-stage UDEC who received four different postoperative adjuvant treatments ($P$ = 0.19) (Figure 3A). Among the patients with advanced UDEC, those who underwent CRT exhibited superior CSS to those who had RT, ChT, and NAT ($P$ < 0.001), whereas no significant difference was observed among those who received RT, ChT, and NAT ($P$ = 0.81, $P$ = 0.58, respectively) (Figure 3B).

Subgroup analyses were further performed on primary tumors, LN involvement, and distant metastases in UDEC patients. The results demonstrated that none of the different postoperative adjuvant treatments exerted a significant effect on CSS in TanyN0M0 patients who underwent surgery at the primary site ($P$ = 0.083), indicating that when the tumor is confined to the pelvis with no LN involvement or distant metastasis, RT, ChT, and CRT do not improve the prognosis (Figure 4A). For TanyN1M0 patients who had undergone surgery at the primary site, CRT resulted in better CSS than RT or ChT alone ($P$ = 0.007) (Figure 4B). In TanyNanyM1 patients, CSS was better in those who received postoperative CRT or postoperative ChT only than in those who did not receive adjuvant therapy (both $P$ < 0.001). No statistically significant difference was found between individuals who received postoperative CRT and those who received ChT only ($P$ = 0.23), but those who received CRT tended to have improved CSS. Similarly, patients who received ChT after surgery were likely

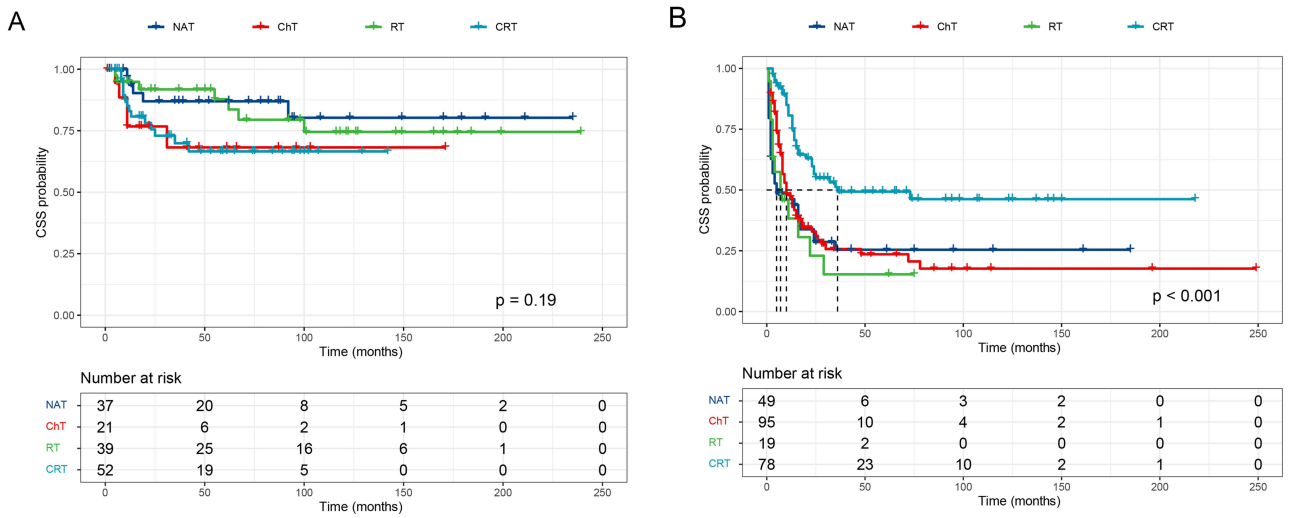


**Figure 3** Kaplan-Meier curves in patients with UDEC at different AJCC stages undergoing different postoperative adjuvant therapies. (**A**) No significant differences in CSS were identified among those with AJCC stages I and II who received four different postoperative adjuvant treatments (P = 0.19). (**B**) Patients treated with CRT had superior CSS to those treated with RT, ChT, and NAT following surgery in patients with AJCC stage III and IV (P < 0.001).

**Abbreviations**: UDEC, undifferentiated and dedifferentiated endometrial carcinoma; AJCC, American Joint Committee on Cancer; CSS, cancer specific survival; NAT, no adjuvant treatment; ChT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

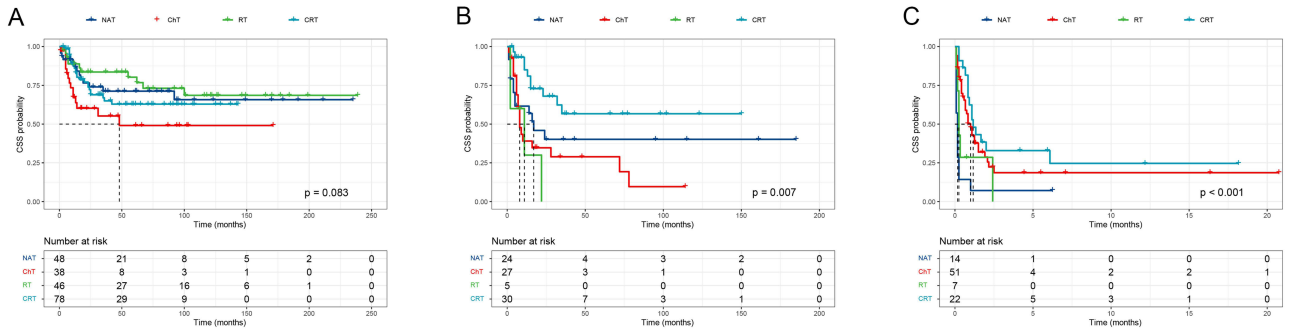


**Figure 4** Kaplan-Meier curves in patients with UDEC undergoing different postoperative adjuvant therapy at different TNM stage. (**A**) No significant differences in CSS were observed among different postoperative adjuvant therapies after surgery for patients at TanyN0M0 stage (P = 0.083). (**B**) The patients at TanyN1M0 stage showed better CSS with CRT than those with RT or ChT alone (P = 0.007). (**C**) CRT and ChT alone after surgery resulted in improved CSS compared to RT alone or NAT for patients with TanyNanyM1 stage (P < 0.001).

**Abbreviations**: UDEC, undifferentiated and dedifferentiated endometrial carcinoma; TNM stage, pathological tumor, node, metastasis stage; CSS, cancer specific survival; NAT, no adjuvant treatment; ChT, chemotherapy; RT, radiotherapy; CRT, chemoradiotherapy.

to have improved CSS compared to those who received RT alone, but this difference was not statistically significant ($P = 0.102$), which may be attributed to the small number of patients (only seven) who received RT alone (Figure 4C).

These findings imply that CRT can benefit UDEC patients with advanced disease, with LN involvement, or with distant metastases, but it is unclear who benefits from RT alone and who from ChT alone. Accordingly, we did a subgroup analysis for patients who underwent surgical resection of the primary tumor based on the type of post-operative adjuvant therapy they received. As demonstrated in Figure 5A, postoperative ChT alone improved CSS in patients with the primary tumor spread beyond the uterus (pT3, HR = 0.54, $P = 0.004$; pT4, HR = 0.35, $P = 0.033$), when they had lymph node invasion (pN1, HR = 0.64, $P = 0.044$), or distant metastases (pM1, HR = 0.31, $P < 0.001$). In contrast, CSS was worse in patients who did not undergo postoperative RT and instead received ChT alone (HR=1.53, $P = 0.036$). CSS was enhanced with the administration of postoperative RT in patients who underwent postoperative ChT (HR =0.41, $P < 0.001$) and when the primary tumor progressed to pT3 stage (HR = 0.52, $P = 0.002$), which was defined as the involvement of uterine plasma, adnexa, vagina, or parametrium, as well as LN involvement (HR = 0.50, $P = 0.003$)

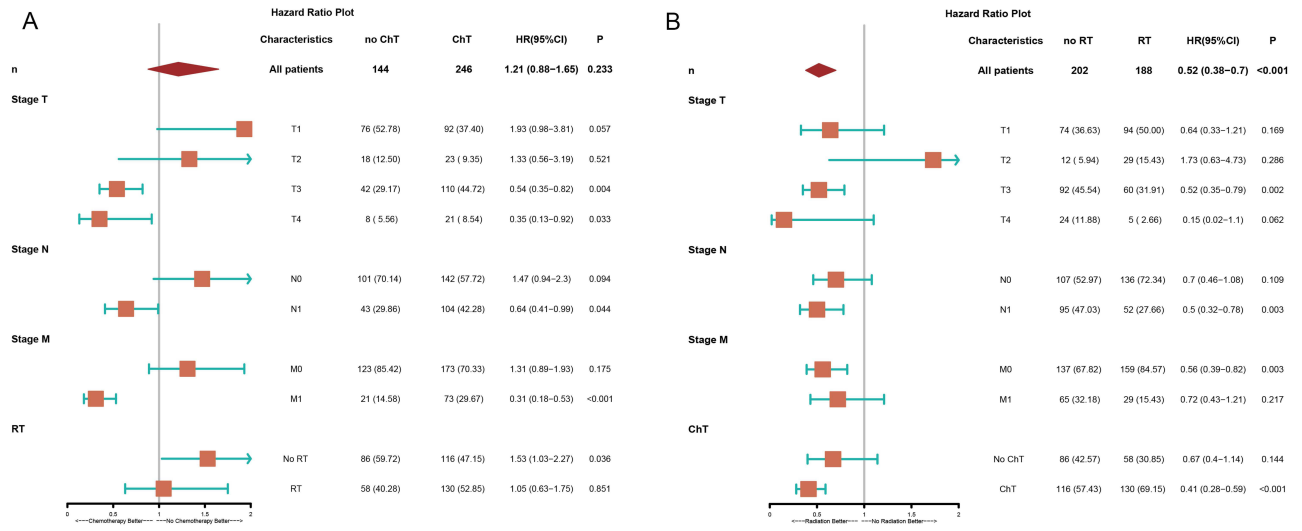


**Figure 5** Forest plot demonstrating the subgroup analysis for patients who underwent surgical resection of the primary tumor in the presence of adjuvant RT or ChT postoperatively based on different TNM stage. (**A**) Subgroup analysis for patients who underwent surgical resection of the primary tumor in the presence of adjuvant ChT postoperatively based on different TNM stage. (**B**) Subgroup analysis for patients who underwent surgical resection of the primary tumor in the presence of adjuvant RT postoperatively based on different TNM stage.

**Abbreviations**: RT, radiotherapy; ChT, chemotherapy; TNM stage, pathological tumor, node, metastasis stage; stage T, pathologic stage of primary tumor; stage N, pathologic stage of lymph nodes; stage M, pathologic stage of metastasis; HR, hazard ratio; CI, confidence interval.

without distant metastasis (HR = 0.56, $P = 0.003$) (Figure 5B). When the primary tumor was confined to uterus without LN metastases, neither postoperative RT nor ChT alone benefited CSS in these UDEC patients (Figure 5).

## Clinical, Pathological, and Molecular Characteristics for the UDEC Patients Diagnosed in Our Center

To attain precision treatment of EC, molecular classification, which involves *POLE* sequencing and immunohistochemical staining of MMR proteins (MLH1, MSH2, MSH6, and PMS2) and p53, has been incorporated into the WHO, NCCN, and European Society of Gynecological Oncology (ESGO) guidelines for risk stratification, treatment advice, and prognosis assessment.[4,5,18] However, the molecular classification of EC is currently unavailable in the SEER database. Therefore, in the present study, we also included 18 patients diagnosed with UDEC (including 3 UEC cases and 15 DEC cases) in our center between January 2018 and August 2023, representing 2.2% (18/832) of diagnosed EC cases in the same period, for further analysis. The clinical characteristics of these patients are shown in Table 2. IHC

**Table 2** Demographic Characteristics, Treatment and Outcome of 18 Patients with Pathologically Confirmed UDEC in Our Center

| Case | Diagnosis Year | Age (years) | Diagnosis | FIGO stage | Surgical Modality | Postoperative Adjuvant Treatment | DFS (Months) | CSS (Months) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 1 | 2018 | 43 | DEC | IIIC2 | TAH+BSO+PLA+PALA +OMX | ChT + EBRT | 6 | 9 | Died of disease |
| 2 | 2019 | 50 | DEC | II | TAH+BSO+PLA+PALA | ChT + EBRT | 51 | 51 | NED |
| 3 | 2019 | 54 | UEC | IA | TLH+BSO+PLA+PALA | ChT + VBT | 44 | 44 | NED |
| 4 | 2020 | 65 | DEC | IB | TLH+BSO+PLA+PALA | NA | 38 | 38 | NED |
| 5 | 2020 | 50 | UEC | IIIC2 | TLH+BSO+PLA+PALA | ChT + EBRT | 35 | 35 | NED |
| 6 | 2021 | 54 | DEC | IA | TLH+BSO+PLA+PALA | ChT + VBT | 29 | 29 | NED |
| 7 | 2021 | 54 | DEC | IIIA | TLH+BSO+PLA+PALA +OMX | ChT + EBRT | 26 | 26 | NED |
| 8 | 2021 | 43 | DEC | IVB | TAH+BSO+PLA+PALA +OMX+PAB | ChT + EBRT | 24 | 24 | NED |

(*Continued*)

**Table 2** (Continued).

| Case | Diagnosis Year | Age (years) | Diagnosis | FIGO stage | Surgical Modality | Postoperative Adjuvant Treatment | DFS (Months) | CSS (Months) | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| 9 | 2020 | 50 | DEC | IIIB | TAH+BSO+PLA+PALA +OMX | ChT | 1 | 3 | Died of disease |
| 10 | 2021 | 62 | DEC | IA | TAH+BSO+PLA+PALA | ChT + EBRT | 23 | 23 | NED |
| 11 | 2022 | 42 | UEC | IA | TLH+BSO+PLA+PALA +OMX | ChT + VBT | 17 | 17 | NED |
| 12 | 2022 | 56 | DEC | IB | TLH+BSO+PLA+PALA +OMX | ChT | 9 | 9 | NED |
| 13 | 2022 | 70 | DEC | IA | TLH+BSO+PLA+PALA +OMX | ChT | 9 | 9 | NED |
| 14 | 2022 | 56 | DEC | IA | TLH+BSO+PLA+PALA +OMX | ChT + VBT | 14 | 14 | NED |
| 15 | 2023 | 59 | DEC | IA | TLH+BSO+PLA+PALA +OMX | NA | 6 | 6 | NED |
| 16 | 2023 | 67 | DEC | IIIC1 | TAH+BSO+PLA+PALA +OMX | ChT | 1 | 5 | Recurrence |
| 17 | 2023 | 50 | DEC | IIIC1 | TAH+BSO+PLA+PALA | ChT + EBRT | 3 | 3 | NED |
| 18 | 2023 | 55 | DEC | IIIC2 | TAH+BSO+PLA+PALA +OMX | ChT + EBRT | 2 | 2 | NED |

**Notes**: As of August 2023, the median follow-up time of UDEC patients in our center was 15.5 (range: 2–51) months, the median CSS time was 15.5 months.
**Abbreviations**: UEC, undifferentiated endometrial carcinoma; DEC, dedifferentiated endometrial carcinoma; UDEC, undifferentiated and dedifferentiated endometrial carcinoma; FIGO, Federation International of Gynecology and Obstetrics; TAH, total abdominal hysterectomy; TLH, total laparoscopic hysterectomy; BSO, bilateral salpingo-oophorectomy; PLA, pelvic lymphadenectomy; PALA, para-aortic lymphadenectomy; OMX, omentectomy; ChT, chemotherapy; VBT, vaginal brachytherapy; EBRT, external beam radiotherapy; NA, not applicable; DFS, disease free survival; CSS, cancer-specific survival; NED, no evidence of disease.

analysis of the 18 UDCE patients revealed that 6 (33.3%) had p53wt and 12 (66.7%) had p53abn, 12 (66.7%) showed MMRp and 6 (33.3%) showed MMRd (Table 3). Of these six MMRd patients, one had a MSH6 loss, two had a PMS2 loss, and three had a simultaneous PMS2 and MLH1 loss. *POLE* sequencing is not yet available at our center. All 18

**Table 3** Immunohistochemical Staining Results of the 18 Patients with UDEC in Our Center

| Case | ER | PR | Ki-67 | P53 | MLH1 | MSH2 | MSH6 | PMS2 |
|---|---|---|---|---|---|---|---|---|
| 1 | + | + | 80% | MT | + | + | + | + |
| 2 | + | + | 90% | MT | + | + | + | + |
| 3 | - | - | 90% | WT | + | + | + | + |
| 4 | + | - | 30% | MT | + | + | + | + |
| 5 | - | - | 20% | MT | + | + | + | + |
| 6 | - | - | 50% | WT | - | + | + | - |
| 7 | + | + | 70% | WT | + | + | + | + |
| 8 | - | - | 80% | WT | + | + | + | + |
| 9 | - | - | 90% | MT | - | + | + | - |
| 10 | + | + | 80% | MT | + | + | + | + |
| 11 | - | - | 40% | MT | + | + | + | - |
| 12 | - | - | 90% | WT | - | + | + | - |
| 13 | - | - | 90% | MT | + | + | + | + |
| 14 | + | + | 90% | MT | + | + | + | - |
| 15 | + | + | 75% | WT | + | + | + | + |
| 16 | - | - | 90% | MT | + | + | + | + |
| 17 | - | - | 55% | MT | + | + | - | + |
| 18 | - | - | 80% | MT | + | + | + | + |

**Abbreviations**: UDEC, undifferentiated and dedifferentiated endometrial carcinoma; ER, estrogen receptor; PR, progesterone receptor; MT, mutant type; WT, wild type.

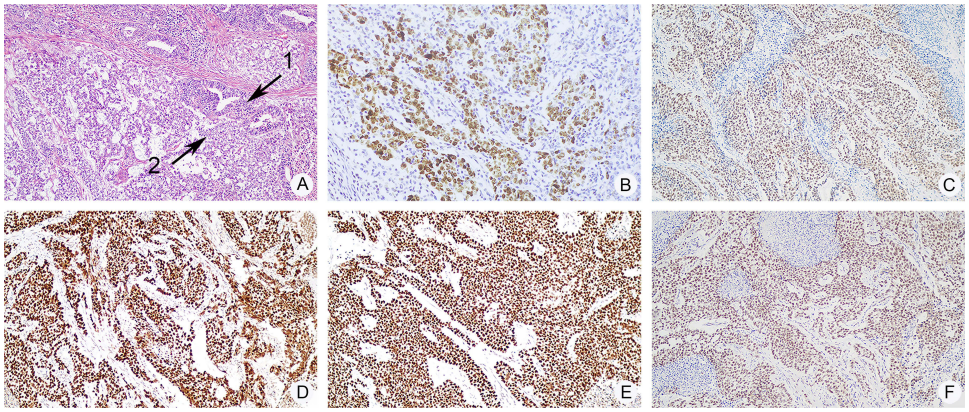


**Figure 6** Histologic morphology and immunohistochemical staining for case 16 with UDEC. (**A**) The undifferentiated component (black arrow 1) and the well-differentiated endometrioid component (black arrow 2) in DEC were well demarcated from each other, and the tumor cells in the undifferentiated component are pleomorphic with prominent nuclear features (HE, ×100); (**B**) Immunohistochemical staining for p53 demonstrates its positive expression in the undifferentiated component (IHC, ×200); (**C**) Immunohistochemical staining for MLH1 demonstrates its positive expression in undifferentiated component (IHC, ×100); (**D**) Immunohistochemical staining for MSH2 demonstrates its positive expression in the undifferentiated component (IHC, ×100); (**E**) Immunohistochemical staining for MSH6 demonstrates its positive expression in the undifferentiated component (IHC, ×100); (**F**) Immunohistochemical staining for PMS2 demonstrates its positive expression in the undifferentiated component (IHC, ×100).
**Note**: Abbreviations: UDEC, undifferentiated and dedifferentiated endometrial carcinoma; Dedifferentiated endometrial carcinoma; HE, hematoxylin-eosin staining; IHC, immunohistochemistry.

patients underwent surgery (including at least hysterectomy), and postoperative pathology results confirmed Federation International of Gynecology and Obstetrics (FIGO) stage I in 9 cases, stage II in 1 case, stage III in 7 cases, and stage IV in 1 case. Following surgery, 12 patients underwent CRT, 4 patients received ChT, and 2 patients did not receive adjuvant therapy due to personal considerations. Upon a median follow-up of 15.5 (range: 2–51) months, 1 FIGO stage IIIC1 patient (case 16) relapsed, 2 patients with FIGO stage IIIC2 (case 1) and IIIB (case 9), respectively, died of UDEC, and the remaining patients were free of tumors. Case 16 developed pelvic and inguinal lymph node metastases one month after surgery and is currently being treated with lenvatinib, panitumumab, and topotecan. She has achieved partial remission after three cycles according to the RESIST criteria. Case 1 experienced extensive intra-abdominal metastases six months after surgery and CRT, which resulted in intestinal obstruction and death, with an overall survival of 9 months. At one month following surgery, case 9 suffered severe tumor metastasis affecting the pubic mound, vagina, rectum, bladder, liver, adrenal glands, and both lungs, with an overall survival of three months. Case 1, case 9 and case 16 showed aberrant p53 expression on IHC staining. The clinical features of the UDEC cases reported from our center are comparable with those from the SEER database, implying that that UDEC is a rare subtype of EC with a low incidence, poor prognosis, and a highly heterogeneous molecular subtype. The histological morphology and immunohistochemical staining for case 16 are shown in Figure 6.

## Discussion

UDEC is a rare malignant tumor of the endometrium. Between January 2000 and December 2019, 485 people with UDEC were identified in the SEER database, accounting for 0.2% of the 232,966 patients with histopathology proven EC diagnosed during the same period. Of them, 443 were eligible for this study: 127 (28.7%) in stage I, 28 (6.3%) in stage II, 145 (32.7%) in stage III, and 143 (32.2%) in stage IV. On follow-up, the 3- and 5-year CSS rates were 45.9% and 44.0%, respectively, with a median survival duration of 14 months (IQR of 5–51 months). The study also included 18 patients with UDEC diagnosed at our center between 2018 and 2023. No UDEC cases were retrieved prior to 2018, which might be attributed to underdiagnosis in the past due to clinicians' insufficient attention to the biological behaviors and clinicopathological characteristics of UDEC. Therefore, clinicians need to place adequate emphasis on the diagnosis of the disease, which requires appropriate sampling of endometrial tissue, supported by IHC staining if necessary; otherwise, the condition can be missed or misdiagnosed as G3 EC, UESS, UNEC, or UCS.[2,19] Ganju et al[20] reported 24 cases of UEC, 10 (42%) of which were advanced at diagnosis. And 2 of them spread to uterine serosa or adnexa, 4 showed pelvic lymph node involvement, and 4 had distant metastases. During a median 14-month follow-up period, 4

relapses, 2 deaths from disease, and 1 death from a treatment-related complication occurred. According to a single-center retrospective cohort study from Canada including 52 patients with UDEC, the largest sample size to date, at a median follow-up of 17.5 months, 8 (58%) patients had local recurrence, 7 (14%) had regional LN recurrence, 15 (29%) had distant recurrence, and 20 (39%) died from the disease. The 5-year disease-free survival (DFS) rate was 80% for FIGO stages I/II, 29% for FIGO stage III, and 10% for FIGO stage IV.[7] The above findings are consistent with our current study, all showing that UDEC is extremely aggressive, usually in advanced stages when diagnosed, and exhibits a poor prognosis.

Using Cox proportional hazard modelling, we investigated the factors affecting UDEC prognosis. Univariate analysis found that a higher pTNM stage was associated with worse CSS, while primary tumor excision, LN dissection, CRT, and multiple primary tumors were favorable for CSS. The multivariate Cox regression analysis showed that only pTNM stage was an independent risk factor for CSS in UDEC patients. In a retrospective study of 53 patients with UDEC, Hamilton et al[7] reported that FIGO stage I/II, adjuvant ChT, adjuvant RT, and better Eastern Cooperative Group (ECOG) performance status were associated with improvement in disease-free survival (DFS), and adjuvant ChT and FIGO stage I/II were independent predictors of OS. AlHilli et al[3] analyzed 3313 UEC patients from the National Cancer Database (NCDB) and discovered that OS was independently affected by age, race, FIGO stage, and the existence of comorbidities. Among them, FIGO stage was the strongest predictor, with a more advanced stage suggesting a worse prognosis. The crucial effect of FIGO stage and postoperative adjuvant therapy on the prognosis of UDEC has been consistently confirmed by the present study.

Currently, there is no consensus on the type of postoperative adjuvant therapy for UDEC. NCCN guidelines recommend systemic treatment ± external irradiation radiotherapy ± vaginal brachytherapy for all FIGO staging patients following surgery because UDEC is a high-risk histologic subtype of EC.[5] According to ESGO guidelines, UDEC patients in stage IA without myometrial infiltration and lymph vascular space invasion (LVSI) are considered as the intermediate-risk group, and postoperative vaginal brachytherapy is recommended to decrease the risk of local recurrence, whereas those in stage IA with myometrial infiltration and those in stages II–IVA without residual lesions after surgery are of the high-risk group, and postoperative external pelvic irradiation combined with chemotherapy is recommended.[18] In this study, we compared the survival outcomes of four postoperative regimens (ChT, RT, CRT, and NAT) in 390 patients with UDEC who underwent surgery and found a significant difference in CSS. Our two-by-two analysis revealed that postoperative adjuvant chemotherapy resulted in decreased CSS, while postoperative RT and CRT improved CSS. Furthermore, subgroup analyses were carried out based on various AJCC stagings to identify the patients who would benefit from postoperative adjuvant therapy. It was found that only in AJCC stage III–IV, patients treated with CRT had superior CSS to those treated with RT, ChT, and NAT following surgery. According to AlHilli et al, patients with stage I, III, and IV UEC who received postoperative adjuvant therapy, including ChT, RT, and CRT, had improved OS at five years.[3] However, stage II patients did not benefit from postoperative adjuvant therapy. It was also found that compared to patients receiving ChT or RT only, those with stages III and IV who received postoperative CRT had better OS. Consequently, the findings regarding the efficacy of ChT for patients with UDEC are inconsistent. It is to be noted that the endpoint of the study was OS, which may be affected by other competing risk factors. Our study focused on UDEC-specific survival and provided a more precise assessment of the effect of postoperative adjuvant therapy on survival outcomes. Furthermore, we conducted subgroup analyses to investigate the effects of pTNM staging on survival outcomes resulting from different adjuvant treatments. There was no significant difference in the CSS of TanyN0M0 staged patients who received different adjuvant therapies after surgery, suggesting that RT, ChT, and CRT fail to improve the prognosis when the tumor is restricted to the pelvis without LN involvement and distant metastasis. Those with pTanyN1M0 stage disease who underwent CRT showed better CSS than those receiving RT or ChT alone, but it is noteworthy that only 5 cases in this population received RT alone. For patients with distant metastases or pTanyNanyM1 stage disease, CRT and ChT alone after surgery resulted in improved CSS compared to RT alone or no treatment at all. These findings imply that CRT can benefit UDEC patients with advanced disease, LN involvement, or distant metastases. To further illustrate which patient may benefit from postoperative ChT or RT, subgroup analyses were conducted and presented in forest plots. The results showed that postoperative ChT improved CSS for the patients with primary tumor beyond uterus (pT3 or pT4), or LN involvement (pN1), or distant metastasis (pM1). Patients who received only ChT without adjuvant RT after surgery had poorer CSS instead, possibly due to ChT-related toxicities. Postoperative RT

was associated with improved CSS in patients with stage pT3, lymph node involvement (pN1), or postoperative ChT. The efficacy of vaginal brachytherapy (VBT) and/or extracorporeal beam radiation (EBRT) was not studied separately because in the current investigation, only 5 and 7 patients in TanyN1M0 and TanyNanyM1 stages received RT alone, respectively. Therefore, patients with UDEC can only benefit from ChT when there are distant metastases, whereas CRT is beneficial for individuals with locally advanced disease, but without distant metastases, and patients at an early stage do not benefit from RT. Hamilton et al[7] also found that postoperative ChT enhanced OS in stage III and IV patients and that postoperative ChT and RT improved disease-free survival, ie, reduced recurrence. The SEER database lacks recurrence-related information. Of the 18 UDEC patients in our center, 12 received RT and 4 received ChT after surgery, except for 2 who did not receive adjuvant therapy for personal reasons. During the follow-up, two patients with FIGO stages IIIC2 and IIIB, respectively, died; one patient with FIGO stage IIIC1 experienced a recurrence and metastasis; the remaining patients were tumor-free and alive. Due to the small number of cases included, further studies are warranted to determine whether postoperative RT can reduce recurrence.

Molecular classification for EC, including The Cancer Genome Atlas (TCGA) and Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE), is increasingly widely used to guide postoperative adjuvant therapy and prognostic judgement.[4,5,18] In clinical practice, the most frequently used method for the molecular typing is IHC staining combined with POLE sequencing.[21] As POLE sequencing is not yet available at our center, the present study only explored the presence of p53abn and MMRd or not in our cases. Of the 3 UEC and 15 DEC patients, 6 (33.3%) displayed MMRd and 12 (66.7%) were MMRp, and 12 (66.7%) showed aberrant p53 expression and 6 (33.3%) were p53wt. Amongst the 12 cases with p53abn, 6 were diagnosed with FIGO stage I–II disease and 6 with stage III. The proportion of MMRd in our study was lower than that reported by Zhang et al (71.4%),[22] whereas p53abn rate was higher than that in recent studies (28.6–52%),[22,23] which could be attributed to the small cohort with different ratio of UEC component in the tumors and different FIGO stages in our study. It is also notable that the co-occurrence of dMMR and p53 aberrant expression were detected in case 9, 11, 14 and 17. These findings suggest that UDECs show multiple molecular profiles, as MMRd, p53abn and the two markers combined. In our study, *POLE* and PD-L1 were not tested with sequencing and IHC staining, respectively. A recently published meta-analysis by Travaglino et al demonstrated four The Cancer Genome Atlas (TCGA) subgroups were represented in UDEC, indicating a great biological heterogeneity in this histologic subtype.[24] Further study with more patients combining traditional clinicopathological features, TCGA molecular profiling and PD-L1 expression is warranted to accumulate evidence for prognostic stratification and tailored treatment of UDEC.

The present study, which include a relatively large number of UDEC patients from the SEER database, has identified factors affecting tumor-specific survival and performed multilevel subgroup analyses to determine the impact of different postoperative adjuvant therapies on survival outcomes, providing strong evidence for treatment decisions and prognosis. In addition, molecular typing heterogeneity among patients with UDEC has been confirmed by exploratory analyses of molecular profiles including p53 and MMR. Undoubtedly, the study has some limitations: First, it was a retrospective study, and there was bias in the clinical characteristics and sample size between the groups receiving different postoperative adjuvant treatments. Second, missing data in the SEER database, such as LVSI, ChT regimen, dose, and duration, might have led to bias in the effect of the variables on CSS. Third, due to the lack of data on disease recurrence and progression-free survival in the SEER database, as well as the small number of patients in our institution, research on recurrence of UDEC was limited in this study.

## Conclusions

The present study has demonstrated that UDEC is characterized by a low incidence but high aggressiveness and poor prognosis. pTNM stage, surgical resection of the primary lesion, and CRT after surgery are independent prognostic factors affecting CSS in UDEC patients. Patients with primary tumors outside of the uterus (pT3 or pT4), involvement of LNs (pN1), or distant metastases (pM1) are shown to benefit from postoperative CRT in terms of improved CSS. Further study with larger sample sizes from prospective multicenter studies is required to determine whether postoperative adjuvant therapy is beneficial for patients with early-stage UDEC.

## Data Sharing Statement

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

## Ethics Approval

The study was conducted in accordance with the Declaration of Helsinki (revised, 2013). The SEER database is an open public database, and therefore an institutional review board approval is not required. Since this retrospective study is based on public data available in the SEER database and no human subjects or personal privacy is involved, informed consent from patients is not required for this study. This study, which also involves 18 cases of undifferentiated and dedifferentiated endometrial carcinoma (UDEC) diagnosed in our center, is approved by the Ethics Committee of First Affiliated Hospital with Nanjing Medical University (No. 2021-SR-239).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

Youren Dai, Huiyun Wu and Jiahui Cao are co-first authors for this study. The authors have no relevant financial or non-financial interests to disclose for this work.

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