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ORIGINAL RESEARCH

The Clinicopathological Features and Prognoses of Lower Uterine Segment Cancer: A Retrospective, Single-Center Cohort Study

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Introduction: This study used single-center data to analyze the clinicopathological features of site-specific endometrial cancer.

Methods: Patients with endometrial carcinoma who had undergone surgery at Peking Union Medical College Hospital, China, between March 2016 and January 2022 were enrolled. Clinical information and pathological characteristics were summarized, and microsatellite status was analyzed using the immunohistochemical method. Patient prognoses were measured in terms of the rates of overall survival and progression-free survival.

Results: The mean patient age was 49 years (ranging: from 25 to 76 years old), and there was no difference in clinicopathological features between endometrioid and type II endometrial carcinoma in LUSC. The ER and PR expression ratios were 80.4% and 64.3%, respectively, in this LUSC cohort, and the MMR deficiency ratio was 33.9%, including 39.6% in endometrioid carcinoma and 15.4% in type II endometrial carcinoma. Combined MSH2&MSH6 loss was more common than combined MLH1&PMS2 being unexpressed (16.1% vs 12.5%), and dMMR patients differed significantly from the pMMR group in terms of vascular invasion (P=0.003). The combination of chemotherapy and radiotherapy did not provide a statistically significant improvement in prognosis compared to chemotherapy alone.

Conclusion: The results of this study showed that LUSC patients tended to be younger and their tumors had less expression of hormone markers. The biological behavior of both endometrioid cancer and type II EC may be similar when EC occurs in this area. Furthermore, this type of tumor also showed a higher incidence of vascular invasion, and the combination of chemotherapy and radiotherapy did not provide significant improvement. Thus, successful treatment of LUSC tumors requires aggressive surgical intervention and a more effective postoperative treatment approach.

Keywords: endometrial cancer, lower uterine segment, prognosis

Introduction

Endometrial cancer (EC) is a common type of cancer of the female reproductive system that accounts for about 2.2% of all cancer cases and over 1.0% of cancer deaths in women globally. Every year, an estimated 417,000 new cases of EC are diagnosed, and 97,000 women die from the disease.[1] The uterine endometrium can be anatomically divided into two regions: the mucosa of the lower uterine segment (isthmus) and the corpus mucosa proper. Depending on where the tumor is located in the uterus, EC can likewise be classified into two different types: uterine corpus endometrial carcinoma (UUEC) and lower uterine segment carcinoma (LUSC). Most cases of endometrial cancer originate from the uterine corpus proper, however. Any EC that originates in the lower uterine segment or extends from the lower uterine segment to the cervix is defined as LUSC. Since LUSC is located at the junction of the uterine body and the

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cervix, its glands and mesenchyme share histological characteristics of both anatomical areas. Therefore, the clinicopathological characteristics of LUSC may differ from those of UUEC.

In addition to the above classification, EC can also be classified as either type I or type II,[2] according to the Bokman system. Type I EC is estrogen-dependent, and type II EC is nonestrogen-dependent and has a worse prognosis than type I.[3,4] In addition, relevant reports have found that the likelihood of mismatch repair (MMR) gene mutations is higher in LUSC than in UUEC, and LUSC is especially susceptible to MSH2 mutations, suggesting that the molecular mutation profile is indeed quite different between UUEC and LUSC.[5,6] As a result, there is a 29% prevalence of Lynch syndrome among women diagnosed with LUSC tumors compared to a 1% to 2% prevalence in the general population. Thus, patients with LUSC can be classified as a high-risk group for Lynch syndrome.[7]

Previous studies on the differences between LUSC and UUEC have been small and have provided varying results. Furthermore, they fail to provide important information on treatment and prognosis (a literature review is summarized in Supplementary Table 1).[3–6,8–13] Thus, in order to gain a better understanding of this type of LUSC specifically we reviewed several cases of LUSC from a single center and analyzed their clinicopathological features and prognostic characteristics in an effort to provide insights into the treatment and needed research directions of this locus-specific EC.

Materials and Methods

Study Participants and Clinical Data

Patients with endometrial carcinoma who underwent surgery at Peking Union Medical College Hospital, China, between March, 2016 and January, 2022 were enrolled in this retrospective study. Those with an initial diagnosis of EC, surgical resection of the primary focus, and postoperative pathological testing that confirmed the diagnosis were screened, and only cases in which the primary tumor was located in the lower uterine segment or extended from the lower uterine segment to the cervix were included. Patients with uterine corpus involvement and those lacking complete follow-up data were excluded from the study. Patients with uterine corpus involvement and those lacking complete follow-up data were excluded from the study.

A total of 56 cases of EC were finally included, and the tumors were mainly located in the lower segment of the uterus. The observational indices of the study included: (1) clinicopathological data such as the patient's age, histological type, depth of tumor infiltration, vascular invasion, and lymph node metastasis; (2) gene mutation status; (3) surgical modality, follow-up, survival, and postoperative treatment; and (4) prognostic risk factor analysis, including disease progression-free survival (PFS) and overall survival (OS).

The patients were followed up with at intervals of 1 to 4 months according to the time between initial treatments, and the follow-up process included medical examinations and transvaginal ultrasound. To detect any disease progression (recurrence and/or metastasis), CT scans of the chest and abdomen were performed every 6 to 12 months. We recorded the patient's status for recurrent disease and survival until October 31, 2023, from which we calculated the overall survival (OS) and progression-free survival (PFS). OS was defined as the duration between the diagnosis date and the date of death from any cause, and PFS was defined as the duration between surgery and the date of disease progression. This study was approved by the Ethical Committee of Peking Union Medical College Hospital (Approved number: K2750).

Histological Analysis

The histology of the female genital tumors was determined based on the 2020 World Health Organization (WHO) Classification.[14] To ensure accuracy, two gynecological pathologists independently reviewed all histological specimens. In cases where the two physicians disagreed on the diagnosis, a third physician reviewed the specimen and cast the deciding vote. Each case of LUSC was surgically staged according to the International Federation of Gynecology and Obstetrics (FIGO 2009) staging system.[15] Pathological information was recorded including tumor grade, myometrial invasion, cervical involvement, lymph node metastasis, and distant metastasis.

Immunohistochemistry Analysis

Immunohistochemistry was performed on one representative block from the paraffin sections of each case. The following antibodies were used: MLH1 (ZM-0152; clone name OTI4H4; ZSGB-Bio); PMS2 (ZM-0407; clone name OTI4B2; ZSGB-Bio); MSH6 (ZA-0541; clone name EP49; ZSGB-Bio); MSH2 (ZA-0702; clone name OTIR1B12; ZSGB-Bio); P53 (ZM-0408; clone name DO-7; ZSGB-Bio); HNF1β (ZA-0129; clone name OTIR2E9; ZSGB-Bio); estrogen receptor (ER) (790–4325; clone name SP1; ROCHE); and progesterone receptor (PR) (790–4296; clone name 1E2; ROCHE). ER, PR, HNF1β, and MMR-related proteins (MLH1, PMS2, MSH6, and MSH2) were positively stained in the nucleus. Proficient mismatch repair (pMMR) was defined as expression of all four MMR proteins, and the loss of any of the MMR proteins was interpreted as deficient mismatch repair (dMMR). Here, the loss of MMR proteins was calculated as a complete loss of tumor nucleus staining for ≥1 protein in the presence of positive staining of the stromal or immune cells as normal control.

For p53 expression, there are wild-type expression and mutation-type expression. Wild-type staining is characterized by an admixture of negative cells and weakly and strongly positive cells that indicates the normal scenario of no TP53 mutation. Mutation-type p53 expression (associated with TP53 mutation) refers to overexpression (strong nuclear expression involving >80% of tumor cell nuclei), complete absence cell of expression in tumor cell nuclei with retained internal control, or unequivocal cytoplasmic expression.

Statistical Analysis

The OS and PFS rates were calculated using the Kaplan-Meier method and compared using the Log rank test. Additionally, the Cox proportional hazards regression model was used to assess the Hazard ratio of the prognosis. The survival curve was plotted using GraphPad Prism 8.0.1, and all statistical analysis was performed using SPSS 23.0. Relationships between different groups of LUSC were assessed using the *t*-test or Fisher exact test as appropriate, and all tests were two-tailed, with statistical significance defined as $P<0.05$.

Results

Patient Clinical Characteristics

A total of 56 cases with a diagnosis of lower uterine segment cancer (LUSC) were enrolled in this study. The mean age was 49 years old (range, 25–76 years; Table 1), including 20 (35.7%, 20/56) cases of postmenopausal women. All patients were admitted to the hospital due to either irregular vaginal bleeding (83.9%, 47/56) or having a suspected tumor in the cervix or endometrium (16.1%, 9/56). 53 patients (94.6%, 53/56) underwent staging surgery for EC with lymph node dissection, and 14 (26.4%, 14/53) of them had positive lymph node metastasis. According to 2023 FIGO stage criteria, 24 patients(42.9%, 24/56) were classified as stage I, 13 (23.2%, 13/56) were stage II, 16 (28.6%, 16/56) were stage III, and 3 (5.4%, 3/56) were stage IV, as shown in Table 1.

Table 1 Clinicopathological Characteristics of 56 Patients in This Study

	***LUSC*(n=56)**
Mean age (range), years	49 (25–76)
Postmenopausal	20 (35.7%)
FIGO stage	
I	24 (42.9%)
II	13 (23.2%)
III	16 (28.6%)
IV	3 (5.4%)

(*Continued*)

Table 1 (Continued).

	LUSC(n=56)
Tumor grade/histology	
Endometrioid	43 (76.8%)
G1	18/43 (41.9%)
G2	14/43 (32.6%)
G3	11/43 (25.6%)
Non-endometrioid	13 (23.3%)
Myometrial invasion	
<1/2	33 (58.9%)
≥1/2	23 (41.1%)
Cervical involvement	26 (46.4%)
Vascular invasion	26 (46.4%)
Lymphadenectomy	
Not done	3 (5.4%)
Performed	53 (94.7%)
Lymph node metastasis	14 (14/53, 26.4%)
Radiation therapy	38/56 (67.9%)
Chemotherapy	35/56 (62.5%)
Distant metastasis	1/56 (1.8%)
Median follow-up (range), months	48 (9–88)
Recurrence	4 (7.1%)
Death	2 (3.6%)

Pathological Findings

As shown in Tables 1 and 2, the main histology type of the LUSCs was endometrioid carcinoma (76.8%, 43/56). The tumor grades of endometrioid carcinoma consisted of 13 (30.2%, 13/43) cases of well-differentiated tumors, 16 (37.2%, 16/43) cases of moderately differentiated tumors, and 14 (32.6%, 14/43) cases of poorly differentiated tumors. There was

Table 2 Clinicopathological Characteristics of Patients by Types of Carcinoma

	Endometrioid carcinoma (n=43)	*Non-Endometrioid carcinoma (n=13)*	*P-value*
Mean age (range), years	49 (25–76)	53 (34–71)	0.178
Postmenopausal	12 (27.9%)	8 (61.5%)	0.027
FIGO stage			
I and II	30 (69.8%)	7 (53.8%)	0.288
III and IV	13 (30.2%)	6 (46.2%)	
Myometrial invasion			
<1/2	26 (60.5%)	7 (53.8%)	0.671
≥ 1/2	17 (39.5%)	6 (46.2%)	
MMR status			
dMMR	17 (39.5%)	2 (15.4%)	0.181
pMMR	26 (60.5%)	11 (84.6%)	
Cervical involvement			
Yes	20 (46.5%)	6 (46.2%)	0.982
No	23 (53.5%)	7 (53.8%)	
Vascular invasion			
Yes	20 (46.5%)	6 (46.2%)	0.982
No	23 (53.5%)	7 (53.8%)	

(*Continued*)

Table 2 (Continued).

	Endometrioid carcinoma (n=43)	*Non-Endometrioid carcinoma (n=13)*	*P-value*
Lymph node metastasis			
Yes	9 (9/40, 22.5%)	5 (5/13, 38.5%)	0.257
No	31 (31/40, 77.5%)	8 (8/13, 61.5%)	
Mean follow-up (range), months	52 (20–88)	47 (9–77)	0.424
OS	48 (20–88)	45 (9–77)	0.374
PFS	48 (7–88)	45 (9–77)	0.108

only one (2.3%, 1/43) case of endometrioid carcinoma that had a morphological MELF (microcystic, elongated, and fragmented) growth pattern, and it was a moderately differentiated stage II endometrioid carcinoma. Besides type I endometrioid carcinoma, there were 4 cases (30.8%, 4/13) of serous carcinomas, 3 (23.1%, 3/13) cases of clear cell carcinomas, 2 cases (15.4%, 2/13) of mixed-type carcinomas, 2 (15.4%, 2/13) cases of neuroendocrine carcinomas, 1 (7.7%, 1/13) case of undifferentiated carcinoma, and 1 (7.7%, 1/13) carcinosarcoma.

There were 26 (46.4%, 26/56) cases where a tumor extended from the lower uterine segment to the cervix, and the incidence of deep muscle infiltration was 41.1% (23/56). Moreover, 53 patients underwent lymphadenectomy, and the positive metastasis ratio was 26.4% (14/53). There was no significant difference in positive lymph node metastasis between endometrioid carcinoma (9/40, 22.5%) and type II endometrium carcinomas (5/13, 38.5%), and there was one case (1.8%, 1/56) that had distant metastasis upon surgical operation.

Regarding ER expression, 45 (80.4%, 45/56) cases showed a positive expression, and the rest had a negative staining pattern. In endometrioid carcinoma, 39 cases (90.7%, 39/43) showed positive expression, with 5 cases (12.8%, 5/39) showing a weak staining pattern (as shown in Figure 1). For type II ECs, there were 6 cases (46.2%, 6/13) that showed a positive pattern, including 3 cases of serous carcinomas, 2 cases of mixed-type carcinomas, and one case of neuroendocrine carcinoma. For PR expression; 36 (64.3%, 36/56) showed positive expression; and 20 cases (35.7%, 20/56) showed negative expression. In endometrioid carcinoma, 33 cases (76.7%, 33/43) showed positive PR expression, including 4 cases (12.1%, 4/33) with mild staining patterns. For type II ECs, 3 cases (23.1%, 3/13) showed positive PR

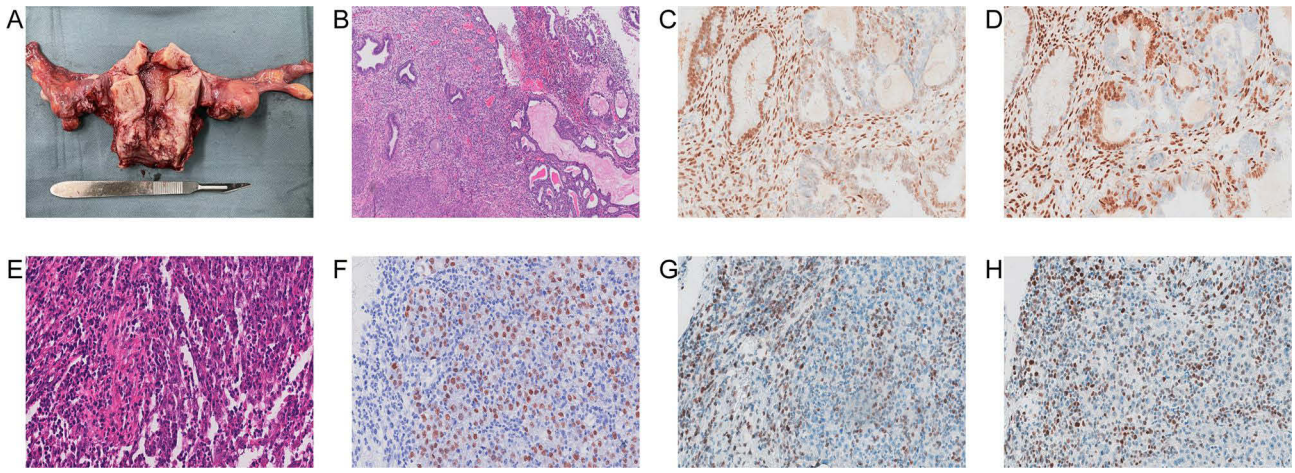

Figure 1 LUSC. (**A**) The anatomical morphology of the uterus. The anterior wall of the uterus was dissected and an ulcerated, bulging mass was seen in the lower segment of the uterus up to the cervical canal; (**B**) Endometrioid carcinoma in the lower segment of the uterus, with the cervical-uterine junction on the left side and endometrioid carcinoma infiltrating the fibrous mesenchymal stroma on the right side, 10×; (**C**) ER staining of LUSC, IHC method, 40×; (**D**) PR staining of LUSC by the IHC method, 40×; (**E**) The dMMR type of clear cell carcinoma HE image, 40×; (**F**) The specific marker HNF1β staining of clear cell carcinoma case, IHC method, 40×; (**G**) MSH2 negative in the clear cell carcinoma, cells with positive intranuclear control, IHC method, 40×; (**H**) MSH6 negative, cells with positive intranuclear control, IHC method, 40×.

expression, including two neuroendocrine and one serous carcinoma. There were 4 cases (9.3%, 4/43) that had an absence of both ER and PR expression in endometrioid carcinomas.

Regarding the p53 expression, the fraction of mutation-type p53 expression was 55.4% (31/56). Furthermore, out of 43 cases of endometrioid carcinoma, 21 cases (48.8%) showed a mutation-type p53 staining pattern. This included 4 cases with strong nuclear staining and 17 cases where the tumor cell nuclear expression was negative. For type II ECs, most of the cases (76.9%, 10/13) had mutation-type p53 expression, including 3 cases with strong nuclear staining and 7 cases with negative tumor expression and positive staining. The wild-type p53 expression cases of type II ECs consisted of two cases of clear cell tumors and one case of neuroendocrine carcinoma.

There was no association between endometrioid carcinoma and type II endometrium carcinomas with respect to their clinicopathological characteristics such as age, stage, myometrial invasion, vascular invasion, lymph node metastasis, and distant metastasis. A significant difference was identified between the different histology types of EC for menopause status, however. We found that postmenopausal patients were more likely to have type II endometrium carcinoma than premenopausal women (P = 0.027).

Expression of Mismatch Repair Proteins

In our cohort, there were 19 patients (33.9%, 19/56) who showed dMMR status, including 7(36.8%) cases with combined MLH1/PMS2 deficiency, and 9 cases (47.3%) with combined MSH2/MSH6 loss. There were 2 cases with isolated loss of PMS2 and one with a single loss of MSH6. Furthermore, MMR protein deficiency in endometrioid carcinomas was higher than in nonendometrioid carcinomas: the dMMR ratio was 39.5% (17/43) in the endometrioid carcinoma patients and 15.4% (2/13) in the nonendometrioid carcinoma patients.

The Association of MMR Status with Clinicopathologic Features

Patients with dMMR had a higher incidence of vascular invasion (P=0.003) than those with pMMR, and pMMR was more common in menopausal women than dMMR (P=0.039). However, there were no significant differences in other clinicopathological characteristics between the dMMR and pMMR groups. Specifically there were no differences in FIGO stage, endometrioid carcinoma grade, Bokman type, myometrial invasion, cervix involvement, lymph node metastasis, or distant metastasis (Table 3).

Table 3 Clinicopathological Characteristics of Patients by Expression of Mismatch Repair Protein

	dMMR (n=19)	*pMMR (n=37)*	*P-value*
Mean age (range), years	47 (32–68)	53 (25–76)	0.083
Postmenopausal	3 (15.8%)	17 (45.9%)	0.039
FIGO stage			
I and II	10 (52.6%)	27 (73.0%)	0.128
III and IV	9 (47.4%)	10 (27.0%)	
Endometrioid	17 (89.5%)	26 (70.3%)	0.181
G1	4 (23.5%)	9 (34.6%)	0.311
G2	5 (29.4%)	11 (42.3%)	
G3	8 (47.1%)	6 (23.1%)	
Non-endometrioid	2 (10.5%)	11 (29.7%)	0.181
Myometrial invasion			
<1/2	10 (52.6%)	23 (62.2%)	0.492
≥ 1/2	9 (47.4%)	14 (37.8%)	
Cervical involvement			
Yes	9 (47.4%)	17 (45.9%)	0.920
No	10 (52.6%)	20 (54.1%)	

(*Continued*)

Table 3 (Continued).

	dMMR (n=19)	*pMMR (n=37)*	*P-value*
Vascular invasion			
Yes	14 (73.7%)	12 (32.4%)	0.003
No	5 (26.3%)	25 (67.6%)	
Lymph node metastasis			
Yes	7 (41.2%)	7 (19.4%)	0.094
No	10 (58.8%)	29 (80.6%)	
Mean follow-up (range), months	49 (20–83)	52 (9–88)	0.651
OS	44 (20–83)	48 (9–88)	0.314
PFS	44 (20–83)	48 (7–88)	0.076

Treatment and Prognostic Analysis

After their operations, 46 patients (82.1%, 46/56) were treated with adjuvant therapy. There were 11 patients (19.6%, 11/56) who received radiation therapy alone, 8 patients (14.3%, 8/56) who received chemotherapy alone, and 27 patients (48.2%, 27/56) who received both radiation and chemotherapy. To analyze prognosis, we selected 53 patients who underwent both bilateral adnexectomy and lymph node dissection in order to eliminate the impact of surgical scope on patient prognosis. The median follow-up time for this cohort was 48 months (ranging: 9–88 months). During the follow-up period, two patients died, and three patients suffered recurrence. The median age of this cohort was 49 years old (range: 25–76 years). Details can be found in Table 1.

Of the 56 patients, 20 (35.7%) were postmenopausal and 36 (64.3%) were not. Additionally, 19 (33.9%) showed dMMR expression, while 37 (66.1%) showed pMMR expression. The 56 patients also suffered from several different stages of cancer: 24 (42.9%) were in stage I, 13 (23.2%) were in stage II, 16 (28.6%) were in stage III, and 3 (5.4%) were in stage IV. One patient was found to have distant metastasis. Based on the information above, the patients in this study were categorized into three subgroups for further analysis: the postmenopausal group, the stage I–III group, the pMMR group, and the nondistant metastasis group. In the menopausal group, chemotherapy alone had a better prognosis than combined radiotherapy and chemotherapy ($P<0.05$). In other groups, such as the nondistant metastasis group and the pMMR group, the prognosis of patients was slightly worse after combined radiotherapy and chemotherapy, but there was no statistically significant difference compared to radiotherapy alone, chemotherapy, or no adjuvant therapy. These results are depicted in Figure 2.

Discussion

The majority of EC is located in the uterine body or uterine fundus and tends to occur more frequently in postmenopausal women more than premenopausal women. The reported mean age at diagnosis of uterine EC is 65–75 years old.[16] Only 14% of ECs are diagnosed in pre-menopausal women, with only 5% occurring in women younger than 40 years. The mean age of LUSC in our cohort was 49 years (range 25–76 years), including 9 (9/56, 16.1%) patients younger than 40 years. Thus, our data indicate that LUSC tended to affect younger patients than uterine EC. Based on of the existing literature, the median age of LUSC cases is 52 years (range 39 to 62 years), which is similar to our result.[3–6,8–13] All the above data show that the lower segment of the uterus is a special anatomic site and that LUSC is more likely to occur in younger patients.

Type II EC, such as clear cell and serous carcinoma, is an invasive histology type with a worse prognosis than type I EC in general EC.[17] However, in our study, there was no significant difference in OS or PFS between the type I EC and type II EC groups (P = 0.374, 0.108; Table 2) of LUSC patients. These results suggest that the biological behavior of both endometrioid cancer and type II EC may be similar when EC occurs in the lower uterine segment. Since this was a small cohort and there were only a few patients who experienced recurrence or metastasis during the follow-up period, the prognostic characteristics of LUSC need to be further investigated with a larger sample.

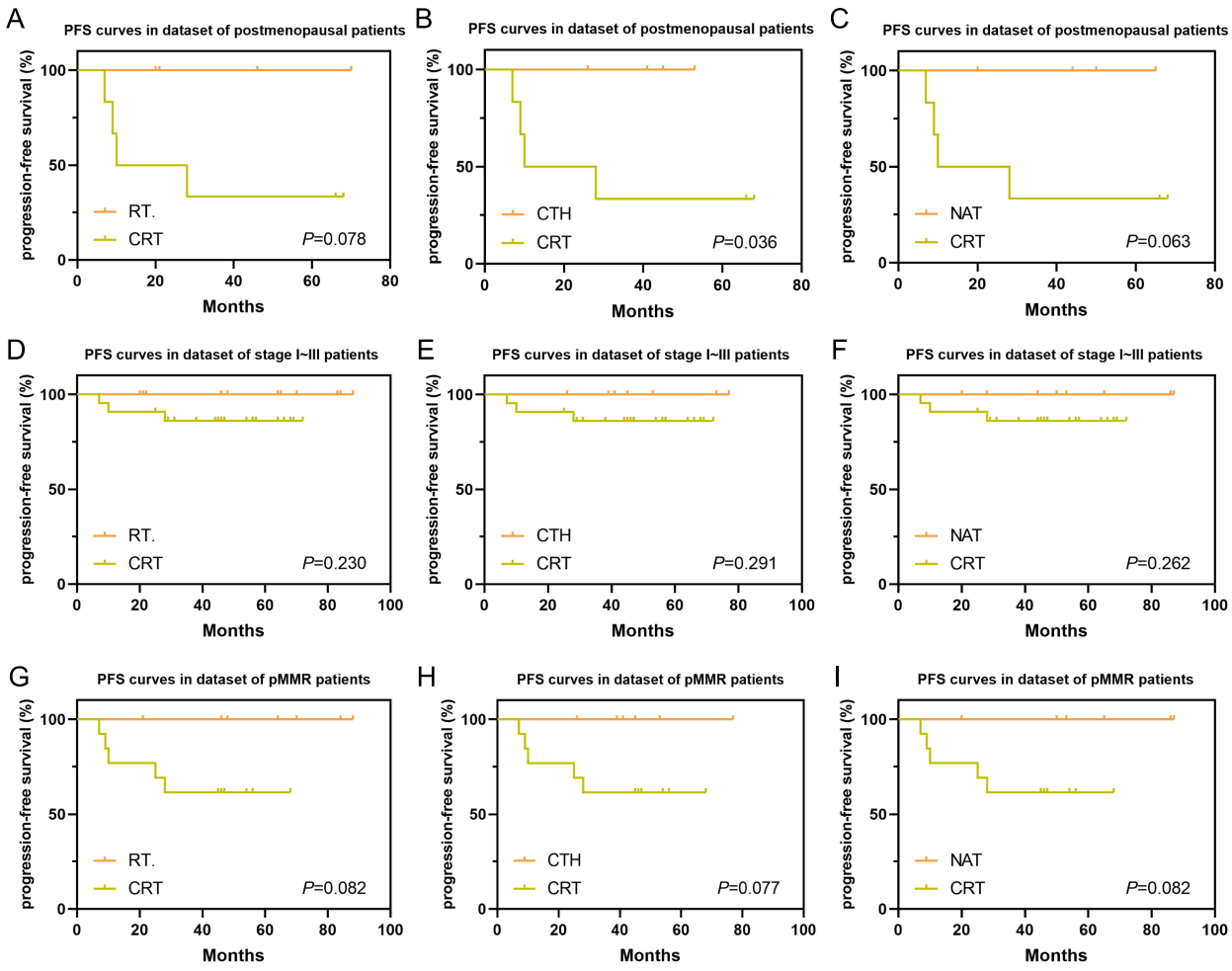

Figure 2 Analyses of Kaplan-Meier curves (Log rank test) for subgroup analyses under different treatment methods. (**A**) The statistical difference in progression-free survival between postmenopausal women receiving RT. alone or CRT (P = 0.078); (**B**) The statistical difference in progression-free survival between postmenopausal women who received CTH alone or CRT (P = 0.036); (**C**) The statistical difference in progression-free survival between postmenopausal women who did not receive postoperative treatment and those who received CRT (P = 0.063); (**D**) The statistical difference in progression-free survival between stage I to III patients receiving RT alone or CRT (P = 0.230); (**E**) The statistical difference in progression-free survival between stage I to III patients receiving CTH alone or CRT (P = 0.291); (**F**) The statistical difference in progression-free survival between stage I to III patients who did not receive postoperative treatment and those who received CRT (P = 0.262); (**G**) The statistical difference in progression-free survival between pMMR patients receiving RT alone or CRT (P = 0.082); (**H**) The statistical difference in the progression-free survival of pMMR receiving CTH alone or CRT (P = 0.077); (**I**) The statistical difference in progression-free survival between pMMR who did not receive postoperative treatment and those who received CRT (P = 0.082).

Abbreviations: CTH, Chemotherapy; RT., Radiotherapy; CRT, simultaneous chemoradiotherapy; NAT, No adjuvant therapy.

Endocrine treatment is an effective method of treating hormone-positive EC patients. Previous studies have demonstrated that the expression of PR is more relevant than ER in predicting the response to progestin treatment or combined estrogen and progestin treatment.[18] In our study, the immunohistochemistry results showed a low expression rate of ER and PR in LUSC. The PR positive ratio was found to be only 64.3% in LUSC, which is lower than the reported ratio of 80% in general EC.[19] Moreover, there is a report that shows a lower correlation (P<0.01) with endometrial hyperplasia in LUSC patients compared to UUSC patients.[10] These results suggest that the lower segment of the uterus corpus is a unique site that is less responsive to estrogen and progesterone compared to the upper uterine corpus. Hence, the biological behavior of both endometrioid cancer and type II EC may be similar when EC occurs in the lower uterine segment, thereby preventing the LUSC patients from benefiting from endocrine therapy.

Accumulating evidence suggests the potential use of novel biomarkers for early diagnosis and management of endometrial cancer.[20,21] MMR is a marker that is associated with the effectiveness of immune checkpoint inhibitors,[22] and the dMMR ratio has been found to be 16–17% in general EC patients.[23] In our cohort, we found a dMMR ratio of 33.9%

in the LUSC patients and an even higher ratio of 39.6% in the type I EC of the LUSC patients. This is consistent with Westin's findings from the largest LUSC cohort to date,[6] in which the unexpressed rate of MMR protein expression was about 34.3% (12/35). Additionally, several other reports have shown that the unexpressed rate of MMR protein expression in LUSC is about 37.3% to 54.5%, which is significantly higher than the unexpressed rate in overall EC cases.[4,13] This suggests that the EC at this particular site of LUSC may be more prone to defects in the DNA mismatch repair system than at other EC sites, which offers these site-specific EC patients an alternative choice in immunotherapy.

In the present study, patients with dMMR had a higher incidence of vascular invasion (p=0.003) than those with pMMR. Since dMMR ECs are more common in the lower uterine segment, and since they show a high likelihood of lymphovascular space invasion (LVSI), they typically require a sentinel or other nodal procedure.[24] Through the analysis of radiotherapy and chemotherapy information and the prognosis of 53 patients in the queue who underwent both bilateral adnexectomy and lymph node simultaneously, we found that the combination of chemotherapy and radiotherapy did not provide a statistically significant improvement compared to chemotherapy alone. In other subgroup analysis, patients who received combined radiotherapy and chemotherapy did not have any advantage in prognosis compared to other treatment methods either, even after excluding advanced patients. Thus, for tumors located in the LUSC, successful treatment requires both aggressive surgical intervention and an effective postoperative treatment method.

Another study has indicated that postoperative adjuvant therapy is not recommended for low-risk EC patients, including stage I and II POLE ultra-mutated patients, and stage I patients with dMMR without lymphovascular space invasion. However, for high-risk patients, combined chemoradiotherapy may be beneficial for prognosis.[25,26] Additionally, research has shown that dostarlimab monotherapy is beneficial for EC patients with dMMR/MSI-H, and clinical trials are underway to explore the combination of immunotherapy with chemotherapy.[27,28] Therefore, future research may further validate the role of combined chemoradiotherapy and immunotherapy in EC.

Our dMMR immunohistochemical results are not only an indication of therapy but also a clue to the association of LUSC with Lynch syndrome. In our cohort, the dMMR loss was composed of 12.5% double unexpressed MLH1&PMS2 and 16.1% double MSH2&MSH6 loss. This is consistent with the findings from the largest LUSC cohort study until now,[6] in which 75% (9/12) were MSH2&MSH6 unexpressed. Furthermore, the authors of that study reported that ten (29%) of 35 women with LUS tumors were confirmed to have Lynch syndrome or were strongly suspected to have Lynch syndrome based on tissue-based molecular assays. Five (14.2%) of these patients had germline MSH2 mutations, a much higher probability than for EC in general.[29] Unfortunately, we did not have the genetic information of somatic alteration for our patients. However, our results do indicate that it is worth investigating the direct relationship between LUSC and LS in the future.

There were still several limitations in our study. First, even though our study has now become the largest LUSC cohort to date, the available prognostic analysis data are relatively limited. We therefore aim to gather a larger volume of data from multiple centers for further validation in the future. Second, TCGA Molecular classification and germline testing for Lynch syndrome were not performed in this study. Subsequent studies could further investigate the direct relationship between LUSC and Lynch syndrome based on both TCGA and NGS results. Third, we only focused on LUSC patients in a single center, decreasing generalizability. Therefore, more prospective clinical studies with a larger patient sample size from multiple centers are needed in order to explore the clinicopathological features of LUSC more comprehensively. Additionally, we intend to continue to perform similar research in the future.

Conclusions

In this study, we aimed to describe the clinicopathological features of LUSC based on a relatively large sample size. The results showed that LUSC patients tended to be younger and that their tumors had less expression of hormone markers. Interestingly, the biological behavior of both endometrioid cancer and type II EC may be similar when EC occurs in the lower uterine segment. This type of tumor also showed a higher incidence of vascular invasion, and the combination of chemotherapy and radiotherapy did not provide significant improvement in prognosis compared to chemotherapy alone.

Patients with LUSC have a high occurrence of dMMR, which suggests that immunotherapy techniques may helpful for treatment. There is also a evidently a relationship between LUSC and Lynch syndrome. Thus, successful treatment of LUSC tumors requires aggressive surgical intervention and an effective postoperative treatment approach.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study has received approval from the Ethics Committee of Peking Union Medical College Hospital, approval number K2750. This study adheres to the principles outlined in the Declaration of Helsinki, ensuring the protection of patient privacy and confidentiality. All patient data used in this research has been anonymized, and no personal identifiers were included in the study. Informed consent was obtained from all participants prior to their inclusion in the study, in accordance with ethical standards and legal requirements.

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Disclosure

The authors declare no conflicts of interest in this work.

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