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Research Article

Characteristics of molecular classification in 52 endometrial cancer and atypical hyperplasia patients receiving fertility-sparing treatment

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ABSTRACT

Objective: To investigate the molecular classification of endometrial cancer (EC) and atypical endometrial hyperplasia (AEH) patients treated with fertility-sparing treatment (FST), and its relationship with clinicopathological factors and treatment efficacy. Methods: A total of 52 EC and AEH patients who received FST and molecular classification tested by next generation sequencing in Peking University People's Hospital from June 2020 to December 2022, were retrospectively collected. We analyzed the relationship between molecular classification and clinicopathological factors and treatment outcomes.

Results: (1) Of the 52 patients, including 46 EC and 6 AEH patients, 42 (80.8%) achieved complete remission (CR) after FST, with a median time to achieve CR of 9 months. Ten cases (23.8%) had recurrence. (2) Patients were distributed into 4 molecular subgroups as 39 cases (75%) of copy number low (CNL) , 7 cases (13.5%) of microsatellite instability-high (MSI-H) , 4 cases (7.7%) of POLE mutations (POLEmut), and 2 cases (3.8%) of copy number high (CNH). Patients with MSI-H subgroup had more family history of tumor (6/7), more with loss of expression of mismatch repair (MMR) protein (7/7), and higher expression level of Ki-67 (3/3). (3) Patients with MSI-H subgroup had the lowest CR rate at 6 months (0/7, $P = 0.014$), and survival analysis showed that such patients were less likely to achieve CR than those with CNL ($P = 0.022$). For CNL patients, median 6-month CR rate was 40.6%. In addition, CR was obtained in 3 (3/4) POLEmut patients and 2 (2/2) CNH patients, respectively.

Conclusions: Molecular classification relates with the treatment response in patients with EC and AEH receiving FST. Patients with MSI-H subgroup have poor treatment efficacy, and patients with CNL need to be further divided to predict treatment benefit. There are also a few successful cases in POLEmut and CNH subtgroups, which needs further research.

1. Introduction

With the increase of incidence of endometrial cancer (EC) in young patients and postponement of childbearing, more and more young EC patients are seeking fertility-sparing treatment (FST). Progesterone based FST has been proved a high remission rate of 72%~76% for early stage EC.[1] While 20%~41% of patients have tumor recurrence after complete remission (CR) and less than 50% patients experience long-term remission.[2] Therefore, it is important to explore biomarkers to predict treatment response and to select patients benefit most from FST.

Since the proposal of molecular classification of EC by The Cancer Genome Atlas (TCGA) in 2013,[3] it provides significant information for prognosis and individualized treatment for EC patients. For EC patients treated with FST, molecular classification can be obtained by testing curettage specimens. The results of the expression status of DNA mismatch repair (MMR) and p53 protein are highly consistent with those from hysterectomy specimen.[4,5] However, the significance of molecular classification in FST is not yet clear. In this study, we retrospectively analyzed the molecular classification and clinicopathological features of patients with early stage EC or atypical endometrial hyperplasia (AEH)

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undergoing FST. We also investigated the relationship between molecular classification and the efficacy of FST, so as to provide reference for the application of molecular classification in fertility-sparing therapy of EC and AEH.

2. Methods

2.1. Study population

Data were collected of early stage EC and AEH patients who received FST and conducted molecular typing by next-generation sequencing in Peking University People's Hospital from June 2020 to December 2022. Inclusion criteria was referred to the Chinese expert consensus on fertility-preserving treatment for young women with early stage well differentiated endometrial cancer (Chinese expert consensus for short),[6] (1) Pathological type of endometrioid cancer, G1～G2, or AEH. (2) Stage Ia and tumor confined to endometrium confirmed by imaging examination (magnetic resonance imaging as first choice). Patients with superficial myometrial invasion who had strong fertility-preserving willing, after fully evaluating and informed the risk of tumor progression and treatment failure, were also included. (3) No contraindications to progesterone therapy or pregnancy. (4) Patients had informed consent and good compliance for follow-up. A total of 52 patients, 46 EC and 6 AEH patients were included. Clinicopathological data were collected by searching the electronic medical record system of our hospital. This study was approved by the Biomedical Ethics Committee of Peking University People's Hospital (approval number: IRB00001052-19142). All patients were given informed consent.

2.2. Fertility-preserving treatment

Pre-treatment evaluation includes history collection, physical examination, pelvic enhanced MRI or ultrasound, hysteroscopic biopsy and pathological examination, as well as complication evaluation.

Treatment regimens: Continuous oral medroxyprogesterone acetate (MPA) 250–500 mg per day or megestrol acetate (MA) 160–320 mg per day as the first choice. If CR was not obtained after the first-line treatment, then second-line treatment can be selected: gonadotropin-releasing hormone agonist (GnRHa) 3.75 mg, subcutaneously injected, once every 28 days, and levonorgestrel-releasing system (LNG-IUS) continuous intrauterine placement. Patients who were not suitable for oral progesterone therapy were treated with LNG-IUS plus GnRHa.

2.3. Follow-up

Endometrial specimen was collected through hysteroscopy every 3 months during initial treatment. The pathological diagnosis was based on the 5th edition of WHO Classification of Female Genital Tumors.[7] Immunohistochemistry was used to detect the expression of estrogen receptor (ER), progesterone receptor (PR), mismatch repair (MMR) gene (including MLH1, PMS2, MSH2, MSH6 genes) related protein and Ki-67.

2.4. Efficacy evaluation

Treatment efficacy was referred to the expert consensus.[6] CR was defined as the absence of hyperplasia or carcinoma. Partial response (PR) was defined as pathological improvement. No response (NR) was defined as persistence of lesion as originally diagnosed. Progression of disease (PD) was defined as evidence of EC for AEH, or the upgrade or later stage for EC. Recurrence was defined as reappearance of EC or AEH after CR.

2.5. Molecular classification procedure

Pathological specimen was obtained by hysteroscopic resection or biopsy. The paraffin-embedded tissue sections with lesion more than 30% were selected, and 5–10 5 μ m-thick slices were taken to extract DNA. Polymerase chain reaction (PCR) was used to construct the sequencing library. Sequencing was carried out by Illumina (Miseq, illumina, USA), a high-throughput sequencer and data analyzed by the system purchased from Xiamen AmoyDx Biopharmaceutical Technology Co., Ltd.. Sequencing results were divided into four subgroups, according to the 2013 TCGA suggestion of molecular classification, as POLE mutations (POLEmut), microsatellite instability-high (MSI-H), copy number low (CNL) and copy number high (CNH). Classification process is as follows: (1) detect the mutation status of POLE gene, if POLE gene mutated then was classified as the POLEmut subgroup; (2) for POLE gene wildtype, then test MSI and was classified as MSI-H subgroup if MSI $\geq$0.4; (3) detect the mutation status of TP53 gene for patients with microsatellite stability and was identified as CNH subgroup, and no mutation was identified as CNL subgroup.

2.6. Post-treatment management

After completion of treatment, follow up was carried out every 3–6 months by ultrasound and hysteroscopy if necessary. Patients were followed up till December 2022, with a median follow-up period of 9 months (3–13.5 months). 52 patients were followed up for remission and recurrence. After CR, patients were suggested for maintenance treatment with cyclic low dose of progesterone or LNG-IUS for those with no temporary pregnancy plan. Otherwise, patients were recommended to reproductive medicine department and encouraged to conceive with or without active assisted reproduction technology (ART).

2.7. Statistical analysis

Statistical analyses are performed using SPSS 25.0 software. Continuous values are presented as medians or means and the intra-group differences are compared by Student's t-test or the Mann-Whitney *U* test. Categorical variables are presented as proportions (25th ～ 75th percentile) and frequency distributions are compared using Chi-squared test or Fisher's exact test. Cumulative CR rate and relapse free survival (RFS) rate are estimated by the Kaplan–Meier method and intergroup difference is compared by log-rank test. P value $<$ 0.05 in two-sided tests is regarded as significant.

3. Results

3.1. General information

Median age of 52 patients with EC or AEH was 33.1 $\pm$ 5.6 years old. Among them, 35 cases (67.3%) were nulliparous,14 cases (26.9%) were complicated with polycystic ovary syndrome (PCOS), 9 cases (17.3%) with diabetes, 7 cases (13.5%) with hypertension, 5 cases (9.6%) with thyroid disease, and 13 cases (25%) with family history of tumor.

Oral MPA or MA was given to 46 patients (88.5%) as the initial treatment regimen. Among them 1 patient received MPA plus chemotherapy because of intra-peritoneal metastasis during treatment. 20 patients changed to second-line regimen as LNG-IUS + GnRHa because of poor response to progesterone. Another 6 patients (11.5%) was given LNG-IUS + GnRHa as initial treatment because of BMI$\geq$28 kg/m^2. See Fig. 1.

Among the 52 patients treated with FST, CR was received in 42 patients (80.8%) with the median therapeutic time to CR 9 months (3–13.5 months), PR in 6 cases (11.5%), NR in 3 cases (5.8%), PD in 1 case (1.9%). During a median follow-up time of 9 months (4.5–13 months), 10 of the 42 patients (23.8%) with CR relapsed, and the median time to recurrence was 8 months (4–11.5 months). Three patients achieved pregnancy among 15 those with pregnancy intention after CR.

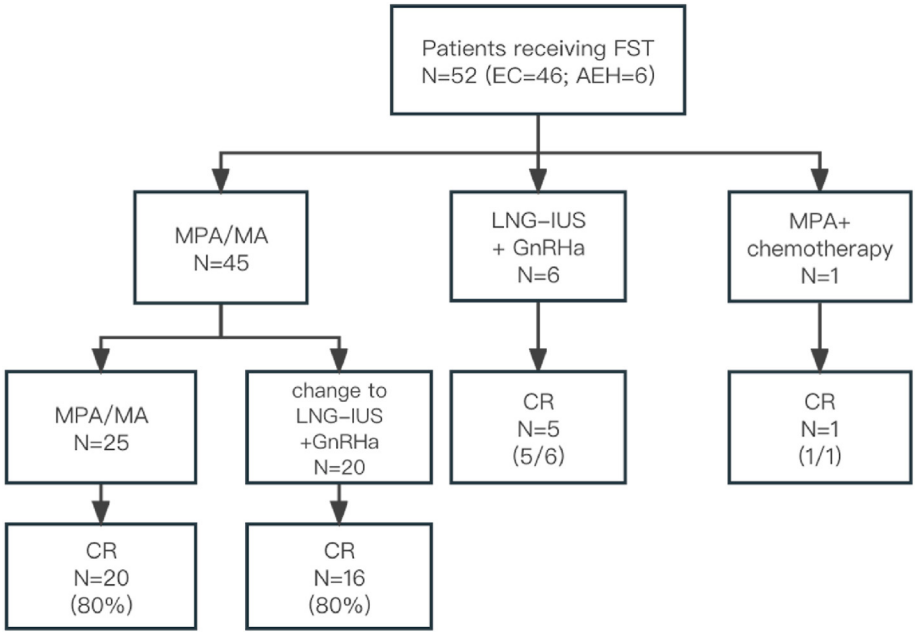

Fig. 1. Flow chat of 52 EC and AEH patients receiving fertility-sparing treatment
EC: endometrial cancer, AEH: atypical endometrial hyperplasia, MPA: medroxyprogesterone acetate, MA: megestrol acetate, LNG-IUS: levonorgestrel-releasing system, GnRHa: gonadotropin-releasing hormone agonist, CR: complete remission.

3.2. Comparison of clinicopathological characteristics among four molecular subgroups

CNL subgroup was the main molecular classification with a total of 39 cases (75%). Others included 7 cases (13.5%) with MSI-H, 4 cases (7.7%) with POLEmut, and 2 cases (3.8%) with CNH. Results are shown in Table 1. Patients with CNL subgroup seemed to be younger (32.1 ± 4.3 years) and have a higher body mass index (BMI) (27.8 ± 5.6 kg/m^2) but with no significant differences. Patients with CNH had the highest serum level of CA125 (34.3 ± 35.2kU/L, $P = 0.046$). And patients with MSI-H subgroup had more family history of tumor (6/7, $P = 0.001$). While waist-hip ratio, nulliparous, medical complications (PCOS, diabetes, thyroid disease, hypertension) showed no significant difference among the four molecular subgroups.

For pathological characteristics of the 52 patients, there was no significant difference in pathological type, depth of myometrial invasion, expression of ER and PR among the four molecular subgroups. While there was significant difference in the expression of MMR protein and Ki-67 in MSI-H patients. These patients all had negative expression of MMR protein (7/7), significantly higher than that in patients with other three molecular subgroups ($P = 0.000$). Also, they had significantly higher expression level of Ki-67 ($P = 0.009$). See Table 2.

3.3. Comparison of therapeutic effects of FST among the four molecular subgroups

Patients with MSI-H tended to have the lowest CR rate (3/7) among the four molecular subgroups ($P = 0.072$). They all failed to achieve CR within 6 months (7/7), with a significantly lower rate than the other three groups ($P = 0.014$). While there was no significant difference in time to CR and recurrence rate among 52 patients ($P = 0.072$, $P = 0.302$, respectively). See Table 3. Furthermore, cumulative CR rate and RFS rate were calculated by Kaplan-Meier method between the MSI-H and CNL subgroups (Fig. 2). Patients with MSI-H subgroup needed significant longer time to achieve CR than patients with CNL ($\chi^2 = 5.234$, $P = 0.022$). While there was no significant difference for the RFS between the two subgroups ($\chi^2 = 0.135$, $P = 0.714$).

For the 7 patients with MSI-H subgroup, 5 were diagnosed with Lynch Syndrome confirmed by MMR gene test. Immunochemistry of tumor specimen showed 4 cases of MSH2/MSH6 deficiency, and 3 of MLH1/PMS2 deficiency. Four of seven patients underwent staging operation including one case with NR after 14 months' treatment, one case with PD after 33 months' treatment, and two cases of disease recurrence. And the final surgical pathology showed three cases of stage Ia endometrioid cancer G1 (including 1 case of synchronous primary endometrial and

Table 1
Clinical characteristics of the 52 EC or AEH patients among the four molecular subgroups.

Variable	Total	POLEmut ($n = 4$)	MSI-H ($n = 7$)	CNL ($n = 39$)	CNH ($n = 2$)	*Statistic*	*P* value
Age at diagnosis (years, $\bar{x} \pm s$)	52	38.5 ± 7.0	34.6 ± 7.8	32.1 ± 4.3	35.5 ± 14.8	$F = 5.393$	0.145
BMI(kg/m^2, $\bar{x} \pm s$)	52	26.5 ± 5.3	24.0 ± 5.5	27.8 ± 5.6	23.9 ± 5.2	$F = 3.414$	0.332
WHR ($\bar{x} \pm s$)	52	0.88 ± 0.65	0.82 ± 0.08	0.86 ± 0.06	0.84 ± 0.15	$F = 1.603$	0.659
CA125 (kU/L, $\bar{x} \pm s$)	52	9.2 ± 2.3	23.7 ± 10.8	18.0 ± 8.5	34.3 ± 35.2	$F = 7.992$	0.046
Infertility, n (%)	35	2 (2/4)	6 (85.7)	26 (66.7)	1 (1/2)	$\chi^2 = 2.018$	0.569
Nulliparous, n (%)	44	3 (3/4)	7 (7/7)	33 (84.6)	1 (1/2)	$\chi^2 = 3.891$	0.273
PCOS, n (%)	13	1 (1/3)	1 (1/7)	10 (29)	1 (1/2)	$\chi^2 = 1.166$	0.761
Diabetes, n (%)	9	1 (1/4)	2 (2/7)	6 (15.4)	0 (0/2)	$\chi^2 = 1.554$	0.670
Thyroid disease, n (%)	5	1 (1/4)	0 (0/7)	4 (10.3)	0 (0/2)	$\chi^2 = 2.629$	0.452
Hypertension, n (%)	7	1 (1/4)	0 (0/7)	6 (15.4)	0 (0/2)	$\chi^2 = 3.101$	0.376
Family history of tumor n (%)	13	2 (2/4)	6 (6/7)	5 (12.8)	0 (0/2)	$\chi^2 = 17.325$	0.001

EC: endometrial cancer, AEH: atypical endometrial hyperplasia, POLEmut: POLE mutations; MSI-H: microsatellite instability-high, CNL: copy number low, CNH: copy number high, BMI: body mass index, WHR: waist-hip ratio, PCOS: polycystic ovary syndrome.

Table 2
Pathological characteristics of the 52 EC or AEH patients among the four molecular subgroups.

Variable	Total	POLEmut ($n = 4$)	MSI-H ($n = 7$)	CNL ($n = 39$)	CNH ($n = 2$)	*Statistic*	*P* value
Pathology, n (%)						$\chi^2 = 5.689$	0.459
AEH	6	1 (1/4)	1 (1/7)	4 (10.3)	0 (0/2)		
EC G_1	39	2 (2/4)	4 (4/7)	32 (82.1)	1 (1/2)		
EC G_2	7	1 (1/4)	2 (2/7)	3 (7.7)	1 (1/2)		
Depth of MI, n (%)						$\chi^2 = 2.104$	0.551
No MI	34	3 (3/4)	4 (4/7)	25 (64.1)	2 (2/2)		
Superficial MI	18	1 (1/4)	3 (3/7)	14 (35.9)	0 (0/2)		
ER, M(P_{25} ~ P_{75})	32	80 (70 ~ 90)	80 (60 ~ 90)	80 (70 ~ 90)	80 (80 ~ 80)	$H = 0.389$	0.942
PR, M(P_{25} ~ P_{75})	32	80 (70 ~ 90)	80 (30 ~ 85)	90 (80 ~ 90)	60 (30)	$H = 2.236$	0.525
MMR protein, n (%)						$\chi^2 = 41.087$	0.000
Negative	7	0 (0/4)	7 (7/7)	0 (0)	0 (0/2)		
Positive	45	4 (4/4)	0 (0/7)	39 (100)	2 (2/2)		
Ki-67, n (%)						$\chi^2 = 11.622$	0.009
> 40%	9	0 (0/4)	3 (3/3)	6 (26.1)	0 (0/2)		
≤40%	23	4 (4/4)	0 (0/3)	17 (73.9)	2 (2/2)		

EC: endometrial cancer, AEH: atypical endometrial hyperplasia, POLEmut: POLE mutations; MSI H: microsatellite instability-high, CNL: copy number low, CNH: copy number high, MI: myometrial invasion, ER: estrogen receptor, PR: progesterone receptor, MMR: mismatch repair.

Table 3
Therapeutic effects of FST of the 52 EC or AEH patients among the four molecular types.

Variable	Total	POLEmut ($n = 4$)	MSI-H ($n = 7$)	CNL ($n = 39$)	CNH ($n = 2$)	*Statistic*	*P* value
CR						$\chi^2 = 6.983$	0.072
Yes	42	3 (3/4)	3 (3/7)	34 (87.2)	2 (2/2)		
No	10	1 (1/4)	4 (4/7)	5 (12.8)	0 (0/2)		
Time to CR ≤ 6months, n (%)						$\chi^2 = 10.634$	0.014
Yes	16	1 (1/3)	0 (0/7)	13 (40.6)	2 (2/2)		
No	26	2 (2/3)	7 (7/7)	17 (59.4)	0 (0/2)		
Time to CR (months), $M(P_{25} \sim P_{75})$	46	7 (4)	12 (8)	9.5 (4.75 ~ 13)	7.5 (3)	$H = 1.726$	0.631
Recurrence, n (%)						$\chi^2 = 3.647$	0.302
Yes	10	1 (1/3)	2 (2/3)	7 (22.6)	0 (0/2)		
No	28	1 (1/3)	1 (1/3)	24 (77.4)	2 (2/2)		

EC: endometrial cancer, AEH: atypical endometrial hyperplasia, POLEmut: POLE mutations; MSI-H: microsatellite instability-high, CNL: copy number low, CNH: copy number high, CR: complete remission.

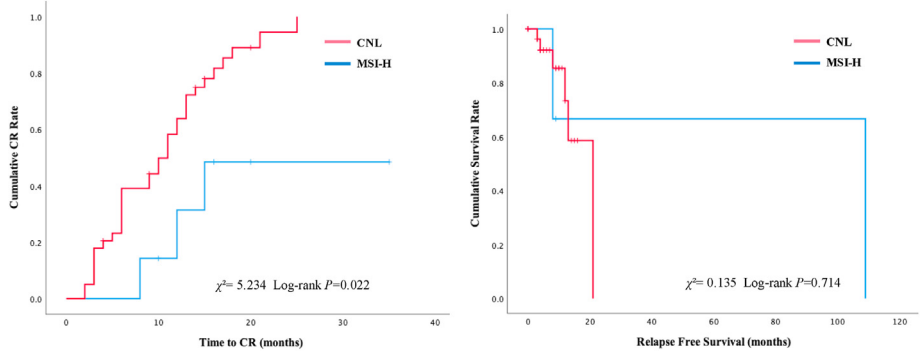

Fig. 2. A. Cumulative CR rates of the 46 EC or AEH patients between the MSI-H and CNL subgroups. B. Cumulative RFS of the 46 EC or AEH patients between the MSI-H and CNL subgroups. MSI-H: microsatellite instability-high, CNL: copy number low, CR: complete remission.

ovarian cancer, thus ovarian endometrioid cancer stage Ia G1) and 1 case of endometrial dedifferentiated cancer stage IIIc1. The other three patients showed one CR after 8 months' treatment, one PR after 20 months' treatment and one NR after 10 months' treatment. No successful pregnancy was achieved in the above 7 patients.

For the 4 patients with POLEmut subgroup, 3 patients achieved CR after 4, 7, 9 months' treatment, respectively. Another patient showed PR after 13 months' treatment. In particular, one patient was found with implantation metastasis of the left colonic sulcus by laparoscopic resection specimen after the initial conservative treatment. Although contradictory with the criteria for FST, she still had strong fertility-sparing willing. After multi-disciplinary team (MDT) discussion, a tentative regimen of paclitaxel plus carboplatin combined with MPA was given to her. The patients showed pathologically CR after 9 months' treatment and imaging showed no lesion residue. She was then given in vitro fertilization-embryo transfer (IVF-ET) and successfully gave full term birth. She was now still in close postpartum follow up.

The two patients with CNH subgroup both achieved CR after 3, 12 months' treatment. And one patient got pregnant by IVF-ET and was in 21 weeks gestational age at last follow-up.

4. Discussion

4.1. Characteristics of molecular classification of EC and AEH patients receiving FST

In recent years, molecular classification of EC has been carried out in young patients. Britton et al. used the proactive molecular risk classifier

for endometrial cancer (ProMisE) to retrospectively analyze 257 young patients with EC.[8] Results showed there were 48 cases (19%) of MMR deficiency (dMMR) type, 34 cases (13%) of POLEmut type, 164 cases (64%) of p53 wild type and 11 cases (4%) of p53 mutant type.[8] Another study for patients with low-grade endometrioid cancer, showed that most of the patients were p53 wild type (60%), dMMR type (29%), and a few were POLEmut type (6%) and p53 mutant type (5%).[3] As most of the young patients receiving FST are low-grade endometrioid cancer, most of them are CNL subgroup, which is consistent with the results of this study. However, patients with CNL showed different treatment responses to FST. It is necessary to combine molecular features with histopathological features for further stratification, so as to predict the real low-risk patients who can benefit from progesterone therapy.

4.2. Correlation between molecular classification and clinicopathological characteristics

There seems to be a correlation between molecular classifications and clinicopathological characteristics. In consistent with our finding, patients with CNL subgroup are the youngest and have the highest BMI, while dMMR and CNH subgroups relate with advanced stage (stage III~IV), a high risk and chemotherapy.[8] This may be attributed to that most of the patients with CNL subgroup often combined with metabolic syndrome such as obesity and diabetes and tumorigenesis is usually estrogen-dependent. Due to related with hyperstimulation of estrogen, it is reasonable to presume that patients with CNL may benefit most from progesterone therapy. Britton's study also showed that obese patients of p53 wild type and of POLEmut type had better oncologic prognosis.[8]

In this study, the seven patients with MSI-H subgroup showed loss of expression of MSH2/MSH6 in 4 cases and loss of MLH1/PMS2 in 3 cases, which was consistent with literature.[9] MSI-H subgroup was considered as moderate prognosis, but it is usually associated with adverse pathological factors in young patients. This study showed that compared with the CNL subgroup, patients with MSI-H had lower BMI, more with family history of tumor and higher expression level of Ki67. Literature also shows that patients with MSI-H type usually presents with lower BMI,[10] lower origin of uterine cavity, higher grade, and lower expression of ER and PR than patients with MMR-proficient.[11] Tumors usually show the characteristics of MSI, including lymphocyte infiltration, undifferentiated or dedifferentiated pathological types.[9] The above adverse pathological factors may be the reason for the poor response to progesterone therapy in patients with MSI-H subgroup.

4.3. Influence of different molecular subgroups on the efficacy of FST

MSI-H subgroup takes 19% of young EC patients. We found none of the 7 patients with MSI-H subgroup got CR within 6 months' treatment. Survival analysis showed that these patients needed longer treatment time to CR than the CNL subgroup. Patients with MSI-H showed a poor response to FST, which was consistent with literature.[9,12] A retrospective analysis by Zakhour et al.[13] showed that for the 84 patients with EC and AEH who received FST, 6 patients (7%) were dMMR patients, and the CR rate was significantly lower than that of non-dMMR patients (0 vs. 53%; $P = 0.028$). Recently, a retrospective study from Korea showed that the response rate to progesterone therapy in patients with dMMR was significantly lower than that in patients with p53 wild type.[14] Burleigh et al. retrospectively analyzed 56 patients under 40 years old, 9 (16%) of them had dMMR who had significantly poorer total survival ($P = 0.028$) and relapse-free survival ($P = 0.042$).[15] Based on the above adverse pathological risk factors, poor progesterone response, poor prognosis, and the increased risk of epithelial ovarian cancer in patients with Lynch syndrome, we suggest that EC or AEH patients with MSI-H subgroup are not suitable for FST. If the patient insists on fertility preserving, the risk of treatment failure should be thoroughly informed and closely monitor taken during treatment.

Patients with CNL subgroup usually have a high expression of ER and PR, which is considered to be an independent risk factor for the prognosis of EC. However, not all patients of this type have a good response to progesterone. In this study, the 6 month CR rate of CNL patients was only 40.6%. Since most of the patients treated with FST are CNL subgroups. It is necessary to further stratify this subgroup to precisely predict treatment response. Some studies have shown that ProMisE molecular classification can be further stratified by combining more biomarkers. For patients with CNL subgroup, mutation of c-terminal cyclin D1 (CCND1), mutation of CTNNB1 gene, amplification of 1q32.1, overexpression of L1 cell adhesion molecule (L1CAM), loss of ER and PR expression and high DNA damage are all identified as markers associated with poor prognosis,[16–20] which indicates that it is possible to make further molecular stratification for the CNL subgroup. Another study combined molecular typing with clinicopathological features which might be a more detailed stratification for EC patients. A total of 614 patients were divided into three groups: patients with substantial lymphovascular space invasion, p53-mutant, and/or >10% L1CAM are defined as group of unfavorable prognosis (15%), patients with POLEmut, no specific molecular profile (NSMP) being microsatellite stable, and CTNNB1 wild-type are defined as favorable prognosis (50%), while patients with MSI or CTNNB1-mutant are defined as intermediate prognosis (35%).[21] This stratification method may be more effective in selecting candidates of EC patients for fertility preserving.

Patients with POLEmut have the best oncologic prognosis and may not be affected by adjuvant therapy[22] which suggests this group may benefit from conservative treatment. Among the 4 POLEmut patients in this study, one EC patient with intraperitoneal implantation metastasis achieved CR after a regimen of chemotherapy plus hormone therapy and gave live birth, but its long-term prognosis still needs further follow-up. For patients with POLEmut, whether the indications of FST can be expanded is worth further study.

On the contrary, patients with CNH subgroup have the worst prognosis with a high risk of recurrence and total survival, and is not supposed to be treated conservatively.[23] However, two patients with CNH subgroup in this study received FST with GnRHa plus LNG-IUS regimen and oral MPA regimen, respectively, and both of them achieve CR, one of them got pregnancy. Therefore, for patients with CNH subgroup, FST might not be the contraindication. But only if they have a high compliance and follow-up condition, could the fertility-preserving treatment be carefully carried out.

This was the first report of molecular classification among EC and AEH patients receiving FST in China. While this study used the TCGA strategy for molecular classification and the method of next generation sequencing is inconvenient in application. In the future, an alternative way like PromisE by testing mutation of POLE gene combined with immunohistochemistry of MMR/p53 protein might be cost-effective and easy popularization. Second, risk factors for treatment response among the CNL patients need to be further studied. Furthermore, there were limited cases for the other three molecular subgroups other than the CNL subgroup. And the findings in this study still needs large-sample research to confirm.

5. Conclusion

In summary, molecular classification is significant for indicating prognosis and progesterone response for EC and AEH patients receiving FST. Based on molecular characteristics, it's reasonable to identify patients who can benefit most from FST. Patients with MSI-H subgroup have poor response to FST and take a high risk of tumor recurrence and hysterectomy, so fertility preservation is not recommended. Patients with CNL subgroup need a more detailed stratified classification by possibly combining the clinicopathological and molecular features. For patients with POLEmut subgroup we might consider broader indications for FST. And there are a few successful cases of fertility preservation for patients

with CNH subgroup under strictly monitor. We look forward to further researches of large sample size to accumulate experience on molecular classification shedding light on the fertility-sparing treatment of EC and AEH.

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Ethics approval

This study was approved by the Biomedical Ethics Committee of Peking University People's Hospital (approval number: IRB00001052-19142).

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Declaration of competing interest

All authors declare no conflict of interest.

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