



Review Article

The prognostic implication of polymerase epsilon-mutated endometrial cancer

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Submission : 14-May-2024
Revision : 22-Jul-2024
Acceptance : 09-Aug-2024
Web Publication : 17-Sep-2024

ABSTRACT

The traditional classification and risk stratification systems of endometrial cancer (EC), which relied on histomorphological features, were limited and poor reproducible. The classification of new molecular subtypes of EC has been developing, including The Cancer Genome Atlas (TCGA)-four molecular subtypes: Polymerase epsilon (POLE) mutation (POLEmut), microsatellite instability hypermutated, copy number-low, and copy number-high and ProMisE-four molecular subtypes: POLEmut, mismatch repair deficiency, no specific molecular profile, and p53 abnormal. POLEmut usually correlates with a favorable outcome. Hence, we reviewed the research since the TCGA molecular subtypes developed in 2013 and summarized the characteristics and prognosis of POLEmut EC patients. In summary, we found POLEmut occurs in 7.3%–9.6% of EC in the previous studies. POLEmut EC consistently exhibits favorable patient outcomes, regardless of adjuvant therapy. The research of POLEmut in EC is absent in Taiwan, and the underlying mechanisms and cost-effectiveness need further investigation.

KEYWORDS: Endometrial cancer, Mismatch repair deficiency, No specific molecular profile, p53, Polymerase epsilon mutation

ENDOMETRIAL CANCER

Endometrial cancer (EC) is the fourth common cancer in females in 2023, with rising incidence and reduced survival. It is estimated that there are 66,200 new cases and 13,030 deaths in the USA [1]. There are two main types of ECs: Type I ECs are mostly well differentiated with endometrioid histology; Type II ECs are poorly differentiated with serous or clear cell histology and show a poor prognosis due to high recurrence rate (80%–90%) [2]. According to the histology and status of differentiation, ECs can be divided into (i) low-grade (Grades 1 and 2) tumors, which are generally associated with a better prognosis, or (ii) high-grade carcinomas (Grade 3) carrying an intermediate prognosis [3].

The diagnosis of EC was based on the evaluation of transvaginal ultrasound, endometrial biopsy, endometrial curettage, and hysterectomy specimens. Chest X-ray, computerized tomography scan, positron emission tomography scan, and blood tests are used for staging EC.

According to the International Federation of Gynecology and Obstetrics staging system of EC, a new staging system was published in 2023 [4]. Stage I includes (IA1) nonaggressive histological type of endometrial carcinoma limited to a polyp or confined to the endometrium; (IA2) nonaggressive

histological types involving <50% of the myometrium with no or focal lymphovascular space invasion (LVSI) as defined by the WHO criteria; (IA3) low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement; (IB) nonaggressive histological types involving 50% or more of the myometrium with no or focal LVSI; and (IC) aggressive histological types such as serous, high-grade endometrioid, clear cell, carcinosarcomas, undifferentiated, mixed, and other unusual types without any myometrial invasion. Stage II encompasses (IIA) nonaggressive histological types that infiltrate the cervical stroma; (IIB) nonaggressive histological types with substantial LVSI; and (IIC) aggressive histological types with any myometrial invasion. Stage III involves (IIIA) differentiation between adnexal versus uterine serosa infiltration; (IIIB) infiltration of the vagina/parametria and pelvic peritoneal metastasis; and (IIIC) refinements for lymph node metastasis to pelvic and para-aortic lymph nodes, including micrometastasis and macrometastasis. Stage IV

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How to cite this article: Wang KH, Ding DC. The prognostic implication of polymerase epsilon-mutated endometrial cancer. Tzu Chi Med J 2025;37(2):135-44.

Access this article online	
Quick Response Code: 	Website: www.tcmjmed.com
	DOI: 10.4103/tcmj.tcmj_120_24

includes (IVA) locally advanced disease infiltrating the bladder or rectal mucosa; (IVB) extrapelvic peritoneal metastasis; and (IVC) distant metastasis.

NEW MOLECULAR SUBTYPES OF ENDOMETRIAL CANCER

Other than the two types of EC, new molecular subtypes of EC were being classified. Type I EC exhibits alterations in the PI3K pathway (over 90%), including PTEN mutations (75%–85%), PIK3CA mutations (50%–60%), and PIK3R1 mutations (40%–50%). However, PIK3CA mutations are also observed in Type II (serous) cancers (42%). Type II (serous) cancers predominantly exhibit HER-2 amplification and p53 mutations, while the p53 mutations are also present in Type I endometrioid cancers (12%) [5,6]. There was no conclusion for discovering the specific markers of the subtype and prognosis of EC.

In 2013, The Cancer Genome Atlas (TCGA) research network analyzed 373 ECs by multiomics. It classified EC into four molecular subtypes with distinct prognoses: (i) DNA polymerase epsilon (POLE) ultramutated (POLEmut) with an excellent prognosis, (ii) microsatellite instability (MSI) hypermutated and (iii) copy number-low with an intermediate prognosis, and (iv) copy number-high with the worst prognosis [7]. Furthermore, Talhouk *et al.* developed ProMisE to identify similar subgroups using a combination of POLE mutation analysis and immunohistochemistry of mismatch repair proteins (including MLH1, PMS2, MSH2, and MSH6) and p53 expression [8,9]. In the ProMisE category, EC could be classified into another four molecular subtypes: (i) POLEmut, (ii) mismatch repair deficiency (MMRd), (iii) no specific molecular profile, and (iv) p53 abnormal (p53abn) [Figure 1]. POLEmut generally had a favorable outcome, while p53abn had the worst prognosis.

POLYMERASE EPSILON GENE AND ITS FUNCTION

POLE, DNA polymerase epsilon (ϵ) catalytic subunit, exhibits not only DNA polymerase activity but also 3'-5' exonuclease proofreading activity, which are crucial for DNA chain elongation and the correction of mismatched bases during DNA replication [10]. POLE mutations are relatively

rare in the germline but predominantly manifest as somatic mutations. Pathogenic mutations of POLE have been identified in exons 9–14, specifically in the exonuclease domain, including P286R, V411 L, S297F, A456P, and S459F, are referred to as “hotspot mutations,” with P286R and V411 L being the most prevalent. However, numerous mutations of POLE’s significance in EC remain unknown [11]. Extensive studies are still required to elucidate the implications of these mutations in EC.

ANALYSIS OF POLYMERASE EPSILON MUTATION IN ENDOMETRIAL CANCER

We summarized the results of the research on POLE mutation in EC from European studies [Table 1], American studies [Table 2], and Asian and Oceania studies [Table 3] since 2013, after the TCGA molecular subtypes developed.

Studies in Europe

In Europe [Table 1], the POLEmut rate was $7.3\% \pm 3.3\%$ (mean \pm standard deviation [SD]), and it was increased to 21.6% in high-grade EC [46] and 13.3% in high-grade endometrioid type of EC (EEC) [24]. POLEmut was specifically high (42.9%) in undifferentiated EC (UDEC) and dedifferentiated EC (DDEC) and associated with improved disease-specific survival (DSS) [40]. POLEmut was also associated with improved DSS, progression-free survival (PFS) [27], recurrence-free survival (RFS) [29], and overall survival (OS) [14,44] in EC patients. Besides, POLEmut was associated with higher CD3+ and CD8+ TILs [13], higher peritumoral lymphocytes and TILs [117], and increased numbers of PD-L1+ immune cells and intratumoral T-cells [15]. Furthermore, POLEmut was few in the SC type of EC (0 of 8) [41], Stage IV EC (3.7%) [34], and mixed and ambiguous EC (5%) [39]. In combination with the status of loss of heterozygosity (LOH) in the BRCA gene, POLEmut was found in the BRCA/LOH-negative (BRCA/LOHneg) population (1 of 16, 6.3%) but none in the BRCA/LOH-positive (BRCA/LOHpos) population (0 of 24, 0%) EC patients [32]. While in combination with the status of p53abn, POLEmut was found in 43 of 107 (40.2%) EC patients, and POLEmut + p53abn obtained better RFS compared with p53abn only [33]. In summary, POLEmut EC patients had favorable outcomes, even in combination with p53abn status.

Studies in America

All American studies were in North America, including Canada and the USA [Table 2]. The POLEmut rate was $7.6\% \pm 3.9\%$ (mean \pm SD) and slightly increased in Grade 3 EC (9.7, 10.7%, and 15.1%) [48,63] and EEC (10.5%) [78]. POLEmut was associated with higher grade, mitotic index, and nuclear grade [49], younger age (<60) [62], and improved PFS [48,50,54,64,79]. On the contrary, in the young EC (age <50) patients, POLEmut was associated with lower grades and LVSI [56]. The POLEmut rate was low in recurrent EC (1.4%) [70], and in the Stage I and Grade 1 EEC population, 0 of 15 POLEmut had recurrence [69]. In an EC combination with the endometrial intraepithelial neoplasia (EIN) cohort, POLEmut was found only in the EIN (4 of 36, 11.1%) group but none in the EC

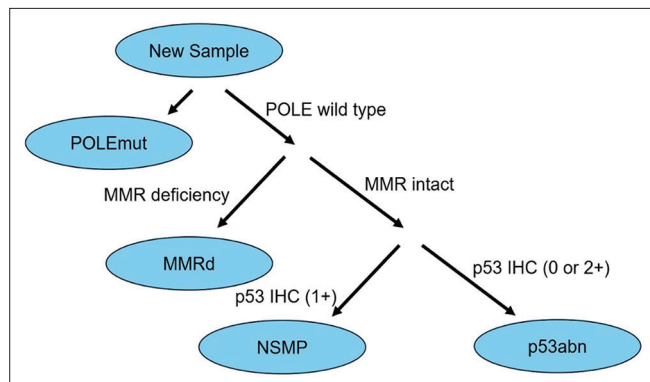


Figure 1: The proactive molecular risk classifier for endometrial cancer (ProMisE) algorithm. POLEmut: POLE mutation. MMRd: mismatch repair deficiency. IHC: immunohistochemistry. NSMP: no specific molecular profile. p53abn: p53 abnormal

Table 1: Polymerase epsilon mutation analysis in endometrial cancer from European studies

POLEmut case (n)	Total cases (n)	Percentage of POLEmut	Population	Significant finding of POLEmut subtype of EC	Methods	Country	References
7	108	6.5	EC	NA	Sanger sequencing	Belgium	[12]
8	120	6.7	EC	Associated with higher CD3+and CD8+ TILs	Sanger sequencing	Belgium	[13]
30	604	5	EC	Associated with lower OS in Stage II-IV EC	Sequencing	Finland	[14]
37	512	7.2	EC	Associated with increased numbers of PD-L1+ immune cells and intratumoral T-cell	Sequencing	Finland	[15,16]
3	90	3.3	EC	NA	Target sequencing	France	[17]
4	125	3.2	EC	NA	Target sequencing	France	[18]
5	80	6.3	EC	NA	Sequencing	France	[19]
10	209	4.8	EC	NA	Sequencing	France	[20]
42	452	9.3	EC	NA	Sequencing	Germany	[21]
7	142	4.9	EC	NA	Sanger sequencing	Germany	[22]
1	15	6.7	EC	NA	Target sequencing	Italy	[23]
2	15	13.3	Grade 3 EC	NA	Sanger sequencing	Italy	[24]
9	125	7.2	EC	NA	NGS	Italy	[25]
27	278	9.7	EC	NA	Sequencing	Italy	[26]
15	94	16	High-risk EC	Associated with better DSS and PFS	NGS	Italy	[27]
16	211	7.6	EC	NA	NGS	Italy	[28]
48	788	6.1	EC	Associated with high tumor grade and better RFS	Sequencing	The Netherlands	[29]
14	116	12.1	EC	NA	Sequencing	The Netherlands	[30]
49	834	5.9	EC	NA	Sequencing	The Netherlands	[31]
1	16	6.3	BRCA/LOHneg EC	0 of 24 in gBRCA/LOHpos EC	Sequencing	The Netherlands	[32]
43	107	40.2	p53abn EC	POLEmut+p53abn obtained better RFS compared with p53abn	Sanger sequencing	The Netherlands	[33]
6	164	3.7	Stage IV EC	NA	Sequencing	The Netherlands	[34]
57	610	9.3	EC	NA	Sequencing	Norway	[35]
14	230	6.1	EC	NA	NGS	Portugal	[36]
12	234	5.1	EC	Associated with lower BMI and higher serum estradiol	Sanger sequencing	Russia	[37]
1	39	2.6	EC	NA	Sanger sequencing	Slovenia	[38]
1	20	5	Mixed and ambiguous EC	NA	Sanger sequencing	Spain	[39]
9	21	42.9	DDEC and UDEC	Associated with improved DSS	Sanger sequencing	Spain	[40]
1	16	6.3	EEC	0 of 8 in SC type of EC	Sanger sequencing	Spain	[41]
16	96	16.7	EC	Associated with early stage	NGS	Spain	[42]
26	339	7.7	EC	NA	Sanger sequencing	Sweden	[43]
38	599	6.3	EC	Associated with better PFS and OS	Sequencing	Sweden and Switzerland	[44]
38	594	6.4	EC	NA	Sanger sequencing	Sweden and Switzerland	[45]
21	97	21.6	High-grade EC	NA	Sanger sequencing	Turkey	[46]
13	173	7.5	EC	NA	Sequencing	UK	[47]

EC: Endometrial cancer, EEC: Endometrioid type of EC, SC: Serous type of EC, DDEC: Dedifferentiated EC, UDEC Undifferentiated EC, TILs: Tumor-infiltrating lymphocytes, OS: Overall survival, DSS: Disease-specific survival, PFS: Progression-free survival, RFS: Recurrence-free survival, BRCA/LOHneg: BRCA/loss of heterozygosity negative, BRCA/LOHpos: BRCA/loss of heterozygosity positive, BMI: Body mass index, gBRCA: Germline BRCA, NA: Not available, p53abn: p53 abnormal, POLEmut: Polymerase epsilon mutation, NGS: Next generation sequencing

group ($n = 22$) [76]. In the CCC subtype of EC, POLEmut was relatively low (1.9% and 6.7%) [59,66], but another study showed a high percentage (16.2%). However, all the patients did not have a hotspot mutation of POLE [55]. In the mixed type of EC, POLEmut was frequently found in EEC/SC (16% and 50%) [72,74]. On a particular kind of EC, high-grade neuroendocrine carcinomas, the POLEmut rate was 7.1% [83]. In combination with the status of SWI/SNF chromatin-remodeling complex in DDEC/UEC

patients, POLEmut was frequently found in SWI/SNF-intact patients (15.4%), but not SWI/SNF-deficient (3.6%) patients [57]. Interestingly, the POLEmut was various in the different races. The POLEmut rate was rare (0.5% and 1.2%) in the Black patients, intermediate in the White patients (4.5% and 5.8%), and higher in the Asian patients (6.1%) [81,82]. These results indicated that the favorable outcome of POLEmut EC patients may be more meaningful in the White and Asian populations.

Table 2: Polymerase epsilon mutation analysis in endometrial cancer from the American studies

POLEmut case (n)	Total cases (n)	Percentage of POLEmut	Population	Significant finding of POLEmut subtype of EC	Methods	Country	References
8	99	8.1	EC	8 of 53 (15.1%) in Grade 3 EC and associated with PFS	Sanger sequencing	Canada	[48]
12	143	8.4	EC	NA	Sequencing	Canada	[8]
47	483	9.7	EC	Associated with higher grade, mitotic index, and nuclear grade	Sequencing	Canada	[49]
39	406	9.6	EC	Associated with improved PFS	Target sequencing	Canada	[54]
10	57	17.5	EC	NA	Sanger sequencing	Canada	[51]
30	319	9.4	EC	NA	Sanger sequencing	Canada	[9]
14	90	15.6	EC	NA	Sequencing	Canada	[52]
1	34	2.9	EC	NA	Sanger sequencing	Canada	[53]
42	460	9.1	EC	Associated with improved PFS	Sequencing	Canada	[54]
6	37	16.2	CCC	0 hot spot mutation	NGS	Canada	[65]
34	257	13.2	ECs <50 years old at diagnosis	Associated with lower grades and LVSI	Sanger sequencing	Canada	[56]
6	82	7.3	SWI/SNF EC	2 of 56 (3.6%) SWI/SNF-deficient DDEC/UEC, 4 of 26 (15.4%) in SWI/SNF-intact	Sequencing	Canada	[57]
2	50	4	EC	NA	Sequencing	Canada	[58]
1	52	1.9	CCC	NA	Sequencing	Canada	[59]
85	1357	6.3	EC	NA	NGS	Canada	[60]
48	376	12.8	Grade 3 EC	Associated with improved RFS	Sequencing	USA, Europe	[61]
30	535	5.6	EC	Associated with younger age (<60)	Sanger sequencing	USA	[62]
7	72	9.7	Grade 3 EC	NA	Sanger sequencing	USA	[63]
11	131	8.4	EC	Associated with improved PFS, increased numbers of PD-1+ CD4+ and PD-1+ CD8+ TILs	Sanger sequencing	USA	[64]
8	75	10.7	Grade 3 EC	NA	Sequencing	USA	[65]
2	30	6.7	CCC	NA	Target sequencing	USA	[66]
39	982	4	EC	NA	Sanger sequencing	USA	[67]
23	451	5.1	EC	NA	Sequencing	USA	[68]
2	29	6.9	Stage I, Grade 1 EEC	0 of 15 in the recurrence group	NGS	USA	[69]
1	74	1.4	Recurrent EC	NA	Sequencing	USA	[70]
28	618	4.5	EC	NA	NGS	USA	[71]
2	8	25	Mixed EC	In 2 of 4 (50%) in EEC/SC, not in CCC/SC (n=1) and EEC/CCC (n=3)	Sanger sequencing	USA	[72]
6	150	4	EC	NA	Sequencing	USA	[73]
4	25	16	EEC/SC mixed EC (age <60)	NA	Sanger sequencing	USA	[74]
6	47	12.8	EC	NA	NGS	USA	[75]
4	58	6.9	EC+EIN	All 4 cases in EIN, n=36 (11.1%)	Target sequencing	USA	[76]
15	310	4.8	EC	NA	SNaPshot assay	USA	[77]
10	95	10.5	Grade 3 EEC	NA	Sequencing	USA	[78]
12	175	6.9	EC	Associated with improved PFS	Target sequencing	USA	[79]
8	140	5.7	EC	NA	NGS	USA	[80]
97	1882	5.2	EC	3 of 259 (1.2%) in Black, 94 of 1623 (5.8%) in White patients	Sequencing	USA	[81]
233	5534	4.2	EC	3 of 590 (0.5%) in Black, 204 of 4520 (4.5%) in White, and 26 of 424 (6.1%) in Asian patients	NGS	USA	[82]
1	14	7.1	High-grade NEC of EC	NA	NGS	USA, UK	[83]

EC: Endometrial cancer, EEC: Endometrioid type of EC, SC: Serous type of EC, CCC: Clear cell carcinoma of EC, DDEC: Dedifferentiated EC, UEC Undifferentiated EC, PFS: Progression-free survival, RFS: Recurrence-free survival, LVSI: Lymphovascular space invasion, SWI/SNF: Switch/sucrose nonfermentable, TILs: Tumor-infiltrating lymphocytes, EIN: Endometrial intraepithelial neoplasia, NEC: Neuroendocrine carcinomas, NA: Not available, POLEmut: Polymerase epsilon mutation, NGS: Next generation sequencing

Studies in Asia and Oceania

In the Asian and Oceania studies [Table 3], the POLEmut rate was 9.6% ±4.9% (mean ± SD), higher than the European and American population. POLEmut was increased

in Grade 3 EEC patients in Japan (29.7%) [108] and high-grade EC (10.4% and 11.8%) in China [91,97] and in Singapore (29.8%) [115]. POLEmut also frequently happens in UDEC/DDEC patients (14.3%) However, POLEmut

Table 3: Polymerase epsilon mutation analysis in endometrial cancer from Asian studies

POLEmut case (n)	Total cases (n)	Percentage of POLEmut	Population	Significant finding of POLEmut subtype of EC	Methods	Country	References
7	79	8.9	EC	NA	NGS	China	[84]
35	467	7.5	EC	Associated with shorter OS in hysterectomy samples of patients (age >60 or Stage I)	Target sequencing	China	[85]
38	426	8.9	EC	Associated with improved OS; POLEmut + MELF pattern increased the tumor recurrence or progression	Sanger sequencing	China	[86]
3	21	14.3	DDEC and UDEC	NA	Sequencing	China	[87]
24	202	11.9	EC	Associated with improved PFS	NGS	China	[88]
73	473	15.4	EC	49 of 291 (16.8%) in open surgery, 24 of 182 (13.2%) in minimally invasive surgery	Sequencing	China	[89]
12	103	11.7	EC	NA	NGS	China	[90]
43	414	10.4	High-grade EC	NA	Sequencing	China	[91]
3	26	11.5	EC	NA	NGS	China	[92]
8	60	13.3	EC	NA	NGS	China	[93]
8	80	10	EC	NA	NGS	China	[94]
14	86	16.3	EC	NA	NGS	China	[95]
3	65	4.6	EC	NA	Sequencing	China	[96]
42	355	11.8	High-grade EC	NA	Sanger sequencing	China	[97]
5	77	6.5	MELF pattern EC	NA	Sanger sequencing	China	[98]
43	628	6.8	EC	NA	Sequencing	China	[99]
6	93	6.5	AEH and EC (age <40), received LNG-IUS	100% CR	Sequencing	China	[100]
28	479	5.8	EC	NA	NGS	China	[101]
1	37	2.7	EC	NA	Sequencing	India	[102]
3	48	6.3	EC	NA	Sanger sequencing	India	[103]
39	151	25.9	EC	Associated with worse DSS and OS	Sanger sequencing	India	[104]
12	138	8.7	EC	Associated with improved PFS	Sequencing	Japan	[105]
5	127	3.9	EC	NA	Sequencing	Japan	[106]
3	36	8.3	EC	NA	NGS	Japan	[107]
22	74	29.7	Grade 3 EEC	NA	NGS	Japan	[108]
7	112	6.3	EC	NA	NGS	Japan	[109]
26	240	10.8	EC	Associated with improved PFS	Droplet digital PCR, NGS	Korea	[110]
16	162	9.9	EC	NA	Droplet digital PCR	Korea	[111]
29	183	15.9	Early-stage EC	NA	Droplet digital PCR	Korea	[112]
8	90	8.9	EC	NA	Sequencing	New Zealand	[113]
2	432	0.5	High-grade EC	NA	Target sequencing, sequencing	Saudi Arabia	[114]
14	47	29.8	Grade 3 EC	Associated with improved RFS	NGS	Singapore	[115]
7	138	5.1	EC	Associated with improved PFS and OS	Sanger sequencing	Thailand	[116]

EC: Endometrial cancer, EEC: Endometrioid type of EC, DDEC: Dedifferentiated EC, UDEC: Undifferentiated EC, OS: Overall survival, DSS: Disease-specific survival, PFS: Progression-free survival, RFS: Recurrence-free survival, MELF: Microcystic elongated and fragmented, AEH: Atypical endometrial hyperplasia, LNG-IUS: Levonorgestrel-releasing intrauterine system, CR: Complete response, NA: Not available, NGS: Next generation sequencing, PCR: Polymerase chain reaction, POLEmut: Polymerase epsilon mutation

was also high in early-stage EC in Korea (15.9%) [112] and rare in high-grade EC in Saudi Arabia (0.5%) [114]. Similar to the results of Western countries, POLEmut obtained a favorable prognosis, which was associated with improved PFS [88,105,110], RFS [115], and OS [86,116]. However, in POLEmut patients, the microcystic elongated and fragmented (MELF) pattern of invasion was associated with a 15.1-fold increase in tumor recurrence or progression risk compared with POLE-wild-type patients [86]. The POLEmut rate in the MELF pattern was 6.5% [98]. POLEmut also obtained worse outcomes, including the association with worse DSS and OS in India [104] and shorter OS in

hysterectomy samples of patients (age >60 or Stage I) in China [85]. Although the rate of POLEmut was high in the Asian population, the prognostic outcome of POLEmut was conflict, not like the results in Western countries.

On the selection of surgical approaches, including open surgery and minimally invasive surgery (MIS), POLEmut was found in 49 of 291 patients (16.8%) who received open surgery and 24 of 182 (13.2%) in MIS. According to the analysis of RFS, the authors suggested that the patients with POLEmut, microsatellite-instability high (MSI-H), homologous recombination repair pathway mutation or

MUC16 mutation, MIS should be recommended, while for patients with TP53 mutation, open surgery is better concerning oncological safety [89]. In consideration of the preservation of fertility, levonorgestrel-releasing intrauterine system was suitable for atypical endometrial hyperplasia and early-stage EC (age <40) patients with POLEmut. All of them ($n = 6$) reached complete response [100]. In summary, the outcome of POLEmut patients is still better than other subtypes in the Asian population.

IMPACT ON THE TREATMENT OF POLYMERASE EPSILON MUTATION ENDOMETRIAL CANCER

PATIENTS

POLEmut EC displayed an increased number of CD8+ TILs and upregulation of the T-cell cytotoxic differentiation and effector markers, T-bet, Eomes, IFNG, PRF, and granzyme B, resulting in enhancement of cytotoxic T-cell response. It also correlated with the enrichment of antigenic neuropeptides [118]. POLEmut ECs were associated with high neoantigen loads and a number of TILs, including CD3+ and CD8+ T-cells. Besides, PD-1 and PD-L1 were counterbalanced by overexpression in these TILs [119]. After ruling out the MMR-deficient cases, the TIL-high pattern showed a moderate accuracy in distinguishing POLE-mutated from POLE-wild-type ECs with sensitivity = 0.85, specificity = 0.66, positive likelihood ratios (LR+) = 2.49, negative LR- = 0.25, and diagnostic odds ratio = 10.30 [120]. These data provide a plausible mechanism for the excellent prognosis in POLEmut EC patients who may be excellent candidates for PD-1-targeted immunotherapies.

POLEmut EC consistently exhibits favorable patient outcomes, regardless of adjuvant therapy [121]. Improved DSS (hazard ratio [HR] = 0.41) and PFS (HR = 0.23) [122], as well as OS, especially in EEC (HR = 0.48) [123], were found in POLEmut EC patients. In the situation of mixed or multiple molecular subtypes of POLEmut, the characteristics of POLEmut-p53abn resembled those of POLEmut, but MMRd-p53abn appeared to be intermediate between MMRd and p53abn [124]. Multiple classifiers EC with POLEmut is characterized by good prognosis even in the presence of MMRd/MSI-H and p53abn [125]. These results suggested de-escalating treatment for EC patients with simple POLEmut or mixed with other subtypes.

PERSPECTIVE AND CONCLUSION

It has been proved that this particular subtype, POLEmut, of EC, obtained a favorable outcome. However, in Black patients, the prevalence of POLEmut is low, suggesting that the other classifications of EC, including traditional and novel molecular subtypes, are still needed. Although there is no POLEmut data in Taiwan, the rate of POLEmut is relatively high in the Asian population. Thus, studying the TCGA and ProMisE classification of EC is urgent in Taiwan.

Other than the TCGA and ProMisE classification of EC, there are some molecular biomarkers, such as *ARID1A*, *CTNNB1*/β-catenin, *LICAM*, and *TTN* [25,126,127], which may be associated with the prognosis of EC patients.

However, the underlying mechanisms of POLEmut are related to the increase of PD-1/PDL-1 axis and TILs, improving the prognosis of EC, and reversing the outcome of POLEmut + p53abn to POLEmut are mainly unknown. Recent studies suggested that POLEmut may be associated with ATM, AMF/AMFR, and cGAS-STING pathway [128-130]. The other detailed mechanisms need further investigation.

Finally, the cost-effectiveness effects of the TCGA and ProMisE classification must be investigated. In a Stage III EC model, the tumor molecular testing was cost-saving [131]. Since the methods for analyzing POLEmut are expensive, and the rate of POLEmut in the Asian population was relatively higher (around 10%), which is correlated with de-escalating treatment, the cost-effectiveness effects should be further evaluated.

In summary, POLEmut analysis in EC is urgent in Taiwan. POLEmut may benefit the prognosis of EC as well as de-escalating treatment. Besides, understanding the underlying mechanisms may provide novel biomarkers for prognosis and therapeutic targets of EC.

Data availability statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Financial support and sponsorship

This work was supported by Hualien Tzu Chi Hospital (TCRD 112-062) and the Buddhist Tzu Chi Medical Foundation (TCMF-CP 111-05).

Conflicts of interest

Dr. Dah-Ching Ding, an editorial board member at the *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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