Chapter 8
Molecular Perspective in Endometrial Carcinoma

Yoichi Kobayashi

Abstract In endometrial cancer, risk evaluation has been made on such as histological types, tumor grade, muscular invasion, lymphovascular infiltration, and lymph node metastasis. But in recent years, molecular analysis of endometrial cancer has been advanced, and novel risk evaluation procedures have been proposed. Especially, The Cancer Genome Atlas (TCGA) and Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) could extract some high-risk groups in previously considered as low-risk groups of low-grade endometrioid endometrial cancer, and some preferable prognosis groups of high-grade endometrioid or type 2 non-endometrioid endometrial carcinoma which are considered as poor prognosis. These new classifications based on the molecular subtypes might be useful to decide the postoperative adjuvant therapy and might improve the quality of life of patients with endometrial cancer.

Keywords The Cancer Genome Atlas (TCGA) · Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) · POLE-ultramutated MSI-hypermutated · Copy-number-high · Copy-number-low · p53 abnormal p53 wild type

8.1 Introduction

Endometrial cancer is the fourth most common malignancy in the United States. Its estimated new cases and deaths were 61,880 and 12,160 in 2018, respectively [1], and both morbidity and mortality are increasing. In Japan, the same tendency is seen [2]. Endometrial cancer is classified into two types: type 1 and type 2 [3]. Type 1

Y. Kobayashi (✉)
Department of Obstetrics and Gynecology, Kyorin University Faculty of Medicine, Mitaka, Tokyo, Japan
e-mail: yoichi@ks.kyorin-u.ac.jp

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endometrial cancer is differentiated endometrioid tumors (grade 1/2) with usually early-staged, associated with estrogen, obesity, and diabetes mellitus, and its prognosis is generally favorable. On the other hand, type 2 endometrial cancer is mostly serous tumors with advanced-staged, and its prognosis is very poor. These distinct criteria according to the histopathology have been widely accepted, but approximately 20% of type 1 cancer cases arise from atrophic endometrium showed recurrence and poor clinical outcomes, then molecular genetic changes might occur in these type 1 cancers [4]. Still, other issues remain unclear in such as mucinous carcinoma, clear cell carcinoma, and mixed carcinoma [5]. So, a novel definition based on the molecular classification to predict prognosis should be developed.

8.2 The Cancer Genome Atlas (TCGA) and Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE): Novel Proposed Molecular Classifications

In 2013, The Cancer Genome Atlas Research Network (TCGA) reported that endometrial cancers could be divided into four groups of tumors based on the genomic analysis [6]. Group 1 is the "POLE ultramutated" subgroup with very high mutational load and mutations in the exonuclease domain of polymerase-ε(POLE). Group 2 is characterized by "microsatellite instability," frequently with MLH-1 promoter hypermethylation and high mutation rates ("hypermutated"). Group 3 is characterized by copy-number-low (CNL) subgroups with TP53-wild type and normal p53 expression ("endometrioid"), and group 4 is copy-number-high (CNH) with low mutation rates of TP53 mutations with aberrant p53 expression ("serous-like") [5–7]. According to these classifications, progression-free survival (PFS) of group 1 is most excellent followed by group 2/3, and group 4 is the worst [5, 6].

Although TCGA classifications could provide better clinical prognosis compared to histological classifications, easier and less expensive methods using immunohistochemistry has been developed (*Pro*active *M*olecular R*i*sk Classifier for *E*ndometrial Cancer; ProMisE) [8]. ProMisE classifications showed four molecular groups of endometrial cancer; POLE-mutated (POLEmt), MMR-deficient (MMR-D), p53-abnormal (p53abn), and p53-wild-type (p53-wt). In recent years, correlations of conventional histological classifications and molecular classifications of TCGA or ProMisE have been reported. Summary of these molecular classifications and prognosis is shown in Tables 8.1 and 8.2.

Table 8.1 Molecular classifications of endometrial cancers

The Cancer Genome Atlas (TCGA)	Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE)
POLE ultramutated	POLE-mutated (POLEmt)
MSI hypermutated	MMR-deficient (MMR-D)
Copy-number-low (endometrioid)	p53-abnormal (p53abn)
Copy-number-high (serous-like)	p53-wild type (p53-wt)

Table 8.2 Histological and molecular classifications and prognosis

	POLEmt	MMR-D	p53wt	p53abn
Low-grade EEC (grade 1,2)	◯	◯	◯	X
High-grade EEC (grade 3)	◯	△	△	X
Serous	◯	◯	X	X
Clear cell	◯	◯	X	X

Prognosis ◯, good; △, intermediate; X, poor; EEC, endometrioid endometrial carcinoma

8.3 Correlation of Histopathological Classifications and Molecular Classifications

8.3.1 Low-Grade Endometrioid Endometrial Carcinoma (EEC)

Low-grade EEC (grade 1/2), characterized by estrogen-dependent, usually develops from endometrial hyperplasia and is associated with obesity and diabetes mellitus. Generally, low-grade EEC is early-staged, and the prognosis is excellent. Overall, 5-year survival is about 95% after surgery without adjuvant therapies, but the subgroup of women with early-staged low-grade EEC are at increased risk of recurrence and death [9]. In conventional histological classifications, such "high-risk" low-grade EEC could not be selected. Moroney et al. reported CTNNB1 mutation, MMR-D, and MSI-H were significantly frequent in recurrent stage 1, grade 1 EEC compared to those without recurrence, and POLEmt was not found in recurrent cases but it was not significant [10].

8.3.2 High-Grade (Grade 3) EEC

In high-grade (grade 3) EEC patients, endocrine and metabolic disturbances are usually absent or occult, with deep myometrial invasion, frequent lymph node metastasis, and unfavorable prognosis [3]. So, grade 3 EEC with muscular invasion is classified as a high-risk group in ESMO Clinical Practice Guideline 2013 [11] and is treated with extended surgery including lymph node resection and adjuvant chemotherapy. In molecular analysis [6, 8], POLE-mutated tumors are endometrioid endometrial cancer (EEC), particularly grade 3 tumors with frequent mutation of PTEN, PIK3CA, PIK3R1, FBXW′, ARID 1A, KRAS, and ARID5B [5]. In cases of PORTEC-3 trial, molecular analysis was performed, and 12.4% of the cases were POLE-ultramutated. In these cases, 56.9% was grade 3 EEC, and although grade 3 EEC is worse histological grade, mainly were early-stage disease (76.4%) with excellent prognosis [12]. A systematic review by Travaglino et al. showed grade 3 EEC was higher prevalent in POLE-hypermutated, MSI, and CNH subgroups, but was lower in CNL subgroup than grade 1/2 EEC [7]. Although small series of study cases, Piulats et al. showed overall survival of high-grade EEC, and disease-specific

48 months survival rates were 100% in POLEmt, 82% in MSI, 77.8% in CNL, and 42.9% in CNH groups [5]. Boose et al. classified grade 3 EEC into four subgroups: P53abn, MMR-D, POLEmt, and no specific molecular profile (NSMP), and they showed 5-year recurrence-free survival rates was best in POLEmt (89%) and was worst in P53abn (47%) [13]. So, at least, grade 3 EEC with POLE-hypermutated could show a preferable prognosis like low-grade EEC. These cases might be over-treated, then those cases should be reclassified by POLE-mutated status in the future.

8.3.3 Serous Carcinoma

Endometrial serous carcinoma is a major component of type 2 endometrial cancers, usually occurs in older patients, and is not associated with estrogen or obesity. Most of serous carcinoma is classified as CNH (serous-like) subtype [14], and its prognosis is generally poor. Raffone et al. performed systematic review and meta-analysis based on ProMisE classifications, and the proportion of non-EEC was highest in the p53abn subgroup (73%), and ESMO 2013 high-risk category was also highest (84.7%) [15]. But in EEC with a "serous carcinoma" component <60 years, 16% of the cases showed MMR-D and 11% were diagnosed with Lynch syndrome, as well as 16% of the cases were POLEmt subtype. Overall survival of cases with MMR-D and POLEmt was significantly better than those without these features [14]. So, even though in serous carcinoma, MMR-D and POLEmt might be associated with preferable prognosis.

8.3.4 Clear Cell Carcinoma

Clear cell carcinoma (CCC) of endometrium accounts approximately for 3% of all endometrial cancers [16] and is classified as type 2 endometrial cancers with advanced stage. Molecular classifications of 52 cases of CCC according to ProMisE revealed 1 (1.9%) POLEmt, 5 (9.6%) MMR-D, 28 (53.8%) p53wt, and 18 (34.6%) p53abn [17], and CCC is molecular heterogeneous disease. Patients with POLEmut or MMR-D CCC had favorable outcomes and the worst in p53abn CCC [17, 18]. Patients with POLEmt or MMR-D subtype showed trends to younger age compared to P53abn subtypes. P53wt subtype accounts for about half of CCC patients [16, 17], but its prognosis was very poor, although the prognosis of other EEC tumors with p53wt is favorable [17, 19, 20].

8.3.5 Neuroendocrine Carcinoma

Neuroendocrine carcinoma (NEC) of the endometrium is a rare disease account for <1% of all endometrial carcinoma [21]. Howitt et al. reported that 15 cases of NEC were sequenced and were classified into four TCGA groups, and 50% of the cases

were in POLEmt (7%) or microsatellite instability/hypermutated groups (43%) [22]. Although the prognosis of NEC according to the molecular status is not yet elucidated, immune checkpoint inhibition may be a reasonable approach to the treatment of microsatellite instability subtype [22].

8.3.6 Endometrial Hyperplasia

Endometrial hyperplasia (EH), precursors of endometrial carcinoma, is classified for endometrial hyperplasia without atypia (non-atypical hyperplasia: NAH) and atypical hyperplasia/endometrioid intraepithelial neoplasia (AH/EIN) [23]. In a cohort of 7947 women diagnosed with EH, progression to endometrial carcinoma of NAH was 4.6% (95%CI, 3.3–5.8%) through 19 years of follow-up; meanwhile, that of AH/EIN was 27.5% (95%CI, 8.6–42.5%) [24]. Russo et al. reported mutations of PTEN, PIK3CA, and FGFR2 commonly detected in endometrial carcinoma were more frequent in EH progressing to endometrial carcinoma [25].

8.3.7 Lynch Syndrome

Lynch syndrome (LS) is an autosomal dominant inherited disease and is characterized by an increasing risk of colorectal and endometrial cancer [26]. Approximately 5% of endometrial cancer is a hereditary tumor, and LS accounts for the majority of inherited endometrial cancers. Lower uterine segment (LUS) cancer is often seen in LS. In a French multicenter study, 25% of the cases were involved LUS [27]. Germline mutations of mismatch repair genes (MMR): MLH1, MSH2, MSH6, and PMS2, are seen in LS, and in most endometrial cancer cases, germline mutations are in MLH1 and MHS2. The cumulative risk of LS-associated endometrial cancer has been reported to be 27–71% [26]. In a retrospective cohort study including 568 females already proven LS [27], 162 (28.5%) women were diagnosed with endometrial cancer, and mutations in MLH1, MSH2, and MSH6 were 53 (32.7%), 83 (51.2%), and 26 cases (16.0%), respectively. Women with MSH6 mutations presented with endometrial cancer at older ages than those with other mutations [28].

Whether the prognosis of LS-associated endometrial cancer is better or worse compared to sporadic ones is still controversial. In a prospective study of the Prospective Lynch Syndrome Database (PLSD), endometrial cancer cases diagnosed <65 years showed preferable 10-year survival rates (89%) [29]. Kim et al. reported women with MMR-D tumors had worse progression-free survival and higher recurrence rates compared with those with MMR-proficient tumors, but there was no significant difference in overall survival between mismatch repair groups [30]. Son et al. reported among all patients aged ≤60 years, MMR-D due to MLH1 methylation was associated with worse progression-free survival (48.6% vs. 83.3%, $p = 0.032$), and overall survival (56.5% vs. 90.0%, $p = 0.025$) [31]. In non-endometrioid endometrial cancer, patients with LS are associated with much better disease-free survival and overall survival than without LS [32].

8.4 Conclusion

Recent advances in molecular analyses could newly classify endometrial cancers for several types. These classifications could compensate for the problems and flaws of conventional pathological diagnosis and could avoid unnecessary adjuvant therapy for so-called "high-risk cancers" actually at low-risk. In the future, these molecular data should be accumulated to improve the prognosis and quality of life of endometrial cancer patients.

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