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Tumor markers and Biomarkers of Gynecological Cancers

Endometrial carcinoma

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Tumor markers

- **CA 125** :

  Cancer antigen (CA) 125 is a glycoprotein encoded by the mucin 16 (*MUC16*) gene

- **HE4:**

  Human epididymis protein 4 is an antigen derived from human epididymis protein, a product of the *WFDC2* gene

Tumor markers:

- The role of tumor markers in EC is unclear, unvalidated, and of low value.
- Does not routinely perform tumor marker testing prior to surgery for EC.
- However, serum cancer antigen 125 (CA 125) can be useful for surveillance of patients after initial treatment if the level was initially elevated.
- Although some gynecologic oncologist routinely order CA 125 in women with type II endometrial cancer and in those with grade 3 endometrial cancers as there is evidence that there is an association with metastatic disease.

Tumor markers

- If a type 2 uterine cancer is suspected or diagnosed on an endometrial biopsy, a serum CA 125 level should be ordered as retrospective studies have consistently reported that elevated levels of CA 125 are associated with :

  -advanced stage

  -poorly differentiated endometrioid adenocarcinomas

  -uterine serous cancers; and uterine clear cell cancers

- Knowing a patient may have an advanced-stage uterine cancer can influence the surgery to be performed and determine the need for a gynecologic oncologist to perform that surgery.

Tumor markers

- Elevations of CA 125 are associated with :
  - positive pelvic node involvement
  - positive peritoneal washings
  - presence of lymphovascular invasion
- However, the prognostic effect of an elevated CA 125 on progression-free survival remains controversial .
- While a correlation between elevated CA 125 preoperatively and lymph node metastases was noted, it was not associated with development of recurrent disease.

Tumor markers

- **CA 125** can be elevated in **carcinosarcoma.**
- If elevated, it appears to correlate with metastases or tumor bulk.
- Preoperative elevation of the tumor marker CA 125 may signify more advanced disease .
- In a retrospective study of 54 patients, CA 125 value **≥30 U/mL** was significantly associated with higher disease stage (62 versus 38 percent with a CA 125 <30 U/mL), presence of a serous component (75 versus 25 percent), and myometrial invasion ≥50 percent (61 versus 39 percent).

Tumor markers

Measurement of serum CA 125 may be useful in the diagnostic work-up of a suspected recurrence, particularly in women that had an associated elevation in their CA 125 at the initial diagnosis.

The level of CA 125 alone should not influence treatment decisions.

Monitoring on treatment :

- For patients receiving systemic treatment for metastatic disease, typically perform CT of the chest, abdomen, and pelvis every two to three cycles, or more frequently in the setting of new or concerning symptoms.
- As in the adjuvant setting, the data do not support the routine monitoring of serum cancer antigen (CA) 125 for women with recurrent or metastatic EC.
- However, in patients whose disease was marked by an elevated CA 125, it may be reasonable to use this as a marker of disease activity alongside imaging and/or clinical examination.

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ORIGINAL PAPER

Assessment of levels of the tumor markers HE4 and CA125 considering staging, grading and histological types of endometrial cancer

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Abstract

Aim of the study was to assess statistical differences of serum levels of HE4 and CA125 between certain endometrial cancer stages, grading and histological types.

Material and methods: A retrospective study of 52 patients admitted to our clinic for a surgical operation because of endometrial cancer was performed. HE4 and CA125 were measured for each patient. The staging was done according to FIGO. The statistical difference of serum levels of tumor markers was analyzed considering different stages, grading and histological types.

Results: Most of the patients (92.31%) were post-menopausal. Serum levels of tumor markers were significantly higher among patients with stage IB-IIIC than stage IA, among patients with stages II-III than stage I and among patients with stage IIIC than stage IA-IIIB. Only HE4 was significantly higher among patients with stage IB than stage IA and among patients with grading G2 and G3 than those with G1. Only CA125 was significantly higher among patients with stage IIIA and IIIB than those with stages I and II. There was no statistically significant difference in level of either tumor marker in differentiation of endometrioid from other histological endometrial cancer.

Conclusions: Both tumor markers HE4 and CA125 can be useful additional tools for pre-surgical differentiation between different stages of endometrial cancer. HE4 can predict advanced histological grades. Neither HE4 nor CA125 can differentiate endometrioid from other histological types of endometrial cancer.

Key words: endometrial cancer, CA125, HE4, staging, grading.

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HE4 and CA125 as preoperative risk stratifiers for lymph node metastasis in endometrioid carcinoma of the endometrium: A retrospective study in a cohort with histological proof of lymph node status

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HIGHLIGHTS

Conclusions

- Preoperative risk stratification aims to identify those at least risk of LNM where lymphadenectomy can be avoided.

- Molecular analysis of endometrioid carcinomas has identified POLE mutation in **better prognosis endometrial cancer** and it is likely that molecular profiling will soon be integrated into our clinical and surgical management of patients.

- It remains to be seen then whether serum markers will continue to have a role. Our study suggests HE4 alone or in combination with CA125 has the potential to supplement stratification of patients into high- or low-risk categories prior to surgery.

Molecular-Genetic Characterization of Endometrial Cancer

- The Cancer Genome Atlas (TCGA) Research Network proposed a novel classification system exclusively based on a profound molecular characterization of the tumors .
- Molecular subtype assignment is highly reproducible and can be done on diagnostic endometrial biopsies , (D&C), hysterectomy specimen.
- The prognostic value of molecular classification has consistently been demonstrated, with predictive value emerging with respect to response to radiotherapy ,chemotherapy ,and targeted treatment.
- According to this, EC is classified into **four different subgroups**

TCGA Cancer Genome Atlas Group

- The ultramutated subclass, characterized by mutations in the exonuclease domain of **DNA polymerase-epsilon** (POLE).
- Patients with POLEmut ECs tend to be younger and thinner, and despite often having seemingly aggressive pathologic features (eg, high-grade, lymphovascular space invasion), they have highly favorable outcomes (>96 percent five-year survival) confirmed across multiple studies .

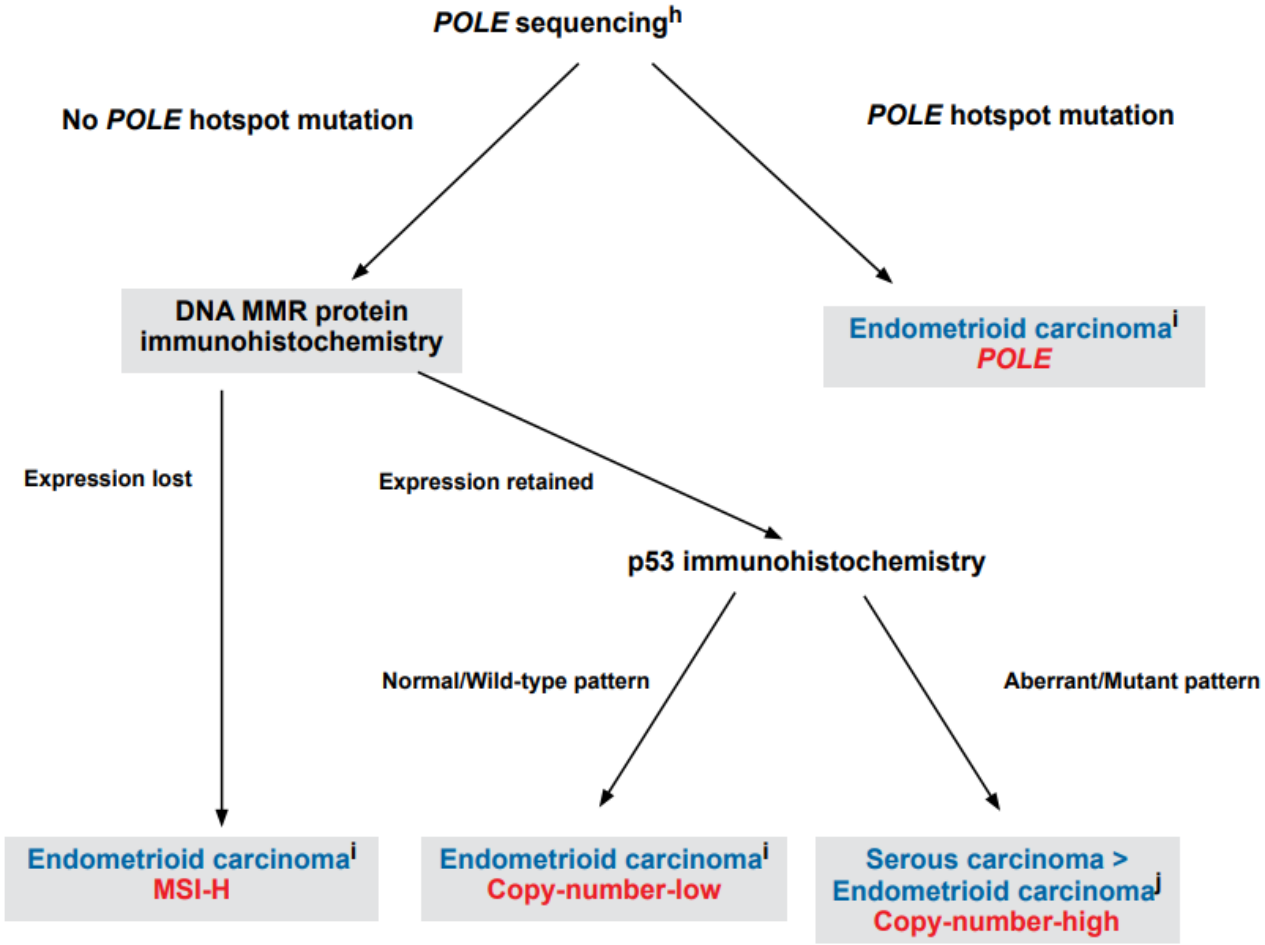
- The hypermutated subclass based on **microsatellite instability (MSI)** has been shown to have an intermediate prognosis. In clinical practice, mismatch repair deficiency (MMRd) is tested by immunohistochemistry of the MMR proteins. It is associated with negative prognostic factors such as higher histologic grade,presence of LVSI and with older age, and advanced stage (III/IV).

- The copy-number low subclass with low mutation frequency (also called subclass with **no specific molecular profile or NSMP**) has also been associated with an intermediate prognosis.

- The copy-number high subclass, characterized by **TP53 mutations**, with mainly serous-type EC, has a very high degree of SCNAs and a low mutation rate and is associated with the most unfavorable prognosis .

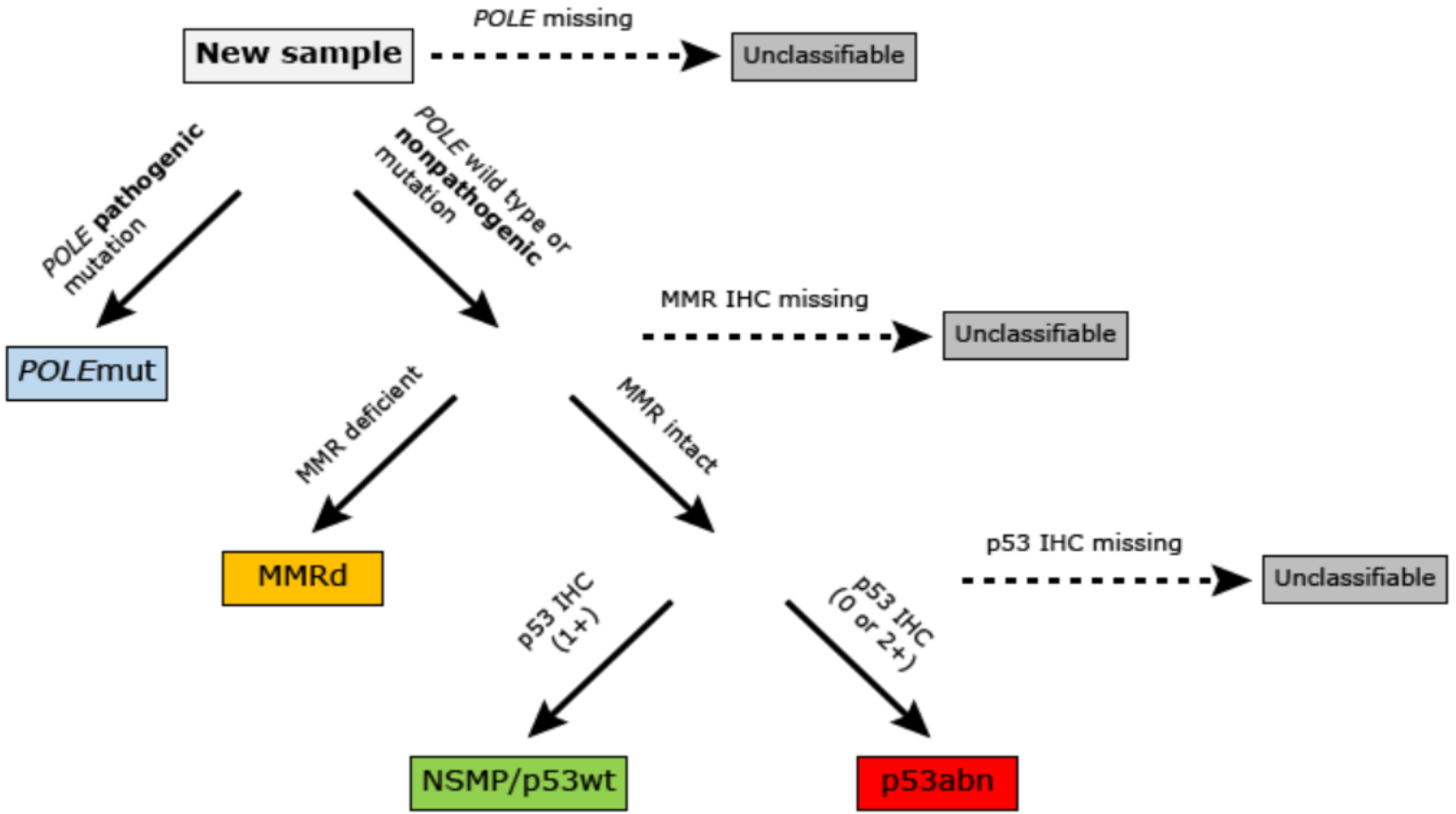
PRINCIPLES OF MOLECULAR ANALYSIS

FIGURE 1: PATHOLOGY AND GENOMICS IN ENDOMETRIAL CARCINOMA[f,g]

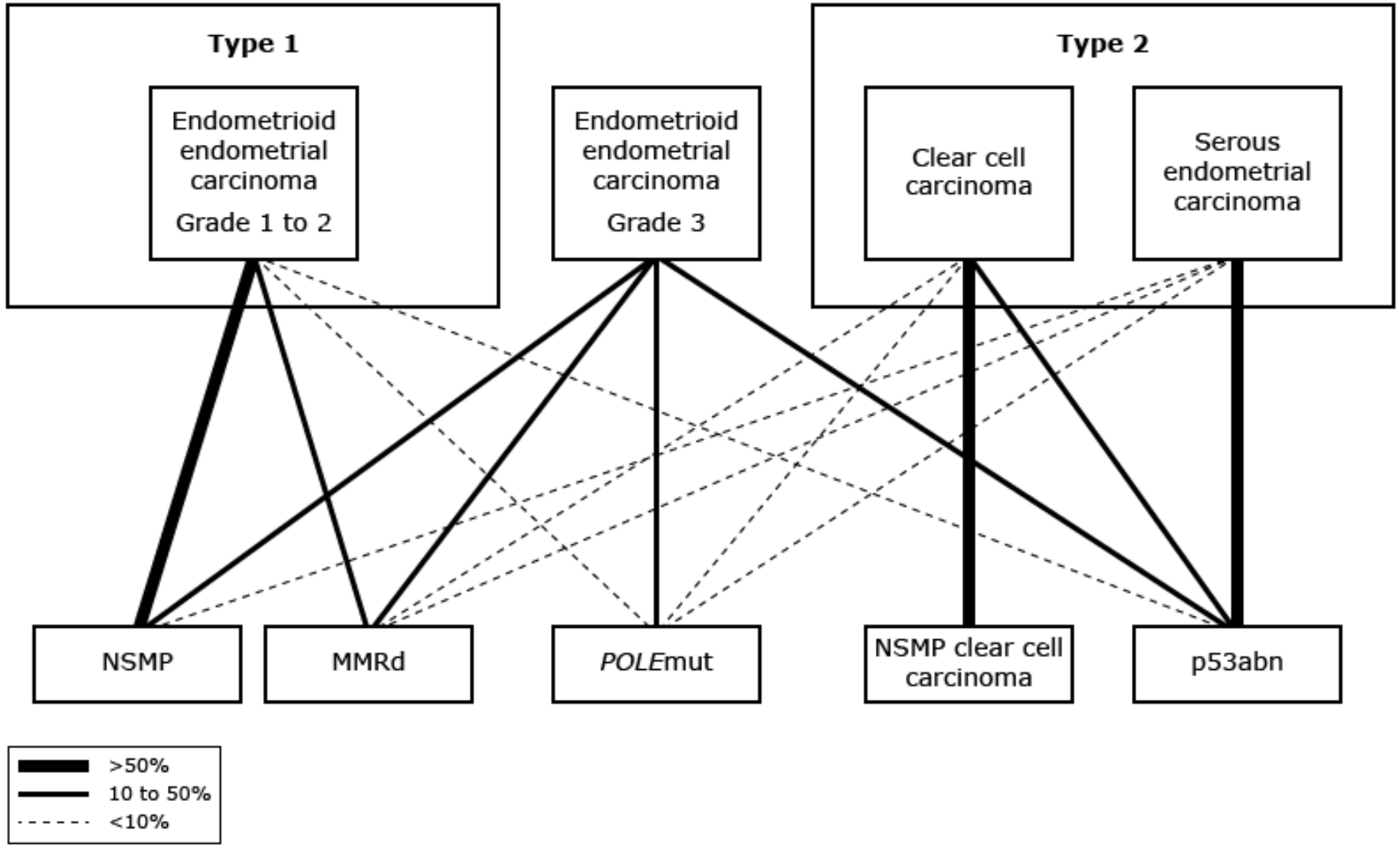


[f]Adapted with permission from Murali R, Delair DF, Bean SM, et al. Evolving roles of histologic evaluation and molecular/genomic profiling in the management of endometrial cancer. J Nat Compr Canc Netw 2018;16:201-209.
[g]Diagnostic algorithm for integrated genomic-pathologic classification of endometrial carcinomas (blue represents histotype; red represents TCGA genomic class).
[h]*POLE* sequencing made by mutational analysis may not be available at all institutions.
[i]May also apply to clear cell carcinomas.
[j]This algorithm does not distinguish between high-grade tumors that cannot otherwise be classified (ie, high-grade carcinoma, serous carcinoma, clear cell carcinoma).

Proactive Molecular Risk Classifier for Endometrial Cancer (ProMisE) molecular classification figure[1-3]



Type 1 and 2 classification and relationship to histomorphologic and molecular endometrial carcinoma classification



Molecular subtypes of endometrial carcinoma: Molecular, pathologic, and clinical features[1-19]

TCGA category	Molecular classification	Molecular features (diagnostic tests)	Pathology features	Clinical features	Outcomes	Treatment options
***POLE* "ultramutated"** (approximately 7% of TCGA)	***POLE*mut** (approximately 7 to 9% of all ECs)	▪ Markedly high TMB ▪ >100 mut/Mb ▪ SCNA very low ▪ *PTEN* mutations (94%) ▪ (*POLE* EDM or hotspot sequencing)	Commonly high grade, LVSI, aggressive features, "ambiguous morphology" prominent TIL, EEC G3-2-1* but can be any	Presents in younger, often thinner women	Highly favorable (>96% five-year survival)	▪ Observation only may be reasonable, even if high-risk features. Clinical trials are needed to establish safety and efficacy. ▪ Checkpoint inhibitors for rare advanced/recurrent
MSI "hypermutated" (approximately 28% of TCGA)	**MMRd** (26 to 30% of all ECs)	▪ 10 to 100 mut/Mb ▪ SCNA low ▪ *PTEN* (88%), *PIK3CA* (54%), *ARID1A* (37%) mutations ▪ (MMR IHC: PMS2, MSH6, ±MSH2, and MLH1; or MSI assay)	LVSI and higher grade, prominent TIL, MELF, EEC G2/3-1* but can be any	Lynch syndrome association	Intermediate	▪ Radiation ▪ Checkpoint inhibitors if advanced/recurrent
Copy-number low (approximately 39% of TCGA)	**p53wt/NSMP** (45 to 50% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA low ▪ *PTEN* (77%), *PIK3CA* (53%), *CTNNB1* (52%), *ARID1A* (42%) mutations ▪ ER+ PR+ ▪ (p53 IHC: wt [normal expression] and absence of *POLE*mut or MMRd)	Squamous differentiation, low TIL, mostly low-grade EEC G1-2-3*	Often presents in younger individuals with higher BMI or exogenous estrogen	Intermediate-favorable	▪ Hormonal therapy ▪ PI3K/mTOR inhibitors?
Copy-number high (approximately 26% of TCGA)	**p53abn** (13 to 18% of all ECs)	▪ Low TMB (<10 mut/Mb) ▪ SCNA high ▪ *PIK3CA* (47%), *PPP2R1A* (22%), *FBXW7* (22%) mutations ▪ (p53 IHC: abnormal or *TP53* mutation)	LVSI, high cytonuclear atypia, mostly high grade, mostly serous but approximately 25% EEC G3	Presents in older, thinner, women; commonly advanced stage	Poor (approximately 50% five-year survival)	▪ Chemotherapy ▪ *HER2*-targeted or *HRD*-targeted therapy?

RESEARCH Open Access

Circulating tumor DNA as a prognostic marker in high-risk endometrial cancer

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Abstract

Background: Currently, there is no reliable blood-based marker to track tumor recurrence in endometrial cancer (EC) patients. Liquid biopsies, specifically, circulating tumor DNA (ctDNA) analysis emerged as a way to monitor tumor metastasis. The objective of this study was to examine the feasibility of ctDNA in recurrence surveillance and prognostic evaluation of high-risk EC.

Methods: Tumor tissues from nine high-risk EC patients were collected during primary surgery and tumor DNA was subjected to next generation sequencing to obtain the initial mutation spectrum using a 78 cancer-associated gene panel. Baseline and serial post-operative plasma samples were collected and droplet digital PCR (ddPCR) assays for patient-specific mutations were developed to track the mutations in the ctDNA in serial plasma samples. Log-rank test was used to assess the association between detection of ctDNA before or after surgery and disease-free survival.

Results: Somatic mutations were identified in all of the cases. The most frequent mutated genes were *PTEN*, *FAT4*, *ARID1A*, *TP53*, *ZFHX3*, *ATM*, and *FBXW7*. For each patient, personalized ddPCR assays were designed for one-to-three high-frequent mutations. DdPCR analysis and tumor panel sequencing had a high level of agreement in the assessment of the mutant allele fractions in baseline tumor tissue DNA. CtDNA was detected in 67% (6 of 9) of baseline plasma samples, which was not predictive of disease-free survival (DFS). CtDNA was detected in serial post-operative plasma samples (ctDNA tracking) of 44% (4 of 9) of the patients, which predicted tumor relapse. The DFS was a median of 9 months (ctDNA detected) versus median DFS undefined (ctDNA not detected), with a hazard ratio of 17.43 (95% CI, 1.616–188.3). The sensitivity of post-operative ctDNA detection in estimating tumor relapse was 100% and specificity was 83.3%, which was superior to CA125 or HE4.

Conclusions: Personalized ctDNA detection was effective and stable for high-risk EC. CtDNA tracking in post-operative plasma is valuable for predicting tumor recurrence.

Keywords: Circulating tumor DNA, High-risk, endometrial cancer, Recurrence

Conclusions. Personalized ctDNA detection was effective and stable for high-risk EC. CtDNA tracking in post-operative plasma is valuable for predicting tumor recurrence.

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