ENDOMETRIAL CANCER: MOLECULAR CLASSIFICATION AND MANAGEMENT IMPLICATIONS

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- Introduction
- Current classification
- Molecular classification
- Management Implications

Disclosure

No conflict of interest to declare

ENDOMETRIAL CANCER

- Most common gynaecological malignancy
- 6th leading cause of cancer-related death among women in USA
  - 11 350 deaths in 2018 (Bastiaan G, Current Onc Reports 2019)
- Increasing incidence
  - Increasing rates of obesity
  - Aging of population
- Early presentation with abnormal uterine bleeding
  - Early stage at diagnosis
  - Favourable outcome (75 – 90% 5 year survival)
- 90% of cases are sporadic

ENDOMETRIAL CANCER

- Treatment
  - Surgical staging
  - Clinicopathological risk factors
    - Age
    - Histological type
    - Stage
    - Grade
    - LVSI
  - Radiation +/- chemotherapy

(Bendifallah S, Brit. J. Cancer, 2015)

ENDOMETRIAL CANCER

- 3 distinct but overlapping dimensions used to categorize EC
  - Pathogenetic
  - Histopathological
  - Molecular

Pathogenetic

- Bokhman 1983
- Dualistic model based on presence or absence of
  - Obesity
  - Hyperlipidaemia
  - Signs of hyperoestrogenism
- Types I
- Type II

(Bell DW, Annu. Rev. Pathol. Mech. Dis, 2019)

Pathogenetic

Type I

- High/moderate degree of differentiation
- Superficial myometrial invasion
- Frequent progesterone sensitivity
- Favourable prognosis

Type II

- Poorly differentiated
- Deep myometrial invasion
- Lower rates of progesterone sensitivity
- Propensity for lymph node metastases
- Unfavourable prognosis

Histopathology

- Based on light microscopic features using WHO classification system
  - Endometrioid carcinoma and its variants
  - Mucinous carcinoma
  - Serous carcinoma
  - Clear cell carcinoma
  - Carcinosarcomas, Mixed-cell, Un/Dedifferentiated
- 3 architectural grades, 1-3
  - < 5%
  - 6-50%
  - > 50%

In clinical practice

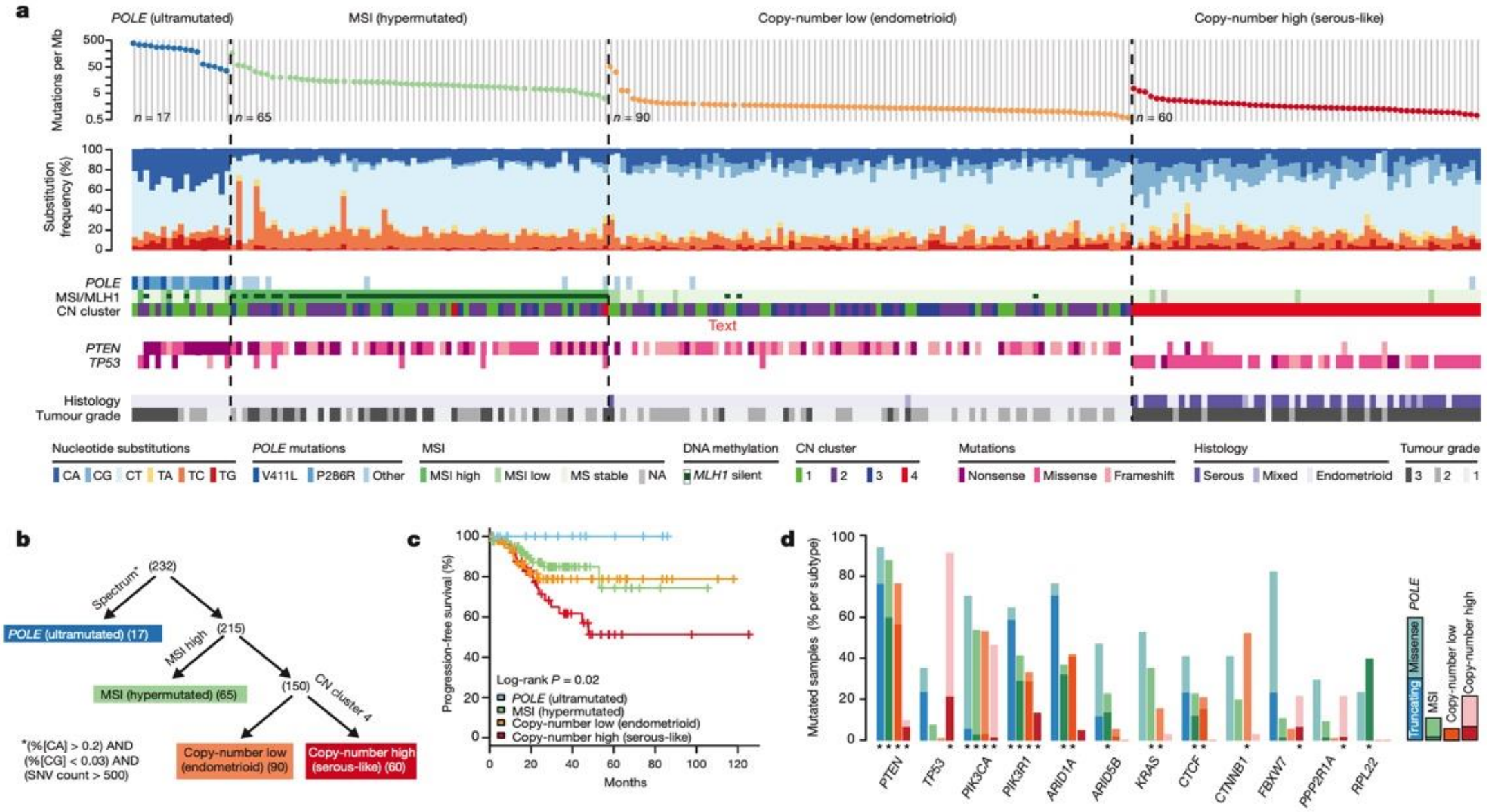
- Less than perfect correlation between histopathologic and pathogenetic subtypes
- Assignment of histopathological type can be difficult in cases of morphological ambiguity
- Minority of EC may exhibit shared characteristics
  - 50% of grade 3 exhibit TP53 mutations – rare in the low grade tumours
- Determining grade is not always clear cut
  - Degree and extent of nuclear atypia sufficient to change grade
  - Intra/inter observer reproducibility is poor (Murali R, J Natl Compr Canc Netw, 2018)

In clinical practice

- Challenges
  - Accurate prognostic assessment
  - Selecting optimal treatment
  - Comparison of treatment interventions
  - Determining eligibility for clinical trials

Molecular pathogenesis

- The Cancer Genome Atlas (TCGA) – Nature, 2013
  - Genomic and proteomic analysis of endometrial cancers
- 4 distinct molecular subgroups
  - *POLE* mutated
  - Microsatellite unstable
  - Copy number low
  - Copy number high
- Correlated with PFS
- Endometrioid histology populate all 4 subgroups
- Serous cancers almost exclusively in the "Copy number high" subgroup


a
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
Mutations per Mb
500
50
5
0.5
n = 17
n = 65
n = 90
n = 60
Substitution frequency (%)
100
80
60
40
20
0
POLE
MSI/MLH1
CN cluster
Text
PTEN
TP53
Histology
Tumour grade
Nucleotide substitutions
CA CG CT TA TC TG
POLE mutations
V411L P286R Other
MSI
MSI high MSI low MS stable NA
DNA methylation
MLH1 silent
CN cluster
1 2 3 4
Mutations
Nonsense Missense Frameshift
Histology
Serous Mixed Endometrioid
Tumour grade
3 2 1
b
Spectrum* (232)
POLE (ultramutated) (17)
MSI high (215)
MSI (hypermutated) (65)
(150)
CN cluster 4
Copy-number low (endometrioid) (90)
Copy-number high (serous-like) (60)
*(%[CA] > 0.2) AND (%[CG] < 0.03) AND (SNV count > 500)
c
Progression-free survival (%)
100
80
60
40
20
0
Log-rank P = 0.02
POLE (ultramutated)
MSI (hypermutated)
Copy-number low (endometrioid)
Copy-number high (serous-like)
0 20 40 60 80 100 120
Months
d
Mutated samples (% per subtype)
100
80
60
40
20
0
PTEN
TP53
PIK3CA
PIK3R1
ARID1A
ARID5B
KRAS
CTCF
CTNNB1
FBXW7
PPP2R1A
RPL22
POLE
Truncating
Missense
MSI
Copy-number low
Copy-number high

Endometrioid carcinoma

1. PI3K-PTEN-mTOR pathway
2. RAS-MEK-ERK pathway
3. WNT-B-catenin pathway
4. High rate of MSI – reflects defects in MMR
5. High incidence of *POLE* mutations

(Bell DW, Annu. Rev. Pathol. Mech. Dis, 2019)

Endometrioid carcinoma

- PI3K-PTEN-mTOR pathway
  - Regulates cell growth, survival, protein synthesis and metabolism
  - 80 – 95%
  - PTEN mutation is an early event
  - Loss of antagonization of PI3K – accumulation of phosphorylated AKT
    - Promotes growth factor mediated cell survival
    - Overcomes cell cycle arrest in G1/2 phases
    - Promotes angiogenesis

Endometrioid carcinoma

- RAS-MEK-ERK
  - Key regulator of cell proliferation, survival and differentiation
  - 15 – 24%
  - Mutation in KRAS gene is predominant pathway
  - Associated with co-occurring alterations in PTEN
- WNT-*B* catenin pathway
  - Regulates cell proliferation and migration
  - 19– 37%
  - More common in microsatellite stable tumours

Endometrioid carcinoma

- Defects in MMR
  - 30%
  - Epigenetic silencing of MLH1 gene
  - Associated with higher tumour grade, LVSI and later-stage disease
- *POLE* mutations
  - 5%
  - more frequent in high grade carcinomas
  - Associated with a favourable prognosis

Serous carcinoma

- Relatively mutationally quiet
- High rates of copy number alterations
- > 85% have TP53 mutations / stabilization of p53 protein
- Lower frequencies of mutations in PTEN and PI3K pathways

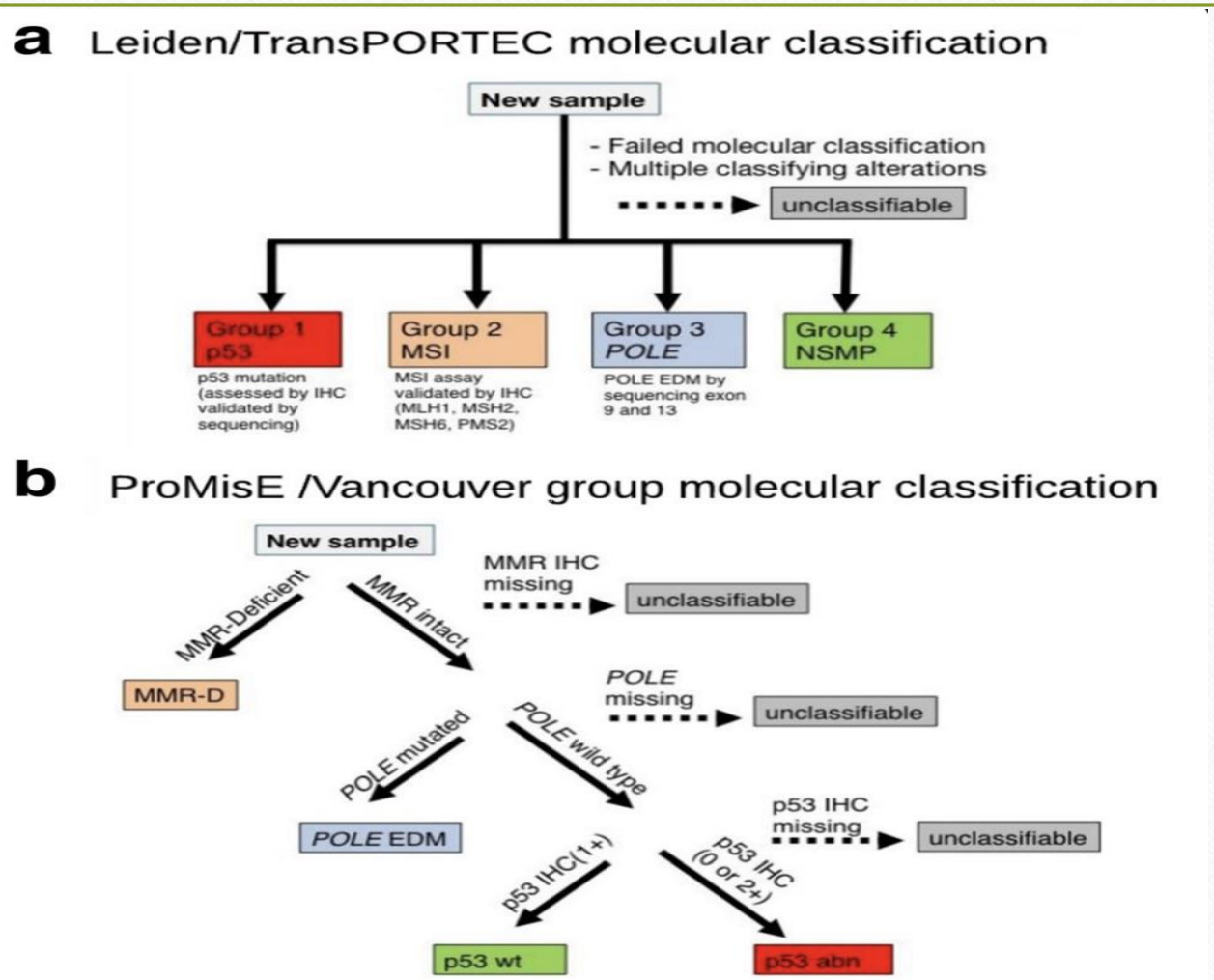


Fig. 1 Schematic of the **a** Leiden/TransPORTEC and **b** ProMisE/ Vancouver molecular classification systems including testing performed, molecular subgroups identified, and by what criteria cases would be considered unclassifiable

- 4 prognostically distinct molecular subgroups
- Can be applied to diagnostic specimens
- Similar survival curves observed with TCGA

(Stello E, Clin. Cancer Res. 2016, Talhouk A, Cancer. 2016)

Management implications

- Personalization of patient care
  - Selecting patients that will need comprehensive surgical staging
  - Selection of patients that need adjuvant treatment
  - Omitting adjuvant treatment in *POLE*-mutant cancers
- Prognosis
  - *POLE* subgroup has most favourable prognosis
  - Copy number high associated with poorest prognosis

Management implications

- Targeted therapy
  - Candidates for immunotherapy
    - *POLE*-mutated and MMR-deficient tumours exhibit infiltrating lymphocytes, high levels of neoantigens and expression of immune checkpoint regulators
    - Immune checkpoint blockade with anti-PD1 antibody (Pembrolizumab)
  - Candidates for MAPK pathway inhibition
    - Several phase II trials underway

Challenges

- Determining whether specific molecular features can be leveraged for patient prognosis and treatment
  - More evidence on selecting adjuvant treatment and targeted therapies based on molecular alterations in EC are needed

CONCLUSION

- Progression from broad categorization of tumours by anatomical site, to distinguishing subgroups by histomorphology and molecular features
- Endometrioid and serous cancers were classified by TCGA into 4 discrete molecular groups
- Increasing knowledge on prognostic significance and possible therapeutic options
- More evidence on treatment selection based on molecular classification is needed