CARCINOME DE L'ENDOMETRE
CLASSIFICATIONS, IMPACT PRONOSTIC

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Plan

- 1- Voies de la carcinogénèse
- 2- Classifications histologiques
- 3- Classifications moléculaires et impact clinique
- 4- Items du CR anapth

- Carcinome de l’endomètre (CE) =
- Cancer le plus fréquent des organes de reproduction féminins
- Prise en charge constitue le principal challenge clinique incluant
  - Stade et caractéristiques histologiques,
  - Nécessité des biomarqueurs pronostiques pour guider le traitement adjuvant

1- *PTEN* mutations

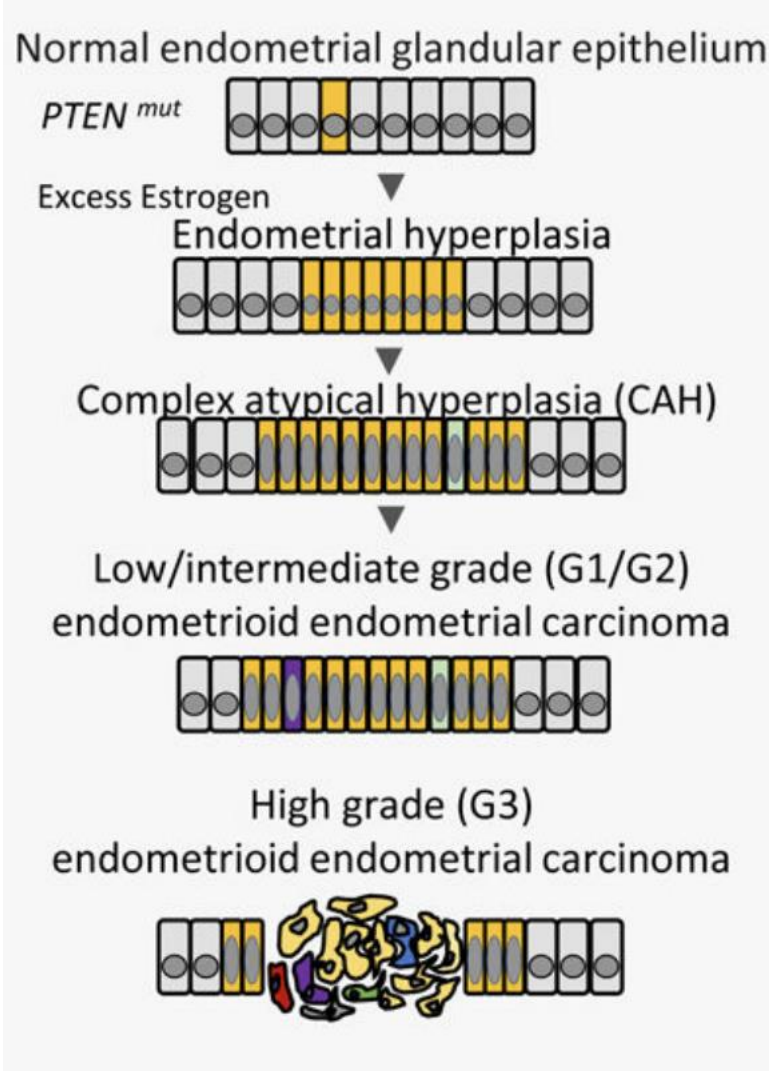
Endometrioid endometrial carcinoma (EEC)

- PTENmut : Early but insufficient tumorogenese event

- Mouse models:
  - Biallelic *Pten* loss leads to CAH;

  but biallelic *Pten* loss together with mutational activation of *Pik3ca* results in progression of CAH to EC
  - Biallelic *Pten* loss, *Ctnnb1* mutation or *Mlh1* inactivation induces EC

- Context of human:
  - *PTEN* mutations commonly co-occur with *PIK3CA* and *PIK3R1* mutations
  - *CTNNB1* mutation and *MLH1* mutation are often co-occur with *PTEN* inactivating mutations



Urick et al, Nat Rev Cancer, 2019 - Mutter et al, Cancer Res 1998

2- *TP53* mutations

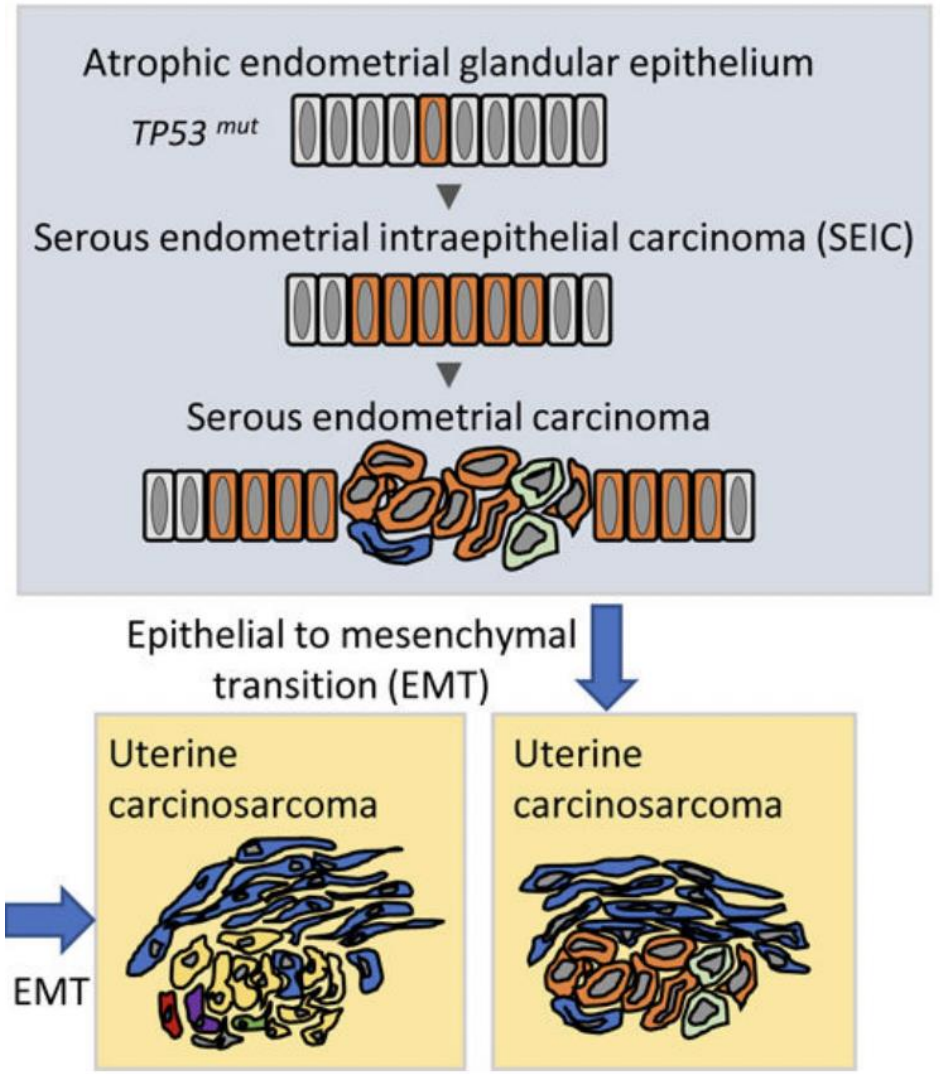
Serous endometrial carcinoma (SEC)

- Early event in SEC pathogenesis

- Aged transgenic mice studies
  - Deletion of *Trp53* leads to SEC as well as other EC
  - Others genes are also aerly events: *FBXW7*, *PIK3CA, PPP2R1A* mutations and *CCNE1* amplification

Uterine carcinosarcoma (UCS)

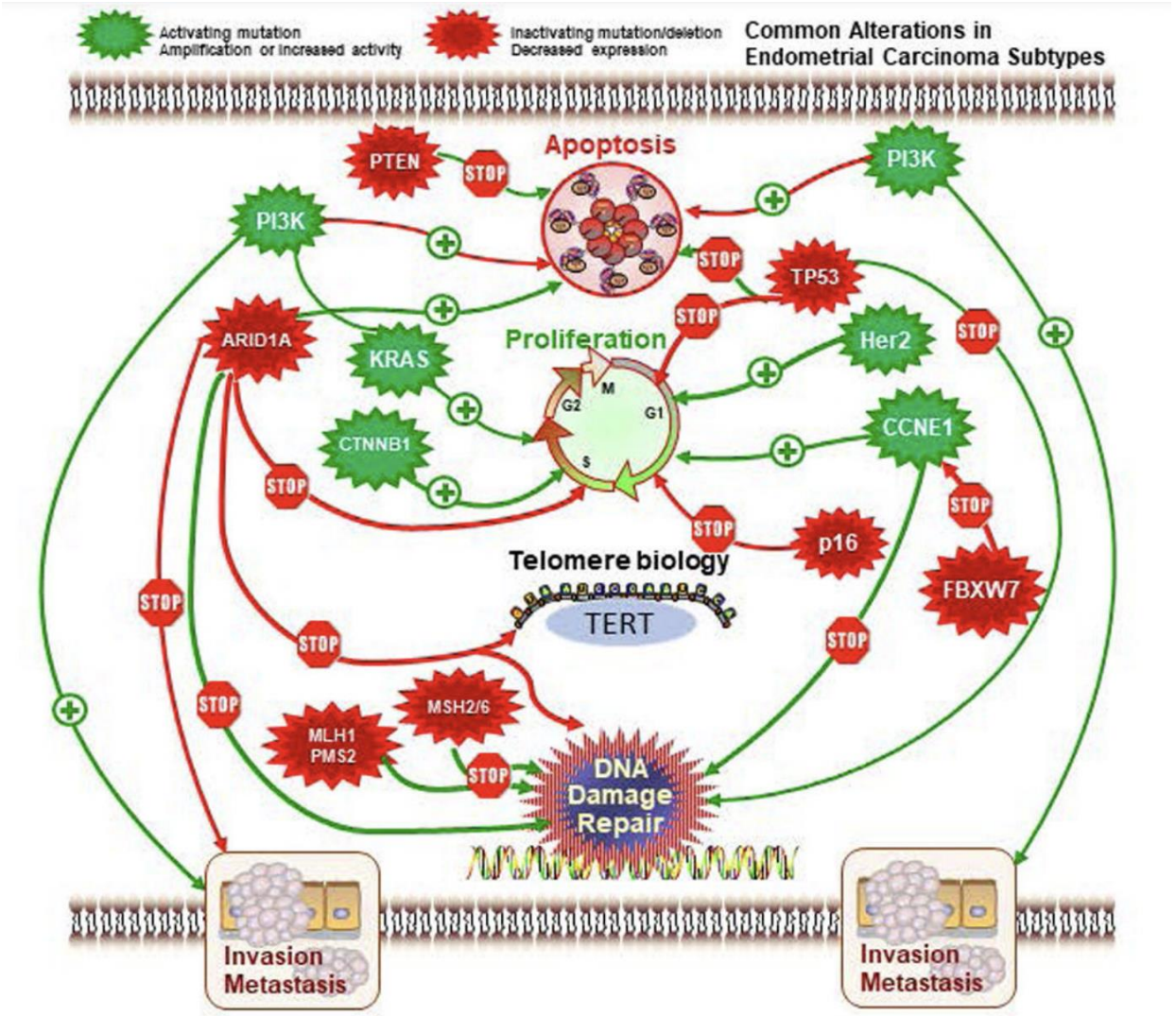
TP53 mutations as in SEC
PTEN mutations associated
EMT transcriptomic gene signature variable high scores



Urick et al, Nat Rev Cancer, 2019 - Sherman et al, Human Pathol 1995 – Cherniack et al, Cancer Cell, 2017

Really

- Several genes
- Several mecanismes

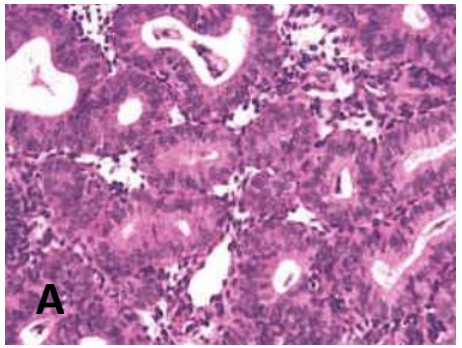


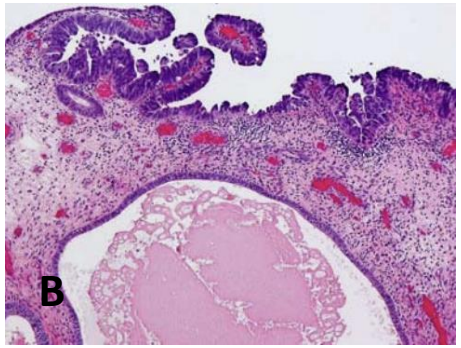
Yen et al, Int J Gynecol Pathol, 2020

Classification de Bokhman (1983)

	Carcinome de type I	Carcinome de type II
Histologie	Carcinome endométrioïde (bas grade)	Carcinome séreux
Précurseur	Hyperplasie avec atypies (A)	Carcinome séreux in situ (B)
Voie de carcinogène	Hormono-dépendante (hyper-oestrogénie)	Hormono-indépendante
Fréquence	80% des cas	20% des cas
Age moyen	59 ans	66 ans
Survie globale à 5 ans	80%	40%
Mutation fréquente	Mutation *PTEN*/β-Caténine	Mutation *P53*

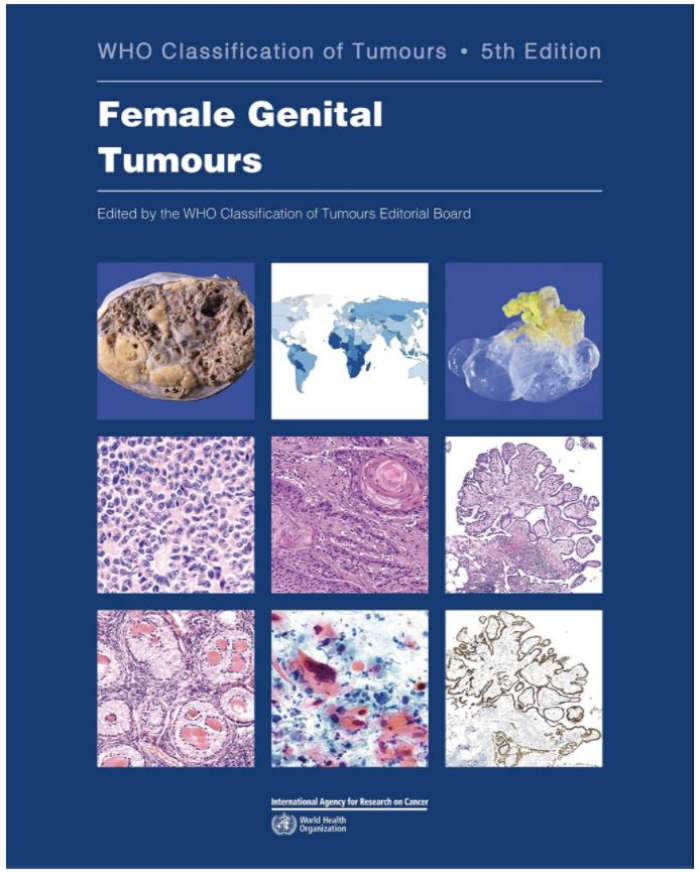
Place des carcinomes endométrioïdes de haut grade?





Bokhman J V, Gynecology Oncology, 1983 – Zannoni et al, Virchows Arch Int J Pathol, 2010

WHO classification (2017)

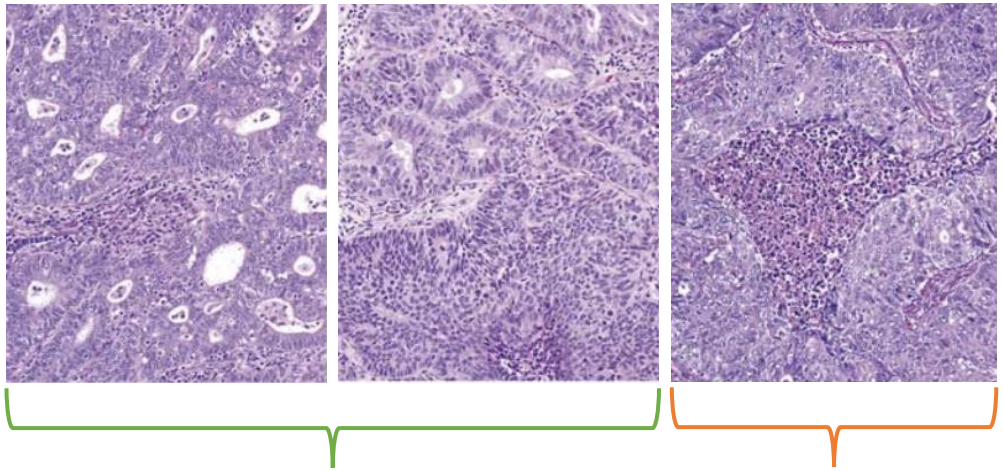


- Carcinome endométrial Endométrioïde (EEC)

- Carcinome séreux (SEE)
- Carcinome à cellules claires (CCEC)
- Carcinosarcome
- Carcinome mixte
- Carcinome indifférencié et dédifférencié
- Carcinomes rares
    - Carcinome neuroendocrine
    - Carcinome mésonéphrique
    - Carcinome mucineux (type gastrique)
    - Carcinome épidermoïde

Grade de FIGO/WHO : only EEC

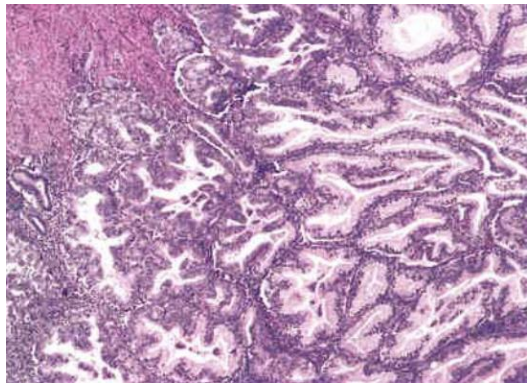
FIGO



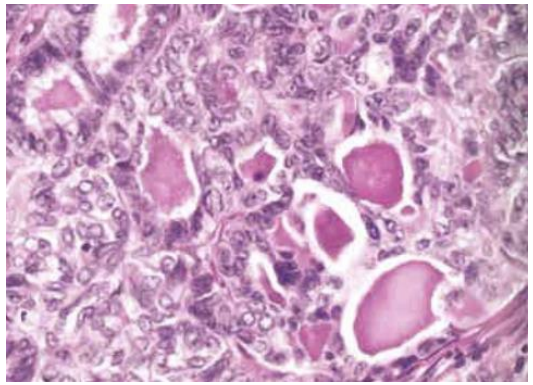
Grade WHO 5th edition

Low-grade

High-grade



Gastric-type EC
Prognosis ?



Mesonephric-type EC
Prognosis ?

> J Pathol Transl Med. 2021 Jan;55(1):43-52. doi: 10.4132/jptm.2020.10.04. Epub 2020 Dec 3.

Interobserver diagnostic reproducibility in advanced-stage endometrial carcinoma

Ho Jin Jung [1], Soo Yeon Lee [1], Jin Hwa Hong [2], Yi Kyeong Chun [1]

> Mod Pathol. 2013 Dec;26(12):1594-604. doi: 10.1038/modpathol.2013.102. Epub 2013 Jun 28.

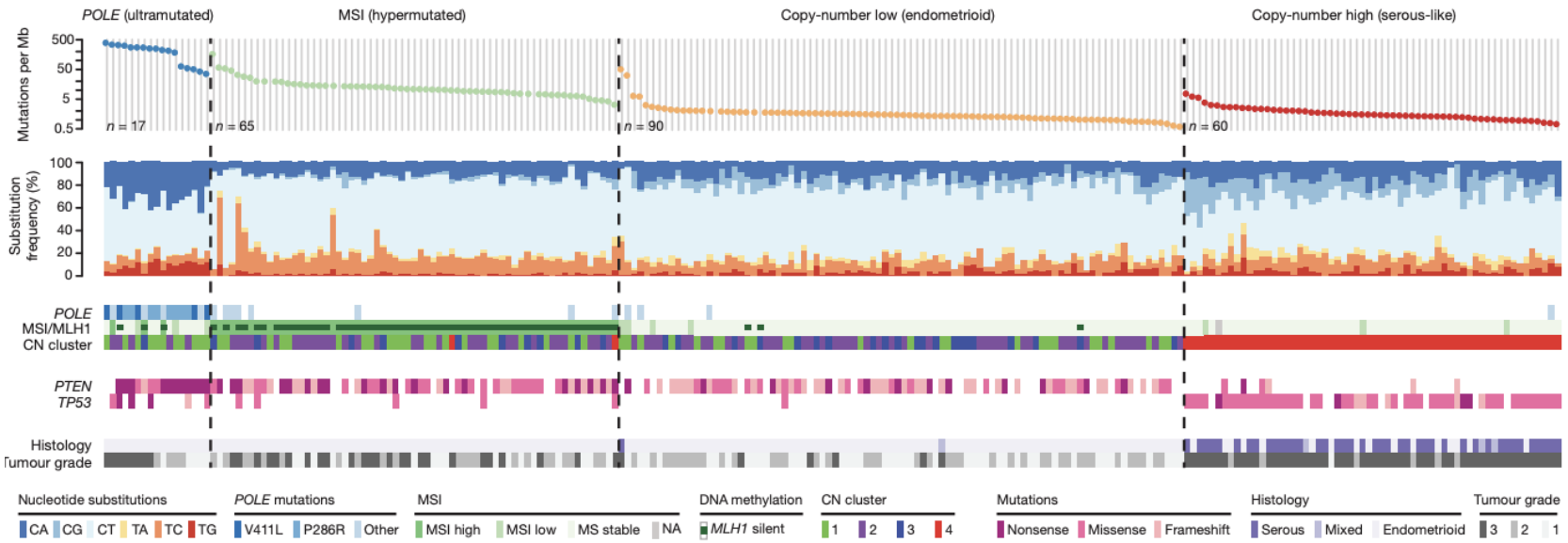
Reproducibility of histological cell type in high-grade endometrial carcinoma

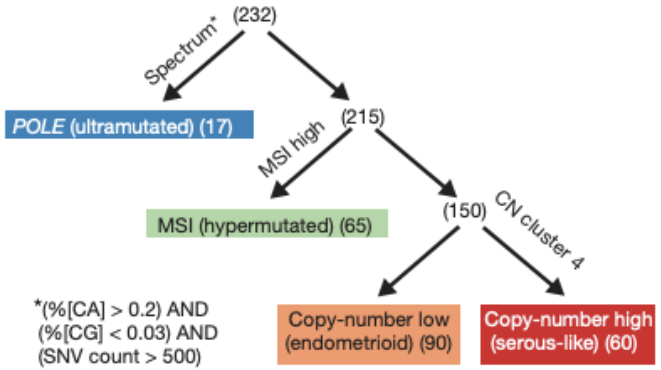
Guangming Han [1], Davinder Sidhu, Máire A Duggan, Jocelyne Arseneau, Matthew Cesari,

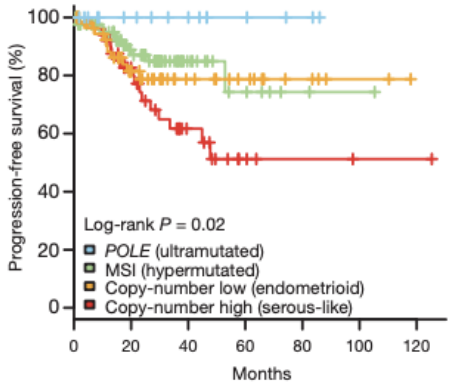
Nécessité nouvel outil afin d'améliorer la reproductibilité et donc mieux guider les options thérapeutiques

Classification TCGA (2013)

373 patients [307 EEC + 66 SEC (53 serous + 13 mixed)] : genomic, transcriptomic et proteomic analysis





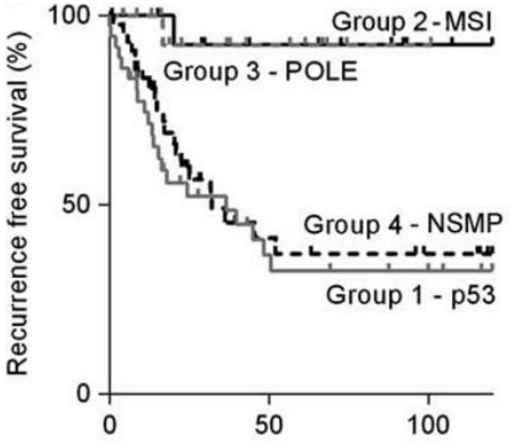


Analyse de recherche, lourde et coûteuse

Douglas and TCGA, Nature, 2013

Leiden/PORTEC group (2015)

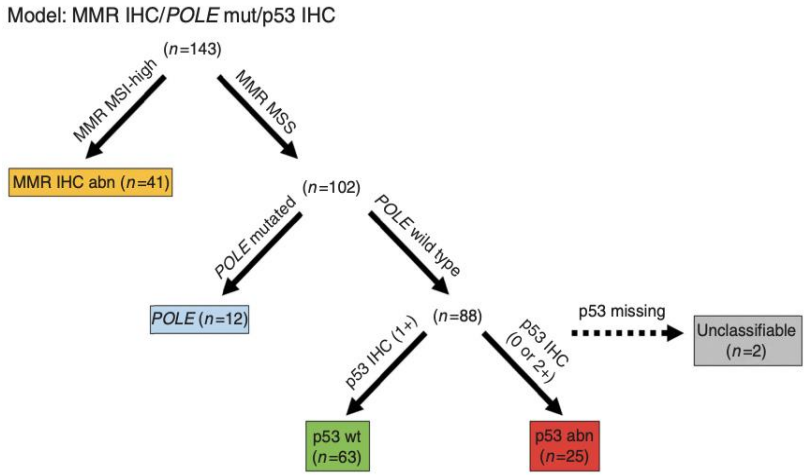
116 high-risk tumours: 86 EEC + 12 SEC + 18 CCEC
p53 IHC, MSI, *POLE* and 12 additional genes
and protein expression ER, PR, PTEN and ARID1

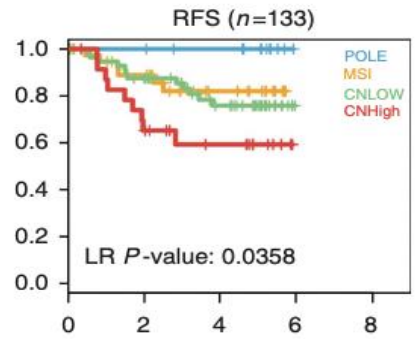


Simplification of TCGA methods
Applicable on FFPE material
MSI testing remplaced by MMR proteins
SCNA testing remplaced by p53
POLE sequencing

Vancouver/ProMisE group (2015, confirmation 2017)

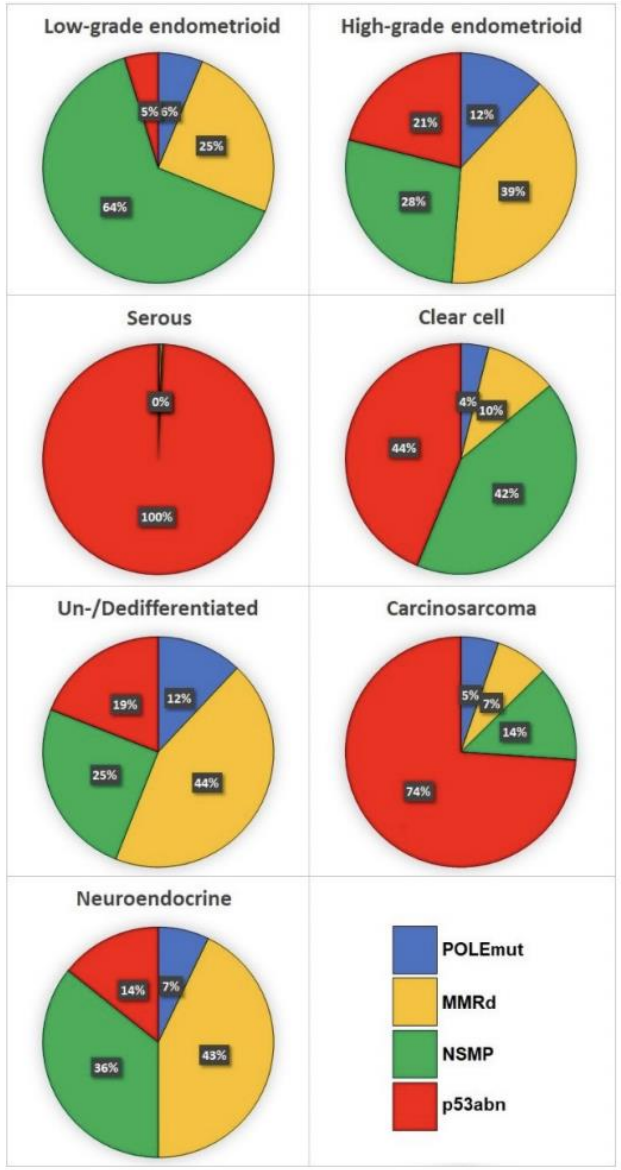
Proactive Molecular Risk Classifier for Endometrial



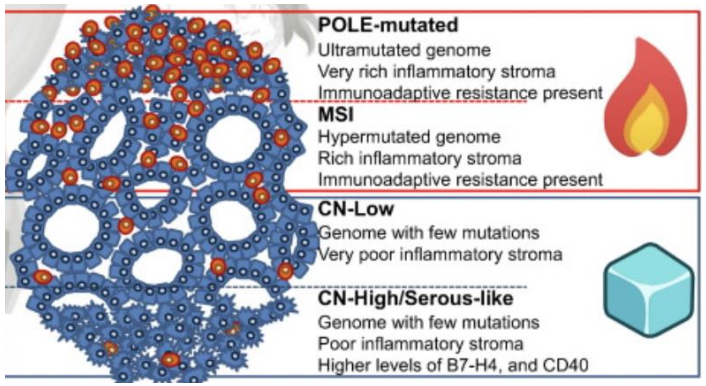


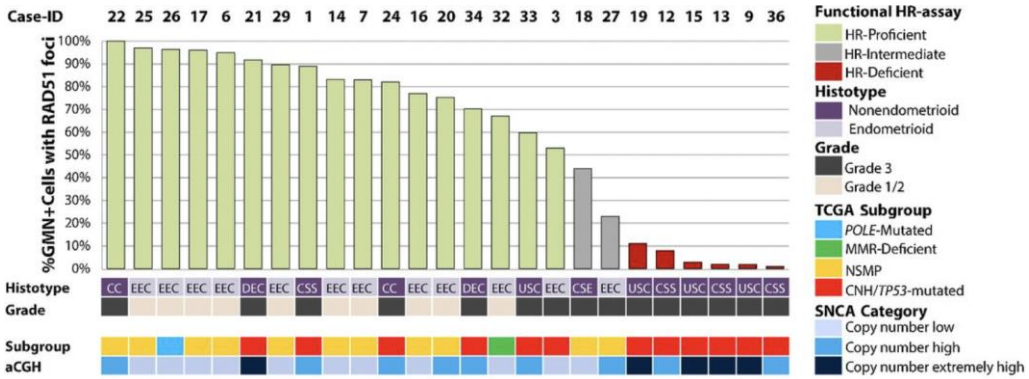
Stelloo et al, MODERN PATHOLOGY, 2015 - Talhouk et al, BJC, 2015 - Talhouk et al, Cancer, 2017

Distribution of TCGA molecular groups according to EC histotype



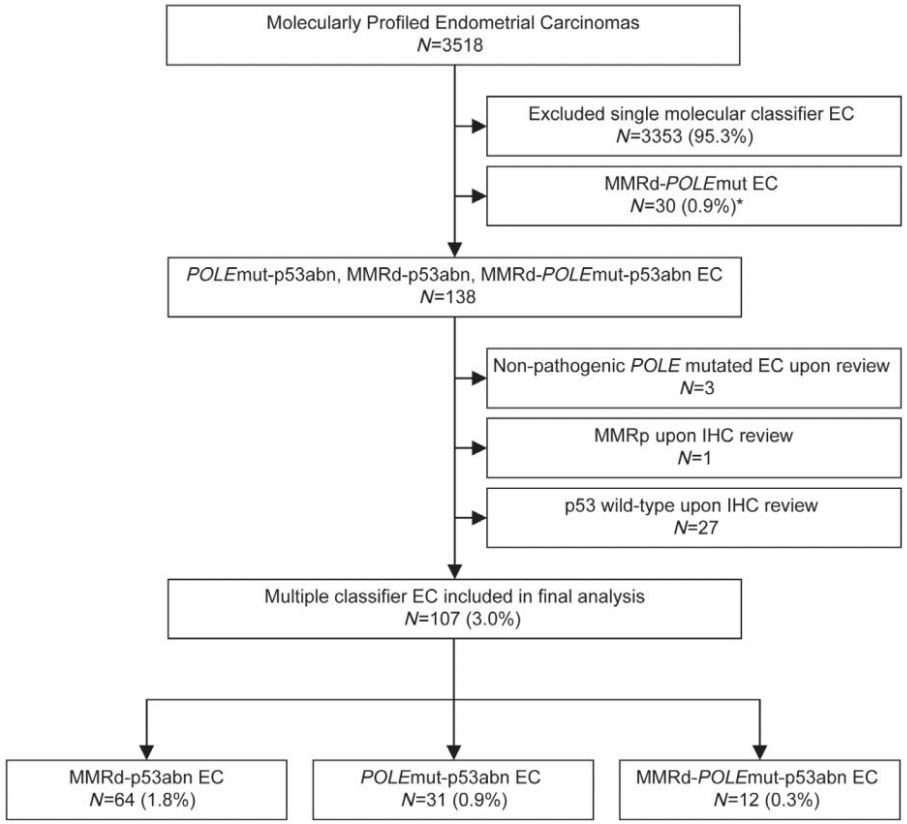
- *Molecular classification encouraged in all EC, especially high-grade*
- *In context of high-grade and/or high-risk molec clissification seems to be relevant for adjuvant Ttt*
  - ✓ *anti-PDL-1 in MMRd signature or POLE signature*
  - ✓ *PARP-inhibitors or anti-HER2 in p53 signature*
- *Decomposition of NSMP: L1CAM expression ? CTNNB1 ?*



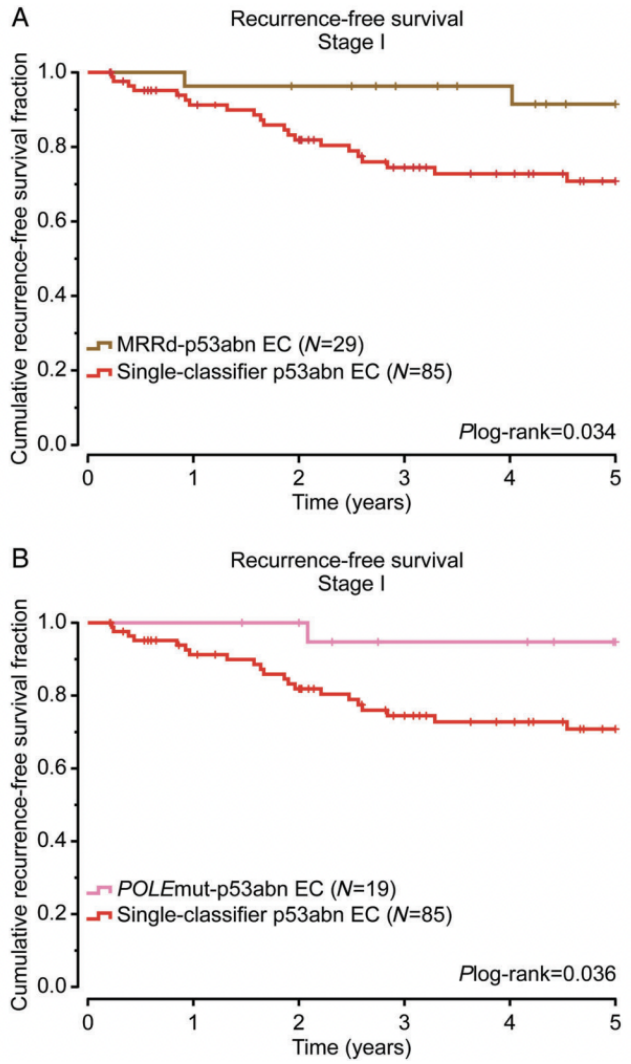


Douglas and TCGA, Nature, 2013 – Santoro et al, Cancers, 2021 – de Jonge et al, Clinical Cancer Research, 2018 – Piulats et al, Genecologic oncology, 2017

Multiple-classifier (5th sous-type)



Multiple-classifier : 3% EC
POLEmut prevails over MMR and p53 status
MMRd signature prevails over P53 status



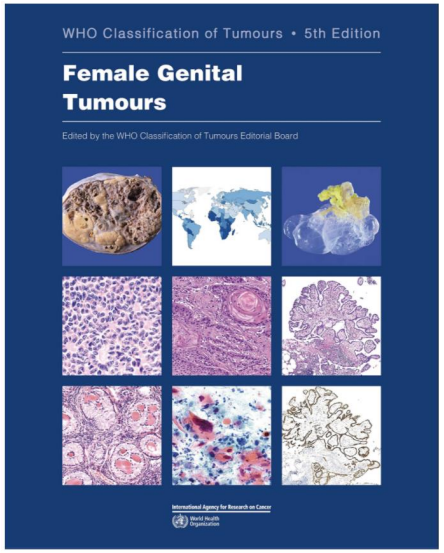
Leon-Castillo, J Pathol, 2020

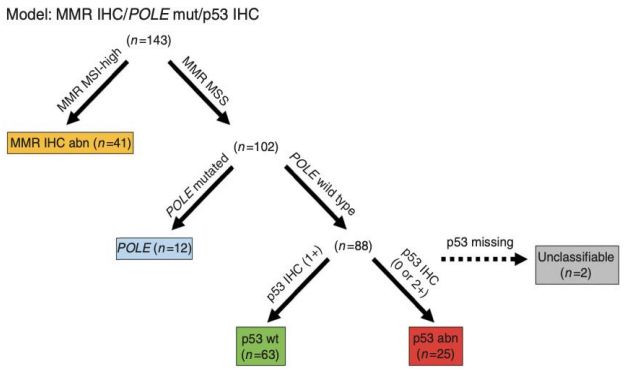
Table 2 Definition of prognostic risk groups

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

T – Primary Tumour

TNM Categories		FIGO Stages	
TX			Primary tumour cannot be assessed
T0			No evidence of primary tumour
T1		I[a]	Tumour confined to the corpus uteri[a]
	T1a	IA[a]	Tumour limited to endometrium or invading less than half of myometrium
	T1b	IB	Tumour invades one half or more of myometrium
T2		II	Tumour invades cervical stroma, but does not extend beyond the uterus
T3		III	Local and/or regional spread as specified here:
	T3a	IIIA	Tumour invades the serosa of the corpus uteri or adnexae (direct extension or metastasis)
	T3b	IIIB	Vaginal or parametrial involvement (direct extension or metastasis)
N1,N2		IIIC	Metastasis to pelvic or para.aortic lymph nodes[b]
	N1	IIIC1	Metastasis to pelvic lymph nodes
	N2	IIIC2	Metastastis to para.aortic lymph nodes with or without metastasis to pelvic lymph nodes
T4[c]		IV	Tumour invades bladder/bowel mucosa





Concin et al, Int J Gynecol Cancer, 2020

> Gynecol Oncol. 2014 May;133(2):197-204. doi: 10.1016/j.ygyno.2014.02.012. Epub 2014 Feb 18.

High concordance of molecular tumor alterations between pre-operative curettage and hysterectomy specimens in patients with endometrial carcinoma

Ellen Stelloo [1], Remi A Nout [2], Lisanne C L M Naves [1], Natalja T Ter Haar [1], Carien L Creutzberg [2], Vincent T H B M Smit [1], Tjalling Bosse [3]

> Gynecol Oncol. 2016 Oct;143(1):46-53. doi: 10.1016/j.ygyno.2016.07.090. Epub 2016 Jul 14.

Molecular classification of endometrial carcinoma on diagnostic specimens is highly concordant with final hysterectomy: Earlier prognostic information to guide treatment

Aline Talhouk [1], Lien N Hoang [2], Melissa K McConechy [3], Quentin Nakonechny [4], Joyce Leo [4], Angela Cheng [5], Samuel Leung [5], Winnie Yang [1], Amy Lum [1], Martin Köbel [6], Cheng-Han Lee [7], Robert A Soslow [8], David G Huntsman [1], C Blake Gilks [4], Jessica N McAlpine [9]

Repeat analysis ?
Curettage/hysterectomy
ESMO : risk group allocation on biopsy is required for adequate

Report of pathology results

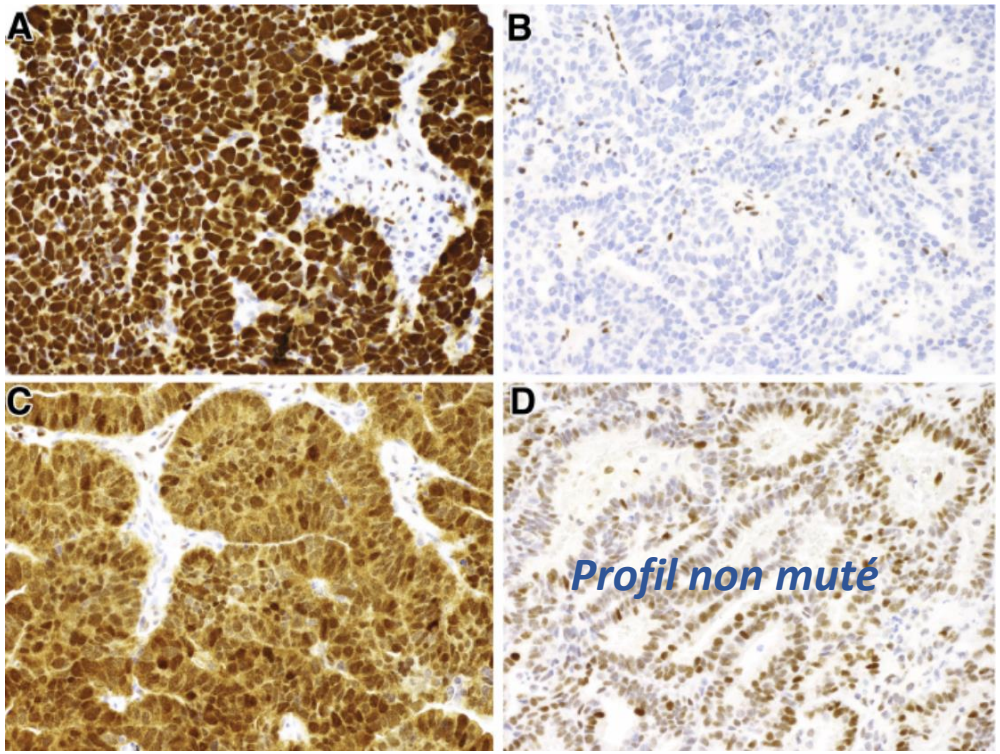
- Tumor type (WHO classification)
  - Endometrioid carcinoma
  - Non Endometrioid carcinoma
- Tumor grade (FIGO/WHO for EEC)
- LVSI
  - Focal
  - Extensive/Substancial (5 or more)
- Others (if surgery): myometrial invasion, cervical stromal invasion…

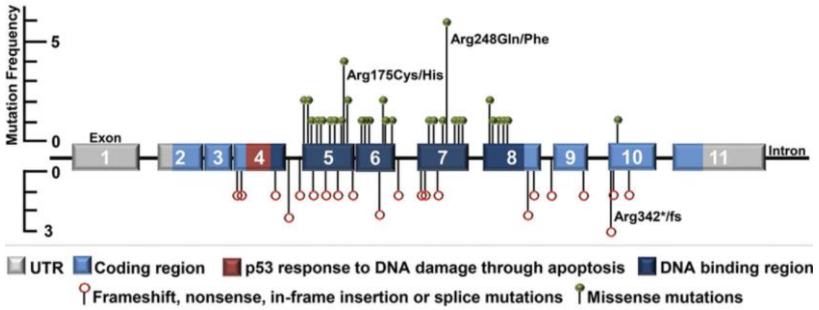
- Ancillary techniques (IHC)
  - ER, RP, p16 et p53,

  Testing MMR (MSH6, PMS2, MLH1, MSH2)

- Somatic mutation analysis of *POLE*

IHC p53





Singh et al, J Pathol, 2020

- Le diagnostic des CE passe par les aspects
  - Cliniques,
  - Radiologiques,
  - Histo-morphologiques,
  - (et aujourd'hui) Moléculaires.

- Les caractéristiques morphologiques et moléculaires dépendent avant tout de la qualité du matériel à analyser.

MERCI POUR VOTRE ATTENTION