Evaluation, Risk-based Stratification & Molecular Classification in Endometrial Cancer

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Burden of Disease

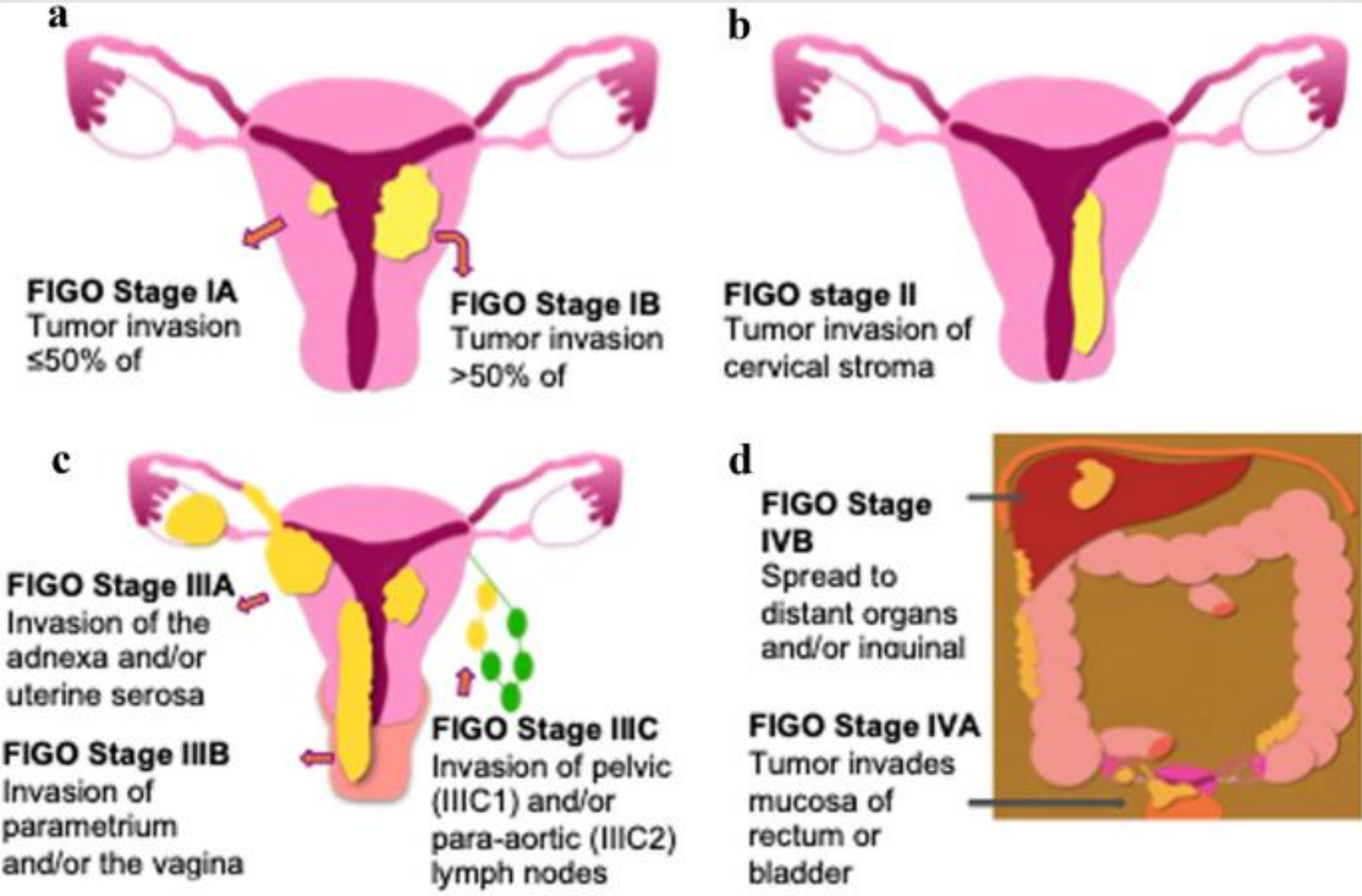
- Endometrial cancer most common Gynecologic malignancy in high-income countries with Age-standardized incidence of 8.7 per 100,000 females (1).
- In India it is the second most common Gynecological malignancy with 16,413 new cases and 6,385 deaths every year (1).
- The incidence peaks between ages 60 and 70 years, but 2 to 5 percent of cases occur before age 40 years (2).

Risk Factors

Estrogen related factors:	Other
1. Early menarche <12- RR- 2.4	1. Advanced age >60
2. Late menopause >55- RR- 1.8	2.Lynch syndrome/ Hereditary non polyposis colon cancer (HNPCC)- 40-60%
3. Nulliparity or history of infertility –RR-3	3. T2 Diabetes – RR-2.1
4. Use of tamoxifen in postmenopausal women- RR-4	4. Metabolic syndrome – RR – 1.89
5. Unopposed estrogen therapy (10-30 fold)	5. overweight/ Obesity – RR- 1.32/2.21
6. Estrogen secreting tumors (Granulosa & thecal cell tumors of ovary)	6. Hypertension – RR- 1.81
7.Polycystic ovarian disease- RR- 2.79	7.Family history of endometrial cancer
8. Liver cirrhosis	8. Prior pelvic irradiation

Ref: Zucchetto Aet Eur J Cancer Prev 2009, Esposito Ket al. Endocrine 2014

Staging in Endometrial Cancer



Histological Classification

Uterine Carcinomas:

- Endometrioid adenocarcinomas (75-80%)
  - Villoglandular
  - Adenoacanthoma (adenoca with benign squamous elements)
  - Secretory
  - Ciliated
- Mucinous adenocarcinoma
- Papillary serous adenoca (1-5%)
- Clear cell adenocarcinoma (5-10%)
- Squamous cell carcinoma
- Undifferentiated carcinoma

Uterine Sarcomas: (3%)

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Adenosarcoma
- Carcinosarcoma (Malignant Mixed Mullerian Tumour/ MMMT)

Histological Grading

FIGO histological grading is based on degree of differentiation:

G1 : ≤ 5% non squamous or non morular solid growth pattern

G2 : 6–50% non squamous or non morular solid growth pattern

G3 : >50% non squamous or non morular solid growth pattern

GX : Grade cannot be assessed

G1 : Well differentiated

G2 : Moderately differentiated

G3 : Poorly differentiated or undifferentiated

High risk histology:

Serous, clear cell and

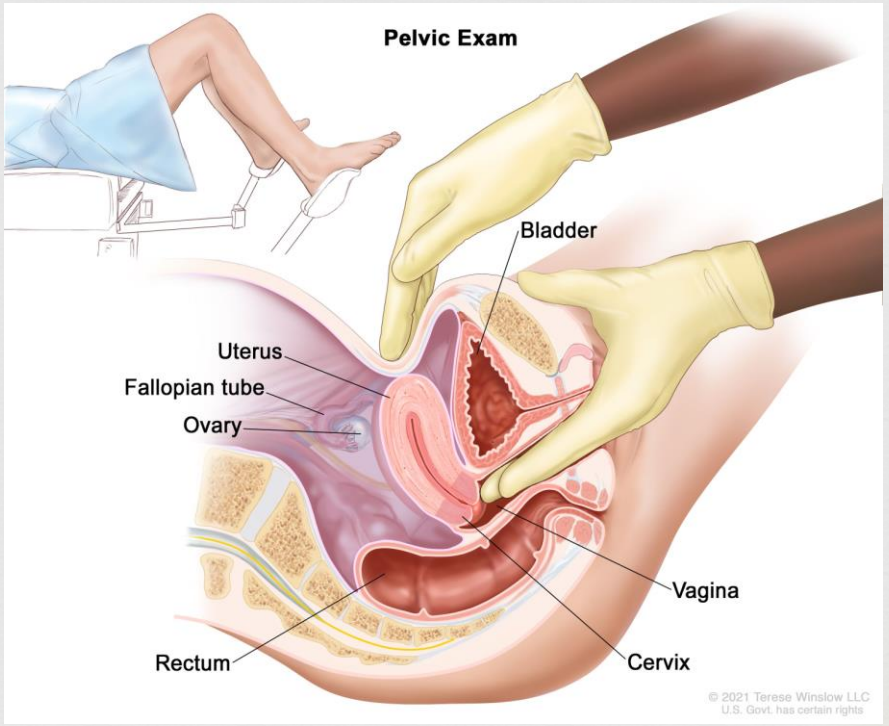
MMMTs- *high risk* – Grade 3

Clinical Presentation

- Abnormal Uterine Bleeding
  present in 75 to 90 percent of cases.
- Abnormal Cervical Cytology
- Incidental finding on Imaging
- Incidental finding after hysterectomy or during abdominopelvic surgery

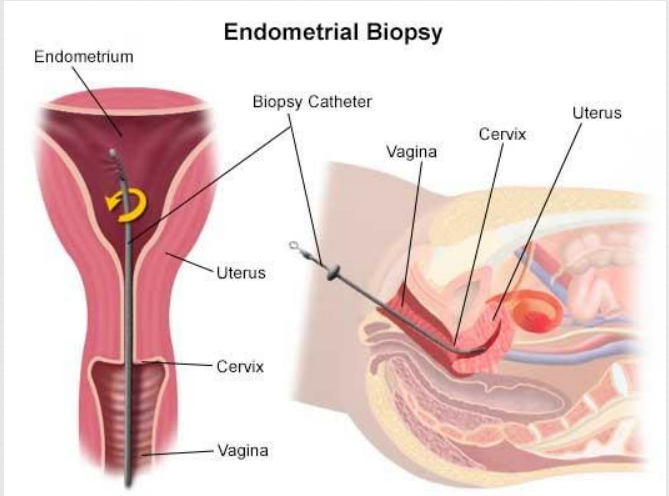
Evaluation

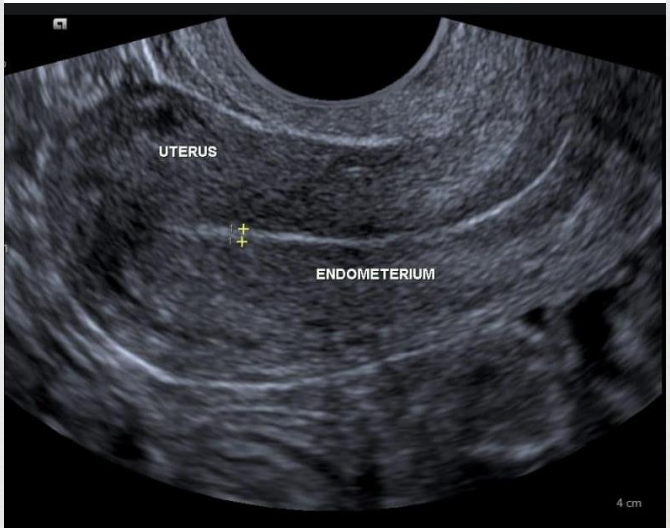
- History ,Physical examination, including bimanual pelvic and bidigital examination
- Assessing baseline fitness of patient:
  - Routine blood investigations
  - Chest X Ray



Establish Diagnosis

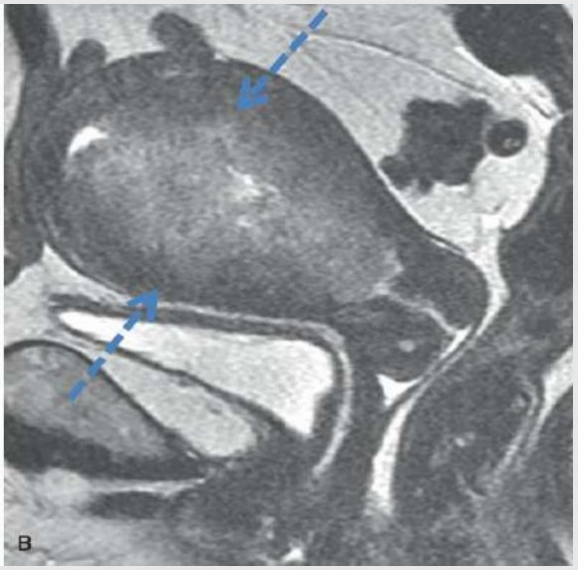
- TVS
  - 5mm thickness in post menopausal women – abnormal
  - Sensitivity of 96%
  - Premenopausal women - endometrial thickness fluctuates with hormone levels
- Endometrial tissue sampling- Gold std
  - Biopsy- Pippelle (Sensitivity 91% in premenopausal, 99.6% in postmenopausal)- OPD Biopsy
  - D and C- Not routinely required if patient is asymptomatic and is planned for surgery
- Hysteroscopy Biopsy
  - If TVS is abnormal but biopsy is inconclusive

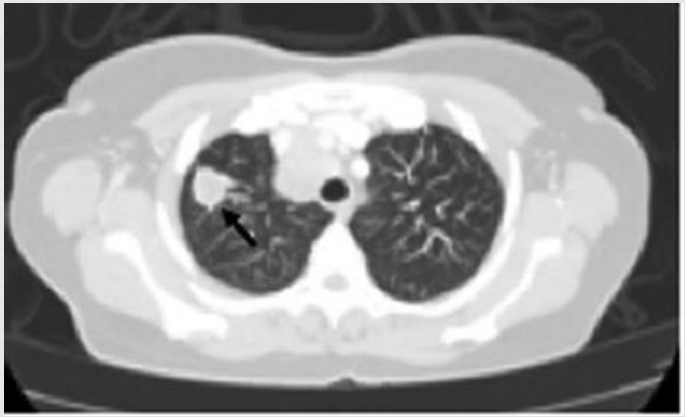




Staging

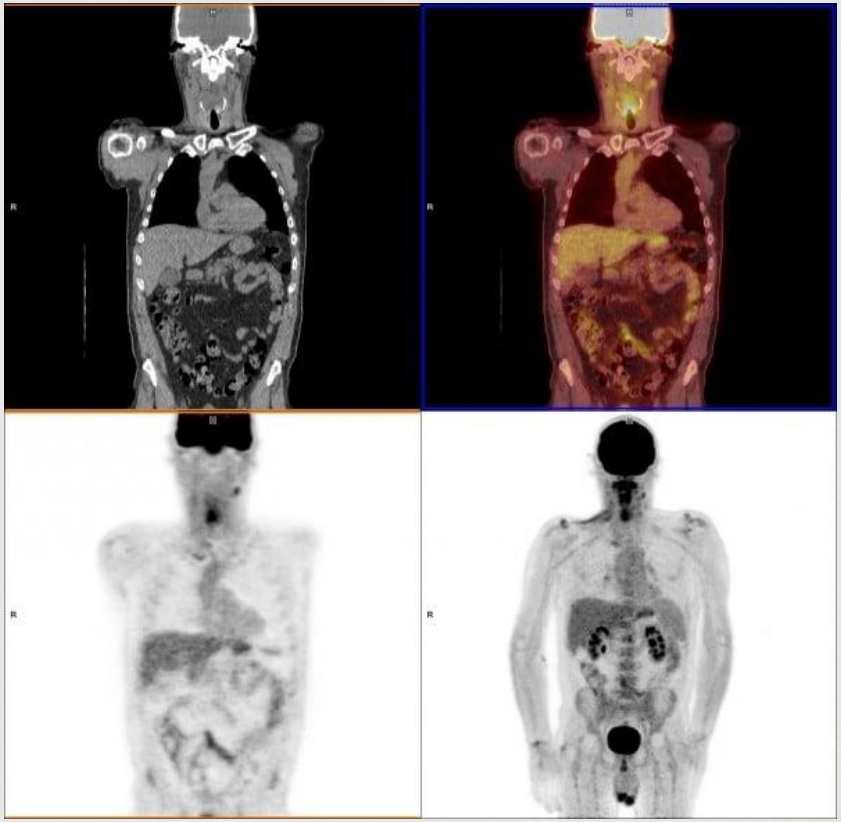
- MRI Pelvis:
  - For determining extent of myometrial invasion
  - To delineate cervical stromal involvement
  - Prior to fertility sparing treatment
  - To rule out residual disease (post incomplete surgery)
  - Status of Pelvis Lymphadenopathy
- CECT Thorax + Abdomen
  - In advanced stages (To rule out distant metastasis).





Additional tests

- PET CECT:
  - In advanced stages
  - LN/ Distant mets
  - Recurrent disease
  - Disadvantage – if <5mm sensitivity is as low as 12%
- CA -125 :
  - Could be elevated in patients with Ca Endometrium
  - Not routinely done
  - Preop levels >40U/mL → s/o regional LN mets and can be used as an indication for full pelvic/ PALND in the absence of metastatic disease.



MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer — A multicenter prospective comparative study

Sofie Leisby Antonsen [a,*], Lisa Neerup Jensen [b], Annika Loft [c], Anne Kiil Berthelsen [c], Junia Costa [c], Ann Tabor [b,o], Ingelise Qvist [d], Mette Rodi Hansen [e], Rune Fisker [f], Erik Søgaard Andersen [g], Lene Sperling [h], Anne Lerberg Nielsen [i], Jon Asmussen [j], Estrid Høgdall [k], Carsten L. Fagö-Olsen [a], Ib Jarle Christensen [l], Lotte Nedergaard [m], Kirsten Jochumsen [n], Claus Høgdall [o]

Models for optimizing predictive value of myometrial invasion, cervical invasion and lymph node metastases in endometrial cancer patients.

Imaging	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Myometrial invasion					
PET/CT + MRI + 2DUS	100	27.8	38.7	100	50.4
PET/CT + MRI	100	35.1	37.0	100	53.0
PET/CT + 2DUS	95.7	35.7	41.7	94.6	55.2
MRI + 2DUS	95.7	45.2	43.6	95.9	60.7
Cervical invasion					
PET/CT + MRI + 2DUS	46.2	81.3	40.0	84.8	73.8
PET/CT + MRI	51.3	89.8	55.6	88.1	82.1
PET/CT + 2DUS	45.2	86.8	48.7	85.2	77.8
MRI + 2DUS	40.5	87.5	47.2	84.2	77.3
Lymph node metastases					
PET/CT + MRI	85.7	88.2	37.5	98.8	88.6

PPV: positive predictive value, NPV: negative predictive value.

Surgical Staging

Surgery - mainstay of treatment

- Extrafascial total hysterectomy with bilateral salpingo-ophorectomy
  - Inspection of the pelvic & abdominal cavities
  - Biopsy of any suspicious extrauterine lesions
  - Peritoneal washings in most cases
  - Surgical assessment of lymph nodes ranges
    - Palpation and Biopsy of suspicious nodes
    - Sentinel lymph node biopsy / Pelvic +/- para-aortic lymphadenectomy
  - Omental bx – in clear cell / serous carcinoma and carcinosarcoma histologies

Risk based Stratification

Need to identify patients with higher chances of local and/or distant recurrences.

In 1983 Bokhran described two risk types:

- Type 1 EC
  - Comprise 65% of EC
  - Estrogen driven
  - Lower grade or endometrioid histologies
  - Favourable prognosis

- Type 2 EC
  - Clinically aggressive histologies
  - Diverse mix of high grade histologies
  - Poor treatment outcomes

Could not capture biological diversity and clinical outcomes of all histologies

RSS	Low	Low Intermediate	High Intermediate	High
PORTEC-1-2000	Stage Ia, grade 1	Stage I with Gr 1 and MMI⩾50% , Gr 2 with any MMI Gr 3 with MMI <50%	Age >60 years with Gr 1 or 2 and MMI >50% Age >60 with Gr 3 and MMI <50%	Stage III–IV disease Uterine serous carcinoma or clear cell carcinoma of any stage
GOG-99-2004	Grade 1 or 2, endometrioid cancers confined to the endometrium stage IA	Age ⩽50 years + ⩽2 RFs Age 50–69 years + ⩽1 RF Age ⩾70 years + no RF	Any age + 3 risk factors Age 50–69 years + ⩾2 RFs Age ⩾70 years + ⩾1 RFs	High-risk Stage III–IV disease-any histology or grade Uterine serous carcinoma or clear cell carcinoma of any stage
SEPAL-2010	Stage IA IB, endometrioid type, LVSI negative	Stage IA grade 3 endometrioid adenocarcinoma; any grade of non-endometrioid carcinoma, any LVSI Stage IB, Gr 1–2 endometroid, LVSI positive Stage IB, Gr 3 endometrioid; non- endometrioid- any LVSI / any grade Stage IC, stage II, any grade, any LVSI		Stage III–IV, any grade, any LVSI
ESMO-2013	Stage IA (Gr 1 & 2) endometrioid type	Stage IA Gr 3 endometrioid , Stage IB (Gr 1 and 2) endometrioid		Stage IB Gr 3 endometrioid type ,All stages with non-endometrioid type
Modified ESMO-2014	Stage I endometrioid, grade 1–2,	Stage I endometrioid, grade 1–2, ≥50% MMI, LVSI negative	Stage I endometrioid, grade 3, <50% MMI, regardless of LVSI status Stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of DOI	Stage I endometrioid, grade 3, ≥50% MMI, regardless of LVSI status Stage II, Stage III endometrioid, no residual disease Non-endometrioid

ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer

Diagnosis, Treatment and Follow-up

Nicoletta Colombo, Carien Creutzberg,† Frederic Amant,‡ Tjalling Bosse,§ Antonio González-Martín,|| Jonathan Ledermann,¶ Christian Marth,# Remi Nout,** Denis Querleu,†† Mansoor Raza Mirza,‡‡ Cristiana Sessa,§§ and the ESMO-ESGO-ESTRO Endometrial Consensus Conference Working Group*

Risk stratification	Factors
Low risk	Stage I endometrioid, grade 1–2
Intermediate low risk	Stage I endometrioid, grade 1–2, ≥50% MMI, LVSI negative
Intermediate high risk	Stage I endometrioid, grade 3, <50% MMI, regardless of LVSI status Stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of DOI
High risk	Stage I endometrioid, grade 3, ≥50% MMI, regardless of LVSI status Stage II, Stage III endometrioid, no residual disease Non-endometrioid

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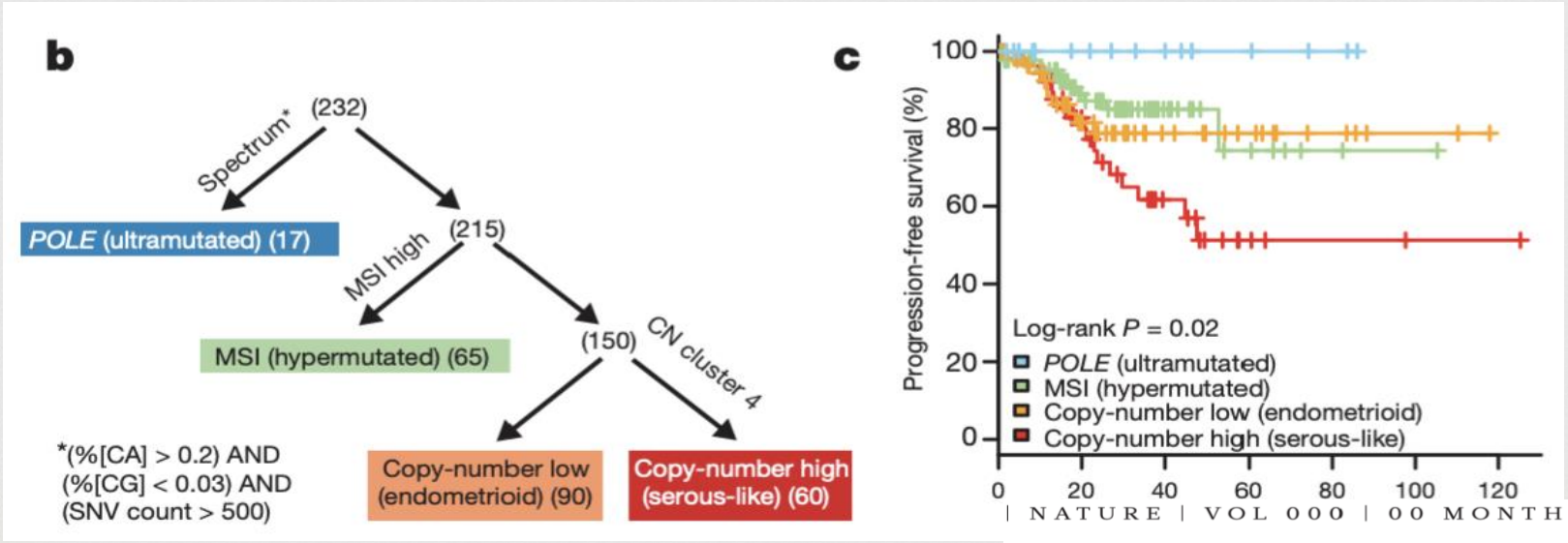
Caveats of Histo-morphological Classification

- Grade and stage migration from endometrial biopsy to hysterectomy specimens in 15-30% of patients (3,4).
- Identifying patients requiring adjuvant therapy remain a tremendous challenge.
- Histologic subtype assignment having moderate concordance among pathologists ranging from 60-70% only (5,6).
- Poor reproducibility in identifying multiple pathologic features
- Need for bringing more reproducibility and objectivity

Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

Group	POLE ultramutated	MSI hypermutated	Copy-number low	Copy-number high
Histology		Primarily endometrioid histology		Most serous/mixed histology tumors and 25% of grade 3 endometrioid tumors
Group identity	POLE exosome domain mutation (100%)	MSI (*MLH1* gene hypermethylation)	Low SCNAs	High SCNAs
Characteristic	Low SCNAs	Low SCNAs	High frequency CTNNB1, SOX17, KRAS, β-catenin mutations	High frequency TP53, ERBB2, CDKN2A mutations and low PTEN expression
	High mutation rate (232×10^{-6}/Mb)	High mutation rate (18×10^{-6}/Mb)	Low mutation rate (2.9×10^{-6}/Mb)	Low mutation rate (2.3×10^{-6}/Mb)
Outcome	Better OS and PFS			Poor OS and PFS



Disadvantages of TCGA Classification

- Needed Fresh frozen tissue for analysis
- Gene sequencing was an integral part of the analysis
- Logistic and Financial constraints for its global implementation

Final validation of the ProMisE molecular classifier for endometrial carcinoma in a large population-based case series

S. Kommoss[1], M. K. McConechy[2], F. Kommoss[3], S. Leung[4], A. Bunz[1], J. Magrill[5], H. Britton[5], F. Kommoss[1,6], F. Grevenkamp[1], A. Karnezis[5], W. Yang[5], A. Lum[5], B. Krämer[1], F. Taran[1], A. Staebler[7], S. Lax[8], S. Y. Brucker[1], D. G. Huntsman[5], C. B. Gilks[5], J. N. McAlpine[9,*†] & A. Talhouk[5†]

- More practical classification
- Could be done on standard formalin fixed and paraffin embedded samples
- Used Immunohistochemistry tests (Except POLE EDM) for testing which serves as surrogate for TCGA classification

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DNA Polymerase epsilon (POLE) mutated

- These are Copy number (CN) stable EC
- Recurrent mutations in exonuclease domain of POLE gene
- Highest somatic mutation frequencies exceeding 100 mutations per megabase (Mb)
- Mostly of endometrioid histologic type
- Excellent prognosis with 5-year OS exceeding 95%

Mismatch repair deficient (MMRd)

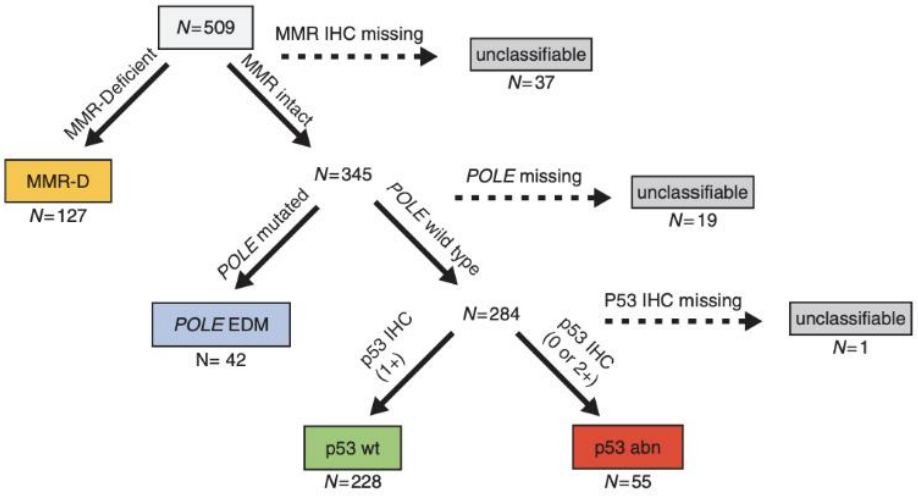
- MMR proteins constitutes: mutL homolog 1 [MLH1], postmeiotic segregation 2 [PMS2], mutS homolog 2 [MSH2], or mutS homolog 6 [MSH6]
- Epigenetic silencing of MLH1 contributes to majority of this subtype
- Lower levels of somatic Copy-number alterations but a high tumor mutational frequency (>10 mutations/Mb)
- Includes both somatic and germline mutations (Lynch syndrome)

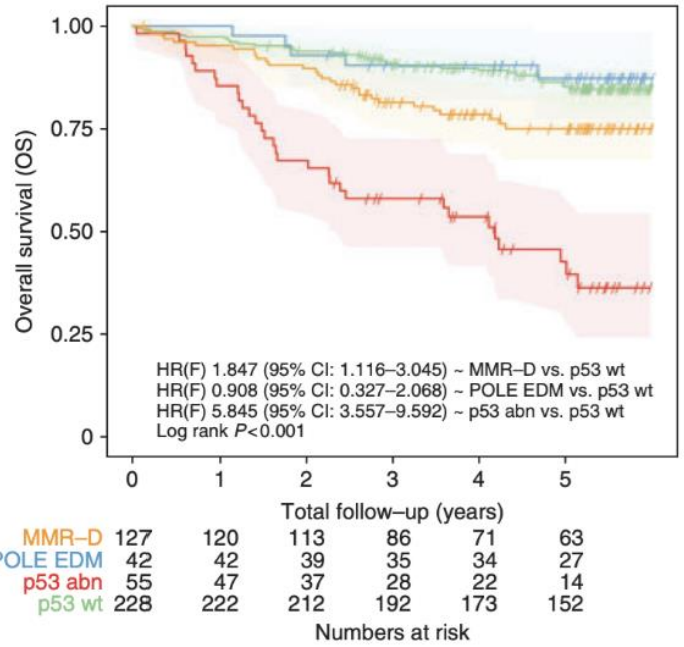
p53 wild-type (p53wt)

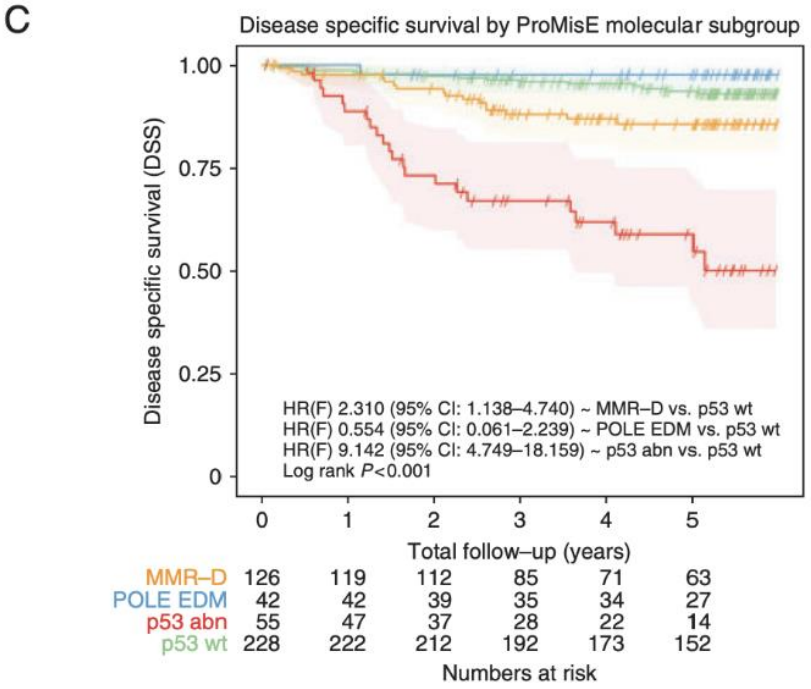
- Genomically stable with moderate mutational load EC
- Involves mostly endometrioid histology with estrogen and progesterone receptor positivity ensuring high response to hormonal therapy
- Has Intermediate to Favorable prognosis

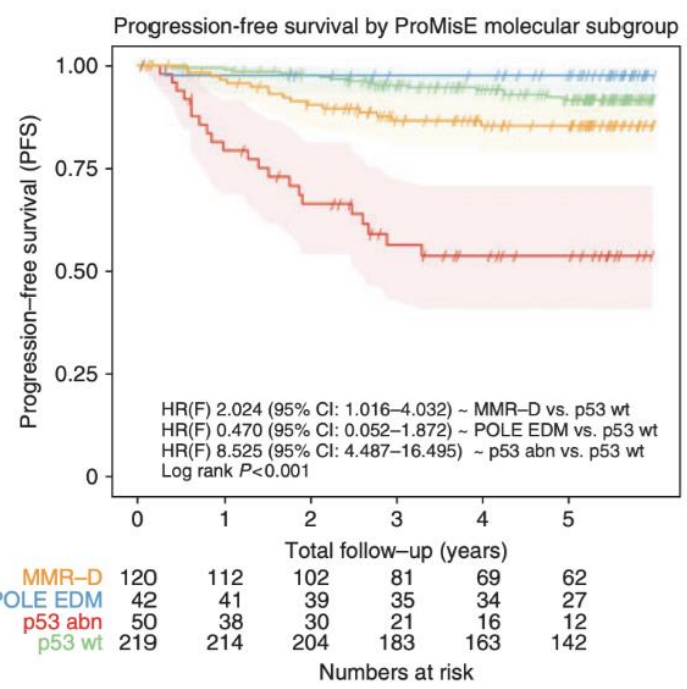
p53 abnormal (p53abn)

- TP53 mutation characteristic of this group
- Has high somatic Copy-number alterations and mutation profiles
- Associated with worse prognosis accounting for 50-70% of endometrial cancer mortality


A
N=509
MMR IHC missing
unclassifiable
N=37
MMR-Deficient
MMR intact
MMR-D
N=127
N=345
POLE missing
unclassifiable
N=19
POLE mutated
POLE wild type
POLE EDM
N= 42
N=284
P53 IHC missing
unclassifiable
N=1
p53 IHC (1+)
p53 IHC (0 or 2+)
p53 wt
N=228
p53 abn
N=55


B
Overall survival by ProMisE molecular subgroup
Overall survival (OS)
1.00
0.75
0.50
0.25
0
HR(F) 1.847 (95% CI: 1.116–3.045) ~ MMR–D vs. p53 wt
HR(F) 0.908 (95% CI: 0.327–2.068) ~ POLE EDM vs. p53 wt
HR(F) 5.845 (95% CI: 3.557–9.592) ~ p53 abn vs. p53 wt
Log rank P<0.001
0 1 2 3 4 5
Total follow–up (years)
MMR–D 127 120 113 86 71 63
POLE EDM 42 42 39 35 34 27
p53 abn 55 47 37 28 22 14
p53 wt 228 222 212 192 173 152
Numbers at risk

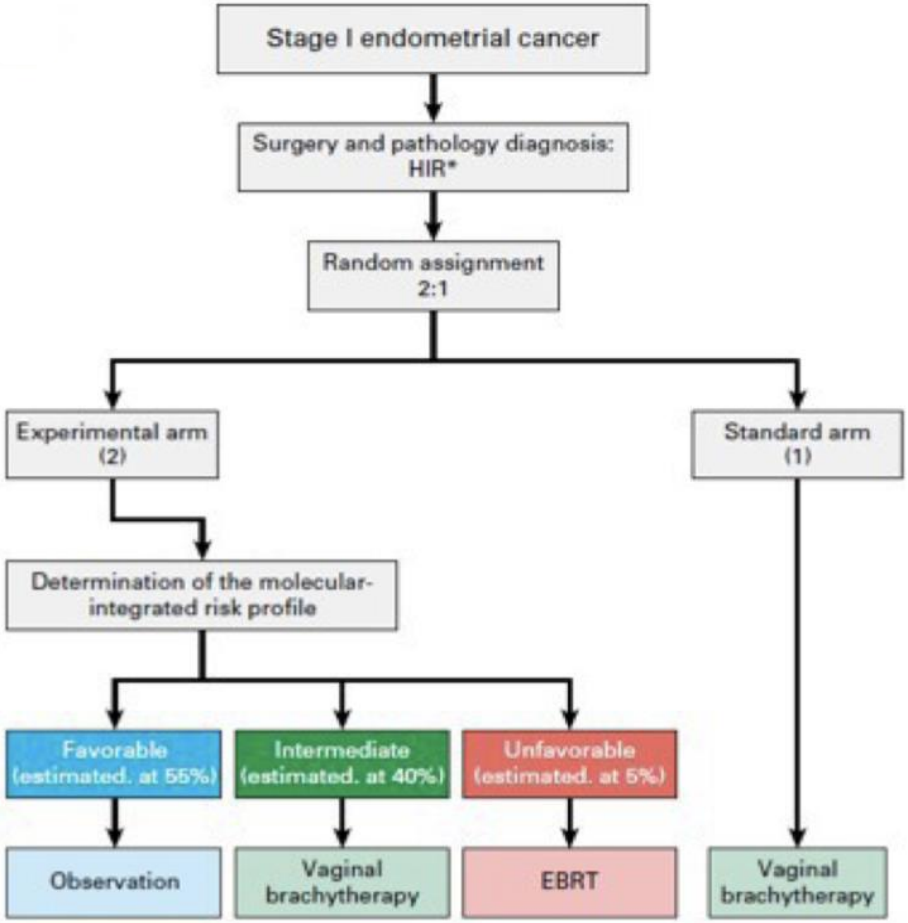

C
Disease specific survival by ProMisE molecular subgroup
Disease specific survival (DSS)
1.00
0.75
0.50
0.25
0
HR(F) 2.310 (95% CI: 1.138–4.740) ~ MMR–D vs. p53 wt
HR(F) 0.554 (95% CI: 0.061–2.239) ~ POLE EDM vs. p53 wt
HR(F) 9.142 (95% CI: 4.749–18.159) ~ p53 abn vs. p53 wt
Log rank P<0.001
0 1 2 3 4 5
Total follow–up (years)
MMR–D 126 119 112 85 71 63
POLE EDM 42 42 39 35 34 27
p53 abn 55 47 37 28 22 14
p53 wt 228 222 212 192 173 152
Numbers at risk

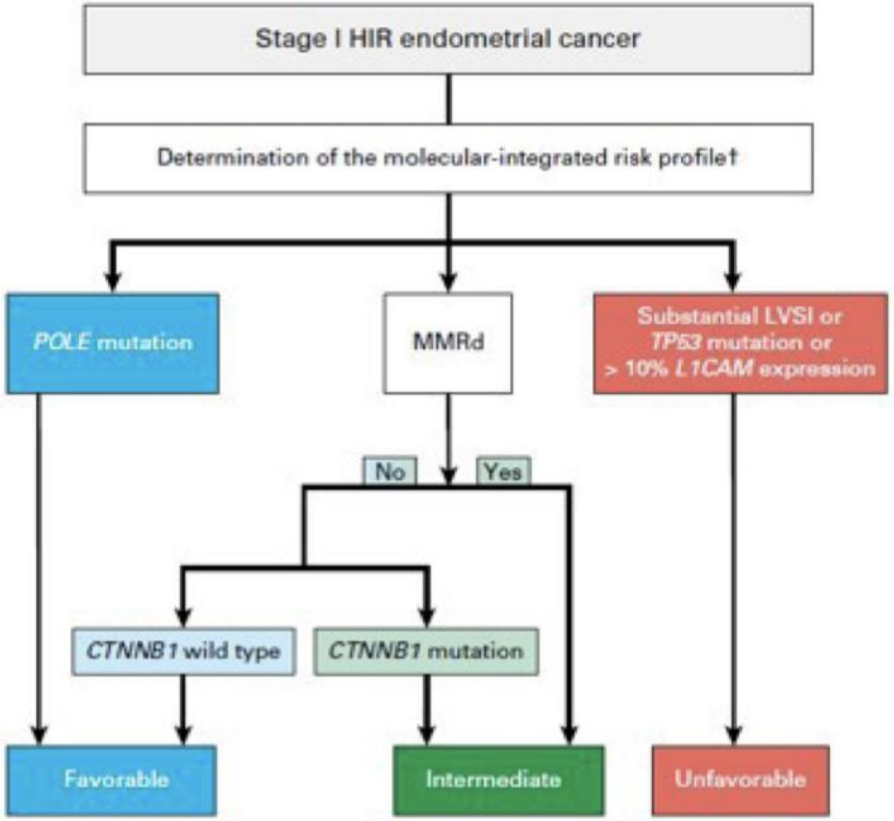

D
Progression-free survival by ProMisE molecular subgroup
Progression–free survival (PFS)
1.00
0.75
0.50
0.25
0
HR(F) 2.024 (95% CI: 1.016–4.032) ~ MMR–D vs. p53 wt
HR(F) 0.470 (95% CI: 0.052–1.872) ~ POLE EDM vs. p53 wt
HR(F) 8.525 (95% CI: 4.487–16.495) ~ p53 abn vs. p53 wt
Log rank P<0.001
0 1 2 3 4 5
Total follow–up (years)
MMR–D 120 112 102 81 69 62
POLE EDM 42 41 39 35 34 27
p53 abn 50 38 30 21 16 12
p53 wt 219 214 204 183 163 142
Numbers at risk

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

ClinicalTrials.gov Identifier: NCT04705649

molecular profile-based adjuvant treatment for women with high-intermediate risk endometrial cancer





van den Heerik ASVM, *et al. Int J Gynecol Cancer* 2020;**30**:2002–2007. doi:10.1136/ijgc-2020-001929

Current impact of Molecular Markers

- Molecular markers introducing more objectivity
- Validation and reliability in Prognostic setting
- Data emerging in its usage as Predictive factor
- Multi institutional collaborative studies needed further for its validation and adaptation in Indian setting

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THANK YOU!!