Endometrial Cancer
FPON - CME Webcast

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UBC

Disclosures

- I have received honoraria and/or travel funding from the following:

- GSK
- Merck
- AstraZeneca
- Abbvie
- Eisai

Learning Objectives

By the end of this session, participants will be able to:

1) Identify endometrial cancer **risk factors**;

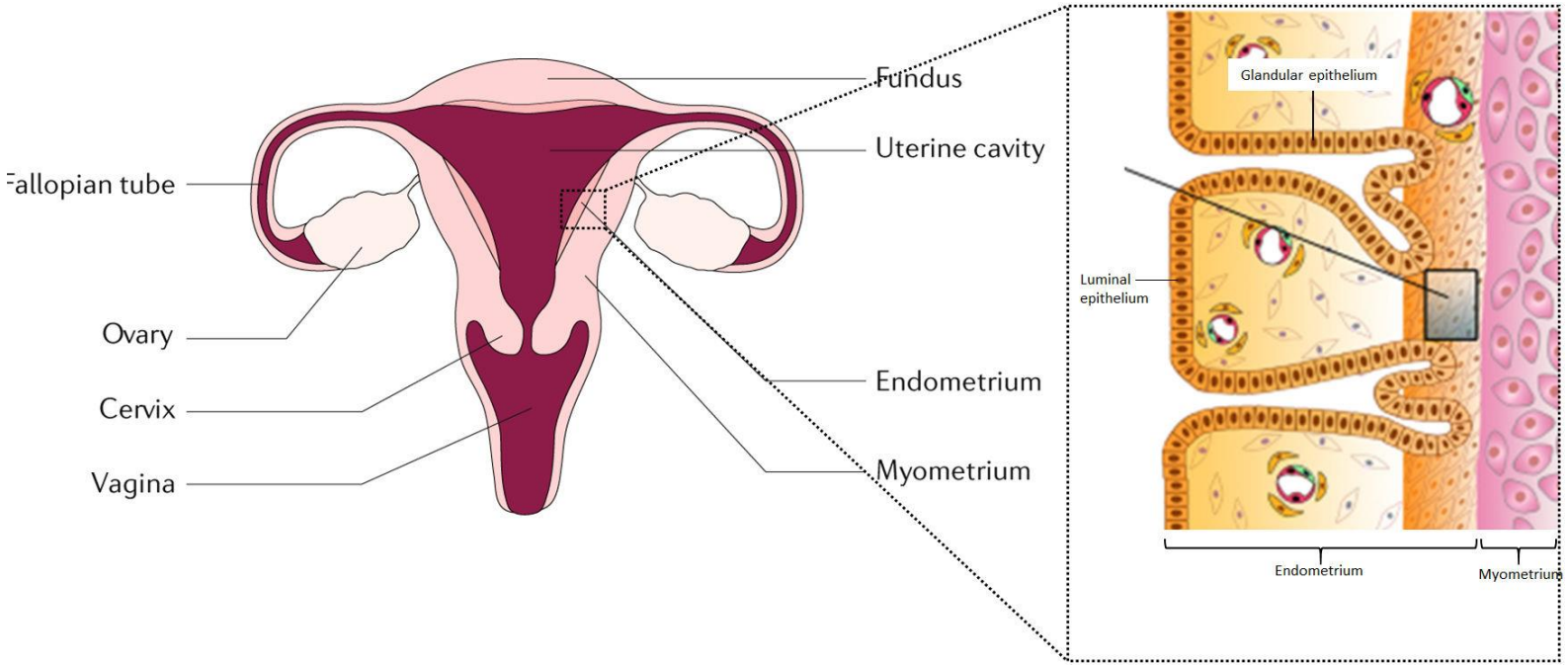
2) Summarize **red flag symptoms**;

3) Review the **diagnostic process**; and

4) Describe **management approach** and post-treatment surveillance recommendations.

Endometrial Cancer (EC) Background

- Most common gynecological malignancy.
- Originates in the **lining of the uterus** (not detected by PAP smear)
- **Average age at diagnosis: 61**
  - 25% of cases occur in premenopausal women, and 5% occurring in women younger than 40 years of age



Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, Oaknin A. Endometrial cancer. Nat Rev Dis Primers. 2021 Dec 9;7(1):88. doi: 10.1038/s41572-021-00324-8. PMID: 34887451; PMCID: PMC9421940.

Endometrial Cancer: Risk Factors

Excess estrogen (relative to progesterone) - impacted by hormonal and reproductive factors.

- **Protective factors**:
  - late menarche
  - parity
  - use of combination estrogen-progesterone birth control pill/HRT/progesterone IUD

- **Risk Factors**:
  - advancing age
  - early menarche (<12) and late menopause (>55)
  - unopposed estrogen (e.g., estrogen only HRT, oligomenorrhea/PCOS)
  - tamoxifen – increased risk in post menopausal women, ~ 1% increase (estrogen agonist effect on endometrium)
  - Lynch Syndrome (rare, affects ~1/400 individuals – women have 40% lifetime risk of EC, 12% risk ovarian ca)
  - Obesity (hyper-estrogenic state due to the peripheral aromatization of adrenal androgens to estrogen by adipose tissue) – 10X increased risk if BMI >30
  - Insulin-resistance and diabetes (increasing the bioavailability of both estrogen and insulin-like growth factor(IGF)-1 by reducing their respective circulating binding proteins)

Modifiable risk factors

Mara Sobel, Andrea N. Simpson and Sarah E. Ferguson. CMAJ September 13, 2021 193 (36) E1423;
Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428. doi: 10.1016/S0140-6736(22)00323-3. PMID: 35397864.

Endometrial Cancer Prevention and Screening

Prevention

- **weight loss** in obese women
- improving **glycemic control** in diabetic women
- use of **combination oral contraceptives** decreases risk by 50% if used for ≥5 years [1].
- addition of a **progestin to estrogen** replacement therapy [2].
- Lynch Syndrome - consider **risk-reducing surgery** (hysterectomy and bilateral salpingo-oophorectomy by the age of 40) to reduce the risk of endometrial and ovarian cancers [3].

Screening

- e.g. endometrial biopsy, transvaginal ultrasound, tumour markers are **NOT proven to decrease the incidence or mortality from cancer in high-risk women**.

1.Kelsey J, Whittemore AS. Epidemiology and primary prevention of cancers of the breast, endometrium and ovary: a brief review. Ann Epidemiology 1994;4:89-95.
2.Miller AB. Planning cancer control strategies. Chronic Dis Can 1992;13:S1-S40.
3.Schmeler KM et al, Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch Syndrome. N Engl J Med 2006;354(3):261-9.

Endometrial Cancer: Incidence

EC incidence rising globally - **132% increase in the last 30 years** (rise in risk factors; in particular **obesity and an ageing population**)[1]

Cases among women **< 40 have double in the US**[1]

The highest rate of EC is currently observed in North America (86·6/100 000)[1]

Lifetime risk: ~1/40 women

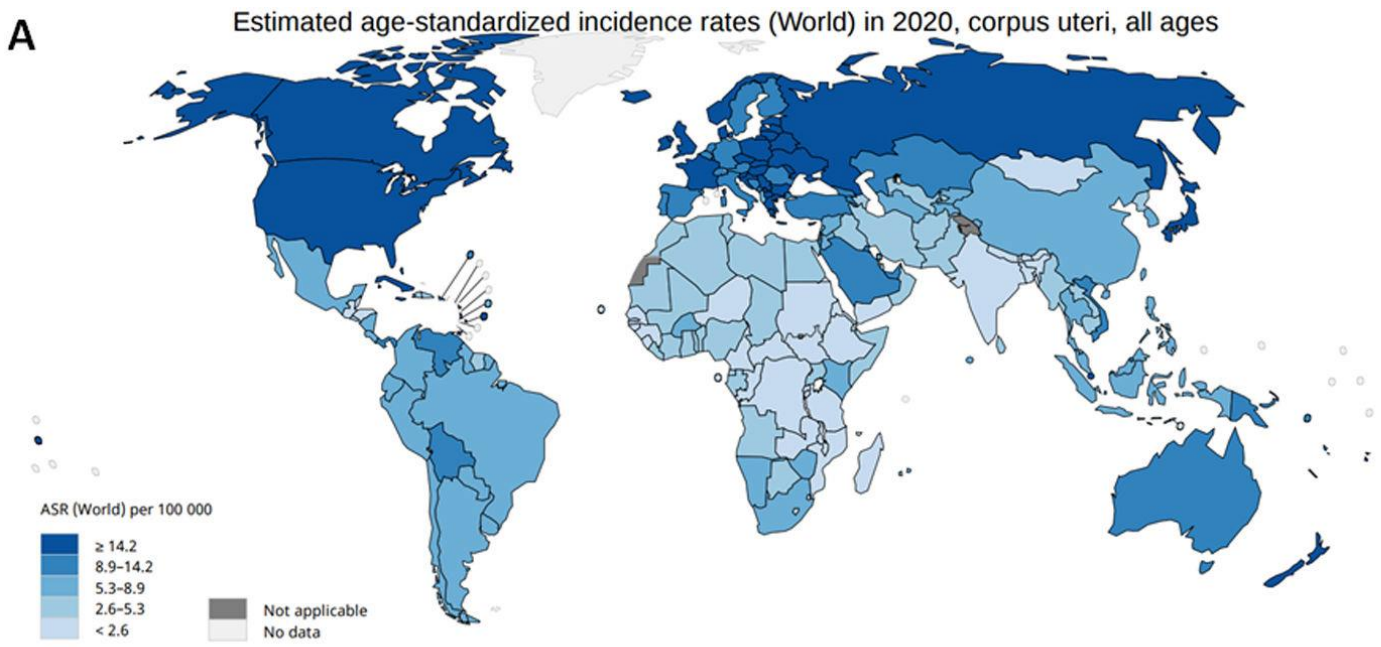
Lifetime risk of EC in women with a BMI greater than 40 kg/m2 is 10–15%, equivalent to the lifetime risk of lung cancer in smokers

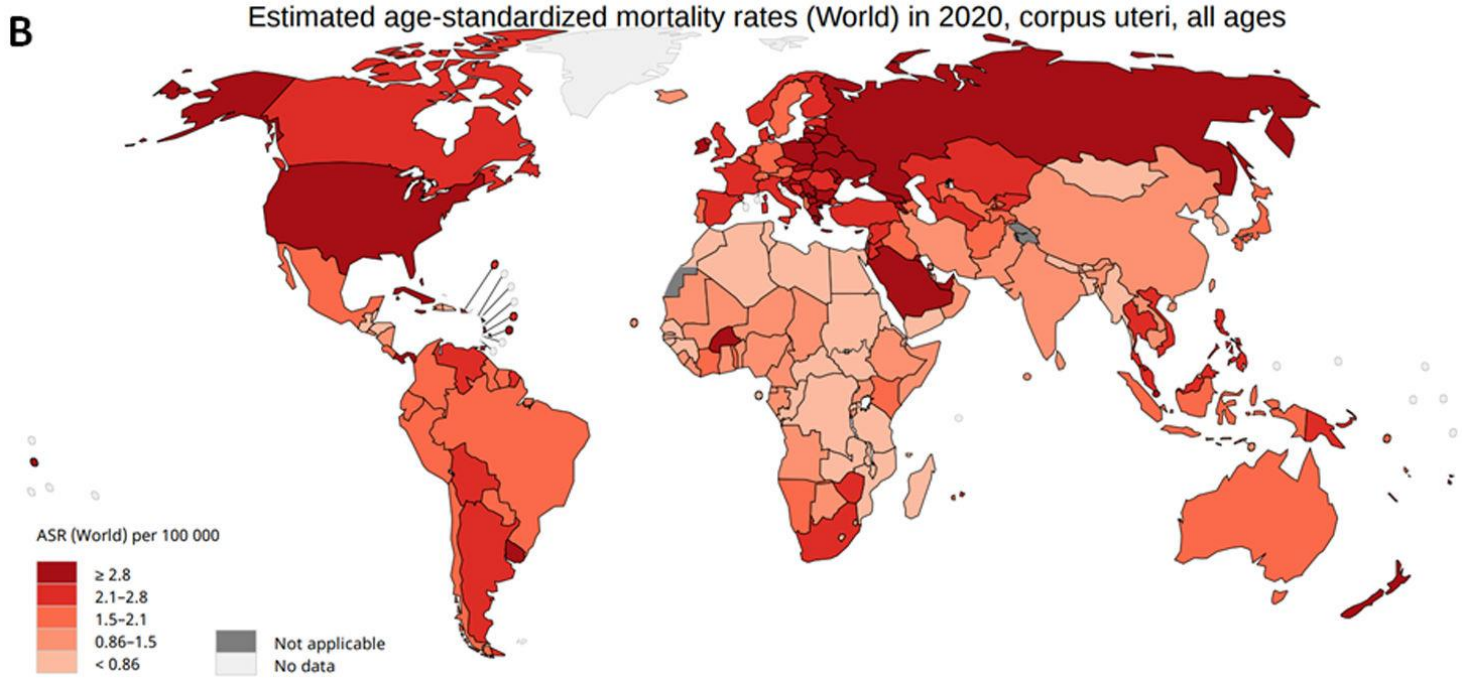
Canadian Cancer Society estimated 8,600 women would be diagnosed with EC and 1,600 would die from it in 2024.

[1] *Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428. doi: 10.1016/S0140-6736(22)00323-3. PMID: 35397864.*

INCIDENCE: EC is more prevalent in high-income countries compared with low-income and middle- income countries

MORTALITY: influenced by socioeconomic status (e.g., income, social class, and educational attainment) as well as access to high-quality healthcare, and oncologist density





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Endometrial Cancer Symptoms and Diagnosis

Post menopausal bleeding - 5–10% of women with postmenopausal bleeding have underlying sinister pathology

The probability of endometrial cancer as a cause of postmenopausal bleeding increases with age

- <1% in women younger than 50 years
- 3% at age 55 years
- 24% in > 80 years

Crosbie et al. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428.

Endometrial Cancer Symptoms and Diagnosis

- Other causes of postmenopausal bleeding (e.g., not EC):
  - Endometrial polyps
  - Submucosal fibroids
  - Endometrial hyperplasia
  - Infections
  - Trauma
  - Vaginal atrophy
  - **Other cancers**: cervical/vaginal, ovarian

Endometrial Cancer Symptoms and Diagnosis

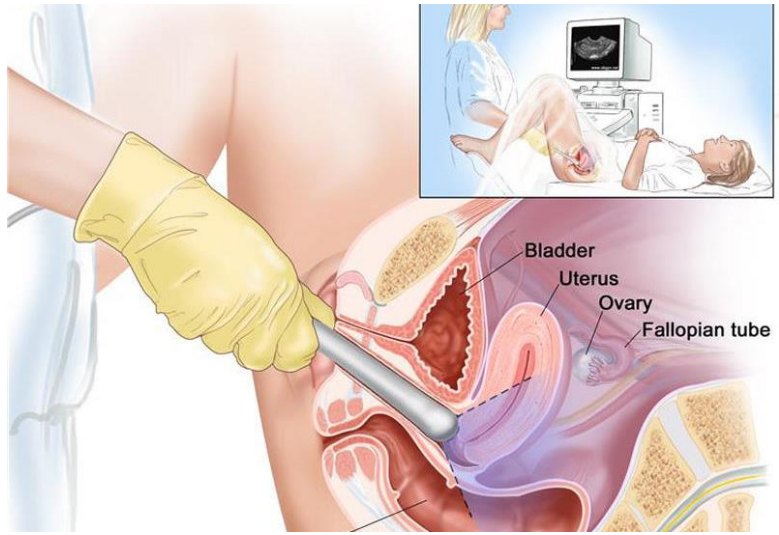
15% of cases are diagnosed **pre-menopause**

- Heavy, prolonged, or **intermenstrual bleeding** (most predictive of EC)
- **CHALLENGE**: common symptom with many causes - EC in 0.3% of cases.
  - Decision to investigate for EC should be guided by **RISK FACTORS**
    - Obesity – symptomatic premenopausal women with a **BMI >30 kg/m² are 10X more likely** to be diagnosed with EC than women with a healthy weight (BMI 18·5–25 kg/m²), in those with **BMI >40 kg/m² this likelihood is 20X increased**
    - Polycystic ovary syndrome (PCOS)
    - Diabetes
    - Family history (Lynch Syndrome)

Crosbie et al. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428.

Diagnosis in Post Menopausal Women: Trans-Vaginal Ultrasound

Transvaginal ultrasound has a high sensitivity, specificity and accuracy in detecting endometrial pathology (including in pre-menopausal women)



- Intra-uterine mass
- Thickened endometrium
- Disease extension into the myometrium
- Disease spread in the pelvis (ovaries, pelvic LNs)

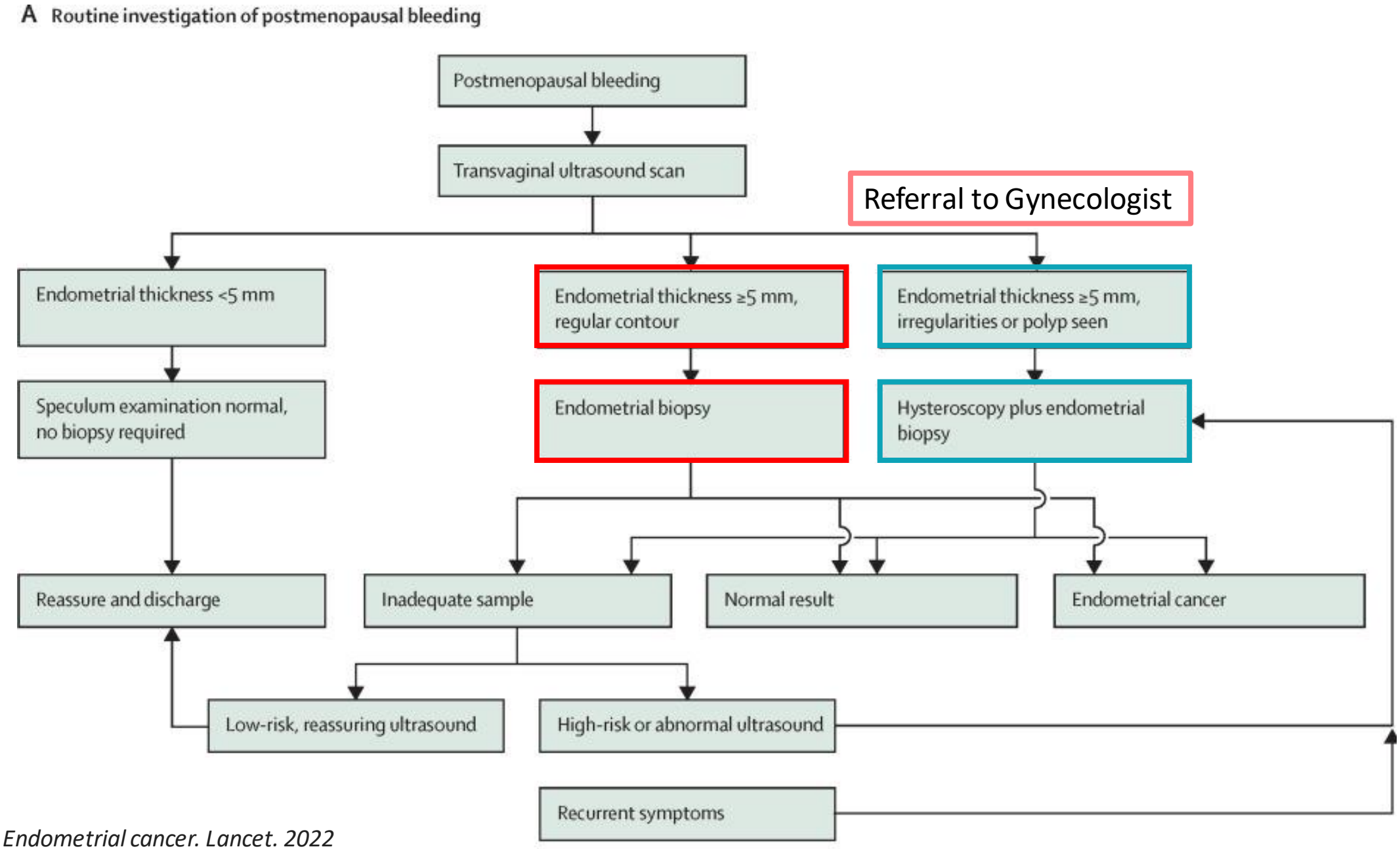
Diagnosis in Post Menopausal Women: Trans-Vaginal Ultrasound

- **Thickened endometrium ≥ 5mm threshold**
- EC detection sensitivity of 96·2% , **specificity of 51.5**% and PPV 21.1
- additional testing (biopsy) required

Table 2
Summary estimates of sensitivity and specificity for different combined cut-off values of ET.

Cut-off	Number of studies	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV	PPV
≥ 3 mm	4	96.2 (92.4–98.2)	42.1 (26.2–59.8)	99.7	7.3
≥ 4 mm	14	95.7 (88.1–98.5)	46.0 (36.7–55.6)	99.4	12.7
≥ 5 mm	20	96.2 (92.3–98.1)	51.5 (42.3–60.7)	99.3	21.1
≥ 6 mm	5	85.2 (70.2–93.3)	64.0 (53.0–73.6)	99.1	17.6
> 8 mm	6	88.0 (71.4–95.5)	66.2 (52.3–77.8)	98.8	22.3
≥ 10 mm	9	78.2 (64.7–87.5)	83.7 (74.4–90.1)	98.1	33.7
> 15 mm	4	58.9 (48.6–68.5)	94.2 (79.6–98.5)	94.0	55.7

B Long, MA Clarke, ADM Morillo, N Wentzensen, JN Bakkum-Gamez
Ultrasound detection of endometrial cancer in women with postmenopausal bleeding: systematic review and meta-analysis
Gynecol Oncol, 157 (2020), pp. 624-633



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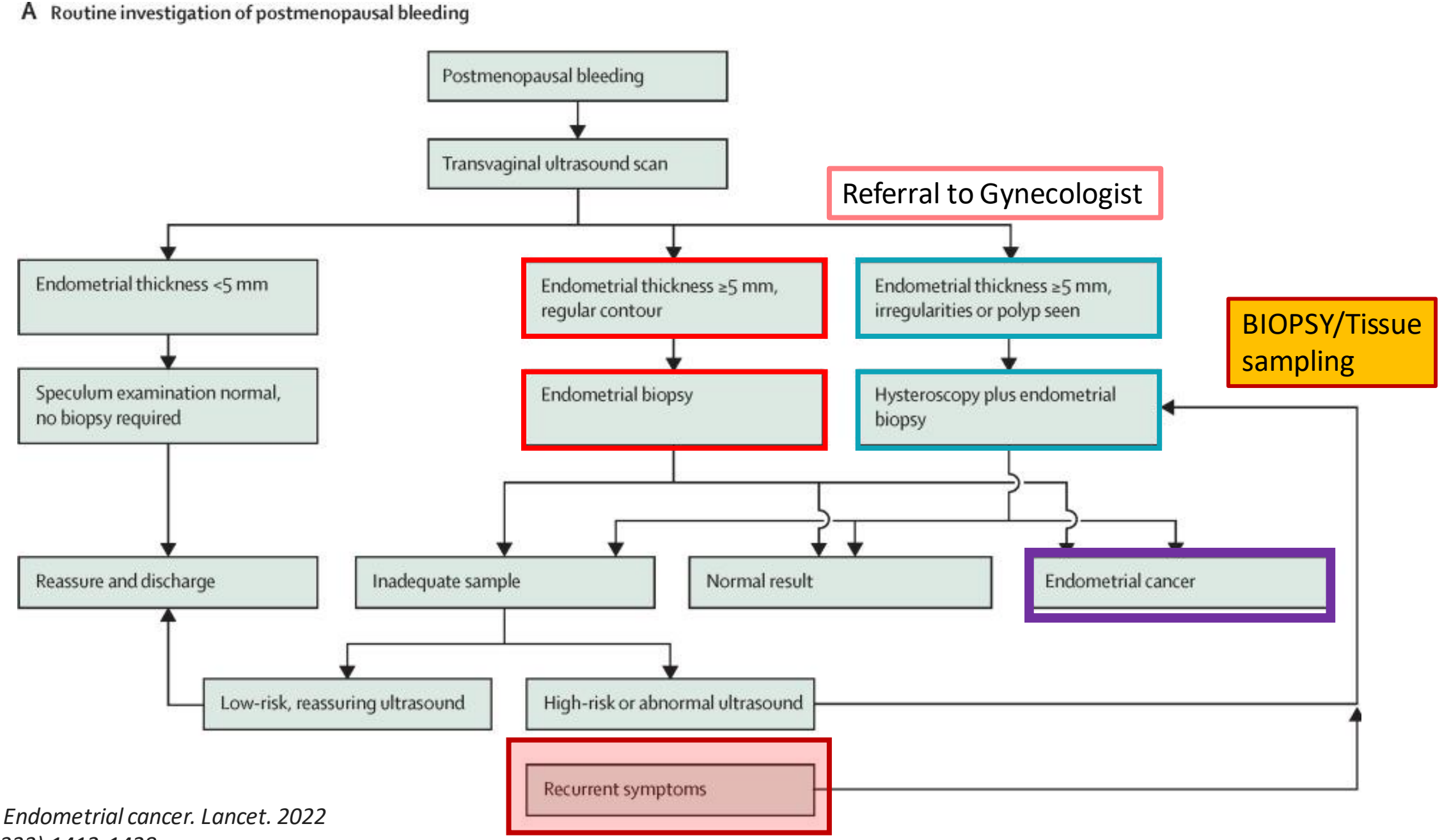


Crosbie et al. Endometrial cancer. Lancet. 2022 Apr 9;399(10333):1412-1428.

Atypical Endometrial Hyperplasia

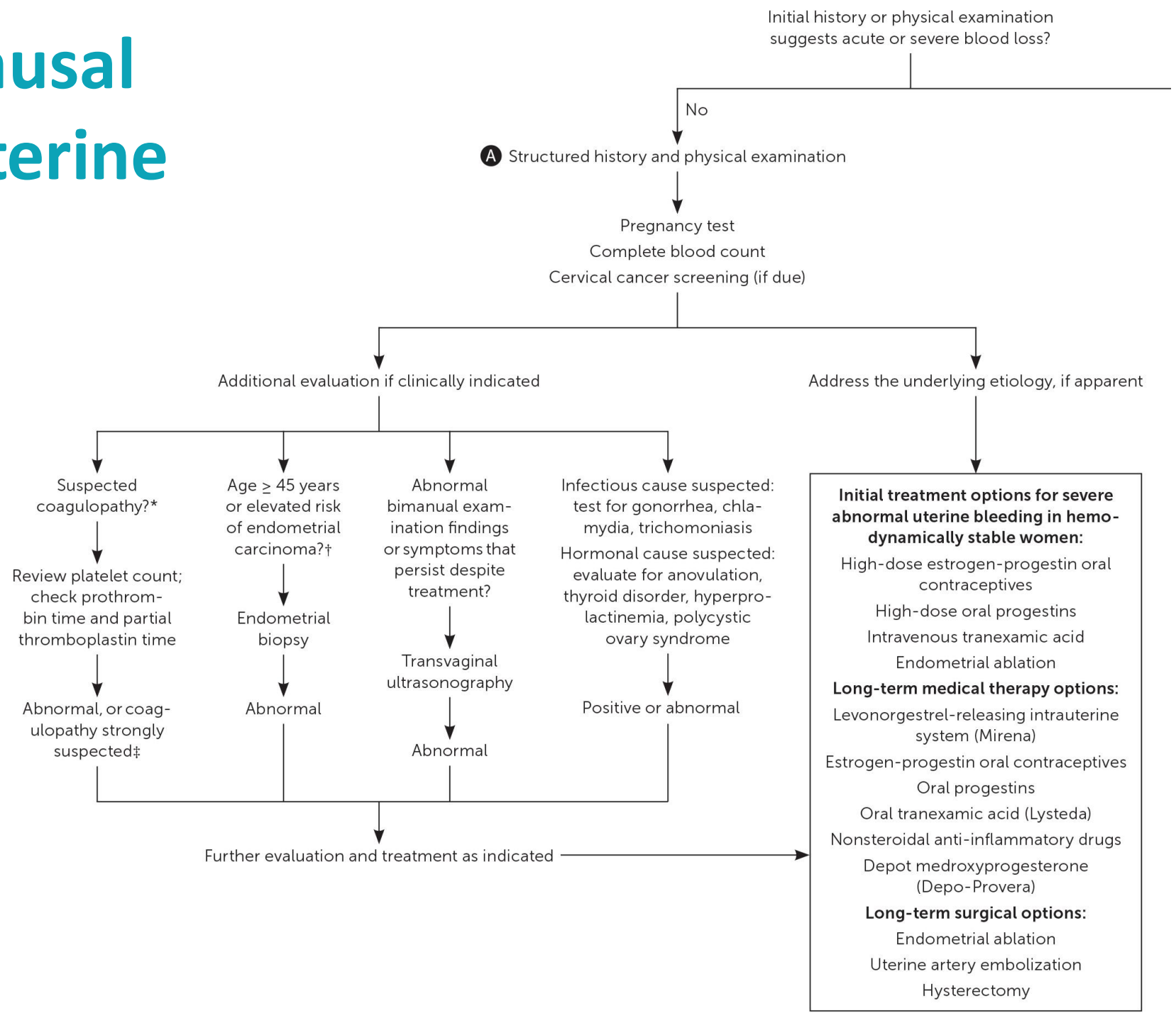
- Atypical endometrial hyperplasia (AEH) is a precursor to endometrioid EC (the most common subtype)
- 29% of untreated AEH will progress to EC
- often a marker of malignancy as more than 40% of women with AEH on biopsy had a diagnosis of EC on their subsequent hysterectomy specimen
- Risk factors are the same as for EC

- standard of care for both AEH and early EC is **definitive surgical management**: hysterectomy with or without bilateral salpingo-oophorectomy and staging

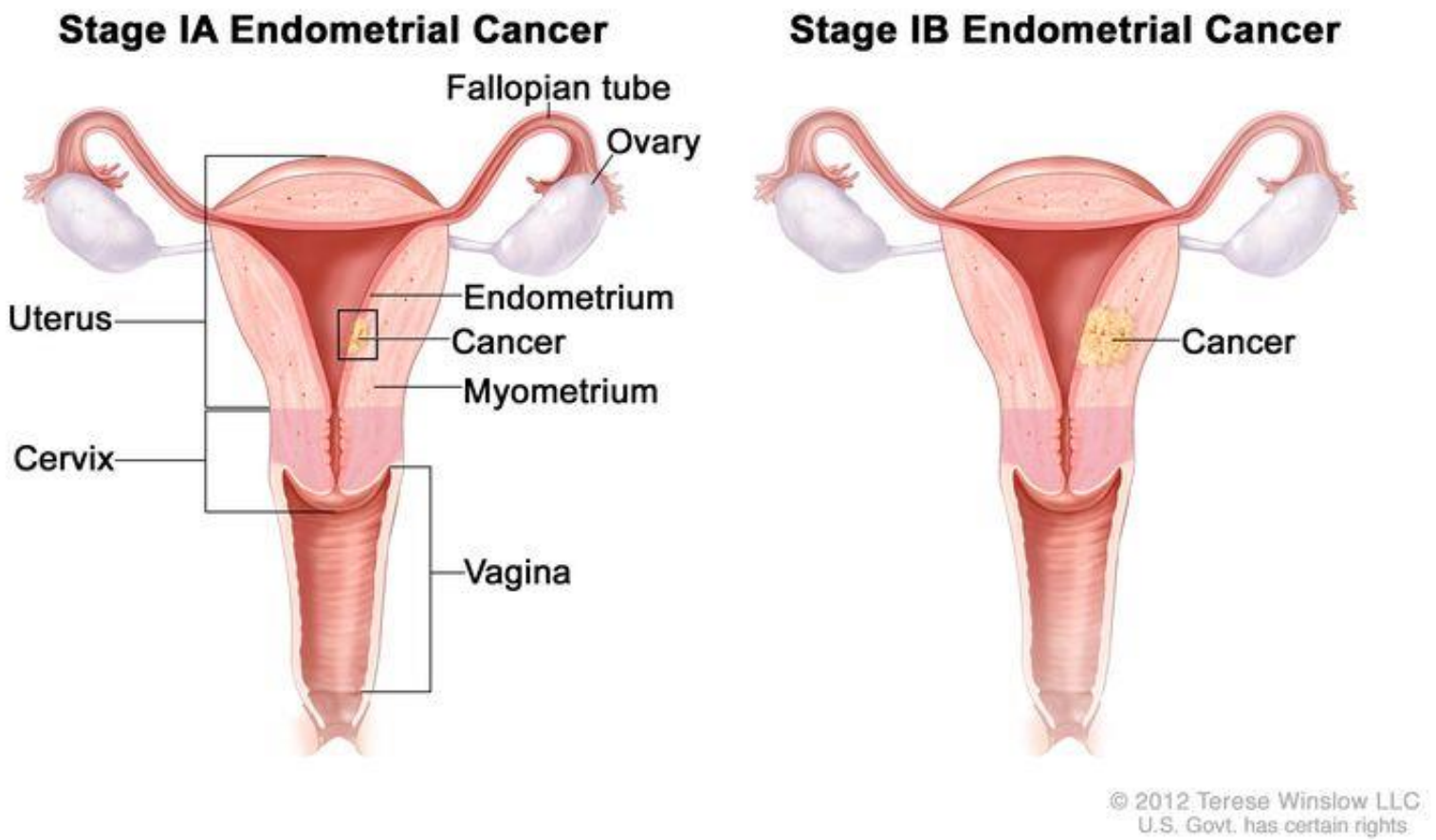
- decision to pursue uterine conservation (for fertility preservation) must be carefully considered since AEH and EC have high recurrence rates

Adjei, N.N., Bowen, M.B., Wilke, R.N. et al. Uterine-Conserving Treatment Options for Atypical Endometrial Hyperplasia and Early Endometrial Cancer. Curr Oncol Rep **26**, *1367–1379 (2024). https://doi.org/10.1007/s11912-024-01603-9*

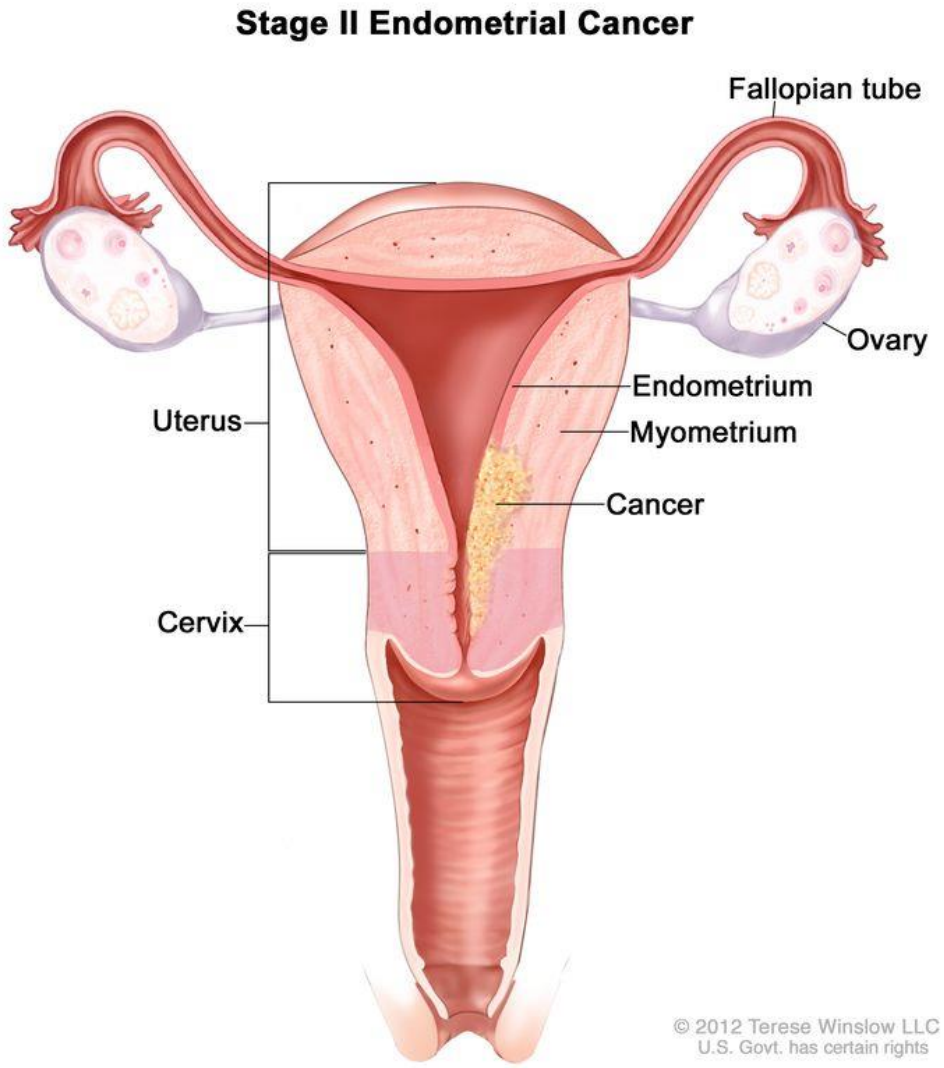
Pre-menopausal abnormal uterine bleeding



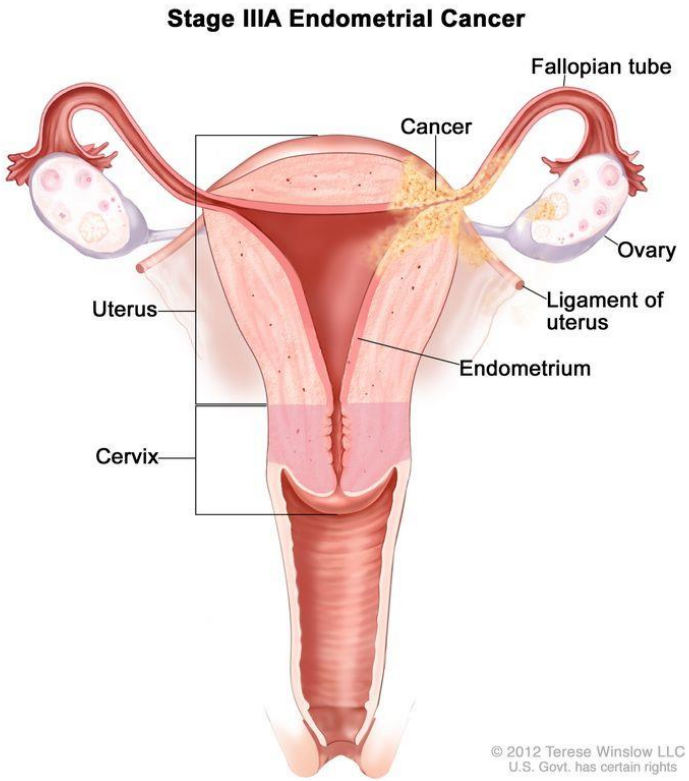
Endometrial Cancer Stage I

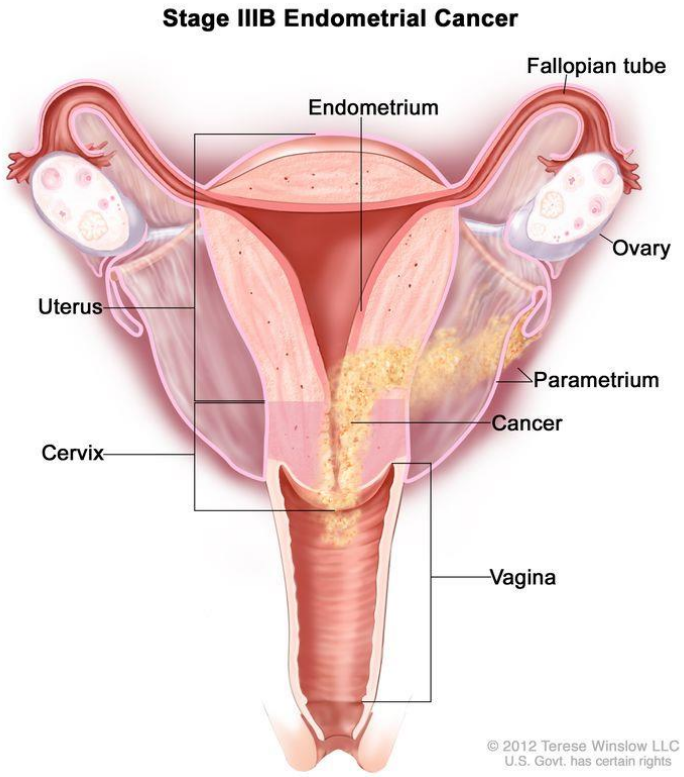


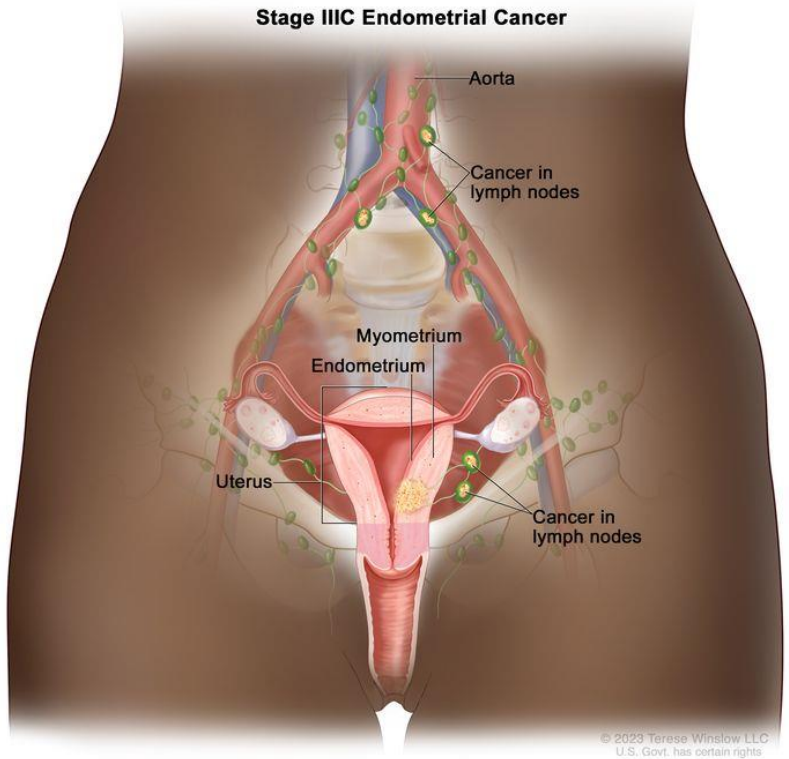
Endometrial Cancer Stage II



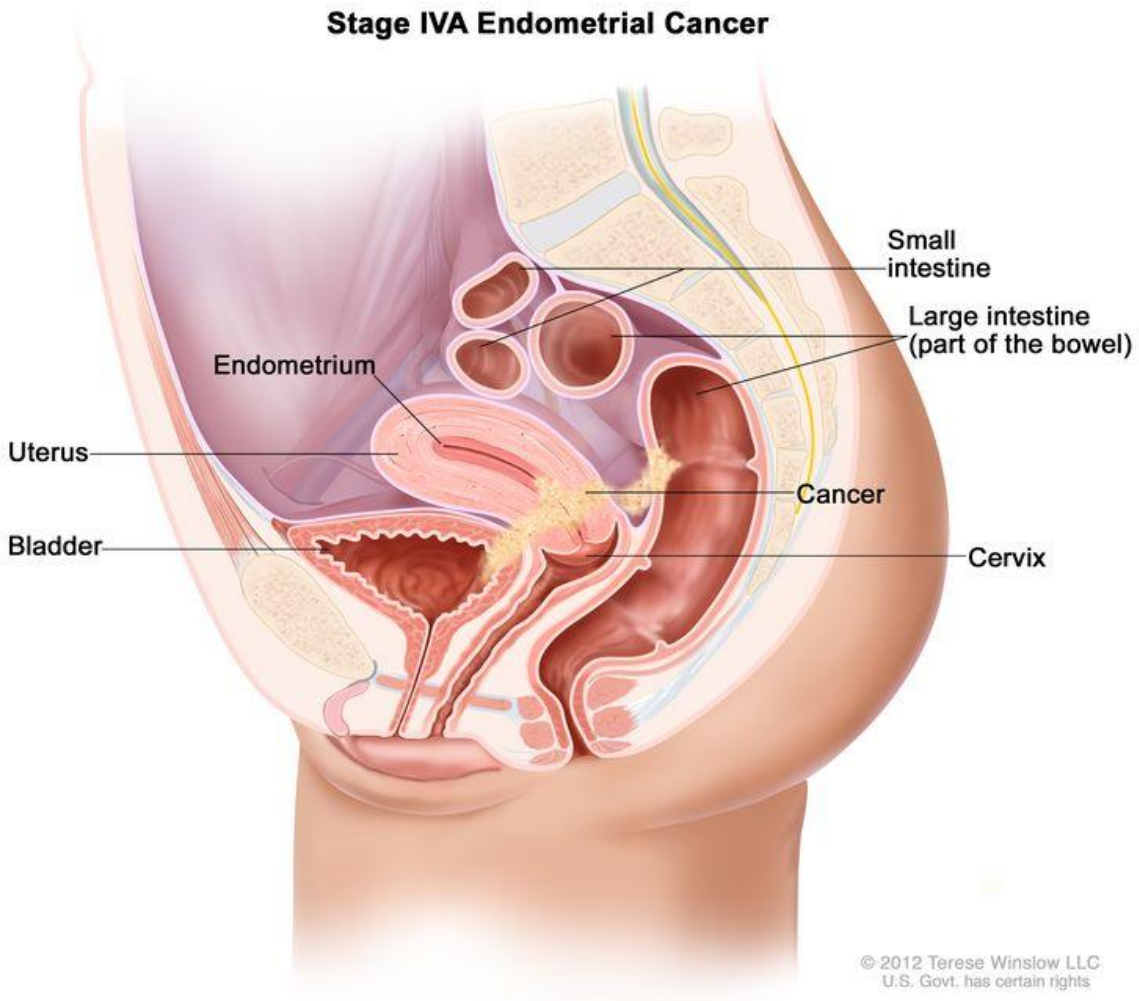
Endometrial Cancer Stage III



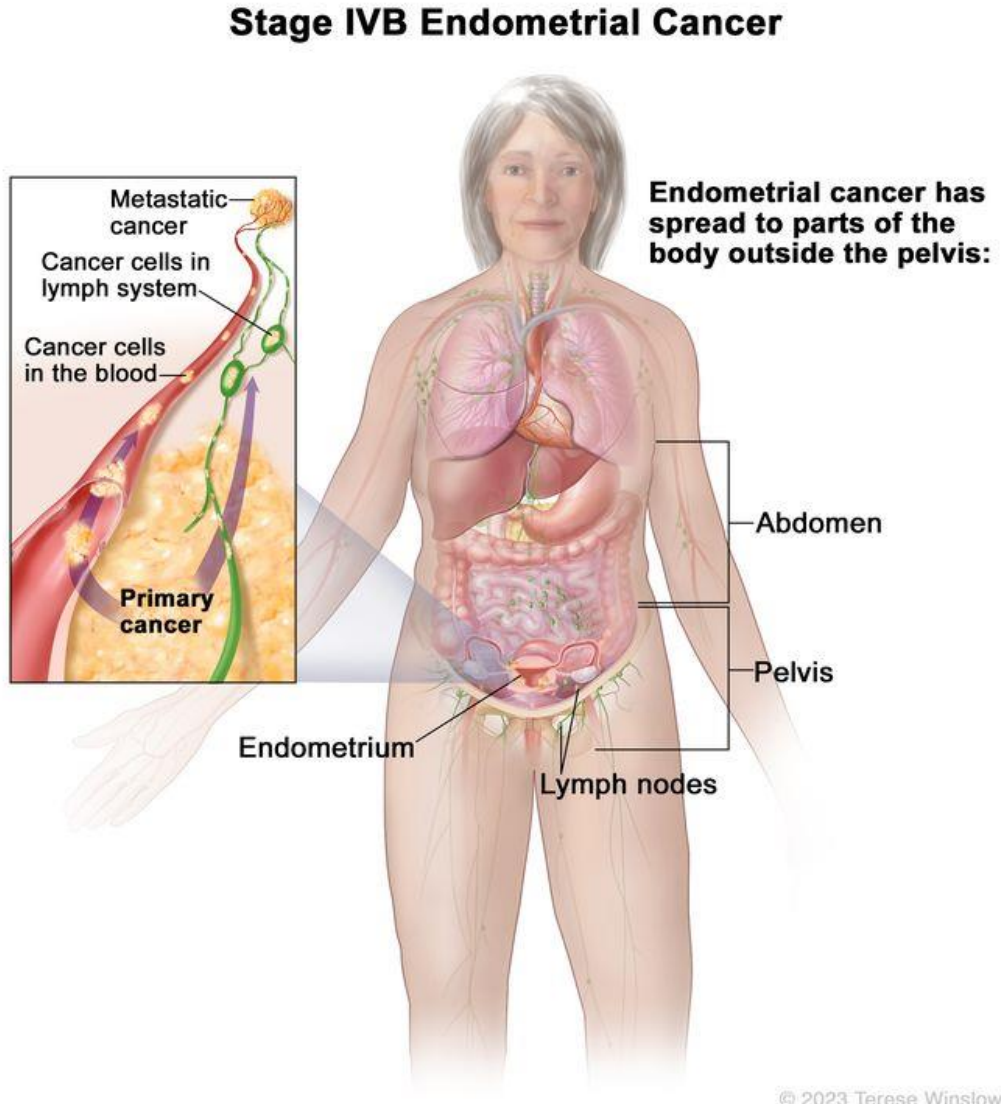




Endometrial Cancer Stage IVA



Endometrial Cancer Stage IVB



Endometrial Cancer Survival by Stage

5-year relative survival rates for endometrial cancer

(These numbers are based on people diagnosed with endometrial cancer between 2013 and 2019.)

SEER* Stage	5-year Relative Survival Rate
Localized	95%
Regional	70%
Distant	18%
All SEER stages combined	81%

*SEER= Surveillance, Epidemiology, and End Results

Endometrial Cancer

- Major advance in understanding EC was the discovery of **4 key molecular groups** of the disease by the TCGA (The Cancer Genome Atlas Program) in 2013

ARTICLE

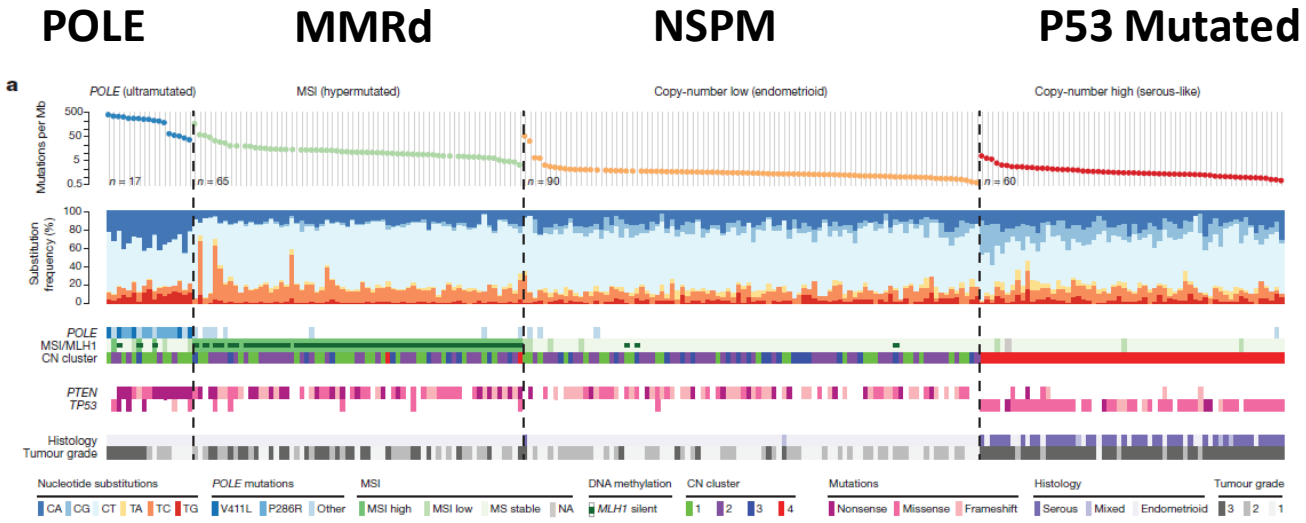
OPEN

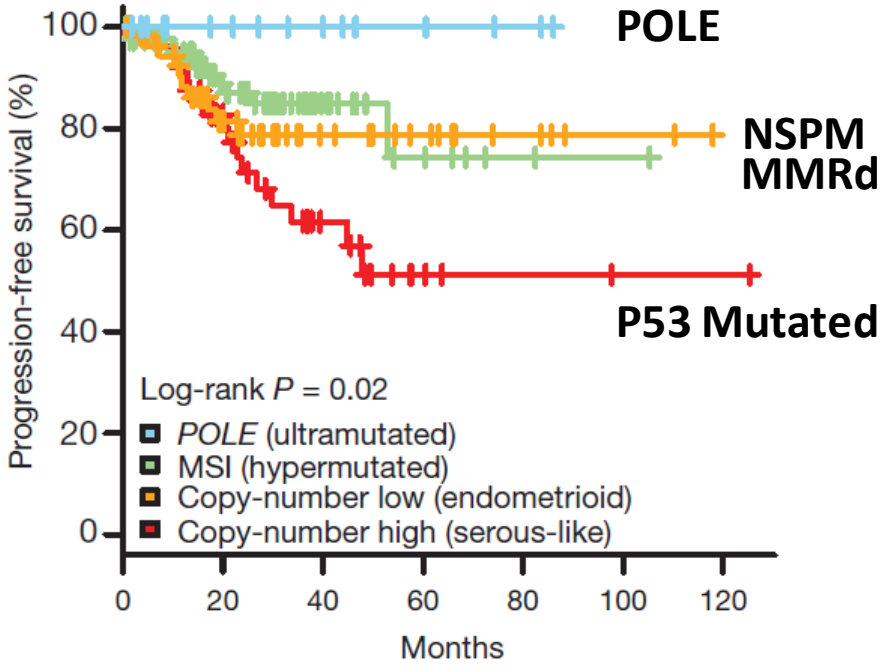
doi:10.1038/nature12113

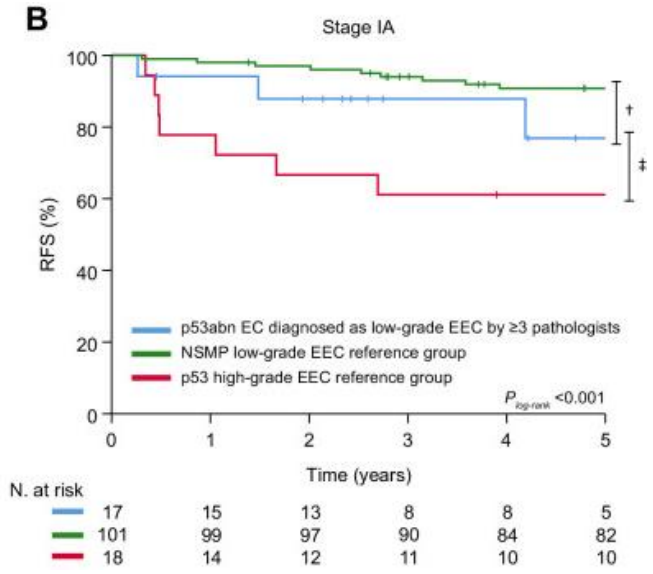
Integrated genomic characterization of endometrial carcinoma

The Cancer Genome Atlas Research Network*

Endometrial Cancer – Molecular Subgroups







Jamieson Clinical Behavior and Molecular Landscape of Stage I p53-Abnormal Low-Grade Endometrioid Endometrial Carcinomas. Clin Cancer Res. 2023 Dec 1;29(23):4949-4957. doi: 10.1158/1078-0432.CCR-23-1397. PMID: 37773079; PMCID: PMC10690141.

Endometrial Cancer – Histology/IHC/Genomics

- Molecular subgroups integrate with (and can override) the common histologic findings
- **Histotypes**: endometrioid, serous and other (clear cell, mucinous, mesonephric etc.)
- **Tumour grade**
- Pathology labs now do **reflexive testing** to help identify the molecular groupings
  - IHC: p53, MMR proteins, estrogen receptor (ER)
  - Genomic sequencing: POLE mutations

ALL NEWLY DIAGNOSED EC CASES IN BC SHOULD BE MOLECULARLY SUBTYPED

Endometrial Cancer – Molecular Subtypes and Disease Management

- Impact **surgical management**
- **Identify potential Lynch syndrome carriers (MMR protein testing)**
  - Lynch syndrome, where inherited pathogenic variants involving one of the four mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2* portends a 13–49% lifetime risk of endometrial cancer, as well as elevated risks for colorectal, gastric, small bowel, ovarian and other cancers
  - **Identification of carriers allows to screening and prevention**
- Influence adjuvant therapy
- Changed the management of metastatic disease

☑

Endometrial Cancer – Surgical Management

Safe and appropriate to be managed by general gynecologists e.g. no justification for lymph node assessment or more complicated staging, low risk of second surgery, high likelihood of surgical cure

General gynecology to manage:→Hysterectomy, BSO only (must meet all of the following criteria)
Grade 1 or 2
Endometrioid histotype
p53wt (wild type)
MMR proficient (MMRp)
Estrogen receptor (ER) positive
Clinical stage I e.g., not suspect disease beyond the uterus
CA125 normal or if elevated explained by other pathology e.g fibroids

High risk disease with greater probability of spread to the pelvic and para-aortic LNs, **need for oncologic staging surgery** including LN dissection +/- disease debulking.

BC Cancer Referral for any of the below parameters
Grade 3
Non-endometrioid histology
MMR deficient (MMRd)
p53abn on IHC and/or *TP53* mutated on sequencing
ER negative
Suspect or confirmed > stage I
CA125 elevated, not otherwise explained (call and discuss if unsure)

http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-management-manual/gynecology/endometrium#Predisposing

Endometrial Cancer – Medical Management

- **Adjuvant chemotherapy - integrate molecular subtype** into treatment recommendations

  - **POLE** mutated cancers have an excellent prognosis.
    - Now enrolling all early-stage POLE mutated ECs into a trial looking at "de-escalation" of therapy
      - No chemotherapy
      - Vagina vault Radiation therapy in place of pelvic radiation

  - **MMRd** – no proven benefit of adjuvant chemotherapy
    - Not offered to early stage MMRd EC, discussed but not strongly endorsed for stage III cases
    - Stage IV MMRd EC – major advance in therapy has been the introduction of immunotherapy

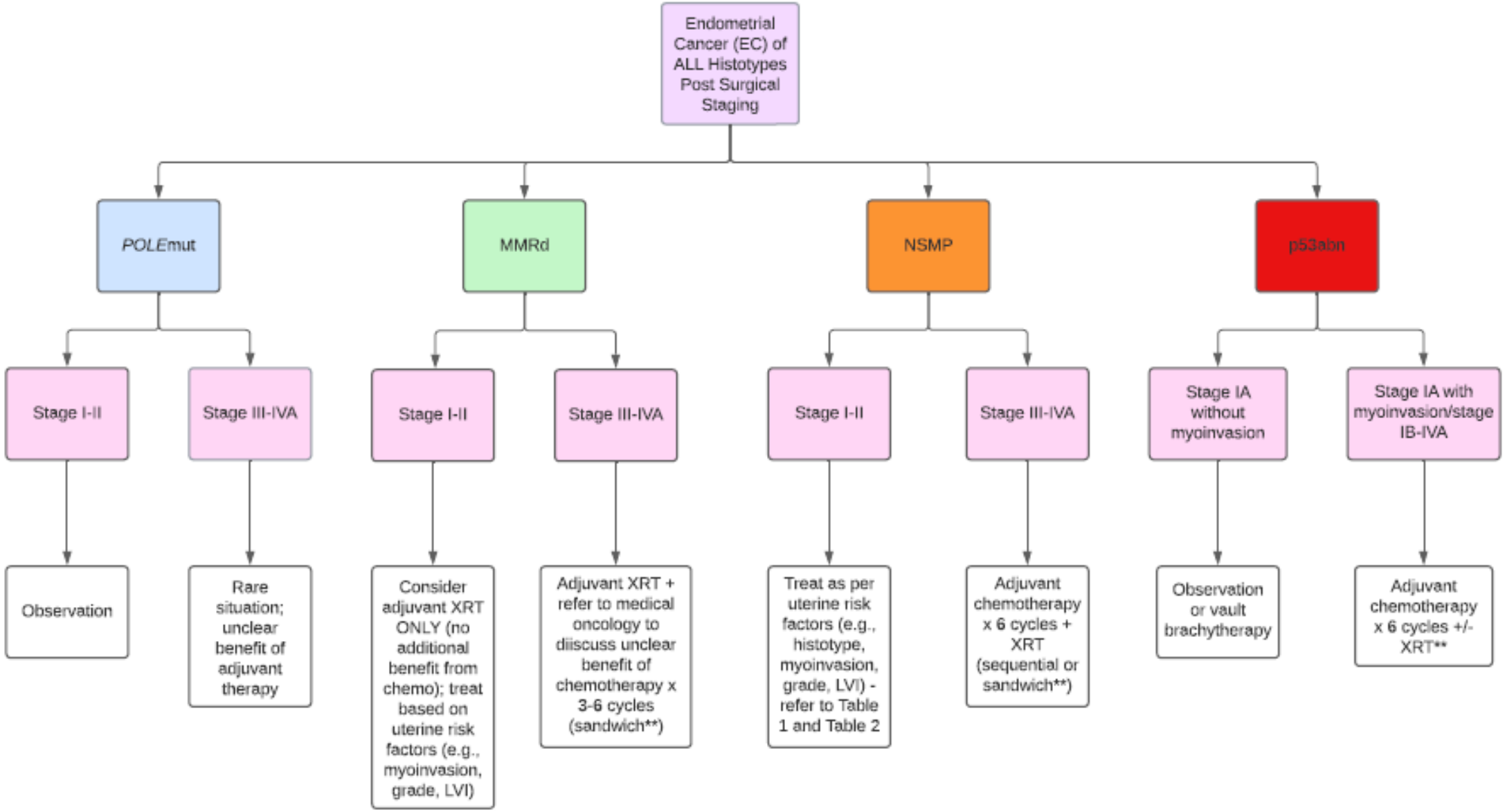
  - **No Specific Molecular Profile** - uncertain if benefit of adjuvant therapy, but is the standard of care for stage IV disease

  - **P53 mutated** – worse prognosis with clear benefit from adjuvant chemotherapy – strongly recommended in stage I-III disease as adjuvant treatment

Endometrial Cancer – Radiation Therapy

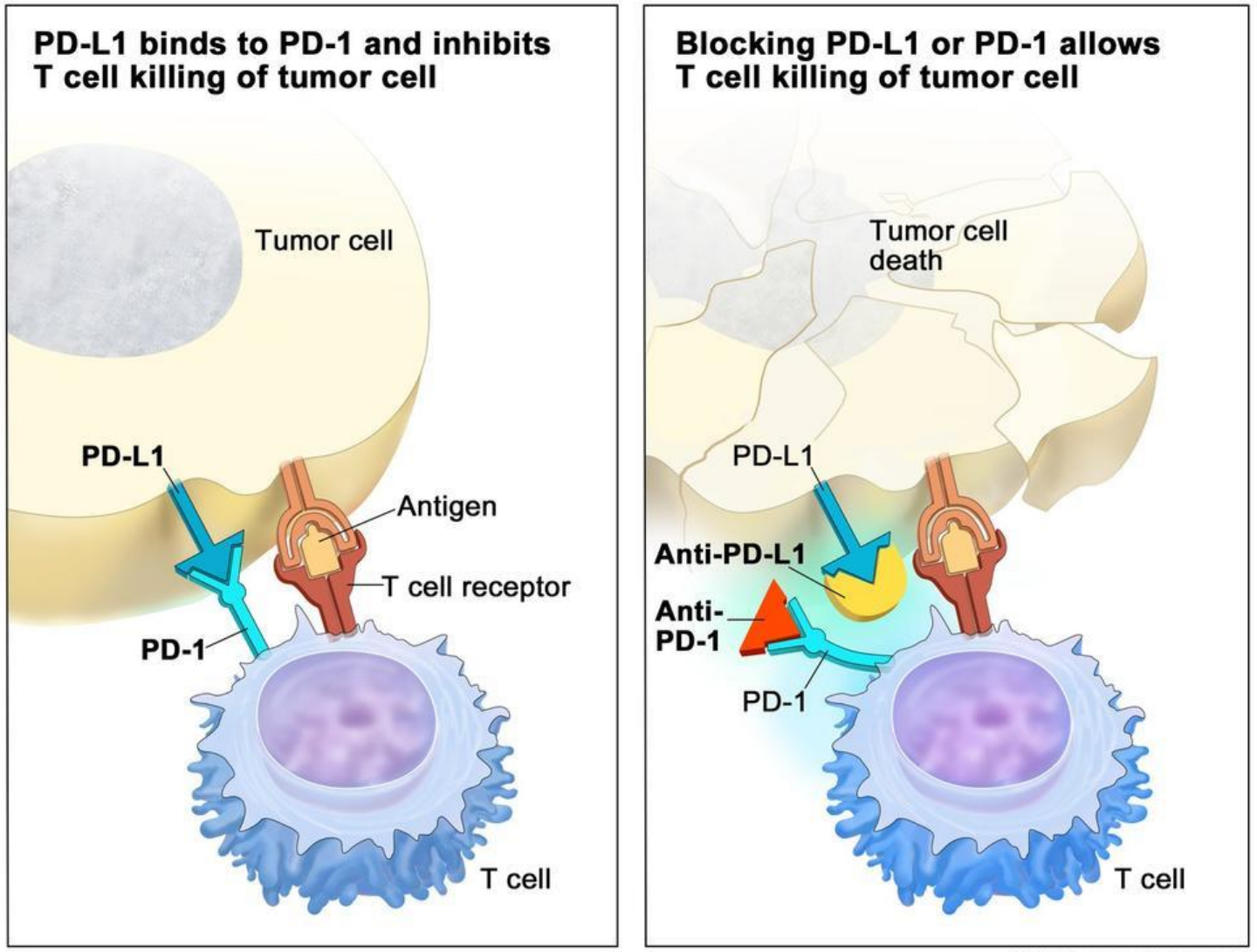
- **Adjuvant radiation** to the vaginal vault, or to the pelvis and para-aortic LNs may be offered to stage I, II, and III
    - MMRd
    - NSMP
    - P53 mutated
- Shown to significantly **reduce the risk of local disease recurrence**

This algorithm should be applied to all surgically resected ECs of any histotype, including non-endometrioid carcinomas.



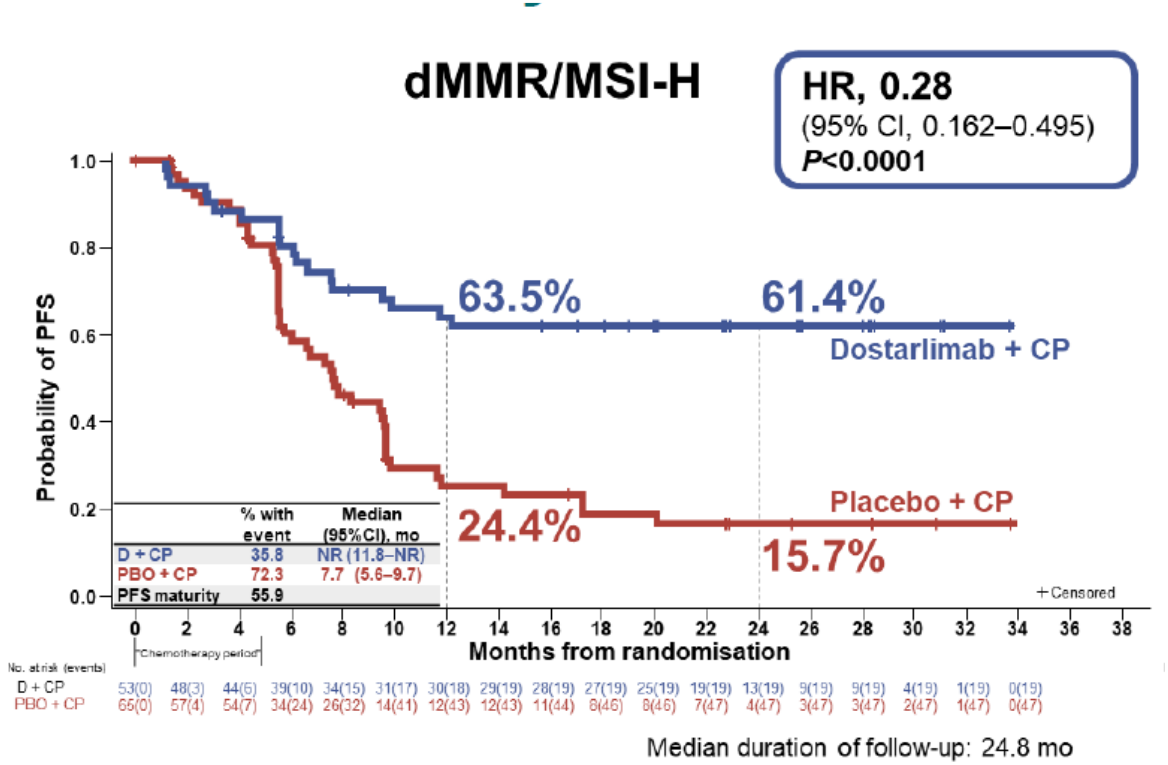
Endometrial Cancer – Recurrent/Metastatic Disease

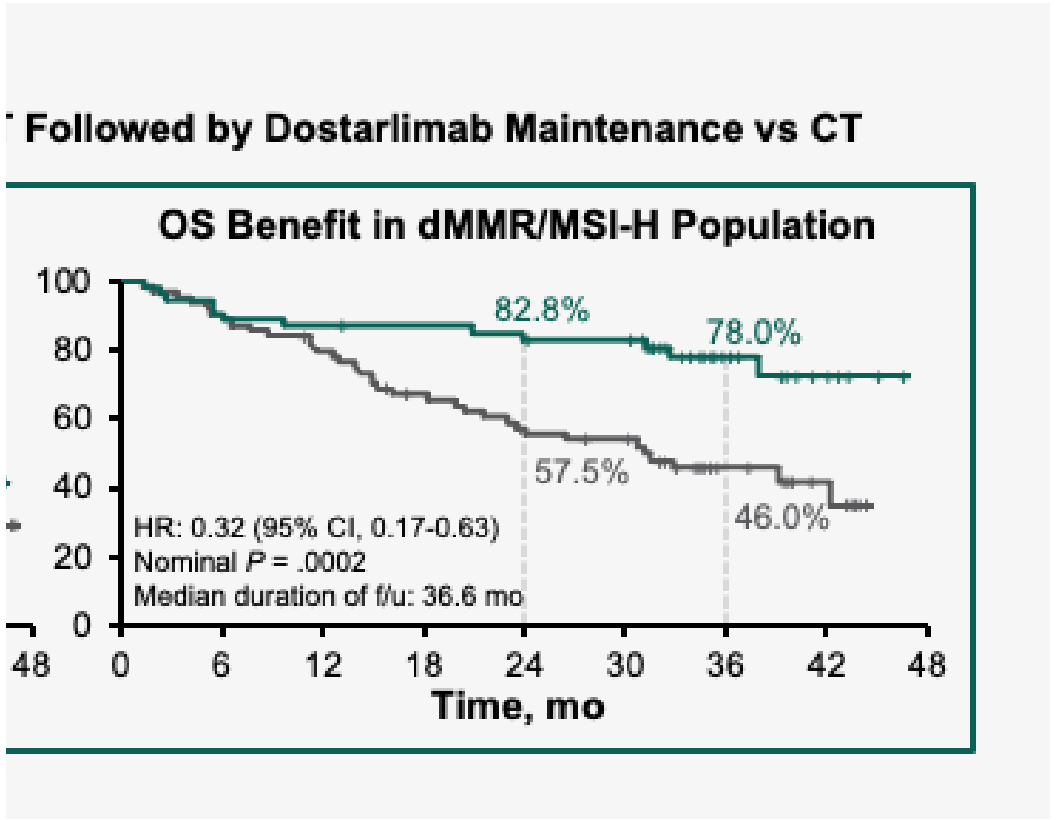
- Basis of treatment is systemic
- Novel therapies have been introduced
- MMRd EC
  - **Addition of immunotherapy, specifically, immune checkpoint inhibitors, to standard chemotherapy**



originally published by the National Cancer Institute

Endometrial Cancer – Immunotherapy in MMRd





Mirza MR; RUBY Investigators. Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer. N Engl J Med. 2023 Jun 8;388(23):2145-2158. doi: 10.1056/NEJMoa2216334. Epub 2023 Mar 27. PMID: 36972026.

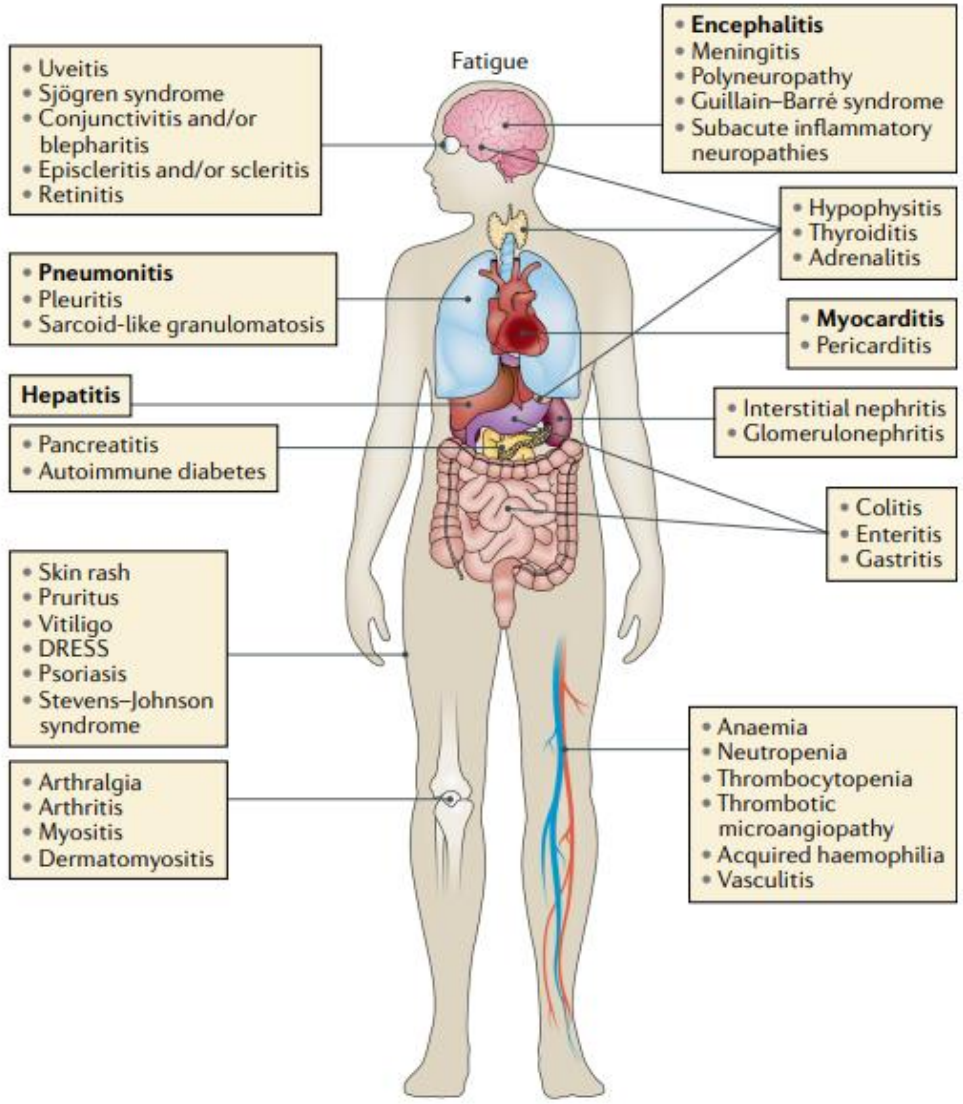
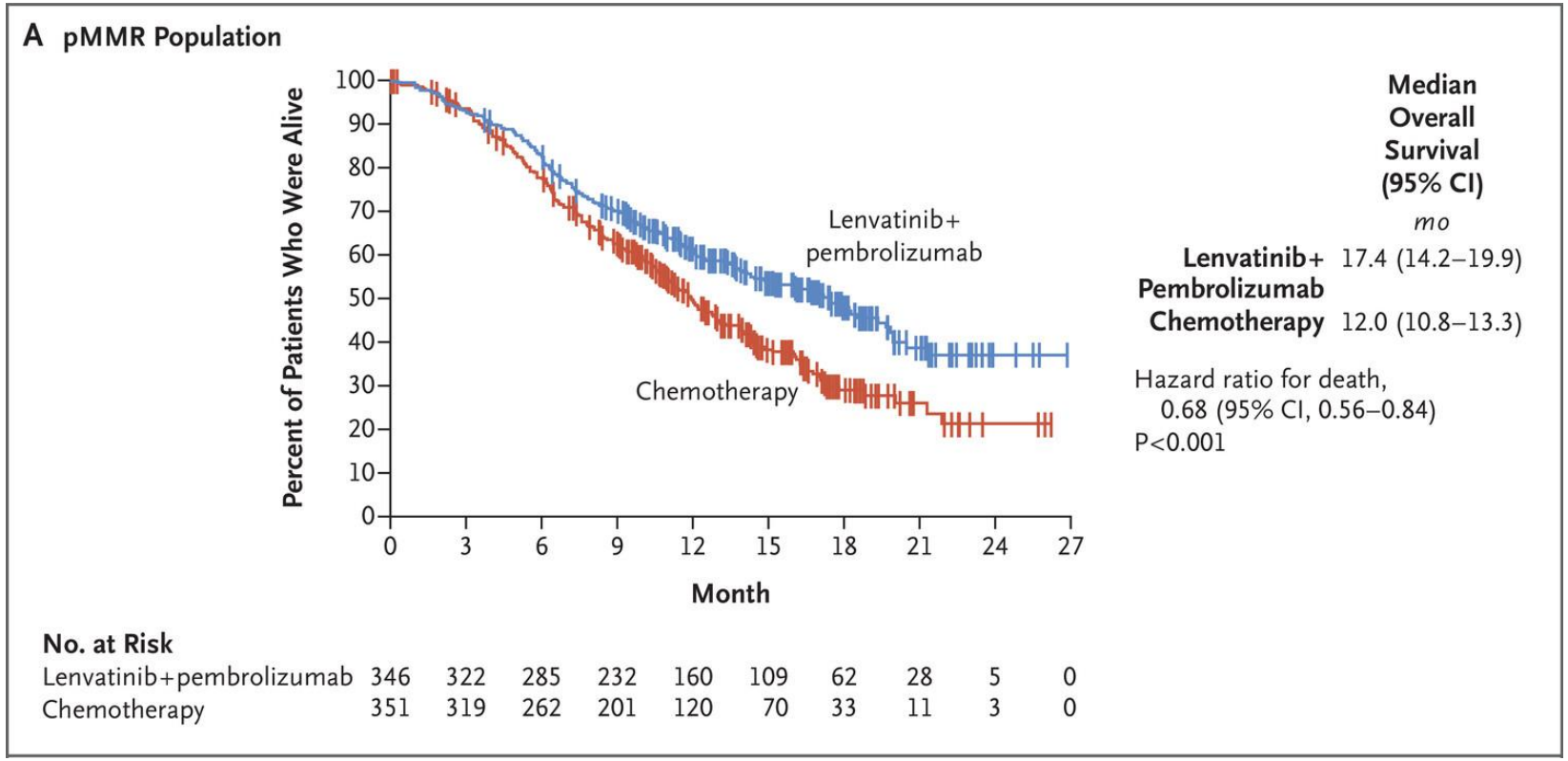


Fig. 2 | **The spectrum of irAEs by affected organ or organs.** Immune-checkpoint inhibitors (ICIs) promote the activation and expansion of T cells. Owing to the diversity of the T cell population and the ability of these cells to infiltrate most organs, ICIs can cause a wide range of immune-related adverse events (irAEs), and these can affect virtually any organ. The most frequently affected organs and the most common specific irAEs are highlighted in boxes. irAEs contributing to most fatalities are highlighted in bold. DRESS, drug rash with eosinophilia and systemic symptoms.

Martins, F., Sofiya, L., Sykiotis, G.P. et al. Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance. Nat Rev Clin Oncol 16, 563–580 (2019). https://doi.org/10.1038/s41571-019-0218-0

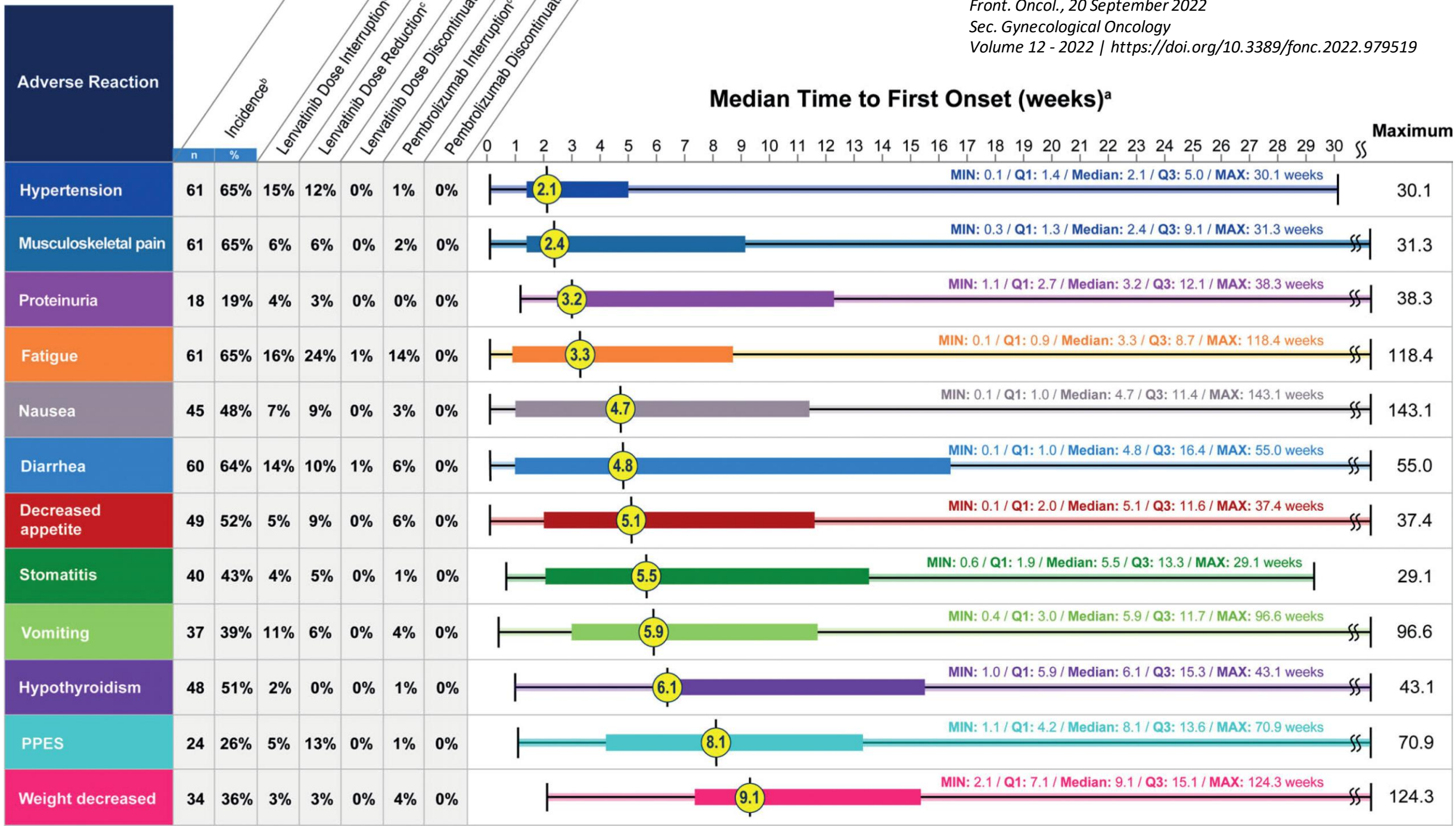
Endometrial Cancer – Recurrent/Metastatic Disease

- Basis of treatment is systemic
- Novel therapies have been introduced
- Non- MMRd
  - **Use of checkpoint inhibitors and a multi-targeted tyrosine-kinase inhibitor (Lenvatinib)**



Makker V, Colombo N, Casado Herráez A, Monk BJ, Mackay H, Santin AD, Miller DS, Moore RG, Baron-Hay S, Ray-Coquard I, Ushijima K, Yonemori K, Kim YM, Guerra Alia EM, Sanli UA, Bird S, Orlowski R, McKenzie J, Okpara C, Barresi G, Lorusso D. Lenvatinib Plus Pembrolizumab in Previously Treated Advanced Endometrial Cancer: Updated Efficacy and Safety From the Randomized Phase III Study 309/KEYNOTE-775. J Clin Oncol. 2023 Jun 1;41(16):2904-2910. doi: 10.1200/JCO.22.02152. Epub 2023 Apr 14. PMID: 37058687; PMCID: PMC10414727.

REVIEW article
Front. Oncol., 20 September 2022
Sec. Gynecological Oncology
Volume 12 - 2022 | https://doi.org/10.3389/fonc.2022.979519



Summary

- EC **incidence is on the rise**, including in younger women, as a result of rising rates of obesity/diabetes
- Post menopausal bleeding - main symptom
- Transvaginal US and biopsy
- New understanding of EC biology/molecular subtypes
- Molecular findings defining therapy (and new therapy has special toxicities)

Thank you!