ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Γ' ΠΑΘΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
ΙΑΤΡΙΚΗΣ ΣΧΟΛΗΣ ΑΘΗΝΩΝ ΕΚΠΑ
ΓΝΑ "Η ΣΩΤΗΡΙΑ"

Γυναικολογικά νεοπλάσματα

Ωραιάνθη Ε. Φιστέ
Παθολόγος – Ογκολόγος, MD, MSc

Κατ' επιλογής μάθημα Παθολογικής Ογκολογίας 2024

Αθήνα, 20/5/2024

Cancer statistics, 2024

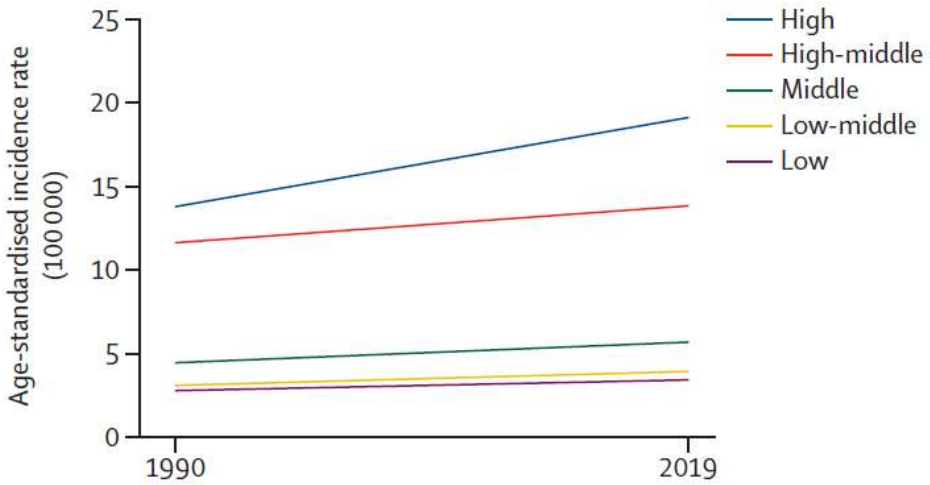
Estimated New Cases		
Breast	310,720	32%
Lung & bronchus	118,270	12%
Colon & rectum	71,270	7%
Uterine corpus	67,880	7%
Melanoma of the skin	41,470	4%
Non-Hodgkin lymphoma	36,030	4%
Pancreas	31,910	3%
Thyroid	31,520	3%
Kidney & renal pelvis	29,230	3%
Leukemia	26,320	3%
All sites	**972,060**	

Estimated Deaths		
Lung & bronchus	59,280	21%
Breast	42,250	15%
Pancreas	24,480	8%
Colon & rectum	24,310	8%
Uterine corpus	13,250	5%
Ovary	12,740	4%
Liver & intrahepatic bile duct	10,720	4%
Leukemia	10,030	3%
Non-Hodgkin lymphoma	8,360	3%
Brain & other nervous system	8,070	3%
All sites	**288,920**	

Siegel RL, et al. CA Cancer J Clin. 2024;74(1):12-49

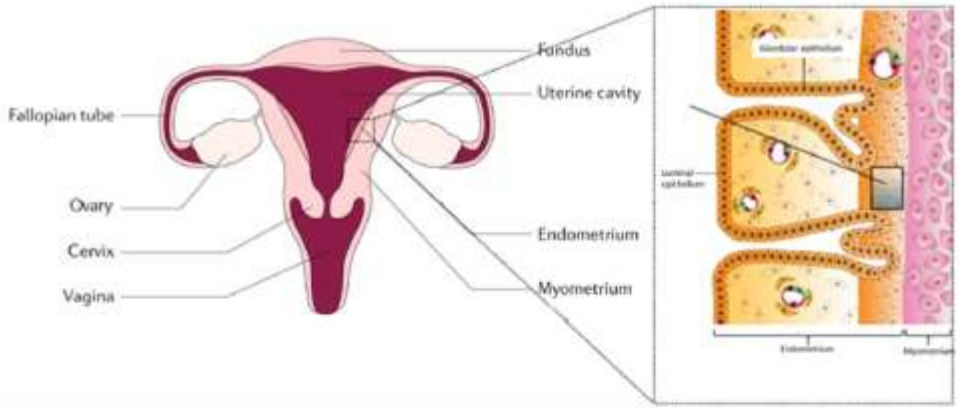
1. Endometrial cancer (EC)
Epidemiology

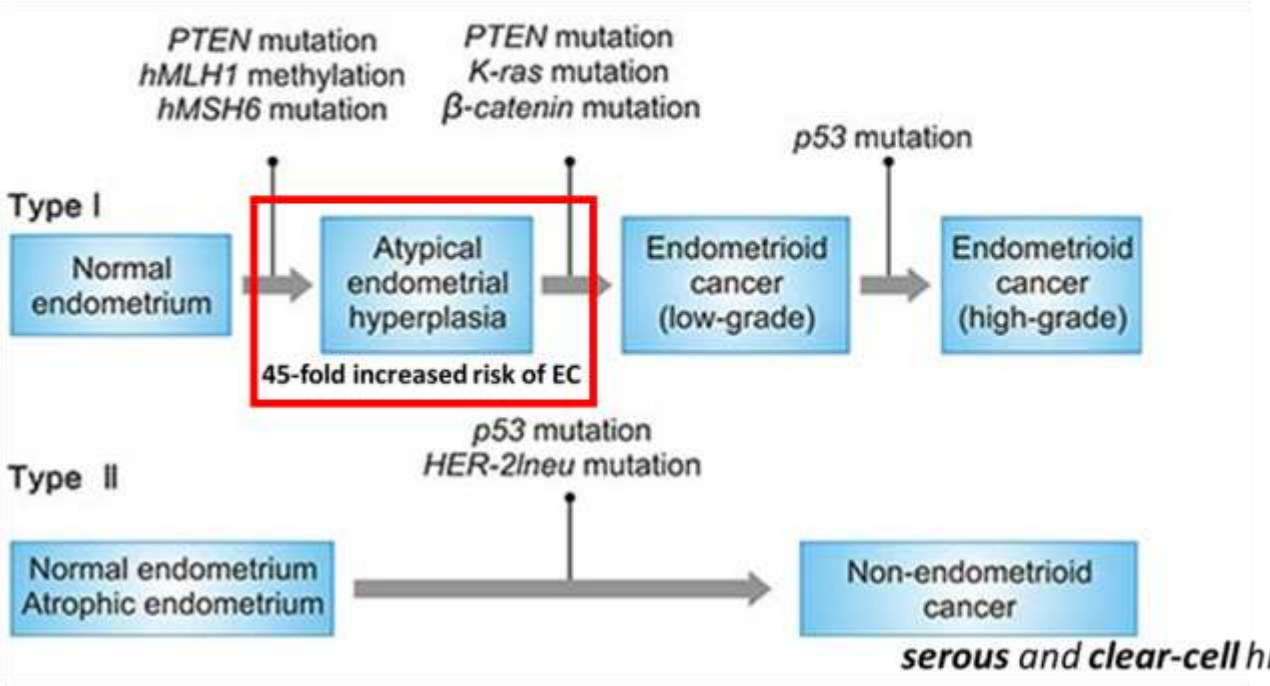
- The most common gynaecological cancer in high income countries
    - US: 66,200 new cases and 13,030 deaths (2023)
- Its **incidence is increasing annually**, by an estimated 1-2%



Somasegar S, et al. Obstet Gynecol. 2023;142(4):978-986
Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

Gene mutations in the carcinogenesis of EC





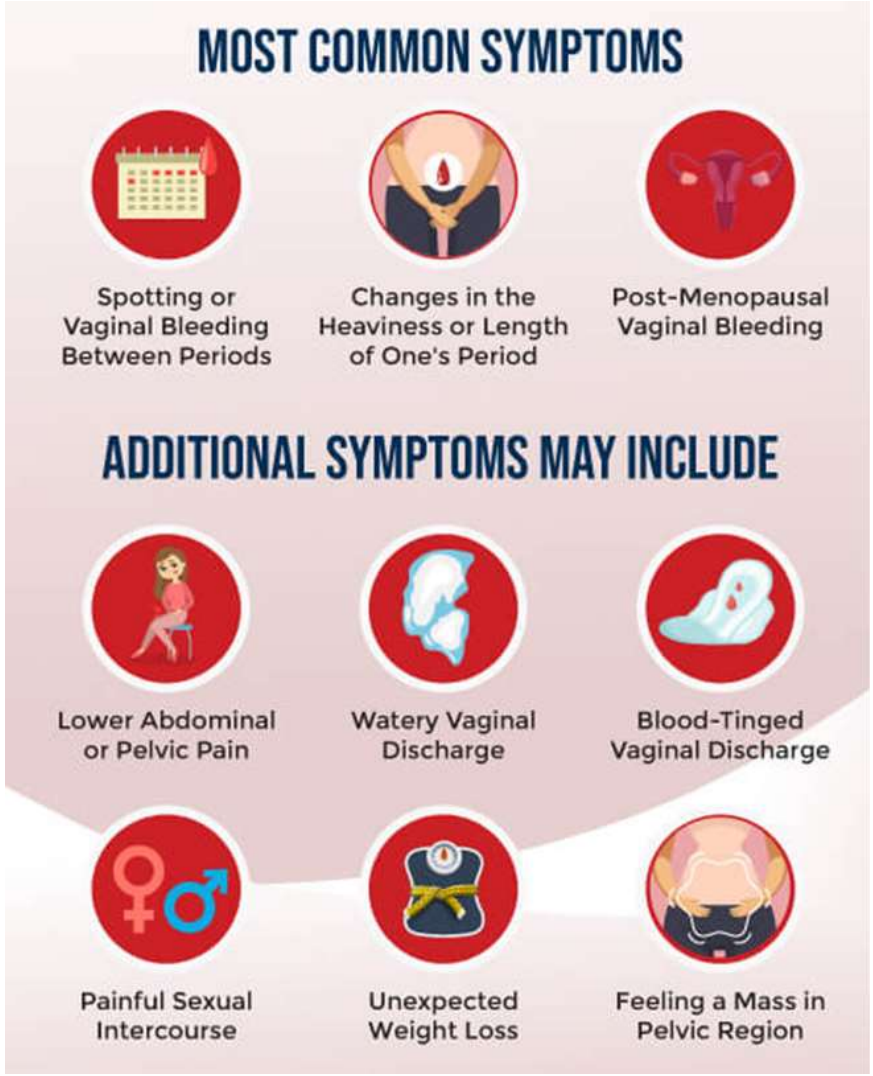
Banno K, et al. J Obstet Gynaecol Res. 2014;40(8):1957-67

Associated risk factors for EC

Characteristic	No. of times risk increased
Obesity	
30-49 lb	3.0
>50 lb	10.0
Nulliparity	2.0
Late menopause	2.4
"Bloody" menopause	4.0
Diabetes mellitus	2.8
Unopposed estrogen	4.0 – 8.0
Complex atypical hyperplasia	29.0
DO NOT forget OLDER AGE !	

Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

Clinical presentation of EC



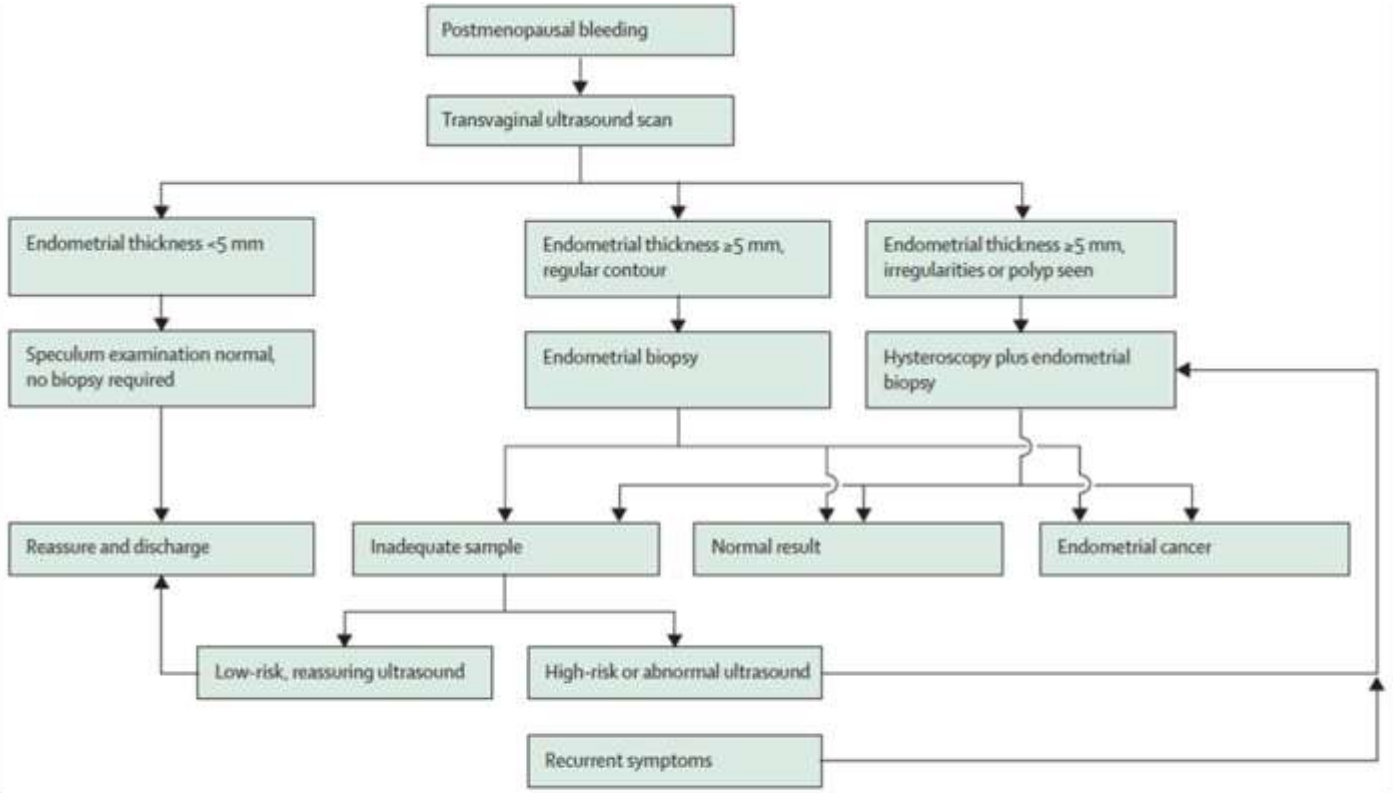
<u>The probability of EC as a cause of postmenopausal bleeding</u>

- <1% in female <50y
- 3% in female aged 55y
- **24% in female >80y**

Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

Diagnosis of EC

Routine investigation of postmenopausal bleeding*



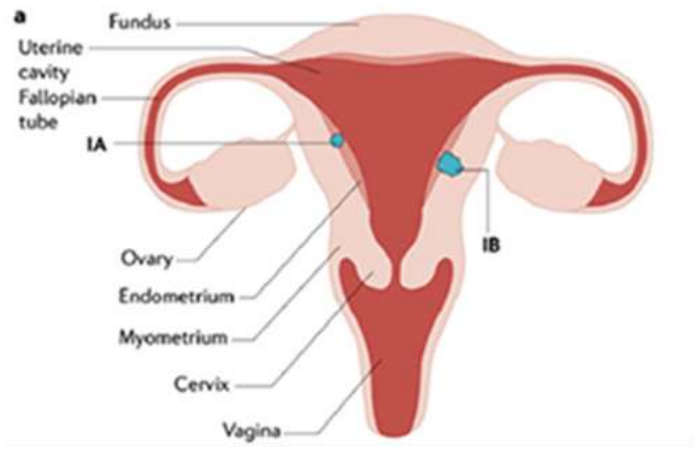
* Decision to **investigate young women** with vaginal bleeding must be guided by **risk factors**:

- family history
- obesity
- polycystic ovary syndrome (PCOS)

- Histological examination of endometrial tissue sample in those with **thickened (>5mm) endometrium**
- Preoperative assesment includes: **pelvic MRI**, **chest/abdomen CT**

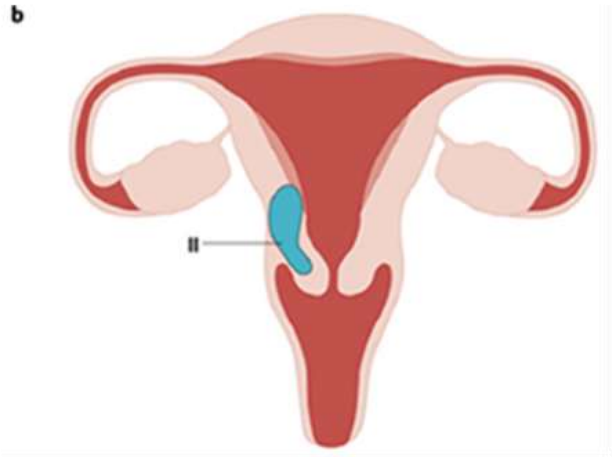
Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

FIGO Staging of EC

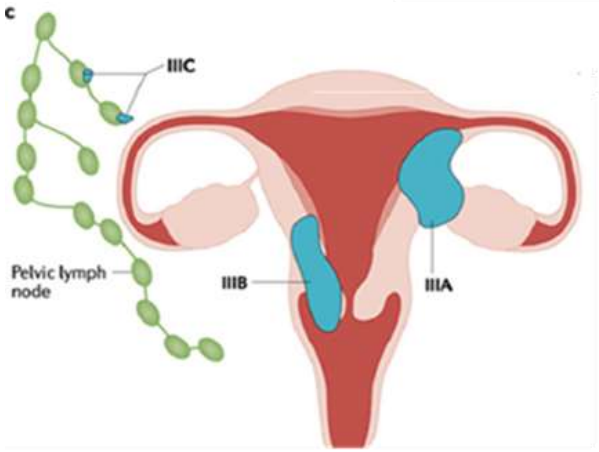


Stage I: tumor confined to the corpus uteri

- IA: <50% myometrial invasion
- IB: ≥50% myometrial invasion

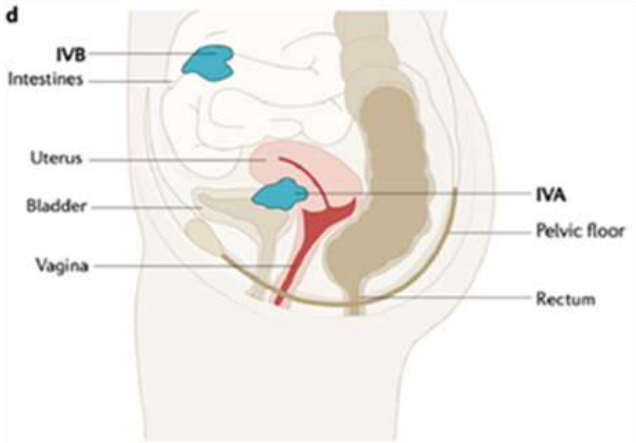


Stage II: tumor invades cervical stroma, but does not extend beyond the uterus



Stage III: local and/or regional spread of the tumor

- IIIA: tumor invades the serosa of the corpus uteri *and/or* adnexae
- IIIB: vaginal *and/or* perimetrial involvement
- IIIC1: positive pelvic lymph nodes
- IIIC2: positive para-aortic lymph nodes with *or* without positive pelvic lymph nodes



Stage IV: tumor invades bladder and/or bowel mucosa, and/or distant metastases

- IVA: bladder and/or bowel mucosa invasion
- IVB: distant metastases, including inguinal lymph nodes

Makker V, et al. Nat Rev Dis Primers. 2021;7(1):88

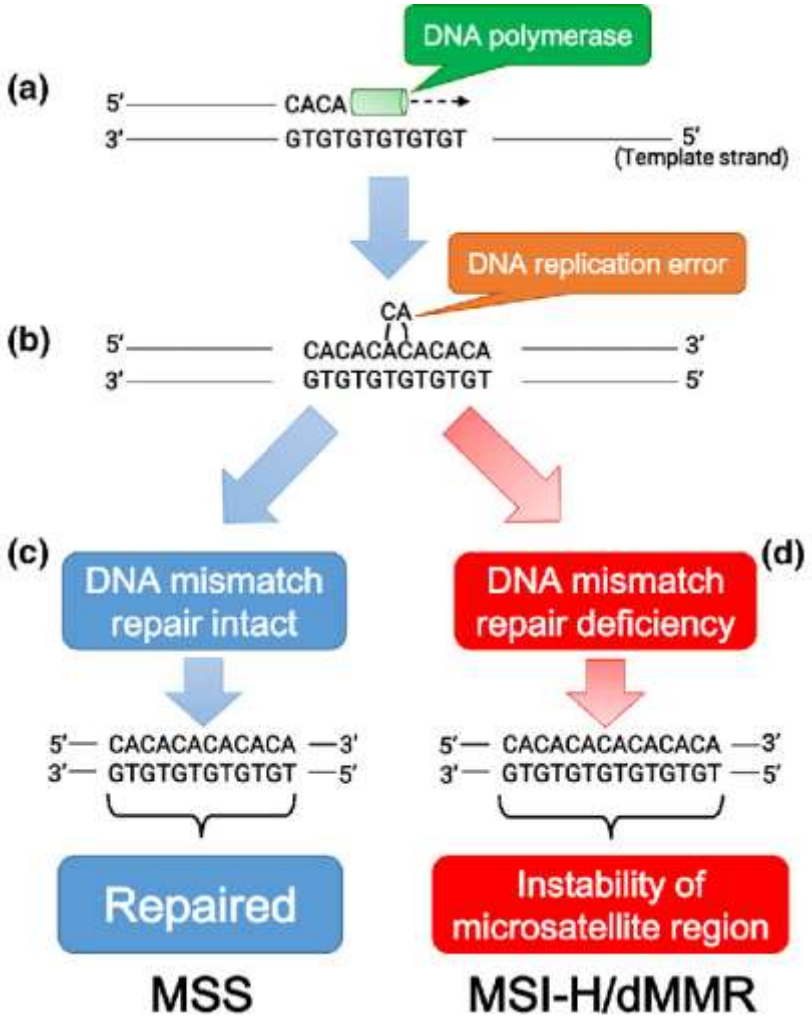
Basic principles for EC treatment

- Surgery
- Radiation therapy (external beam RT, brachytherapy)
- Systemic therapy
  - Chemotherapy
  - Immunotherapy
  - Targeted therapies (multi-targeted TKI, hormone therapy, etc.)

Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

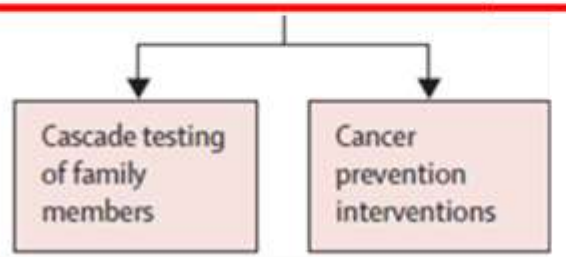
NO screening tools are available for EC

Mismatch repair (MMR)/Microsatellite instability (MSI) status



EC can be classified as:

- MMRp/MSS (70-75%)
- dMMR/MSI-H (25-30%)
- Lynch syndrome (inherited dMMR) accounts for 2-5% of all cases



Hause RJ, et al. Nat Med. 2016;22(11):1342-1350
Crosbie EJ, et al. Lancet. 2022;399(10333):1412-1428

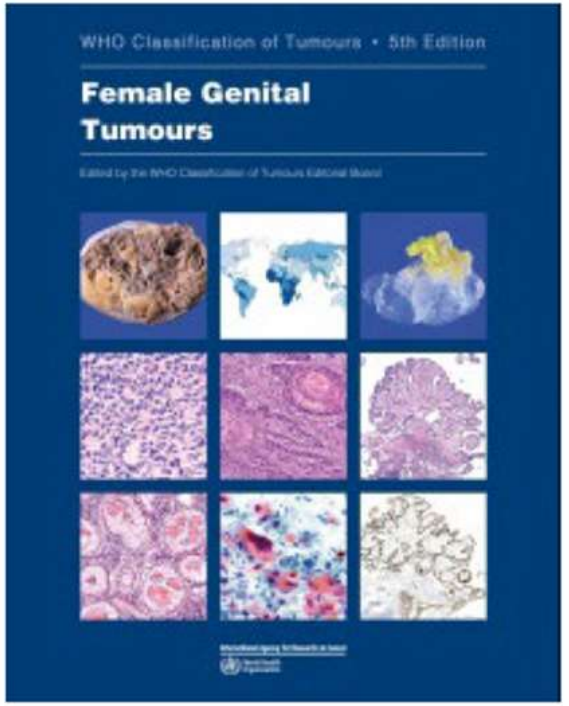
2. Ovarian cancer (OC)
Epidemiology

- The most lethal gynecological cancer in high income countries
    - 313,000 new cases and 208,000 deaths (2020)
- Its **incidence is slowly decreasing** (since 2000s)
- >70% of patients present with late-stage (III-IV) OC
- 5-year survival rates
    - Stage I: 93% → Stage IV: **30%**

Jiang G, et al. Front Oncol. 2022;12:795129

Pathological classification of ovarian tumors

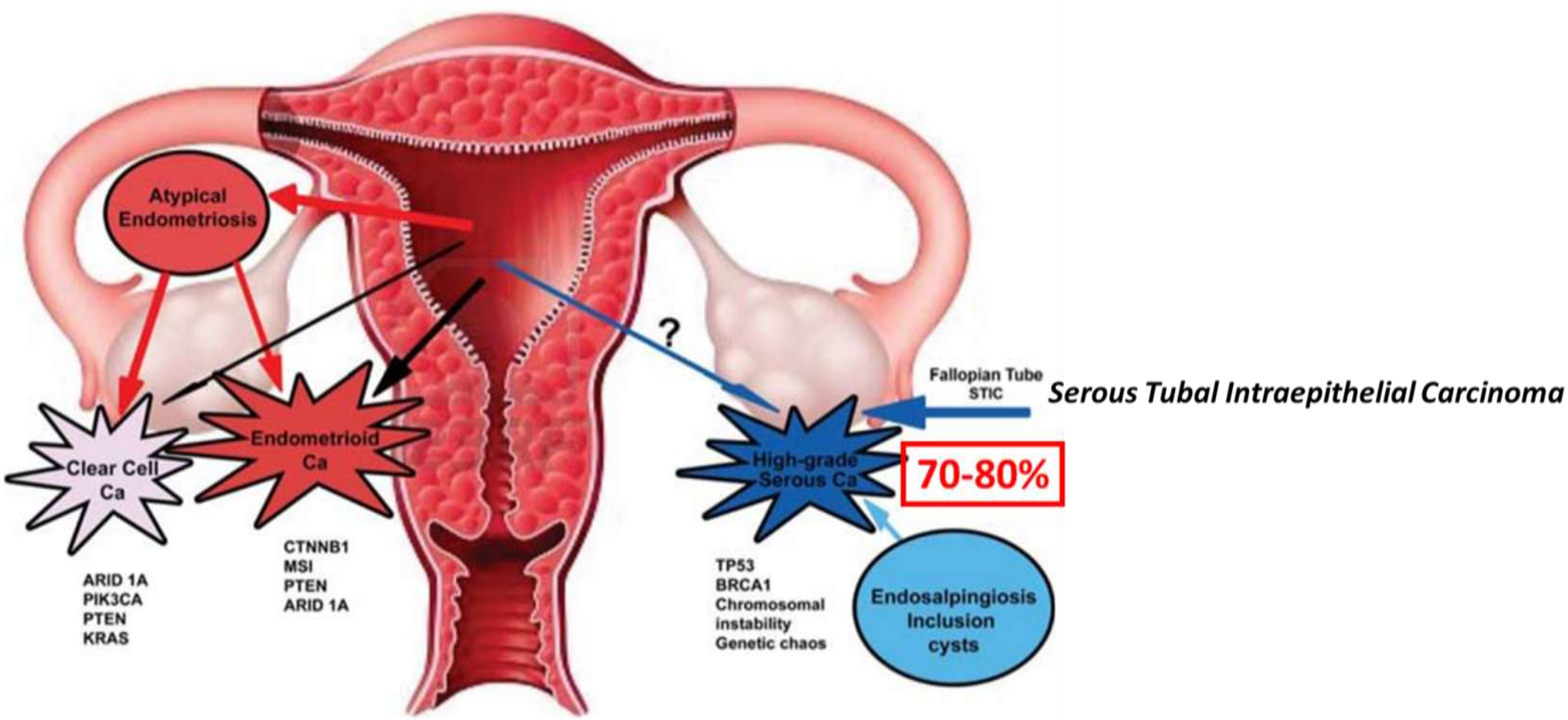
		All tumors	Malignant tumors
1.	Epithelial	55%	80%
2.	Sex-cord stromal	8%	
3.	Germ cell	30%	2%
4.	Mesenchymal (leiomyoma, hemangioma)		
5.	Mixed epithelial/mesenchymal (adenosarcoma)		very uncommon
6.	Miscellaneous (FATWO, small cell carcinoma hypercalcemic type)		
7.	Metastases	6-10%	



WHO classification, 2020

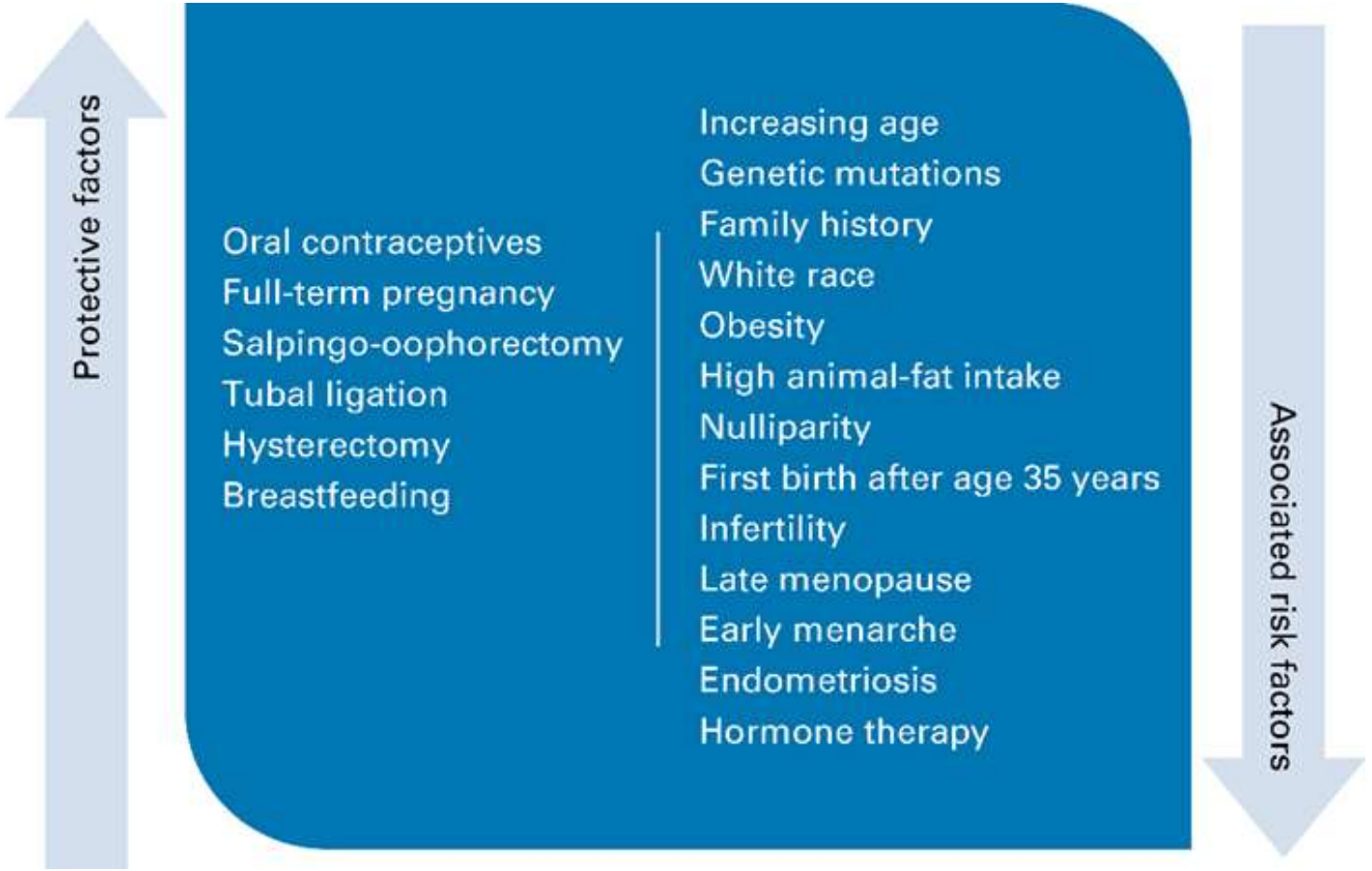
Epithelial OC is **not** a single disease

High-grade serous ovarian cancer (HGSOC) is the most common



Prat J. Ann Oncol. 2012;23 Suppl 10:x111-7

Protective and associated risk factor for OC



ASCO SEP

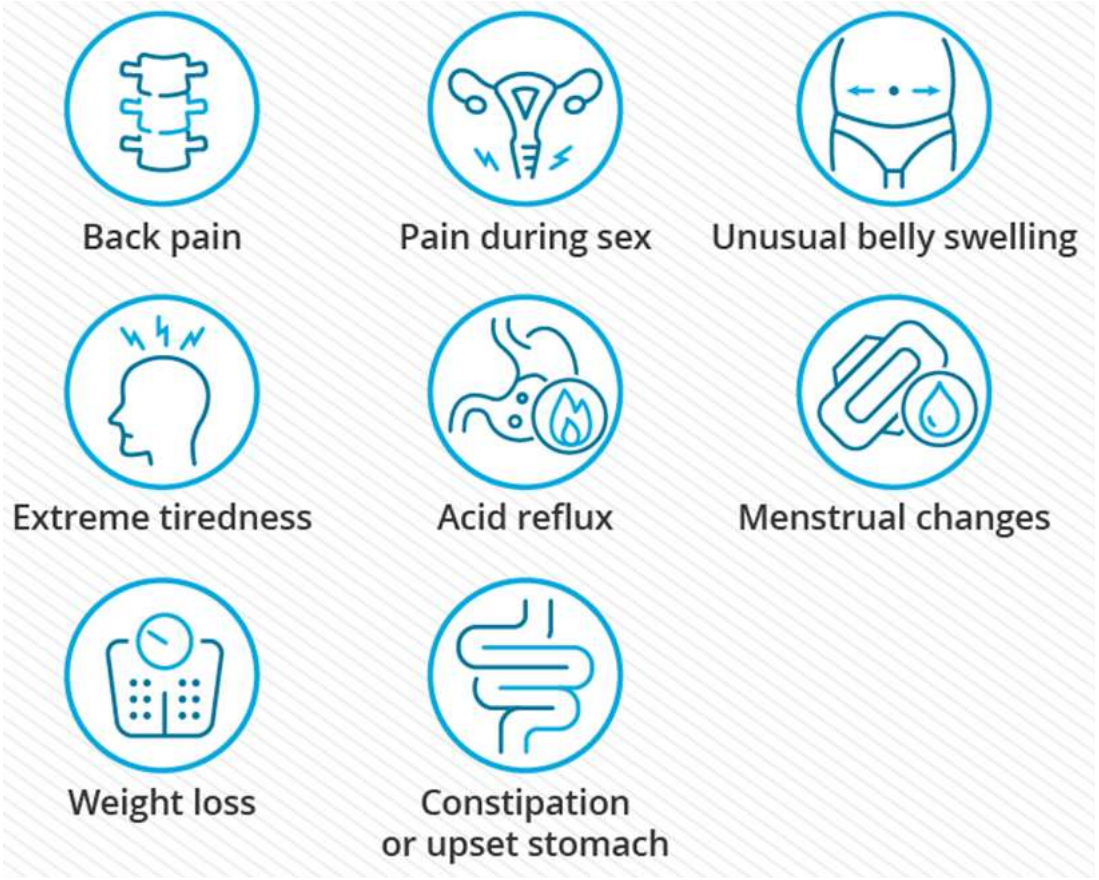
- Carriers of a g*BRCA1/2* pathogenic variant have a high lifetime risk of HGSOC
  - *BRCA1* PV: **44%**
  - *BRCA2* PV: **17%**

  } Vs general population: 1.3% (80 years of age)

- Risk does not start to increase above that of the general population until:
  - *BRCA1* PV: **mid-30s** — between age 35-40 years
  - *BRCA2* PV: **50 years of age** — between age 40-45 years

Risk-Reducing Bilateral Salpingo-Oophorectomy (rrBSO)

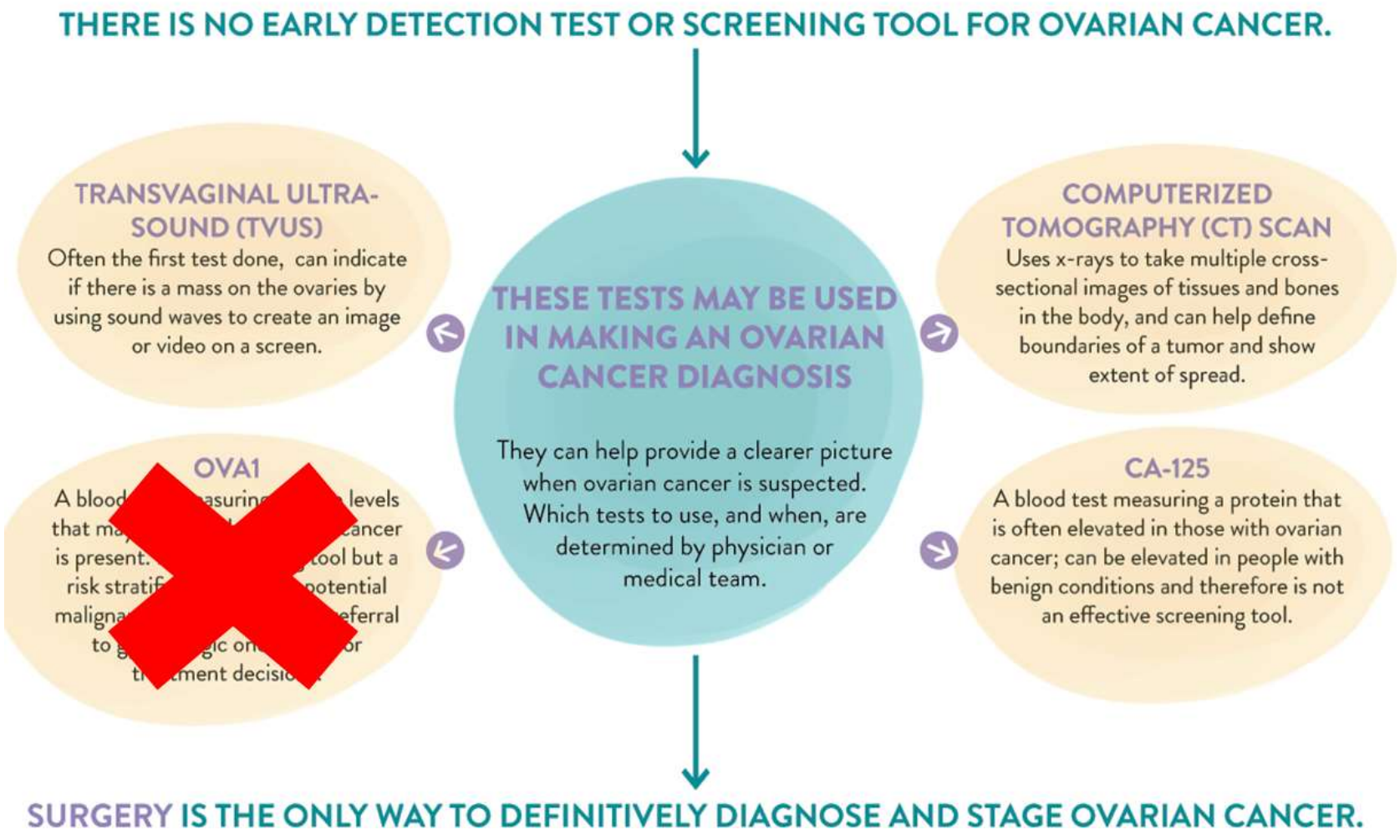
Clinical presentation of OC



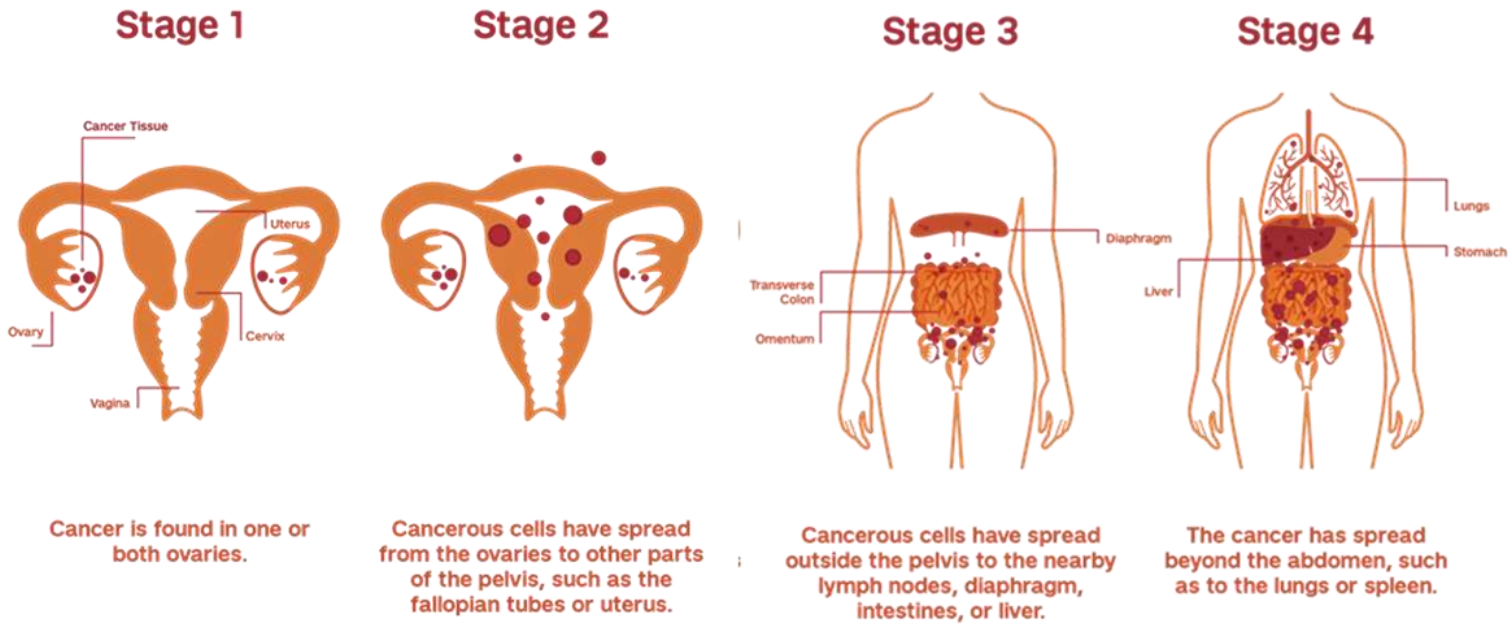
NO screening tools are available!

Lheureux S, et al. Lancet. 2019;393(10177):1240-1253

Diagnosis of OC



AJCC/FIGO Staging of OC



AJCC stages	Number of cases annually	Proportion of all cases diagnosed	Vital status at 10 years		10-year survival
			Alive (proportion of all survivors)	Dead (proportion of all deaths)	
I and II	1,716	13%	944 (35.4%)	772 (7.3%)	55%
III and IV	11,484	87%	1,723 (64.6%)	9,761 (92.7%)	15%

Narod S. Nat Rev Clin Oncol. 2016;13(4):255-61

Basic principles for OC treatment

Early stage (IA-IC) OC

Summary of recommendations	LoE	Go R	Consensus
Laparotomy is the standard surgical approach to treat and stage patients with apparent early stage ovarian carcinoma	V	A	Yes: 100% *(40 voters)*
Whatever the approach used, rupture of an intact tumour with spillage of cancer cells at the time of surgery must be avoided	IV	A	Yes: 100% *(40 voters)*
For patients with early stage disease requiring adjuvant chemotherapy, acceptable treatment regimens are: • carboplatin alone or • carboplatin /paclitaxel	 I II	 A A	 Yes: 100% *(40 voters)* Yes: 100% *(40 voters)*

ESMO/ESGO consensus statement 2018

Can advanced-stage OC be cured?

The three phases of OC treatment

- **Resectability**
  - Aim to achieve a status of no (visible) residual disease
- **Eradication**
  - Aim to eliminate all cancer cells present after debulking surgery with (neo)adjuvant chemotherapy
- **Prevention of recurrence**
  - Aim to prevent or delay recurrence after surgery and chemotherapy with maintenance therapy

Narod S. Nat Rev Clin Oncol. 2016;13(4):255-61

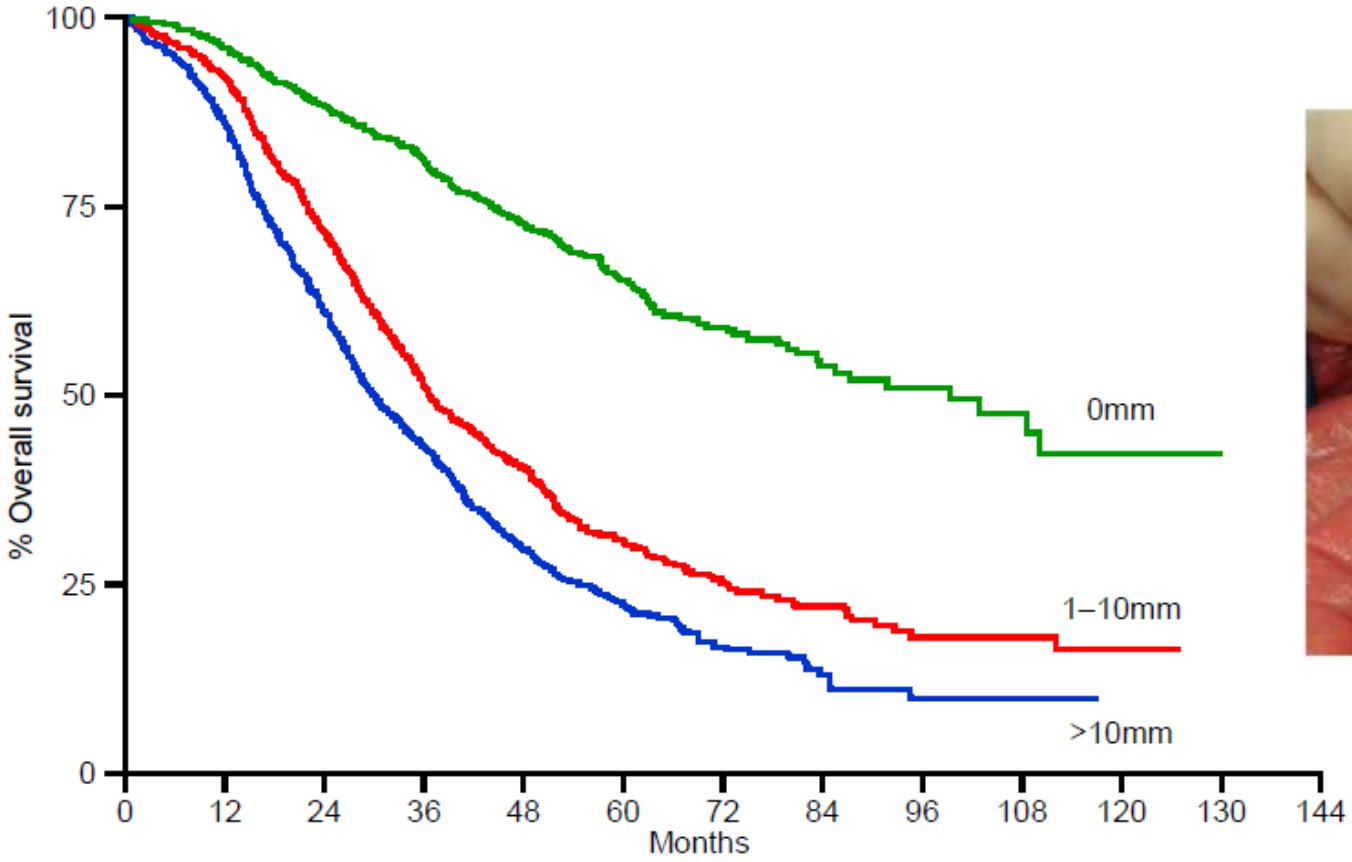
R0 cytoreduction

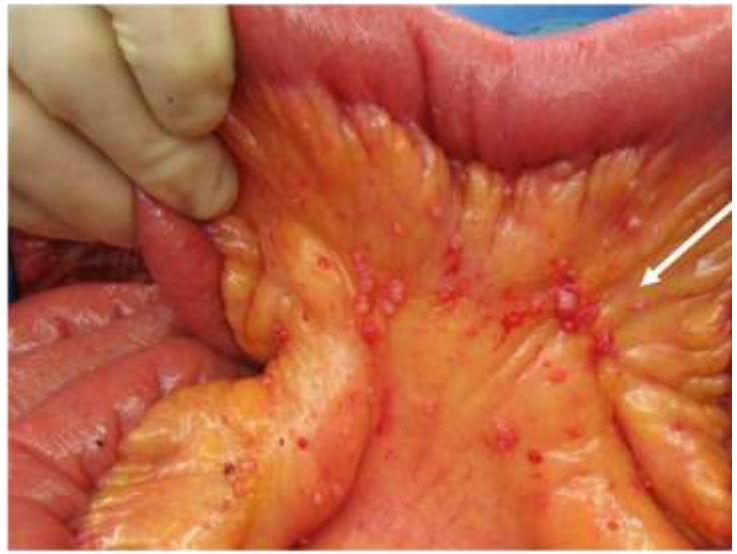
The most significant prognostic factor in advanced EOC

70%
no
gross
resid.
disease

20%
1–10mm
res.-disease

10%
>10mm

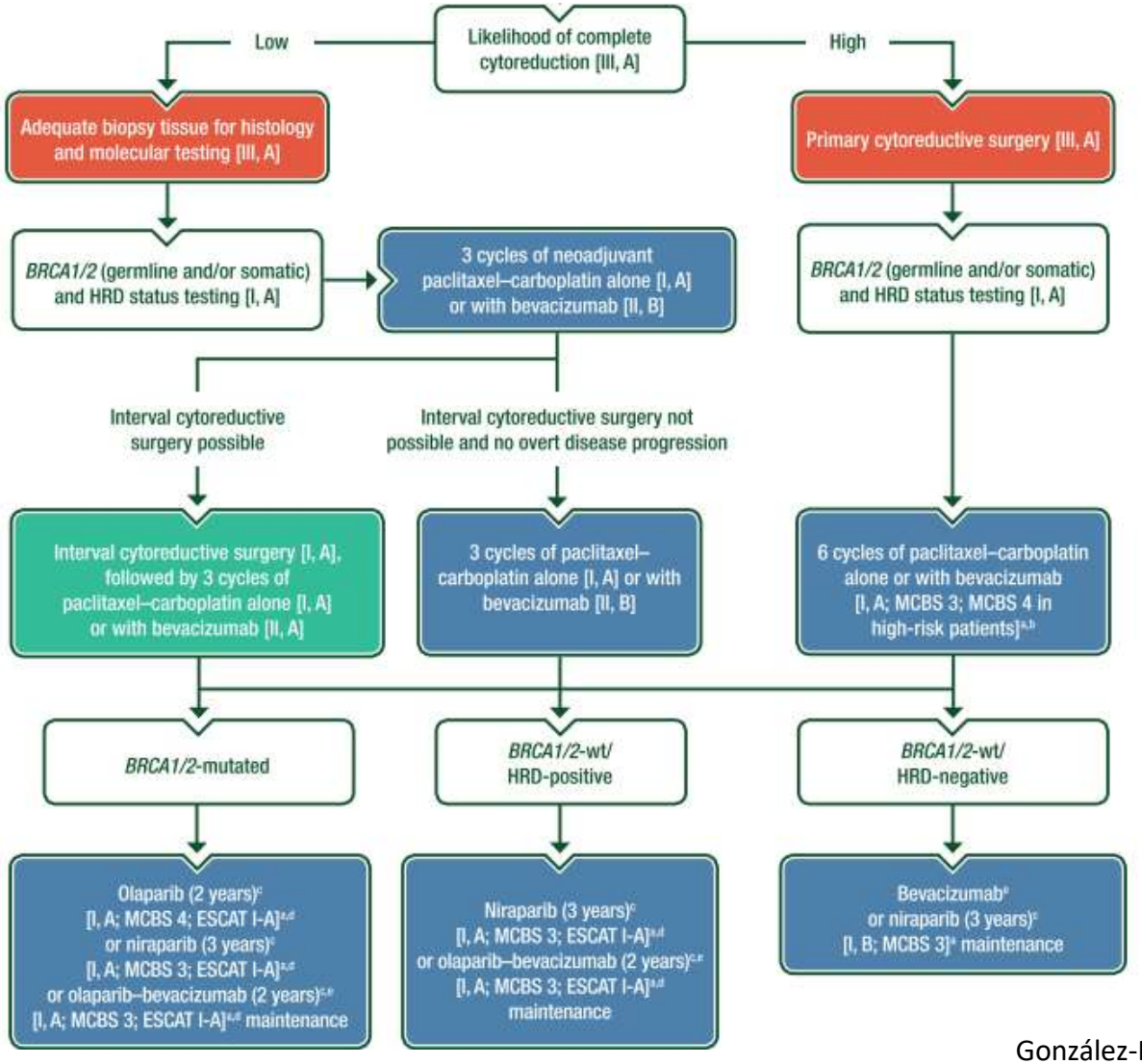




du Bois A, et al. Cancer. 2009;115(6):1234-44

Basic principles for OC treatment

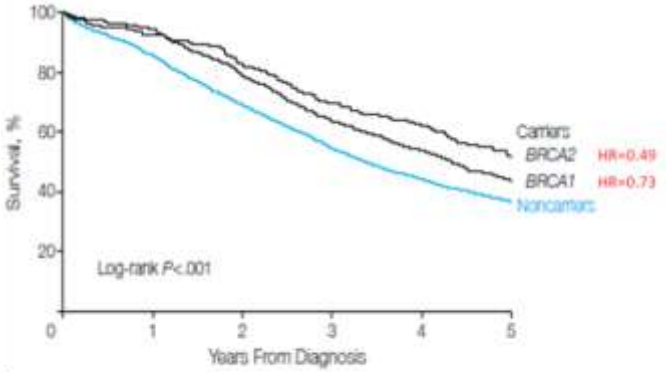
Advanced stage (II-IV) OC



González-Martín A, et al. Ann Oncol. 2023;34(10):833-848

Basic principles for OC treatment
Maintenance therapy in advanced stage (II-IV) OC

- **All HGSOC patients**, regardless of stage and/or age, should be referred for **genetic counseling**
  - ***BRCA1/2mut*** in **~25%** of cases
  - ***BRCA1/2mut*** OC is associated with **better prognosis**
  - ***BRCAmut*** OC patients derive unprecedented **benefit from PARP inhibitors**



Meta-analysis of 26 studies BRCA1 (n=909), BRCA2(n=304) et 2666 non-carriers

Bolton, *JAMA* 2012

Konstantinopoulos PA, et al. Cancer Discov. 2015
DiSilvestro P. ESMO 2022
González-Martín A. ESMO 2019
Ray-Coquard I.L. ESMO 2022

Basic principles for OC treatment

Recurrent disease

Assessment of the following factors [I-II, A]:

- Histotype
- *BRCA1/2* status
- Number of prior lines
- Exposure and response to prior treatment
- TFIp
- Potential for surgery
- Residual toxicity
- Patient's general condition
- Patient preference

Platinum resistant disease

Platinum-free interval <6 months

(mOS <9-12 months)

Early palliative care [I, A]

Single agent (non-platinum)[c] [I, B]

+ bevacizumab, if not contraindicated or previously exposed [I, A; MCBS 4][d]

Trabectedin–PLD (if TFIp >6 months and platinum intolerant) [II, C; MCBS 2][d]

Platinum sensitive disease

Platinum-free interval >6 months

(mOS: 24-36 months)

Platinum-based doublet[e] (PLD preferred) + PARPi maintenance[f,g], if responsive and PARPI-naive [I, A]

(preferred option if *BRCA1/2*-mutated)

or platinum-based doublet[e] (PLD preferred) + bevacizumab[f] [I, A]

(if no contraindication or previous exposure to bevacizumab)

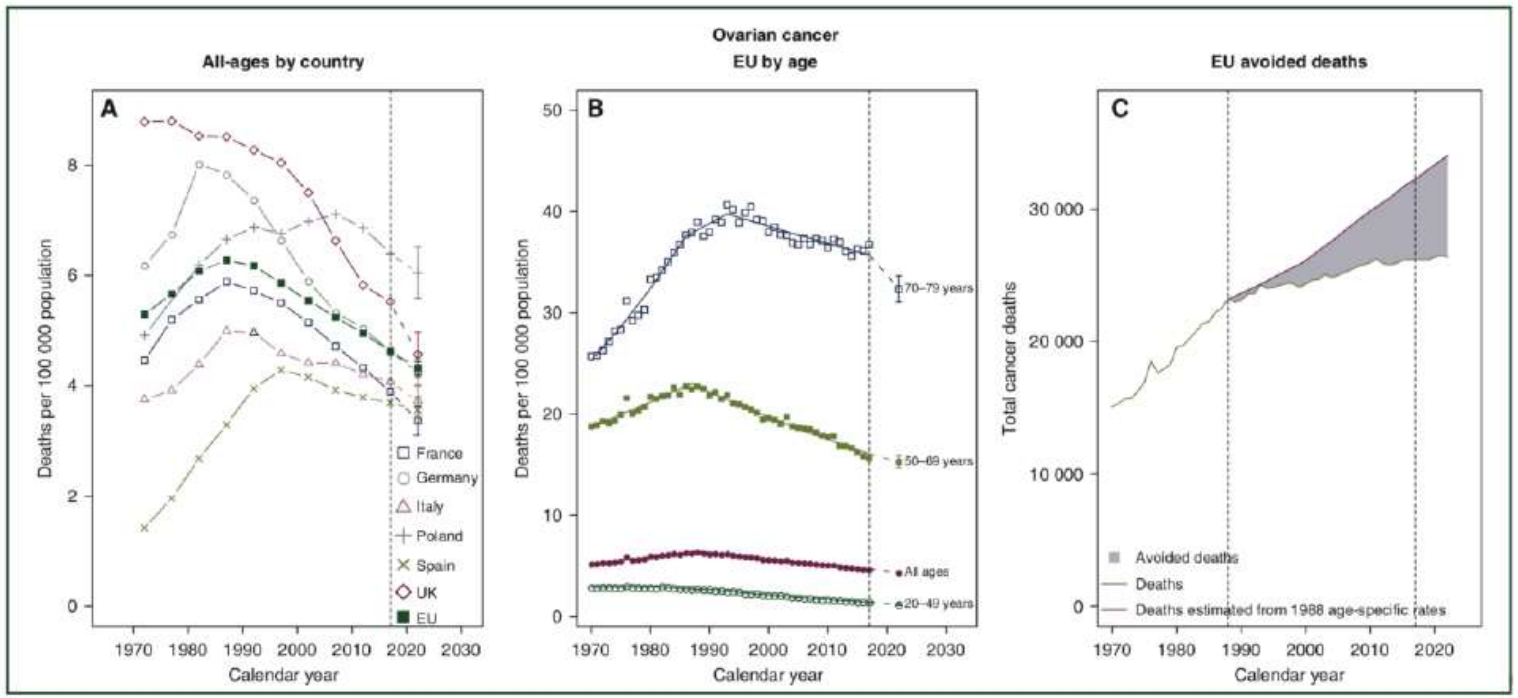
Do NOT forget the feasibility of Secondary Cytoreductive Surgery (CRS)

González-Martín A, et al. Ann Oncol. 2023;34(10):833-848

European cancer mortality predictions for the year 2022 with focus on ovarian cancer

M. Dalmartello[1], C. La Vecchia[1*], P. Bertuccio[1], P. Boffetta[2,3], F. Levi[4], E. Negri[1,3,5] & M. Malvezzi[1]

111 000 cancer deaths have been avoided (during a period of 34 years).
In 2022 alone, 8000 are predicted to be avoided



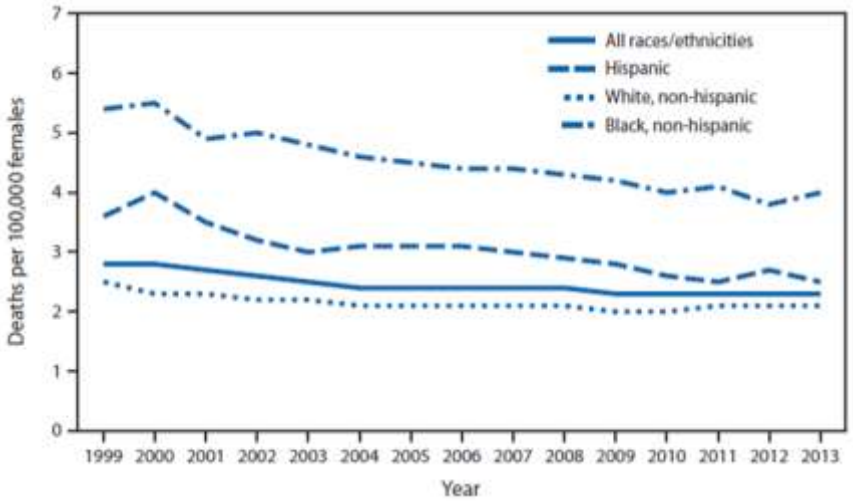
Main driving factors (by Dalmartello et al)

- Use of oral contraceptives
- Early diagnosis ?
- Improved surgery
- Platinum in the 80s
- Taxanes in the 90s
- ~~Gemcitabine~~
- ~~Intraperitoneal CT~~
- Possibly bevacizumab ?
- Prophylactic BSO in BRCAmut carriers
- PARPi

Annals of Oncology Volume 33 - Issue 3 - 2022

3. Cervical cancer (CC)
Epidemiology

- The 4th most common malignancy in female, worldwide
  - 604,000 new cases and 342,000 deaths (2020)
- Its **incidence is decreasing** (>**25%** since the early 1990s)
  - Global HPV vaccine uptake
- 5-year survival rates
  - Stage I: 92% → Stage IV: **18%**

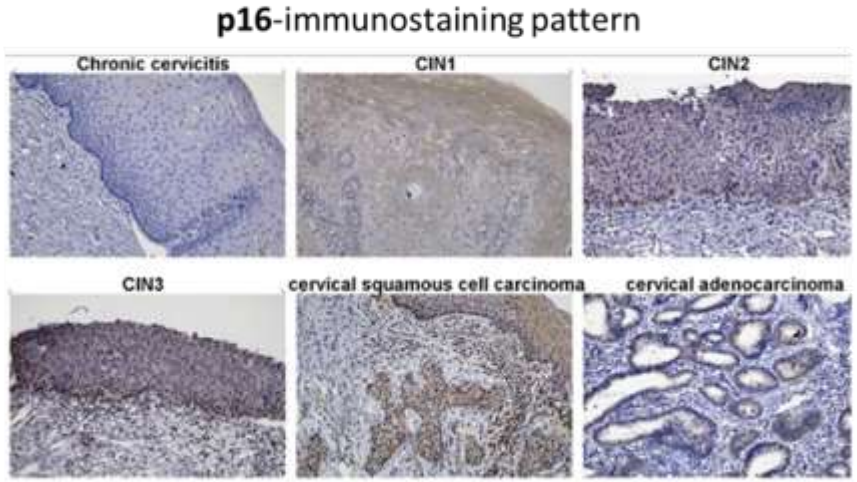


Duranti S, et al. Cancers (Basel). 2021;13(9):2089

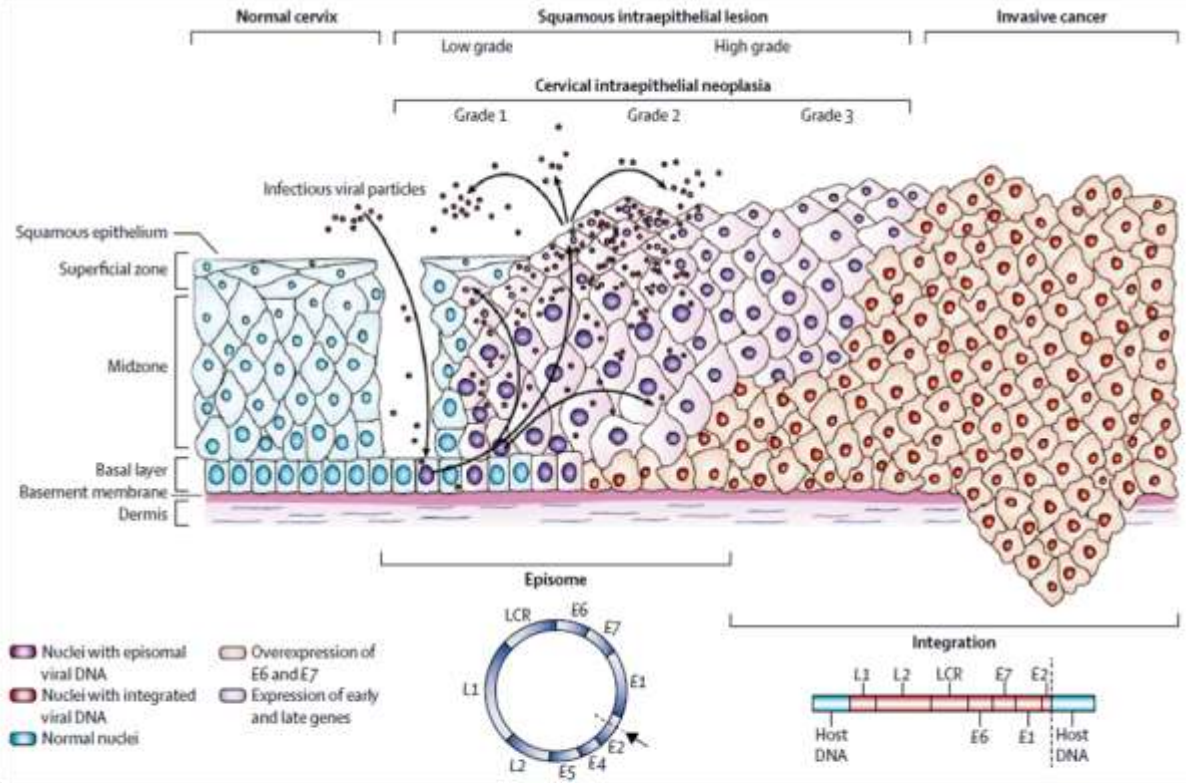
Pathogenesis of CC

Chronic HPV infection causes almost all cases

- Risk factors include:
  - early age of sexual debut
  - multiple sexual partners
  - history of sexually-transmitted infection
  - tobacco smoke

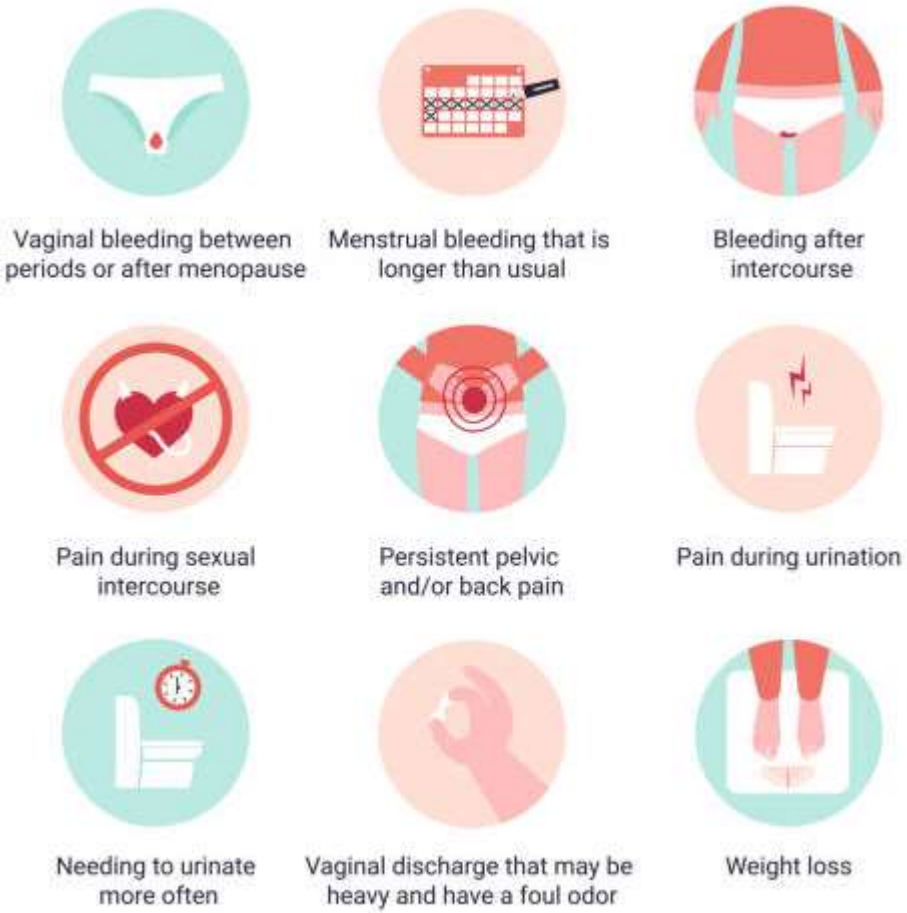


IHC stains of the HPV16 E7 protein in cervical lesions



Cohen PA, et al. Lancet. 2019;393(10167):169-182
Voidăzan ST, et al. Biology (Basel). 2022;11(7):956

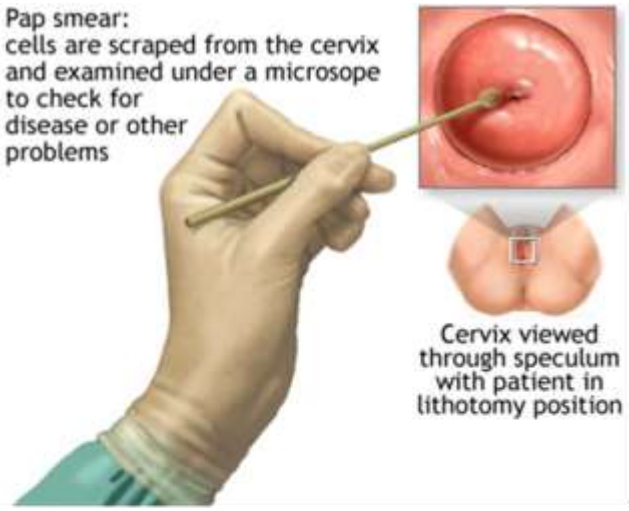
Clinical presentation of CC

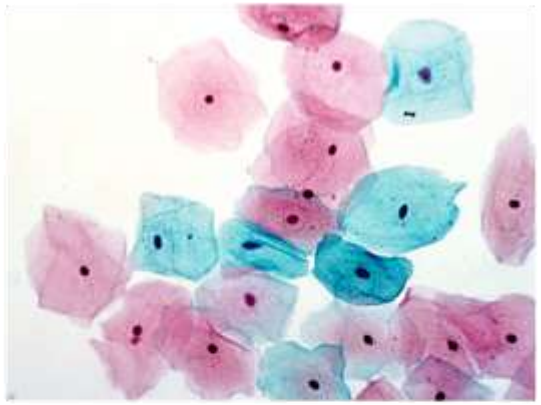


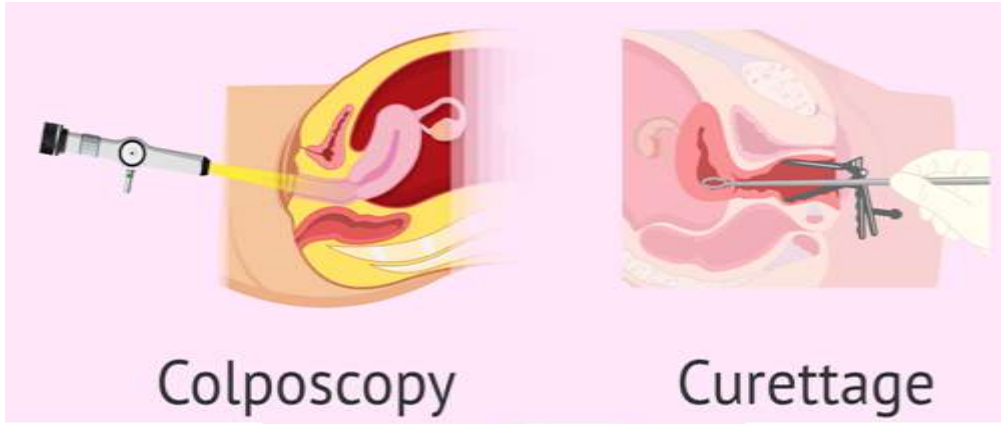
- In its early stages, CC is often **asymptomatic**
- The trial of lower limb oedema, flank pain, and sciatica suggest pelvic sidewall invasion

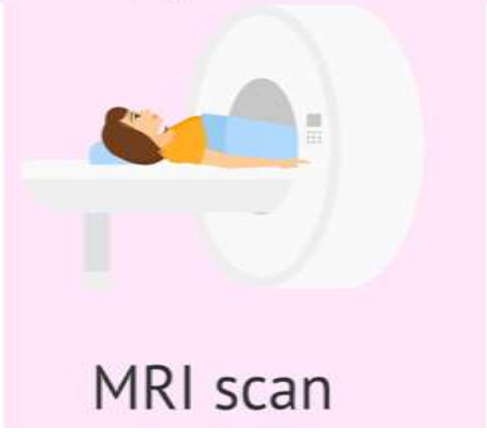
Cohen PA, et al. Lancet. 2019;393(10167):169-182

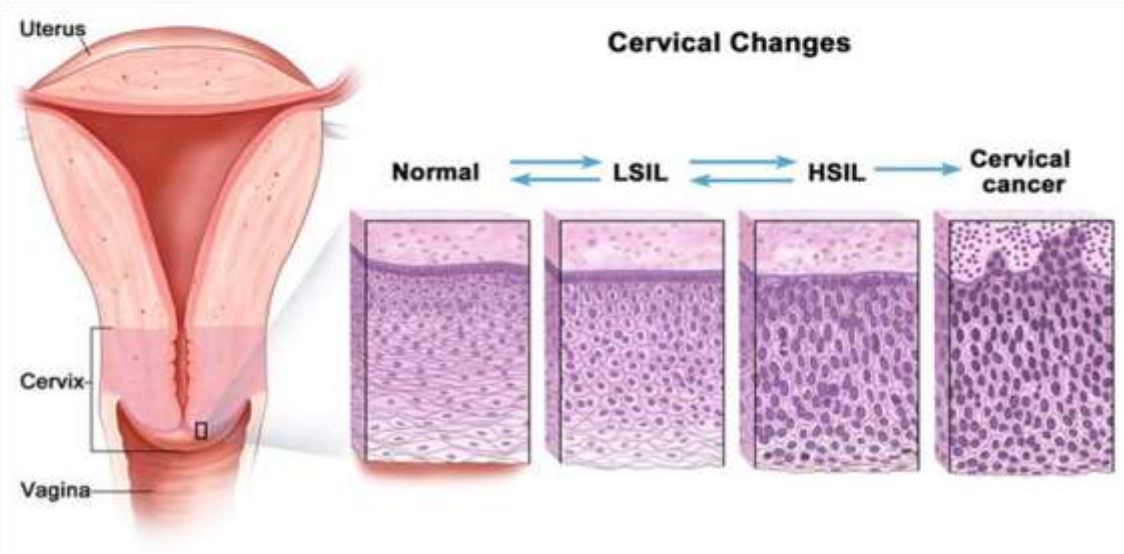
Diagnosis of CC











Cohen PA, et al. Lancet. 2019;393(10167):169-182

Who should be screened?!

- Women **aged 21-29** should receive **PAP smear screening** **every 3 years**, with the choice to continue until 65

OR

- Women **aged 30-65** should receive combination **high-risk HPV testing plus PAP smear** **every 5 years**

U.S. Preventive Services TASK FORCE

Who should NOT be screened?!

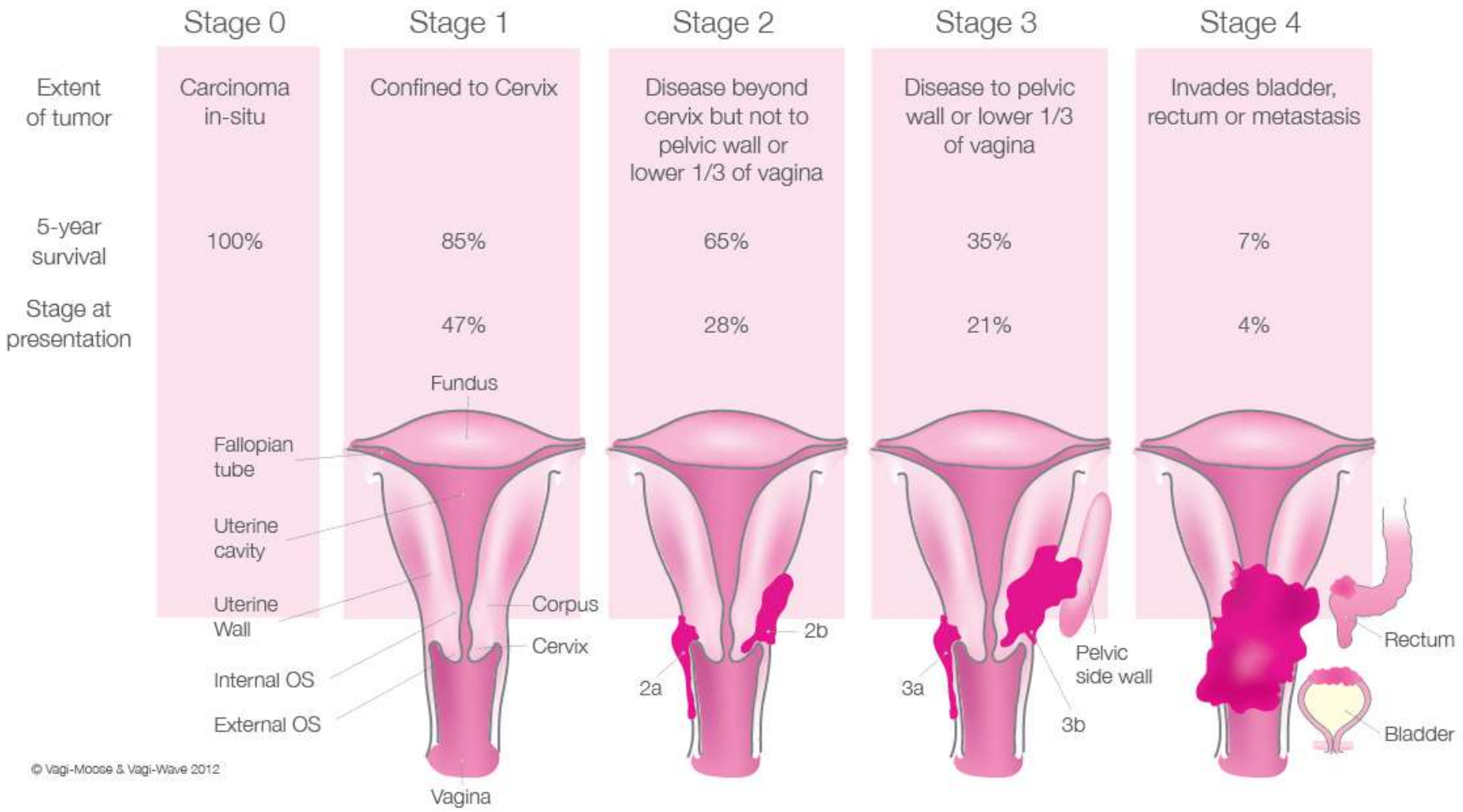
- Women **under 21 years**
- Women **older than 65** who have had **three consecutive negative cytology results** *or* **two consecutive negative HPV tests**

U.S. Preventive Services
TASK FORCE

Δ. Η γνωμοδότηση της Εθνικής Επιτροπής Εμβολιασμών

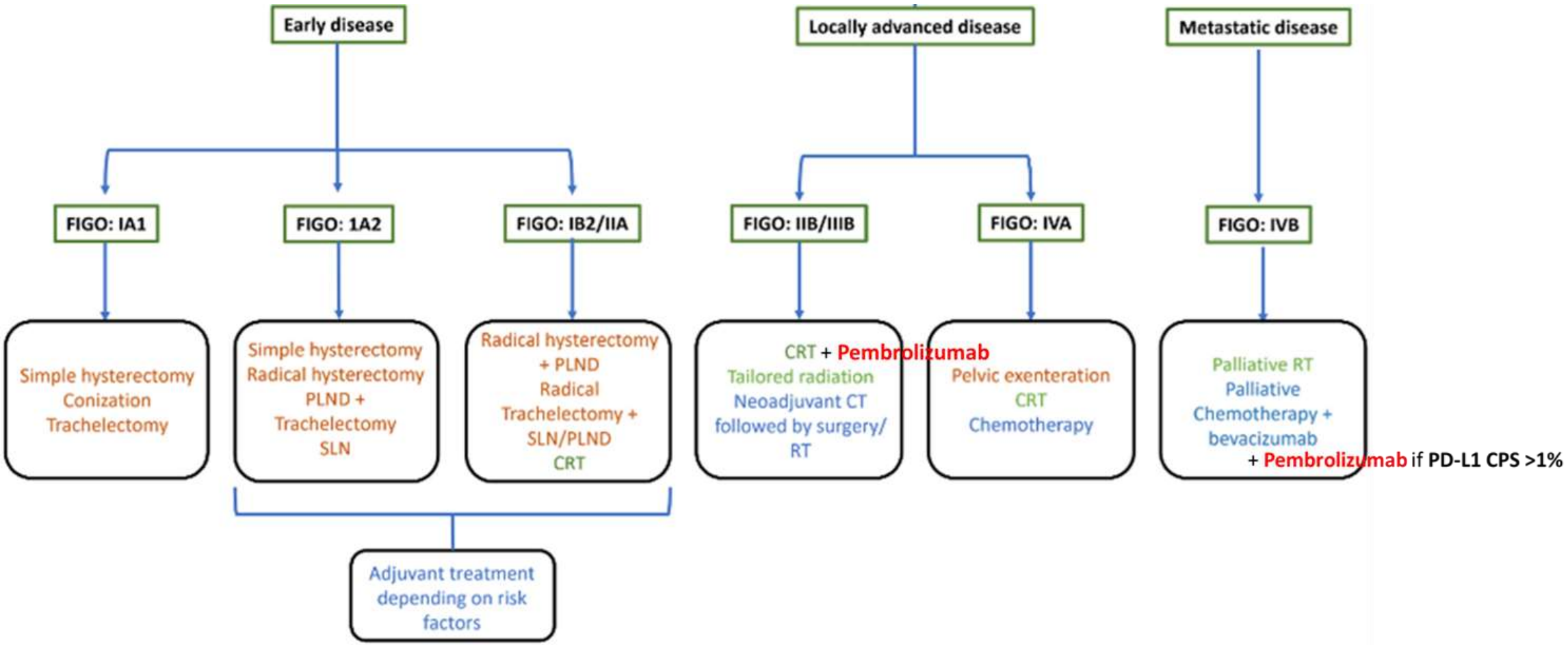
Με βάση τη διεθνή βιβλιογραφία και συνεκτιμώντας τα παραπάνω δεδομένα, η γνωμοδότηση της Εθνικής Επιτροπής Εμβολιασμών περιλαμβάνει τις ακόλουθες αλλαγές στο εμβολιαστικό σχήμα έναντι του HPV: (α) σύσταση για γενικό εμβολιασμό αγοριών και κοριτσιών, (β) το ενδεικνυόμενο διάστημα εμβολιασμού και για τα δύο φύλα είναι η ηλικία 9 έως 11 ετών, (γ) σε περίπτωση που ο εμβολιασμός και για τα δύο φύλα δεν πραγματοποιηθεί στη συνιστώμενη ηλικία, μπορεί να γίνει αναπλήρωση (catch-up) του εμβολιασμού, (δ) επισημαίνεται ότι το εμβόλιο HPV θα αποζημιώνεται πλήρως σε αγόρια και κορίτσια ηλικίας 15-18 ετών μέχρι 31.12.2023, και (ε) ο περιορισμός στην αποζημίωση μετά τις 31.12.2023 δεν αφορά τις ομάδες αυξημένου κινδύνου.

FIGO Staging of CC



Cohen PA, et al. Lancet. 2019;393(10167):169-182

Basic principles for CC treatment



Burmeister CA, et al. Tumour Virus Res. 2022;13:200238

@OraianthiF