Multidisciplinary approach

to gynecological malignancies

UNIWERSYTET JAGIELLOŃSKI
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UNIWERSYTECKI
W KRAKOWIE

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Introduction

Axioms & definitions

Radical treatment

- Cure – the highest priority
- Aggressive, multimodality treatment
- Relatively short treatment duration
- Quality of life during treatment is of secondary concern (supportive care– yes, reduction of intensity – last resort)

Palliative treatment

- Balance: quality of life vs life extension
- Symptom control, delaying progression, complication avoidance
- Indefinite duration – „chronization”
- Minimizing toxicities (intensity reduction & supportive care)

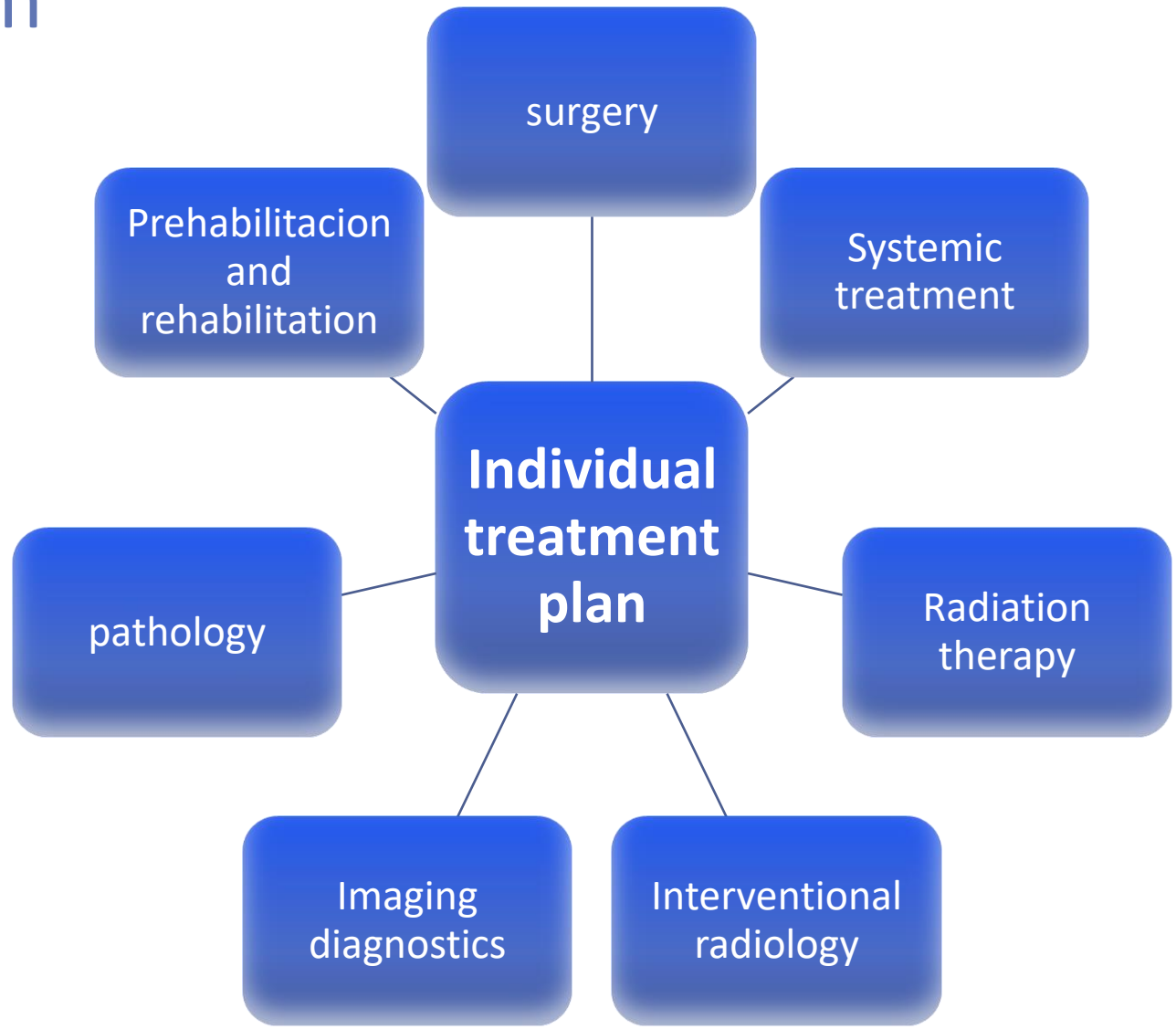
Axioms & definitions

- **Metastatic disease is incurable – treatment can be only palliative**
  - Typically: available treatment options do no have enough efficacy/toxicity ratio to eradicate all the disease foci
  - Exceptions:
    - „chemo-curable” cancers – great chemosensitivity
    - Single metastasis from a cancer of indolent biology
    - Immunotherapy (percentage of patients)
    - „therapeutic miracles” (probabilistic extremes)
- **In metastatic disease, proportion of the foci will always be indetectable**
  - Typically : some of the foci remain below the spatial or tissue resolution of a given imaging method
  - Exceptions : Single metastasis from a cancer of indolent biology

Who should plan treatment?
MDT – multidisciplinary team

MDT:

- Multiple specialities
- Sub-specialization in a given disease group – role of „high volume centres”
- Infrastructure
  - people
  - facilities/ equipment
  - organization
- Close teamwork



How to devise a treatment plan

Tumor biology:
- Histo-pathology
- Molecular factors
- Metabolic consequences

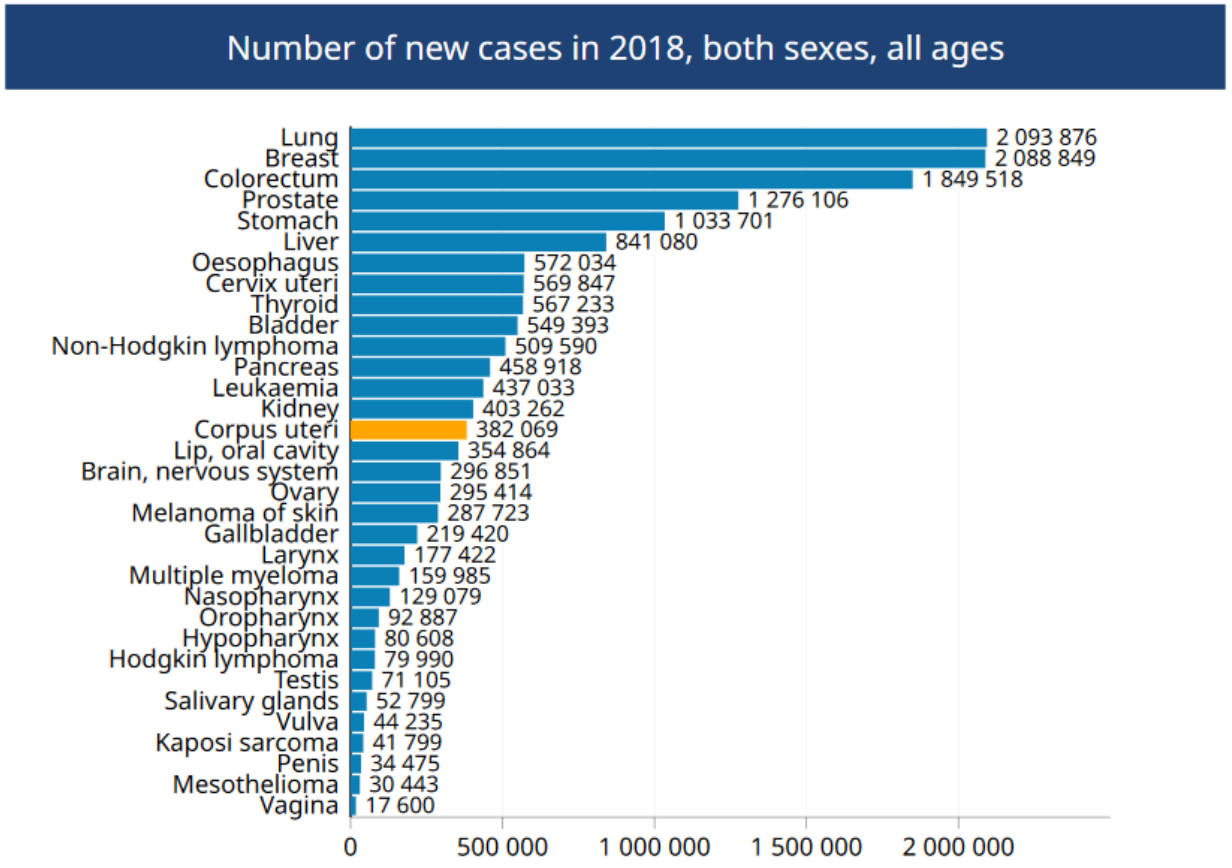
Clinical stage:
- Clinical, pathological, imaging
- Primary tumour, regional lymph nodes, distant metastases

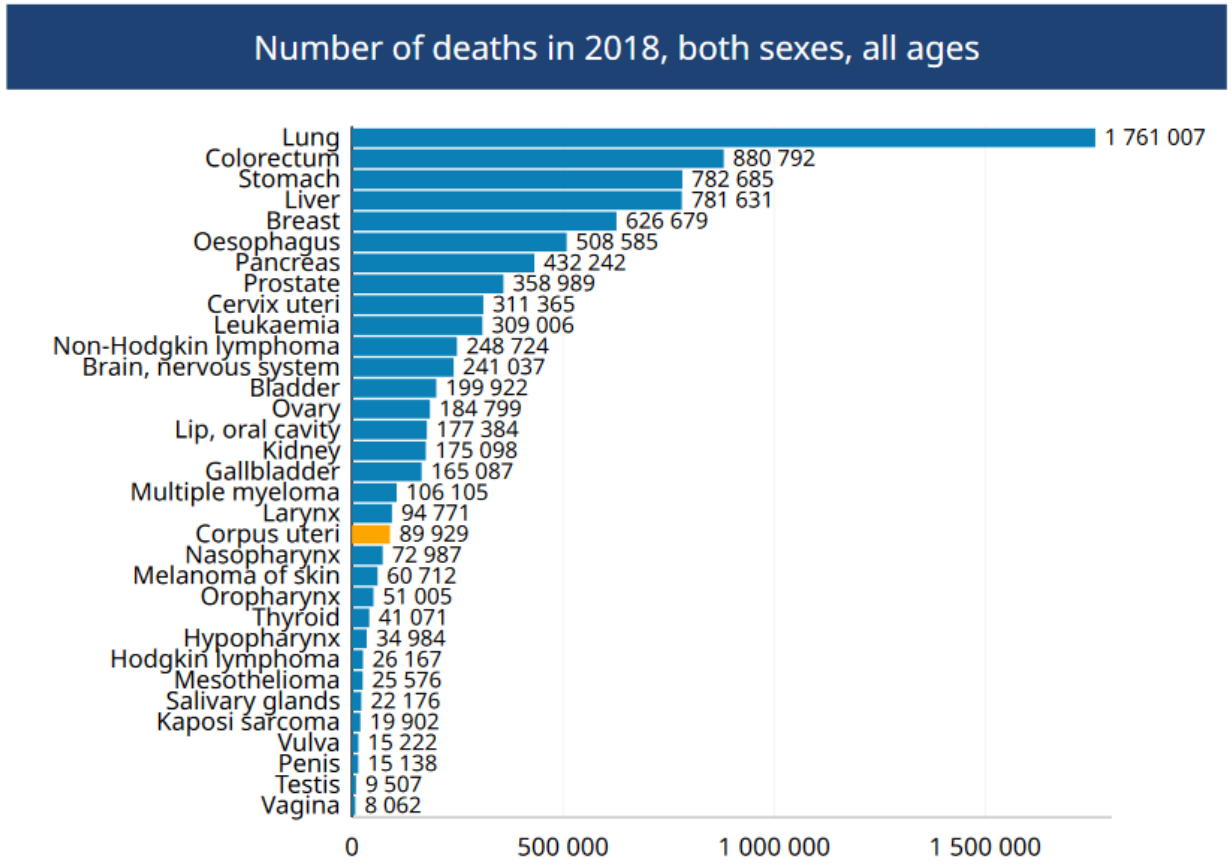
Patients general condition:
- Performance status
- Comorbidities
- Biological age
- Social support

Treatment Plan:
- Aim (radical / palliative)
- Priorities
- Treatment modalities & their sequence
- Anticipated problems
- Survivorship plan / care
- Treatment failure plan

Endometrial cancer

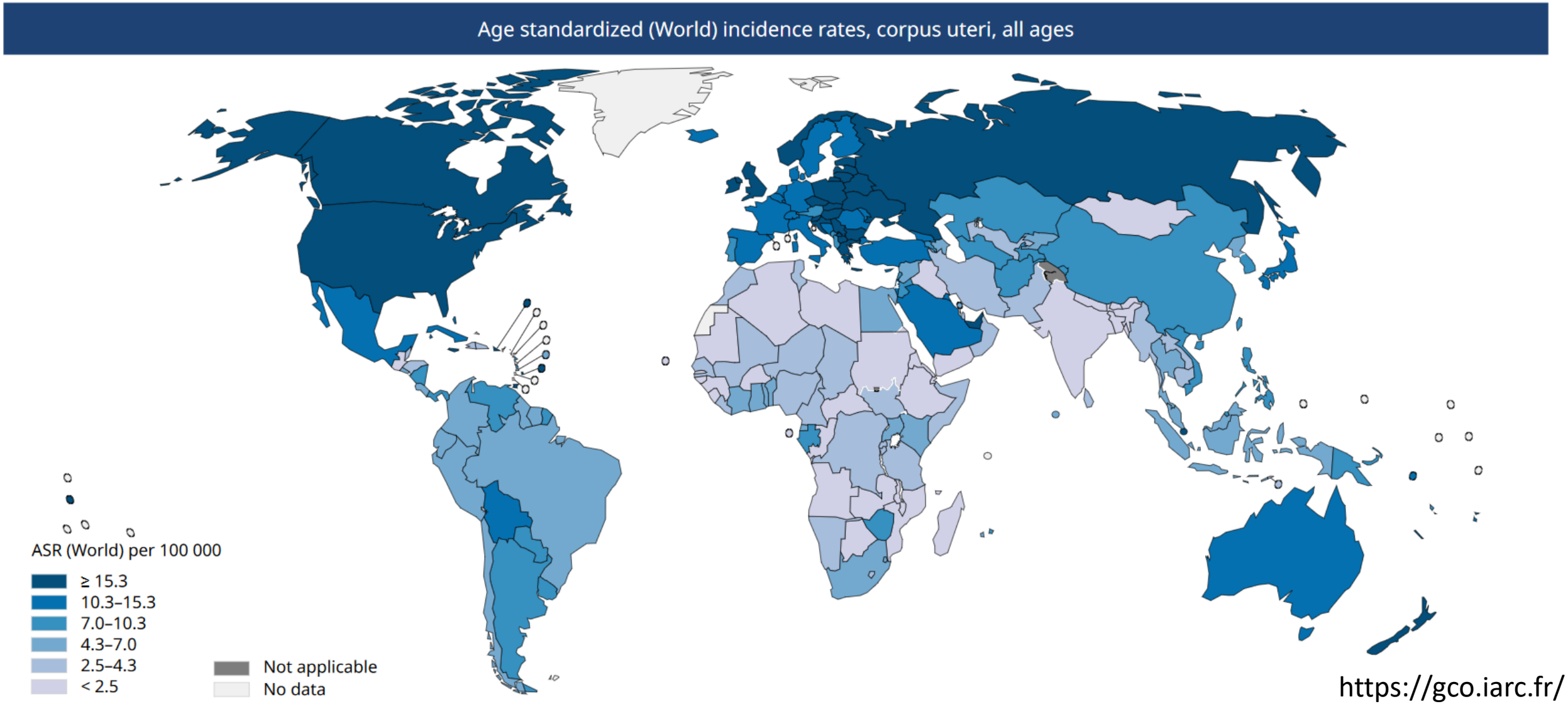
Endometrial cancer





https://gco.iarc.fr/

Endometrial cancer



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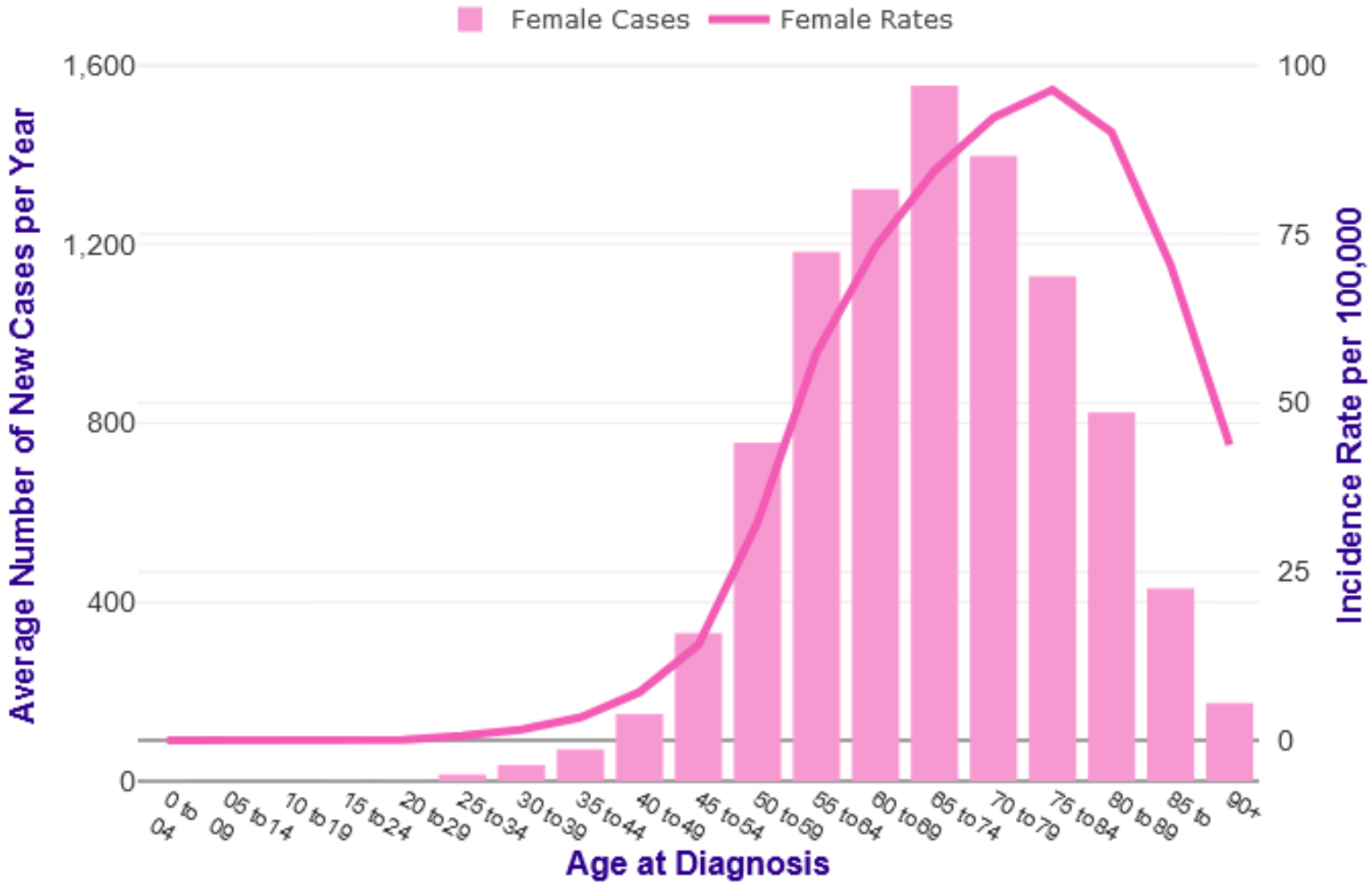
Endometrial cancer



www.cancerresearchuk.org

Endometrial cancer

- **Risk factors**
  - Estrogen exposure
    - Oral contraceptives (without progestagen), hormone replacement (without progestagen), tamoxifen
    - Chronic anovulation (especially polycystic ovaries syndrome)
    - Obesity (peripheral production)
    - Early menarche / late menopause
  - Metabolic syndrome
  - Genetic
    - dMMR (Lynch Syndrome)
    - dHRR (BRCA)

Endometrial cancer

- **Protective factors**
  - High gravidity and parity
  - Breastfeeding
  - Progestagenes
    - Oral contraceptives (protective effect of progestagenes prevails over that of estrogens)

Endometrial cancer

Presentation

- Abnormal uterine bleeding (present in 75-90% cases)
- Uterine abnormality on imaging
  - Mass or endometrial thickening
  - Role of myoma surveillance
- Abnormal cervical cytology (displastic endometrioid cells)

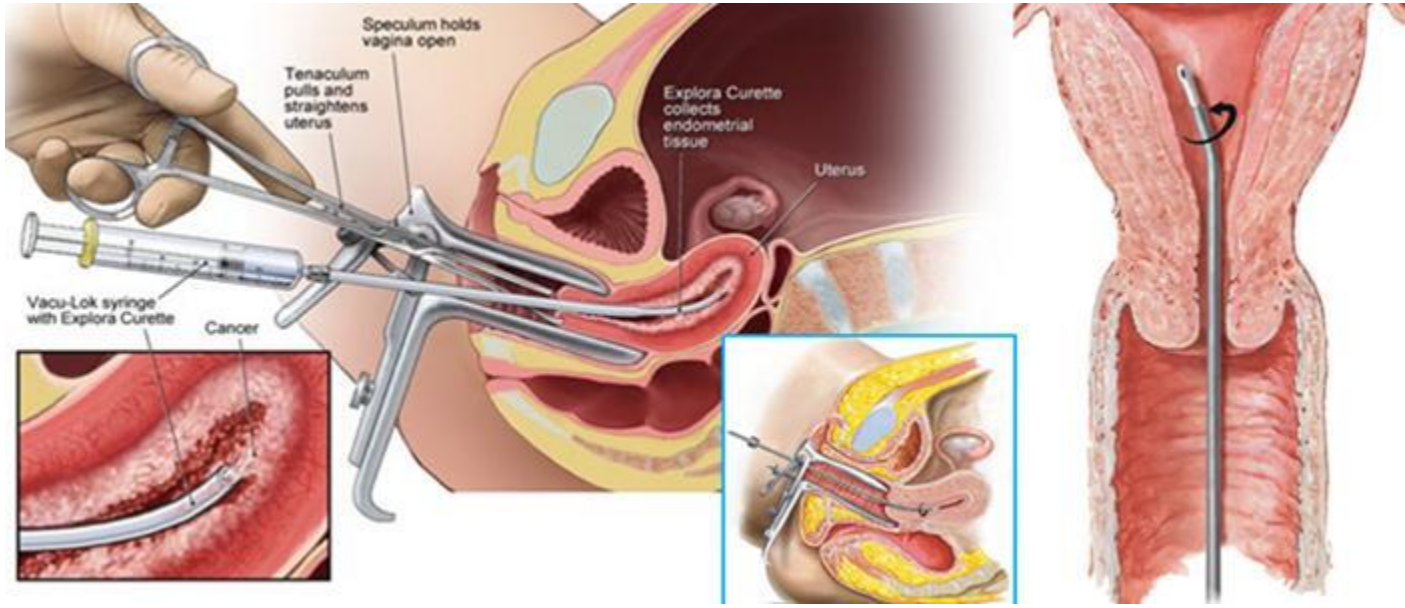
- Screening not viable in general population
  - effecive for patients on tamoxifen? (limited data)

Endometrial cancer

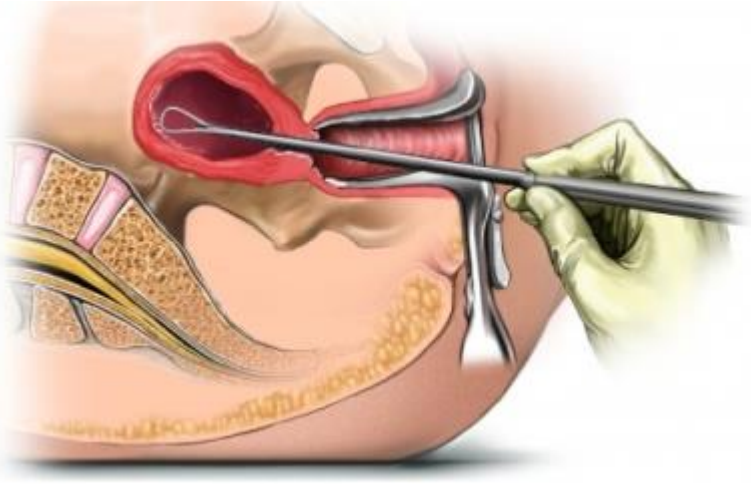
Diagnosis

- Endometrial sampling (blind biopsy)
  - Sufficient in most cases
- Excochleation (curettage)
  - May be therapeutic in case of heavy bleeding
- Hysteroscopy
  - if blind biopsy insufficient

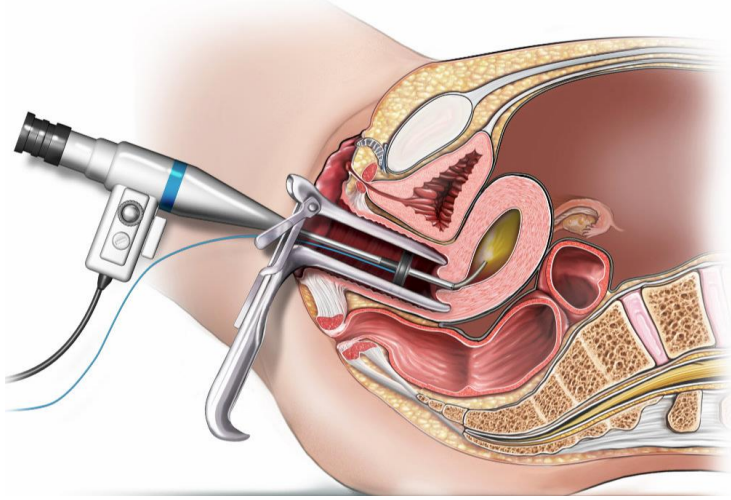
- Blind sampling



- curettage



- hysteroscopy



Endometrial cancer

Pathology

- Precursor lesions
  - endometrioid intraepithelial neoplasia
  - Serous endometrial intraepithelial carcinoma
- Type I
  - ~70% cases
  - Estrogen-driven
  - Favourable prognosis
- Type II
  - ~30% cases
  - Various histologies
  - Estrogen-independent
  - Poor prognosis

Endometrial cancer

Pathology - Cancer subtypes

- Endometrioid carcinoma
  - Most common subtype
  - Favourable prognosis
- Serous endometrial carcinoma
  - Worse prognosis
  - Clinical picture often similar to ovarian cancer
- Clear cell carcinoma
  - Aggressive, poor prognosis
- Sarcomas
  - Multiple subtypes, variable biology

Endometrial cancer

Staging

- Locoregional assessment (TN)
  - Pelvic exam
  - Transvaginal ultrasound
  - MRI
    - If resectability uncertain
    - If fertility preservation desired
  - **surgery**
- Metastasis assessment (M)
  - Typically abdominal ultrasound and chest X-ray sufficient for type I cancers (relatively low risk of metastases)
  - CT
    - always for type II cancers
    - when indicated for type I

Endometrial cancer

Treatment for localized disease

- Hysterectomy + bilateral salpingo-oophorectomy
  - Laparoscopic approach less toxic and equally effective to open surgery
  - Peritoneal sampling only if dissemination is suspected
- Regional lymph node dissection / sampling
  - Subject of controversy
    - Improves survival vs only diagnostic?
    - Extent? Sentinel vs selective vs pelvic vs pelvic+paraaortic?
  - Instrumental in shaping the postoperative treatment

Endometrial cancer

Adjuvant treatment - risk assessment

- Low-risk — grade 1 endometrioid cancers confined to the endometrium – no adjuvant
- Intermediate-risk - combination of risk factors – adjuvant radiation +/- chemotherapy
  - myometrial invasion (especially outer one-third of wall thickness)
  - occult cervical stromal invasion myometrial invasion,
  - grade 2 or 3 tumours
  - evidence of lymphovascular invasion
- High-risk
  - Lymph node involvement – chemotherapy + radiation
  - Clear-cell or serous histology (regardless of stage) – chemotherapy

Endometrial cancer

Adjuvant treatment

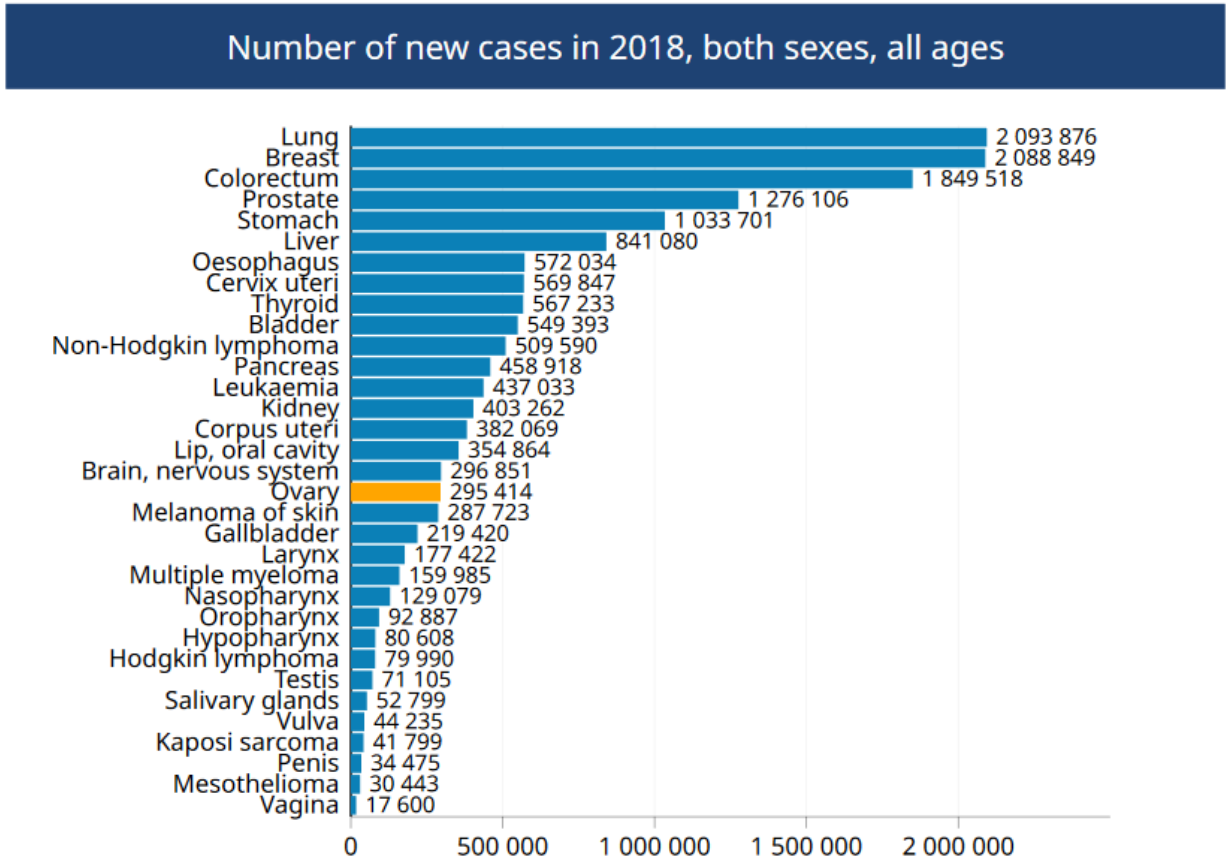
- Intermediate-risk
  - Vaginal brachytherapy preferred over tele-RT (less toxicities)
  - Chemotherapy in rare cases of intermediate-high risk
- High-risk
  - Chemotherapy alone (PXL+CBDCA) for low stage adverse histologies (type II)
  - Chemoradiation -> chemotherapy or radiation-> chemotherapy for positive lymph nodes

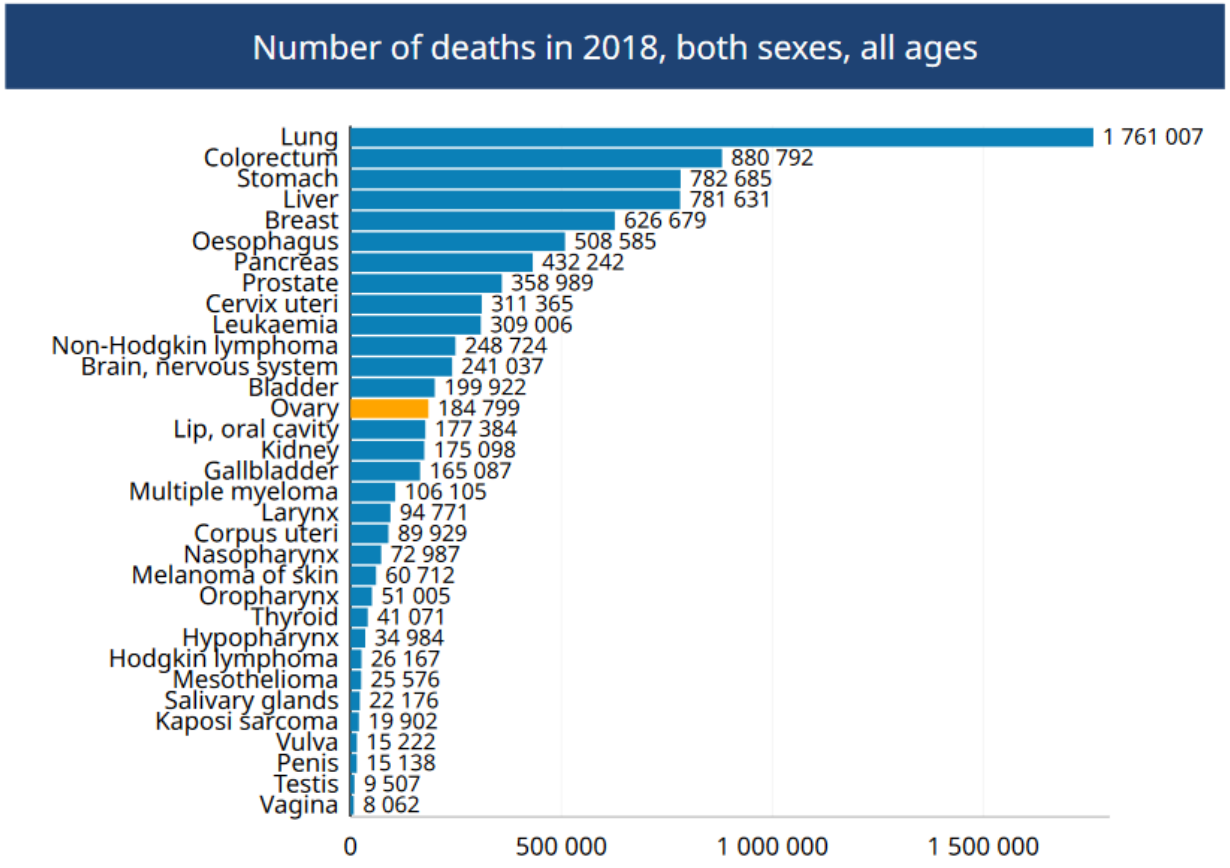
Endometrial cancer

- **Metastatic disease**
  - cytoreduction of the primary – low quality data suggest it may be beneficial
  - Endocrine therapy (progestagenes or /and anti-estrogenes) for G1-2, mildly symptomatic cancers
  - Chemotherapy - effective
    - Platins
    - Taxanes (paclitaxel)
    - Topotecan
    - Anthracyclines
  - Targeted therapies
    - Bevacizumab – active in 2nd and subsequent lines
    - Immunotherapy – active if dMMR present

Ovarian cancer

Ovarian cancer





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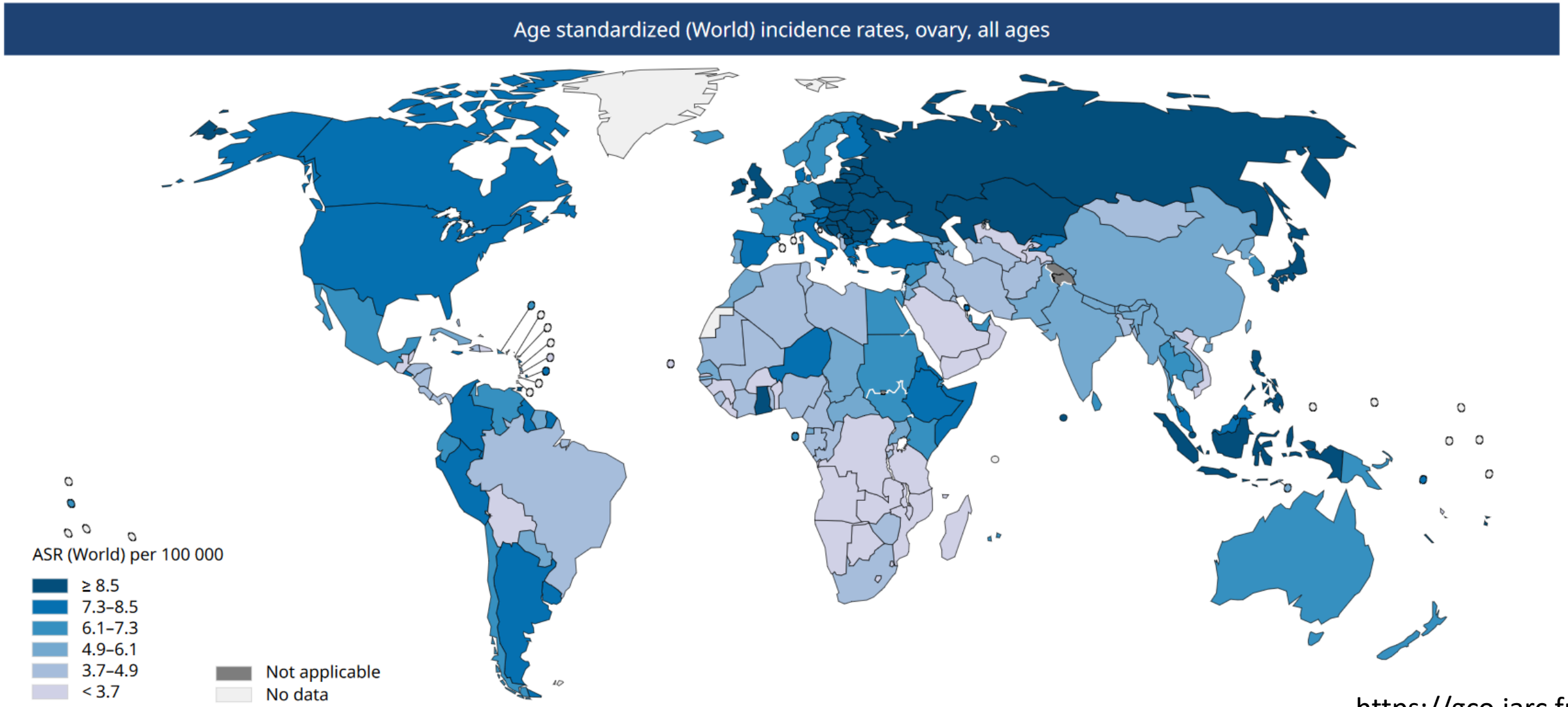
Ovarian cancer



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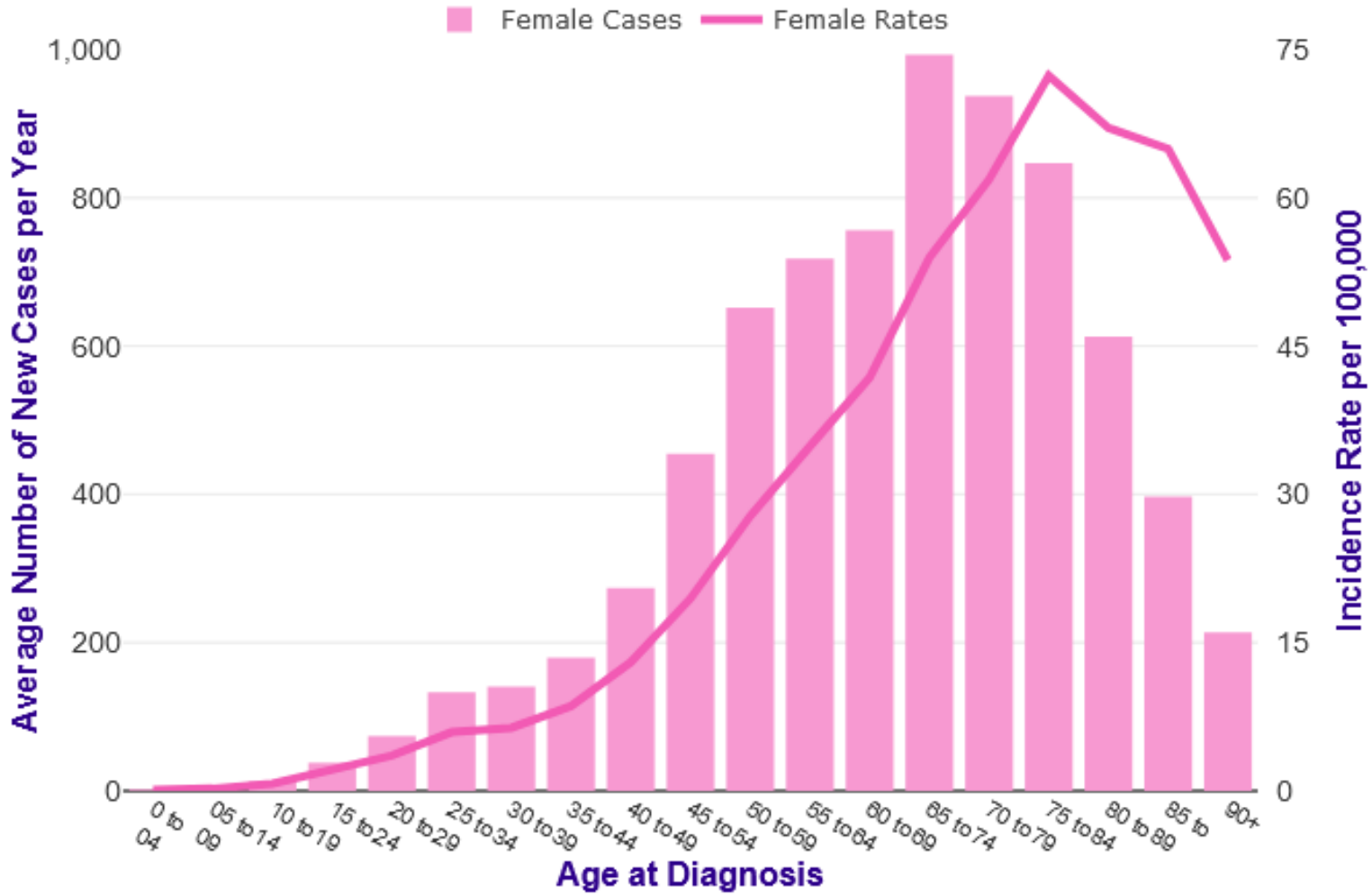
Ovarian cancer



Ovarian cancer

- **Risk factors**
  - Estrogen exposure
    - Oral contraceptives (without progestagen), hormone replacement (without progestagen), tamoxifen
    - Obesity (peripheral production)
    - Early menarche / late menopause
    - Polycystic ovaries?
  - Metabolic syndrome
  - Endometriosis
  - Asbestos exposure
  - Genetic
    - dHRR (BRCA, PALB, CHEK, RAD51)
    - dMMR (Lynch Syndrome)

Ovarian cancer

- **Protective factors**
  - High gravidity and parity
  - Breastfeeding
  - Progestagenes
    - Oral contraceptives (protective effect of progestagenes prevails over that of estrogens)
  - Hysterectomy
  - Tubal ligation

Ovarian cancer

Presentation

- Early symptoms
  - Adnexal mass
  - Bloating
  - Urinary urgency & frequency, change in bowel habits
  - Pelvic & abdominal pain
- Late symptoms
  - Ascites and/or hydrothorax
  - Subileus / ileus
  - Recurrent vein thrombosis, PE
  - cachexia

Cachexia – complex disturbance of protein and energy balance

Decreased intake

GI tract involvement
(passage, digestion, absorption)

Treatment-related GI impairment
(passage, digestion, absorption)

Systemic treatment
(hospital diet, altered appetite and taste, nausea and vomiting)

Anxiety and depression
(low drive, decreased appetite)

Systemic inflammation
(flu-like symptoms, decreased appetite)

Increased usage

Systemic inflammation

Cancer metabolic needs

Healing of cancer-damaged tissues

Healing of treatment-related injuries

Cachexia – complex disturbance of protein and energy balance

Cancers particularly associated with cachexia

- Esophageal
- gastric
- pancreatic
- biliary
- lung
- ovarian
- bladder
- lymphomas

Clinical findings associated with cachexia

- Signs of generalize inflammation
  - B symptoms (weight loss, fever, night sweats)
  - Glasgow prognostic index (albumin, CRP)
- Body cavity implants and effusions
- High proliferative index

Khorana score – ambulatory risk of VTE		ponts
Cancer type	Gastric, pancreatic, glioblastoma	2
	Lung, gynaecologic, urologi (except prostate), lymphomas	1
Obseity	BMI >35	1
Anemia	HGB <10g/dl or usage of ESA	1
leucocytosis	WBC >11k/ul	1
trombocytosis	PL >350k/ul	1

Ovarian cancer

Diagnosis

- Pelvic examination
- TV-ultrasound or MRI
- Lab studies
- HP typically obtained during the resection

Ovarian cancer

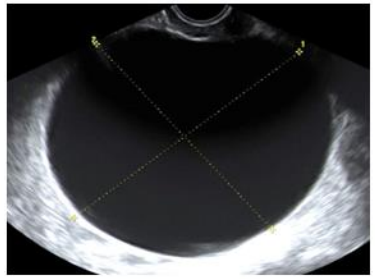
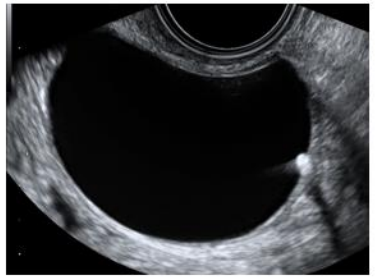
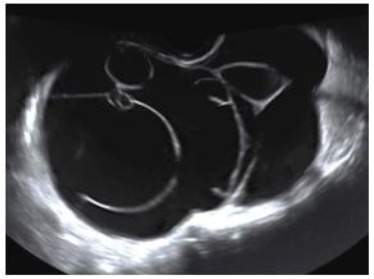
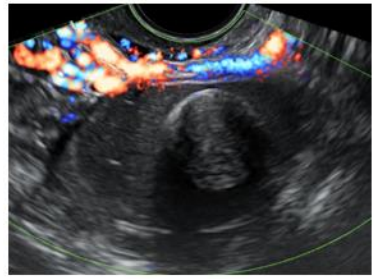
IOTA criteria for managing ovarian mass

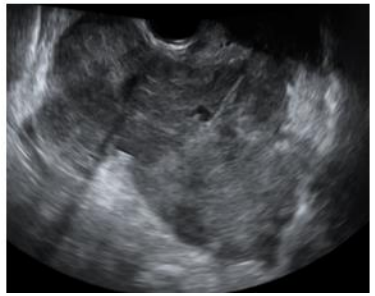
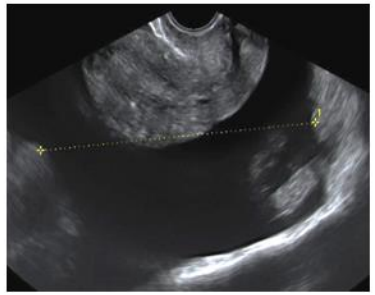
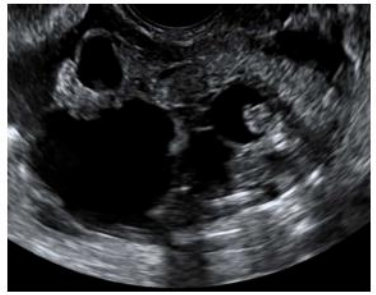
- **Benign features**
- If an ovarian lesion has at least one of these features and no malignant features it can be confidently considered benign:
  - unilocular cyst
  - smooth multilocular tumor <10 cm
  - solid components <7 mm in diameter
  - presence of acoustic shadow
  - no detectable Doppler signal

- **Malignant features**
- If an ovarian lesion has at least one of these features and no benign features it can be confidently considered malignant:
  - irregular solid tumor
  - irregular multilocular-solid mass >10 cm in diameter
  - ≥4 papillary structures
  - ascites
  - high Doppler signal (colour score 4)

Ovarian cancer

IOTA criteria for managing overian mass

B1 Unilocular	B2 Presence of solid components with largest diameter < 7 mm	B3 Presence of acoustic shadows	B4 Smooth multilocular tumor with largest diameter < 100 mm	B5 No blood flow (color score 1)
				

M1 Irregular solid tumor	M2 Presence of ascites	M3 At least 4 papillary structures	M4 Irregular multilocular-solid tumor with largest diameter ≥ 100 mm	M5 Very strong blood flow (color score 4)
				

https://www.iotagroup.org

Ovarian cancer

Circulating tumor markers

- HE4 (Human Epididymis Protein 4)
  - Specific mainly to ovary and ovarian cancer
  - Can rarely be produced by different cancers

Circulating tumor markers

- Ca 125
  - Specific to mesothelium (pericardium, pleura, peritoneum)
  - Can rise whenever mesothelium is damaged (malignant implants, endometriosis, trauma, inflammation, effusion etc)

ROMA (Risk of Ovarian Malignancy Algorithm)

- Based on HE4, Ca125 and age
- assesses the malignancy risk of a benign-looking lesion (as per IOTA criteria)

Ovarian cancer

Pathology

- High-grade serous carcinoma (HGSC; 70 - 80 %)
- Endometrioid carcinoma (10 %)
- Clear cell carcinomas (10 %)
- Mucinous carcinoma (3 %)
- Low-grade serous carcinoma (LGSC; <5 %)
- Germ-cell tumors (~1%) .

Ovarian cancer

Treatment for localized disease

- Optimal resection is key and must comprise of:
  - Hysterectomy
  - bilateral salpingo-oophorectomy
  - omentectomy
  - appendectomy
  - resection of all visible peritoneal implants or peritoneal sapling if no macroscopic lesions present
  - Effusion fluid cytology
  - Epigastric peritoneal smear cytology (to exclude extrapelvic involvement)
- regional lymph node dissection / sampling
  - Subject of controversy
    - Improves survival vs only diagnostic?
    - Extent? Sentinel vs selective vs pelvic vs pelvic+paraaortic?
  - Instrumental in shaping the postoperative treatment

Ovarian cancer

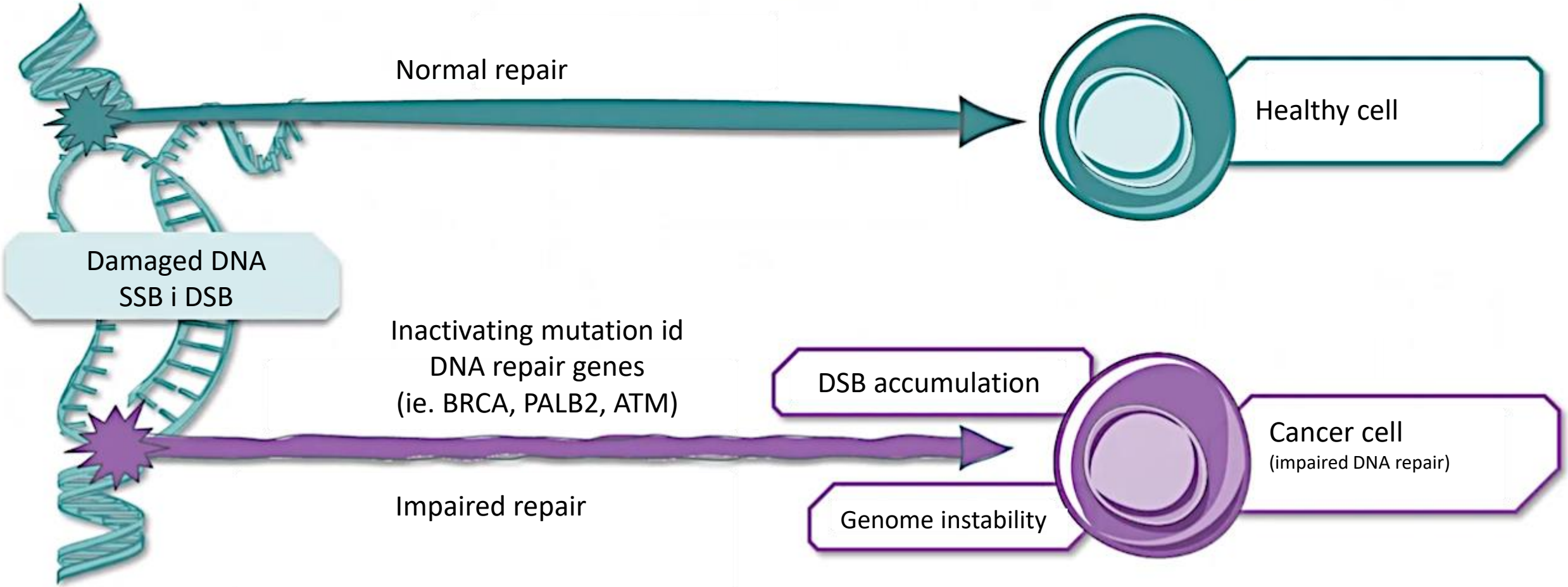
Adjuvant treatment

- All the patiens shoul be considered, except for low-risk stage I A, all
- Patinum + taxane (paclitaxel + carboplatinum)
- Regimen and dosing variable (typically paclitaxel 175mg/m2 and carboplatinum AUC6)
- 4-6 cycles

Ovarian cancer

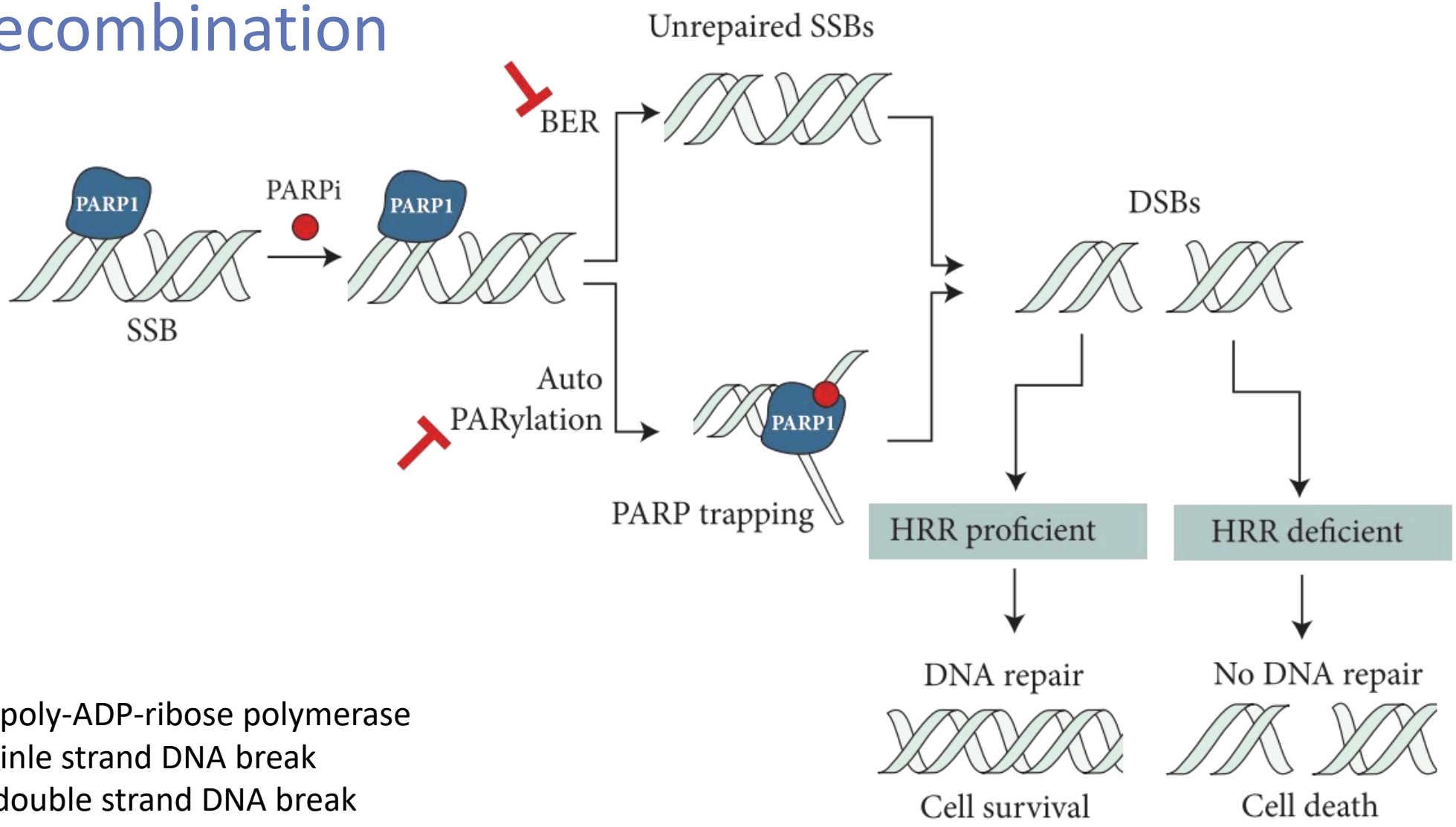
- **Metastatic disease**
  - cytoreduction of the primary – low quality data suggest may be beneficial
  - Chemotherapy - effective
    - Platins
    - Taxanes (paclitaxel)
    - Topotecan
    - Anthracyclines
  - Targeted therapies
    - Bevacizumab – active in 1nd and subsequent lines
    - PARP inhibitors – effective in HRRd cancers
    - Immunotherapy – active if dMMR present

Ovarian cancer and homologous recombination



1. Cerrato A, et al. *J Exp Clin Cancer Res*. 2016;35:179. **2.** Javle M, et al. *Ther Adv Med Oncol*. 2011;3:257-267.

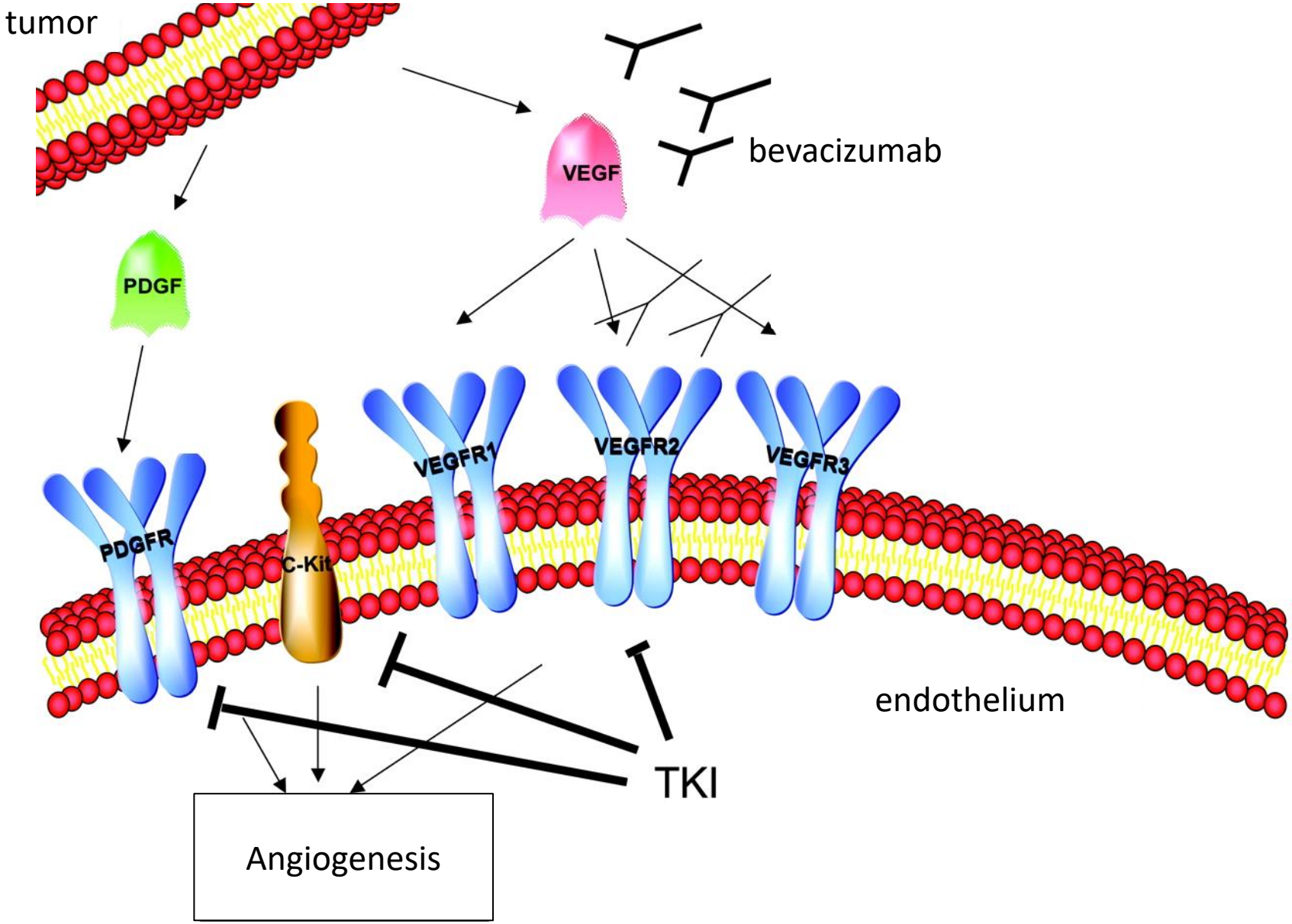
Ovarian cancer and homologous recombination



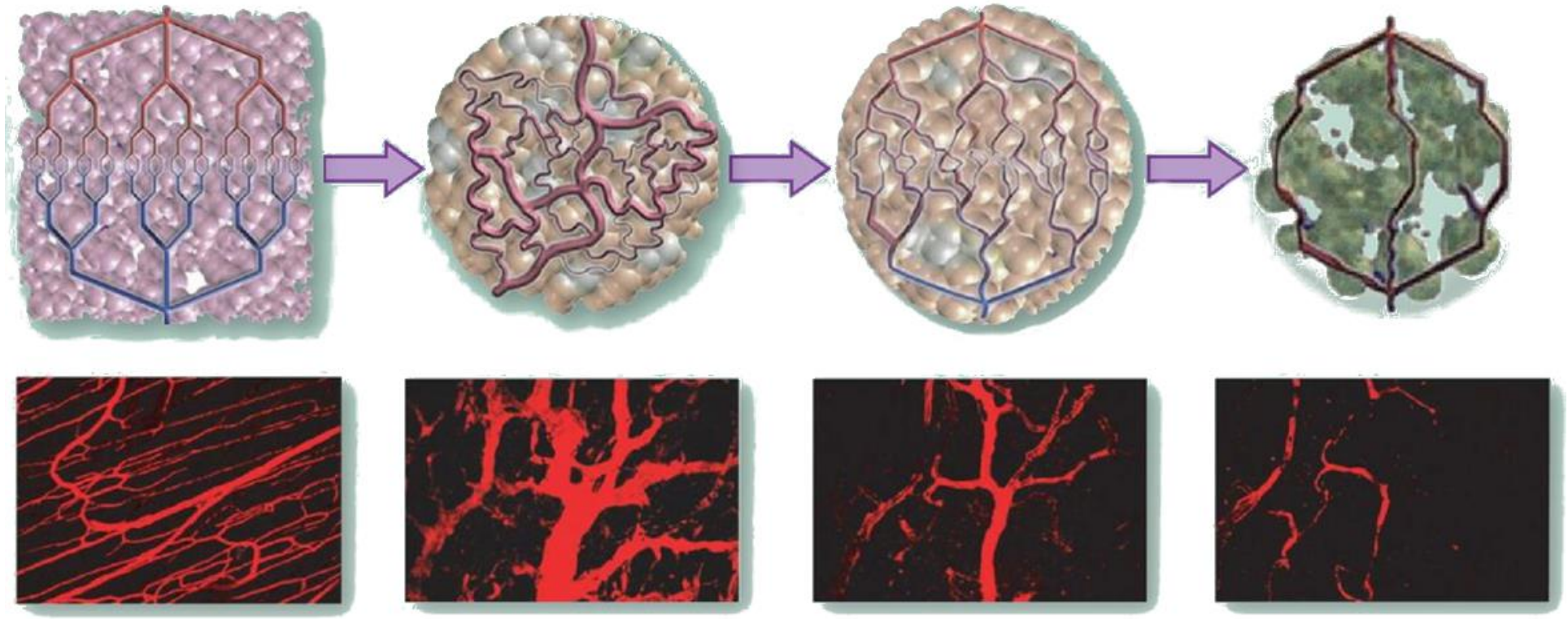
PARP –poly-ADP-ribose polymerase
SSB – sinle strand DNA break
DSB – double strand DNA break
BER – base excision repair
HRR – homologous recombination repair

Lord CJ, Ashworth A, *Nature*, 2012,

Angiogenesis inhibitors



Angiogenesis inhibitors



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Thank you