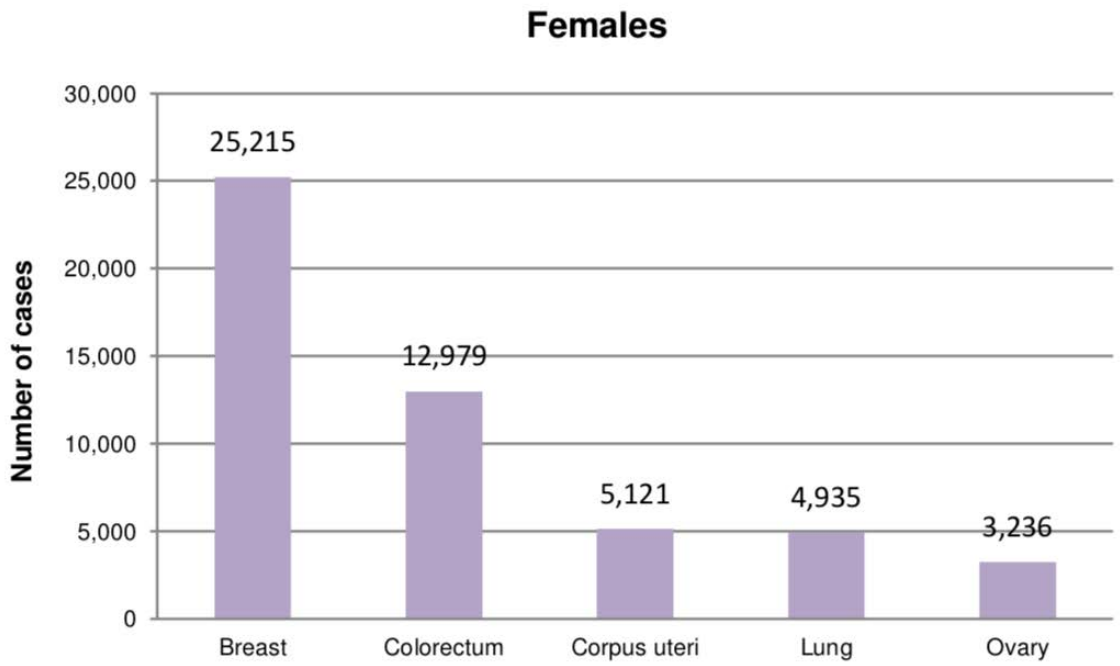
Information and detection of ovarian cancer

DRA. LUISA SÁNCHEZ LORENZO

Epidemiology

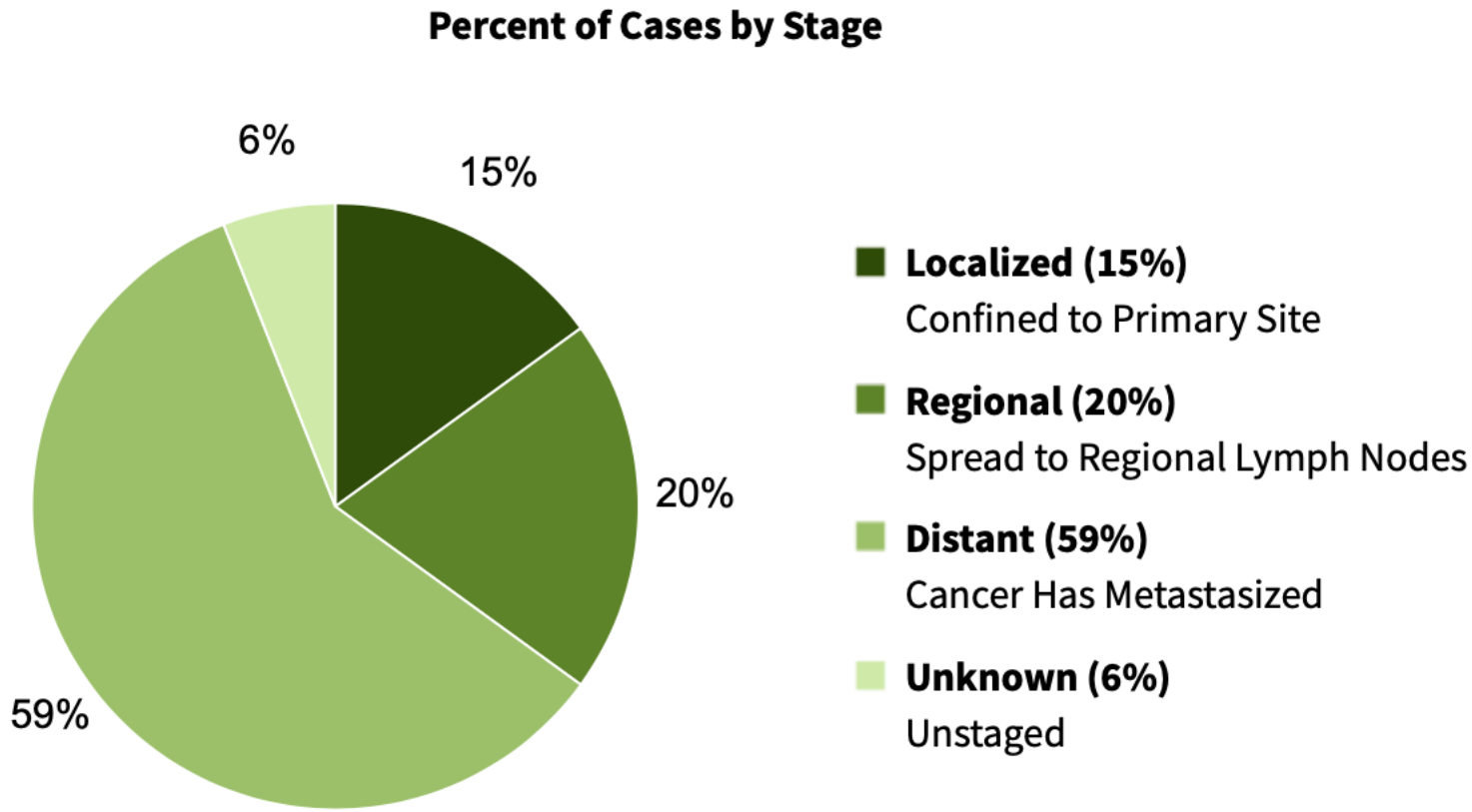
	Common Types of Cancer	Estimated New Cases 2018	Estimated Deaths 2018
1.	Breast Cancer (Female)	266,120	40,920
2.	Lung and Bronchus Cancer	234,030	154,050
3.	Prostate Cancer	164,690	29,430
4.	Colorectal Cancer	140,250	50,630
5.	Melanoma of the Skin	91,270	9,320
6.	Bladder Cancer	81,190	17,240
7.	Non-Hodgkin Lymphoma	74,680	19,910
8.	Kidney and Renal Pelvis Cancer	65,340	14,970
9.	Uterine Cancer	63,230	11,350
10.	Leukemia	60,300	24,370
	-	-	-
17.	**Ovarian Cancer**	**22,240**	**14,070**

Cancer Statistics. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/. Accessed 17 Nov 2018



World Health Organization - Cancer Country Profiles, 2014 (SPAIN)

Epidemiology



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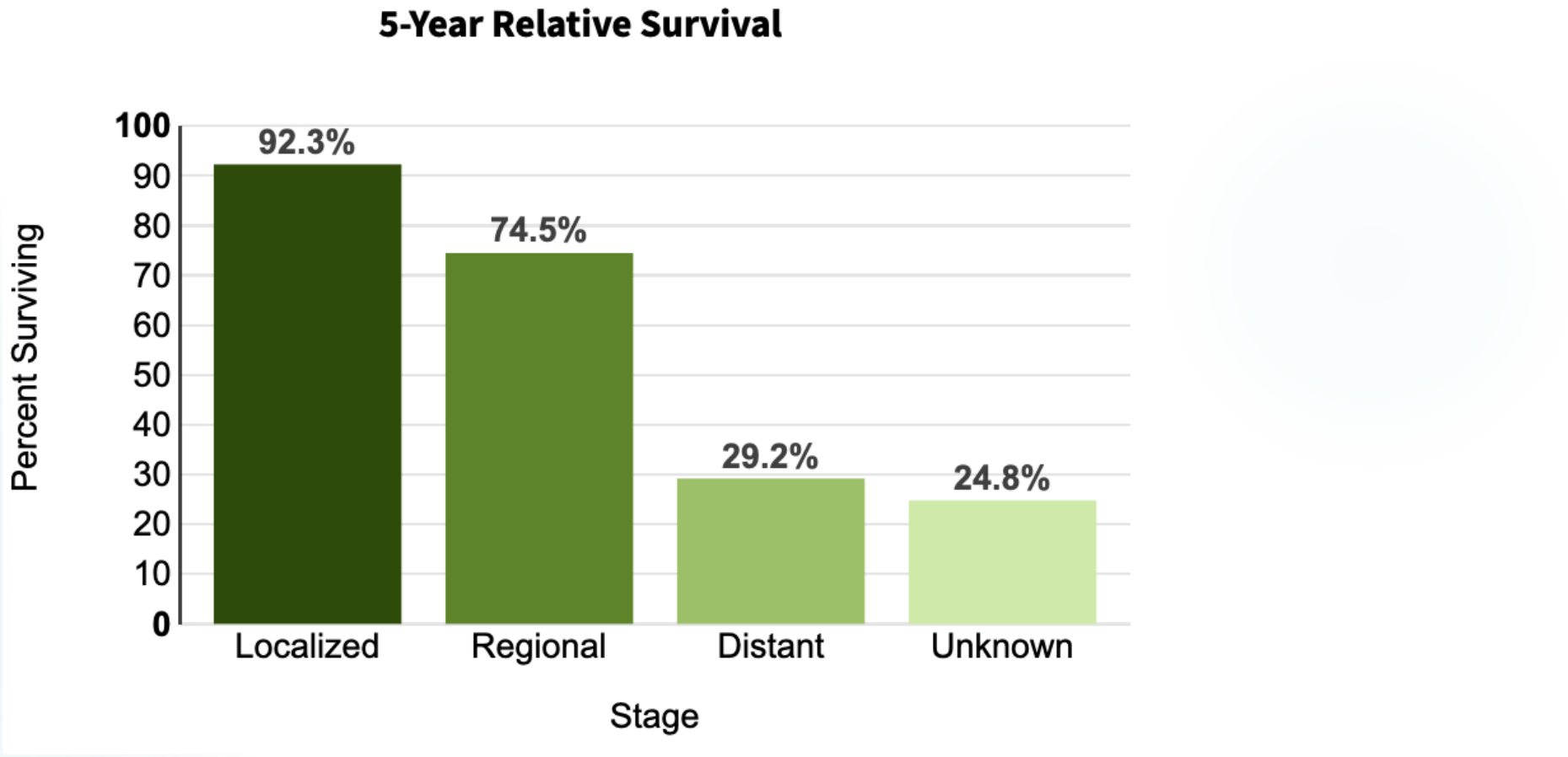

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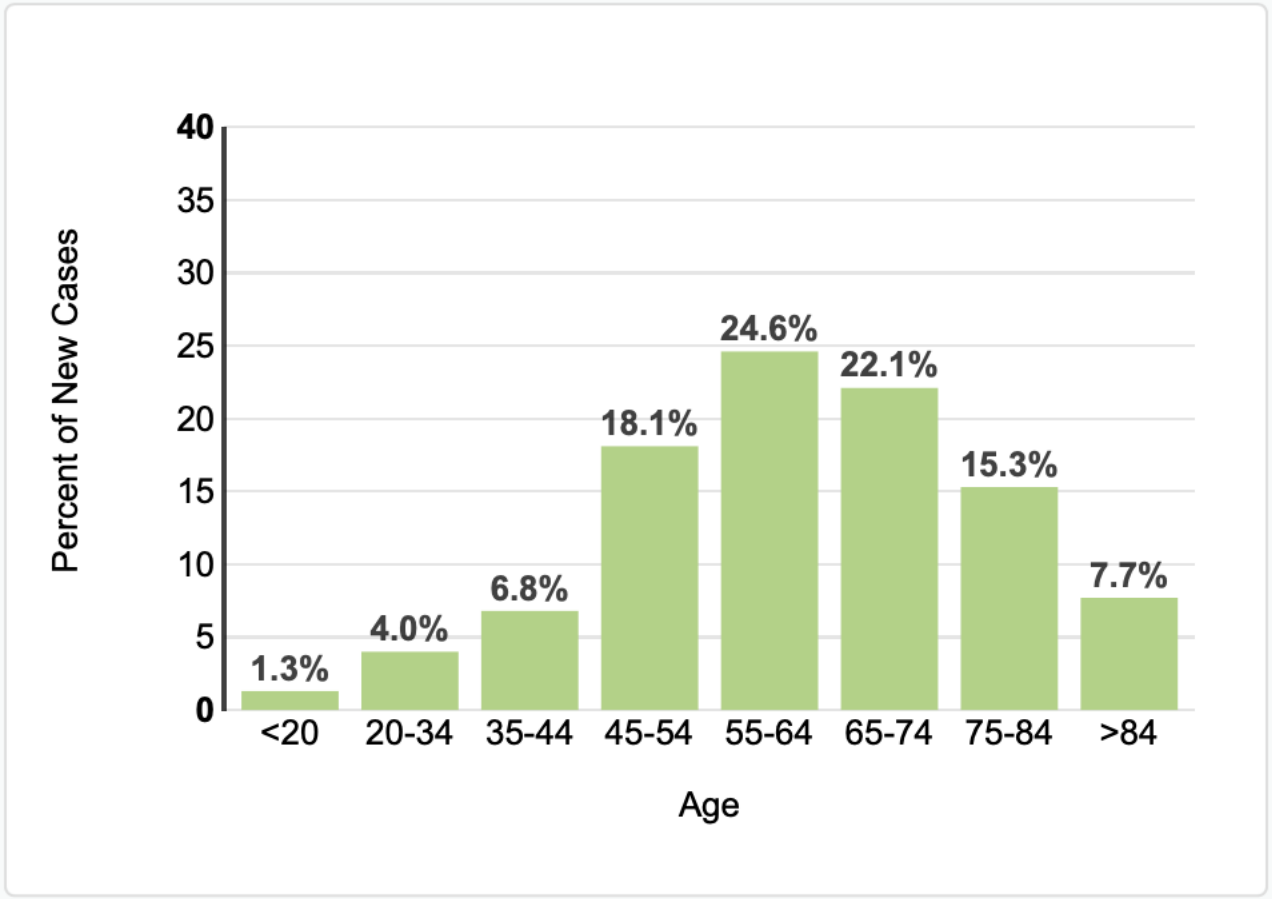


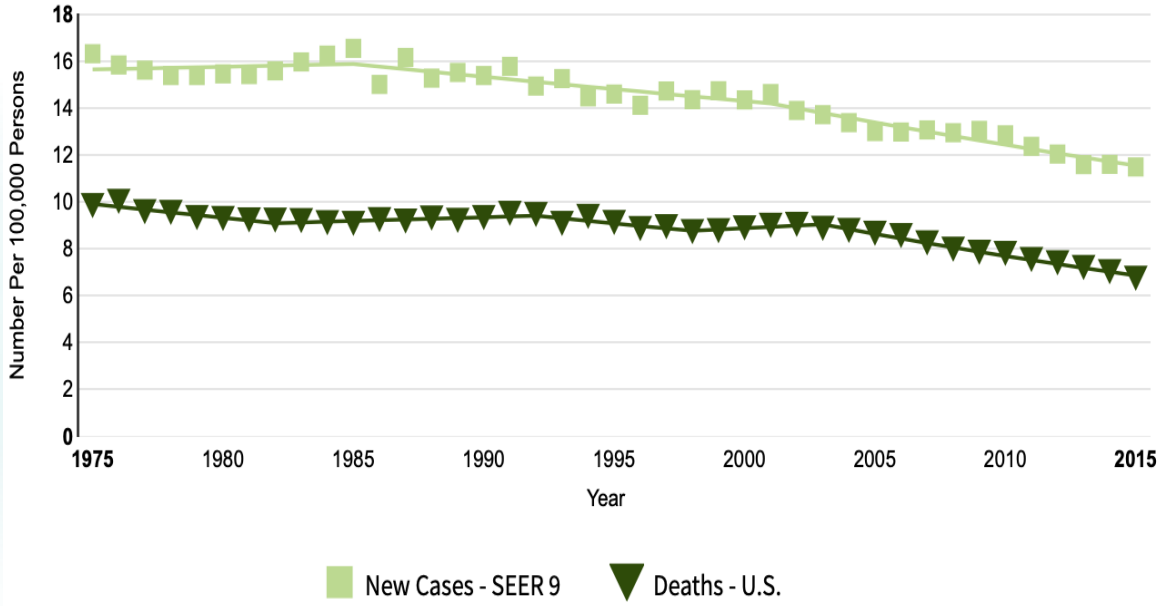
Ovarian cancer is most frequently diagnosed among women aged 55-64.

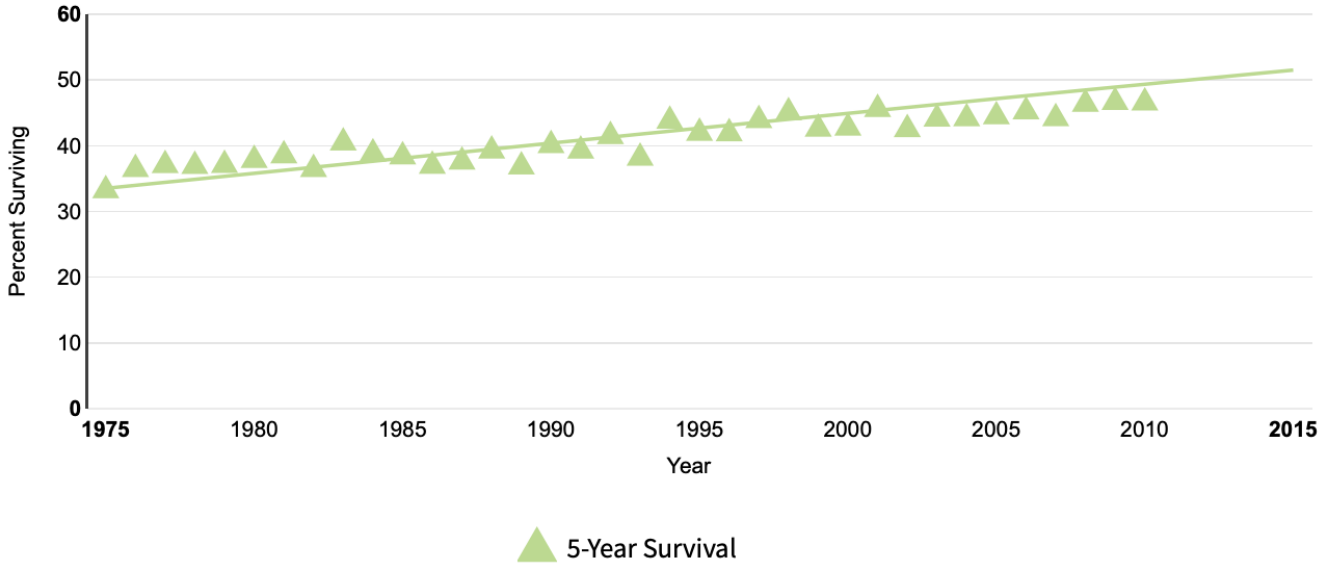
Median Age At Diagnosis

63

Cancer Statistics. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/. Accessed 17 Nov 2018

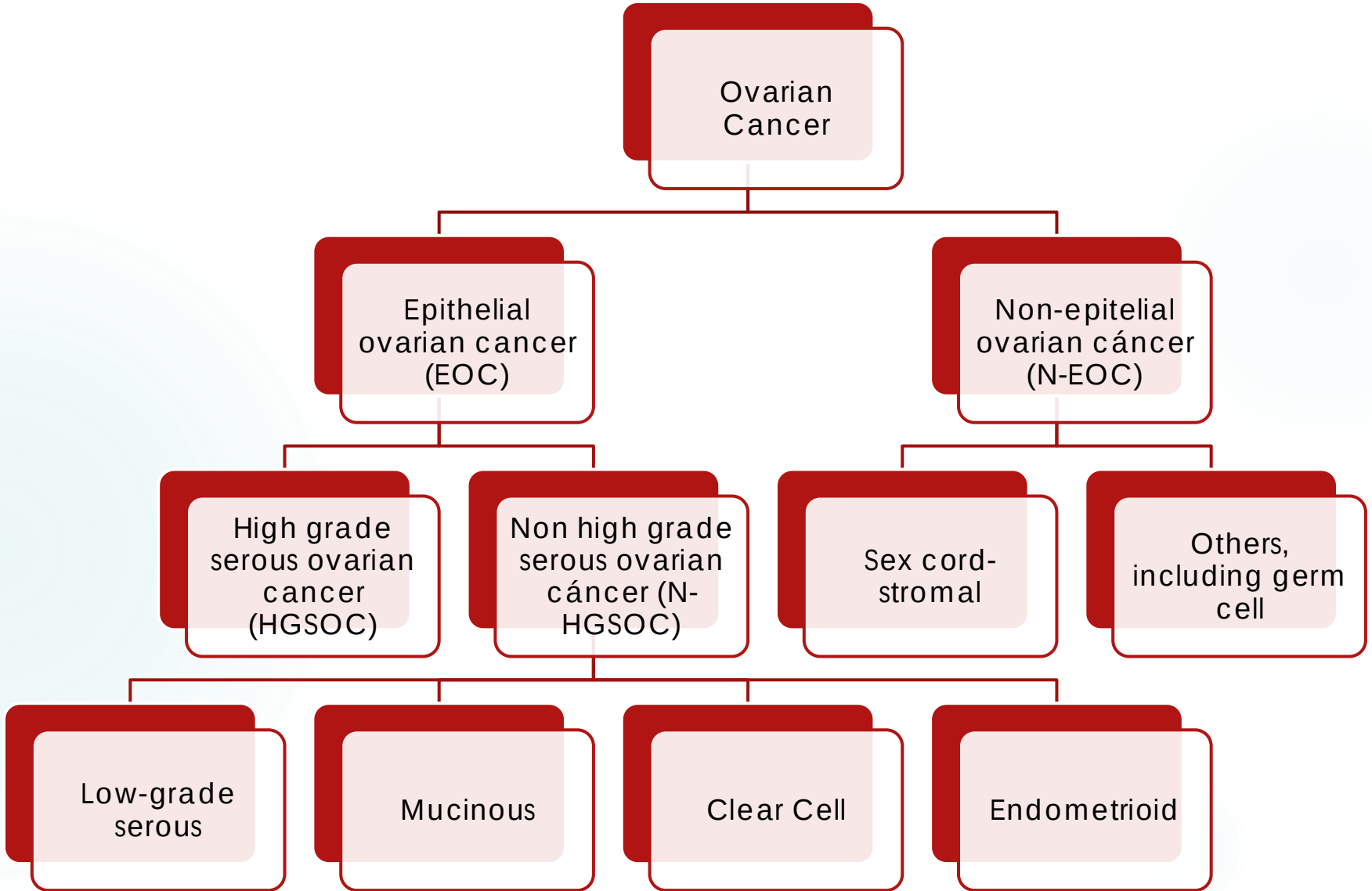
Epidemiology



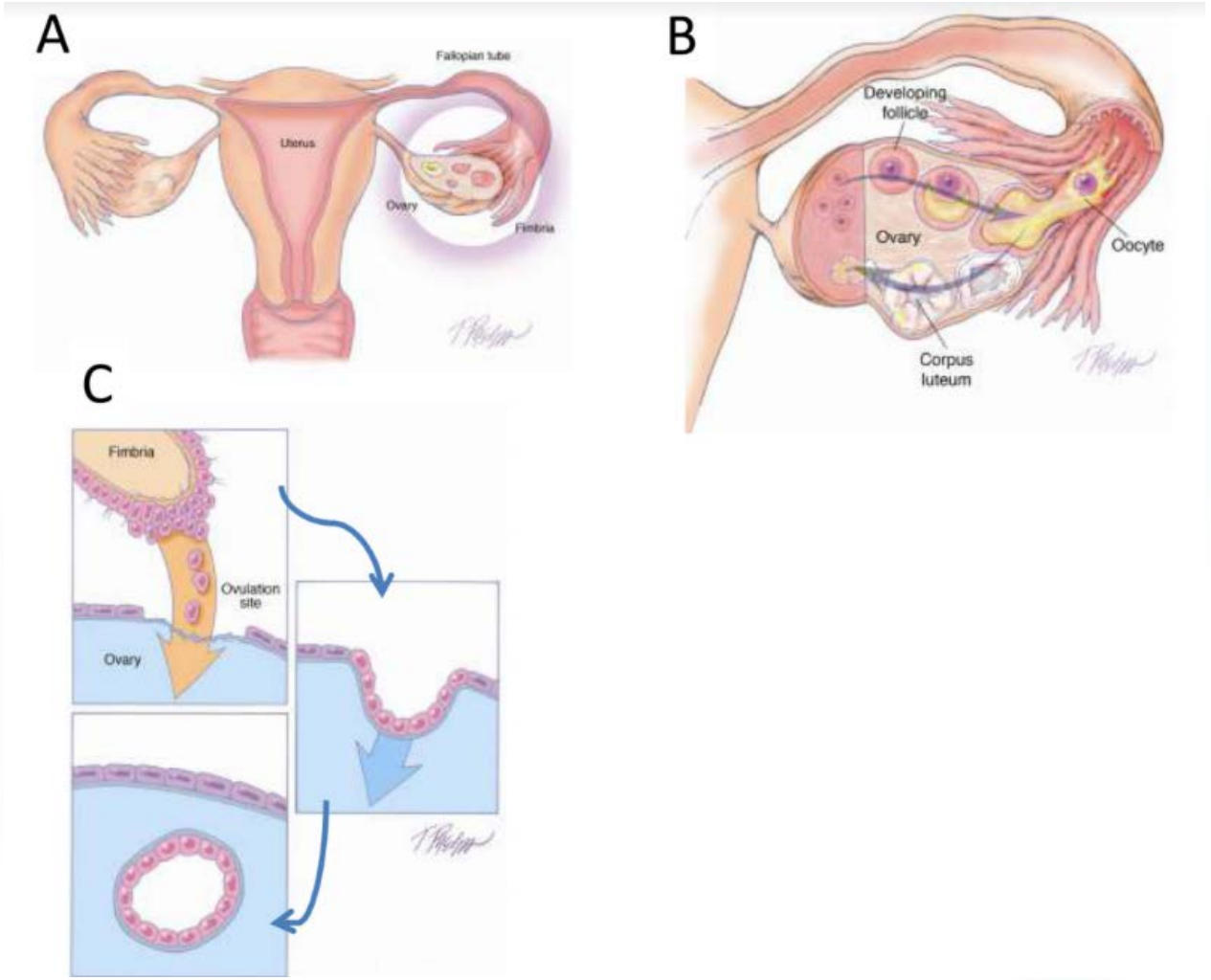


Cancer Statistics. National Cancer Institute, Surveillance, Epidemiology, and End Results Program. http://seer.cancer.gov/. Accessed 17 Nov 2018

Classification of ovarian cancer

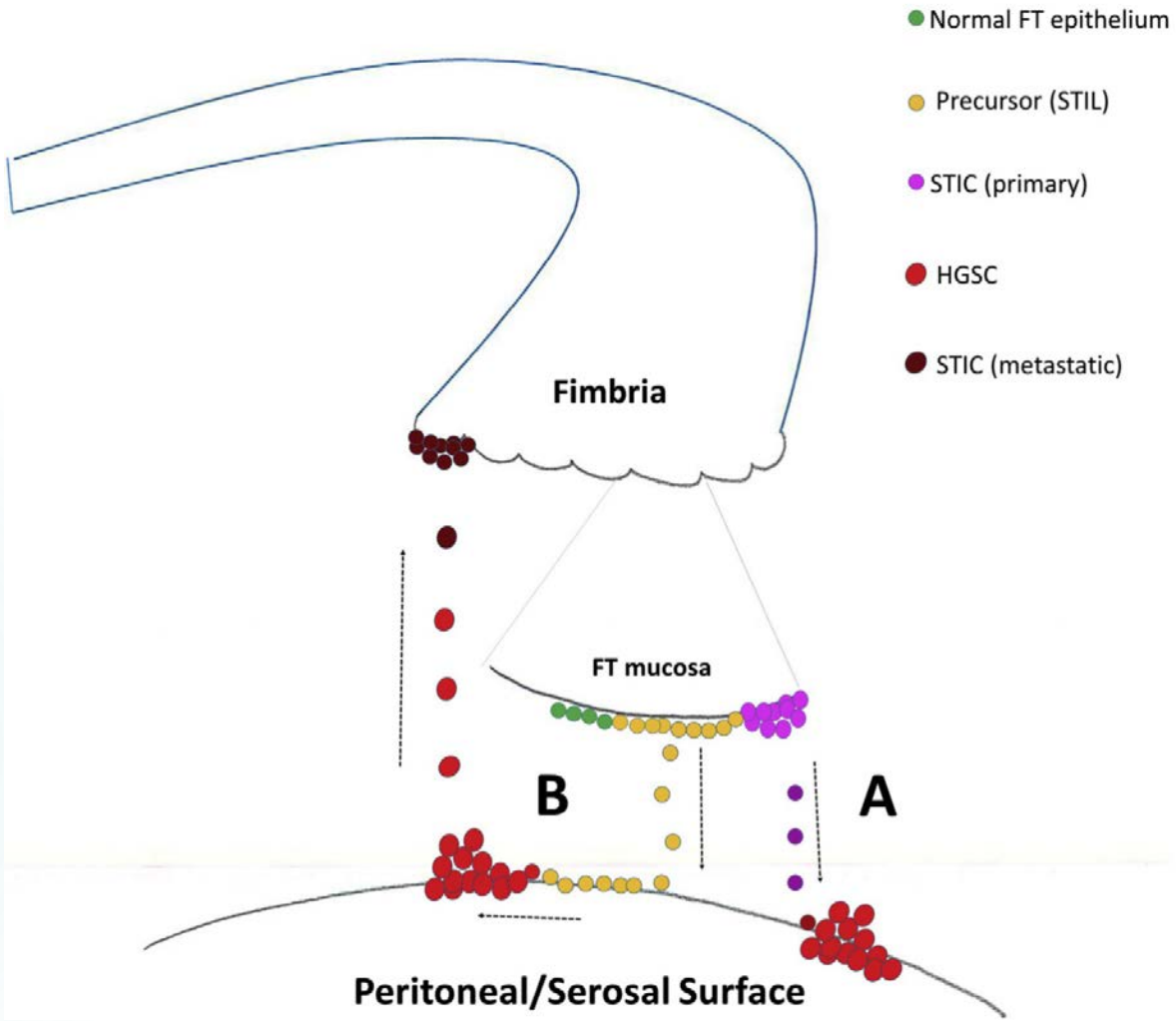


Etiology & Pathology of EOC



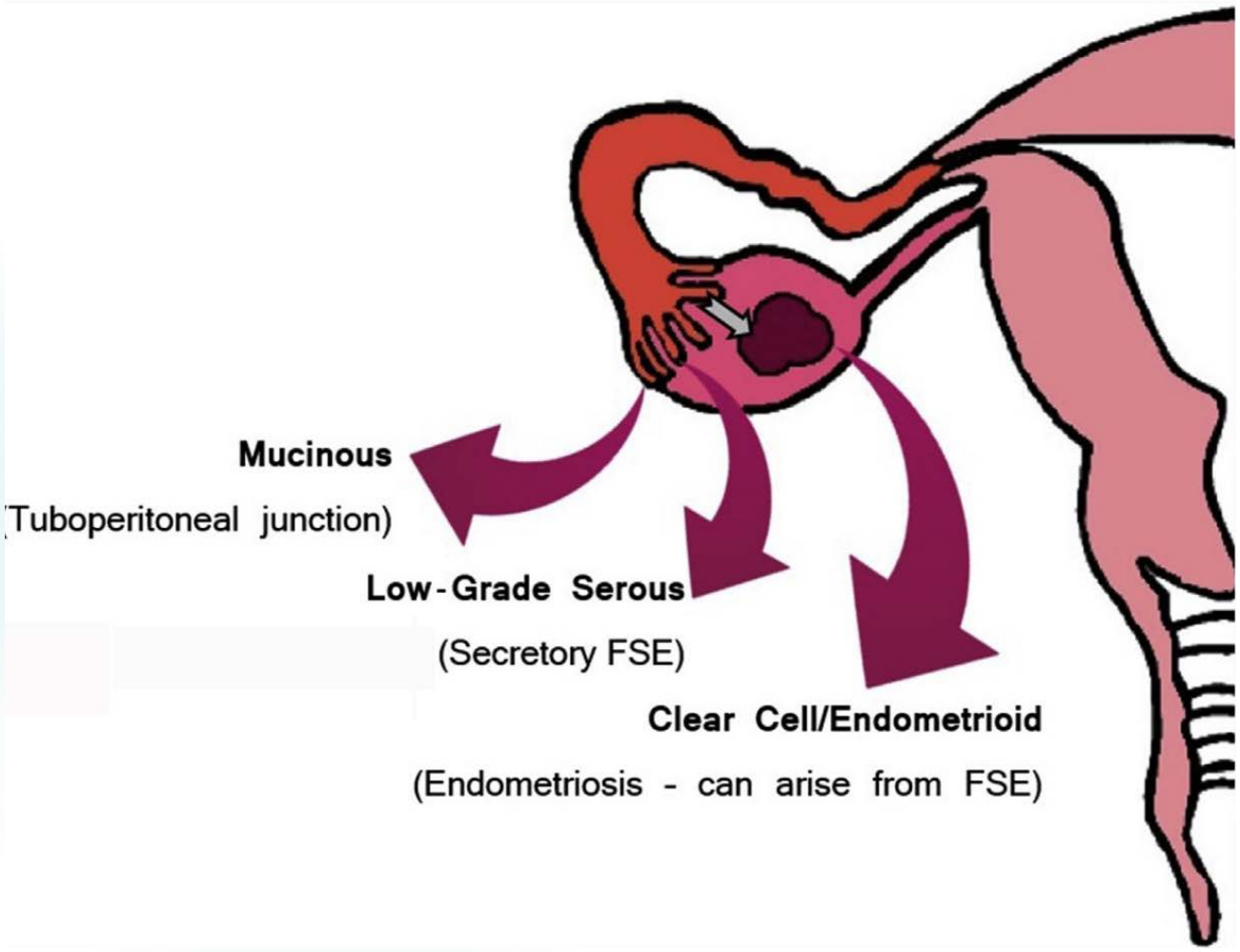
Kurman et al, Am J Surg Pathol. 2010 March ; 34(3): 433–443

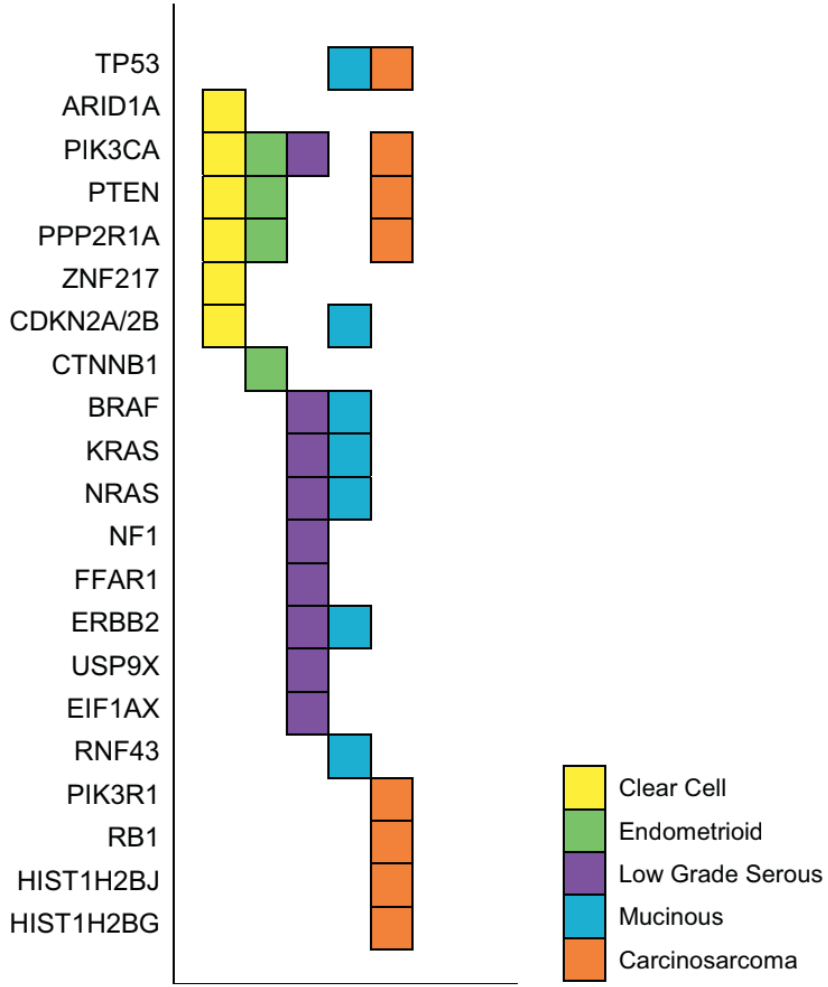
Etiology of HGSOC



Soong et al Hemat Oncol Clin N Am 32 (2018) 915-928

Etiology non-HGSOC





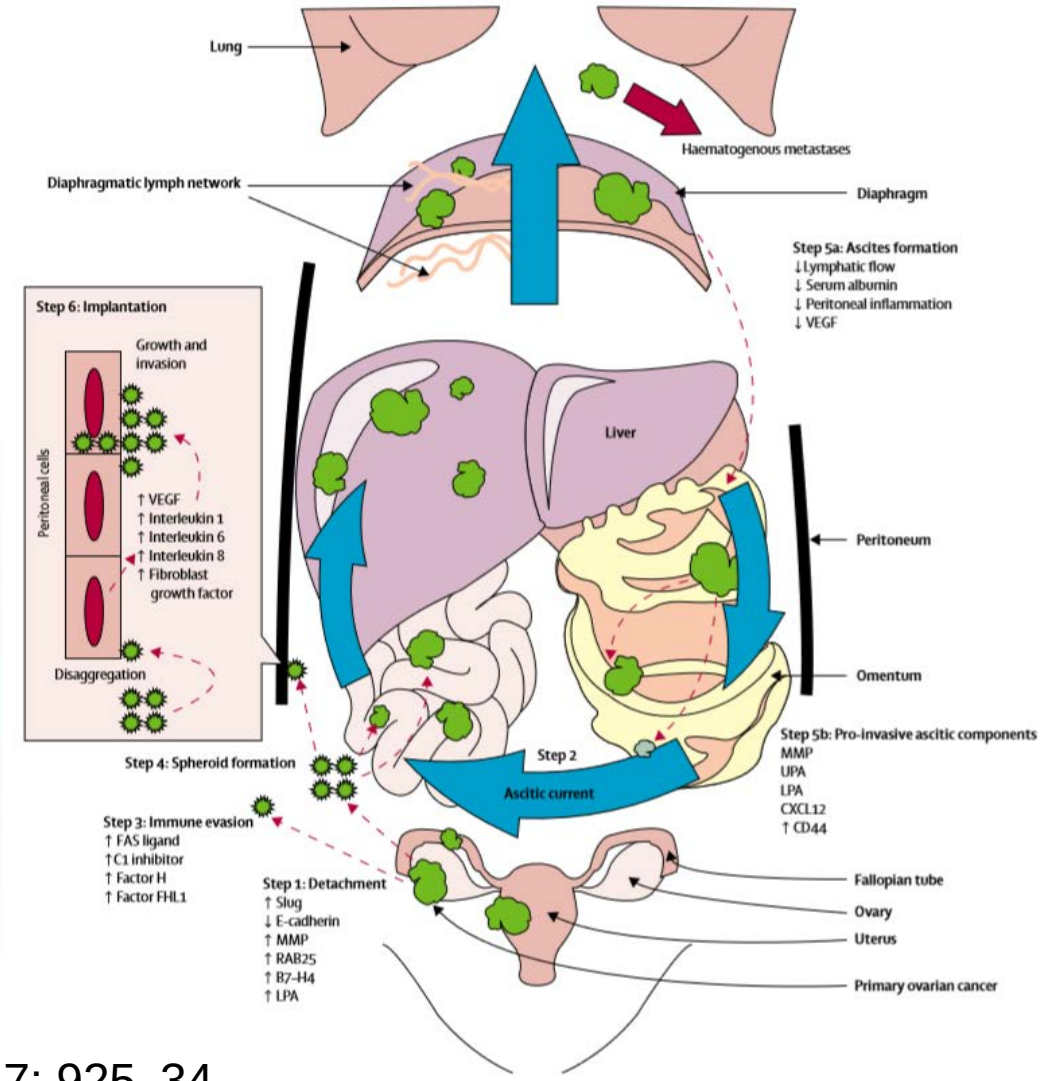
Ilenkovan et al Hemat Oncol Clin N Am 32 (2018) 929-942

Etiology

	High-grade serous	Low-grade serous	Mucinous	Endometrioid	Clear cell
Usual stage at diagnosis	Advanced	Early or advanced	Early	Early	Early
Presumed tissue of origin/precursor lesion	Tubal metaplasia in inclusions of ovarian surface epithelium or fallopian tube	Serous borderline tumor	Adenoma–borderline–carcinoma sequence; teratoma	Endometriosis, adenofibroma	Endometriosis, adenofibroma
Genetic risk	*BRCA1/2*	?	?	HNPCC	?
Significant molecular abnormalities	p53 and BRCA pathways	*BRAF* or K-RAS	*K-RAS* *HER2*	*PTEN*, β-catenin, *ARID1A* *PIK3CA* *K-RAS* MI	HNF-1β *ARID1A* *PIC3CA* *PTEN*
Proliferation	High	Low	Intermediate	Low	Low
Response to primary chemotherapy	80%	26%–28%	15%	?	15%

Prat et al; Int J Gynecol Obstet 2018; 143 (Suppl. 2): 93–108

A unique mechanism of dissemination



Tan et al Lancet Oncol 2006; 7: 925–34

Risk Factors

Increased	Decreased	Indeterminate

• Hereditary
  • Family history of ovarian cáncer
  • Personal history of breast cáncer
  • Alteration in BRCA1 or BRCA2
  • Lynch Syndrome
• Reproductive
• Hormonal
  • Early menarche
  • Late menopause
  • Hormone replacement therapy
  • Estrogen
  • Androgen
• Inflammatory
  • Endometriosis
  • Pelvic inflammatory disease
• Lifestyle
  • Obesity
	• Reproductive
	  • Multiparity
	  • Breastfeeding
	• Surgery
	  • Hysterectomy
	  • Tubal ligation
	• Hormonal
	  • Oral contraceptives
	  • Progestagens
		• Fertility drugs
		• Cigarette smoking
		• Perineal Talc exposure

Hereditary ovarian cancer

Gene	Protein	Protein function
BRCA1	Breast cancer type 1 susceptibility protein	• Crucially involved in the repair of double-strand breaks by homologous recombination • Serves as a scaffold for other proteins involved in double-strand DNA repair, mostly through defective homologous recombination • Stabilizes RAD51–ssDNA complexes
BRCA2	Breast cancer type 2 susceptibility protein	
BARD1	BRCA1-associated RING domain protein 1	• Forms a heterodimer with BRCA1 • The BRCA1–BARD1 complex is essential for mutual stability
BRIP1	BRCA1-interacting protein 1 (also known as Fanconi anaemia group J protein)	• Binds to BRCA1 • The BRCA1–BRIP1 complex is required for S phase checkpoint activation
PALB2	Partner and localizer of BRCA2	• A bridging protein that connects BRCA1 and BRCA2 at sites of DNA damage • Helps load RAD51 onto ssDNA
RAD51C	DNA repair protein RAD51 homologue 3	• Strand exchange proteins that bind to ssDNA breaks to form nucleoprotein filaments and initiate DNA repair
RAD51D	DNA repair protein RAD51 homologue 4	
MSH2	MutS protein homologue 2	• Mismatch repair proteins that recognize and repair base-pairing errors occurring during DNA replication • Mutations in mismatch repair genes are associated with Lynch syndrome
MLH1	MutL protein homologue 1	
MSH6	MutS protein homologue 6	
PMS2	Mismatch repair endonuclease PMS2	

Matulonis et al Nature Reviews. Disease Primers Article number 16061

Hereditary ovarian cancer

Grupo Español de Investigación en Cáncer de Ovario

SEOM Sociedad Española de Oncología Médica

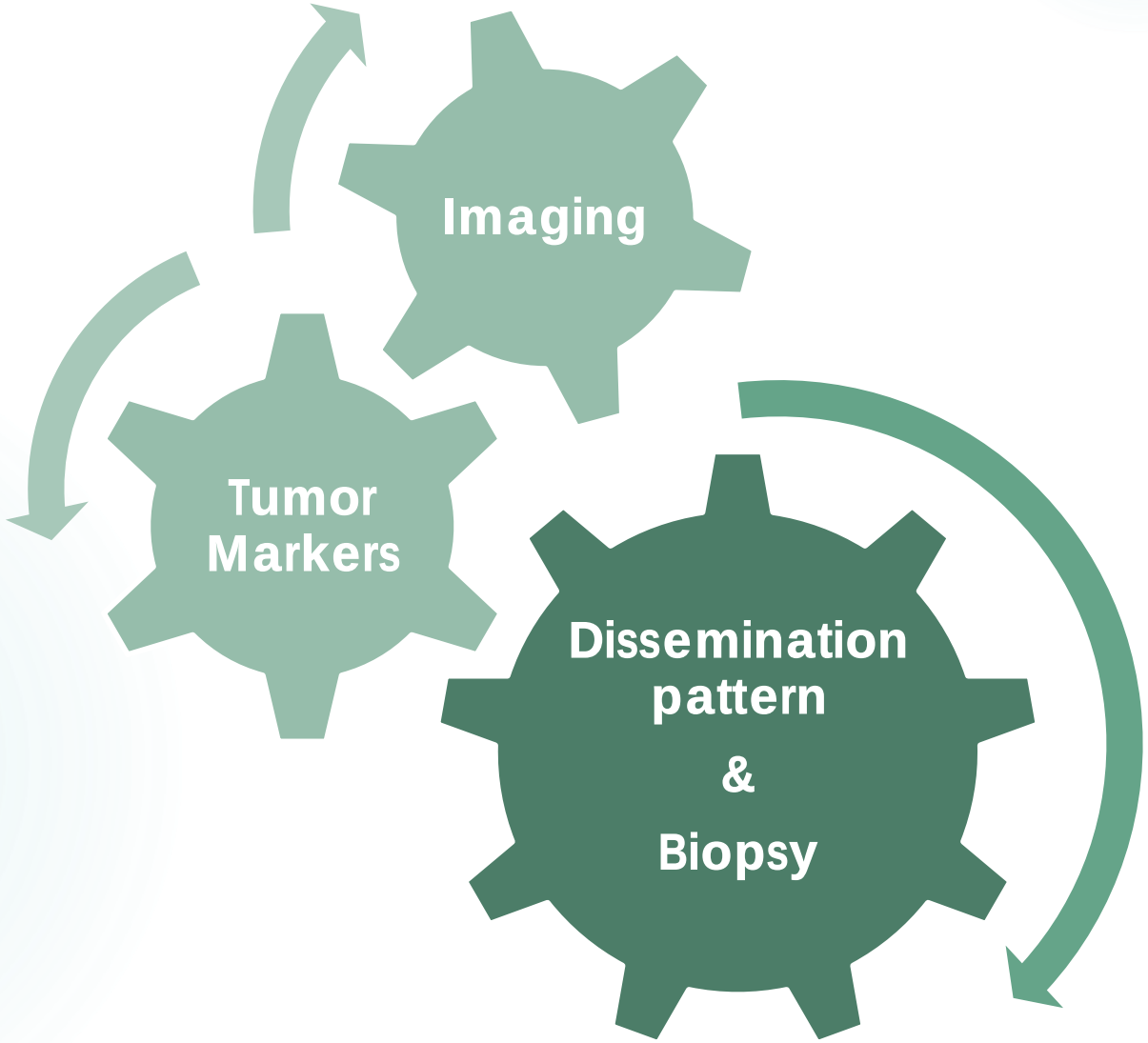
ALL Patients diagnosed with high grade non-mucinous epithelial ovarian cancer independently of age, family history or platinum sensivity

Clinical Presentation

- Prodromal symptoms tend to be VAGUE:
  - Abdominal distension
  - Constipation
  - Vague pelvis pressure
- PAIN usually minimal
- INSIDIOUS progression to advanced disease
- LACK of SENTINEL SYMPTOMS of early disease
- FREQUENTLY present with symptoms at distant sites to the ovary
- Differential diagnosis: gastrointestinal or metastatic breast cancer

Physical Examination Findings

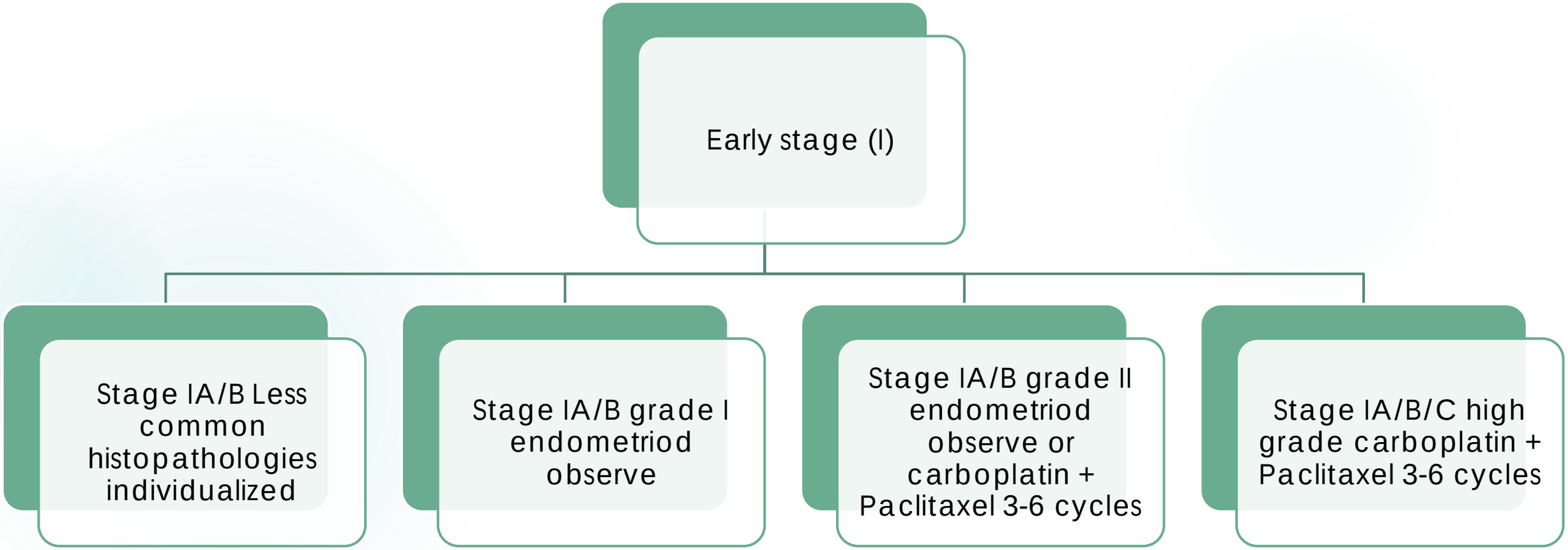
- Abdomen:
  - Distented
  - Palpable mass,
  - Apparent ascites
- Cardiovascular:
  - Taquycardia
  - Deep venous thrombosis
  - Lower extremity edema
- Pulmonary:
  - Decreased breath sounds in lung bases (pleural effusion)
- Pelvic:
  - Adnexal mass, fixed mobility of uterus, cul de sac nodularity
- Nodal:
  - Palpably enlarged inguinal and cervical nodes (infrequently encountered)


Imaging
Tumor Markers
Dissemination pattern
&
Biopsy

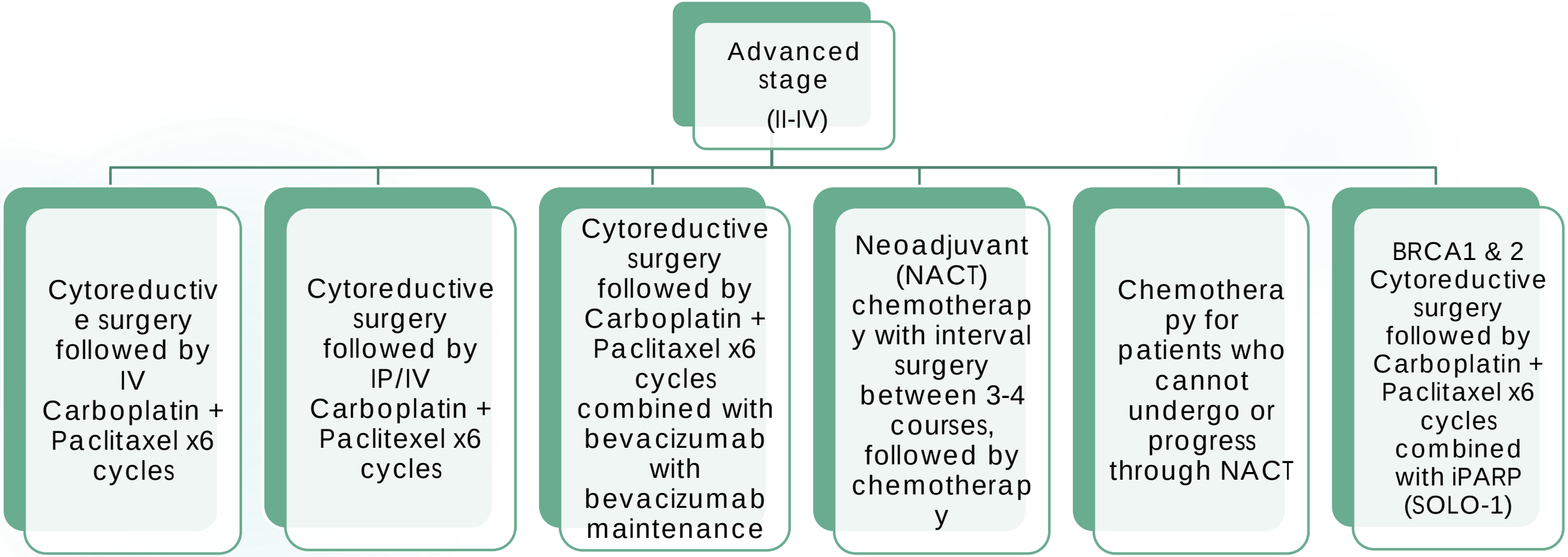
Imaging and Diagnostic Evaluation

- Imaging:
  - Computed tomography (CT)
  - Magnetic resonance
  - PET-CT (improved detection of occult nodal metastasis)
- Tumor markers: CA 125, CEA and CA19.9
- Dissemination pattern: extra-abdominal nodal involvement, bone or parenchymal liver metastases are uncommon …
- Biopsy:
  - Advanced disease above the diaphragm: percutaneous core biopsy
  - Disease limited the abdominal cavity:
    - Laparoscopic assessment is often necessary to assess stage and diagnosis
    - Debilitated patients or biopsy not feasible: cytology from pelvic mass or ascitis aspiration

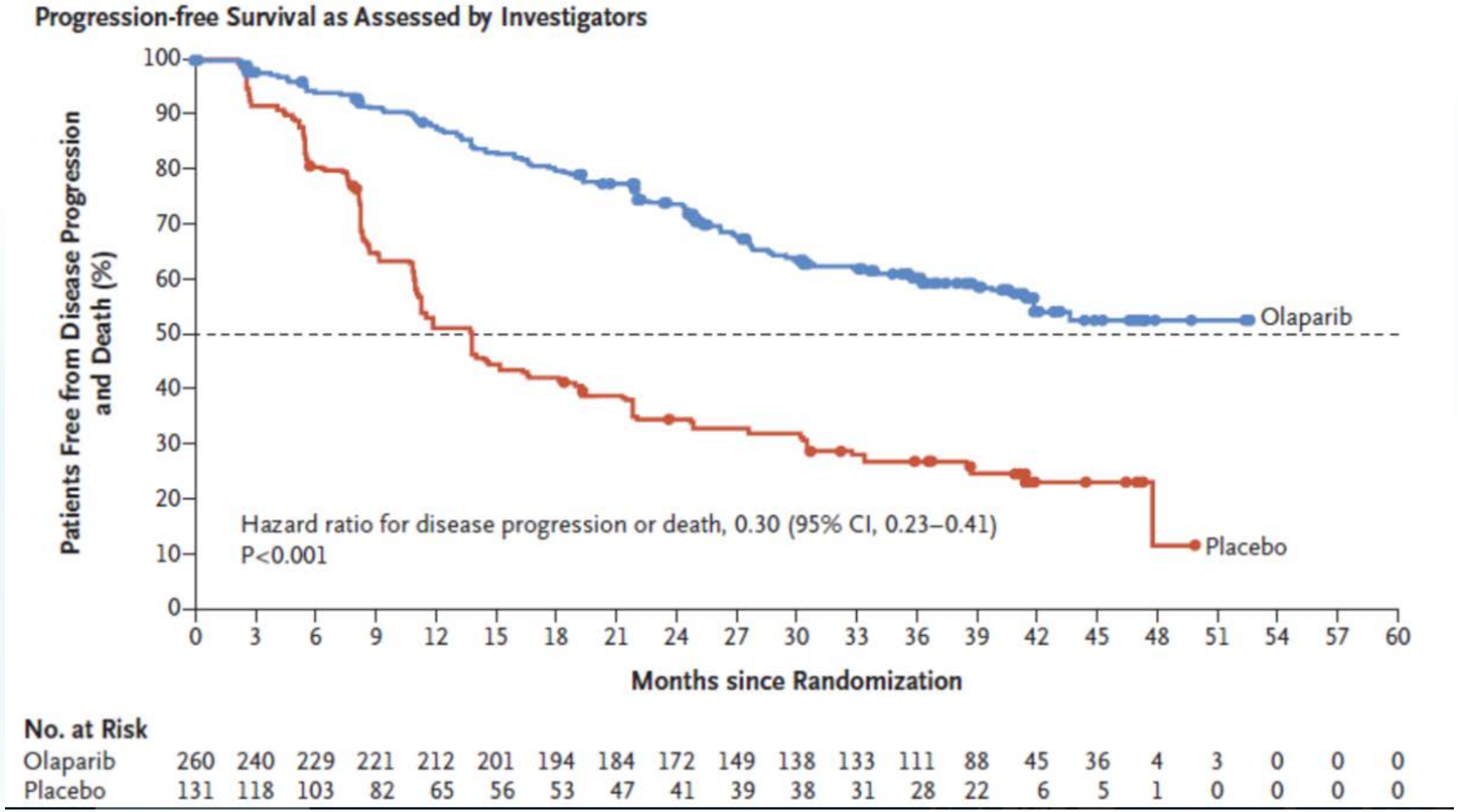
Strategies for the management



Strategies for the management



Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer … But many other trials ongoing



Moore et al NEJM 2018; doi: 10.1056/NEJMoa1810858

Acute and long-term toxicities of chemotherapy

- Chemotherapy-induced neuropathy
  - At least 50% of ptes
  - Dose dependent and exacerbated by concurrent neurotoxic drugs
  - Rarely may start or progress after chemotherapy completation.
  - Prevention strategies:
    - Aminofostine
    - Omega-3 fatty acid supplementation
  - Treatment strategies:
    - Duloxetine (leve 1 efficacy data)
    - Others gabapentine, lamotrigine and nortriptyline
    - Moderate physical activity

Acute and long-term toxicities of chemotherapy

- Sexual Function/Menopausal Symptoms
  - Decreased sexual activity
  - Physical and Phycological distress
  - Symptoms:
    - Vaginal Dryness
    - Decreased libido
    - Increased dyspareunia
  - Often remain unrecognized and undertreated
  - Treatment:
    - Hormonal ??
    - Non-hormonal: mirtazapine, bupropion and gabapentine. Physical therapy

Please answer the following questions about your overall sexual function:

1. Are you satisfied with your sexual function? ❑ Yes ❑ No

If no, please continue.

2. How long have you been dissatisfied with your sexual function? _____

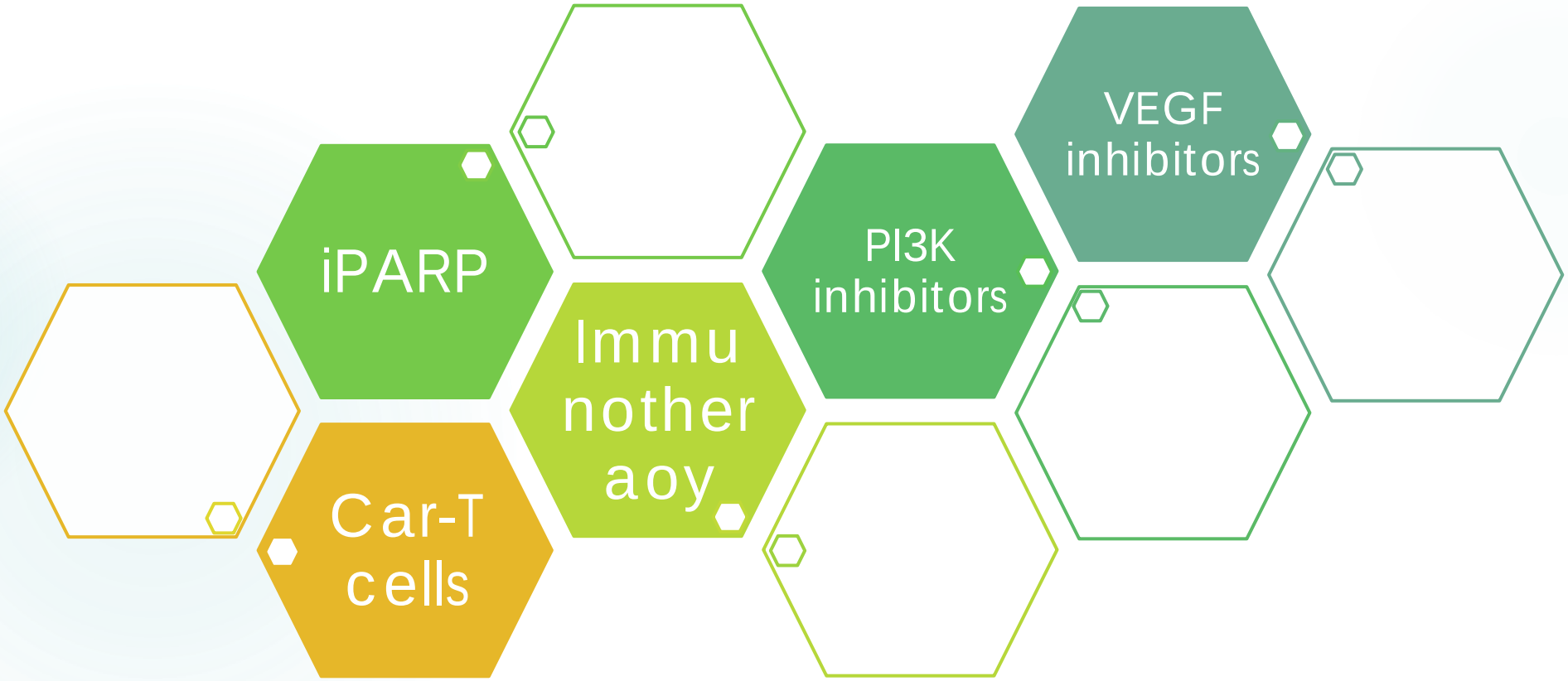
3. Mark which of the following problems you are having, and circle the one that is most bothersome:
   - ❑ Little or no interest in sex
   - ❑ Decreased genital sensation (feeling)
   - ❑ Decreased vaginal lubrication (dryness)
   - ❑ Problem reaching orgasm
   - ❑ Pain during sex
   - ❑ Other: _____

4. Would you like to talk about it with your doctor? ❑ Yes ❑ No

Acute and long-term toxicities of chemotherapy

- Cognitive dysfunction, mood disorders and fatigue
  - 25% experience cognitive decline in at least one domain
  - 20% experience depression
  - 75% pathologic anxiety around the time of surgery
  - Cancer-related fatigue:
    - Exercise
    - Nutrition optimization
    - Cognitive behavioral therapy
    - Pshycosocial interventions
    - In certain cases consider: methylphenidate or modafinil

New treatments



New treatments

PARPi trials in ovarian cancer (results awaited).

Agent	Trial	Population	Line of treatment
Olaparib (Astrazeneca)	**SOLO-1 (NCT01844986):** Phase III maintenance (olaparib vs placebo)	$BRCA^{mut}$; AOC	First line
	SOLO-2 (NCT01874353): Phase III maintenance (olaparib vs placebo)	$BRCA^{mut}$; PSROC	After ≥2 lines platinum based CT
	SOLO-3 (NCT02282020): Phase III olaparib vs physician choice CT (standard of care non-platinum based)	$BRCA^{mut}$; PSROC	After ≥2 lines of platinum based CT
Rucaparib (Clovis)	**ARIEL 2 (part 2) (NCT01891344):** Single arm study	HGROC	Received ≥2 prior lines of CT
	ARIEL 3 (NCT01968213): Phase III maintenance (rucaparib vs placebo)	HGROC	After ≥2 lines of platinum based CT
	ARIEL 4 (NCT02855944): Phase III rucaparib vs chemotherapy	$BRCA^{mut}$; ROC	Received ≥2 lines prior CT
Niraparib (Tesaro)	**QUADRA study (NCT02354586):** Single arm phase II study	HGROC	Must have had 3/4 prior lines of CT
	PRIMA study (NCT02655016): Phase III maintenance (niraparib vs placebo)	HRD+ve; AOC	First line
	AVANOVA study (NCT02354131): Phase I/II niraparib ± bevacizumab	HRD+ve; PSROC	No limits on number of previous lines of CT
Veliparib (AbbVie)	Phase III combination CT followed by maintenance **(NCT02470585)**	$BRCA^{mut}$; AOC	First line
Talazoparib (Medivation/Pfizer)	Phase I/II study **(NCT01989546)**	$BRCA^{mut}$ solid tumours	After ≥1 standard CT or no standard Rx options
	Phase II study **(NCT02326844)**	$gBRCA^{mut}$; ROC	Progression following a PARPi

CT – chemotherapy; Ph – phase; gBRCAm – germline BRCA mutation; PSROC – 'platinum-sensitive' recurrent ovarian cancer; HGROC – high-grade recurrent ovarian cancer; HRD – homologous recombination deficient; AOC – advanced ovarian cancer; Rx – treatment.

Screening and Prevention

- PLCO trial : transvaginal sonography and CA125;
  - 1993-2001
  - 39110 pts
  - 388 cases diagnosed
  - ...but 1080 false positive (15% with major complications)
- NROSS trial : increase in baseline CA125
  - 5729 pts
  - <1% referred for sonography
- UKCTOCS trial: control, anual TVS and anual CA125
  - >200.000 ptes

Screening and Prevention

- Serum biomarkers:
  - CA125
  - CA15.3
  - HE4
- ROMA INDEX
  - Aid in assessing wheter a premenopausal or postmenopausal woman with an ovarian adnexal mass is at high or low probability of finding malignancy on surgery.
  - NOT INTENDED FOR SCREENING or STAND-ALONE diagnostic assay.
- Circulating tumor DNA
- Proximate tumors fluids

Ovarian Cancer Screening and Prevention in the High-Risk Population

Ovarian Cancer Screening and Prevention in the High-Risk Population

- Hereditary breast and ovarian cancer syndrome accounts for 5%–10% of breast cancers and 15-20% of invasive ovarian cancers
- Mutations in two genes, BRCA1 and BRCA2
- Women with BRCA mutations have a markedly increased risk of early-onset breast, ovarian, pancreatic, and other cancers when compared to the risks in the general population
- The overall occult gynecological carcinoma has been detected in 9.1% of BRCA carriers

Ovarian Cancer Screening and Prevention in the High-Risk Population

- Risk-Reducing Salpingo-Oophorectomy (RRSO)
  - significant reduction in the risk of breast and ovarian cancer-specific mortality
  - between 35 and 40 years of age, upon completion of childbearing and based on the age of the youngest affected relative with an ovarian cancer diagnosis, regardless of the type of BRCA mutation
- Risk-Reducing Salpingectomy (RRS)
- Other recommendations:
  - pelvic examinations, transvaginal ultrasounds, and serum CA125 levels every 6 months beginning at age 30 or 5–10 years earlier than the youngest diagnosed relative with ovarian cancer

PRIMEVIEW

OVARIAN CANCER

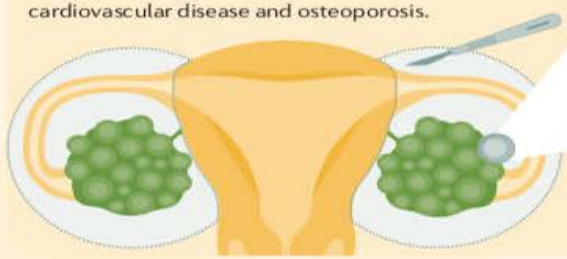
nature REVIEWS DISEASE PRIMERS

For the Primer, visit doi:10.1038/nrdp.2016.61

Ovarian cancer can be subdivided into different histological subtypes, such as high-grade serous, low-grade serous, clear-cell, mucinous and endometrioid carcinomas. Each subtype has different risk factors, molecular characteristics and clinical features.

PREVENTION

Women at increased genetic risk of developing ovarian cancer can undergo risk-reducing surgery, such as bilateral salpingo-oophorectomy (removal of the fallopian tubes and ovaries). The timing of surgery is important, as this can be associated with adverse effects; in women <45 years of age, the hormonal effects of oophorectomy (that is, surgical menopause) can increase the risk of cardiovascular disease and osteoporosis.



MANAGEMENT

The main treatment for women with ovarian cancer is surgical cytoreduction, which is followed by adjuvant chemotherapy for high-risk cancers. In some patients, such as those with extensive inoperable cancer burden, neoadjuvant chemotherapy can be administered before surgery with additional chemotherapy given post-surgery.

Most women with advanced-stage ovarian cancer will experience recurrence of disease

MECHANISMS

Angiogenesis is important for the growth of ovarian cancer and metastasis

Alterations in genes encoding proteins involved in homologous recombination, for example, *RAD51*, *BRCA1*, *BRCA2* and *BARD1*, have been identified in up 50% of ovarian carcinomas

Of these, germline *BRCA1* and *BRCA2* mutations are the most significant known genetic risk factors for ovarian cancer and are found in up to 17% of patients

Other alterations associated with ovarian cancer include those in *TP53* and in genes involved in DNA mismatch repair, such as *MLH1* and *PMS2*

HOMOLOGOUS RECOMBINATION AND DNA REPAIR

QUALITY OF LIFE

Ovarian cancer is associated with reductions in quality of life, which can affect physical, functional, social and sexual well-being.

Measures of quality of life, such as patient-reported outcomes, are being incorporated into clinical trials for ovarian cancer

OUTLOOK

Now is an exciting time for ovarian cancer research, with genomic analyses yielding more information about the histological subtypes of cancer and the pathophysiology of disease. Rational design of new treatments for ovarian cancer is also poised to move forward.

EPIDEMIOLOGY

225,000 new cases of ovarian cancer are diagnosed globally each year, with >140,000 cancer-specific deaths. Incidence and survival rates have been shown to vary by country. Risk factors for ovarian cancer include genetic, reproductive and lifestyle factors. In postmenopausal women, the use of hormone replacement therapy is associated with an increased risk. Other factors that affect risk include parity and the use of oral contraceptives, NSAIDs and cigarette smoking.

Genetic risk factors for ovarian cancer include mutations in *BRCA* and in genes involved in the Fanconi anaemia pathway

DIAGNOSIS

The median age of diagnosis of ovarian cancer is 63 years. Most ovarian cancers are asymptomatic in the early stages; symptoms such as ascites, gastrointestinal dysfunction, abdominal bloating and pain might initially be missed or attributed to another disease. Because of the lack of screening tests and the propensity for intra-abdominal tumour spread, ovarian cancer is most often diagnosed at a late stage.

Staging of ovarian cancer is based on surgical assessment of the cancer at initial diagnosis and requires assessment of the lymph nodes, abdominal fluid and histological examination of tissue

Designed by Laura Marshall

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