EPITHELIAL OVARIAN CANCER [1,2]

General Overview

- 2nd most lethal and 3rd most common gynecological malignancy worldwide
- Risk factors: older age, early menarche/late menopause, nulliparity, endometriosis, pelvic radiation, genetic: germline *BRCA1/2* mutation 16-65% increased risk, Lynch syndrome mostly due to mutations in MLH1 (4-20% lifetime risk), MSH2/EPCAM (8-38% lifetime risk) and MSH6 (1-10% lifetime risk), Li-Fraumeni syndrome (TP53), RAD51C/D, BRIP1, PALB2
- Protective factors: oral contraceptive use, breastfeeding, parity
- Symptoms: vague, abdominal/pelvic pain, constipation, diarrhoea, urinary frequency, vaginal bleeding, abdominal distension and fatigue
- 90% epithelial ovarian cancer (EOC); classification based on histopathology, immunohistochemistry and molecular analysis (WHO 2020): 70% high-grade serous (HGSC), 10% endometrioid (EC), 6-10% clear cell (CCC), 5% low grade serous (LGSC), 3-4% mucinous carcinoma (MC), and other rare entities.

Pathology and molecular biology of EOC subtypes					
IHC staining	**HGSC**	**EC**	**CCC**	**LGSC**	**MC**
p53	Abnormal	Abnormal / normal	Normal	Normal	Normal
p16	+	-	-		
WT-1	+	-	-	+	-
ER	+/-	+	-	+	-
PAX8	+	+		+	-
Vimentin		+			
HFN1b			+		
CDX2					+
Molecular alterations	*TP53, BRCA1/2, HRD*	*CTNNB1, ARID1A, PTEN, KRAS, TP53,* ***MSI/dMMR***	*ARID1A, PIK3CA, PTEN,* ***MSI/dMMR***	***KRAS, BRAF,*** *RAF*	*CDKN2A, KRAS,* ***HER2***

Staging (2014 FIGO classification) and Prognosis

- Full lab including CA-125
- Pelvic ultrasound
- (PET)-CT of thorax, abdomen, pelvis (may underestimate bowel and mesenteric involvement)
- MRI pelvis in case of indeterminate pelvic mass
- Cytological assessment of ascites and/or pleural fluid if present
- CEA and CA 19-9 in case of MC, endoscopy if either elevated
- Tissue diagnosis: see Figure 1. Surgical staging preferable when disease appears suitable for cytoreduction as assessed by imaging. Image-guided biopsy of the ovary not recommended.
- Somatic testing: somatic *BRCA1/2* testing in FIGO stage III-IV HGSC and EC; homologous repair deficiency (HRD) in FIGO stage III-IV *BRCA1/2*wt HGSC and EC; MSI/MMR in EC and CCC; KRAS/BRAF in LGSC, HER2 in MC
- Genetic testing: germline NGS panel in high grade epithelial ovarian cancer (excl MC)

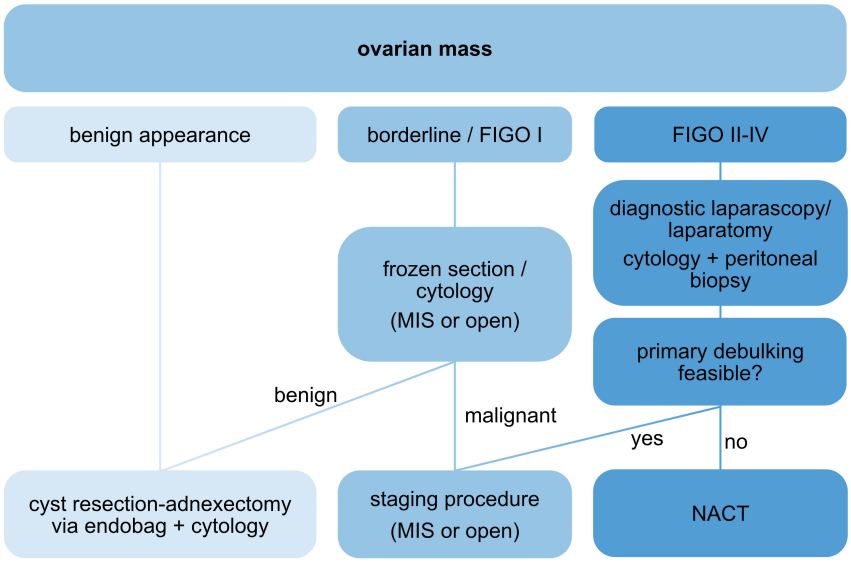
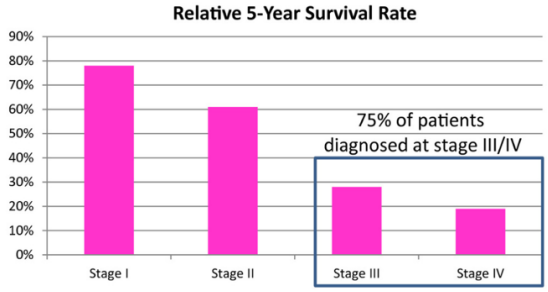


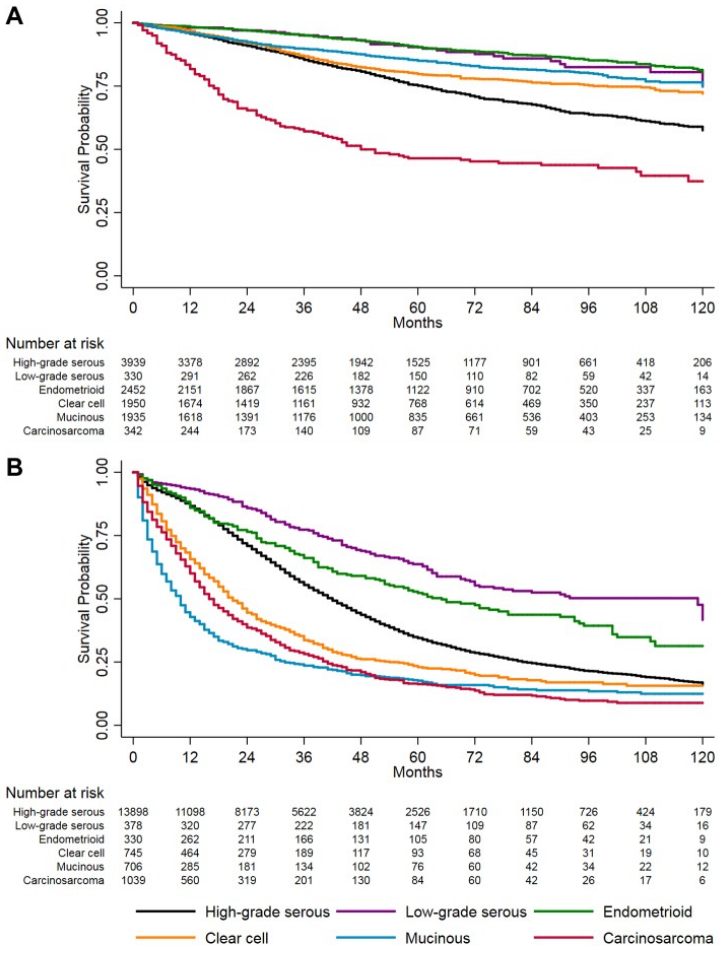
Figure 1: flowchart for staging of ovarian mass

FIGO 2014 classification
Stage 1: Tumor confined to ovaries or fallopian tube(s) **IA**: Tumor limited to one ovary (capsule intact) or fallopian tube, without tumor on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings. **IB**: Tumor limited to both ovaries (capsules intact) or fallopian tubes, without tumor on ovarian or fallopian tube surface and without malignant cells in the ascites or peritoneal washings. **IC**: Tumor limited to one or both ovaries or fallopian tubes, with any of the following **IC1**: Surgical spill **IC2**: Capsule ruptured before surgery or tumor on ovarian or fallopian tube surface **IC3**: Malignant cells in the ascites or peritoneal washings **Stage 2: Tumor involves one or both ovaries or fallopian tubes with pelvic extension (below pelvic brim) or primary peritoneal cancer** **IIA:** Extension and/or implants on uterus and/or fallopian tubes and/or ovaries **IIB:** Extension to other pelvic intraperitoneal tissues **Stage 3: Tumor involves one or both ovaries or fallopian tubes or primary peritoneal cancer, with cytologically or histologically confirmed spread to the peritoneum outside the pelvis and/or metastasis to the retroperitoneal lymph nodes** **IIIA1:** Positive retroperitoneal lymph nodes only (cytologically or histologically proven **IIIA1(i)**: Metastasis ≤10 mm in greatest dimension **IIIA1(ii)**: Metastasis >10 mm in greatest dimension **IIIA2**: Microscopic extra-pelvic (above the pelvic brim) peritoneal involvement with or without positive retroperitoneal lymph nodes **IIIB**: Macroscopic peritoneal metastasis beyond the pelvis ≤2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes **IIIC**: Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ) **Stage 4: Distant metastasis excluding peritoneal metastases** **IVA**: Pleural effusion with positive cytology **IVB**: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

- Prognosis:
  - Depends on stage, histological subtype, age, ECOG, response to treatment, degree of postoperative residual disease, volume of center in which operation takes place
  - Risk factors: abundant ascites, > 70 y, poor ECOG
  - Neo-adjuvant setting
    - CA-125 KELIM predicts likelihood of complete interval cytoreductive surgery (ICS) and risk of subsequent platinum-resistant relapse [3]
    - Chemotherapy response score (CRS) on omental specimens is a prognostic tool to assess the response to neoadjuvant chemotherapy
  - Relative 5-year survival rate of epithelial ovarian cancer: [4]



  - Kaplan-Meier survival curves of epithelial ovarian cancer survival by stage and histotype, 2004–2014, SEER 18 registries, A. Localized and regional-stage disease, B. Distant-stage disease [5]



Treatment

FIGO STAGE I-II

SURGERY

- Aim is complete resection of the tumor and adequate staging
- Midline laparotomy, inspection and palpation of the whole abdominal cavity, peritoneal washing with cytological examination, biopsies from – and if possible, resection of – all visible lesions and all abdominal fields (paracolic, bladder, diaphragm, adhesions and suspicious lesions), bilateral salpingo-oophorectomy, hysterectomy, infra-colic omentectomy, appendicectomy in MC
    - + systematic pelvic and para-aortic lymphadenectomy in high-grade disease
    - 30% of patients with FIGO I disease are upstaged during surgical staging, this has impact on the adjuvant therapy and demonstrates the importance of correct staging
    - Laparoscopic approach may be a safe alternative in some patients with early-stage ovarian cancer [6], although ESGO and NCCN guidelines still recommend an open approach
- Consider fertility-sparing surgery in young patients after discussion of the potential risks; in case of borderline tumours, non-epithelial tumours, low-grade stage IA (serous, endometrioid or mucinous expansile subtype) and selected IC1 stages; unilateral salpingo-oophorectomy with surgical staging; minimally invasive surgery avoiding tumour rupture is acceptable

ADJUVANT CHEMOTHERAPY

- Prolongs PFS and OS [7–9]
- Standard schedule: carboplatin AUC 6 (or 5 if frail) + paclitaxel 175mg/m^2 q3w
    - x 6 for HGSC / HGEC / high-risk MC or any stage IC-II regardless of histotype
    - x 3 as a minimum for others
- Alternative schedule: carboplatin AUC 6 (or 5 if frail) q3w x 6, consider weekly carboplatin +/- paclitaxel in case of comorbidities
- Benefit uncertain for LGSC stage IB-IC, CCC stage IA-IB, low-grade EC stage IB-IC, expansile MC stage IC, and infiltrative MC stage IA [1,2]
- Not recommended in completely staged LGSC stage IA, low-grade EC stage IA, and expansile MC stage IA-IB [1]

FIGO STAGE III-IV

SURGERY

- Aim is complete or optimal cytoreduction, defined as total macroscopic tumor clearance with no residual visible disease (important prognostic factor)
- At least one attempt by an experienced surgical team should be done
- No benefit from systematic lymphadenectomy if macroscopic complete resection and clinically negative nodes cf. LION trial [10]
- Gold standard is primary cytoreductive surgery if physically able to undergo surgery and complete resection seems achievable; also recommended in patients with less chemo-sensitive subtypes (e.g. MC or LGSC), even if uncertainty about achieving complete resection and a small residual tumor (<1 cm) is likely to remain

- Interval debulking (preceded by and followed by 3 cycles platinum-based chemotherapy) option in bulky IIIC or IV disease if complete resection upfront unlikely or extensive surgery not tolerable
- Hyperthermic intraperitoneal perioperative chemotherapy (HIPEC) is an option, but careful patient selection required [11]

SYSTEMIC TREATMENT

		FIGO	Histology	First-line	Maintenance*2	OS benefit
BRCA1/2 **mt**		III + IV	high-grade + epithelial	Chemotherapy*1	Olaparib*3	no
BRCA1/2 **wt**	HRD **positive**	III + IV	HGSC or HGEC	Chemotherapy*1 + Bevacizumab*4	Bevacizumab*4 + Olaparib*5	yes
	HRD **negative**	IV	epithelial	Chemotherapy*1 + Bevacizumab*4	Bevacizumab*4	no
		III + IV*6	HGSC or HGEC	Chemotherapy*1	Niraparib*7	no

- ***1** Standard schedule carboplatin AUC 6 (or 5 if frail) + paclitaxel 175mg/m^2 q3w x 6 cycles [12]
  - If contraindications to paclitaxel: replace with docetaxel or pegylated liposomal doxorubicin (PLD) [13,14]
  - Very frail patients: carboplatin AUC 2 + paclitaxel 60mg/m^2 q1w x 18 cycles [15]
- ***2** In case of partial or complete response to chemotherapy (max 6 cycles)
- ***3** Start within 8 weeks after end of chemotherapy for a total of 2 years, PFS benefit cf. SOLO-1 trial [16]
- ***4** Total of 15 months (22 cycles), including period in combination with chemotherapy[17–19]
- ***5** Start within 3-9 weeks after end of chemotherapy for a total of 2 years, OS benefit cf. PAOLA-1 trial [20]
- ***6** Inoperable FIGO III-IV, operable FIGO IV, FIGO III-IV after NACT and interval debulking, FIGO III with or without residual disease after primary debulking
- ***7** Start within 12 weeks after end of chemotherapy for a total of 3 years, PFS benefit cf. PRIMA trial [21]
- Retrospective data suggest possible value of maintenance anti-estrogen therapy in LGSC

RECURRENT DISEASE

FACTORS TO CONSIDER

- Up to 70% of pt with stage III-IV high-grade ovarian cancer relapse within 3 years
- Definition of platinum-sensitivity as “6-month treatment-free interval from last platinum (TFIp)” is debated
- Assess histotype, *BRCA1/2* status, number of prior lines, exposure and response to prior therapy, TFIp, possibility of achieving complete secondary surgical cytoreduction, residual chemotherapy toxicity, patient’s general condition and preferences

SURGERY

- In selected cases (positive AGO score[22]: complete resection at first surgery, good performance status, absence of ascites) if first relapse > 6 months of last platinum [23–25], to be followed by adjuvant platinum-based chemotherapy

SYSTEMIC TREATMENT

- When platinum is an option
  - Indication: prior response to platinum and no contra-indication
  - Carboplatin in combination with paclitaxel, PLD, or gemcitabine (or alone if contra-indication for combination); 4-6 cycles [26–29]
  - + bevacizumab, continued as maintenance if partial/complete response; only PFS benefit; in theory preference for carboplatin-PLD backbone (OS benefit over carboplatin-gemcitabin backbone) but not reimbursed in this combination in Belgium (only carboplatin-paclitaxel or carboplatin-gemcitabine) [30]; preference if rapid symptom control required; only if TFIp > 6 months and if not received prior bevacizumab
  - Maintenance olaparib or niraparib if response to platinum rechallenge and not received prior bevacizumab, irrespective of *BRCA1/2* and HRD status [31–34]; only if PARPi-naïve; recommended length unclear [35]
- Non-platinum-based
  - Indication: progression during platinum or shortly after, platinum-intolerance
  - Options: trabectedin-PLD if intolerance to platinum and TFIp 6-12 months and received prior platinum; single-agent weekly paclitaxel, topotecan, gemcitabine, PLD, oral metronomic cyclophosphamide
  - + bevacizumab in case of paclitaxel, PLD or topotecan if no contra-indication, not received previously, and not received more than 2 prior lines
  - Clinical trials
  - Consider hormonal therapy for LGSC
  - Best supportive care

Follow-up

- Physical examination and symptom review every 3 months first 3 years, then every 6 months until year 5; longer follow-up in case of *BRCA1/2*-mut carriers
- Imaging in case of symptoms
- Regular follow-up of CA-125 is debated: no OS advantage if treatment is initiated based solely on CA-125 increase [36]

What's new

- Mirvetuximab soravtansine in folate-receptor alpha positive platinum-resistant ovarian cancer, after 2-4 prior lines of prior therapy, available via medical need program [37]

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