

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	<i>TP53</i> , <i>BRCA1/2</i> , <i>HRD</i>	<i>CTNNB1</i> , <i>ARID1A</i> , <i>PTEN</i> , <i>KRAS</i> , <i>TP53</i> , <i>MSI/dMMR</i>	<i>ARID1A</i> , <i>PIK3CA</i> , <i>PTEN</i> , <i>MSI/dMMR</i>	<i>KRAS</i> , <i>BRAF</i> , <i>RAF</i>	<i>CDKN2A</i> , <i>KRAS</i> , <i>HER2</i>

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)

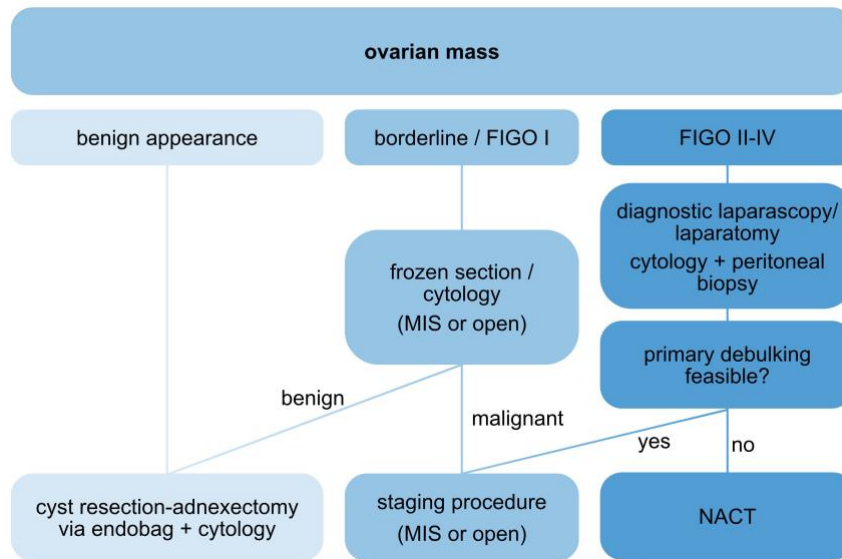


Figure 1: flowchart for staging of ovarian mass

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

IIIB: 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

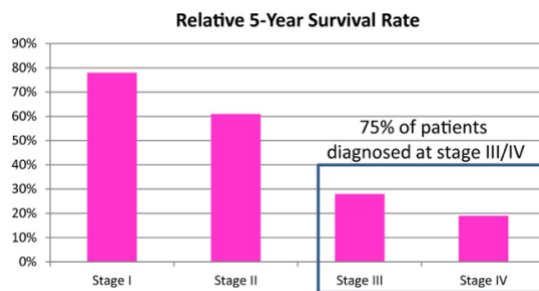
IIIC: Macroscopic peritoneal metastasis beyond the pelvis >2 cm in greatest dimension, with or without metastasis to the retroperitoneal lymph nodes (includes extension of tumor to capsule of liver and spleen without parenchymal involvement of either organ)

Stage 4: Distant metastasis excluding peritoneal metastases

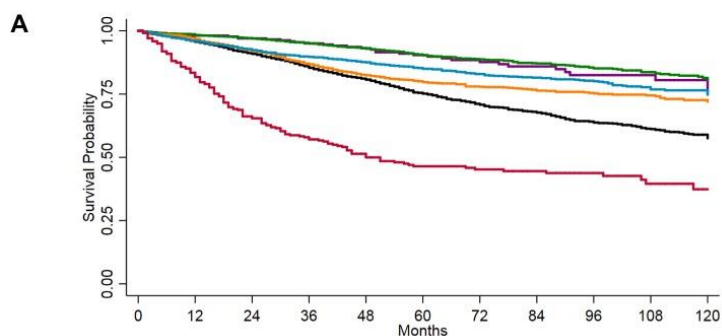
IVA: Pleural effusion with positive cytology

IVB: Parenchymal metastases and metastases to extra-abdominal organs (including inguinal lymph nodes and lymph nodes outside of the abdominal cavity)

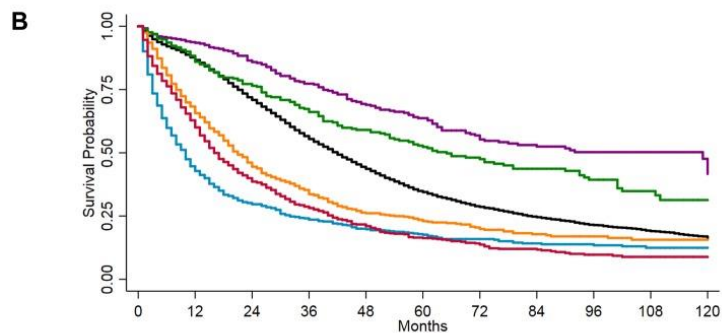
- Prognosis:
 - Depends on stage, histological subtype, age, ECOG, response to treatment, degree of postoperative residual disease, volume of center in which operation takes place
 - Risk factors: abundant ascites, > 70 y, poor ECOG
 - Neo-adjuvant setting
 - [CA-125 KELIM](#) predicts likelihood of 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



Number at risk	0	12	24	36	48	60	72	84	96	108	120
High-grade serous	3939	3378	2892	2395	1942	1525	1177	901	661	418	206
Low-grade serous	330	291	262	226	182	150	110	82	59	42	14
Endometrioid	2452	2151	1867	1615	1378	1122	910	702	520	337	163
Clear cell	1950	1674	1419	1161	932	768	614	469	350	237	113
Mucinous	1935	1618	1391	1176	1000	835	661	536	403	253	134
Carcinosarcoma	342	244	173	140	109	87	71	59	43	25	9



Number at risk	0	12	24	36	48	60	72	84	96	108	120
High-grade serous	13898	11098	8173	5622	3824	2526	1710	1150	726	424	179
Low-grade serous	378	320	277	222	181	147	109	87	62	34	16
Endometrioid	330	262	211	166	131	105	80	57	42	21	9
Clear cell	745	464	279	189	117	93	68	45	31	19	10
Mucinous	706	285	181	134	102	76	60	42	34	22	12
Carcinosarcoma	1039	560	319	201	130	84	60	42	26	17	6

— High-grade serous — Low-grade serous — Endometrioid
— Clear cell — Mucinous — Carcinosarcoma

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/m² 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	no
		III + IV HGSC or HGEC	Chemotherapy* ¹	Niraparib* ^{6,7} Rucaparib* ⁸	no no
	HRD negative	IV epithelial	Chemotherapy* ¹ + Bevacizumab* ⁴	Bevacizumab* ⁴	no
		III + IV HGSC or HGEC	Chemotherapy* ¹	Niraparib* ^{6,7} Rucaparib* ⁸	no no

- *¹ Standard schedule carboplatin AUC 6 (or 5 if frail) + paclitaxel 175mg/m² 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/m² 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, [ESMO MCBS score 4](#) ¹⁶
- *⁴ Total of 15 months (22 cycles), including period in combination with chemotherapy¹⁷⁻¹⁹
- *⁵ Start within 3-9 weeks after end of chemotherapy for a total of 2 years, PFS benefit in HRD-positive BRCA-wt group cf. PAOLA-1 trial, no ESMO MCBS score available for BRCAwt group 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, [ESMO MCBS score 2](#) ²¹
- *⁸ Start within 8 weeks after end of chemotherapy for a total of 2 years, PFS benefit cf. ATHENA-MONO trial, [ESMO MCBS score 3](#) ²²
- 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 score²³: complete resection at first surgery, good performance status, absence of ascites) if first relapse > 6 months of last platinum^{24–26}, 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^{27–30}
 - + 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)³¹; 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^{32–35}; only if PARPi-naïve; recommended length unclear³⁶
- 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 increase³⁷

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