# RECOMMENDATIONS AND GUIDELINES

# Summary INITIAL MANAGEMENT OF EPITHELIAL OVARIAN CANCER CASES









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The French National Cancer Institute (INCa) is the health and scientific expertise agency in the field of cancer care responsible for coordinating cancer control in France.

The document was drafted by the FRANCOGYN Group (French oncological and gynaecological research group), in partnership with SFOG (French Society of gynaecological oncology) and with ARCAGY-GINECO, and under the aegis of the National College of French Gynaecologists and Obstetricians (CNGOF) who holds the copyright.



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# **ABBREVIATIONS**

MA: marketing authorisation
BRCA: BRCA1 (breast cancer 1) or BRCA2 (breast cancer 2) gene mutation
CCS: complete cytoreductive surgery
HIPEC: hyperthermic intraperitoneal chemotherapy
CPH-I: Copenhagen index
GFR: glomerular filtration rate
FIGO: International Federation of Gynecology and Obstetrics
GnRH: gonadotropin-releasing hormone

HE4: human epididymal protein 4 MRI: magnetic resonance imaging IP: intraperitoneal LoE: level of evidence PARP: poly ADP-ribose polymerase PCI: Peritoneal Carcinosis Index PET: Positron Emission Tomography ROMA: risk of ovarian malignancy algorithm HRT: hormone replacement therapy

# INTRODUCTION

Ovarian epithelial, fallopian tube and primary peritoneal cancer affects one out of every 70 women in industrialised countries. Its incidence is approximately 4600 new cases in France in 2015. It is the 8<sup>th</sup> most common female cancer and represents the 4<sup>th</sup> cause of female cancer-related mortality, with 3100 deaths each year. It mainly affects postmenopausal women. The prognosis of ovarian cancer remains poor with a 5-year overall survival of 43%, regardless of stage, and most deaths occurring within the first two years post-diagnosis. Three-quarters of patients are diagnosed at an advanced stage (International Federation of Gynecology and Obstetrics (FIGO) stage IIIC and IV), i.e. with disease that has spread outside the ovaries, over the entire peritoneal surface or to distant sites. These stage IIIC-IV patients have a 5-year overall survival of less than 20%.

The natural course of ovarian cancer is marked by a good initial response to proposed treatments (surgery and chemotherapy) in 80% of patients. However, 70% of these present with recurrence within two years, generally with the

reformation of diffuse peritoneal disease such as peritoneal carcinosis. When recurrence occurs less than one year after the end of chemotherapy, the disease is considered to be "resistant to platinum salts" and when it occurs after more than one year, it is considered to be "sensitive to platinum salts".

The surgical work done determines both the patient's oncological prognosis, through its ability to result in zero macroscopic tumour residue or not, and perioperative morbi-mortalities. This modulation of the benefit of cytoreductive surgery is correlated with the care structure, with in particular the number of surgical procedures carried out on advanced-stage cases.

The adjuvant treatment of ovarian cancer has been based on a systemic treatment based on paclitaxel (Taxol<sup>®</sup> and generics) and carboplatin since the 1990s. Drugs for treating ovarian cancer have recently emerged: anti-angiogenic agents and PARP inhibitors. Besides the benefit of these new therapeutic classes for ovarian cancer treatment, a question remains as to the method of administration of chemotherapy.

# **OBJECTIVES AND TARGETS**

These guidelines come from the FRANCOGYN Group (French oncological and gynaecological research group), under the aegis of the National College of French Gynaecologists and Obstetricians (CNGOF), in partnership with SFOG (French Society of gynaecological oncology), with ARCAGY-GINECO, accredited by the French National Cancer Institute (INCa). They are intended for healthcare professionals involved in the diagnosis, initial treatment and followup of ovarian epithelial cancer patients: surgeons, medical gynaecologists, gynaecologists-obstetricians, medical oncologists, anatomopathologists, general practitioners, radiologists, anaesthetists, molecular biologists (oncogenomic platform), oncogenetics consultants, oncogeriatrics consultants, nutritionists, nuclear medicine physicians, nurses, midwives, hospital or dispensing pharmacists.

These guidelines apply to ovarian epithelial cancers of all types and stages, affecting adult patients (focusing separately on fertility preservation for young patients and on older patients). Borderline ovarian tumours, ovarian non-epithelial cancers and ovarian cancer recurrences do not fall within the scope of this document and are therefore excluded.

The objective of these guidelines for clinical practice is to enable optimal care provision that is homogeneous throughout the territory, for women treated for ovarian epithelial, fallopian tube and primary peritoneal cancer. The ultimate objective is to improve these patients' survival and quality of life.

This document summarises the main findings based on the data developed in the thesaurus, available to download on the e-cancer site. In this thesaurus, the reader will find all the justifications supporting these findings.

The methodology is described on page 25. A list of abbreviations is available on page 5.

It should be noted that all cases of ovarian epithelial, fallopian tube and primary peritoneal cancer require a prior review as part of a multidisciplinary consultative meeting (RCP). All major treatment changes and treatments for relapse must also be reviewed as part of an RCP review.

# **ALGORITHMS**

# Algorithm 1: Early-stage (FIGO I to IIA) ovarian or fallopian tube cancers



<sup>1</sup>Definition of suspected malignant lesion with imaging:

- ultrasound: The mass is classified as malignant if it has at least one malignant rule with no benign rule (as per the simple rules);
- MRI as per the ADNEX Score: lesion with risk and high risk of malignancy.

# Simple ultrasound rules

Benign lesion rules		Malign	Malignant lesion rules		
B1	Unilocular	M1	Irregular solid tumour		
B2	Presence of solid components with largest	M2	Presence of ascites		
	diameter < 7 mm				
B3	Presence of acoustic shadows	M3	≥ 4 papillary structures		
B4	Smooth multilocular tumour with largest	M4	Irregular multilocular-solid tumour with largest diameter		
	diameter < 100 mm		≥ 100 mm		
B5	No blood flow	M5	Very strong blood flow on Doppler		

# ADNEX MR score system [RUIZ2016]

	Malignancy risk*	Classification
Disappearance of lesion in MRI	0%	Very low risk
Unilocular cyst or hydrosalpinx with high T2-weighted signal (type 5) and no solid tissue Endometriotic unilocular cyst, with no internal enhancement Fatty lesion, with no solid tissue No enhancement of a wall Solid tissue with low T2-weighted and low DW signal	0-1.7%	Low risk
Unilocular cyst with high T1-weighted signal (type 3-4) (not fatty or endometriotic) Multilocular cyst, with no solid tissue Solid tissue enhanced according to a Type 1 curve	5.1-7.7%	Intermediate risk
Solid tissue enhanced according to a Type 2 curve	26.6-57.1%	High risk
Solid tissue enhanced according to a Type 3 curve Peritoneal implants	68.3-100%	Very high risk

\* Percentage observed in both external validation studies [RUIZ2016, PEREIRA2018]

Algorithm 2: Advanced-stage (FIGO III) ovarian, fallopian tube or primary peritoneal cancers



# Categories as per Makar

Category 1	The main tumour bulk located in the small pelvis No massive ascites No intestinal resection required
Category 2	The main tumour bulk located in the small pelvis No massive ascites Intestinal resection required
Category 3	The main tumour bulk located in the upper abdomen No massive ascites No intestinal resection required
Category 4	The main tumour bulk located in the upper abdomen No massive ascites Intestinal resection required
Category 5	The main tumour bulk restricted to the upper abdomen, Massive ascites or presence of miliary spread on mesentery. Multiple intestinal resections required

# Fagotti score

Parameters	Score
Omental cake	0: isolated sites
	or 2: diffuse infiltration up to the greater curvature of the stomach
Peritoneal carcinosis	0: carcinosis involving limited regions (paracolic gutter or pelvic peritoneum suitable for surgical
	resection by peritonectomy)
	or 2: NON-RESECTABLE massive peritoneal infiltration or miliary spread
Diaphragmatic	0: all other cases
carcinosis	or 2: extensive infiltration or confluent nodules infiltrating most of the diaphragmatic surface
Mesenteric retraction	0: no mesenteric retraction
	or 2: mesenteric retraction
Bowel infiltration	0: all other cases
	or 2: intestinal resection is envisaged
Stomach infiltration	0: all other cases
	or 2: nodules infiltrating the stomach and/or spleen and/or lesser omentum
Liver metastases	0: all other cases
	or 2: any lesion having a surface area > 2cm

Algorithm 3: Advanced-stage (FIGO IV) ovarian, fallopian tube or primary peritoneal cancers



# Algorithm 4: Post-therapeutic follow-up of ovarian, fallopian tube or primary peritoneal cancers



# GUIDELINES

KEY

 recommended courses of action
 unadvised courses of action or no recommendation possible due to a lack of data or insufficient data

# **PREDICTIVE DECISION MODELS AND TOOLS**

# **OVARIAN CANCER DIAGNOSIS**

# Imaging (ultrasound, MRI)

# INDICATIONS

- Supra-pubic, endovaginal ultrasound is recommended for ovarian tumour analysis (Grade A).
- In the case of ultrasound carried out by an experienced sonographer, subjective analysis is the recommended technique (Grade A).
- In the case of ultrasound carried out by a non-expert sonographer, use of the Simple Rules (described on page 7) is recommended (Grade A) and should be preferably combined with subjective analysis in order to be in line with the performances of an expert sonographer (Grade A).
- In cases of indeterminate ovarian lesions in supra-pubic endovaginal ultrasound examinations, it is recommended to carry out an MRI of the pelvis (Grade A).

# PELVIC MRI PROTOCOL AND REPORT

- In adnexal tumour analysis, if an MRI is carried out, the MRI protocol with injected dynamic T2, T1, T1 sequences with fat saturation, diffusion and after injecting gadolinium, is recommended (Grade B).
- To characterise an adnexal MRI image, it is recommended to include a malignancy risk score (such as ADNEX MR, described on page 6) (Grade C) in the report and to formulate an anatomopathological hypothesis (Grade C).

# Tumour markers, clinical and biological scores

# TUMOUR MARKERS

- Serum CA125 quantification is recommended for the diagnosis of a suspected malignant ovarian tumour following imaging (Grade A).
- Serum HE4 quantification is recommended for the diagnosis of an indeterminate ovarian mass following imaging (Grade A). HE4 quantification is not reimbursed at the present time.
- If a single serum marker is used, no guidelines can be formulated on the choice between CA125 and HE4 quantification for the diagnosis of a suspected malignant ovarian tumour when presented with an indeterminate ovarian mass in imaging (Grade B).
- The use of urine HE4 is not recommended for the diagnosis of a suspected malignant ovarian tumour (Grade A).
- The use of free serum circulating tumour DNA (Grade A) or of a tumour-associated autoantibody (Grade B) is not recommended for the diagnosis of a suspected malignant ovarian tumour.
- Failing scientific data of sufficient quality, no guidelines can be formulated on the use of CEA and CA19.9 quantification in cases of an indeterminate ovarian mass.

# CLINICAL AND BIOLOGICAL SCORES

- In cases of an indeterminate ovarian mass following imaging, use of the ROMA (Risk of Ovarian Malignancy Algorithm) score may be proposed (Grade A).
- In cases of an indeterminate ovarian mass following imaging, use of the following for diagnostic purposes:
   Copenhagen index (CPH-I);
  - R-OPS score;
  - OVA500 score;
  - is not recommended (Grade C).

# DISEASE STAGING AND SURGICAL RESECTABILITY

# Imaging

- It is recommended to carry out a CT scan of the thorax, abdomen and pelvis with injection for the pretherapeutic disease staging and resectability assessment of peritoneal carcinosis appearing to be of ovarian, fallopian tube or primary peritoneal origin (Grade B).
- MRI may be proposed, supplemented by a CT scan of the thorax without injection in cases of contraindication to iodinated contrast medium injection (severe kidney failure, GFR < 30 mL/min) (Grade C).</p>

The report should specify (Grade C):

- extensive disease spread (including massive ascites);
- mesenteric involvement;
- extensive gastrointestinal involvement;
- lesser omentum (hepatic portal) involvement;
- suprarenal periaortic adenopathies;
- abdominal (liver, etc.) parenchymal metastases;
- extra-abdominal (umbilical or parietal, lung, mediastinal lymph node, etc.) metastases.

# Laparoscopy and descriptive surgical scores

### LAPAROSCOPY

Laparoscopy is recommended for the pretherapeutic resectability assessment of ovarian, fallopian tube and primary peritoneal cancers (Grade A).

### SURGICAL SCORES

- It is recommended to use a score (at least Fagotti type, described on page 8) with laparoscopy to assess the non-resectability risk for initial or interval surgery for ovarian, fallopian tube, primary peritoneal carcinosis (Grade C).
- In cases of cytoreductive laparotomy for peritoneal carcinosis of ovarian, fallopian tube or primary peritoneal origin, it is recommended to assess the tumour load using the Peritoneal Cancer Index (PCI) (Grade C).

### **Tumour markers**

- It is not recommended to use serum CA125 as the sole basis for assessing the resectability of peritoneal carcinosis of ovarian, fallopian tube or primary peritoneal origin (Grade A).
- Failing specific data for the HE4 count in respect of surgical resectability, no guidelines can be formulated on the use of this assay for assessing ovarian, fallopian tube or primary peritoneal carcinosis resectability.
- Failing data, no guidelines can be formulated on the use of other biomarkers (CEA, CA19.9) for assessing ovarian, fallopian tube or primary peritoneal carcinosis resectability.
- Failing published data, no guidelines can be formulated on the diagnostic value of new biomarkers in respect of resectability.

### POST-NEOADJUVANT CHEMOTHERAPY THERAPEUTIC RESPONSE IMAGING AND TUMOUR MARKERS

- No guidelines can be formulated on the type of imaging to be carried out for assessing ovarian, fallopian or primary peritoneal carcinosis resectability, post-neoadjuvant chemotherapy.
- Failing sufficient data, no guidelines can be formulated on the use of CA125 or HE4 quantification for assessing resectability in cases of peritoneal carcinosis of ovarian, fallopian or primary peritoneal origin, post-neoadjuvant chemotherapy.
- Failing data, no guidelines can be formulated on the use of CEA, CA19.9 type biomarkers, and new biomarkers for assessing peritoneal carcinosis of ovarian, fallopian tube or primary peritoneal origin post-neoadjuvant chemotherapy.

# SCORES, MODELS, TOOLS AND ALGORITHMS FOR ASSESSING DIAGNOSIS AND POST-CHEMOTHERAPY THERAPEUTIC RESPONSE

Based on the data available, no guidelines can be formulated on the use of scores for predicting prognosis or response to chemotherapy in ovarian, fallopian tube or primary peritoneal cancers.

# **BIOPATHOLOGY**

# BENEFIT OF EXTEMPORANEOUS EXAMINATION IN CASES OF SUSPECTED OVARIAN CARCINOMA

Extemporaneous examination may be proposed in cases of surgery for a suspicious ovarian mass if the findings modify the intraoperative strategy (Grade B). The consistency between the final examination and the extemporaneous examination may vary according to the anatomopathologist's expertise in ovarian disease.

LAPAROSCOPIC SURGICAL SAMPLING QUALITY CRITERIA, SURGICAL SPECIMEN TRANSPORT, STORAGE AND SAMPLING METHODS APPLIED BY PATHOLOGISTS

# Laparoscopic surgical samples (number, sites, sampling volume)

- Prior to any chemotherapy, it is recommended to obtain a positive diagnosis of ovarian carcinoma (carcinoma histological type and grade) on biopsied material and not based on cytology (Grade C).
- It is recommended to perform biopsies with multiple good-sized samples on different tumour sites prior to neoadjuvant chemotherapy (Grade C).
- If imaging-guided microbiopsies are performed, it is recommended to remove three core biopsies with a needle greater than 16 G in size (Grade C).

# Tissue fixing, transport and storage methods

- It is recommended to fix the tissue samples in neutral buffered formol (with 4% formaldehyde), no later than 1 hour post-excision (Grade C).
- Vacuum sealing and storage at + 4°C may be an alternative, only for large surgical specimens, making it possible to extend this interval for not more than 48 hours (Grade C).
- It is recommended to fix tissue samples at least 6 hours (for biopsies) prior to anatomopathological examination (Grade C).

# Surgical specimen sampling methods

- It is recommended to sample ovarian, fallopian tube and primary peritoneal carcinomas by positioning samples particularly on solid areas, on the tumour capsule and on areas of different macroscopic appearance (Grade C).
- Given the tumoral heterogeneity of mucinous ovarian lesions, it is recommended to sample 1 to 2 blocks per cm of tumour (Grade C).
- In order to determine the origin of high-grade serous carcinoma (ovary versus fallopian tube, versus peritoneum), sampling on the fallopian tube and the entire pavilion of the oviduct may be proposed (Grade C).
- In the absence of macroscopic omental involvement after thorough macroscopic examination, it is recommended to sample at least 3 systematic sampling blocks on an omentectomy specimen in order to detect most of the microscopic involvement (Grade B).
   In cases of macroscopic omental involvement, it is recommended to only sample a single block on the largest macroscopic tumour nodule (Grade B).

# REQUIRED HISTOLOGICAL AND IMMUNOHISTOCHEMICAL CRITERIA TO ALLOW DIAGNOSIS OF THE VARIOUS HISTOLOGICAL SUBTYPES OF OVARIAN EPITHELIAL CANCERS

- It is recommended to use the 2014 WHO classification for diagnosing the histological subtype and grade of ovarian carcinoma (Grade C). In cases of diagnostic uncertainty in respect of the histological type on the morphological appearance alone, it is recommended to conduct an immunohistochemical study. An antibody panel including EMA, CK7, CK20, PAX8, WT1, p53, RE, RP, HNF1b and napsin A may be of use (Grade C).
- In cases of somatic BRCA gene mutation, the patient must be referred for oncogenetic counselling. Constitutional BRCA screening and its benefit in the monitoring of patients and their at-risk relatives is the subject of a specific INCa publication: "Inhibiteurs de PARP : préconisations pour un parcours en génétique oncologique" (PARP inhibitors: recommendations for an oncogenetics pathway), Outils pour la pratique collection, French National Cancer Institute, October 2019.

# ANATOMOCYTOPATHOLOGICAL QUALITY CRITERIA AND MINIMUM ITEMS TO INCLUDE IN REPORT

- The microscopic study should specify the histological tumour type, tumour grade, potential presence of serous tubal intraepithelial carcinoma (STIC), tumour sites, peritoneal cytology, lymph node status and FIGO classification with year of classification (Grade B).
- In cases of diagnostic uncertainty on the ovarian carcinoma histological type or grade, it is recommended to conduct an immunohistochemical study with an optimal antibody panel (Grade C).
- It is recommended to include in the anatomopathological report, the macroscopic examination including the description of the samples received and their intactness (intact or ruptured ovarian or serous tubal capsule), the tumour sites and the description of the omentum (size, tumour invasion, and size of the largest tumour site post-chemotherapy) (Grade B).
- It is recommended to state the size and site of the largest residual nodule in the post-chemotherapy surgical specimen report (Grade C).
- It is recommended to state in the histological report whether there are no or less than 5% residual tumour cells remaining post-chemotherapy (Grade C).

# EARLY-STAGE (STAGES IA-IIA) OVARIAN CANCER SURGERY

# BENEFIT AND NATURE OF SURGICAL (RE)STAGING IN CASES OF DETECTION OF PRESUMED STAGE I OR IIA STAGE OVARIAN CANCER

# Omentectomy

- Omentectomy (at least infracolic) is recommended to conduct complete initial surgical staging of presumed early-stage ovarian cancer (Grade C).
- In cases where initial staging is not conducted or incomplete (without omentectomy), restaging including omentectomy is recommended, particularly in the absence of an established indication of chemotherapy (Grade C).

# Appendicectomy

- Appendicectomy is recommended to conduct complete initial surgical staging of presumed early-stage ovarian cancer (Grade C).
- In cases where initial staging is not conducted or incomplete (without appendix investigation or resection), restaging including appendicectomy is recommended, particularly in the absence of an established indication of chemotherapy (Grade C).

# Cytology

Peritoneal cytology is recommended to conduct complete initial surgical staging of presumed early-stage ovarian cancer (Grade C).

### **Staged peritoneal biopsies**

- Peritoneal biopsies are recommended to conduct complete initial surgical staging of presumed early-stage ovarian cancer (Grade C).
- If surgical restaging is indicated, peritoneal biopsies are recommended (Grade C).

# Pelvic and periaortic lymphadenectomies

- Pelvic and periaortic lymphadenectomy is recommended to conduct complete initial surgical staging of presumed early-stage ovarian cancer, with the exception of the expansile mucinous subtype (Grade B).
- In cases where initial lymph node staging is not conducted or incomplete, restaging including lymphadenectomies is recommended, particularly in the absence of an established indication of chemotherapy, with the exception of the expansile subtype (Grade B).

# ROLE OF MINI-INVASIVE SURGERY IN PRESUMED STAGE I OR IIA OVARIAN CANCER (RE)STAGING

- The choice of initial surgical staging approach in respect of presumed early-stage ovarian cancer is dependent on the local conditions (particularly tumour size) and surgical expertise. If complete surgery without any risk of tumour rupture with protected surgical specimen removal is possible, the laparoscopic route is recommended (Grade B). Otherwise, median laparotomy is recommended (Grade B).
- The laparoscopic route is to be preferred for surgical restaging (Grade B).
- Failing sufficient data, no guidelines can be formulated on the use of the robot-assisted laparoscopic route over the conventional laparoscopic route.

# IMPACT OF INTRAOPERATIVE RUPTURE ON PRESUMED STAGE I OR IIA OVARIAN CANCER SURVIVAL

It is recommended to take all necessary measures to prevent intraoperative ovarian tumour rupture, including the intraoperative laparoscopic conversion decision (Grade B).

ROLE OF IMMEDIATE STAGING FOLLOWING EXTEMPORANEOUS ANATOMOPATHOLOGICAL DIAGNOSIS OF PRESUMED STAGE I OR IIA OVARIAN CANCER (RE)STAGING

- Failing specific data, no guidelines can be formulated in respect of conducting surgery in 1 stage with extemporaneous diagnosis or in 2 stages with definitive anatomopathological diagnosis for the treatment of presumed early-stage ovarian cancer.
- For patients seeking to preserve their fertility, the decision to administer conserving surgery or not should be made after a discussion between fertility specialists and medical or surgical oncologists on a definitive anatomopathological examination (see page 17).

# FERTILITY PRESERVATION STRATEGIES FOR YOUNG WOMEN IN CASES OF STAGE I OVARIAN CANCER

# PATIENT INFORMATION

It is recommended to inform stage IA ovarian cancer patients of childbearing age of the option of conserving treatment (Grade C).

# INDICATIONS OF FERTILITY-PRESERVING SURGERY IN CASES OF OVARIAN CANCER

- Surgical treatment conserving the uterus and the contralateral adnexa after unilateral adnexectomy may be proposed for low-grade stage IA ovarian cancer in a woman of childbearing age, subject to the requirement of negative staging (complete peritoneal and lymph node for all histologies and associated with uterine curettage for endometrioid and mucinous subtypes) (Grade C). For the specific case of expansile mucinous ovarian cancer, lymph node staging is not required.
- It is recommended to inform the patient on the risk of recurrence between 6 and 13% in the contralateral ovary if fertility preservation is sought (Grade C).
- It is recommended to hold a multidisciplinary review of the benefit/risk balance of conserving surgery based on definitive anatomopathology between oncologists (medical and/or surgical) and a reproductive specialist (Grade C).
- Failing data, no guidelines can be formulated on the bilateral adnexectomy strategy with uterus preservation with a view to oocyte donation.

# Indications of fertility-preserving surgery in cases of "borderline" (stage IC) ovarian cancer

- Bilateral adnexectomy with uterine preservation may be proposed to be able to envisage subsequent pregnancy through oocyte donation for high-grade FIGO IA or low-grade FIGO IC1 or IC2 serous, mucinous or endometroid cancer (Grade C).
- Preservation of the uterus and contralateral adnexa may be discussed on a case-by-case basis as part of a multidisciplinary consultative meeting in respect of rare tumours for stage I clear-cell cancer.
- Uterus-conserving surgery is not recommended for epithelial cancer that has spread beyond the ovaries, regardless of the histological type (Grade C).

# ROLE OF COMPLEMENTARY FERTILITY PRESERVATION STRATEGIES

It is recommended to inform the patient seeking fertility preservation that, despite conserving surgery, unilateral adnexectomy is associated with diminished ovarian reserve and with a risk of onset of premature ovarian insufficiency (Grade C).

# **Ovarian tissue cryopreservation**

Failing sufficient fata, no guidelines can be formulated on ovarian cortex freezing with a view to a future ovarian tissue graft in the context of ovarian epithelial cancers.

# **Ovarian stimulation of contralateral ovary**

Failing sufficient data, no guidelines can be formulated on ovarian stimulation for medically-assisted reproduction on the contralateral ovary after conserving surgery for ovarian epithelial cancer.

### In vitro oocyte maturation

Failing sufficient data, no guidelines can be formulated on *in vitro* oocyte maturation after *ex vivo* oocyte retrieval on ovarian cancer adnexectomy surgical specimens.

# **GnRH** analogues (agonists)

Failing sufficient data, no guidelines can be formulated on the use of GnRH analogues for preserving fertility in cases of ovarian cancer conserving treatment.

# **PERIOPERATIVE OVARIAN CANCER CARE**

# PREOPERATIVE PHASE

# Preoperative correction of nutritional deficiencies

- It is recommended to screen for nutritional deficiencies in patients presenting with ovarian, fallopian tube or primary peritoneal cancer (Grade B).
- Failing specific data on ovarian, fallopian tube and primary peritoneal cancer, no guidelines can be formulated on the preoperative nutritional deficiency improvement strategy.

Preoperative pharmaconutrition (or immunonutrition)

Failing specific data on ovarian, fallopian tube and primary peritoneal cancer, no guidelines can be formulated on preoperative immunonutrition in ovarian, fallopian tube or primary peritoneal cancer.

# Preoperative anaemia correction

- It is recommended to screen for anaemia in patients presenting with ovarian, fallopian tube or primary peritoneal cancer (Grade C).
- Failing specific data on ovarian cancer, no guidelines can be formulated on the preoperative anaemia correction strategy in ovarian, fallopian tube or primary peritoneal cancer.

# Digestive preparation prior to advanced ovarian cancer surgery

Failing specific data on ovarian, fallopian tube or primary peritoneal cancer, no guidelines can be formulated on whether to carry out preoperative digestive preparation in cases of ovarian, fallopian tube or primary peritoneal cancer.

# **INTRAOPERATIVE PHASE**

# Intraoperative filling monitoring

- It is recommended to conduct personalised intraoperative filling monitoring of patients presenting with ovarian, fallopian tube or primary peritoneal cancer (Grade B).
- Failing sufficient specific data, no guidelines can be formulated on personalised intraoperative filling monitoring for patients presenting with early-stage ovarian or fallopian tube cancer.

# Intraoperative tranexamic acid infusion

Infusion of a single dose of tranexamic acid may be proposed for ovarian, fallopian tube or primary peritoneal cancer surgery patients (Grade C).

### **PERIOPERATIVE PHASE**

- Epidural analgesia is recommended for patients undergoing laparotomy-based cytoreductive surgery for ovarian, fallopian tube or primary peritoneal cancer. (Grade B). Failing epidural analgesia, self-controlled administration of morphine is recommended, not associated with the continuous flow rate (Grade B).
- Failing sufficient data, no guidelines can be formulated on intravenous lidocaine or ketamine administration during surgery or the prescription of gabapentin or pregabalin in the perioperative phase.
- Failing data, no guidelines can be formulated on analgesic combinations for ovarian, fallopian tube or primary peritoneal cancer surgery.

# POSTOPERATIVE PHASE: EARLY REFEEDING AND MOBILISATION (ENHANCED POST-SURGERY REHABILITATION)

- Early resumption of feeding is recommended, including in cases of digestive resection after ovarian, fallopian tube or primary peritoneal cancer surgery (Grade B).
- It is recommended to set up enhanced post-surgery rehabilitation regimens, including early mobilisation, after ovarian, fallopian tube or primary peritoneal cancer surgery (Grade C).

# ADVANCED-STAGE (STAGES IIB TO IV) OVARIAN CANCER SURGERY

# INDICATIONS AND METHODS

- Complete surgery (i.e. with no macroscopic tumour residue) is recommended for advanced-stage ovarian, fallopian tube or primary peritoneal cancers (Grade B).
- It is recommended that ovarian cancer surgery be performed in a centre treating at least 20 cases of advancedstage cancer per year (Grade C).
- An interval of less than 6 weeks between surgery and commencing adjuvant chemotherapy is recommended for advanced-stage ovarian, fallopian tube and primary peritoneal cancers (Grade C).
- Surgery is recommended for stage IV advanced ovarian, fallopian tube or primary peritoneal cancers, where total abdominal peritoneal resection is possible (Grade C).

# LYMPHADENECTOMIES

- It is recommended to conduct periaortic and pelvic lymphadenectomies for advanced ovarian, fallopian tube of primary peritoneal cancers, regardless of the histological type, in cases of clinical or radiological suspicion of pelvic and/or periaortic metastatic adenopathy (Grade B).
- In the absence of suspected clinical or radiological adenopathy and in cases of total macroscopic peritoneal surgery following initial surgery, lymphadenectomy may be omitted because this does not modify the adjuvant medical treatment or overall survival, while increasing morbidity (Grade B).
- Suprarenal, mesenteric, coeliohepatic, cardiophrenic angle lymphadenectomies are not recommended in the absence of invasion (Grade C).

### **NEOADJUVANT CHEMOTHERAPY**

- Neoadjuvant chemotherapy is recommended for advanced ovarian, fallopian tube and primary peritoneal cancers in the following cases:
- unsuitability for total resection in primary surgery (Grade B);
- impaired general health or significant comorbidities (Grade B);
- stage IV (particularly with multiple intrahepatic lesions, or lung metastases) or massive ascites with miliary spread (Grade B).

# APPROACHES

Failing sufficient data, no guidelines can be formulated on the role of surgical laparoscopy (as opposed to diagnostic laparoscopy) for primary FIGO stage III or IV ovarian cancer surgery.

### SURGERY IN CASES OF NON-ZERO MACROSCOPIC TUMOUR RESIDUE AT END OF PROCEDURE

- Complete surgery, i.e. with no macroscopically visible peritoneal tumour residue, is recommended for FIGO stage III or IV ovarian cancers (Grade B).
- Failing data, no guidelines can be formulated on the type of surgical procedure to be carried out in cases of palliative surgery or of intraoperative detection of the inability to carry out zero macroscopic residue surgery in a FIGO stage III or IV cancer patient. If a surgical procedure is carried out, its morbidity should be as low as possible.

# MINIMUM INFORMATION IN SURGICAL REPORT

- It is recommended to describe the peritoneal carcinosis prior to any excision as well as tumour residue at the end of surgery (size, location and reason for non-extirpability) (Grade B).
- Use of a peritoneal carcinosis score suitable for assessing the tumour load objectively, such as the Peritoneal Carcinosis Index (PCI), is recommended (Grade C).
- Use of a standardised surgical report is recommended (Grade C).

# SYSTEMIC TREATMENTS

# EARLY STAGES (I-IIA)

# **Chemotherapy: general guidelines**

For stage I ovarian tumours, it is important first of all to ensure that surgical staging has been carried out as per the guidelines (see section on surgery). Besides the histological type, the FIGO stage (2014 version), the tumour grade is an item that can be used to establish whether complementary chemotherapy is indicated; it is therefore essential to obtain this information from the anatomopathologist.

# **ADJUVANT CHEMOTHERAPY**

Adjuvant chemotherapy is recommended for all early-stage (stage I-IIA) high histological grade (serous, endometrioid, undifferentiated, carcinosarcomas) ovarian, fallopian tube or primary peritoneal cancers (Grade A).

ADJUVANT CHEMOTHERAPY REGIMEN

- A platinum salt (Grade A), preferentially carboplatin (Grade A), as monotherapy (Grade A) or combined with another chemotherapy (Grade B), is recommended for early-stage ovarian or fallopian tube adjuvant chemotherapy. For combination therapy, the carboplatin (AUC 5-6) D1 and paclitaxel (175 mg/m2) D1 combination every 3 weeks is recommended (Grade B).
- For early-stage high-grade serous ovarian carcinomas, a combination is recommended over monotherapy (Grade B).

# **DURATION OF CHEMOTHERAPY**

- A chemotherapy regimen of at least 3 cycles and not more than 6 cycles is recommended for IA or IB ovarian cancers (Grade A).
- Six chemotherapy cycles are recommended for FIGO stage  $\geq$  IC ovarian or fallopian tube cancers (Grade C).
- Six chemotherapy cycles are recommended for FIGO stage ≥ IA high-grade serous ovarian or fallopian tube carcinomas (Grade C).

# Specific recommendations for rare tumours

Failing data, no guidelines can be formulated for the adjuvant treatment of early-stage ovarian mucinous, clearcell, low-grade endometrioid carcinomas and low-grade serous carcinomas. Reference may be made to the rare ovarian tumour guidelines.

# **Targeted therapies**

Failing data, no guidelines can be formulated on the use of antiangiogenic treatments, targeted therapies or immunotherapy in early-stage ovarian or fallopian tube cancers.

# ADVANCED STAGES (IIB-IV)

# Chemotherapy

# SYSTEMIC CHEMOTHERAPY

Chemotherapy is recommended for all advanced-stage (stages IIB-IV) ovarian, fallopian tube or primary peritoneal cancers (Grade A).

# CHEMOTHERAPY REGIMEN

- A platinum salt (Grade A), preferentially carboplatin (Grade A), combined with another drug (Grade A) is recommended as the standard chemotherapy for advanced ovarian, fallopian tube or primary peritoneal cancers.
- Preferential use of the carboplatin (AUC 5-6) D1 and paclitaxel (175 mg/m2) D1 combination every 3 weeks is recommended, considered the standard regimen for advanced ovarian, fallopian tube or primary peritoneal cancers (Grade A).
- Alternative to this standard ovarian, fallopian tube or primary peritoneal cancer regimen may be proposed as follows:
- Weekly fractionation of chemotherapy with carboplatin (AUC 2) on D1, D8 and D15, and paclitaxel (60 mg/m2) on D1, D8, D15 every 3 weeks to reduce adverse effects (reduction of alopecia and neurological toxicity) (Grade B). In cases where paclitaxel is contraindicated, the carboplatin (AUC 5) D1 and pegylated liposomal doxorubicin (30 mg/m2) D1 combination every 4 weeks may be proposed (Grade B), as well as carboplatin (AUC 5) monochemotherapy every 3 weeks (Grade B).
- In cases where carboplatin is contraindicated, cisplatin (75 mg/m2) may be combined with paclitaxel (175 mg/m2) every 3 weeks (Grade A).

# **DURATION OF CHEMOTHERAPY**

A duration of at least 6 treatment cycles is recommended for advanced ovarian, fallopian tube or primary peritoneal cancer chemotherapy (Grade A).

PERIOPERATIVE CHEMOTHERAPY

- The carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m2) regimen every 3 weeks is recommended in cases of neoadjuvant treatment of advanced ovarian, fallopian tube or primary peritoneal cancers (Grade A).
- It is recommended to perform interval surgery after 3 to 4 advanced ovarian, fallopian tube or primary peritoneal cancer treatment cycles (Grade C). The number of adjuvant treatment cycles should be 2 to 4, after interval cytoreductive surgery, for a total (neoadjuvant cycles + adjuvant cycles) of not more than 6 to 9 cycles (Grade C)

TIME INTERVAL BETWEEN CYTOREDUCTIVE SURGERY AND CHEMOTHERAPY

It is recommended to commence chemotherapy less than 6 weeks post-cytoreductive surgery for advanced ovarian, fallopian tube or primary peritoneal cancers (Grade C).

# **Targeted therapies**

# ANTIANGIOGENIC TREATMENTS

- Bevacizumab may be proposed as a treatment for advanced ovarian, fallopian tube or primary peritoneal cancers in combination with carboplatin and paclitaxel chemotherapy for up to 6 cycles followed by maintenance therapy until disease progression or for up to not more than 15 months or until unacceptable toxicity for advanced-stage (stages IIIB and IIIC (FIGO 1988) and IV) patients, particularly for patients with a poorer prognosis (stage IV, postoperative tumour residue and patient not having undergone surgery) (Grade A).
- Bevacizumab in combination with chemotherapy should be omitted in cycle 1 if the treatment commences less than 4 weeks after initial (Grade A) or interval (Grade B) cytoreductive surgery.
- Failing sufficient data and failing evidence of clinical benefit, no guidelines can be formulated on the use of bevacizumab in combination with neoadjuvant chemotherapy. Interval surgery after bevacizumab may be proposed (Grade B).

# **HORMONE THERAPY**

Hormone therapy treatment is not recommended in high-grade ovarian, fallopian tube or primary peritoneal carcinomas (Grade A).

### PARP INHIBITORS

- Olaparib monotherapy is recommended for the maintenance treatment of adult advanced (FIGO stages III and IV) high-grade ovarian epithelial, fallopian tube or primary peritoneal cancer with BRCA1/2 gene mutation (germinal and/or somatic) who have had a partial or complete response to first-line platinum-based chemotherapy (Grade B).<sup>1</sup> Patients must commence olaparib treatment no later than 8 weeks after the end of their platinum-based treatment. Patients may continue treatment until radiological disease progression, until unacceptable toxicity or for up to 2 years if there is no radiological sign of the disease after 2 years of treatment. Patients presenting with signs of disease at 2 years, who, in the attending physician's opinion, may benefit from continuing treatment, may be treated after the 2-year limit.
- To enable the prescription of olaparib for advanced ovarian, fallopian tube or primary peritoneal cancer patients with BRCA 1 or 2 mutations, it is recommended to screen for BRCA 1 or 2 mutation from the diagnostic stage, therefore at the time of the initial assessment laparoscopy (Grade B).<sup>2</sup>

# **CHEMOTHERAPY APPROACHES**

# NON-HYPERTHERMIC INTRAPERITONEAL ROUTE

Intraperitoneal (IP) adjuvant chemotherapy, administered by a trained team, may be proposed after initial surgery with tumour residue < 10 mm for ovarian, fallopian tube or primary peritoneal carcinosis. The recommended regimen is: paclitaxel 135 mg/m<sup>2</sup> over 3 hrs or 24 hrs intravenously (IV) D1, cisplatin 75 to 100 mg/m<sup>2</sup> IP D2 and paclitaxel 60 mg/m<sup>2</sup> IP D8 administered every 3 weeks for 6 cycles. It is recommended to discuss the benefit/risk ratio of the IP route compared to the IV route with the patient, due to a higher risk of complications. Should it be necessary to discontinue IP chemotherapy, treatment should be continued by the IV route (Grade B).
 No data are available enabling the formulation of guidelines on the part IP chemotherapy use of hervasizumab

No data are available enabling the formulation of guidelines on the post-IP chemotherapy use of bevacizumab.

# HYPERTHERMIC INTRAPERITONEAL ROUTE: HIPEC

- Hyperthermic intraperitoneal chemotherapy (HIPEC) may be proposed for FIGO stage III ovarian, fallopian tube or primary peritoneal carcinosis, at the time of interval surgery with a residue < 10 mm, conducted after 3 cycles of intravenous (IV) chemotherapy, for patients with initially non-resectable disease (Grade B).</p>
- The regimen should be: cisplatin 100 mg/m<sup>2</sup> distributed at a rate of 50 mg/m<sup>2</sup> at the start of the procedure, 25 mg/m<sup>2</sup> at 30 min and 25 mg/m<sup>2</sup> at 60 min, for a total duration of 90 min at 40-41°C, combined with hyperhydration and nephroprotection with IV sodium thiosulphate, bolus of 9 g/m<sup>2</sup> at the start of HIPEC, followed by 12 g/m<sup>2</sup> over 6 hours (Grade B). At the time of publication of these guidelines, sodium thiosulphate is only available under a named-patient temporary authorisation for use.
- No data are available enabling the formulation of guidelines on the post-HIPEC use of bevacizumab.

<sup>&</sup>lt;sup>1</sup> At the time of writing of these guidelines, olaparib is available for this indication, via a cohort temporary authorisation for use (ATUc) granted by the French National Medicines and Health Products Safety Agency, pending its reimbursement via marketing authorisation, awarded on 12 June 2019. The procedure for accessing this treatment in the ATUc context is described in the protocol for therapeutic use and information collection (PUT) available on the ANSM website (ansm.sante.fr)

protocol for therapeutic use and information collection (PUT) available on the ANSM website (ansm.sante.fr) <sup>2</sup> "Inhibiteurs de PARP : préconisations pour un parcours en génétique oncologique" (PARP inhibitors: recommendations for an oncogenetics pathway), Outils pour la pratique collection, French National Cancer Institute, October 2019.

# **ELDERLY SUBJECTS**

# GENERAL PRINCIPLE

Subject to comorbidities and the possibility of complete surgery, it recommended to conduct complete surgery on the elderly (Grade B).

# ADAPTATION OF SURGICAL STRATEGY ACCORDING TO AGE AND/OR GERIATRIC CRITERIA

- In cases of ovarian, fallopian and primary peritoneal cancer in the elderly, it is recommended to carry out cytoreductive surgery in a centre performing over 20 surgical procedures for advanced cancer annually (Grade C).
- It is recommended to conduct an oncogeriatric assessment prior to the provision of care for an elderly ovarian, fallopian tube or primary peritoneal cancer patient (Grade C).
- It is recommended to account for at least the following items in vulnerability assessments for elderly ovarian, fallopian tube or primary peritoneal cancer patients:
  - age  $\geq$  80 years, particularly if blood albumin  $\leq$  37g/L;
  - age ≥ 75 years and FIGO stage IV;
  - age  $\geq$  75 years, FIGO stage III and  $\geq$  1 comorbidity (Grade C).

# ADAPTATION OF CHEMOTHERAPY ACCORDING TO AGE AND/OR GERIATRIC CRITERIA

Systemic treatment identical to that for younger patients (platinum salt-based bitherapy) is recommended for the treatment of ovarian, fallopian tube and primary peritoneal cancers in non-vulnerable elderly patients (Grade B).

ADAPTATION OF THERAPEUTIC SEQUENCE BETWEEN CHEMOTHERAPY AND SURGERY

Initial chemotherapy may be proposed after 70 years in cases of comorbidities and/or extensive peritoneal carcinosis requiring complex initial surgery (Grade C).

# POST-THERAPEUTIC FOLLOW-UP, ROLE OF HORMONE REPLACEMENT THERAPY AND CONTRACEPTION

# MONITORING TO BE SET UP AFTER INITIAL OVARIAN EPITHELIAL TUMOUR TREATMENT

- It is recommended to review symptoms at 3 months, 6 months, 12 months, 18 months and 24 months and once a year post-treatment for ovarian epithelial, fallopian tube or primary peritoneal cancer (Grade B).
- If paraclinical monitoring is indicated, serum HE4 quantification may be proposed (Grade C). HE4 quantification is not reimbursed by French Social Security. If HE4 monitoring is impossible, serum CA125 quantification may also be proposed (Grade B).
- In cases of serum HE4 or CA125 elevation after ovarian epithelial, fallopian tube or primary peritoneal cancer treatment, imaging tests are recommended (Grade B).
- If no ascites is present, systematic peritoneal cytology is not recommended after ovarian, fallopian tube or primary peritoneal cancer treatment (Grade C).
- Systematic CT scanning of the thorax, abdomen and pelvis is not recommended after ovarian, fallopian tube or primary peritoneal cancer treatment (Grade C).
- For ovarian, fallopian tube or primary peritoneal cancer follow-up, it is recommended to monitor patients with complete initial surgery (zero macroscopic tumour residue, CCS) and in good general health (ECOG 0) with serum quantification (HE4 or CA125) from 6 months after the end of chemotherapy and subsequently every 6 months, in the case of initially elevated serum markers (Grade C).

# POST-OVARIAN EPITHELIAL TUMOUR HORMONE REPLACEMENT THERAPY OPTIONS

# Post-high-grade serous ovarian, fallopian tube or primary peritoneal cancer

- It is recommended to propose hormone replacement therapy (HRT) to patients under 45 years of age following non-conserving high-grade serous ovarian, fallopian tube or primary peritoneal cancer treatment (Grade C).
- HRT may be proposed in cases of climacteric syndrome, in the context of an individual review of the benefit/risk balance to patients over 45 years of age with previous history of high-grade serous ovarian, fallopian tube or primary peritoneal cancer (Grade B).

### Post-ovarian municous adenocarcinoma

- It is recommended to propose HRT to patients under 45 years of age following non-conserving mucinous ovarian cancer treatment (Grade C).
- HRT may be proposed to patients over 45 years of age with previous history of mucinous ovarian cancer in cases of climacteric syndrome, in the context of an individual review of the benefit/risk balance (Grade C).

# Post-low-grade serous adenocarcinoma or low-grade endometrioid adenocarcinoma

Failing specific data for these histological types, no guidelines can be formulated on the use of HRT for patients with previous history of low-grade serous or low-grade endometrioid ovarian cancer.

# **HRT type**

In any case, the prescription conditions for HRT are subject to the same guidelines as for the general population [ANAES-AFSSAPS2004] [HAS2014].

# CONTRACEPTION OPTIONS AFTER INITIAL OVARIAN EPITHELIAL TUMOUR TREATMENT

Failing specific data, no guidelines can be formulated on the use of hormonal contraception after fertilityconserving ovarian and fallopian tube cancer treatment.

# METHODOLOGY

# Guideline formulation methodology

The guideline formulation methodology is detailed in the thesaurus, available to download on the INCa and CNGOF website.

It is based on:

- critical analysis of the best scientific data available used to assign a level of evidence to the findings from the literature;
- and the justified opinion of the experts of the working group.

A systematic bibliographic search was conducted over the period between 1 January 2005 and 8 June 2018. The bibliographic search, methodological analysis and summary of the scientific data were conducted by the working group. The guidelines were formulated by the multidisciplinary working group. The guidelines were subsequently reviewed by a panel of independent reviewers from the working group by means of quantitative (grading) and qualitative (observations) reviews. The members of the working group finally reviewed the compiled observations with a view to finalising the document at a final meeting.

# Level of evidence

The level of evidence consists of the ranking of the data of the literature on which the formulated guidelines are based. It is dependent on the type and quality of the studies available, as well as the consistency or lack of consistency of their findings. Details of the levels of evidence used are provided in the thesaurus. The findings of the literature were subsequently summarised and assigned a level of evidence according to the scale described in the thesaurus.

# **Grading of guidelines**

Each guideline is associated with a grade according to the scale described in the thesaurus and based on the level of evidence of the literature and the expert review by the working group and the reviewers.

# In respect of the medicinal product

It should be noted that the marketing authorisations of some older drugs (particularly paclitaxel, carboplatin), for which generic versions are now available, have never been reviewed despite changes in knowledge and practices. In this way, some of the courses of action recommended by the expert group for these medicinal products are based on the findings of trials conducted after the marketing authorisations were granted and on the ensuing clinical practices.

The adverse effects of medicinal product treatments are mostly mentioned in the summary of product characteristics of the marketing authorisation of the corresponding drugs. Some adverse effects occurring after the drug was

# Working group set-up

These national guidelines were formulated by a multidisciplinary working group, representing the medical fields involved, practice methods and geographic divisions and formed by the FranCOGyn Group (French oncological and gynaecological research group), under the aegis of the National College of French Gynaecologists and Obstetricians

introduced on the market and not yet mentioned in the marketing authorisation are reported on the ANSM website. In cases of severe (serious) adverse reactions that could be attributed to the cancer treatment, the treatment may be discontinued and the temporary discontinuation must be confirmed by the oncologist within 24 hours. As a general rule, temporary or permanent discontinuation of a cancer treatment as well as dose modifications fall within the remit of the medical oncologist and may give rise to a further multidisciplinary consultative meeting for a further therapeutic proposal if relevant.

Healthcare professionals are required to report any suspected adverse effects (online via the dedicated portal <a href="http://solidarites-sante.gouv.fr/soins-et-">http://solidarites-sante.gouv.fr/soins-et-</a>

maladies/signalement-sante-gouv-fr, information also available on the ANSM website).

(CNGOF), in partnership with SFOG (French Society of gynaecological oncology), with ARCAGY-GINECO.

The professional members of the national review group were proposed by the learned societies concerned by the scope of these guidelines and the regional oncology networks (detailed in the thesaurus).

# WORKING GROUP, COORDINATION AND EXPERT REVIEWERS

The experts of the working group were contacted *intuitu personae* and not as a representative of an organisation, learned society or group of professionals.

The French National Cancer Institute ensured that the experts proposed by the sponsor availed of the independence needed to carry out the expert reviews required based in particular on a review of their declarations of interest, published on the dedicated DPI-SANTE website.

Within the scope of the accreditation procedure, the review of the connections of interest was submitted by INCa's Expert Review Commission.

# Coordination

# Accreditation coordinators

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# **National review**

The list of all 99 reviewers is available on the thesaurus available to download on the website of the French National Cancer Institute and of the National College of French Gynaecologists and Obstetricians (CNGOF).

# /Summary INITIAL MANAGEMENT OF EPITHELIAL OVARIAN CANCER CASES



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