Management of epithelial cancer of the ovary, fallopian tube, primary peritoneum. Long text of the joint French clinical practice guidelines issued by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY, endorsed by INCa. (Part 2 systemic, intraperitoneal treatment, elderly patients, fertility preservation, follow-up)

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Summary:

Adjuvant chemotherapy by carboplatin and paclitaxel is recommended for all high-grade ovarian and tubal cancers (FIGO stages I-IIA) (grade A). After primary surgery is complete, 6 cycles of intravenous chemotherapy (grade A) are recommended, or a discussion with the patient about intraperitoneal chemotherapy, according to her risk-benefit ratio. After complete interval surgery for FIGO stage III, hyperthermic intraperitoneal chemotherapy (HIPEC) can be proposed, in accordance with the modalities of the OV-HIPEC trial (grade B). In cases of postoperative tumor residue or in FIGO stage IV tumors, chemotherapy associated with bevacizumab is recommended (grade A).

Key words: ovarian cancer; tubal cancer, primary peritoneal cancer, surgery; chemotherapy; guidelines

Introduction

Initial management of epithelial ovarian cancers is relatively heterogeneous in France, with treatment sequences that differ substantially between centers for primary or interval surgery. Similarly, the extent of surgery and the surgical staging procedures vary according to patient characteristics (young vs elderly women, for example). Perioperative management, whether it concerns early recovery or fertility preservation, has not been standardized, although it can cause physical or psychological morbidity. Finally, cancer centers vary widely in their use of chemotherapy (and how they administer it), as well as of targeted therapies; a national strategy remains to be defined, according to different clinical contexts. Work to develop clinical practice guidelines is therefore necessary to enable practices to be in accordance with the best evidence and to improve prognosis for all patients.

Accordingly, the French research group for oncologic gynecologic surgery (FRANCOGYN), the French national college of gynecologists and obstetricians (CNGOF), the French society of gynecologic oncology (SFOG), and the national investigators' group for studies in ovarian and breast cancer (GINECO-ARCAGY) brought together a working group to develop such guidelines. This text is a synthesis of clinical practice guidelines for the initial management of epithelial ovarian, tubal, or primary peritoneal cancers (excluding recurrence of ovarian cancer and borderline tumors).[1] The development of these clinical practice guidelines followed the standards set by the French national authority for health (HAS) and the national cancer institute (INCa), with reviews by experts both within and outside the working group. INCa has endorsed these clinical practice guidelines.

This article deals with the role of systemic and intraperitoneal treatments, the treatment of elderly women, fertility preservation, and the follow-up of women with ovarian, tubal, or primary peritoneal cancers.

Their aim is to aid professionals (gynecologic surgeons, medical gynecologists, gynecologist-obstetricians, pathologists, medical oncologists, radiologists, anesthetist-critical-care specialists, nuclear physicians, general practitioners, midwives, and paramedical personnel) in managing women with ovarian cancer or with suspected ovarian, tubal, or primary peritoneal cancer.

Role of intravenous systemic treatments of early-stage ovarian or tubal cancer (FIGO stages I-IIA)[4]

An analysis of the literature has shown that at early stages adjuvant chemotherapy based on a platinum compound alone (especially carboplatin) or with another compound improves both relapse-free survival and 10-year overall survival (LE1). The optimal number of cycles of chemotherapy ranges from 3 to 6 (LE1).

Adjuvant chemotherapy is recommended for all high-grade ovarian and tubal cancers (FIGO stages I-IIA) (grade A). Adjuvant chemotherapy for early-stage ovarian or tubal cancer must include a platinum compound (grade A), preferably carboplatin (grade A). For high-grade serous carcinomas, an additional drug is recommended rather than use of this single agent (grade B). The chemotherapy recommended for early-stage ovarian or tubal cancer is based on the combination of carboplatin (AUC 5-6) on D1 and paclitaxel (175 mg/m2) on D1 every 3 weeks (grade B). Chemotherapy for stage IA or IB ovarian or tubal cancer must include at least 3 cycles and a maximum of 6 (grade A). For stage I high-grade serous carcinoma of the ovary or fallopian tubes and for the other histologic types of FIGO stages ≥ IC tumors, 6 cycles of chemotherapy are recommended (grade C).

No guidelines can be issued about chemotherapy indications for early-stage ovarian carcinomas of the following types: low-grade serous, low-grade endometrioid, or clear-cell mucinous. It may be useful to refer to the guidelines of the network of rare ovarian tumors.

Role of systemic intravenous treatments of advanced (FIGO stages IIB-IV) ovarian, tubal, or primary peritoneal cancers)[4] (Figures 1 and 2)

In advanced ovarian, tubal, or primary peritoneal cancers, polychemotherapy based on a platinum compound and taxane is superior to other combinations of chemotherapy for both overall survival and progression-free survival (LE1). The reference combination used in most clinical trials is carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m² for 3 hours), every 3 weeks. Carboplatin is not inferior to cisplatin for either overall or progression-free survival, combined with paclitaxel; the latter combination has the best tolerance profile (LE1). A trial in Japan found that weekly fractionation of paclitaxel with an increase of dose-intensity to 80 mg/m2 combined with carboplatin AUC 5 or 6 every 3 weeks was superior (LE1). This superiority was not observed in a trial of a white population (LE1), except among those who had not received bevacizumab both with chemotherapy and then as maintenance (LE2). Weekly fractionation of carboplatin and paclitaxel without increased dose-intensity (carboplatin AUC 2 on D1, D8, and D15, and paclitaxel 60 mg/m2 on D1, D8, and D15 every 3 weeks) is not inferior to the standard regimen and has a somewhat favorable tolerance profile (for neuropathy and alopecia) (LE1). As an alternative to paclitaxel, carboplatin can be combined with docetaxel, gemcitabine, or pegylated liposomal doxorubicin, but none of these combinations is superior to the standard treatment by carboplatin-paclitaxel (LE1). Although the efficacy of cisplatin is equivalent to that of carboplatin, cisplatin has a higher risk of nonhematologic toxicity, especially renal, gastrointestinal, and infectious (LE1). Oxaliplatin was assessed in association with cyclophosphamide in one trial with efficacy similar to that of the combination of cisplatin and paclitaxel (NP2). No clinical trial has demonstrated the superiority of any combination of 3 chemotherapy substances over the standard two-therapy combination (LE1). The number of cycles of chemotherapy administered in randomized clinical trials has ranged from 6 to 9. Moreover, the trials assessing the utility of strategies of chemotherapy maintenance have not shown any advantages over the standard regimen (LE1). The randomized clinical trials aimed at assessing the value of neoadjuvant chemotherapy

generally tested the standard regimen of carboplatin (AUC 5 or 6) on D1 and paclitaxel (175 mg/m2) on D1 every 3 weeks. Neoadjuvant chemotherapy was given for 3 to 4 cycles before interval cytoreduction surgery, then resumed in the postoperative period for 3 adjuvant cycles, for a total of 6 to 9 cycles overall. Most clinical trials begin adjuvant chemotherapy less than 4 weeks after surgery; a retrospective study of 3 randomized clinical trials reported the prognostic value of chemotherapy started after 19 days (LE3). Bevacizumab at a dose of 7.5 and 15 mg/kg every 3 weeks, combined with chemotherapy and then as maintenance, improved median progression-free survival of advanced stage III and IV ovarian cancer by 4 months for all stages combined, with the most benefit for the subgroups of women with poorer prognosis (i.e., stage IV and the Stage III women with postsurgery tumor residue and those with no surgery) (LE1). We note that more than 20% of the women had grade-3 toxicity (especially those with hypertension). Bevacizumab with chemotherapy must be omitted in cycle 1 if the treatment begins less than 4 weeks after surgical resection (NP1). Bevacizumab can be used in combination with a chemotherapy protocol including intensified weekly administration of paclitaxel at 80 mg/m² (LE3). The administration of bevacizumab after interval surgery does not increase its toxicity (LE2), and its use in combination with neoadjuvant chemotherapy does not increase perioperative morbidity during interval surgery (LE2). Nor does the use of bevacizumab in combination with neoadjuvant chemotherapy significantly increase the number of patients undergoing surgery or the rate of complete interval surgery (LE2). The role of hormone therapy has not been assessed for the treatment of advanced high-grade ovarian cancer. Olaparib is currently used for maintenance after chemotherapy in women with platinum-sensitive relapsed ovarian cancer who have a BRCA1/2 tumor or germline mutation. Its demonstrably high efficacy in this situation led to its authorization in 2014. The results of the SOLO-1 phase III randomized double-blinded, placebo-controlled trial that assessed olaparib as maintenance therapy after standard first-line

treatment were published in the *New England Journal of Medicine*. The principal objective of this trial was to demonstrate the superiority of olaparib as maintenance treatment for progression-free survival. Overall, 391 women with FIGO stages III-IV high-grade serous or endometrioid cancer with a BRCA1/2 mutation were included; they were randomized 2:1 between olaparib and placebo after the end of the initial treatment sequence including primary or interval surgery and carboplatin-based chemotherapy. The maintenance treatment continued until progression or for a maximum of 24 months in its absence. The median follow-up was 41 months. The principal objective of the study was largely achieved, with a median progression-free survival corresponding to around 3 years in the olaparib group vs 13.8 months in the placebo group; HR=0.30; 95% CI 0.23-0.41; P<0.0001. The analyses of second progression-free survival (PFS2) (time from randomization to second disease progression or death), first subsequent treatment or death, and second subsequent treatment or death were also positive and confirm the principal endpoint. The data for overall survival remain immature. The groups did not differ for quality of life. From the perspective of toxicity, no new signal was observed for patients treated at relapse. The role of immunotherapy (anti-PD1 and PD-L1 and anti-CTLA4) is under evaluation for the management of advanced high-grade ovarian cancer as a first-line treatment.

Chemotherapy is recommended for all advanced (FIGO stages IIB-IV) ovarian, tubal, and primary peritoneal cancers (Grade A). A platinum compound (Grade A), preferentially carboplatin (Grade A), together with another substance (Grade A), is recommended as the standard chemotherapy for these advanced cancers.

The preferential use of the combination of carboplatin (AUC 5-6) on D1 and paclitaxel (175 mg/m2) on D1 every 3 weeks is recommended and considered the standard regimen for advanced ovarian, tubal, and primary peritoneal cancers (Grade A).

The following alternatives to this standard regimen may be proposed:

- Weekly fractionation of chemotherapy with carboplatin (AUC 2) on D1, D8, and D15, and paclitaxel (60 mg/m2) on D1, D8, and D15 every 3 weeks to limit their adverse effects (reduction in both alopecia and neurological toxicity) (Grade B).

- If paclitaxel is contraindicated, the combination of carboplatin (AUC 5) on D1 and pegylated liposomal doxorubicin (30 mg/m2) on D1 every 4 weeks can be proposed (Grade B), as can single-agent chemotherapy with carboplatin (AUC 5) every 3 weeks (Grade B).

- If carboplatin is contraindicated, cisplatin (75 mg/m2) can be combined with paclitaxel (175 mg/m2) every 3 weeks (Grade A).

A duration of at least 6 treatment cycles is recommended for chemotherapy for advanced ovarian, tubal, and primary peritoneal cancers (Grade A).

A regimen of carboplatin (AUC 5 or 6) and paclitaxel (175 mg/m2) every 3 weeks is recommended for neoadjuvant treatment for these advanced cancers (Grade A).

Interval surgery is recommended after 3 to 4 cycles of treatment for these cancers (Grade C). The number of cycles of adjuvant chemotherapy after interval cytoreduction surgery will be 2 to 4, for a minimum total of 6 cycles and a maximum of 9 (Grade C).

Chemotherapy should begin less than 6 weeks after cytoreduction surgery in advanced ovarian, tubal, and primary peritoneal cancer (grade C).

Bevacizumab can be proposed together with chemotherapy by carboplatin and paclitaxel for up to 6 cycles of treatment and then alone as maintenance for a maximum of 15 months or until toxicity becomes unacceptable for women with FIGO stages III and IV cancers (FIGO 2014), especially those with the worst prognosis (stage IV, postoperative tumor residue, or no surgery) (grade A). Bevacizumab with chemotherapy must be omitted in cycle 1 if the treatment begins less than 4 weeks after primary (grade

A) or interval (Grade B) cytoreduction surgery. In the absence of any demonstration of the clinical utility of bevacizumab together with neoadjuvant chemotherapy, no recommendation in this situation is currently justified. Interval surgery after bevacizumab is not contraindicated. Olaparib as maintenance treatment after primary or interval surgery and first-line chemotherapy is recommended at a dose of 300-mg tablets × 2/24 h orally for 24 months or until progression in women with FIGO stages III-IV high-grade serous or endometrioid ovarian, tubal, or primary peritoneal cancer and a BRCA1/2 mutation (Grade B). At the time these guidelines were drafted, olaparib is not yet authorized as first-line treatment. As of now, no data are available about the combination of bevacizumab and olaparib. **Rapid testing for BRCA mutations is necessary at diagnosis of ovarian cancer to determine if olaparib is indicated (figure 3).**

Role of the intraperitoneal approach for administering chemotherapy (hyperthermic (HIPEC) or normothermic) in advanced ovarian, tubal, or primary peritoneal cancers)[5] (Figure 1)

Intraperitoneal (IP) chemotherapy without hyperthermia

The meta-analysis by Jaaback et al. published in 2016 (LE1) covered 2119 women and 9 randomized trials comparing the intravenous (IV) and intraperitoneal (IP) administration of adjuvant chemotherapy after so-called optimal surgery (i.e., tumor residue < 1 cm). It reported that IP chemotherapy produced a significant gain in overall survival (8 studies), with a HR of 0.81 (95% CI 0.72-0.90) (LE1). This result is nearly identical to that found in considering only the 6 high quality studies (HR: 0.80 (95% CI 0.72-0.90) (LE1). This improvement in overall survival is independent of both the number of medications used and the dose. It should be noted that 6 of the 9 studies included in this meta-analysis did not use paclitaxel, and only 2 used carboplatin, due to the age of the studies; the most recent dated back to 2006 and used a control arm that did not correspond to current standards of IV chemotherapy. IP

administration leads to a significant increase in fever, fatigue, gastrointestinal effects, infections, metabolic effects, pain, and neurological toxicity, with a concomitant reduction in the quality of life during and for 6 weeks after the chemotherapy, compared with IV administration (LE2). The IP pathway has complications specific to the level of the intraperitoneal trocars, notably, occlusion in 7 to 25% of cases and infection in 5 to 19%. Tolerance is better experienced teams perform the IP chemotherapy (LE4). The data in the current literature do not enable a definitive conclusion about the efficacy of IP carboplatin or about the use of IP chemotherapy after interval surgery.

Experienced teams can offer adjuvant IP chemotherapy after primary surgery with tumor residue < 10 mm for ovarian, tubal, or primary peritoneal carcinomatosis. The recommended protocol is paclitaxel 135 mg/m² for 3 h or 24 h intravenous (IV) on D1, cisplatin 75 to 100 mg/m² IP on D8, every 3 weeks for 6 cycles. The risk-benefit ratio of the IP versus the IV pathway should be discussed with the woman in view of the higher complication rate with IP. If IP chemotherapy must be interrupted, treatment must be continued by the IV pathway (Grade B). No data exist to justify a recommendation about the use of bevacizumab after IP chemotherapy.

Intraperitoneal pathway with hyperthermia: HIPEC

As of today, one phase III randomized trial has assessed the role of HIPEC for ovarian cancer with interval surgery. It demonstrated that, with strict OVHIPEC protocol adherence, median relapse-free survival in the surgery-only arm was 10.7 months and in the surgery + HIPEC arm, 14.2 months (P=0.003), with median overall survival 33.9 and 45.7 months (P=0.02), respectively, with a median follow-up of 4.7 years. Toxicity rates were equivalent in both arms (25% and 27% P=0.74; the most frequent grade 3-4 toxicity reports concerned abdominal pain, infections, and ileus. Durations of hospitalization were similar (8 *vs* 10 days).

The time to resumption of chemotherapy was almost the same in both arms (30 vs 33 days); 90% of the women in the surgery-only arm and 94% in the surgery + HIPEC arm received the 3 planned cycles of postoperative chemotherapy (LE1). These results underline the potential role of HIPEC but require confirmation, at a minimum by prospective registries.

In initially nonresectable FIGO stage III ovarian, tubal, and primary peritoneal cancers, hyperthermic intraperitoneal chemotherapy (HIPEC) can be offered after interval surgery expected to be complete or optimal (tumor residue < 1 cm), performed after 3 cycles of intravenous (IV) chemotherapy (grade B). The protocol must include cisplatin 100 mg/m^2 distributed at 50 mg/m^2 at the beginning of the procedure, 25 mg/m^2 at 30 min, and 25 mg/m^2 at 60 min, for a total duration of 90 min at 40-41° C, combined with hyperhydratation and nephroprotection by IV sodium thiosulfate, by a bolus of 9 g/m^2 at the start of HIPEC, then 12 g/m^2 for 6 hours (grade B). At the publication of these guidelines, sodium thiosulfate is available only on temporary authorizations for a named patient (nominative ATU). No data exist to justify a recommendation about the use of bevacizumab after HIPEC.

Modalities and strategies for fertility preservation for young women with FIGO stage I ovarian cancer [6]

The possibility of fertility preservation in a woman with ovarian cancer concerns a small number of women: approximately 52 women per year in France. It must not be neglected, however, because 12.1% of the women with ovarian cancer are younger than 44 years, and their 5-year survival rate for stages IA and IB is 91.2%. The risk of recurrence for the contralateral ovary ranges from 6% to 13% for women of child-bearing age receiving conservative treatment of stage IA cancer.

Women of child-bearing age should be informed about the possibility of conservative management of their fertility in cases of stage IA epithelial ovarian cancer (Grade C). Conservative surgical management of the uterus and the contralateral adnexa after a unilateral adnexectomy for a low-grade serous, mucinous, or endometrioid stage IA ovarian cancer may be offered to a woman of child-bearing age, on condition that complete peritoneal and lymph node staging are negative, along with the findings of the uterine curettage for the endometrioid and mucinous histologic subtypes (Grade C). Women who wish for fertility preservation must be informed that there is a risk of recurrence ranging between 6 and 13% in the contralateral ovary.

For serous, mucinous, and endometrioid ovarian cancers that are either high-grade FIGO stage IA or low-grade stage IC1 or IC2, a bilateral adnexectomy may be proposed, with uterine preservation to envision a pregnancy later by oocyte donation (Grade C). No data exist to justify guidelines about uterine preservation in women with FIGO stage IB tumors. **For FIGO stage I clear-cell cancer, preservation of the uterus and contralateral adnexa can be discussed on a case-by-case basis in a multidisciplinary meeting for consultation on rare tumors. Surgery to preserve the uterus is not recommended for women with epithelial ovarian cancers at a FIGO stage ≥ IIa (beyond the pelvis) (Grade C).**

Despite conservative surgery, a unilateral adnexectomy is associated with diminution of the ovarian reserve and with a risk of premature ovarian insufficiency (LE4). Adjuvant platinum-based chemotherapy does not appear to affect either ovarian reserve or subsequent fertility, but the data are limited (LE4). **Before any decision is made about conservative surgery of stage I ovarian cancer, it is recommended that the risk-benefit balance of fertility-preserving surgery be assessed in a multidisciplinary consultation with the oncologist and a physician specializing in reproduction (grade C).**

Adequate evidence does not currently exist to justify a recommendation to freeze ovarian cortex tissue for future grafting for women with epithelial ovarian cancers, or to judge the oncologic safety (or lack thereof) of ovarian stimulation by pituitary gonadotropins after conservative surgery for a stage IA grade 1 epithelial ovarian tumor**.**

Management of older women with ovarian, tubal, or primary peritoneal cancer[7]

Characteristics of treatments for older women

Women aged 70 years or older account for a constantly increasing portion of the population, given its continuous aging. Those with ovarian cancer have a poorer prognosis than younger women: overall survival at 1 year for women aged ≥ 80 years is 36.9%, from 75-79 years 59.3%, from 70-74 years 68.4%, and from 65-69 years 73.5% (LE4). In the different cohorts published, age is correlated with a reduction in recurrence-free survival and in overall survival (LE4). The characteristics of ovarian cancer in woman ≥ 70 years are generally more unfavorable: tumors that are less differentiated, more frequent mixed tumors, and more frequent high-grade serous carcinomas (LE4). Advanced age currently leads to especially heterogeneous management of ovarian cancer. The lower rates of complete and optimal surgery and of complete chemotherapy indicate undertreatment of elderly women with ovarian cancer. The rate of radical surgery falls significantly with age, including in expert centers. In the SEER database, the rate of radical surgery considered optimal (residues less than 1 cm) was 73.7% for the women younger than 60 years, 29.5% between 60 and 79 years and 21.7% at and after 80 years (LE4). Nonetheless, in the case of complete surgery, the benefit for elderly women is the same as that for their younger counterparts. The rate of exclusively surgical management, with no chemotherapy, increases with age: in the SEER database it is 8.1% for the women aged 65 to 69 years, 10.3% for those aged 70 to 74, 15.1% for those 75 to 79, 21.6% for those 80-84, and 37.5% for those ≥ 85 (LE4). Similarly, age is

significantly associated with a delay in chemotherapy after surgery and a reduction in its dose intensity (LE4). For the women ≥ 75 years in the SEER database, the rate of standard surgery was 37.6%, of standard chemotherapy 51.2%, and of a standard medical/surgical strategy, 18.9% (LE4).

Toxicity of treatments in older women with ovarian cancer

Postoperative mortality is higher in elderly, than in younger, women with ovarian cancer: 30-day postoperative mortality in women ≥ 80 years is 5.4% versus 2.4% for the younger women (OR = 2.3, P=0.036) (LE4). This excess mortality may be linked to a higher rate of emergency surgery (25% vs 14%, P<0.0003) and a lower rate of surgery in expert centers (6.6% vs 18.6%, P=0.001); elderly women with ovarian cancer had surgery more often in general hospitals than in specialized cancer centers or university hospitals (LE4). The risk of postoperative morbidity is higher in women ≥ 75 years. Three variables play a role in the postoperative morbidity rate: age ≥ 75 years, an ASA score ≥ 3, and surgical complexity (LE4). Similarly, chemotherapy toxicity is higher in elderly women with ovarian cancer, which results in a reduction in dose intensity (LE4).

What adaptation of treatment can be offered to elderly women with ovarian cancer?

The centralization of surgery for ovarian cancer has been identified as a major factor in better management. A study by Bristow et al. shows that the only independent risk factor for postoperative mortality in multivariate analysis is the number of annual surgical procedures for ovarian cancer performed (more than 20 procedures by hospital per year, and more than 10 per surgeon per year) (LE4). Age ≥ 60 years was correlated only with prolonged hospitalization. Another German study estimated that a "surgeon effect" reduced perioperative mortality by 29% when the surgeon performed more than 12 ovarian cancer procedures annually (LE4).

Several studies have shown the effect of geriatric and nongeriatric covariables on postoperative morbidity and mortality: gait speed, dependence assessed by the IADL (Instrumental Activities of Daily Living) and the SPPB (Short Physical Performance Battery) scores are all significantly correlated with postoperative mortality (LE4). Several studies identified some categories of women who do not appear to benefit from primary cytoreduction surgery because of their high mortality in the first 60 days after surgery: mortality in the SEER database is 12.7% for the women older than 74 years with a FIGO stage IV tumor or with one or more comorbidities and a FIGO stage III tumor (LE4). In another retrospective study, the 60-day postoperative mortality for women older than 80 years who had surgery for advanced ovarian cancer (74% optimal) was 20%; moreover, among these women, 13% did not receive adjuvant chemotherapy, 22% were treated with a single chemotherapy agent, and 37% had only three chemotherapy cycles (LE4).

Older women with ovarian, tubal, or primary peritoneal cancer should receive cytoreduction surgery in high-volume centers (performing more than 20 procedures for advanced ovarian cancer annually (grade C). This surgery is recommended in elderly women (Grade B) provided that comorbidities and the likelihood of complete surgery allow it.

The risk-benefit ratio of surgery for ovarian, tubal, and primary peritoneal cancer should be assessed on a case-by-case for the populations at the highest risk of complications (LE4), defined by:

- **Age ≥ 80 years, especially with albuminemia ≤ 37 g/L**
- **Age ≥ 75 years and FIGO stage IV**
- **Age ≥ 75 years, FIGO stage III and ≥ 1 comorbidity.**

A geriatric oncology assessment is recommended before the decisions about management of elderly women with ovarian, tubal, or primary peritoneal cancer (grade C).

Geriatric vulnerability can be assessed by various scores. Some of these scores are correlated with the performance of complete chemotherapy. The Geriatric Vulnerability Score (GVS) score has been correlated with the performance of 6 cycles of carboplatin alone (LE2) and the IADL score was predictive of the performance of at least 4 chemotherapy cycles in 70-year-old women (LE2). Authors have proposed chemotherapy protocols adapted for these vulnerable women, such as:

- carboplatin as a single agent
- carboplatin AUC2 and paclitaxel 60 mg/m² 3 weeks/4.
- carboplatin AUC 4-5 and paclitaxel 135 mg/m²
- carboplatin AUC5 D1; paclitaxel 60 mg/m² D1, D8, D15; D1=D28.

Elderly but not especially frail women with ovarian, tubal, or primary peritoneal cancers should receive intravenous chemotherapy identical to that for younger women (i.e., two agents, platinum-based) (grade B).

Neoadjuvant chemotherapy was most cost-effective in elderly women at high risk of complications (i.e., age ≥ 75 years and FIGO stage IV or age ≥ 75 years and stage III and at least 1 comorbidity) in the SEER database (LE4); in the EORTC study, it was associated with a lower complication rate and a higher rate of optimal surgery for elderly women (LE4).

In advanced ovarian, tubal, and primary peritoneal cancers, neoadjuvant chemotherapy diminishes the complexity of the surgical procedure and the perioperative morbidity and mortality of the interval surgery (LE1). In these advanced stage, starting with chemotherapy is a good alternative for those 70 years or older with comorbidities or with extensive peritoneal carcinomatosis requiring complex initial surgery (LE4).

Post-treatment follow-up of ovarian, tubal, and primary peritoneal cancers and the role of hormone therapy[8] (Figure 4)

Follow-up of high-grade serous epithelial cancers

Data specific to the follow-up of women treated for high-grade non-serous ovarian, tubal, or primary peritoneal cancers are sparse. The following guidelines concern women treated for a high-grade serous ovarian, tubal, or primary peritoneal carcinoma. In women in complete remission after surgery and chemotherapy for an advanced cancer of this type, 75 to 80% have a recurrence in the 2 years after the end of treatment (LE3). These recurrences are most often abdominal. Nonetheless the route of chemotherapy administration as well as the type of therapy chosen change the sites of recurrence. They may increase the rate of extra-abdominal and lymph node sites (LE4). The sensitivity of clinical examination to screen for recurrence of an epithelial ovarian tumor after initial treatment ranges from 7% to 78% for the diagnosis of a recurrence of ovarian, tubal, or primary peritoneal cancer (LE4). Personalized follow-up with a telephone interview asking about symptoms of recurrence, delegated to trained healthcare workers, at 3, 6, 12, 18 and 24 months after the end of treatment is equivalent to clinical monitoring (LE2).

After the conclusion of treatment of epithelial ovarian, tubal, or primary peritoneal cancer, an assessment of symptoms is recommended at 3, 6, 12, 18, and 24 months, and then yearly (Grade B)

In ovarian, tubal, and primary peritoneal cancers, CA125 at more than twice the upper limit of normal precedes clinical signs by 4.8 months (LE1). After treatment of these cancers, women are most satisfied when they receive the CA125 results for the monitoring consultation (LE4).

Elevation of the HE4 serum assay is more sensitive and earlier than that of CA125 for screening for the recurrence of these cancers (LE3). **If paraclinical monitoring is indicated for a woman after treatment of an epithelial ovarian, tubal, or primary peritoneal cancer, HE4 serum assays can be recommended (grade B). The CNAM-TS does not reimburse the HE4 serum assay. In the absence of possible HE4 monitoring, CA125 serum assays can also be proposed (grade B).**

After treatment of epithelial ovarian, tubal, or primary peritoneal cancer, any finding of elevated serum HE4 or CA125 levels should be followed by an imaging examination (grade B).

Peritoneal cytology is not only invasive but also has poor sensitivity for the detection of a recurrence of ovarian cancer (LE4). **Unless ascites is present**, **routine peritoneal cytology is not recommended for the diagnosis of a recurrence of ovarian, tubal, or primary peritoneal cancer (grade C).**

After treatment of these cancers, the strategy of monitoring by CT thorax/abdomen/pelvis scan for the first two years is less effective and three times more expensive per diagnosis of recurrence than the CA125 assay alone (LE4). **After treatment of ovarian, tubal, or primary peritoneal cancer, routine monitoring by CT scan of the thorax/abdomen/pelvis is not recommended (Grade C).**

If epithelial ovarian, tubal, or primary peritoneal cancer recurs in asymptomatic women, treatment based solely on an elevated serum CA125 level does not increase overall survival, and it impairs their quality of life (LE1).

Early diagnosis of recurrence of ovarian, tubal, or primary peritoneal cancer that is accessible to complete surgical treatment (i.e. no macroscopic tumor residue) improves survival (LE3). Surgical management of a recurrence of epithelial ovarian, tubal, and primary peritoneal cancer is beneficial for overall survival only if surgical resection is macroscopically complete

(CC0) (LE1). In cases of platinum-sensitive recurrence (i.e., recurrence > 6 months after the last line of chemotherapy) of ovarian, tubal, or primary peritoneal cancer, the AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) score (based on a primary complete surgery (CC0), good overall condition (ECOG 0), and a limited recurrence (ascites <500 cc)) allows the selection of women eligible for complete surgical resection (LE3). After treatment of ovarian cancer, regular monitoring by other examinations for early screening of a recurrence, that is, before the onset of symptoms, is beneficial only if the second cytoreduction surgery is complete (with no macroscopic residue: CC0).

For the follow-up of ovarian, tubal, or primary peritoneal cancer, women with complete initial surgery (no macroscopic tumor residue, CC0) and in good overall condition (ECOG 0) should be monitored by serum assays (HE4 or CA125) starting 6 months after the end of chemotherapy, then every 6 months, if the serum markers were initially high (Grade C) (5).

Role of hormone therapy after the treatment of ovarian, tubal, or primary peritoneal cancer.

Women younger than 45 years whose mucinous ovarian adenocarcinoma has been treated benefit from HRT in terms of cardiovascular and overall survival (LE3). **Women younger than 45 years of age who have undergone nonconservative treatment for high-grade serous ovarian, tubal, or primary peritoneal cancer should be offered hormone replacement treatment (HRT) for menopause (grade C)**

HRT does not increase the risks of recurrence or mortality in women older than 45 years (LE2). **HRT can be offered for menopausal symptoms to women with a history of high-grade serous ovarian, tubal, or primary peritoneal cancer, after an individual evaluation of her risk-benefit ratio (Grade B).**

Women younger than 45 years whose mucinous ovarian adenocarcinoma has been treated benefit from HRT in terms of cardiovascular survival and overall survival (LE4). **HRT should be offered to women younger than 45 years after non-conservative treatment of mucinous ovarian cancer (grade C). HRT can be offered to a woman older than 45 years with a history of mucinous ovarian cancer for menopause symptoms after an individual evaluation of her risk-benefit ratio.**

Low-grade serous or endometrioid adenocarcinomas are hormone-sensitive histologic types, for which HRT use is a potential risk (LE4). **Nonetheless, no specific data for these histologic types justify a guideline about HRT use in women with a history of low-grade serous or endometrioid ovarian cancer.**

In all cases, the prescription of HRT and its dosage and administration must follow the same guidelines as those for the general population (see, HAS guidelines 2014).

Declaration of interests

The authors' potential relationships of interests are listed at:

https://www.transparence.sante.gouv.fr.

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https://www.e-cancer.fr/Professionnels-de-sante/Recommandations-et-outils-d-aide-a-la-pratique).

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Figure 1: **Management of a FIGO stage III ovarian, tubal, or primary peritoneal cancer**

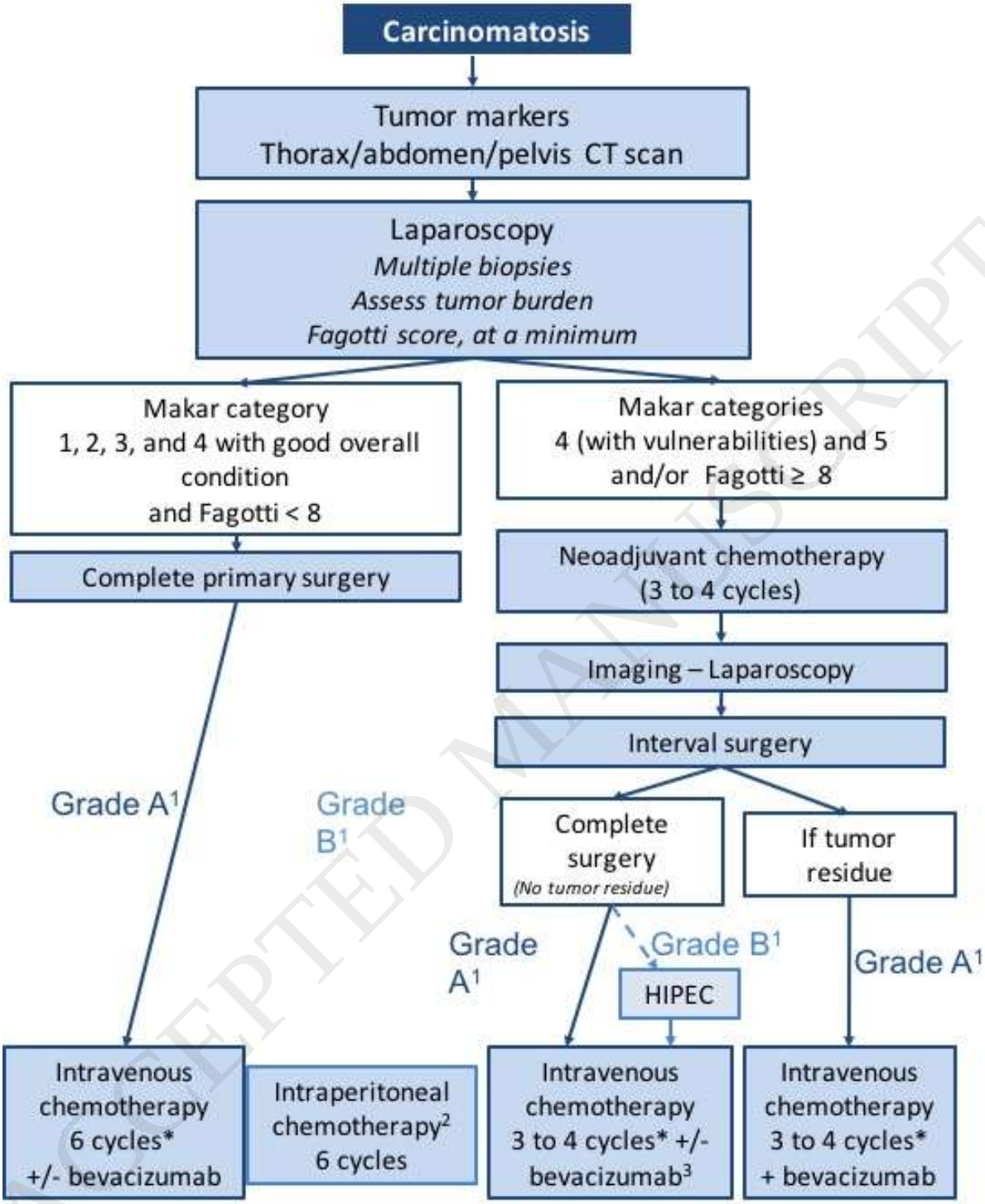
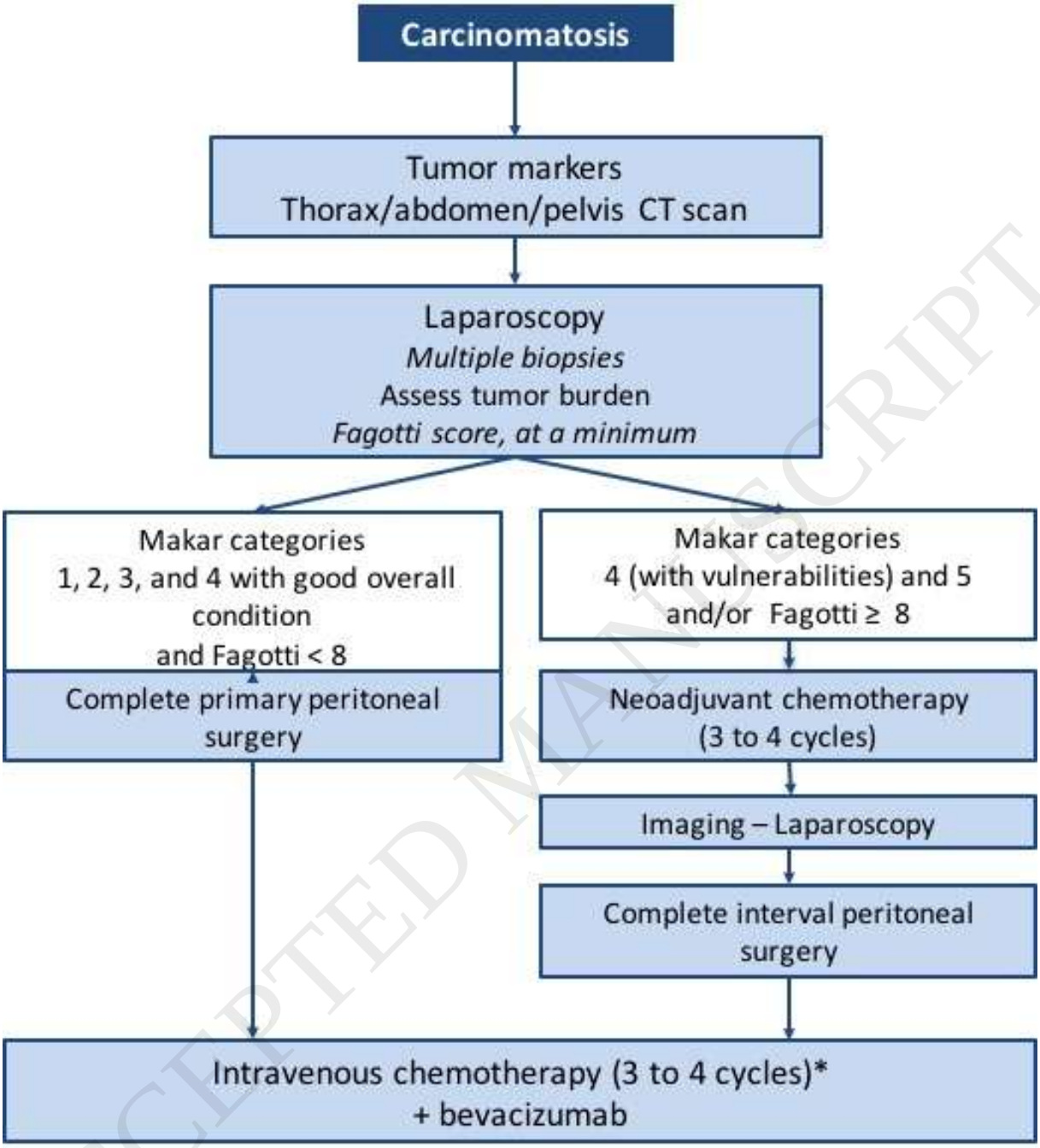


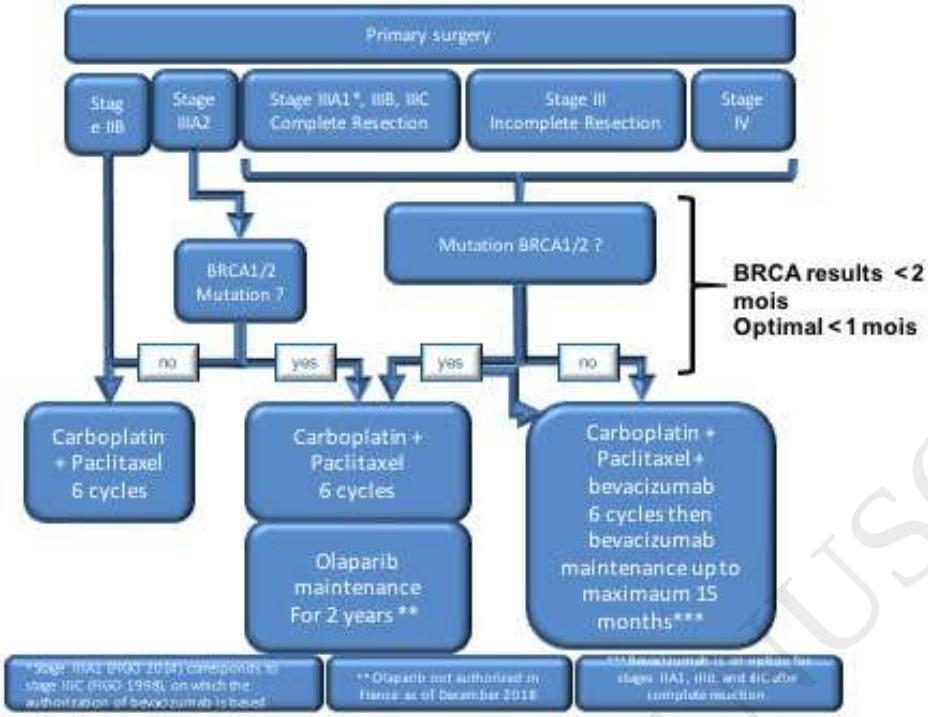
Figure 2: **Management of a FIGO stage IV ovarian, tubal, or primary peritoneal cancer**



Makar categories	
Category 1	**Tumor located in pelvis** **Little or no ascites** **No need for gastrointestinal resection**
Category 2	**Tumor located in pelvis** **Little or no ascites** **Gastrointestinal resection is envisioned**
Category 3	**A large portion of the tumor is localized in the supramesocolic space** **Little or no ascites** **No need for gastrointestinal resection**
Category 4	**A large portion of the tumor is localized in the supramesocolic space** **Little or no ascites** **Gastrointestinal resection is envisioned**
Category 5	**A large portion of the tumor is localized in the supramesocolic space** **Abundant ascites or miliairy patterns on the mesentery.** **Need for several gastrointestinal resections**

Figure 3: **Management strategy in the era of first-line Olaparib**

A: in cases of primary surgery



B: in cases of primary chemotherapy

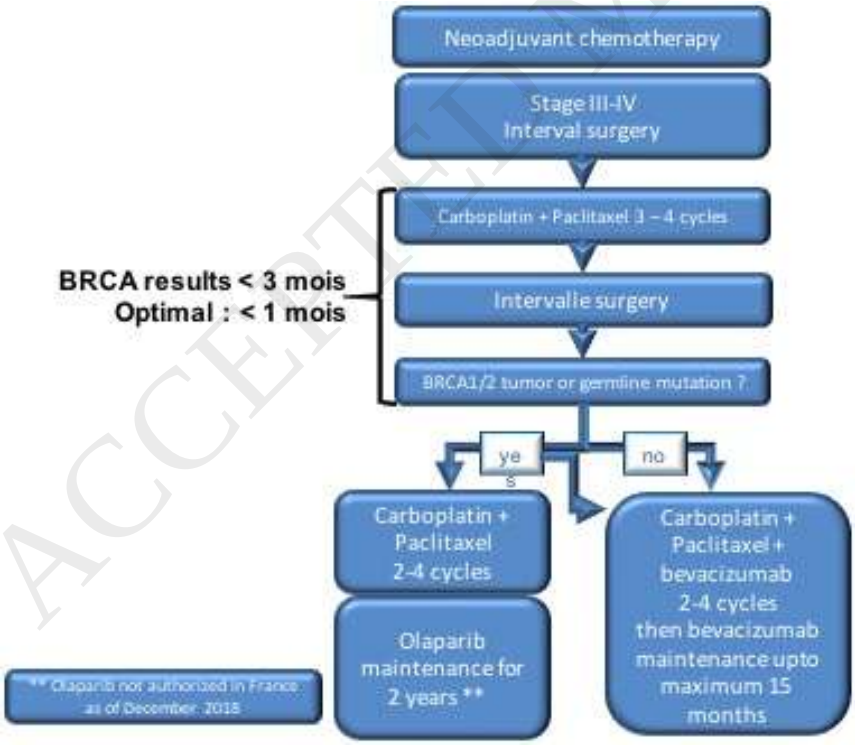


Figure 4: **Post-treatment follow-up of women with ovarian, tubal, or primary peritoneal cancer**