



Optimization of surgical treatment of advanced ovarian cancer: a Spanish expert perspective

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Abstract

Background Optimal upfront treatment of patients with advanced ovarian cancer is complex and requires the adequate function of a multidisciplinary team. Specific standard of quality of care needs to be taken into consideration.

Methods A literature search in PubMed was performed using the following criteria: (“ovarian neoplasms”[MeSH Terms] OR (“ovarian”[All Fields] AND “neoplasms”[All Fields]) OR “ovarian neoplasms”[All Fields] OR (“ovarian”[All Fields] AND “cancer”[All Fields]) OR “ovarian cancer”[All Fields]) “[Date - Publication]: “2018/01/14”[Date - Publication]).

Results This article describes how to optimize the surgical management of advanced ovarian cancer, to achieve the best results in terms of survival and quality of life. For this purpose, this document will cover aspects related to pre-, intra- and postoperative care of newly diagnosed advanced ovarian cancer patients.

Conclusion Optimizing upfront treatment of patients with advanced ovarian cancer is complex and requires a structured quality management program including the wise judgment of a multidisciplinary team. Surgeries performed by gynecologic oncologists with formal training in cytoreductive techniques at referral centers are crucial factors to obtain better clinical and oncological outcomes. However, other factors such as the patient’s clinical status, the hospital infrastructure and equipment, as well as the tumor biology of each individual patient should also be taken into account before deciding on an initial therapeutic strategy for advanced-stage ovarian cancer to offer patients the best quality of care.

Keywords Ovarian cancer · Peritoneal carcinomatosis · Quality of care · Advanced stage · Optimization of treatment

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Introduction

Ovarian cancer is known as the leading cause of death from gynecological cancer in western countries. Among women, it is the seventh most frequent, according to different registers, and the fifth main cause of death after breast, lung, colorectal and pancreatic cancers [1].

Since it frequently presents with non-specific symptoms, this neoplasm is often detected at an advanced stage [2], where the combination of surgery and chemotherapy is the cornerstone of upfront treatment [3]. Surgery, however, can be performed either before adjuvant chemotherapy [called primary debulking surgery (PDS)], or after neoadjuvant chemotherapy (NACT), called interval debulking surgery (IDS). The ultimate goal of surgical treatment is, in any case, to achieve a complete macroscopic tumor resection with the least number of complications and a better quality of life. The decision whether women should undergo PDS or NACT-IDS, is sometimes difficult and, should be made by a multidisciplinary tumor board [3–5]. To decide the most

appropriate therapeutic, factors such as the patient's characteristics, the tumor extension, as well as the binomial center/surgeon—volume/expertise are among the most important factors to be considered. A large body of evidence has demonstrated that an appropriate surgical treatment, as part of a multidisciplinary management, can have a positive impact on the survival of patients in advanced stages of the disease [4, 5]. Several international scientific societies have developed guidelines and recommendations for the surgical treatment of advanced ovarian cancer [3, 6, 7], although its implementation is not always homogenous amongst countries or, even centers within the same geographical region [8].

Focusing on Spain, and considering the importance of a proper implementation of such recommendations, the authors of this document have reviewed the management of this disease taking into account not only the recommendations of specialized organizations but also the characteristics of the country. Specifically, this paper intends to describe how to optimize the surgical management of advanced ovarian cancer, to achieve the best results in terms of survival and quality of life. For this purpose, this article will cover aspects related to pre-, intra- and postoperative care of newly diagnosed advanced ovarian cancer patients. Level of evidence will be classified according to the Agency for the

Healthcare Research and Quality (<https://www.guidelines.gov>) (Table 1).

1. Clinical and radiological evaluation of the patients to decide upfront treatment

Several clinical and radiological factors need to be considered before deciding upfront treatment in women with advanced stage epithelial ovarian cancer (Table 2).

Patient characteristics

Surgical cytoreduction can be associated with morbidity and mortality in over 30% and 2–4% of patients, respectively [9, 10]. Therefore, determining if a patient is suitable for either PDS or NACT followed by IDS is crucial to avoid preventable complications. Thus, some studies tried to correlate pre-operative clinical predictors of an unacceptable risk of post-operative morbidity after primary cytoreduction [11, 12]. One of them [11] showed the combination of advanced age (> 75 years) with either FIGO stage III or IV and coincident comorbidity as a reliable predictor of a poor outcome. Other study [12] identified a subgroup of patients either aged over 75 and serum albumin < 3 g/dl or who had a score ≥ 4 in the American Society of Anesthesiology (ASA) classification

Table 1 Level of evidence

Level	Definition
IA	Evidence from meta-analysis of randomized controlled trials
IB	Evidence from at least one randomized controlled trial
IIA	Evidence from at least one controlled study without randomization
IIB	Evidence from at least one other type of quasi-experimental study
III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both

Table 2 Associated factors to decide upfront treatment in women with advanced ovarian cancer

Factor	Characteristic
Non-modifiables	
Disease	Extension and localization of the disease Tumor biology
Patient	Age Comorbidities and poor performance status
Modifiables	
Surgeon	Adequate skills and training
Institutional infrastructure	Ovarian cancer multidisciplinary surgical team Availability of prolonged operative time Appropriate surgical armamentarium ICU: well-trained personnel and well equipped

ICU intensive care unit

and high initial tumor burden (stage IV or high-volume stage IIIC) with unacceptably high rates of morbidity and peri-operative mortality after upfront debulking surgery. This subgroup could account for about 10% of advanced ovarian cancer cases. Taking together these results, we recommended that in high-risk women with an Eastern Cooperative Oncology Group (ECOG) score > 1, ASA score 4–5, and aged > 75 years, NACT should be considered as the upfront treatment (III).

Evaluation of tumor extension

Several studies have shown significantly better oncological outcomes in terms of progression-free survival (PFS) and overall survival (OS) when a complete tumor resection (R0) is achieved [13, 14] (IA). A tumor debulking not reaching true R0, but leaving residual tumor of less than 1 cm in the maximum diameter of the biggest nodule, in the past known as “optimal tumor debulking”, still provides a modest survival benefit for the patient compared to suboptimal resection (III). However, neoadjuvant approach will be preferred when an excessive surgical effort is needed and just “optimal” debulking can be expected. Having this in mind, it is important to carry out an evaluation of the tumor extension before and during the surgical intervention, to properly assess the tumor resectability and decide the most appropriate treatment in each patient (IV).

Preoperative evaluation of tumor extension

It is necessary to rule out a peritoneal carcinomatosis from a non-ovarian origin, as well as unresectable tumor dissemination. For this purpose, imaging techniques, tumor markers as well as ultrasound or laparoscopy guided biopsies can be used [3]. Pre-operative tumor markers can provide information that helps to determine if a peritoneal carcinomatosis has an ovarian or extra-ovarian origin [15] (IIA). In this case, if the CA-125 (UI/mL)/CEA (ng/mL) ratio is < 25, mammography and endoscopy (gastroscopy and colonoscopy) with biopsy if applicable are mandatory to exclude primary breast, gastric, or colon cancer [15] (IB).

Different guidelines reviewed imaging techniques useful in the preoperative setting [3, 6, 7]. CT scan of the chest, abdomen and pelvis is the most commonly used technique as part of the initial evaluation. It has the advantage of its reduced cost and its widespread availability, although it has drawbacks such as high radiation, limited resolution (< 5 mm) or insufficient tissue characterization. It is applicable in the diagnosis of stage IVB disease and the need for extended procedure (III). Although predictive models of surgical results have been proposed [16, 17], there are no external validated studies with a good predictive performance for residual disease [18]. Other imaging techniques, however,

have revealed interesting advances in the diagnostic field. Recent publications have advocated the fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) as a potential tool for improved staging of this condition, mainly in women with suspected stage IV in the CT scan [19] (III). Diffusion-weighted magnetic resonance imaging (DW-MRI) is another tool under investigation used to predict resectability in women with advanced-stage ovarian cancer. The evidence for using the DW-MRI in improving detection of the true extent of the disease seems promising [20–22]. A recent study in 32 patients with ovarian cancer found that the main benefit of using DW-MRI was the detection of disease in the serosa and mesentery of the bowel, with 91% accuracy for detecting peritoneal disease compared with 75% when using a CT scan and 71% when using FDG-PET/CT [22] (III). This encouraging data from a small number of studies should, however, be prospectively evaluated and validated with a larger sample of patients to reach stronger conclusions in this matter.

Finally, video-assisted thoracoscopic surgery (VATS) is a useful tool for patients with pleural effusion; as it can help to detect pleural disease and determine ideal candidates for surgical cytoreduction [23] (III).

Recommendations

Considering the available evidences, the preoperative evaluation of a patient should include a CT scan of the thorax, abdomen and pelvis and determination of tumor markers: CA125, CEA and CA 19.9. In suspected stage IV disease, the use of PET-CT is recommended. If symptoms of gastrointestinal cancer are present or if the CA 125: CEA ratio is less than 25, mammography, gastroscopy and colonoscopy should be requested. In patients with preoperative criteria for primary cytoreduction and pleural effusion, a previous evaluation by VATS is recommended.

The presence of at least one of the radiological findings included in Table 3 confirms the non-resectability and NACT would be recommended after having obtained an adequate tissue sample by means of a thick needle transcutaneous ultrasound-guided or laparoscopic biopsy [3]. Finally, NACT should be preferred in high-risk women, defined as: ECOG > 1, ASA = 4 and age > 75 years.

Intraoperative evaluation

Laparoscopy has proven to be a reliable method for exploring peritoneal carcinomatosis in selected cases of advanced-stage ovarian cancer. For this purpose, specific scores have been previously validated [24, 25]. It can identify patients who qualify for complete PDS and reduce not

Table 3 Criteria to indicate neoadjuvant chemotherapy

Characteristic
Radiological
Massive celiac trunk involvement
Infiltration of the pancreas head or body
Multiple intra-hepatic metastases
Upper mediastinal adenopathies
Pulmonary metastases
Bone/brain metastasis
Surgical
Diffuse involvement/deep infiltration of the stomach/duodenum (limited excision is possible)
Head or body involvement of the pancreas (the tail of the pancreas can be resected)
Deep infiltration of the root of the mesentery
Diffuse serous carcinoma of the small intestine that would require a large resection causing a short bowel syndrome (remaining intestine < 1.5 m)
Infiltration of the celiac trunk, hepatic arteries, left gastric artery

only the number of futile laparotomies in patients found to have unresectable disease, but also adverse complications and an unwanted delay in the initiation of chemotherapy, contributing to a better quality of life, without increasing medical health care costs [24–26] (IIB).

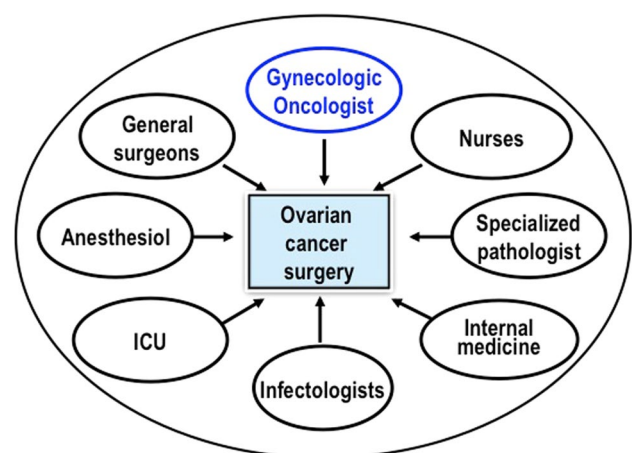
Once a laparotomy is decided, and before starting the tumor resection and to avoid reaching the “point of no return”, a systematic method of assessment that rules out any criterion of non-resectability needs to be implemented. Thus, according to the European Society of Gynaecological Oncology (ESGO) [3], NACT would be indicated when one of the criteria included in Table 3 is found (IV).

Methodology of tumor resection

A xipho-pubic midline incision will allow a full exposure of the abdomino-pelvic organs to establish the true extension of the disease. In this sense, before starting tumor removal, a stepwise systematic evaluation of the abdominal cavity is performed to avoid the so-called “point of no return” which may result in unnecessary patient morbidity [27]. This standardized strategy has been described previously [27], and includes two points of stop-or-go decisions. Initially, the falciform ligament is resected, and the peritoneum of the paracolic gutters and the omentum are dissected from the transverse colon. Then, the lesser sac is opened allowing the evaluation of the pancreas, the celiac trunk, the liver, and the hepatoduodenal ligament with portal vein, hepatic artery and main biliary duct. If a non-resectable tumor is present, surgery is stopped. If not, the second point of decision is the evaluation of the mesentery root and the small bowel surface by dissecting the adhesions and separating the small bowel from the colon and the greater omentum [27].

Center and surgery team characteristics

It is important to have a surgical team (Fig. 1) with formal training in cytoreductive techniques such as: modified posterior exenteration with pelvic peritonectomy with colorectal resection and anastomosis, pelvic and abdominal peritonectomy, retroperitoneal lymph node dissection, liver mobilization with diaphragmatic stripping and resection, splenectomy, as well as hepatic and gastric surgery in selected cases, among others. Moreover, a survival benefit has been clearly demonstrated for patients treated by experienced gynecologic oncologists in high-volume tertiary centers [4, 5] (III).

**Fig. 1** Surgical multidisciplinary team to treat women with advanced ovarian cancer

Minimum requirements of the center and surgical team to perform a surgical debulking

To optimize the surgical treatment of advanced ovarian cancer, Institutions must meet minimum requirements, including some of the stated in the Quality Assurance in Advanced (III–IV) Ovarian Cancer Surgery of the European Society of Gynaecological Oncology ESGO document [3]:

- The minimum number of cases submitted to primary debulking by center and year should be at least 20. There is a direct association between OS and hospital surgical case volume [28]. The combination of high-volume hospitals (≥ 20 cases/year) and high-volume physicians (≥ 10 cases/year) is an independent predictor of improved disease-specific survival [29] (III).
- The minimum rate of patients scheduled for PDS should be at least 60% [3]. Complete primary tumor debulking should be achieved in at least 70% of these patients (IV).
- Pathology diagnosis is mandatory before any cytoreductive procedure. Therefore, if ultrasound- or laparoscopic-guided biopsy was not performed before surgery, an intraoperative histology diagnosis needs to be done (IV).
- A properly trained multidisciplinary surgical team should be available, composed of gynecologic oncologist [4], general surgeons, thoracic surgeons, vascular surgeons, anesthesiologists and nurses [4, 30] (Fig. 1) (IV).

- Availability of intensive care unit or similar (units of intermediate or resuscitation care) with all the necessary personnel and equipment (transfusion, interventional radiology, etc.) (IV)
- All cases need to be discussed in a multidisciplinary tumor board that should include gynecological oncologists, medical oncologists, as well as radiologists and pathologists specialized in gynecological cancer, among others (Fig. 2).
- It is highly advisable that centers should have experience in participating in national or international clinical trials [31, 32] (IV).
- Adjuvant chemotherapy after IDS need to be based on 3 cycles of carboplatin and paclitaxel intravenously. Maintenance treatment with Bevacizumab should be recommended in cases of stage IIIB to IV disease at diagnosis (I).

Surgical report

All patients undergoing surgical cytoreduction must have a detailed surgical report including surgical findings, intraoperative complications with estimated blood loss and transfusion, as well as a detailed description of residual disease if applicable. Thus, complete cytoreduction (R0) is defined as the absence of macroscopic residual disease after surgery; while incomplete cytoreduction means macroscopic residual disease left at the end of the procedure measured, in

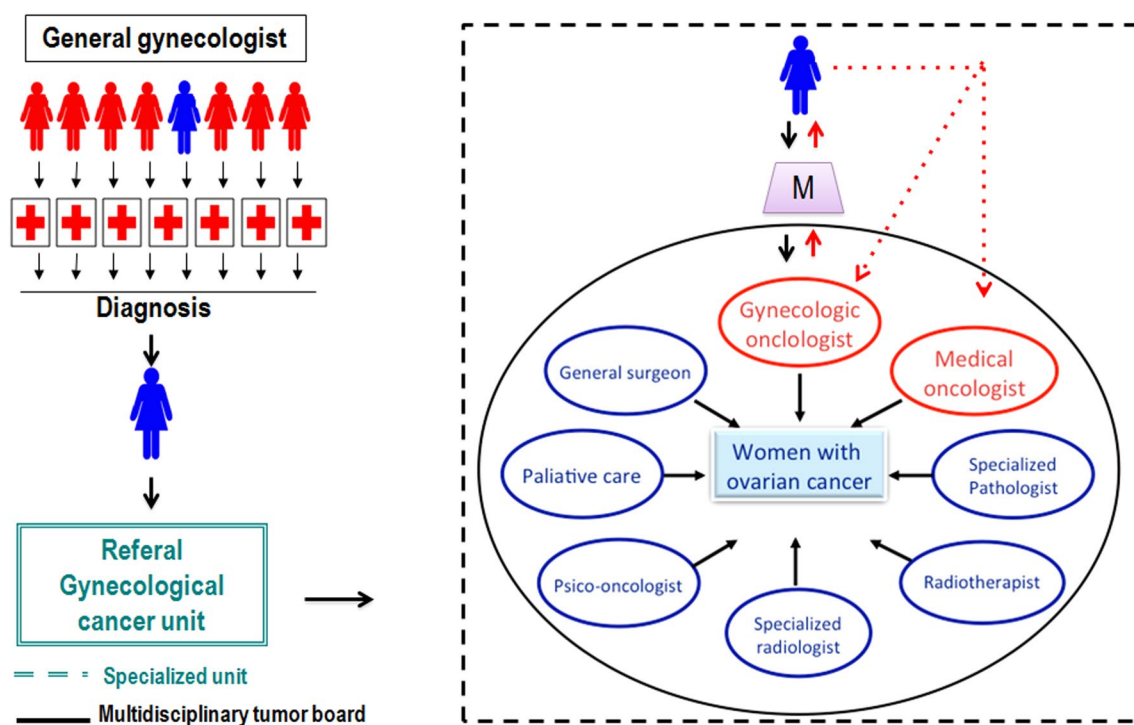


Fig. 2 Multidisciplinary approach of women with advanced ovarian cancer

millimeters, as the maximum diameter of the biggest metastases. Residual disease must be described as the maximum size of the biggest metastasis in each organ and anatomical structure of the abdominal–pelvic cavity. It is recommended to detail the abdominal cavity divided into nine quadrants, and then, the peritoneal and retroperitoneal disease following the ESGO surgical report [33].

Prospective tumor registry

A prospective collection of data from each patient is recommended as a quality indicator of surgery for advanced ovarian cancer [3]. This not only can help to reduce the sub-registry in the number of patients and the incidence of complications, but also can serve as an internal quality control to confirm whether the results in each institution are or not in line with the standard of care. A structured database can be found in this document as a supplementary file.

Time intervals

The treatment process of patients with advanced ovarian cancer has several time intervals which have been proposed as an important quality indicator [7] (IV). Thus, recording the following time intervals is recommended:

- The time between the first visit and the start of treatment should be less than 30 days: a longer time interval might indicate either an inappropriate waiting list for imaging or operating room, or an ineffective communication among the specialists of the multidisciplinary team.
- The time between surgery and the initiation of adjuvant chemotherapy should be less than 50 days (4–6 weeks): a longer time interval might be due to either a higher incidence of postoperative complications with prolonged hospitalization time, or an ineffective communication between gynecologic oncologists and medical oncologists.
- The time between the last course of NACT and IDS should be less than 40 days: although a longer time interval could be explained by a chemotherapy-related neutropenia in some cases, other factors such as an inappropriate waiting list for imaging or operating room, or an ineffective communication among specialists of multidisciplinary team may also be the causes of this delay.

Centralization

Centralization of gynecologic oncology services can improve outcomes, since the access to specialized care and multidisciplinary teams allows a greater optimization of shared knowledge [4, 5]. Against the trend of being treated in centers close to their homes, which may not

be adequately prepared for that purpose, the centralization of ovarian cancer treatment is already a fact that has shown promising results in terms of OS, PFS and rates of complete PDS, as have been observed in various countries [30, 34–38] (III). In addition, treatment centralization has demonstrated to be cost effective [39, 40] (III).

2. Pre-, intra- and postoperative care: ERAS protocol (enhanced recovery after surgery) and PROFAST project (postoperative recovery in advanced ovarian cancer, fast-track protocol)

In the perioperative care, the implementation of the ERAS program [41, 42] has been proposed to reduce hospitalization without increasing the rate of complications or readmissions (IB). Even though guidelines for women with gynecological cancer have been recently published [41, 42], the available information of the ERAS protocols in advanced ovarian cancer is still scarce [43]. For this reason, a Spanish research team launched the PROFAST, a randomized clinical trial designed to compare fast-track protocol versus classical management to improve the results of complex surgical procedures, based on preoperative optimization, improvement of the surgical process and postoperative standardization which involves all related parties in the overall result. In the implementation of the program, a multidisciplinary teamwork integrates specialists in gynecology and obstetrics, anesthesia and resuscitation, nutritional support and nursing, with the prominent figure of the “physician in charge”, responsible for monitoring patients from preoperative to postoperative, coordinating the teams, expediting the complementary tests, and advising and accompanying their follow-up.

The study was recently finished, pending for the final analysis and publication. The study compared conventional management with that following the ERAS protocol. The primary objective was the reduction in the median length of hospitalization, and secondary objectives included the incidence of perioperative complications and readmissions rates and related costs. An intermediate analysis in 29 patients proved that ERAS is a safe measure that can significantly reduce hospitalization time and patient-related costs [43]. While waiting for definitive results, some measures should be recommended. Before surgery, all patients should receive a thrombo-embolic prophylaxis scheme, which should be maintained for up to 30 days after surgery. In addition, compression stockings should be placed during surgery, which should be maintained until walking normally. Bladder catheter should be maintained during the first 24–48 h, while abdominal drains are not recommended routinely in gynecologic/oncology surgery including for patients undergoing lymphadenectomy or bowel surgery. [42].

3. Postoperative radiological evaluation

Even in patients who underwent optimal primary cytoreduction, residual disease detected in an early post-surgical CT scan is associated with significant worse outcomes [44–46] (III). Different studies have demonstrated discrepancies between surgeons' operative assessments of residual disease and what is identified on postoperative CT scan [44, 47]. Heitz and colleagues [48] analyzed the surgical results of residual tumor taking into account the surgeon's assessment, the radiological observation and the joint assessment (surgeon and radiological). According to this study, 29% of the R0 considered by the surgeon had residual disease detected by radiological assessment, out of which 23% were R0 according to the joint assessment based on the physician's and the radiological assessment. One possible explanation is that the discordance is related to the time elapsed between surgery and the pre-chemotherapy CT scan, which leads to the idea of a tumor regrowth. From these data, it is agreed that post-surgical CT scan should be performed within 4 weeks after surgery to determine the disease status just before the initiation of adjuvant chemotherapy (III). Performing a post-surgical CT scan might help clinicians to identify a high-risk group of patients, thus, to offer patients the most beneficial adjuvant systemic regimens.

Conclusion

Optimizing upfront treatment of patients with advanced ovarian cancer is complex and requires a structured quality management program including the wise judgment of a multidisciplinary team. Surgeries performed by gynecologic oncologists with formal training in cytoreductive techniques at referral centers are crucial factors to obtain better clinical and oncological outcomes. However, other factors such as the patient's clinical status, the hospital infrastructure and equipment, as well as the tumor biology of each individual patient should also be taken into account before deciding on an initial therapeutic strategy for advanced-stage ovarian cancer to offer patients the best quality of care.

Compliance with ethical standards

Conflict of interest The authors declare that there are no conflicts of interest.

Ethical approval This paper involves no human participants or animals.

Informed consent No informed consent was necessary.

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