

A multidisciplinary approach remains the best strategy to improve and strengthen the management of ovarian cancer (Review)

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Abstract. Ovarian cancer represents one of the most aggressive female tumors worldwide. Over the decades, the therapeutic options for the treatment of ovarian cancer have been improved significantly through the advancement of surgical techniques as well as the availability of novel effective drugs able to extend the life expectancy of patients. However, due to its clinical, biological and molecular complexity, ovarian cancer is still considered one of the most difficult tumors to manage. In this context, several studies have highlighted how a multidisciplinary approach to this pathology improves the prognosis and survival of patients with ovarian cancer. On these bases, the aim of the present review is to present recent advantages in the diagnosis, staging and treatment of ovarian cancer highlighting the benefits of a patient-centered care approach and on the importance of a multidisciplinary team for the management of ovarian cancer.

Contents

1. Introduction
2. Risk and protective factors for ovarian cancer
3. Ovarian cancer symptoms, diagnosis and staging
4. Ovarian cancer surgical treatments
5. Ovarian cancer pharmacological treatments
6. Ovarian cancer management: From linear to multidisciplinary patient-centered care approach
7. Conclusions

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1. Introduction

Ovarian cancer represents the eighth most frequently diagnosed tumor and the seventh most lethal cancer in women leading to almost 185,000 deaths annually worldwide (1). Despite the improvement of screening strategies and the advancement of anticancer surgical and pharmacological treatments, ovarian cancer is still considered one of the most commonly diagnosed and aggressive urogenital female tumors, with a 5-year relative survival rate of 93% and 5-year cause-specific survival rates of 82, 71, 66 and 43% for endometrioid, mucinous, clear cell carcinoma and serous ovary carcinoma, respectively (2,3). The majority of ovarian cancer cases are epithelial, which accounts for 85-90% of all diagnosed ovarian tumors. This type of tumor usually affects women aged between 55 and 65 years old (4); contrariwise, germ cell ovarian cancer accounts for ~5% of all diagnosed tumors with an average age of onset of 20 years old (4).

2. Risk and protective factors for ovarian cancer

Several risk factors have been recognized for ovarian cancer. It was demonstrated that the risk of developing ovarian cancer increases significantly with age and in particular after menopause, probably due to hormonal imbalance (5). In this regard, it was observed that post-menopause hormone therapies, based on the administration of estrogens alone or in combination with progesterone, significantly increased the risk of developing ovarian cancer (relative risk, 1.53; confidence interval, 1.40-1.66) (6). Strictly associated with menopause and hormone imbalance risk factors, weight gain and obesity have also been associated with an increased risk of ovarian cancer (7). Of note, obesity represents one of the main important modifiable risk factors for different tumors. In patients suffering from ovarian cancer, it was also demonstrated that obesity negatively affects the prognosis of patients leading to therapeutic failure and worse overall survival time (7). As widely described for other tumors such as breast and prostate cancer (8,9), besides these physiological variations of hormone levels, occupational and environmental risk factors as well as endocrine disruptors and other chemical substances have been associated with the development of ovarian cancer (10-13).

Other well-recognized risk factors are gene mutations and hereditary syndromes that represent the most notable predisposing causes for the development of ovarian cancer (14). A growing body of literature has demonstrated that individuals harboring germline mutations affecting *BRCA1* and *BRCA2* genes have an increased risk of breast and ovarian cancer (15-18). Overall, ~25% of ovarian cancer tumors are positive for *BRCA1* or *BRCA2* mutations (19). As explained in the following sections, the evaluation of such mutations is important for the choice of anticancer pharmacological treatments (20,21). Other hereditary syndromes related to ovarian cancer include hereditary non-polyposis colon cancer syndrome, Peutz-Jeghers syndrome and adenine DNA glycosylase (*MUTYH*)-associated polyposis syndrome affecting several mismatch repair genes (including *MSH2*, *MSH6* and *MLH1*), *STK11* and *MUTYH* (22-24), respectively.

Other controversial and not yet ascertained risk factors are represented by tobacco smoking, androgens, diet and talc powder. For all these risk factors, observational, case-control, retro- and prospective studies have generated conflicting results thus limiting the awareness about the causative effects of these factors (25). It was demonstrated that tobacco smoking is associated with the development of mucinous ovarian cancer, but it does not increase susceptibility to other types of ovarian tumors (26,27). Unconvincing data have been obtained for the association between powder use in the genital area and the risk of ovarian cancer. In this context, some studies highlighted a slightly increased risk of ovarian cancer in women using talc powder in the genital area (28-30). However, a recent observational study on 250,000 women observed for 11 years has demonstrated that the use of powder does not significantly increase the incidence of ovarian cancer (28-30).

Besides these risk factors, numerous studies have also identified some protective factors able to reduce the incidence of ovarian cancer. Among these factors, pregnancy and breastfeeding are both associated with a reduced risk of developing this tumor. In particular, a significantly reduced risk for ovarian cancer has been observed in women carrying full-term pregnancies before 26 years old (31). In addition, the increased number of full-term pregnancies, together with the time of breastfeeding, is associated with a lower risk of ovarian cancer (31). Finally, the use of oral contraceptives for birth control seems to play an important protective role against ovarian cancer with higher protective effects the longer the treatments are administered (32). In this context, other birth control strategies, including intrauterine devices and tubal ligation, have also been associated with a reduced risk of ovarian cancer (33).

3. Ovarian cancer symptoms, diagnosis and staging

During the early stages, ovarian cancer is not associated with clinical symptoms, therefore the diagnosis of this tumor is often delayed. Mild ovarian cancer symptoms may be often confused with other benign pathologies, including gastrointestinal disorders, urogenital infections and benign ovarian lesions (including ovarian cysts, teratomas and fibromas) (34). However, unlike benign diseases, ovarian cancer symptoms are persistent and worsen over time (34). Generally, moderate or severe symptoms are associated with the spread of the disease in adjacent anatomical regions. Among these symptoms, the

most frequently observed are pelvic distension, abdominal and pelvic pain and urgent or frequent urination (34). Other symptoms may include pain during sex, back pain, constipation, altered menstruation, fatigue and weight loss (35). The correct self-assessment of these symptoms by the patients may improve the timing of diagnosis allowing the gynecological surgeon and oncologist to intervene promptly by increasing the patient response to treatments (36).

Regarding ovarian cancer staging, two main staging systems are used worldwide for ovarian cancer, which are the International Federation of Gynecology and Obstetrics (FIGO 2018) system and the American Joint Committee on Cancer (AJCC 8th edition) system both based on the Tumor-Node-Metastasis (TNM) parameters (37,38). Table I shows both FIGO and AJCC staging in terms of the pathological characteristics of tumors: Tumor dimension (T), lymph node involvement (N) and presence of distant metastasis (M) (Table I).

At present, several diagnostic strategies are available to make a correct and timely diagnosis of ovarian cancer when recurrent symptoms are observed. The first step for a correct diagnosis of ovarian cancer is based on the collection of patient's medical history and on a correct physical exam performed by a gynecologist with expertise in gynecological oncology (39,40). The aim of these procedures is the collection of all relevant data about the presence of pre-existing conditions or risk factors that could increase the risk of developing ovarian cancer. In particular, as previously mentioned, the presence of a family member with ovarian cancer or the presence of hereditary syndromes and genetic mutations may lead the clinician to make a diagnosis of suspected ovarian cancer in the presence of specific abdominal symptoms. In the same manner, the physical examination of the abdomen and pelvis is of fundamental importance to observe pelvic mass, ascites or abdominal distension suggestive of ovarian cancer (41). The physical examination could include a rectovaginal exam performed with empty bladder to evaluate the presence of abdominal or pelvic masses. However, although important and easy to perform, physical investigations have a low sensitivity and a low specificity, especially in overweight patients or in presence of small tumors, as abdominal or pelvic distention may be caused by other benign pathologies (42,43).

After the physical examination, patients with suspected ovarian cancer are subjected to various laboratory and imaging tests useful to detect the presence of the tumor, its severity and extent (41). Among the most used laboratory tests both for preventive and diagnostic purposes is the evaluation of blood tumor markers, namely cancer antigen (CA) 125 and human epididymis protein 4 (HE4), alongside the normal hematological parameters (red and white blood cells count, platelets and hemoglobin). In particular, CA 125 is considered the main predictive serum biomarker for ovarian cancer as it is elevated in 50% of patients with early-stage ovarian cancer and in over 80% of all patients with this tumor (44).

Regarding HE4, this marker is evaluated together with CA 125 as it appears to be elevated in a significant fraction of patients with ovarian cancer negative for CA 125 (45,46). Therefore, the use of HE4 is of fundamental importance in screening strategies to intercept all those ovarian carcinomas negative for other tumor biomarkers. The evaluation of these

Table I. Ovarian cancer staging and pathological features.

FIGO stage	AJCC stage	TNM characteristics	Description of tumor
I	I	T1 N0 M0	The tumor is limited to the inner part of one ovary (T1) and there is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
IA	IA	T1a N0 M0	The tumor is limited to the inner part of one ovary without the involvement of the outer surface (T1a) and there is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
IB	IB	T1b N0 M0	The tumor is limited to the inner part of both ovaries and there are no cancer cells in ascites or in the abdominal and pelvic cavities (T1b) and there is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
IC	IC	T1c N0 M0	The tumor is in one or both ovaries and the tumor capsule is broken during surgery (IC1); the tumor capsule is broken before surgery or the tumor is on the outer surface of the ovary(ies) (IC2); tumor cells are present in the ascitic fluid or in the washing liquid obtained from the abdomen and pelvis (IC3). There is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
II	II	T2 N0 M0	The tumor is in one or both ovaries and has spread to other adjacent pelvic organs or to the peritoneum (T2). There is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
IIA	IIA	T2a N0 M0	The tumor has invaded or grown into the uterus or the fallopian tubes (T2a). It has not invaded lymph nodes (N0) or distant sites (M0).
IIB	IIB	T2b N0 M0	The tumor has invaded the outer and inner surface of pelvic organs including, uterus, fallopian tubes, bladder and sigmoid colon (T2b). There is no involvement of neighboring lymph nodes (N0). There are no metastases (M0).
IIIA1	IIIA1	T1-2 N1 M0	The tumor has invaded ovaries, the peritoneum and other pelvic organs (T1-2). The tumor has spread to the retroperitoneal (pelvic and/or para-aortic) lymph nodes (N1) without forming distant metastasis (M0).
IIIA2	IIIA2	T3a N0-1 M0	The tumor affects one or both ovaries and has invaded the peritoneal cavity and organs outside the pelvis; however, it is not visible during surgery (T3a). The tumor is present or not on the retroperitoneal lymph nodes (N0-1). There are no metastases (M0).
IIIB	IIIB	T3b N0-1 M0	The tumor affects one or both ovaries and has invaded the peritoneal cavity and organs outside the pelvis. During surgery the tumor is visible but is <2 cm (T3b). The tumor is present or not on the retroperitoneal lymph nodes (N0-1). There are no metastases (M0).
IIIC	IIIC	T3c N0-1 M0	The tumor affects one or both ovaries and has invaded the peritoneal cavity and organs outside the pelvis. During surgery the tumor is visible and is >2 cm (T3c). The tumor is present or not on retroperitoneal lymph nodes (N0-1). There are no metastases (M0).
IVA	IVA	T1-4 N0-3 M1a	The tumor is present or not on retroperitoneal lymph nodes (N0-3). Tumor cells have invaded the bloodstream leading to malignant pleural effusion. However, cancer cells have not invaded the spleen, intestine, liver neither lymph nodes outside the abdominal cavity (M1a).
IVB	IVB	T1-4 N0-3 M1b	The tumor is present or not on retroperitoneal lymph nodes (N0-3). The tumor has spread to the liver or spleen, to extra abdominal lymph nodes and/or to other extra peritoneal organs or tissues, such as the lungs and bones (M1b).

FIGO, International Federation of Gynecology and Obstetrics; AJCC, American Joint Committee on Cancer; T, tumor; N, node; M, metastasis.

two markers, together with the evaluation of six symptoms predicting the presence of ovarian cancer (pelvic pain, abdominal pain, urinary urgency/frequency, increased abdominal size, bloating and difficulty eating/feeling full) showed a significant

improvement in diagnostic accuracy from 83.8 to 98.5% (46). Other tumor biomarkers, such as serum α -fetoprotein and quantitative β -human chorionic gonadotropin (β -hCG), are less used and are used for the diagnosis of germ cell ovarian cancer (47).

After these preliminary assessments, women who present symptoms and biomarkers predictive for ovarian cancer undergo imaging tests, including ultrasound, computed tomography (CT) scan, magnetic resonance imaging (MRI) scan and positron emission tomography (PET) scan (48).

Generally, the first imaging test to be performed is a transvaginal ultrasonography. Several studies have shown how transvaginal ultrasonography is able to distinguish benign lesions from tumors with an excellent rate of accuracy (pooled sensitivity and specificity of 92 and 88%, respectively) thus allowing the clinician to evaluate the structure and vascularization of the ovarian parenchyma, the presence of cysts or masses and any ascitic effusions (49-52).

Both CT, MRI and PET are not widely used for the diagnosis of ovarian cancer but for the evaluation of the extent of the tumor and the possible presence of distant metastases. Specifically, CT scan can be used to perform biopsies of suspected metastases in a procedure called CT-guided needle biopsy (53,54). Meanwhile, PET and MRI are mostly used to evaluate the spread of diseases in neighboring lymph node stations and in distant organs, such as the medulla and brain, through the use of radiotracers or contrast agents (for example gadolinium) (55).

Finally, after tumor diagnosis, it is essential to perform molecular tests and genetic counseling to determine the presence of relevant mutations in tumor specimens useful for prognostic and therapeutic purposes (56-60). As aforementioned, the most frequent mutations observed in ovarian cancer are those affecting the *BRCA1* and *BRCA2* genes as well as other mutations within *STK11*, *MSH2*, *MSH6*, *MLH1*, *PMS6* and *MUTYH* (56,57). Besides molecular evaluations, previous studies have demonstrated that immunohistochemical investigations are fundamental both for diagnostic and prognostic purposes for different abdominal tumors, including that of ovaries (58-60).

4. Ovarian cancer surgical treatments

Over the decades, the therapeutic options for the treatment of advanced ovarian cancer have been improved significantly through the development of more precise and less invasive surgical techniques as well as the availability of novel effective drugs able to extend the life expectancy of patients, especially for metastatic ovarian cancer (61,62). Different studies have demonstrated that in the last 20-35 years there was a significant improvement in the survival rates of patients with ovarian cancer; however, some reports have shown that the advancements of the anticancer treatment have not ameliorated the long-term survival and the cure rate of ovarian cancer (63-65). In particular, a recent study showed that both incidence and 5-year survival rates have improved in the last 30 years. Indeed, the 5-year survival rate increased from 39.3% in the 80s to 45.4% observed in 2012; similarly, the survival time was also improved passing from 34 months observed in 1983 to 52 months observed in 2012, highlighting how the latest treatments have improved the survival time of patients with ovarian cancer (62).

At present, surgery represents the gold standard for the treatment of ovarian cancer. Ovariectomy and adnexectomy are used for both staging, debulking and treatment of early

ovarian cancer, thus being curative in such tumors limited to the ovaries (66,67). Ovarian cancer surgery can be performed by open surgery with midline incision or by minimally invasive surgery (MIS). MIS, performed by laparoscopic surgery, is generally performed for newly diagnosed tumors limited to one or both ovaries and to the pelvic cavity without metastatic dissemination (68). However, MIS is generally used only in structured centers equipped with experienced gynecological surgeons (68). In the case of advanced tumors (stages II, III and IV), open surgery is always used in order to perform extended cytoreduction (debulking) aimed at eliminating all cancer lesions with a thickness of >1 cm (69,70). Briefly, in both MIS and open surgery, the first steps consist in the collection of ascitic fluid and in the execution of peritoneal lavage used for immunocytochemistry evaluations useful to establish the presence of tumor cells in the peritoneal cavity (71). Subsequently, surgeons check the entire peritoneal cavity to assess the absence of any suspicious extra ovary lesions. In the case of no suspicious masses, biopsies from different parts of the peritoneal cavity (paracolic gutters, pelvis and diaphragm) should be obtained to exclude cancer dissemination (71). After these preliminary steps, surgeons can remove the primary tumor through bilateral salpingo-oophorectomy, hysterectomy, omentectomy and lymph node dissection (both pelvic and paraaortic nodes). To avoid post-surgery cancer dissemination, the tumor has to be removed encapsulated. In the case of young patients (20-45 years old) with monolateral stage IA and IC ovarian cancer that would maintain fertility, the surgeon could opt for unilateral ovariectomy and adnexectomy, thus preserving the contralateral ovary and uterus (71).

Overall, the main objectives of ovarian cancer surgery are the removal of the primary tumor and the maximal debulking of pelvic and peritoneal masses. In presence of advanced tumors, the clinicians can opt for neoadjuvant chemotherapy (NAC) followed by debulking surgery. If the NAC plus surgery approach is chosen, tumor biopsies are collected before chemotherapy to assess the molecular features of the tumors (through immunohistochemistry or molecular tests) thus allowing administration of appropriate anticancer drugs (72). In those patients undergoing NAC and debulking surgery, a whole-abdominal radiation treatment should be applied if residual disease is still observed after a second-look laparotomy; however, this approach needs to be carefully evaluated to avoid bowel toxicity (73,74).

5. Ovarian cancer pharmacological treatments

Besides surgery, anticancer pharmacological treatments are the best therapeutic option for the management of ovarian cancer. Over the years, several chemotherapeutic agents have been used for the treatment of ovarian cancer. Thanks to the evolution of anticancer pharmacological treatments, it is now possible to effectively treat the different histological and molecular subtypes of ovarian cancer, contributing to the improvement of the quality of life and life expectancy of these patients (2,75).

Ovarian cancer chemotherapy. After surgery, chemotherapy can be optionally administered in patients with low-grade tumors (stage IA or IB), while the first-line treatment for

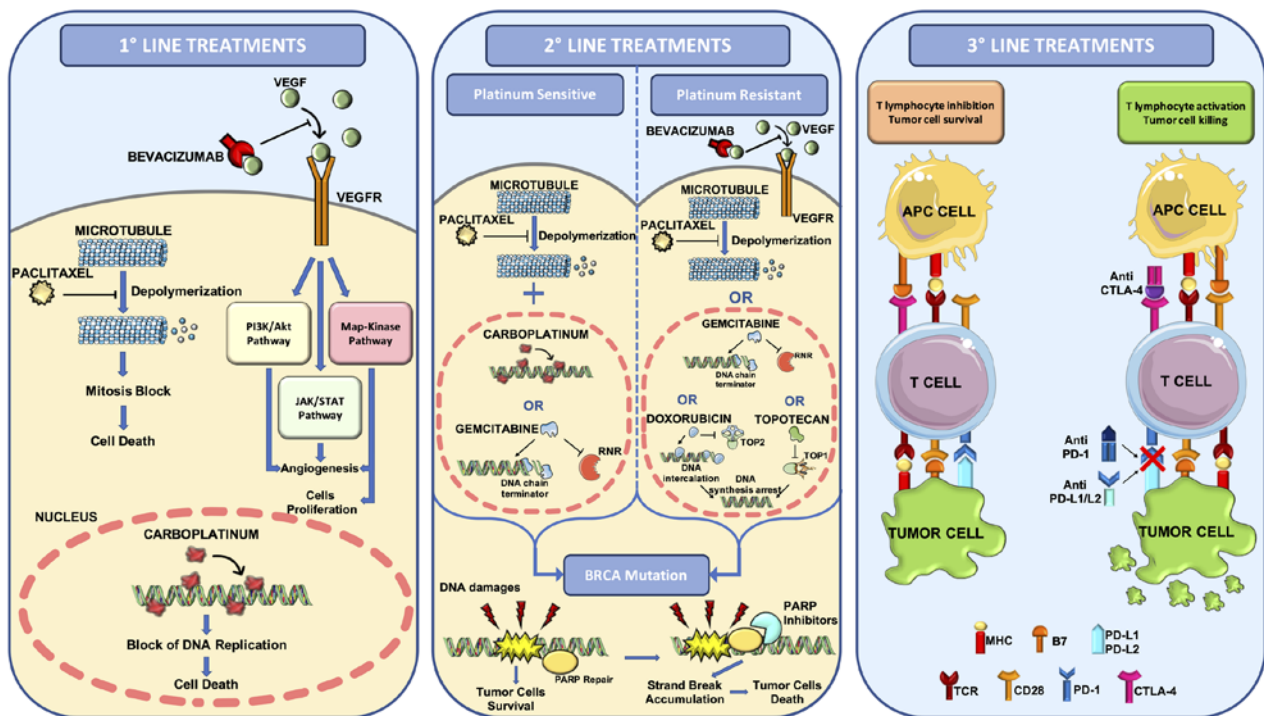


Figure 1. Overview of the pharmacological treatments for the management of ovarian cancer. First-line treatments based on the administration of platinum/taxane regimen plus anti-VEGF mAb bevacizumab. Second-line treatments based on the administration of paclitaxel plus carboplatin or gemcitabine in the case of platinum sensitive tumors or bevacizumab plus paclitaxel, gemcitabine, doxorubicin or topotecan in the case of platinum resistant tumors. For BRCA mutated ovarian cancer, PARP inhibitors can be used for first-line or second-line treatments. Third-line treatments consist in the administration of the first-line and second-line drugs plus immune checkpoint inhibitors. MHC, major histocompatibility complex; RNR, ribonucleotide reductase; TCR, T-cell receptor; TOP1, type 1 topoisomerase; TOP2, type 2 topoisomerase.

ovarian cancer with more advanced stages is based on the administration of platinum-based chemotherapy. Indeed, the first-line regimen consists of the administration of intravenous platinum/taxane every three weeks for six cycles (76). The same compounds are usually administered also in patients with stage III/IV ovarian cancer undergoing NAC protocols for three cycles followed by debulking surgery plus six additional cycles of platinum/taxane (76,77).

Thus, for >20 years, the first-line treatment for ovarian cancer has been based on the administration of carboplatin (used instead of cisplatin because it is less toxic and equally effective) and paclitaxel administered every three weeks in a six-cycle schedule. The preferred route of administration is the intravenous systemic one, although several studies have also proposed intraperitoneal administration, which has not given improved results in terms of improvement of progression-free survival (PFS) (78,79). Similarly, several trials have investigated the beneficial effects of paclitaxel weekly administration compared with the conventional 3-week schedule; however, this therapeutic option is not widely used as conflicting data have been generated in three different clinical studies (JGOG 3016, GOG 262 and MITO 7) (80-82) (Fig. 1).

More recently, the introduction of anticancer targeted therapies has improved the efficacy of first-line treatments for patients with ovarian cancer who can benefit from treatments based on the administration of carboplatin, paclitaxel and bevacizumab (83,84). Bevacizumab is a monoclonal antibody against the pro-angiogenic factor VEGF-A that has prolonged the PFS and OS time of patients, especially of those patients with advanced tumors (83). In particular, it was

demonstrated that the prolonged administration of 15 mg/kg 3-weekly of bevacizumab up to 15 months together with standard carboplatin/paclitaxel chemotherapy is associated with a prolonged PFS time; however, due to the expensive cost of treatments and the related gastrointestinal and vascular toxicities, novel protocols based on a low dose of bevacizumab for 30 months is still under evaluation and it is awaiting approval as a therapeutic standard for this tumor (76,85,86) (Fig. 1).

After the first-line chemo- and targeted therapy, the patients can completely respond to treatments or develop a relapse. In the case of a partial or complete response, patients can undergo maintenance chemotherapy with the same drugs used in the first-line treatment to improve PFS (87,88).

In the case of tumor recurrence, patients are treated with a second-line treatment that is different depending on whether the tumor is resistant or sensitive to platinum compounds (89,90). Tumor recurrence can be observed through biochemical (increased expression of CA125 and other biomarkers) or clinical (imaging techniques) examinations (91) after which patients are assigned to standard treatment for recurrent disease or to experimental clinical trials using novel drugs or different drug combinations (92,93).

For patients with ovarian cancer developing a platinum-resistant disease, the second-line treatments consist of single non-platinum-based therapies using different agents, including docetaxel, paclitaxel, topotecan and gemcitabine, with a therapeutic efficacy ranging from 19 to 27% of the treated patients (71). Similar percentages of response have been obtained treating ovarian cancer relapse with bevacizumab (therapeutic response observed in ~20% of patients) (94). More

recently, in absence of severe adverse events, combined therapies with bevacizumab plus one agent among doxorubicin, topotecan and paclitaxel have shown a significant improvement of OS in patients with platinum-resistant recurrent disease (95) (Fig. 1).

In the case of platinum-sensitive recurrence, there are different therapeutic options based on the administration of several drug combinations including carboplatin plus paclitaxel (or docetaxel with weakly or 3-weeks administration), carboplatin plus gemcitabine and bevacizumab, carboplatin plus liposomal doxorubicin and cisplatin plus gemcitabine (96). In addition, patients with ovarian cancer who are platinum-sensitive are often eligible for novel clinical trials assessing the efficacy of novel agents or combined therapies. Among these trials, recent evidence has demonstrated the therapeutic efficacy of poly (ADP-ribose) polymerase (PARP) inhibitors in both platinum-sensitive and -resistant ovarian cancer harboring *BRCA1* or *BRCA2* mutations. In particular, patients with platinum-sensitivity with complete or partial response to at least two lines of treatments can benefit from olaparib single-agent maintenance therapy improving their PFS from 5.5 to 19.1 months (97). Similarly, olaparib single-therapy can be used also in patients with platinum-resistant *BRCA* mutated ovarian cancer who failed three or more lines of chemotherapy (98) (Fig. 1).

Novel first-line and second-line treatments with PARP inhibitors. As aforementioned, some patients with ovarian cancer can benefit from novel first-line and second-line treatments based on the administration of selective inhibitors of PARP. PARP proteins are a family of 17 enzymes involved in numerous cellular processes, and in particular PARP-1 and PARP-2 play a crucial role in DNA damage repair (99,100).

The development of PARP inhibitors has represented the turning point in the treatment of ovarian cancer, both in the first-line and in case of tumor recurrence, highlighting the importance of studying the molecular profile of tumors to improve the selection of patients eligible for these innovative treatments. Indeed, these drugs, including olaparib, rucaparib, niraparib and talazoparib, find application in tumors with germline mutations affecting *BRCA1* and *BRCA2* or in advanced ovarian cancer refractory to three or more lines of treatment (101).

Recent evidence has demonstrated that patients with ovarian cancer harboring *BRCA1* or *BRCA2* mutations could benefit from a first-line or a second-line treatment with olaparib, which reduces the risk of progression or death by 70% compared with placebo in patients who achieved a complete or partial response to the first platinum-based line. In particular, 60.4% of patients treated with olaparib showed a progression-free survival of 36 months compared with 26.9% of women in the placebo arm (102). These data are further corroborated by the results presented during the European Society for Medical Oncology 2019 and European Society of Gynecological Oncology 2019 conferences regarding two clinical trials using niraparib and olaparib plus bevacizumab (PRIMA and PAOLA 1 trials, respectively) as first-line treatments (103-105). The therapeutic efficacy of PARP inhibitors has been demonstrated mainly in patients with *BRCA1/2*-positive ovarian cancer who develop platinum-sensitive relapse. In these patients,

maintenance treatment with olaparib significantly improves overall survival time (SOLO2 and E19 trials) (106-108).

The therapeutic efficacy of PARP inhibitors has been demonstrated also in patients without *BRCA* mutations. The NOVA trial based on the administration of niraparib in patients with ovarian cancer demonstrated that all patients can benefit from this treatment, although improved results were obtained for patients with homologous recombination deficiency (HRD) compared with patients without mutations affecting the HR system (105).

In December 2016, the Food and Drug Administration launched an accelerated approval process for the use of rucaparib as a single agent for the treatment of patients with ovarian cancer at an advanced stage and with a *BRCA* mutation (germline or somatic) who had been previously treated with two or more lines of chemotherapy (109). In addition, rucaparib is also used as second-line maintenance therapy in patients with platinum-sensitivity with or without *BRCA1/2* mutations as reported in the Ariel 3 Trial (100).

Novel therapeutic approaches for the treatment of ovarian cancer. Besides these conventional therapies, novel approaches for the treatment of advanced or metastatic ovarian cancer are being developed and studied. Modest results have been obtained in several clinical trials assessing the efficacy of immune checkpoint inhibitors (ICIs) already used for the treatment of several advanced and metastatic tumors (110-112). In particular, the administration of anti-PD-1 (nivolumab or pembrolizumab) or anti-PD-L1 (atezolizumab) in advanced ovarian cancer has a good response only in 10-15% of patients (113-115). Similar results have been obtained with the single administration of the anti-CTLA-4 ICI ipilimumab, which is effective only in a small fraction of patients who has previously received an anticancer therapeutic vaccine (116). Overall, single-agent ICI administration shows limited efficacy in advanced ovarian cancer, therefore novel protocols assessing the concomitant administration of ipilimumab and nivolumab have been proposed (117). Such studies have demonstrated an improved and longer response rate in patients treated with two ICIs compared with patients treated with nivolumab alone, thus replacing the single-agent ICI regimens (117). A recent review of the literature collected all the completed and ongoing clinical trials using different combinations of ICIs, selective inhibitors or chemotherapeutic agents showing encouraging and conflicting results based on the clinical and molecular features of the patients enrolled (118) (Fig. 1).

Other investigated therapeutic options for advanced ovarian cancers are represented by therapeutic vaccines, adoptive cellular therapy, T cell transfer and chimeric antigen receptor T-cell therapy; however, further clinical studies are needed to assess the efficacy and safety of these further treatments (119).

Finally, several treatments are available as maintenance or palliative therapy for disseminated and metastatic ovarian cancer. Similarly, VEGFR inhibitors, including pazopanib, nintedanib and cediranib, are often used for the treatment of recurrent platinum-resistant ovarian cancer (100). In line with these treatments, VEGF inhibitors such as aflibercept are used in case of malignant ascites showing an improvement of time to next paracentesis but not of OS (120).

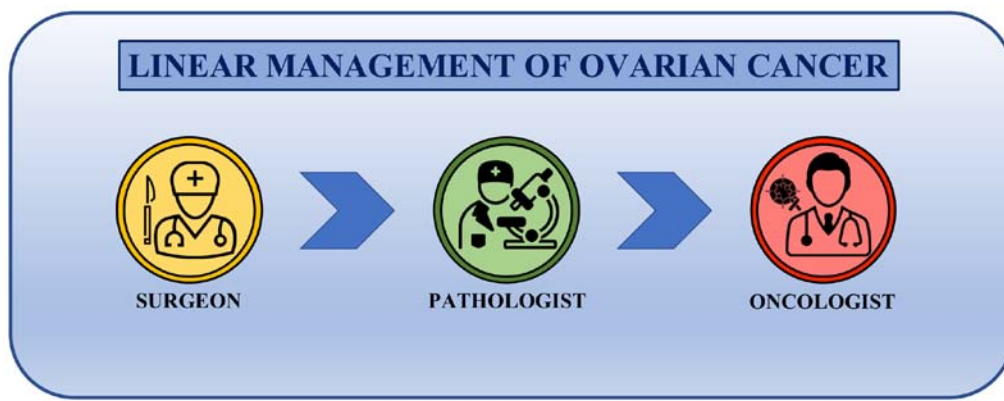


Figure 2. Linear management of ovarian cancer. Main players of ovarian cancer management are the surgeon who removes the tumor, the pathologist who assesses the tumor histotype and the medical oncologist who selects and starts the pharmacological treatments. There is no interaction between these three main specialists in the management of the patient with ovarian cancer.

Despite the availability of all these surgical and pharmacological treatments, the prognosis of patients with ovarian cancer is often poor. To improve the quality of life and life expectancy of these patients, it is necessary to opt for therapeutic choices that take into account the patient's comorbidities, the adverse effects of therapies and the patient's age. Therefore, the management of the patient with ovarian cancer is extremely complex and requires the convergence of different professional skills to ensure high standards of care.

5th ovarian cancer consensus conference of Tokyo. The 5th ovarian cancer consensus conferences held in Tokyo, Japan, in 2015 (121), established that platinum-based regimens are doubtless the standard of care in the first-line treatment of ovarian cancer. However, for the first time, besides highlighting the importance of the platinum-free interval (PFI) as a stratification factor or to define patient eligibility for clinical trials, great importance was given to treatment-free interval useful to improve selection of successive chemotherapy regimens for patients with recurrent disease.

The main decision criterion for second-line treatments is the definition of platinum-sensitivity or resistance. Sensitivity to platinum-based treatments must be assessed after a period of at least 6 months; however, there is a linear relationship between PFI and platinum sensitivity, therefore the evaluation of PFI is of primary importance in future therapeutic choices and must be considered as a continuous variable in the decision-making process leading to the new therapy. Furthermore, PFI will be used as a parameter for the eligibility of patients in novel clinical trials, therefore the evaluation of PFI cannot be limited to a fixed 6-month window but should be evaluated periodically.

Overall, platinum-based therapy remains the most effective therapy in the management of epithelial ovarian cancer, and primary PFI provides relevant prognostic and predictive information. A significant fraction of patients receives different lines of platinum-based therapy, thus evaluating the interval of time after the most recent line can provide prognostic information about acquired resistance and clonal evolution of the tumor due to intervening non-platinum treatments. Over the years different non-platinum agents have been integrated into conventional therapy; this led to the need of new prognostic

and predictive markers to make the best treatment decisions for the management of recurrence (121).

6. Ovarian cancer management: From linear to multidisciplinary patient-centered care approach

As aforementioned, the symptomatology, diagnosis, staging and treatments of ovarian cancer are extremely complex and require the convergence of various specialists able to provide the gynecological oncologist with a clinical picture as detailed as possible, useful for designing the appropriate therapeutic protocol for each patient. Therefore, at present, the approach to the patient with advanced ovarian cancer should be multidisciplinary. This includes a team of experts who follow the patient step by step during the diagnosis, surgical therapy, pharmacological therapy, rehabilitation and follow-up, creating a collaborative network where the patient is at the center and can benefit of high standards of care in the perspective of personalized medicine and patient-centered care (122).

In this context, over the decades, great advancements in the management of patients with ovarian cancer have occurred, passing from a linear approach to care, where the patient is treated by individual specialists without communication between them, to a multidisciplinary and integrated approach where different specialists share clinical information and chose the best therapeutic options together (123,124).

Until 30 years ago, the therapeutic approach followed a linear trend where the main stakeholders of cancer management were the surgeon, who operated the surgical resection of the tumor, the pathologist, who made the histological diagnosis, and the medical oncologist, who dealt with the therapeutic schedule to be administered (Fig. 2). Although other professionals participated in the clinical management of ovarian cancer (including gynecologists, radiologists and laboratory technicians), they did not actively take part in the clinical-therapeutic decisions. In addition, the interactions between the patient, the surgeon, the pathologist and the oncologist rarely occurred and each of these three professional figures made therapeutic choices without first discussing with colleagues (125,126).

Since the late 80s, some studies have highlighted the benefits of the multidisciplinary management of patients with

cancer in terms of diagnosis, therapeutic response, survival and quality of life, suggesting that an integrated approach to cancer could lead to improved outcomes for patients (127-129). With regards ovarian cancer, it was demonstrated that a collegial discussion can lead all the specialists to evaluate the diagnostic-therapeutic areas beyond those of their own competence, leading to an increase of awareness in the number of potential treatments available and expected pitfalls thus improving the effectiveness of treatments (130,131).

The development of multidisciplinary teams has changed the previous linear approach to patients into a circular one. Indeed, the main players of ovarian cancer management are now working together, comparing their clinical findings each other in a patient-centered care approach where the patients are in the middle of a circular decision-making pathway receiving information and therapeutic options shared between the gynecological surgeon, the pathologist and the medical oncologist (Fig. 3). This circular approach to ovarian cancer treatment has introduced different therapeutic opportunities that are continuously evaluated and re-elaborated according to the clinical information received from the different specialists involved in the collaborative care network. Therefore, this approach results in a improved management of ovarian cancer and patient awareness about the status of the disease, as well as greater confidence in the therapeutic options that they will undergo (132).

Although patient-centered care has significantly improved the standard of ovarian cancer care, several studies have demonstrated that patients treated in specialized structures where multidisciplinary teams operate have an improved prognosis compared with patients treated in non-specialized centers (133-135). A possible explanation of this trend could be related to the well-organized approach to treatment in specialized hospitals with a high volume of patients with ovarian cancer per year where the components of the multidisciplinary team meet together weekly to discuss the periodic clinical, laboratory and instrumental findings useful to take appropriated and shared clinical decision. Of note, despite the undoubted advantages of a multidisciplinary team in terms of the quality of the assistance provided, this type of interdisciplinary display requires appropriate organization, time for periodic meetings, willingness to collaborate and adequate IT support; it is useful to share medical records and clinical data, favoring a continuous constructive debate for the better management of each patient (136).

As shown in Fig. 3, the gynecologist (or gynecological surgeon), the pathologist and the oncologist are the key nodes of this circular multidisciplinary network. However, as aforementioned, due to the current complexity of ovarian cancer diagnosis, staging and treatments other professionals, including the general surgeon, urologist, vascular surgeon, radiologist, nuclear medicine physicians, geneticist, molecular biologist and psycho-oncologist are fundamental in the circular patient-centered model (Fig. 4).

Only a structured center can offer well-structured multidisciplinary teams able to address all of the patient needs. In this context, the Mercado *et al* (137) study shows that patients treated in referral centers and treated by expert physicians have a 40% higher survival compared with patients treated in a peripheral center.

As surgery represents the gold standard for the treatment of ovarian cancer, it is well established that patients treated in experienced centers benefit from maximum cytoreductive surgical resection which positively correlates with the overall survival of patients (135,138). Besides the importance of surgery, the discussion of clinical cases in the multidisciplinary team does not end with the diagnosis and surgical resection of tumor masses, but it takes place at every decision-making point, especially in case of recurrent diseases (139). In these cases, the interaction of the various specialists can lead to the design of novel and effective therapeutic strategies tailored to each patient (139). Thus, such strategies may involve new surgical interventions in the peritoneal cavity or other body districts, which requires the expertise of different types of surgeons, including urologists, vascular surgeons and general surgeons, or could lead to novel anticancer treatments using both chemo- and radiation therapies when distant metastases are observed (140,141).

It is important to note that each specialist within the multidisciplinary team has a fundamental role in the diagnostic or therapeutic process. Indeed, the use of imaging techniques performed by the radiologist is fundamental to formulate a diagnosis of suspected ovarian cancer and to establish the localization of lesions (142,143). In the same manner, the precise histological and biomolecular evaluation of ovarian cancer is now essential for modern cancer treatments (144,145). In this context, the pathologist, geneticist and molecular biologist are fundamental for the assessment of grading, histotyping and molecular typing of ovarian cancer (146,147). In addition, the multidisciplinary network of specialists is further enriched by the inclusion of breast specialists and nutritionists. In particular, breast specialists intervene in the case of BRCA1- and BRCA2-positive ovarian cancer who could develop a secondary neoplasm affecting the breast (148,149); while nutritionists are now a key professional figure in medical oncology departments. In fact, several studies have demonstrated that nutrition represents an important protective factor against the development of tumors (150) but also represents an effective therapeutic intervention for patients with cancer (151,152). In this context, several studies have demonstrated that dietary and lifestyle interventions during cancer treatments can ameliorate the adherence to treatment as well as patient quality of life and prognosis [hazard ratio (HR) for physical activity, 0.60; 95% CI, 0.39-0.92; $P=0.02$; HR for highest vs. lowest tertile of quality diet, 0.73; 95% CI, 0.55 to 0.97; $P=0.03$] (153-156). These data, together with the clinical features of patients allow clinicians to determine the best therapeutic approach as well as to predict the prognosis and outcomes of patients (157).

The importance of a multidisciplinary team for the management of ovarian cancer has emerged during the COVID-19 pandemic where patients with ovarian cancer have experienced difficulties in accessing medical treatment (158). Indeed, due to the spread of infection, patients with cancer have experienced delays in treatment or missed some therapies with a negative impact on the treatment response (159). In addition, patients with cancer are considered vulnerable individuals with an increased risk of COVID-19 infection and severe symptomatology (160). In this context, the multidisciplinary team involved in the management of ovarian cancer has improved novel telemedicine strategies useful to monitor

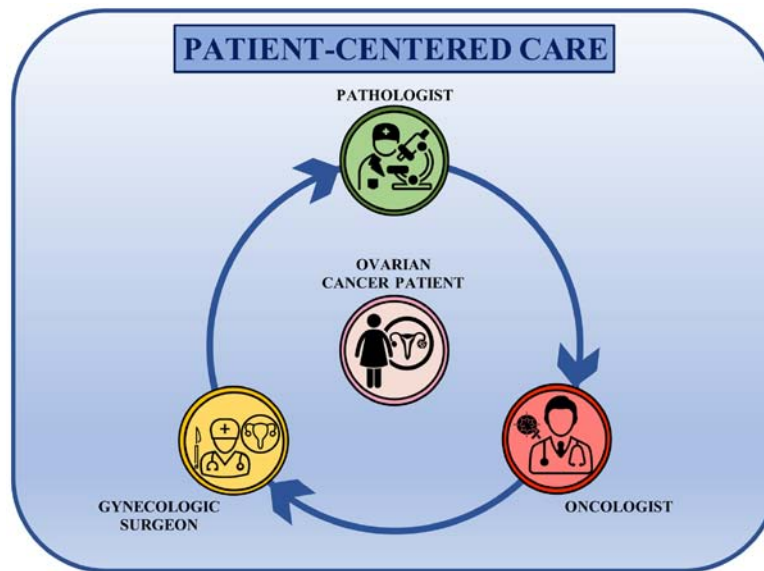


Figure 3. Circular approach to the management of patients with ovarian cancer patients. Main specialists involved in ovarian cancer care interact with each other sharing all of the relevant information and all clinical decisions are patient-centered.

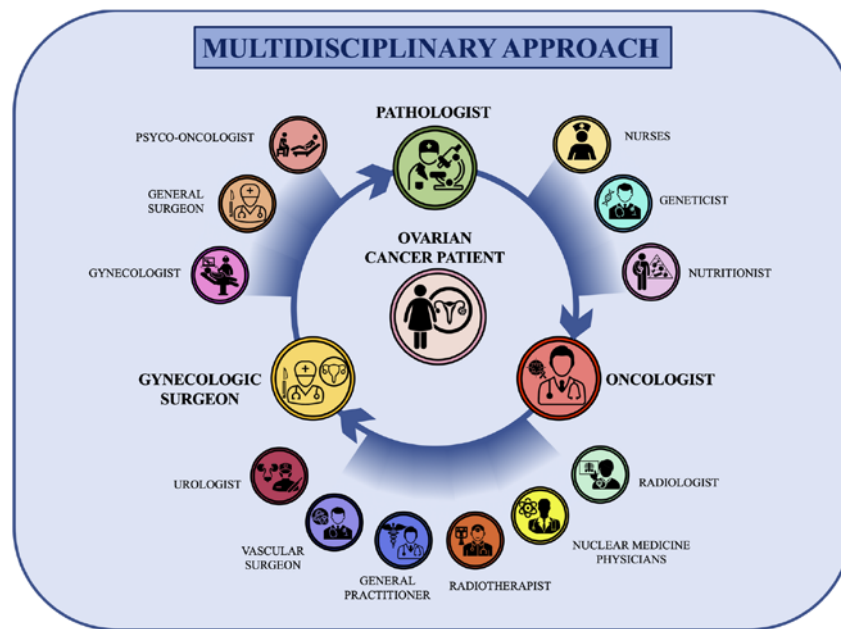


Figure 4. Circular and multidisciplinary network for the management of patients with ovarian cancer. The gynecological surgeon, pathologist and oncologist are the key nodes of the patient-centered circular multidisciplinary network. Other specialists, including nurses, geneticists, nutritionists, radiologists, nuclear medicine physicians, radiotherapists, general practitioners, vascular surgeons, urologists, gynecologists, general surgeons and psycho-oncologists, actively participate in all the decision-making steps of ovarian cancer management.

patients with ovarian cancer at a distance, thus following the progression of the disease and patient health status during the treatment. In addition, thanks to the patient-centered circular multidisciplinary network the information is easily transferred among specialists, thus increasing the speed of the implementation of therapeutic strategies and follow-up visits (161-163).

7. Conclusions

In recent years, the management of ovarian cancer has been significantly improved through the introduction of novel

pharmacological treatments and mini-invasive surgical techniques. Besides these advancements, a multidisciplinary approach for the treatment of ovarian cancer has significantly improved the quality of life and prognosis of patients. Overall, a multidisciplinary team is able to face clinical, molecular, pathological and psychological issues of patients with ovarian cancer, ensuring a high standard of care supporting the process of personalized medicine. The importance of a multidisciplinary team and periodic meetings lays also on the constant improvement of molecular, biological and therapeutic knowledge in the field of ovarian cancer care. Indeed, the active discussion performed within a multidisciplinary

team improves the adoption of the best therapies for patients as well as the efficacy of treatments.

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LF, GSca and PS conceived the manuscript, performed bibliographic research and wrote the article. VL, GG and AL performed the bibliographic research and prepared the table and figures. GSca and ABD provided critical revisions. All authors provided critical revisions and read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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