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A multidisciplinary approach for complete cytoreduction after neoadjuvant chemotherapy in advanced-stage ovarian cancer: a case report

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ABSTRACT

Background. The Portuguese standardized incidence rate of ovarian cancer is 9.5/10,000 women, with 75% of cases diagnosed at an advanced-stage. Presenting an illustrated description of a multidisciplinary surgical approach combining upper and lower abdominal debulking surgery reaching R0 after neoadjuvant chemotherapy in advanced ovarian cancer is the main objective of the presented case.
Case presentation. A 63-year-old patient presented with abdominopelvic pain and suspicious bilateral ovarian lesions. Diagnostic laparoscopy met the criteria for unresectability and tumour biopsy revealed high-grade serous adenocarcinoma of the ovary. A cytoreductive interval surgery was performed after neoadjuvant chemotherapy involving extensive resections of the upper abdomen. R0 was successfully achieved. At the 24-month follow-up, she is free of recurrence.
Conclusions. Maximal debulking is one of the main determinants of survival in advanced-stage ovarian cancer. Meticulous preoperative planning with multidisciplinary surgical coordination is the key to achieving this goal.

INTRODUCTION

Ovarian cancer represents the second most common and the deadliest form of gynaecological malignancy, with *BRCA* 1-2 as the most common genetic variants which predispose to develop this type of disease [1-3]. According to GLOBOCAN, an estimated total of 313,959 cases of ovarian cancer were diagnosed and 207,252 succumbed to this neoplasia in 2020 [4]. An increase of 36.6% in cases and 47.6% in the number of fatalities is expected in 2040 [5]. For the Portuguese population, the standardized incidence rate of ovarian cancer is 9.5/10,000 women [6].
Based on data from the United States National Cancer Database Surveillance, Epidemiology, and End Results (SEER), approximately 1.2% of women will be diagnosed with ovarian cancer in their lifetime, mostly between the sixth and seventh decades [1, 7]. The five-year survival rate depends on the stage at diagnosis, ranging from 92.6% for initial stages to 30.3% for metastatic cancer [7].

Epithelial ovarian cancer is the most common type of ovarian cancer (90%) [8]. High-grade serous carcinoma, the most frequent subtype, which represents 70 to 80% of all malignant ovarian neoplasms, is a woman's silent enemy due to its nonspecific symptoms and signs, even in cases of advanced-stage at diagnosis [8-10].

The standard of care for advanced ovarian cancer is primary aggressive cytoreductive surgery followed by systemic platinum-based chemotherapy [11]. The maximum effort is mandatory for achieving the goal of complete cytoreduction (R0), meaning no residual tumour after surgical debulking, even using a minimally invasive approach [12-14]. In selected cases, who may not be good surgical candidates due to unresectable disease, visceral metastasis, poor performance status or severe comorbidities, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) shows an equivalent survival rate with less morbidity when compared to primary debulking surgery (PDS) [15].

A comprehensive preoperative evaluation decides the most suitable approach [6]. Advanced-stage ovarian cancer always implies high surgical complexity demanding an orchestra of multiorgan surgical procedures encompassing the upper abdomen proximal to the Treitz ligament or intestinal resections, in addition to the standard steps for removal of uterus and adnexa, coordinated by a multidisciplinary team [16].

Presenting an illustrated description of a multidisciplinary surgical approach combining upper and lower abdominal debulking surgery reaching R0 after neoadjuvant chemotherapy in advanced ovarian cancer is the main objective of the following case.

CASE PRESENTATION

A 63-year-old patient was referred to the Gynaecology Outpatient Unit due to diffuse abdominopelvic pain, accompanied by abdomen bloating and constipation; these symptoms had started five months beforehand and had worsened in the last two months. She had no post-menopausal uterine bleeding. Concerning her prior clinical history, she was hypocoagulated in relation to medicated hypertension and atrial fibrillation. She had also undergone gastric sleeve surgery and right knee arthroscopy. Body Mass Index was 28.5 kg/m^2 and Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was 1. The initial workup included a normal colonoscopy. A transvaginal gynaecological ultrasound revealed suspicious bilateral ovarian lesions with irregular borders, multiple echogenic patterns within the mass mostly solid, and dense multiple irregular septa. Vaginal and rectal examination revealed large bilateral palpable adnexal masses, solid, fixed, with irregular outer contour. Painless mobilization of the uterus and adnexa was registered. Her CA-125 was 973.3 U/mL with ROMA score positive of 97.4% (HE4 620.2 pmol/L). CEA was negative (1.6 ng/mL). Magnetic resonance imaging showed 60 mm left and 50 mm right heterogeneous adnexal masses, without cleavage plane with the uterus, massive ascites, and enlarged left internal iliac lymph nodes. A priority laparoscopic surgery with multiple biopsies was performed, attributing the Fagotti score to the patient of ten. The left adnexal biopsy revealed high-grade serous adenocarcinoma with immunohistochemistry displaying diffuse labelling of the neoplastic cell population for estrogen receptors, progesterone receptors, PAX8, p53 and p16, and ki-67 of 60-70%. The genetic study did not detect pathogenic variants in the *BRCA1*, *BRCA2*, *BRIP1, RAD51C, RAD51D, MLH1, MSH2, MSH6,* or *PALB2* genes. The Gynaecological Oncology Multidisciplinary Tumour Board decided in favour of performing NACT. The patient completed four cycles of carboplatin and paclitaxel with good tolerance. Thoraco-abdominopelvic tomography following NACT showed an absence of thoracic disease, but three nonspecific liver lesions with 7-14 mm in segments II and VII, 3 nodular implants with 15-20 mm close to the left splenic hilum, a 23mm lesion in the left adrenal gland, without ascites. CA-125 after the neoadjuvant approach was 21.5 U/mL.

A cytoreductive interval surgery was planned. Detailed informed consent was obtained before the procedure, explaining the desired benefit balanced with possible risks, mainly related to the need for transient stoma formation or loss of organ function. She underwent a debulking surgery about four weeks after neoadjuvant therapy in collaboration with the General Surgery team, in a highly complex surgery that lasted around eight hours. The diagnostic laparoscopy showed a fixed uterus without a rectouterine cleavage plane, enlarged adnexa with similar dimensions of previous resonance imaging, omental cake, enlarged single

pelvic lymph node, solid lesions 20-40 mm at the level of diaphragmatic cupulas and infiltrating left splenic hilum and a 30mm solid lesion in the left adrenal gland. Subsequent midline laparotomy included en bloc extrafascial hysterectomy, bilateral salpingo-oophorectomy, and anterior resection of the rectum with primary colorectal anastomosis (**Figure 1**). Consecutive surgical steps for achieving complete cytoreduction were: selective pelvic lymphadenectomy after extensive adhesiolysis, liver mobilization with resection of diaphragmatic metastasis, intraoperative ultrasound excluding suspicious hepatic lesions, en bloc left splenectomy and adrenalectomy, omentectomy and appendectomy (**Figures 2-6**). No residual macroscopic tumour lesions were recorded after IDS. The FIGO stage was IIIB.

The patient was monitored in the initial postoperative period in a specialized Surgical Intermediate Care Unit (day 0 to day 5), where there was an increase in inflammatory parameters on day 4, and abdominopelvic tomography excluded intra-abdominal complications. A rise in the right hemidiaphragm was diagnosed without respiratory compromise and she underwent daily kinesiotherapy with complete resolution. She was discharged from the hospital on postoperative day 10. Two cycles of adjuvant chemotherapy followed the interval surgery, starting approximately 1.5 months later. In the first post-operative review, there was an intact vaginal vault and a skin wound dehiscence of about 10 mm, which finally healed one month later. She is still under regular surveillance in the Gynaecological Oncology Unit according to the national Consensus and is free of recurrence after a 24-month follow-up. During this surveillance period, the patient was followed up every 3 months, performing clinical evaluation including gynaecological examination, without symptoms/signs of recurrence. Periodic measurements of CA-125 (8, 7.1, 5.3, 3.5, 14, 3.6, 3.1 and 3 U/mL) were performed, with thoraco-abdominopelvic tomography requested at 15 months of surveillance, by analytical elevation compared to previous values, showing no recurrence of the disease.

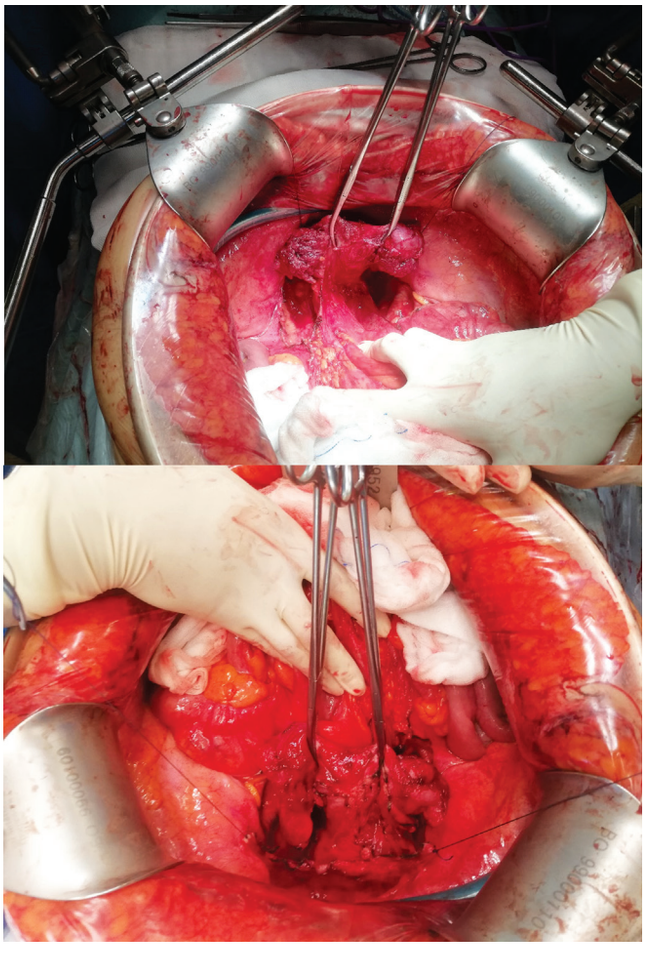

Figure 1. *En bloc anterior resection of the rectum, uterus and adnexa.*

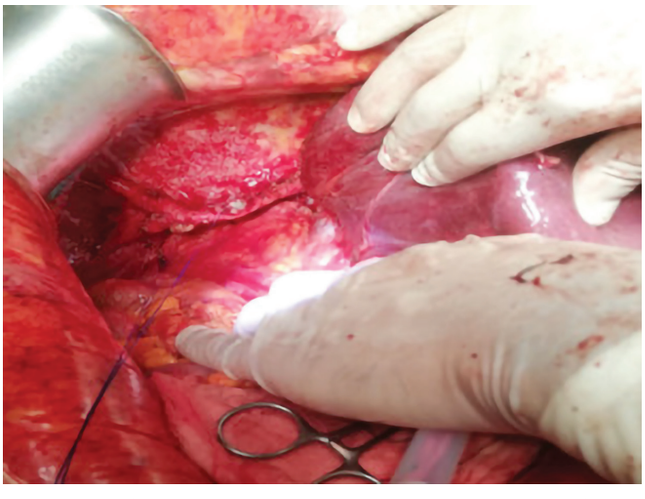

Figure 2. *Left rotation of the right liver exposing the vena cava and posterior right diaphragm.*

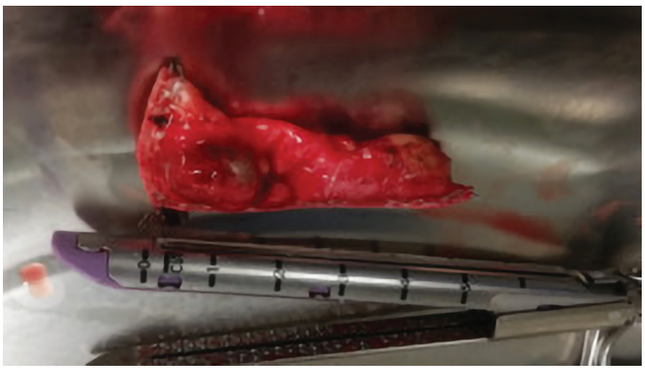

Figure 3. *Excision of diaphragmatic metastases.*

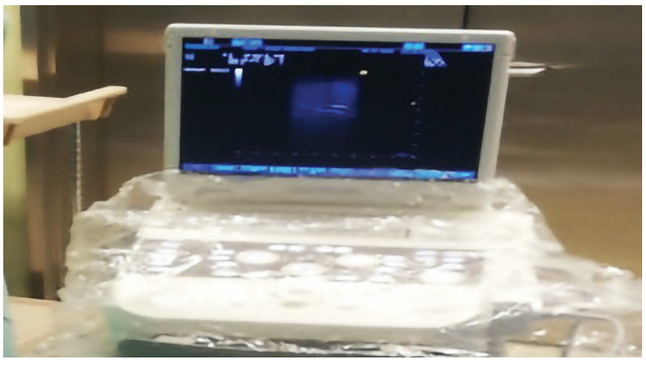

Figure 4. *Intraoperative hepatic ultrasonography, excluding hepatic malignant lesions.*

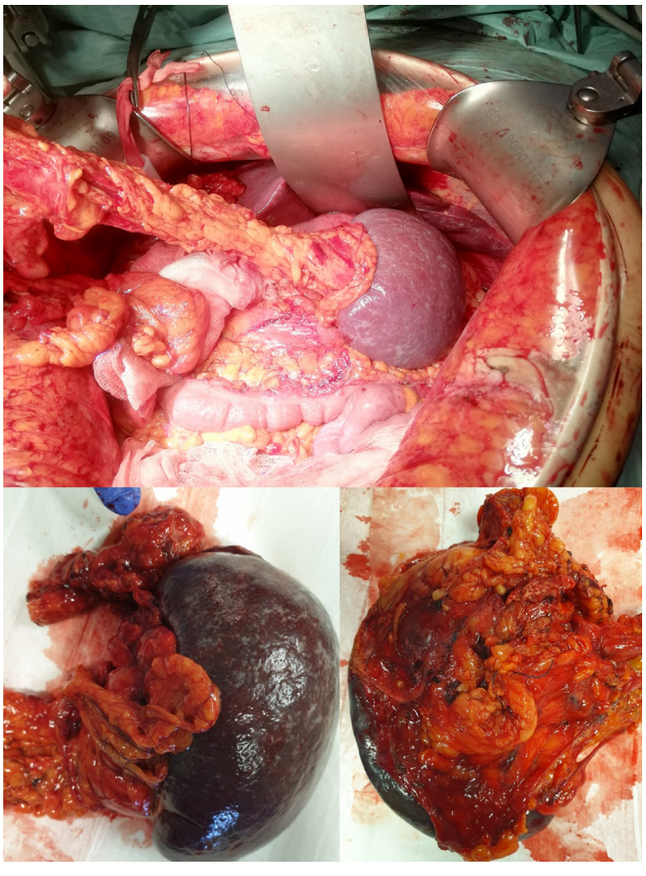

Figure 5. *En bloc left splenectomy and adrenalectomy.*

DISCUSSION

Despite a lot of genomic and medical advances in understanding and treating the disease, ovarian cancer is the leading cause of death from gynaecological cancer in the developed world, and, unfortunately, most patients are still diagnosed in advanced-stages [1]. Additionally, even in those who respond well to the initial treatment, about 80% will develop a recurrence, due to several immunological and non-immunological mechanisms [17-19].

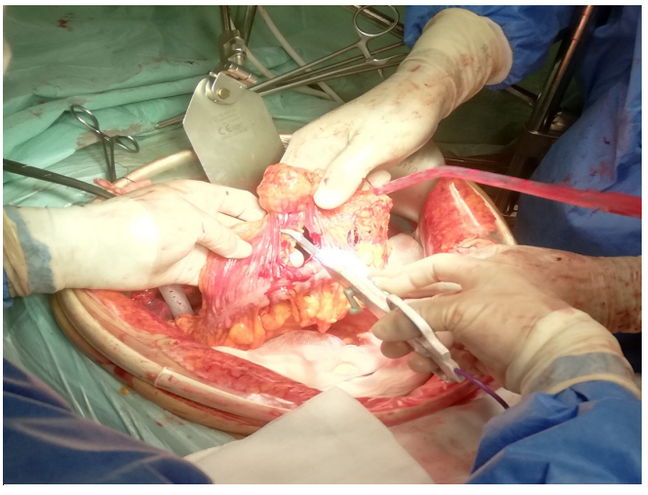

Figure 6. *Omental cake and respective omentectomy.*

Cytoreductive surgery remains a cornerstone of treatment for ovarian cancer [20]. Complete resection of all grossly visible disease – primary cancer and all metastatic disease –, whether performed as primary treatment or after neoadjuvant chemotherapy, remains the goal whenever cytoreductive surgery is performed [9, 21]. The residual disease is the key determinant of success in the control of oncological disease and, on a broader horizon, is inversely proportional to survival and directly proportional to recurrence in advanced ovarian cancer [22, 23]. Total resection of macroscopic disease, leaving only residual microscopic disease, has the best overall survival. 30 to 40% of patients in this category will be free of the disease in five years and a 10% increase in cytoreduction represents a 5.5% increase in median survival [9].

Biomarkers, histological and genetic factors, intestinal invasion, extra-pelvic disease, hormone levels, and patient profile are just some of the prognostic factors that should be considered before making a surgical decision [24].

Berman *et al*. stated that it is unknown whether complete resection has direct proportionality to the surgeon's expertise or to the intrinsic biological behaviour of the tumour [25]. Indeed, total debulking, with tolerable morbidity, reflects surgical experience, technical skills, quality in anaesthesia, nursing, and intensive care [26]. Assuming that residual disease and radical surgery independently predict disease-specific overall survival rates for patients with carcinomatosis, aggressive surgical efforts with extensive resection of upper abdomen metastases are associated with improved progression-free survival and overall survival in later stages of ovarian cancer [1, 26].

As ovarian cancer in 75% of cases is diagnosed in advanced-stages and more often in older patients, the burden of disease and individual comorbidity prevent all patients from being good candidates for primary debulking surgery. Selected patients with histologically-proven advanced-stage disease may benefit from three to four cycles of neoadjuvant chemotherapy that can be administered initially, reducing the tumour burden and making the disease resettable in an IDS with less technical complexity [15, 27]. NACT supplemented by IDS may be particularly suitable in patients with advanced age, poor performance status, frailty, severe medical comorbidities, visceral metastases, pleural effusion, macroscopic ascites, or other criteria of unresectable disease or predicted suboptimal upfront resection (≥ 10 mm of residual disease at the end of surgery) [1, 15, 28].

This alternative approach has been proven by five pioneering randomized prospective trials. EORTC 55971 showed complete cytoreduction in 19% of the patients receiving upfront debulking surgery followed by adjuvant chemotherapy whereas 51% in patients receiving NACT and IDS and there was less surgical morbidity in NACT and IDS group while progression-free and overall survival rates showed no difference in both groups [21]. CHORUS trial included 550 patients and revealed that NACT followed by IDS was superior regarding complete cytoreduction (43% *vs* 17% in PDS) and surgical complications such as postoperative death, infection, thrombosis, or haemorrhage with overall survival rates similar in both groups [29]. JCOG 0602, once again, showed noninferiority of NACT followed by IDS compared to upfront debulking surgery with the former group showing shorter operation time, less organ resection, and fewer adverse events postoperatively in general [30]. In the SCORPION study, interval debulking surgery was associated with significantly better complete resection (67% *vs* 47.6% in PDS), lower postoperative early major complication rates (7.6% *vs* 25.9% in PDS), including postoperative deaths (0% *vs* 8.3% in PDS) [31, 32]. TRUST, an ongoing trial, will clarify the optimal timing of surgical therapy in advanced ovarian cancer with overall survival as the primary endpoint [33]. Despite the heterogeneity among these clinical trials, the results, in general, demonstrate that patients treated with NACT benefited from better surgical outcomes, including shorter operative time, less blood loss, less surgical complexity to achieve complete debulking, less intra- and post-operative morbidity, and lower risk of postoperative mortality and shorter hospital stay compared to upfront surgery. The variables progression-free survival and overall survival did not find significant differences between the two therapeutic groups for advanced ovarian cancer [1].

The upper abdomen approach integrates the multiorgan resection strategy in the debulking of advanced ovarian cancer and allows an increase in overall survival with acceptable morbidity [24]. In addition, excision of intestinal metastases can restore proper bowel function and strengthen the nutritional status of the patient, increasing the tolerability of adjuvant chemotherapy. Besides, a large tumour mass has areas of poor vascularization and oxygenation, and clusters of cells in a quiescent state, whose sensitivity to chemotherapy will be suboptimal [9]. When performed by experts in oncology, surgeries will be successful in 70% to 90% of patients, with primary morbidity of approximately 5% and operative mortality of 1%. Bowel resection in these patients does not seem to elevate the general morbidity caused by the surgical intervention [9]. The overall rate of complications related to en bloc resection of the uterus and adnexa with rectosigmoid without protective ileostomy is about 2%, minimized with careful patient selection and close postoperative surveillance [24].

The limit for what is surgically feasible or prudent may lie in the surgeon's ability to master the disease associated with patient fragility. The arduous task of achieving complete resection in advanced ovarian cancer is based on the progressive refinement of preoperative techniques by examinations of image and by laparoscopy using the Fagotti score that better allow selection of the ideal candidates for R0 surgical debulking with acceptable morbidity and those most likely to benefit from a neoadjuvant chemotherapy treatment obtaining resettable residual disease in a second time [34]. Then, it will depend on the skills of a multidisciplinary team, which in the case described was made up of gynaecological oncologists and dedicated general surgeons and anaesthesiologists, who combined maximum efforts to address all signs of disease, always bearing in mind a common goal, that of prolonging the patient's survival and quality of life [16]. Our patient fulfilled some criteria against primary debulking – omental caking, peritoneal carcinomatosis, diaphragmatic

carcinomatosis, bowel infiltration, stomach infiltration –, a Fagotti score of ten confirmed irresectability. NACT protocol followed by IDS and adjuvant chemotherapy was successfully applied and she has now gained two years with no evidence of relapse [22, 35]. The illustration of the coordination of a multidisciplinary surgical team in the common goal of macroscopic disease depletion, thus increasing the patient's disease-free survival, is the main highlight of this case. The limitation of this case lies in the fact that it is a common example in the day-to-day of an experienced Oncology Centre.

Another issue to be discussed concerns the role of lymphadenectomy for staging and therapeutic goals in advanced ovarian cancer. There are great debates between those who defend lymphadenectomy as a useful procedure in the surgical removal of micro metastases and those who contest it for the importance of preserving lymphatic tissue with beneficial immune functions and minimizing morbidity. According to the literature, patients with advanced ovarian cancer have a high incidence of pelvic and para-aortic lymph node metastases [36]. Retrospective studies attribute better survival to the group submitted to lymphadenectomy in cytoreductive surgery [37, 38]. However, some recent studies have shown that retroperitoneal staging is associated with unnecessary morbidity and mortality without survival benefits [39-41]. One such study, a European prospective multicentre study (LION-AGO Study Group) investigated the role of systematic pelvic and para-aortic lymphadenectomy in advanced epithelial ovarian cancer with optimal intra-abdominal debulking without macroscopically visible metastasis. In this context, lymphadenectomy did not present better results, with more complications and mortality being reported [40]. It has been documented that lymphadenectomy represents an increase of 60 minutes in operative time, an increase of 150 ml of blood loss, and a 7.4% increase in the transfusion rate, in addition to increasing the rate of hospitalization in intensive care by 8.6% [40, 41]. The higher morbidity and mortality may be due to the sum of the intrinsic procedures or to the subsequent immunological fragility [42, 43]. Until new data supporting systematic lymphadenectomy in the setting of advanced ovarian cancer are available, the ESMO Guidelines advocate: "a maximal surgical effort is required, including intestinal resection, peritoneal stripping, diaphragmatic resection, removal of bulky para-aortic lymph nodes and splenectomy […] the value of systematic pelvic and para-aortic lymphadenectomy in advanced disease remains controversial […] should not be regarded as a standard procedure" [44]. This recommendation is reinforced by the NCCN Guidelines stating that "suspicious and/or enlarged nodes should be resected, if possible […] systematic lymph node dissection and resection of clinically negative nodes is not required" [1].

Another topic intensely debated by the scientific community concerns the potential of targeted therapies applied to ovarian cancer. This incessant discussion is related to the fact that ovarian cancer is the most lethal gynaecological tumour, due to the high percentage of recurrence associated with poor prognosis with any therapeutic regimen adopted [45].

Bevacizumab, the most widely used antiangiogenic (anti-VEGF) agent, has been approved for first- and second-line treatment of advanced epithelial ovarian tumours [45]. The efficacy of bevacizumab plus carboplatin and paclitaxel for first-line treatment was proven in 2 multicentre, double-blind, randomized studies [46, 47]. Study GOG-218 compared 3 groups of patients with FIGO stage III-IV ovarian cancer: 3-weekly cycles of carboplatin plus paclitaxel in cycles 1-6 (group A), the same chemotherapy with concomitant bevacizumab in cycles 2-6 and placebo in cycles 7-22 (group B), or the same chemotherapy plus bevacizumab in cycles 2-22 (group C). This study revealed a significant increase in progression-free survival in the group that received bevacizumab plus standard chemotherapy followed by maintenance with bevacizumab (14.1 months) compared to those treated with standard chemotherapy alone (10.3 months) or without maintenance bevacizumab (11.2 months). Overall survival was not significantly improved by adding bevacizumab to background chemotherapy. However, applying only to high-risk disease (stage IV), an improvement in median overall survival was demonstrated and this was significantly higher in the group undergoing maintenance with bevacizumab (40.6 months) compared to the groups without maintenance therapy (32.8 months) or who did not use bevacizumab (32.9 months) [46]. The phase III randomized ICON7 trial confirmed these results. Patients with FIGO stage I-IIA (clear-cell histology or grade 3) and IIB-IV epithelial ovarian cancer were allocated to receive 6 cycles of 3-weekly carbopla-

tin and paclitaxel with or without bevacizumab for 12 months. The median progression-free survival was significantly higher in the bevacizumab group (19.8 months) compared to the control group (17.4 months) and the complete/partial response rate was 48% in the chemotherapy-alone group and better results were obtained in the bevacizumab group (67%). Overall survival did not change significantly between the two groups at 49 months of follow-up [47]. Despite its wide use in adjuvant therapy with beneficial effects on tumour reduction and inherent survival, there is still debate about patient selection, better dosage and temporal distance in relation to cytoreductive surgery [45]. Regarding the application of anti-VEGF in the neoadjuvant setting, several studies are promising but have not yet proved to be sufficient to recommend in clinical practice, due to the increased risk of complications of the surgical wound, formation of fistulas, gastrointestinal perforations or thromboembolic events [45, 48, 49]. Also in recurrent disease, the addition of antiangiogenic agents to chemotherapy has been shown to increase progression-free survival [45]. In the case of isolated lymph node recurrence, due to its less aggressive behaviour, secondary cytoreductive surgery followed by chemotherapy is defended as safe, and viable, with less postoperative morbidity compared to the use of chemotherapy alone [50].

Another targeted therapy with positive results in the treatment of high-grade serous ovarian cancer (HGSOC) is PARP inhibitors. 15-20% of HGSOCs can be hereditary, with mutations in the BRCA1 and BRCA2 genes being the most frequent. When there is a defect in these genes, DNA repair mechanisms require the action of PARP proteins. By inhibiting this mechanism, PARP inhibitors cause cell death, called synthetic lethality, a key therapeutic target in HGSOCs [51]. It was the Solo 1 trial that changed the paradigm of patients with BRCA mutation and advanced ovarian cancer, demonstrating that a PARP inhibitor, Olaparib, significantly improved progression-free survival in these patients, with a steep decrease in disease progression or death of 70% over placebo [52]. Currently, guidelines advocate testing for BRCA in all patients with epithelial ovarian cancer, to investigate the potential use of targeted therapy and implement prevention strategies in relatives with a BRCA mutation. However, this test is not evenly distributed across all locations [51].

CONCLUSIONS

In conclusion, for those who are not candidates for standard primary debulking surgery, neoadjuvant chemotherapy followed by interval surgery represents an alternative to achieve the lowest possible surgical morbidity without compromising patient survival. A cooperative surgical approach among different specialties for combined upper and lower abdominal debulking surgery in patients with advanced ovarian cancer is safe, feasible, and should be performed in experienced Centres for the fundamental goal of maximal resection.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

S.L.O.: Conceptualization, formal analysis, data curation, writing - original draft. A.M.: Data curation, formal analysis. S.G., J.P.: Writing – review & editing. N.N.M.: Conceptualization, writing – review & editing.

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Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

A formal IRB approval was obtained by the Institutional Ethics Committee (reference07/19/11/2021).

Informed consent

The patient enrolled in this study gave written informed consent to allow data collection and analysis for research purposes prior to the start of the study.

Data sharing

Data are available under reasonable request to the corresponding author.

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