Updates in Surgery (2019) 71:389–394
https://doi.org/10.1007/s13304-018-0600-y

ORIGINAL ARTICLE

Cytoreductive surgery followed by HIPEC repetition for secondary ovarian cancer recurrence

Stefano Cianci[1] · Carlo Ronsini[2] · Giuseppe Vizzielli[1] · Alessandro Tropea[3] · Antonio Biondi[4] · Giovanni Scambia[5] · Anna Fagotti[5]

Received: 30 September 2018 / Accepted: 29 October 2018 / Published online: 8 November 2018

Abstract

Secondary and tertiary cytoreductive surgery was associated with improved overall survival in platinum-sensitive recurrent ovarian cancer (ROC). Hyperthermic intraoperative intra-peritoneal chemotherapy (HIPEC) is considered an attractive method in the treatment of ROC to deliver chemotherapy with enhanced effect directly at the tumor site. However, another deserving aspect is the feasibility and the oncologic role of HIPEC repetition. Twelve patients affected by secondary ovarian cancer recurrence previously submitted to cytoreduction followed by HIPEC were enrolled for the present study to receive tertiary cytoreduction followed by HIPEC repetition. The median operative time, including time for HIPEC procedure, was 360 min (range 240–540). Average EBL was 325 ml (from 100 to 500 ml). The median hospital stay was of 5 days, from 4 to 10. Low-grade post operatory complications occurred in 2 patients (16.6%) and high-grade complication in 1 case (8.3%). Our study report encouraging data about safety of HIPEC repetition in ovarian cancer treatment.

Keywords HIPEC · HIPEC repetition · Ovarian cancer · Loco-regional treatment · Carcinosis · Chemotherapy · Cytoreduction

Introduction

Gynecological surgery represents the mainstay treatment for several benign [1–9] as well as malign conditions [10–17], which may play a detrimental role on patient's quality of life and wellbeing [18–23].

Ovarian cancer is the leading cause of death among gynecological malignancies. Even if a complete cytoreduction is achieved at the time of first surgery, about 60–70% of stage III patients develop a recurrence [13].

Surgical treatment represents the cornerstone for the management of several benign [24–29] as well as malignant gynecological diseases, even using minimally invasive approach [13–16, 30–32].

The role of surgical approach in the therapeutic management of relapsed epithelial ovarian cancer (REOC) is still debated by oncologists. Secondary and tertiary cytoreductive surgery (SCS) was associated with improved overall survival (OS) in platinum-sensitive recurrent ovarian cancer (ROC) [32]. Data reported from a meta-analysis by Bristow et al. showed that the residual tumor is the most important factor for survival rate also in relapsed disease [33].

✉ Stefano Cianci
stefanoc85@hotmail.it; stefano.cianci@policlinicogemelli.it

[1] Unità Operativa Ginecologia Oncologica, Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Univeristario A. Gemelli, IRCCS, Rome, Italy

[2] Department of Medicine and Aging Sciences, University "G. D'Annunzio" of Chieti-Pescara, Chieti, Italy

[3] Department for the Treatment and Study of Abdominal Diseases and Abdominal Transplantation, IRCCS-ISMETT, (Istituto Mediterraneo per i Trapianti e Terapie ad alta specializzazione), University of Pittsburgh Medical Center Italy, Palermo, Italy

[4] Department of General Surgery and Medical Surgical Specialties, University of Catania, Catania, Italy

[5] Unità Operativa Ginecologia Oncologica, Dipartimento Scienze della Salute della Donna e del Bambino, Fondazione Policlinico Univeristario A. Gemelli, IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy

In the last years, one of the most debated topics is the role of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of REOC. It is considered an attractive method to deliver chemotherapy with enhanced effect directly at the tumor site.

The use of such loco-regional approach has proved to improve prognosis of peritoneal carcinomatosis from different origins (bowel, appendix, pseudomyxoma peritonei and peritoneal mesothelioma). Regarding ovarian cancer, some studies have demonstrated its effectiveness to prolong post-recurrence survival [34]. However, another deserving aspect is the feasibility and the oncologic role of HIPEC repetition in patients previously treated. This study is aimed to assess the role of HIPEC repetition, in terms of clinical and oncological outcomes, in a group of women affected by secondary ovarian cancer recurrence and previously treated with HIPEC, receiving secondary cytoreduction and HIPEC repetition.

Materials and methods

This retrospective study was conducted at Policlinico Agostino Gemelli Foundation, between February 2009 and November 2016. The Ethical Committee approved the HIPEC treatment in platinum-sensitive recurrent ovarian cancer patients submitted to SCS. Data for the current analysis were retrieved from the electronic database of the Department of Obstetrics and Gynecology at the same University and informed consent was obtained from all subjects. Clinical charts of the patients submitted to SCS + HIPEC have been reviewed for the purpose of the study.

12 women affected by platinum-sensitive [platinum-free interval (PFI) of 6 months or longer] secondary recurrent ovarian cancer were selected for the purpose of the present study. The second relapse was defined as the presence of one or more exclusive intra-abdominal relapses detected at FDG-PET/CT scan and/or staging laparoscopy (S-LPS).

Required criteria for SCS + HIPEC were: age ≥ 8 and ≤ 70 years; Eastern Cooperative Group Performance Status (ECOG PS) ≤ 2; life expectancy of at least 3 months; normal cardiac, hepatic, respiratory, bone marrow and renal functions (creatinine clearance > 60 µl/min according to Cockcroft formula [35], absolute neutrophil count > 1500/µl, a platelet count > 150,000/µl, bilirubin levels and creatinine < 1.5 times upper the range); compliant patients. Women with distant (extra-abdominal) unresectable metastases, diffused carcinosis and/or no evidence of intra-abdominal disease were excluded, as well as platinum-resistant patients and cases where a sub-optimal SCS was achieved.

Patients received either a standard laparotomic or laparoscopic approach with the aim to achieve complete cytoreduction (removal of all macroscopically detectable disease, RT = 0) followed by HIPEC repetition. The extension of peritoneal spread at the time of recurrence was classified according with the peritoneal cancer index (PCI) [36].

Patient's clinicopathological characteristics are reported in Table 1.

Patients were similar for age, BMI, and ECOG-graded functional status, DFI from primary treatment to first recurrence and DFI from first to second and third recurrence. Furthermore, operative variables as EBL, operative time (OT), early and late complications, histological type and grading, chemotherapy drugs used for HIPEC, hospital length of stay, mortality, and disease-free and overall survival were recorded for each patient. Surgical complications were defined and classified according to Dindo classification [37].

Table 1 Patients' clinicopathological characteristics and first recurrence data

Variable	Cases	
	No.	(%) (range)
All	12	
Median age (years)	49	(35–70)
Median BMI (kg/m^2)	24	(22–27)
Median ECOG PS at I recurrence	0	100%
Median PCI at I recurrence	3	(1–16)
Type of approach		
PDS	9	75%
IDS	3	25%
Tumor histotype		
Serous	11	91.67%
Endometrioid	0	
Undifferentiated carcinoma	1	8,33%
Clear cells	0	
Residual tumor at primary surgery		
RT = 0 (PDS)	9	100%
RT = 0 (IDS)	3	100%
RT > 0	0	
Early post-op complications		
Grade 1–2[a]	1	8.33%
Grade 3–4[b]	4	33.33%
Hipec at I recurrence		
Cisplatin	6	50%
Oxaliplatin	4	33.33%
None	2	16,67%
Adjuvant chemotherapy	12	100%
Median DFI-1 (months)[c]	32	(12–71)
Median DFI-2 (months)[d]	23	(11–65)
Residual tumor at second surgery	0	100%

[a]Pharmacological or injection treatment

[a]Re-operation, invasive procedures

[c]Months from date of I surgery to date of I recurrence

[d]Months from date of II surgery to date of II recurrence

The follow-up period started at the date of third surgery plus second HIPEC procedure, with the censor date of September 2018. The disease-free interval (DFI-3) was calculated at time from third CRS and second HIPEC to fourth recurrence or end-time of analysis. Overall survival (OS) was calculated from the date of primary CRS to the date of death from any case or to the end-time of analysis.

Procedure

The surgical procedures performed during tertiary cytoreduction are summarized in Table 2. The HIPEC infusion was performed using four drains positioned in the four abdominal quadrants after completion of surgery or using laparoscopic accesses in the only case of laparoscopic procedure. Intra-peritoneal platinum-based drugs were administered (oxaliplatin 360 mg/m^2 for 30 min or cisplatin 75 mg/m^2 for 60 min) at the temperature of 41.5 °C. Perfusion was performed with closed technique and the abdomen was carefully re-explored after HIPEC completion.

Results

From 2009 to 2016, 12 patients underwent tertiary cytoreductive surgery (CRS) + HIPEC procedures in our center for a second platinum-responsive (> 6 months PFI) ovarian cancer recurrence and were selected for the present study.

As reported in Table 1, mean age was of 49-year-old (range 35–70), mean BMI was 24 kg/m^2 (range 22–27).

All patients had diagnosis of second recurrence of epithelial ovarian cancer, platinum responsive, which was an inclusion criteria, 11 serous histological types, 1 patient had an undifferentiated solid tumor in a personal history of serous ovarian cancer (Table 1).

Every patient underwent complete cytoreductive surgery at first diagnosis (RT = 0). 9 patients received primary debulking surgery (PDS), the other 3 patients were previously treated with 3 cycles of neoadjuvant chemotherapy (carboplatin + paclitaxel) followed by interval debulking surgery (IDS).

All patients, after first surgery, such as second one, received an adjuvant chemotherapy treatment (carboplatin + paclitaxel; or gemcitabine + paclitaxel).

At first diagnosis, 11 patients had an advanced-stage ovarian cancer (5 stages IIIB; 5 stages IIIC; 1 stage IVB), and one patient had an early stage ovarian cancer (IC3), according to FIGO classification.

At first recurrence, every single patient received secondary cytoreductive surgery with RT = 0 achieved; All procedures were followed by HIPEC procedure, 8 cases using cisplatin 75 mg/m^2 at the temperature of 41.5 °C C for 60 and 4 patients received oxaliplatin 360 mg/m^2 at the temperature of 41.5 °C C for 30 min.

Table 2 Second recurrence data and intra- and post-operative outcomes of secondary cytoreductions

Variable	Cases	
	No.	(%)
All	12	
LPS	1	8.33%
LPT	11	91.67%
Median ECOG PS at II recurrence	0	100%
Median PCI at II recurrence	2	(2–6)
Surgical procedure		
Peritonectomy/omentectomy	1	8.33%
Bowel resection	5	41.67%
Splenectomy	2	16.67%
Diaphragmatic stripping/resection	3	25.00%
Liver resection	1	8.33%
LNF	4	33.33%
Peri-operative outcome		
Median operative time (min)	360	(240–540)
Median EBL (ml)	325	(100–500)
Median hospital stay (days)	5	(4–10)
RT = 0	12	100%
Early post-op complications		
Grade 1–2[a]	2	16.67%
Grade 3–4[b]	1	8.33%
HIPEC drugs at II recurrence		
Oxaliplatin	3	25.00%
Cisplatin	9	75.00%
Median CA125 serum levels at II recurrence (UI/ml)	70	14–82.9
Adjuvant chemotherapy	12	100%
Median DFI-3 (months)[c]	28	(6–94)
Death	1	8.30%
Median OS	99	(45–217)

[a]Pharmacological or injection treatment

[b]Re-operation, invasive procedures

[c]Months from date of III surgery to date of III recurrence

Median first DFI-1 (from first surgery to diagnose of first recurrence) was 32 months, with a range from 12 to 71 (Table 1).

Median second DFI-2 (from second surgery to second recurrence) was 23 months, from 11 to 65.

Every patient enrolled started from a good and stable clinical condition (ECOG < 2).

7 patients were investigated for BRCA 1 or 2 mutations. 2 were positive for BRCA 1 mutation.

All patients occurred with abdominal second recurrence underwent tertiary CRS and submitted to explorative laparoscopy, to assess peritoneal involvement. Mesenteric

retraction, or massive disease spread was considered an exclusion criterion for surgical procedure.

As shown in Table 2, 11 patients were converted into a laparotomic debulking, and a single patient was treated by laparoscopy. In every case, the treatment reached the complete debulking of the abdominal disease (RT = 0), followed by repetition of HIPEC perfusion.

During laparoscopic evaluation, an intra-peritoneal (IP) metastasis was detected in all patients, but 4 patients had also an extra-peritoneal (EP) involvement (positive lombo-aortic lymphnodes).

Surgical procedures performed were proportional of disease spread: 1 omentectomy, 5 bowel resections, 2 splenectomies, 3 diaphragmatic peritoneal stripping (in one case with full thickness diaphragmatic resection), 1 liver resection, 4 lombo-aortic lymphadenectomies, 1 excision of iliopsoas muscle localization.

The median operative time (OT), including time for HIPEC procedure, was 360 min (range 240–540). Average EBL was 325 ml (from 100 to 500 ml). The median hospital stay was 5 day, (from 4 to 10). Low-grade (G1–G2) post operatory complications occurred in 2 patients (16.6%), and were a lung and a wound infection, treated with antibiotics.

In a single case, a G3 complication was recorded, which was represented by a vaginal-rectal fistula (8.3%) that required surgical treatment of bowel resection with termino-terminal anastomoses and ileostomy.

All patients after surgery underwent adjuvant systemic chemotherapy treatment.

Follow-up

Median follow-up period was 35 months and was set on September 2018.

During this period, only 5 cases of third recurrence were detected (41.6%). 4 of them were represented by a singular, isolated localization. The other case concerned in 3 different sites. One case of recurrence occurred in a patient with a mutation of BRCA 1.

Median DFI-3 (month from date of third surgery to third recurrence) for whole patients was 28 months, from 6 to 94.

One patient died after third disseminate recurrence, four patients were lost in follow-up on September 2017, one of them was one of the third recurrence patients. The other patients with third recurrence were still alive. Mean overall survival (OS) was 99 months, from 45 to 217.

Discussion

The rational to perform HIPEC in ovarian cancer is particularly convincing, based on the prevalent intra-abdominal diffusion of the disease, which is also the main driver of survival in AEOC patients. Indeed, this approach combines the advantage of the intraperitoneal chemotherapy administration with the complete diffusion of the drug in the whole abdomen, all enhanced by hyperthermia [38].

However, although several literature data have shown an improvement in survival rates of patients underwent HIPEC procedure [39], results are still conflicting due to the heterogeneity in settings of patients included, as well as in drugs/doses administered. Thus, besides thousands of women treated, we are still stacked, with no definitive conclusions assumed up to date.

Actually, several other randomized trials are currently in progress (HORSE NCT01539785, CHORINE NCT01628380, MMC 2014 NCT02124421) to clarify all these aspects.

The local chemotherapy administration represents an important innovation and some studies have investigated this aspect. The first point of HIPEC procedure is the hyperthermia. Indeed, in vivo and in vitro studies have demonstrated that high temperature can increase the cytotoxic function of chemotherapy drugs [38]. To furnish concrete data about this point, an interesting study reported that at a temperature of 41.5 °C, the platinum efficacy is increased up to 50% [38].

Considering all these aspects, new technologies to deliver loco-regional chemotherapy are actually suitable [40, 41].

In an attempt to better investigate the clinical outcomes of HIPEC repetition in patients affected by ovarian cancer recurrence, we conducted this study evaluating post operatory morbidity and survival rate after repetition of HIPEC administration. To our knowledge, this is the first study evaluating only ovarian cancer patients.

This aspect represents a point of strength of our study because we evaluated the specific role of second HIPEC in a specific subset of patients. In fact, our series represent a "pure series" whereas a limit of our study is the small number of our cohort.

Our data are in accordance with available literature, demonstrating the safety of second HIPEC. Indeed, we recorded only one peri-operative incidence of grade 3 complication (8.33%). This data are coherent even with complication rate of first HIPEC treatment [31, 42].

Even the complication incidence in our study is comparable with available literature, infact in a study focused on tertiary cytoreductive surgery [43], the major complication rate of tertiary cytoreductive surgery was 9.7%.

Since our study to our knowledge is the only one to report pure series of ovarian cancer patients, a comparison with other studies regarding survival rates is inappropriate. In a recent study by Fanfani et al. [32], the authors evaluated the role of tertiary and quaternary CRS in recurrent ovarian cancer. They reported a median disease-free interval (from the end of chemotherapy to third recurrence) of 22 months after second recurrence submitted to CRS. Considering that

in our series the DFI-3 recorded after second recurrence is 28 months, the data are encouraging. However, considering the small number of our series, further studies are needed to confirm this data.

Another interesting data is the fact that in our series the DFI-3 is longer than DFI-2, respectively, 28 months vs 23 months.

In conclusion, this study represents the effort to improve the survival rate of patients affected by ovarian cancer; however, guaranteeing a good quality of life and reducing morbidity. Obviously, more other aspects take place to improve all the aspects of physical and psychological health [44–50].

Conclusions

Although further studies with higher number of patients are needed to give definitive conclusion about the role of HIPEC in ovarian cancer treatment, our study report encourages data about safety of second HIPEC in the treatment of this disease. Even from an oncologic point of view, our results could give a new point of reflection about this topic.

Funding The work was not supported by any fund/Grant.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants and/or animals All procedures performed in studies involving animals were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all subjects.

References

1. Laganà AS, Vitale SG, Trovato MA et al (2016) Full-thickness excision versus shaving by laparoscopy for intestinal deep infiltrating endometriosis: rationale and potential treatment options. Biomed Res Int 2016:3617179. https://doi.org/10.1155/2016/3617179
2. Caruso S, Cianci S, Vitale SG et al (2017) Effects of ultralow topical estriol dose on vaginal health and quality of life in postmenopausal women who underwent surgical treatment for pelvic organ prolapse. Menopause 24:900–907. https://doi.org/10.1097/GME.0000000000000851
3. Caruso S, Rugolo S, Bandiera S et al (2007) Clitoral blood flow changes after surgery for stress urinary incontinence: pilot study on TVT versus TOT procedures. Urology 70:554–557. https://doi.org/10.1016/j.urology.2007.04.045
4. Lagana AS, Vitale SG, De Dominici R et al (2016) Fertility outcome after laparoscopic salpingostomy or salpingectomy for tubal ectopic pregnancy a 12-years retrospective cohort study. Ann Ital Chir 87:461–465
5. Vitale SG, Laganà AS, Gulino FA et al (2016) Prosthetic surgery versus native tissue repair of cystocele: literature review. Updates Surg 68:325–329. https://doi.org/10.1007/s13304-015-0343-y
6. Vitale SG, Sapia F, Rapisarda AMC et al (2017) Hysteroscopic morcellation of submucous myomas: a systematic review. Biomed Res Int 2017:6848250. https://doi.org/10.1155/2017/6848250
7. Sturlese E, Triolo O, Grasso R et al (2017) Thromboembolism prophylaxis in laparoscopic surgery for gynecologic benign diseases. Results of a single center experience in 922 procedures. Ann Ital Chir 88:342–347
8. Di Sardo Spiezio A, Vieira MDC, Laganà AS et al (2017) Combined systemic and hysteroscopic intra-amniotic injection of methotrexate associated with hysteroscopic resection for cervical pregnancy: a cutting-edge approach for an uncommon condition. Eurasian J Med 49:66–68. https://doi.org/10.5152/eurasianjmed.2017.16215
9. Di Sardo Spiezio A, Di Guardo F, Santangelo F, Cianci S, Giampaolino P (2017) Commentary on "Assessment of risk factors of intrauterine adhesions in patients with induced abortion and the curative effect of hysteroscopic surgery". J Investig Surg 18:1–3. https://doi.org/10.1080/08941939.2017.1400133
10. Bellia A, Vitale SG, Laganà AS, Cannone F, Houvenaeghel G, Rua S, Ladaique A, Jauffret C, Ettore G, Lambaudie E (2016) Feasibility and surgical outcomes of conventional and robot-assisted laparoscopy for early-stage ovarian cancer: a retrospective, multicenter analysis. Arch Gynecol Obstet 294(3):615–622
11. Cignini P, Vitale SG, Laganà AS, Biondi A, La Rosa VL, Cutillo G (2017) Preoperative work-up for definition of lymph node risk involvement in early stage endometrial cancer: 5-year follow-up. Updates Surg 69(1):75–82
12. Rossetti D, Vitale SG, Tropea A, Biondi A, Laganà AS (2017) New procedures for the identification of sentinel lymph node: shaping the horizon of future management in early stage uterine cervical cancer. Updates Surg 69(3):383–388
13. Tozzi R, Giannice R, Cianci S et al (2015) Neo-adjuvant chemotherapy does not increase the rate of complete resection and does not significantly reduce the morbidity of Visceral–Peritoneal Debulking (VPD) in patients with stage IIIC–IV ovarian cancer. Gynecol Oncol 138:252–258. https://doi.org/10.1016/j.ygyno.2015.05.010
14. Gueli Alletti S, Rossitto C, Cianci S, Scambia G (2016) Telelap ALF-X total hysterectomy for early stage endometrial cancer: new frontier of robotic gynecological surgery. Gynecol Oncol 140:575–576. https://doi.org/10.1016/j.ygyno.2016.01.018
15. Gueli Alletti S, Rossitto C, Cianci S et al (2016) Telelap ALF-X vs standard laparoscopy for the treatment of early-stage endometrial cancer: a single-institution retrospective cohort study. J Minim Invasive Gynecol 23:378–383. https://doi.org/10.1016/j.jmig.2015.11.006
16. Gueli Alletti S, Rossitto C, Perrone E et al (2017) Needleoscopic conservative staging of borderline ovarian tumor. J Minim Invasive Gynecol 24:529–530. https://doi.org/10.1016/j.jmig.2016.10.009
17. Chiofalo B, Palmara V, Laganà AS et al (2017) Fertility sparing strategies in patients affected by placental site trophoblastic tumor. Curr Treat Options Oncol 18:58. https://doi.org/10.1007/s11864-017-0502-0
18. Vitale SG, La Rosa VL, Rapisarda AMC, Lagana AS (2017) The importance of fertility preservation counseling in patients with gynecologic cancer. J Reprod Infertil 18:261–263
19. Vitale SG, La Rosa VL, Rapisarda AMC et al (2018) Fertility preservation in women with gynaecologic cancer: the impact on quality of life and psychological well-being. Hum Fertil (Camb) 21:35–38. https://doi.org/10.1080/14647273.2017.1339365

20. Laganà AS, La Rosa VL, Rapisarda AMC et al (2017) Psychological impact of fertility preservation techniques in women with gynaecological cancer. Ecancermedicalscience 11:ed62. https://doi.org/10.3332/ecancer.2017.ed62
21. Gueli Alletti S, Vizzielli G, Lafuenti L, Costantini B, Fagotti A, Fedele C, Cianci S, Perrone E, Gallotta V, Rossitto C, Scambia G (2018) Single-institution propensity-matched study to evaluate the psychological effect of minimally invasive interval debulking surgery versus standard laparotomic treatment: from body to mind and back. J Minim Invasive Gynecol 25(5):816–822
22. Laganà AS, La Rosa VL, Rapisarda AMC et al (2017) Anxiety and depression in patients with endometriosis: impact and management challenges. Int J Womens Health 9:323–330. https://doi.org/10.2147/IJWH.S119729
23. Vitale SG, La Rosa VL, Rapisarda AMC, Laganà AS (2017) Impact of endometriosis on quality of life and psychological well-being. J Psychosom Obstet Gynaecol 38:317–319. https://doi.org/10.1080/0167482X.2016.1244185
24. Rossitto C, Gueli Alletti S, Rotolo S et al (2016) Total laparoscopic hysterectomy using a percutaneous surgical system: a pilot study towards scarless surgery. Eur J Obstet Gynecol Reprod Biol 203:132–135. https://doi.org/10.1016/j.ejogrb.2016.05.007
25. Gueli Alletti S, Rossitto C, Cianci S et al (2018) The Senhance™ surgical robotic system ("Senhance") for total hysterectomy in obese patients: a pilot study. J Robot Surg 12:229–234. https://doi.org/10.1007/s11701-017-0718-9
26. Gueli Alletti S, Perrone E, Cianci S et al (2018) 3 mm Senhance robotic hysterectomy: a step towards future perspectives. J Robot Surg. https://doi.org/10.1007/s11701-018-0778-5
27. Rossitto C, Cianci S, Gueli Alletti S et al (2017) Laparoscopic, minilaparoscopic, single-port and percutaneous hysterectomy: comparison of perioperative outcomes of minimally invasive approaches in gynecologic surgery. Eur J Obstet Gynecol Reprod Biol 216:125–129. https://doi.org/10.1016/j.ejogrb.2017.07.026
28. Cosentino F, Vizzielli G, Turco LC et al (2018) Near-infrared imaging with indocyanine green for detection of endometriosis lesions (Gre-Endo Trial): a pilot study. J Minim Invasive Gynecol. https://doi.org/10.1016/j.jmig.2018.02.023
29. Rapisarda AMC, Cianci A, Caruso S et al (2018) Benign multicystic mesothelioma and peritoneal inclusion cysts: are they the same clinical and histopathological entities? A systematic review to find an evidence-based management. Arch Gynecol Obstet 297:1353–1375. https://doi.org/10.1007/s00404-018-4728-2
30. Gallotta V, Conte C, Giudice MT et al (2017) Secondary laparoscopic cytoreduction in recurrent ovarian cancer: a large, single-institution experience. J Minim Invasive Gynecol 25:644–650. https://doi.org/10.1016/j.jmig.2017.10.024
31. Fagotti A, Costantini B, Gallotta V et al (2015) Minimally invasive secondary cytoreduction plus HIPEC versus open surgery plus HIPEC in isolated relapse from ovarian cancer: a retrospective cohort study on perioperative outcomes. J Minim Invasive Gynecol 22:428–432. https://doi.org/10.1016/j.jmig.2014.11.008
32. Fanfani F, Fagotti A, Ercoli A et al (2015) Is there a role for tertiary (TCR) and quaternary (QCR) cytoreduction in recurrent ovarian cancer? Anticancer Res 35:6951–6955
33. Bristow RE, Puri I, Chi DS (2009) Cytoreductive surgery for recurrent ovarian cancer: a meta-analysis. Gynecol Oncol 112:265–274. https://doi.org/10.1016/j.ygyno.2008.08.033
34. Petrillo M, De Iaco P, Cianci S et al (2016) Long-term survival for platinum-sensitive recurrent ovarian cancer patients treated with secondary cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol 23:1660–1665. https://doi.org/10.1245/s10434-015-5050-x
35. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41. https://doi.org/10.1159/000180580
36. Sugarbaker PH, Jablonski KA (1995) Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg 221:124–132
37. Dindo D, Demartines N, Clavien PA (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 240:205–213
38. Issels RD (2008) Hyperthermia adds to chemotherapy. Eur J Cancer 44:2546–2554. https://doi.org/10.1016/j.ejca.2008.07.038
39. Fagotti A, Costantini B, Vizzielli G et al (2011) HIPEC in recurrent ovarian cancer patients: morbidity-related treatment and long-term analysis of clinical outcome. Gynecol Oncol 122:221–225. https://doi.org/10.1016/j.ygyno.2011.04.008
40. Cianci S, Vizzielli G, Fagotti A et al (2018) A novel HIPEC technique using hybrid CO_2 recirculation system: intra-abdominal diffusion test in a porcine model. Updates Surg. https://doi.org/10.1007/s13304-018-0557-x
41. Cianci S, Abatini C, Fagotti A et al (2018) Hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancies using new hybrid CO_2 system: preliminary experience in referral center. Updates Surg. https://doi.org/10.1007/s13304-018-0578-5
42. Paris I, Cianci S, Vizzielli G et al (2018) Upfront HIPEC and bevacizumab-containing adjuvant chemotherapy in advanced epithelial ovarian cancer. Int J Hyperth. https://doi.org/10.1080/02656736.2018.1503346
43. Falcone F, Scambia G, Benedetti Panici P et al (2017) Tertiary cytoreductive surgery in recurrent epithelial ovarian cancer: a multicentre MITO retrospective study. Gynecol Oncol 147:66–72. https://doi.org/10.1016/j.ygyno.2017.07.008
44. Vitale SG, Caruso S, Rapisarda AMC et al (2018) Isoflavones, calcium, vitamin D and inulin improve quality of life, sexual function, body composition and metabolic parameters in menopausal women: result from a prospective, randomized, placebo-controlled, parallel-group study. Prz Menopauzalny 17:32–38. https://doi.org/10.5114/pm.2018.73791
45. Caruso S, Cianci S, Fava V et al (2018) Vaginal health of postmenopausal women on nutraceutical containing equol. Menopause 25:430–435. https://doi.org/10.1097/GME.0000000000001061
46. Caruso S, Cianci S, Cariola M et al (2017) Improvement of low sexual desire due to antiandrogenic combined oral contraceptives after switching to an oral contraceptive containing 17β-Estradiol. J Womens Health (Larchmt) 26:728–734. https://doi.org/10.1089/jwh.2016.5801
47. Caruso S, Cianci S, Cariola M et al (2017) Effects of nutraceuticals on quality of life and sexual function of perimenopausal women. J Endocrinol Investig 40:27–32. https://doi.org/10.1007/s40618-016-0500-2
48. Caruso S, Rapisarda AM, Cianci S (2016) Sexuality in menopausal women. Curr Opin Psychiatry 29:323–330. https://doi.org/10.1097/YCO.0000000000000280
49. Caruso S, Cianci S, Amore FF et al (2016) Quality of life and sexual function of naturally postmenopausal women on an ultralow-concentration estriol vaginal gel. Menopause 23:47–54. https://doi.org/10.1097/GME.0000000000000485
50. Caruso S, Agnello C, Malandrino C et al (2014) Do hormones influence women's sex? Sexual activity over the menstrual cycle. J Sex Med 11:211–221. https://doi.org/10.1111/jsm.12348