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Centralizing surgery for ovarian cancer in a 'non-centralizing' country (Belgium): the UNGO (UCLouvain Network of Gynaecological Oncology) experience

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ABSTRACT

Objective In Belgium there is no centralization of surgery for ovarian cancer, with more than 100 centers treating around 800 cases per year. In 2017 a network with several collaborating hospitals was established to centralize surgery for ovarian cancer (UCLouvain Network of Gynecological Oncology; UNGO) following publication of the European Society of Gynecological Oncology (ESGO) recommendations and quality criteria for surgery of advanced ovarian cancer. We obtained ESGO accreditation in 2019.

Methods We retrospectively collected data associated with patients undergoing surgery in our institution from 2007 to 2016, before the creation of the network (cohort 1) and, following the establishment of UNGO (2017–2021), patients undergoing surgery were prospectively registered in a REDCap database (cohort 2). The outcomes of the two cohorts were compared.

Results A total of 314 patients underwent surgery in our institution from 2007 and 2021: 7.5 patients/year in cohort 1 (retrospective, 2007–2016) and 40.8 patients/year in cohort 2 (after network creation, 2017–2021). Median disease-free survival was increased from 16.5 months (range 13.2–20.4) in cohort 1 to 27.1 months (range 21.5–33.2) in cohort 2 (p=0.0004). In cohort 2, the rate of patients with residual disease at the end of the surgery was significantly less (18.7% vs 8.8%, p=0.023), although more patients in cohort 1 received neoadjuvant chemotherapy (89% vs 54%, p<0.001). However, there was a higher rate of complications in the patients in cohort 2 (18.8% vs 30%, p=0.041).

Conclusion Our study shows that, with the help of ESGO and its recommendations, we have been able to create an efficient advanced ovarian cancer centralized network and this may provide an improvement in the quality of care.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Surgery is the cornerstone of treating advanced ovarian cancer. Following the European Society of Gynecological Oncology (ESGO) guidelines should increase the quality of surgery and the survival of patients.

WHAT THIS STUDY ADDS

⇒ By following the ESGO recommendations and quality criteria for surgery of advanced ovarian cancer, we established a network to centralize surgery for ovarian cancer in Belgium based solely on the best medical interest of patients. This study shows that centralization may improve the survival of patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study shows that centralization is possible in a non-centralizing country. We encourage gynecologists and oncologists to join ESGO and to organize care for patients with ovarian cancer on a medical basis.

INTRODUCTION

Cytoreductive surgery with multiple organ resection and peritonectomy to achieve complete cytoreduction improves survival in patients with epithelial ovarian cancer with reasonable complications, according to retrospective studies.[1 2] In suitable patients it is the standard treatment for advanced ovarian cancer.[3] At the same time, the experience of the surgeon and the number of cases she/he operates on per year, along with adequate patient selection, improves the quality of the cytoreduction and the cancer-related survival of patients.[4] In 2015 the European Society of Gynecological Oncology (ESGO) set up an accreditation process for centers to improve the quality of the surgery for advanced ovarian cancer. Candidate centers were required to operate on 24 advanced ovarian cancer cases (International Federation of Gynecology and Obstetrics (FIGO) stage III–IV) per hospital per year.

In Belgium, the gynecologic oncology subspeciality is not recognized. There is no restriction for centers or surgeons to perform surgery for ovarian cancer, so cases are spread across hospitals. The Belgian Healthcare Knowledge Center performed a review of all cases of ovarian cancer and borderline tumors treated in Belgium from 2014 and 2018 and

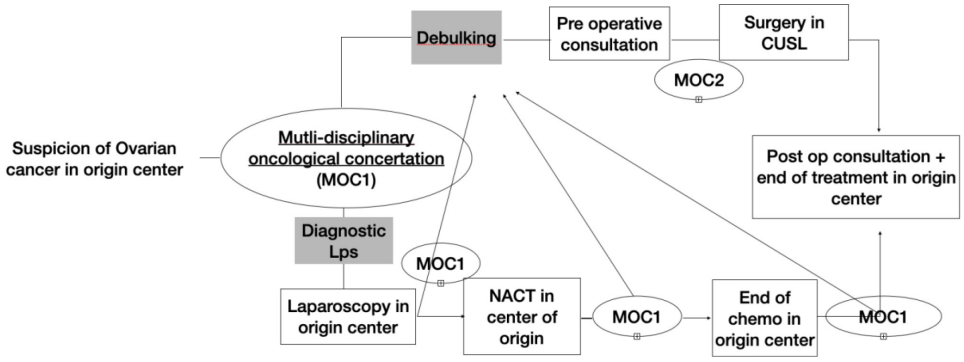


Figure 1 General overview of the UCLouvain Network of Gynecological Oncology (UNGO) organization. CUSL, Cliniques Universitaires Saint-Luc; MOC1, multidisciplinary discussion at center of origin; MOC2, multidisciplinary discussion at reference center; NACT, neoadjuvant chemotherapy.

the conclusion was similar to their previous report for the period 2004–2008,[5] that 100 hospitals continue to treat ovarian cancer. More than 50% treated <10 cases/year and only five treated >25 cases/year. In their recent publication, the authors have shown that survival in centers treating <8 cases/year was 2.5 years less than in centers treating >8 cases/year.[6]

To address this problem, and realizing that even our academic center (Cliniques universitaires Saint Luc – UCLouvain Academic Hospital) failed to reach the recommended 24 cases per year, we contacted several centers with which we already had collaboration and proposed building a network to improve the quality of the care offered to patients with advanced ovarian cancer, called the 'UCLouvain Network of Gynecological Oncology' (UNGO). With the clear guidelines provided by ESGO on the criteria for ovarian cancer surgery quality, surgeons were more open to collaborate. In 2017, the network initially included three hospitals (Tournai Center Hospitalier de Wallonie Picarde, Brussel Cliniques de l'Europe (two sites) and Cliniques universitaires St Luc). Cliniques St-Jean Brussel joined in 2018, followed by Cliniques St-Pierre Ottignies in 2019 and finally Centre Hospitalier Regional from Mons in 2021.

The originality of our network is that only surgery and multidisciplinary discussion were centralized. The majority of the care remains in the center of origin with the local team. We also implemented a system whereby the patient's primary gynecologic oncologist performs the surgery together with the center's gynecologic oncologist at the reference center. The academic hospital (Cliniques universitaires Saint-Luc) was chosen to be the reference center.

The practical organization and flow of the patients is shown in Figure 1. When a patient presents with suspected advanced ovarian cancer in her center of origin, her assessment and the first multidisciplinary discussion take place in the center of origin. If primary surgery with curative intent is decided upon (debulking), the patient is referred to the reference center for a pre-operative consultation where she meets the oncology gynecology team and the anesthesiology team. A second multidisciplinary discussion takes place in the reference center to validate the therapeutic strategy and the patient is operated on in the reference center, Cliniques Universitaires Saint-Luc, with her gyneco-oncologist from the center of origin. The immediate post-operative period is managed in the reference center and the patient is then returned to her center of origin for post-operative consultation and organization of the rest of her treatment. If diagnostic laparoscopy is proposed, this is performed at the center of origin and a second multidisciplinary discussion is held at the center of origin. If debulking is proposed, the patient is referred to the reference center and follows the same care pathway. If neoadjuvant chemotherapy is proposed, this is organized at the center of origin. After three treatments, a check-up is performed and a new multidisciplinary discussion takes place in the center of origin and, if surgery is proposed, she is referred to the reference center and follows the same care pathway. If surgery is not possible after three courses, the next three courses are performed in the center of origin, with a new multidisciplinary discussion in the center of origin at the end of the courses. If surgery is proposed, she is referred to the reference center and follows the same care pathway. If surgery is not possible, the patient continues her follow-up in the center of origin unless a clinical study is available in the reference center. Fagotti et al[7] showed that laparoscopy carried out in referring centers by trained local onco-gynecologists is reliable for assessing resectability in patients with advanced ovarian cancer.

We report on the results of the first 5 years of the UNGO set-up to centralize the treatment of ovarian cancer in Belgium. ESGO accreditation for advanced ovarian cancer surgery was received in 2019.

METHODS

We conducted a retrospective comparison of the outcomes of the patients before and after centralization of the treatment of advanced ovarian cancer at the Cliniques universitaires Saint-Luc inside the UNGO.

We retrospectively reviewed the files of all the patients with advanced ovarian cancer treated at the Cliniques universitaires Saint-Luc from 2007 to 2016 (before the creation of the network) and registered the pre- and post-operative information as well as the clinical evolution. Within UNGO, we prospectively registered all the operated cases using REDCap electronic data capture tools hosted at Clinique universitaire Saint-Luc[8 9] (with the authorization of the ethical committee for this registry) and followed their evolution using follow-up surveys sent by email with the agreement of the gynecologic oncologist from the referring center.

The primary end point of the study was disease-free survival, which is known to be most influenced by the quality of the

surgery or patient selection. Secondary end points were overall survival, rate of complete cytoreduction (by collecting information on residual disease in the surgical report and defining complete surgery as no visible residual disease), the length of hospitalization, and post-operative complications. Confounding factors considered were the use of maintenance therapy with poly(ADP-ribose) polymerase (PARP) inhibitors and/or the anti-VEGF monoclonal antibody (bevacizumab),[10–12] recently introduced in Belgium. In particular, PARP inhibitors were not available for frontline treatment (outside of clinical studies) before May 2020.

Statistical analysis

Comparison of patient characteristics, hospital stay and post-operative complications in the two cohorts was performed for continuous variables with an unpaired Student's t-test or Wilcoxon–Mann–Whitney test for non-normal data. For discrete variables a χ^2 test or Fisher's test was used when the expected minimum number of patients was <5. Disease-free survival and overall survival were estimated using the Kaplan–Meier method and the two cohorts were compared using the log-rank test. Univariate and multivariate analysis was performed using the Cox proportional-hazards model.

RESULTS

A total of 314 patients underwent surgery at the Cliniques universitaires Saint-Luc for ovarian cancer between 2007 and 2021 and were included in the study; 35 patients were excluded from the analysis because of FIGO stages less than III. Between 2007 and 2016 (cohort 1), 75 patients were treated for advanced ovarian cancer at the Cliniques universitaires Saint-Luc (7.5 patients/year). After centralization from 2017 to 2021 (cohort 2), 204 patients were treated within the UNGO (40.8 patients/year) (Figure 2). Median follow-up was 39.75 months from diagnosis (range 24.6–65.5) for cohort 1 and 17.43 months (range 10.7–31.0) for cohort 2.

More patients in cohort 1 than in cohort 2 received neoadjuvant chemotherapy (89% vs 54%, p<0.001), even though significantly more patients in cohort 1 had residual disease at the end of the surgery, both in primary and interval surgery (18.7% vs 8.8%, p=0023) (see Table 1 and Online supplemental table 1 for details of the amount of residual disease). For patients receiving neoadjuvant chemotherapy, in cohort 1 the majority of patients (65.7%) received six cycles before surgery whereas, in cohort 2, the majority of patients underwent surgery after three cycles (45.9%), as recommended in ESGO guidelines (see Online supplemental table 2). However, patients in cohort 1 had a higher initial CA125 and a greater volume of ascites. Histologically, more patients in cohort 2 presented with serous carcinoma and more patients in cohort 1 presented with undifferentiated carcinoma (Table 1).

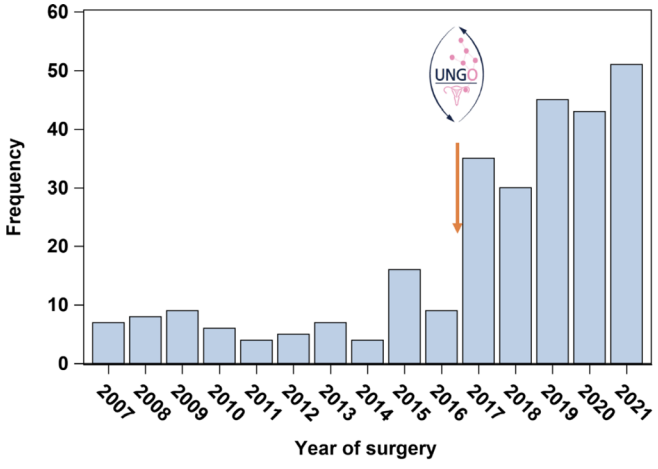


Figure 2 Change in the number of cases operated on per year from 2007 to 2021. Since the creation of UNGO (UCLouvain Network Of Gynecological Oncology) and the subsequent centralization of cases, the number of cases operated on is >25/year and has increased each year to 2021.

We observed a significantly longer hospital stay for patients in cohort 2, linked to a significant increase in post-operative complications from 18.8% to 30% (p=0.041) (see Table 2 and Online supplemental table 3 for details of complications). There was an increase in Dindo–Clavien grade III complications in cohort 2 requiring radiological or surgical intervention, in particular fecal peritonitis (11%), secondary hemorrhage (6%), pneumothorax (4.8%), and abdominal wall complications (11%).

With centralization and the higher number of patients operated on per year, radical surgery with upper abdominal surgery was also implemented when needed (see Online supplemental table 4). The standard procedures (hysterectomy with bilateral salpingo-oophorectomy, omentectomy and colo-rectal resection) were not statistically significantly different in the two cohorts, but the use of upper abdominal procedures was higher in cohort 2 (right diaphragm stripping 22.7% vs 52.5% (p<0.001), left diaphragm stripping 5.3% vs 19.6% (p=0.004), splenectomy 2.7% vs 14.2% (p=0.007), small omentum removal 6.7% vs 18.6% (p=0.014)). Digestive procedures were performed in cohort 1 by a colorectal surgeon without a gynecologic oncologist. In cohort 2, digestive procedures were always performed jointly by the reference center's gynecologic oncologist and a colorectal or hepatobiliary surgeon.

Patients in cohort 1 had a median disease-free survival of 16.5 months (range 13.2–20.4) compared with 27.1 months (range 21.5–33.2) for cohort 2 (p=0.0004) (see Figure 3). The median overall survival was not reached for cohort 2, and was 57.7 months for cohort 1. To ensure that any improvement in disease-free survival in cohort 2 over cohort 1 was not due to maintenance therapy (bevacizumab and PARP inhibitor) offered to more recent patients, we removed all patients who received maintenance therapy from the analysis (n=7 in cohort 1 and n=47 in cohort 2). However, this did not change the median disease-free survival observed (16.5 vs 27.1 months, p<0.001) because most patients who received maintenance therapy were included late into the cohorts (Online supplemental figure 1).

Among patients with complete cytoreduction, the median disease-free survival remained better in cohort 2 (28.1 months vs 18.7 months, p<0.001) (see Online supplemental figure 2).

We next performed a univariate and multivariate analysis on disease-free survival (see Online supplemental table 5). The univariate analysis showed that the surgery performed after centralization was associated with increased disease-free survival (HR 0.56 (range 0.399–0.774), p<0.001). Other factors influencing disease-free survival were also found on univariate analysis, including residual disease, grade 3 histology, age, and neoadjuvant chemotherapy use. FIGO stage IV did not significantly influence disease-free survival,

Table 1 Patient characteristics

	2007–2016 (n=75)	2017–2021 (n=204)	P value
Age, years, mean±SD	63.2±12.14	60.80±14.90	0.216
FIGO stage at diagnosis, n (%)			0.435
III	57 (76.0%)	144 (70.6%)	
IV	18 (24.0%)	58 (28.4%)	
Missing	0 (0.0%)	2 (1.0%)	
Neoadjuvant chemotherapy, n (%)			<0.001*
Yes	67 (89.3%)	111 (54.4%)	
No	8 (10.7%)	93 (45.6%)	
Missing			
Residual disease, n (%)			0.023*
Yes	14 (18.7%)	18 (8.8%)	
No	61 (81.3%)	185 (90.7%)	
Missing	0 (0.0%)	1 (0.5%)	
BRCA mutation, n (%)			0.842
No mutation	24 (32.0%)	53 (26.0%)	
BRCA 1 or BRCA 2 mutation	8 (10.7%)	16 (7.8%)	
Missing	43 (57.3%)	135 (66.2%)	
Initial CA125, median (P25–P75)			<0.001*
Initial CA125 (IU/L)	1283 (257–2424)	336 (96–861)	
Histological type, n (%)			<0001*
Serous/serous papillary	50 (74.6%)	167 (85.6%)	
Mucinous	0 (0.0%)	5 (2.6%)	
Endometrioid	6 (8.9%)	5 (2.6%)	
Clear cells	1 (1.5%)	1 (0.5%)	
Undifferentiated	10 (14.9%)	2 (1.0%)	
Other	0 (0.0%)	15 (7.7%)	
Missing	8 (10.7%)	9 (4.4%)	
Grade, n (%)			0.571
Low grade (I–II)	7 (9.3%)	24 (11.8%)	
High grade (III)	60 (80.0%)	159 (77.9%)	
Missing	8 (10.7%)	21 (10.3%)	
Ascites, n (%)			0.267
Yes	49 (65.3%)	122 (59.8%)	
No	8 (10.7%)	32 (15.7%)	
Missing	18 (24.0%)	50 (24.5%)	
Ascites volume, n (%)			<0.001*
No ascite	8 (10.7%)	32 (15.7%)	
0–500 mL	14 (18.7%)	72 (35.3%)	
500 mL–1 L	3 (4.0%)	13 (6.4%)	
1–3 L	18 (24.0%)	13 (6.4%)	
>3 L	14 (18.7%)	24 (11.8%)	
Missing	18 (24.0%)	50 (24.5%)	
Maintenance therapy, n (%)			0.011*
Yes	7 (9.3%)	47 (23.0%)	

Continued

Table 1 Continued

	2007–2016 (n=75)	2017–2021 (n=204)	P value
No	67 (89.3%)	157 (77.0%)	
Missing	1 (1.3%)	0 (0.0%)	
Maintenance therapy drug (patients with maintenance therapy: n=54)			<0.001*
PARPi	0 (0.0%)	43 (91.5%)	
Bevacizumab	7 (100.0%)	4 (8.5%)	

*Statistically significant.
BRCA, breast cancer gene; CA125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics; PARPi, poly(ADP-ribose) polymerase inhibitor.

but only patients with a complete response to neoadjuvant chemotherapy or who were completely resectable were offered surgery. Patients with persistent multi-metastatic disease or metastases that did not respond after six cycles of neoadjuvant chemotherapy were either referred for a new chemotherapy regimen (with or without a therapeutic window) or, if eligible, were given bevacizumab or PARP inhibitor. The multivariate analysis showed that only age (HR=1.02 (range 1.00–1.45), p=0.045), residual disease (HR=3.16 (range 1.45–6.91), p=0.004) and BRCA mutation (HR=0.38 (range 0.18–0.80), p=0.011) significantly influenced disease-free survival.

DISCUSSION

Summary of the Main Results

This study shows that it is possible to centralize treatment based only on a medical decision. After our original centralization process, we were able to show an improvement in disease-free survival in relation to the rise in the number of patients operated on per year from 7.5 to 40.8. The ESGO guidelines and the accreditation processes have been instrumental in setting up the UNGO collaborative network. We have confirmed that centralization, by increasing the number of surgeries performed in one hospital and also with better patient selection, improves patient survival.[13]

Results in the Context of Published Literature

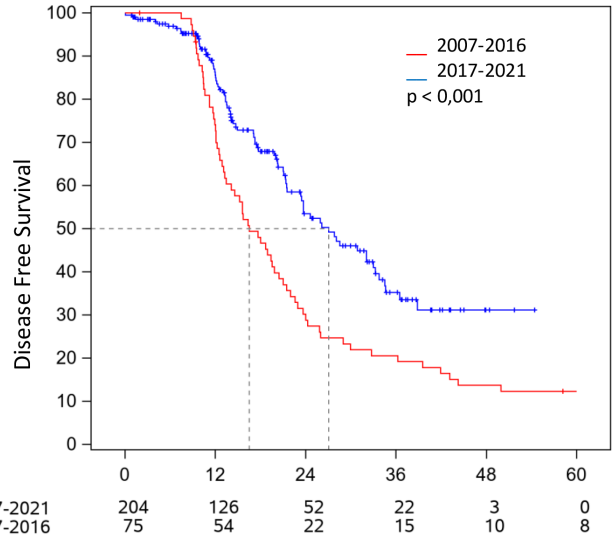
Several different factors can explain the improvement in disease-free survival observed in the UNGO cohort. First, there is better stratification of patients and selection of treatment regimens following the double multidisciplinary discussion of all cases. In our experience, this resulted in an important reduction in systematic neoadjuvant chemotherapy and more primary debulking surgery with a higher level of complete cytoreductive surgery. In cohort 1, most of the residual disease was in the superior abdomen or mesentery, which was not routinely managed. In cohort 2, in which radical surgery had been implemented, residual disease was in millimeters in cases of diffuse disease in the small bowel which could not be completely resected. The cases of supra-centimetric disease in this cohort were in patients where surgery was aborted because the carcinomatosis had spread extensively and complete resection was not possible.

Second, the increase in the number of cases operated on per referral surgeon (J-LS and ML) has also increased the expertise

Table 2 Comparison of length of hospital stay and the rate of post-operative complications in the two cohorts

	2007–2016 (n=75)	2017–2021 (n=204)	P value
Hospital stay, days, median (P25–P75)	7 (6–10)	9 (7–11)	0.007
Post-operative complications			
Missing	0 (0.0%)	1 (0.5%)	0.041
Yes	14 (18.7%)	63 (30.9%)	
Dindo–Clavien classification			
Missing	0 (0.0%)	16 (7.8%)	0.258
I	5 (6.7%)	9 (4.4%)	
II	8 (10%)	19 (9.3%)	
III	1 (1.3%)	13 (6.3%)	
IV	0 (0.0%)	3 (1.4%)	
V	0 (0.0%)	3 (1.4%)	

Length of hospital stay is significantly longer after centralization and the rate of post-operative complications is significantly increased with mainly an increase in grade III complications according to the Dindo–Clavien classification.



	2007-2016 N = 75	2017-2021 N = 204	p-value
Kaplan Meier of disease free survival (months)			
Median	16.5	27.1	<0,001
Confidence Interval 95%	(13.2 – 20.4)	(21.5 – 33.2)	

Figure 3 Kaplan–Meier curves of disease-free survival of all patients in the two cohorts showing that centralization of ovarian cancer care increases disease-free survival by 10 months.

and quality of the surgery. Centralization and the higher number of patients operated on per year have facilitated the development of radical surgery with upper abdominal surgery, enabling higher rates of optimal cytoreduction even in patients with more extensive disease.[14] Neoadjuvant chemotherapy was systematically used before centralization, given that radical surgery and upper abdominal surgery were not routinely performed when disease was found on the diaphragm or in the upper abdomen. Finally, we noted that before centralization, surgery was mostly performed after six cycles of neoadjuvant chemotherapy, which is not standard of care (see Online supplemental table 2).

Pairing surgeons during cytoreduction also improves the expertise of the referring gynecologic oncologists and their ability to assess resectability without having to centralize diagnostic laparoscopy. The combination of the European guidelines edited by ESGO and the increase in the number of cases has contributed to better adherence to the guidelines in all participating centers. Indeed, it has been shown that, in high-volume centers, there is better adherence to the guidelines.[15]

There are only 10 million inhabitants in Belgium, meaning that only approximatively 800 new cases of ovarian cancer are treated each year, a strong argument for limiting the number of centers authorized to treat ovarian cancer.

Our study has shown that there is a significant increase in postoperative complications, mostly grade III complications, that has already been described in other centers implementing radical surgery.[16]

Strenghts and Weaknesses

Here we report real-life data and show that it is possible to centralize oncological pathologies on a medical basis solely for the benefit of our patients. We also show that centralization based on ESGO recommendations rapidly improves patient survival.

The limitations of our study are the long time frame over which it was conducted and its retrospective nature. The number of patients is also quite low, especially in cohort 1, limiting the number of possible comparisons of factors that could influence the observed difference in disease-free survival. In particular, we were not able to compare disease-free survival in patients who had neoadjuvant chemotherapy and then optimal cytoreduction before and after centralization. As more patients in cohort 1 received neoadjuvant chemotherapy, the groups were not balanced.

Even with the important increase in the number of cases treated in the reference center after centralization, it cannot yet be considered to be a high-volume center, especially considering that there was more than one gynecologic oncologist.

Our study is a before-and-after study and it is well known that, when performing sequential comparisons, the 'after' group is always going to have a more favorable response because more selective patients are included, better surgery is performed, and follow-up is shorter.

During the study period the timing of surgery when neoadjuvant chemotherapy was used changed substantially, with a large majority of patients in cohort 1 undergoing surgery after six courses of treatment and, in cohort 2, many more undergoing surgery after three courses, which represents a major change in medical management. Furthermore, there were very few patients who benefited from maintenance therapy, and limited follow-up of those patients who were included late, given the recent reimbursement of these treatments. We cannot therefore conclude that these treatments have no influence on the observed difference in disease-free survival.

Implications for Practice and Future Research

Encouraged by these results and by the accreditation processes for other gynecological cancers undertaken by the ESGO, new

discussions have been started within UNGO to also centralize cervical cancer surgery and radiotherapy. Furthermore, in endometrial cancer, data collected in the different expert centers of our network (not yet published) show that surgical skills and adhesion to the ESGO guidelines are increasing and discussions are underway to also organize the management of these more frequent cancers.

CONCLUSION

Centralization of ovarian cancer surgery is key to raising the quality of care for patients. Centralization of care is achievable and results in a major improvement in disease-free survival of patients with advanced ovarian cancer. The ESGO guidelines and accreditation process were an important incentive and very guiding in establishing UNGO.

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Contributors ML collected the data, built the UNGO with J-LS, operated on the patients and wrote the manuscript. MJ, MW, FG, J-PVG, ND, VM, LV, and PG are representatives of their institutions in UNGO and recruited and operated on the patients, and reviewed the manuscript. KS performed the statistical analysis. PJ, CM, and AG are in charge with ML and J-LS of the post-operative care of the patients, participating in the multidisciplinary board, and reviewing the manuscript. J-FB is the medical oncologist of the reference center and participated in the building of UNGO. He also reviewed the manuscript. He is in charge with ML of the clinical research in gynecological oncology. J-LS co-built and supervised UNGO, operated on the patients as one of the referent gynecologist oncologists, and reviewed the manuscript. AMB review the text and corrected the English. ML is the guarantor of this work.

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