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## What underlies the observed hospital volume-outcome relationship?

Marius Huguet, Xavier Joutard, Isabelle Ray-Coquard, Lionel Perrier

### Abstract:

Studies of the hospital volume-outcome relationship have highlighted that a greater volume activity improves patient outcomes. While this finding has been known for years in health services research, most studies to date have failed to delve into what underlies this relationship. This study aimed to shed light on the basis of the hospital volume effect by comparing treatment modalities for epithelial ovarian carcinoma patients. Hospital volume activity was instrumented by the distance from patients' homes to their hospital, the population density, and the median net income of patient municipalities. We found that higher volume hospitals appear to more often make the right decisions in regard to how to treat patients, which contributes to the positive impact of hospital volume activities on patient outcomes. Based on our parameter estimates, we found that the rate of complete tumor resection would increase by 10% with centralized care, and by 6% if treatment decisions were coordinated by high volume centers compared to the ongoing organization of care. In both scenarios, the use of neoadjuvant chemotherapy would increase by 10%. As volume alone is an imperfect correlate of quality, policy makers need to know what volume is a proxy for in order to devise volume-based policies.

### Keywords:

Volume outcome relationship, France, Epithelial Ovarian Cancer, Instrumental variable, Organization of care, Care pathway, Learning effect, Centralization of care.

### JEL codes:

C31, C36, I11, I18, L11

# What underlies the observed hospital volume-outcome relationship?

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## SUMMARY

Studies of the hospital volume-outcome relationship have highlighted that a greater volume activity improves patient outcomes. While this finding has been known for years in health services research, most studies to date have failed to delve into what underlies this relationship. This study aimed to shed light on the basis of the hospital volume effect by comparing treatment modalities for epithelial ovarian carcinoma patients. Hospital volume activity was instrumented by the distance from patients' homes to their hospital, the population density, and the median net income of patient municipalities. We found that higher volume hospitals appear to more often make the right decisions in regard to how to treat patients, which contributes to the positive impact of hospital volume activities on patient outcomes. Based on our parameter estimates, we found that the rate of complete tumor resection would increase by 10% with centralized care, and by 6% if treatment decisions were coordinated by high volume centers compared to the ongoing organization of care. In both scenarios, the use of neoadjuvant chemotherapy would increase by 10%. As volume alone is an imperfect correlate of quality, policy makers need to know what volume is a proxy for in order to devise volume-based policies.

**Keywords:** Volume outcome relationship; France; Epithelial Ovarian Cancer; Instrumental variable; Organization of care; Care pathway; Learning effect; Centralization of care.

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## **1. INTRODUCTION**

The volume outcome relationship (VOR) in health economics has been the subject of extensive investigation. Most of the studies to date have found that higher volume hospitals have better outcomes (e.g., lower mortality rates). Two recent studies performed a systematic review, either of the surgeon VOR or of the hospital VOR, in order to obtain an overview of all of the types of procedures and/or diseases for which the VOR has been investigated and found to have an important role (Morche, Mathes, & Pieper, 2016; Pieper, Mathes, Neugebauer, & Eikermann, 2013). However, an observed correlation between the hospital volume and patient outcomes does not necessarily imply a causal impact of volume on outcomes. Luft et al. have proposed two hypotheses for how volume could correlates outcomes (Luft, Hunt, & Maerki, 1987). These are, on the one hand, the “practice-makes-perfect” hypothesis, which states that physicians and hospitals with a greater number of patients develop better skills, and on the other hand the “selective-referral” hypothesis, which is based on the opposite notion, namely that physicians and hospitals that have better outcomes attract more patients. The correlation between hospital volume and outcomes is likely to be a combination of these two hypotheses, making hospital volume endogenous in an outcome model. Furthermore, failing to properly control for differences in case-mix according to hospital volume activities also makes hospital volume endogenous if they are correlated to patient outcomes. To overcome these econometric issues, several studies have instrumented hospital volume activities by the number of potential patients and other hospitals in a defined area (Gaynor et al., 2005; Gowrisankaran, Ho, & Town, 2006; Hentschker & Mennicken, 2017; Ho, Town, & Heslin, 2007b; Kahn, Ten Have, & Iwashyna, 2009).

Identifying the causal impact of volume on outcomes has major policy implications, since centralization of care would only be beneficial if hospital volume improves patient outcomes. These studies tend to support the notion assumed in the medical literature that practice indeed makes perfect. What most volume-outcome studies lack, however, is “delving into” what underlies the observed or estimated relationship. Identifying the causal impact of volume on outcomes does not provide information about the learning process that it implies. The learning effect implied by the ‘practice makes perfect’ hypothesis could either relate to improvement in the clinicians’ skills at performing a specific procedure (e.g., a surgical intervention), or relate to a better ability of clinicians to choose the optimal treatment, especially for complex diseases with multiple treatment options. A study by Mesman et al. identified intermediate factors that could explain part of the observed VOR (Mesman, Westert, Berden, & Faber, 2015). They identified three categories of intermediate factors: compliance with an evidence-based process of care, the level of specialization, and hospital-related factors (e.g., capacity, staffing, health services, etc.). A recent study of advanced cancer surgery proposed instrumentation of hospital volume by exploiting exogenous variation of hospital volume due to the creation or decommissioning of entire cancer clinics (Avdic, Lundborg, & Vikström, 2014). They also proposed several alternative interpretations of the positive impact of an increase in hospital volume on patient outcomes. They tested whether the positive impact of an increase in volume could be due to organizational changes, staff transfers, a change in the patient-hospital distance, technology, and waiting times. Ultimately, they rejected all of their alternative interpretations of the impact of hospital volume and they concluded that the effect of volume on outcomes is consistent with the ‘learning by

doing' hypotheses, in which experience with treating highly heterogeneous patients plays a fundamental role in the learning process.

We chose to study the case of Epithelial Ovarian Carcinoma, which is characterized by a complex care pathway with multiple treatment options that depend on the patient's condition and the clinician's decisions. As stipulated by the French ministerial order of 27 March 2007, French legislation requires a minimum hospital volume activity of 20 cases per year in order to receive authorization to treat gynecological cancers. The cutoff for gynecological cancers includes ovarian, vulvar, cervical uterine, and vaginal cancers. It has been shown that this cutoff is not enough to guarantee sufficient hospitals volume activities for ovarian cancer surgery in France (Huguet et al., 2018).

Although there has been extensive research on the VOR, very few changes have been implemented in regard to the organization of care. Luft (2017) has pointed out that "The goal should be understanding what accounts for the relationship when it is observed so as to then learn how to improve outcomes". While several studies have identified differences in treatments according to hospital volume activities, none of them have linked these differences to patient outcomes to see whether they contributed to the observed VOR. In this study, we distinguish between a learning effect on the ability to perform a procedure and a learning effect on the ability to make the right decisions in the causal impact of hospital volume on outcomes. The hypothesis tested in this paper is that, depending on the patient's characteristics, the care pathway could differ according to hospital volume activities, and that these differences could explain part of the positive impact of hospital volume on outcomes for EOC patients. More specifically, we tested whether they are differences in the use of neoadjuvant chemotherapy according to hospital

volume activities, and we examined whether this led to a heterogeneous effect in regard to the treatment received. We also compared the way hospitals used neoadjuvant chemotherapy in the time between the initiation of chemotherapy and surgery, and how this was linked to patient outcomes.

Centralized care at high volume hospitals is thought to be the optimal organization of care (Friebel, Hauck, & Aylin, 2017). Nevertheless, very few countries have moved to centralized care for several reasons. One limitation of centralized care is that it decreases competition between care providers, and it has been clearly shown that competition between providers in a fixed-price market improves the quality of care, since providers compete in regard to aspects other than price, such as the quality or hospital's amenities (Gaynor & Town, 2012). A study that took into account the changes in the market structure that would occur with centralized care found that regionalization of care for complex cancer surgeries would increase consumer surplus, while controlling for the negative impact of a reduction in competition between providers that it would incur (Ho, Town, & Heslin, 2007a). The second major limitation of centralized care is that it could increase inequalities in access to quality care by increasing in the distance between patients and the site where they receive treatment. The impact of the implementation of minimal volume standards in Germany and its impact on the travel time for patients (C Hentschker & Mennicken, 2015) has been modeled. This indicated that centralized care for aortic aneurysms without rupture and hip fracture would improve patient outcomes while having a negligible impact on patient travel times. However, in their analysis they assumed that patients would be redirected to their nearest high volume center in order to centralize the care. By making this assumption,



they failed to account for the patients' freedom to choose their preferred provider, which is in fact the case in most developed countries.

An alternative solution to improve patient outcomes without centralizing care is to improve the quality of care of low volume providers. Thus, in order to reduce the differences in outcomes according to hospital volume activities, it is important for policy makers to understand the process by which high volume providers achieve better outcomes. Unraveling the process of learning and determination of the extent to which the decisions by clinicians play a role in the volume outcome relationship could have major implications and offer alternatives to centralized care for improvement of the overall quality of care.

In this study, we have highlighted several factors that characterize the observed part of VOR for EOC patients. Higher volume hospitals appear to more often make the right decisions in regard to how to treat patients, which contributes to the positive impact of hospital volume activity on patient outcomes. Based on our parameter estimates, we found that the rate of complete tumor resection would increase by 10% with centralized care, and by 6% if treatment decisions were coordinated by high volume centers compared to the ongoing organization of care. In both scenarios, the use of neoadjuvant chemotherapy would increase by 10%. As volume alone is an imperfect correlate of quality, policy makers need to know what volume is a proxy for in order to devise volume-based policies.

The remaining part of this paper is structured as follows: section 2 describes the data and the empirical strategy; section 3 presents the results, and section 4 provides a discussion of the results and the conclusions.

## **2. DATA and METHODS**

### **2.1. Data**

Several databases were used for this retrospective study. These comprised three clinical databases from clinical registries, the “Hospi Diag” public database of hospital characteristics, and open access datasets from the National Institute for Statistics and Economic Studies (INSEE).

The three clinical databases contained exhaustive datasets of patients in first-line treatment for EOC in 2012 in three regions of France (Basse Normandie, Bourgogne and Rhone-Alps). These three regions account for 15% of the metropolitan French population<sup>1</sup>. The Rhone-Alpes region is located in the southeast of France, and has several large cities; the three biggest being Lyon, Grenoble, and Saint-Etienne. Basse Normandie is located in the northeast of France, and Bourgogne is in the east. The database was generated by the EMS team (Medical Evaluation and Sarcomas) at the Leon Berard cancer research center (Lyon, France), the registry of Caen, and the registry of Dijon. They established an exhaustive list of all of the patients newly diagnosed with ovarian cancer in these regions using existing lists from oncology treatment-coordinated centers (3C), and from pathologists in these regions. The inclusion criteria were: first-line treatment for EOC, diagnosed in 2012, an incident case, more than 18 years of age, residing in France, and being treated at a hospital in one of these three regions. The exclusion criteria were: non-epithelial disease, relapsed disease, less than 18 years of age, or patients living in the region who had

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<sup>1</sup> <https://www.insee.fr/fr/statistiques/>

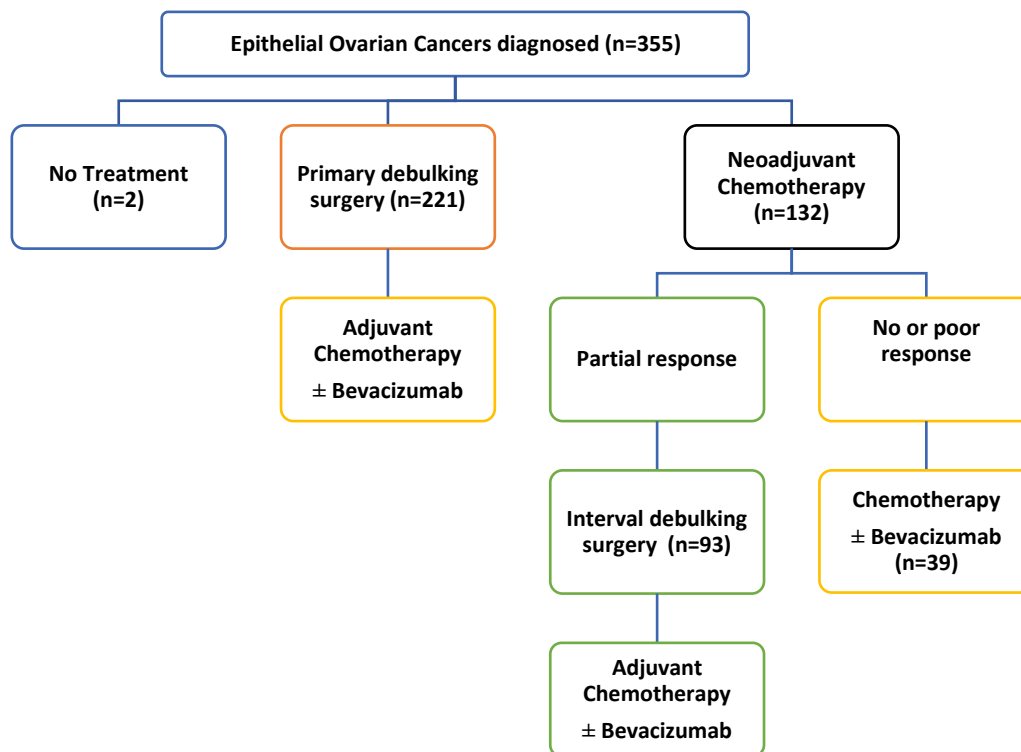
undergone treatment in another region of France. Finally, two years after diagnosis period, clinical research assistants collected the data at all of the included hospitals.

The databases include information on patient characteristics, such as age, cancer history (yes or no), patient residential postal codes, and — above of all — detailed information on the severity of the cancer: the presence of ascites (yes or no), histology (e.g., high-grade serous carcinoma, other histological subgroup, or unknown), the FIGO stage (I to IV), and the tumor grade (1 to 3).

The presence of ascites determines the level of liquid in the abdomen that can be identified at the time of diagnosis and that is likely to worsen the patient's outcome. Epithelial ovarian tumors are classified into different histological subgroups based on several characteristics of the tumor (Kaku et al., 2003). Large differences in survival have been noted between different histological subgroup (Ji, Försti, Sundquist, Lenner, & Hemminki, 2008). The FIGO stage relates to the size of the tumor, while the grade reflects the speed at which the tumor is growing.

We obtained detailed information on first-line treatments for each patient. Figure 1 provides an overview of the treatment options for patients diagnosed with EOC. Primary surgery has been the standard treatment for decades. It aims to remove all of the tumor (i.e., complete tumor resection), which correlates strongly with overall survival (Bois et al., 2009). Neoadjuvant chemotherapy followed by surgery is a treatment strategy for advanced stage EOC patients, and its aim is to reduce the size of the tumor before the surgery in order to increase the likelihood of a complete resection, and to avoid a primary surgery that would be too aggressive for patients who are particularly ill (Qin, Jin, Ma, Zhang, & Pan, 2018).

Figure 1 - Care pathway of EOC patients



Several hospital characteristics were taken into account. This was done by matching this database with the “Hospi Diag”<sup>2</sup> public database of hospital characteristics for the year 2012 using the FINESS number (i.e., Fichier National des Etablissements Sanitaires et Sociaux, which is a unique identifier for French hospitals). Several hospital characteristics were included, such as the share of the activity represented by cancerology, the bed occupation rates in the surgery unit, the number of beds, the hospital’s accreditation by the National Authority for Health (Giraud, 2001), and the number of surgical interventions per surgeon.

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<sup>2</sup> <https://www.data.gouv.fr/fr/datasets/hospi-diag/>

In order to instrument hospital volume activities and to be able to identify a causal impact of volume on outcome, we also used patient residential postal codes. First, by computing the distance between each patient's residential postal code and the exact location of their hospital for first-line treatment. Driving distances were computed using the function *'mapdist'* of the package *'ggmap'* in *R statistical software*. Secondly, by matching the patients' residential postal codes with open access databases from the National Institute for Statistics and Economic Studies (INSEE). Information about the patients' municipalities was included, such as the median household income and the population density per square kilometer.

We used complete tumor resection as a quality indicator that is known to be the gold standard for first-line treatment (Bois et al., 2009). For EOC patients, survival is strongly associated with the size of the residual disease after surgery (Chang, Bristow, & Ryu, 2012). Primary surgery with either complete (i.e., < 1 mm) or optimal tumor resection (i.e., 1-10 mm) improves survival compared to suboptimal tumor resection (i.e., > 10 mm), while only complete tumor resection affects patient survival with neoadjuvant chemotherapy (Vermeulen, Tadesse, Timmermans, Kruitwagen, & Walsh, 2017). As we only considered the hospital of first-line treatment in the data, complete tumor resection is the most direct outcome for comparing first-line treatments. Use of survival could have introduced bias in the analysis, as some patients may have received secondary treatment at another hospital.

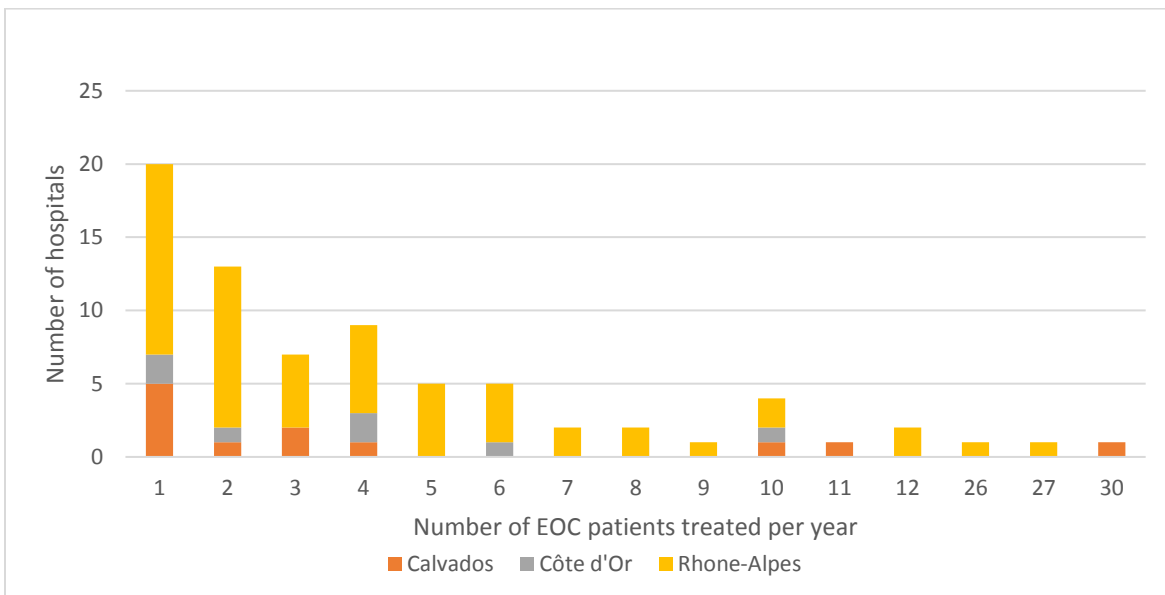
Of the 355 patients recorded in the database, 41 patients did not undergo surgery, either because they did not receive any treatment (n=2), or because they were treated by chemotherapy only (n=39). Since our outcome of interest was a quality indicator of the surgery, and we were interested in differences in outcomes according to the first-line treatment, these 41 patients were

excluded from the analysis. Finally, 37 of the 314 eligible patients were excluded due to missing data in regard to patient characteristics, outcomes, or instrument variables.

## **2.2. Descriptive statistics**

In 2012, 355 patients were identified in first-line treatment for EOC and they were treated in 74 different hospitals in the Basse Normandie, Bourgogne and Rhone-Alpes region. The high number of hospitals compared to the low number of patients led to a mean hospital volume activity of 4.8 patients treated in first-line per year and per hospital. The distribution of hospital volume activities varied from a minimum of 1 patient per year, to a maximum of 30. This wide variation in the distribution is readily apparent in Figure 2, which depicts the number of hospitals for each volume activity and by region.

*Figure 2 - Distribution of hospital volume activities*



Twenty of the 74 facilities (27%) had treated one patient in 2012, and 54 had treated five patients or less (73%). The top 10 hospitals with the highest volume activities treated 45% of the patients. An overview of the market structure and the geographical concentration of the providers is shown in Table 1, which displays the share of patients that had at least ‘N’ hospitals treating gynecologic cancer to choose from in a radius of ‘K’ kilometers around the municipalities. It can be seen that 47% of the patients had at least one hospital within a radius of 10 kilometers from their place of residence. Approximately half of the patients had at least two providers that they could choose from within 20 kilometers of their place of residence.

Table 1: The share of patients that have a choice of N hospitals located within K kilometers from where they reside.

Distance (K) in Kilometers	Number (N) of hospitals				
	N=1	N=2	N=3	N=4	N=5
K=10	46.9	36.2	27.1	20.6	11
K=20	70.1	55.6	41	34.5	22.9
K=30	83.3	70.6	57.6	49.7	32.2
K=40	90.4	81.6	72	58.2	45.2
K=50	93.2	89.3	83.1	74.6	66.7

Table 2 displays the hospital characteristics according to their volume activity. In order to not make the descriptive statistics overly complex, we compared the 10 hospitals with the highest volume versus the other hospitals. It can be seen that the higher volume hospitals tended to be more specialized in oncology ( $p < 0.001$ ), and they had a higher number of beds in the surgery unit ( $p < 0.001$ ), a higher number of surgery rooms ( $p < 0.001$ ), a higher number of surgeons ( $p < 0.001$ ), and a higher number of gynecologists or obstetricians ( $p = 0.005$ ). The type of hospital also appears to be a strong correlate of volume activity ( $p < 0.001$ ), with 70% of the high volume hospitals being

teaching hospitals versus only 5% of the low volume hospitals. Conversely, 50% of the low volume hospitals were private for profit hospitals, and 39% were public hospitals.

Table 2: Hospital characteristics

	Top 10 High Volume Hospitals	Low Volume Hospitals (n=64 hospitals)	p-value
Hospital volume activity	15.80	3.08	0.000
Fraction of the hospital activity represented by oncology	38.42	11.40	0.000
Bed occupation rate in surgery (%)	81.40	80.90	0.983
Number of beds in surgery	373.67	115.62	0.001
Number of surgery rooms	37	11.63	0.001
Number of Surgeons	61.27	20.88	0.001
Number of Gynecologists and Obstetricians	18.16	7.10	0.005
Aggregate score for nosocomial infection prevention	87.25	85.14	0.476
<u>Type of hospital (%):</u>			
- Private for profit	20	50	0.000
- Private not for profit	10	6.45	
- Public	0	38.70	
- Teaching Hospital	70	4.85	
<u>Accreditation (French National Authority for Health) (%):</u>			
- Accreditation	37.50	38.98	0.732
- Accreditation with recommendations for improvement	37.50	22.03	
- Accreditation with mandatory improvement	25	33.91	
- Conditional accreditation due to reservations	0	5.08	

Note: The differences were analyzed using the Student's t-test or the Chi square test.

While the hospital characteristics differ according to hospital volume activities, this is also the case for the patient characteristics (Table 3). Higher volume hospitals tended to treat patients with a higher tumor grade ( $p=0.007$ ) and a higher share of primary inoperable tumors ( $p=0.005$ ).



Patients treated in lower volume hospitals tended to be swayed more by the distance from their place of residence to the hospital, since 41% of them opted for treatment at the nearest hospital, versus 13% of the patients treated in higher volume hospitals ( $p < 0.001$ ). Patients living in more populated areas also appear to prefer higher volume hospitals ( $p = 0.047$ ), which may also be explained by the fact that high volume settings are often located in large cities.

Table 3: Patient and municipality characteristics

	Top 10 High Volume Hospitals (n=158 patients)	Low Volume Hospitals (n=197 patients)	p-value
<b>Patient characteristics</b>			
Age	60.255	62.399	0.139
Prior history of cancer (%)	15.19	15.46	0.944
Presence of ascites (%)	67.72	58.25	0.068
Primary inoperable (%)	45.57	31.12	0.005
<u>Histology (%):</u>			
- HGSC	55.70	44.67	0.062
- LGSC	3.80	7.61	
- Mucinous	5.06	10.15	
- Endometrioid	8.23	14.21	
- Clear cell	6.33	6.09	
- Unknown	20.88	17.27	
<u>FIGO Stage (%):</u>			
- I	17.99	30.09	0.080
- II	5.89	5.61	
- III	60.64	52.55	
- IV	15.48	11.75	
<u>Tumor Grade (%):</u>			
- 1	6.96	17.77	0.007
- 2	17.09	17.26	
- 3	61.39	46.70	
- Unknown	14.56	18.27	
<b>Patient municipality</b>			
Distance to hospital (km)	42.92	36.21	0.414
Hospital chosen is the closest (%)	13.29	41.12	0.000
European Deprivation Index	3.21	2.82	0.414
Population density	1,477.50	981.62	0.047
Median income	20,653	20,593	0.857

Note: High-Grade Serous Carcinoma (HGSC); Low-Grade Serous Carcinoma (LGSC). The differences were analyzed using the Student's t-test or the Chi square test.

### **2.3. Econometric specification**

In this study, we investigated whether the care pathways differed according to hospital volume activities conditionally on patient characteristics, and we linked these differences to patient outcomes to see if they could explain part of the positive impact of hospital volume on outcomes.

For the comparison, we first employed a methodology that has been widely used in the existing literature to discern volume outcome relationships (Cowan et al., 2016). We estimated the correlation between hospital volume and our outcome of interest (i.e., complete tumor resection) conditionally on patient characteristics using a logistic regression. The set of patient characteristics included age, a prior history of cancer, the presence of ascites, histology, the FIGO stage, and the tumor grade. This methodology is aimed at discerning associations between hospital volume activities and outcomes. However, it does not control for the endogeneity of hospital volume activity. Indeed, hospital volume is very likely to be endogenous when entering models as explanatory variable for three reasons. First, due to omitted explanatory variables, since it is not reasonable to think that our set of patient characteristics includes all of the prognostic factors of EOC. For example, we did not control for co-morbidities or for human Breast Cancer (BRCA) gene mutations, which are known to increase the probability of developing ovarian cancer (Antoniou et al., 2003). Since they were omitted, they fall in the error term, which could cause hospital volume to be correlated to the error term if these characteristics differ on average according to hospital volume activity. Secondly, tumor staging is subject to measurement errors, and it has been shown that patients are more often properly staged at high volume centers (Kumpulainen et al., 2006). Again, these systematic measurement errors fall in the error term and are directly correlated to hospital volume, which in turn makes the error term correlated to

hospital volume. Thirdly, due to the simultaneous relationship between hospital volume and outcomes as a result of selective referral. To eliminate these endogeneity issues, hospital volume has often been instrumented in the existing literature (Gaynor et al., 2005; Gowrisankaran et al., 2006; Corinna Hentschker & Mennicken, 2017). We employed a similar methodology by instrumenting hospital volume by the logarithm of distance, the population density of the patients' municipalities, and the median net income in the patients' municipalities.

The standard methodology presented above seeks to discern the relationship between hospital volume and patient outcomes. However, it does not provide information about the process of learning that the relationship implies. To unravel this effect, we jointly estimated the following model:

$$\left\{ \begin{array}{l} \text{Log}(\text{Volume}_i) = \beta_1 X_i + \beta_2 g(\text{Distance})_i + \beta_3 \text{Pop\_density}_m + \beta_4 \text{Income}_m + \gamma_1 \alpha_i + \epsilon_{1i} \\ \text{NACT}_i = \beta_3 \text{Volume}_i + \beta_4 \text{Volume}_i^2 + \beta_5 X_i + \gamma_2 \alpha_i + \epsilon_{2i} \\ \text{Log}(\text{TTS}_i) = \beta_6 \text{Volume}_i + \beta_7 \text{Volume}_i^2 + \beta_8 X_i + \gamma_3 \alpha_i + \epsilon_{3i} \\ \text{Outcome}_i = \beta_9 \text{Volume}_i + \beta_{10} (\text{Volume} \times \text{NACT})_i + \beta_{11} \text{NACT}_i + \beta_{12} X_i + \gamma_4 \alpha_i + \epsilon_{4i} \end{array} \right.$$

Where  $i = 1, \dots, N$  are patient identifiers, and  $m = 1, \dots, M$  are the patients' municipality identifiers.  $X_i$  are the patients' characteristics, including age, prior history of cancer, the presence of ascites, histology, the FIGO stage, and the tumor grade.  $\alpha_i \sim N(0; 1)$  is a normally distributed random term at the individual level, and it is independent of the idiosyncratic errors terms  $\epsilon_{1i}, \epsilon_{2i}, \epsilon_{4i}$ . The idiosyncratic error terms  $\epsilon_{1i}, \epsilon_{2i}, \epsilon_{4i} \sim N(0; 1)$  and  $\epsilon_{3i} \sim \text{Weibull}(\lambda; k)$ . We defined the function  $g(\cdot)$  of the distance as  $g(\text{Distance})_i = \alpha_1 \text{Closest}_i + \alpha_2 \text{Log}(\text{Distance})_i + v_i$ . The model is identified through our set of instruments

for hospital volume, which includes the function  $g(\cdot)$  of the distance, the population density in patients' municipalities, and the median net income in the patients' municipalities. What links the four equations is the individual's random terms (i.e.,  $\alpha_i$ ), which represents the unobserved (to the econometrician) patient's state of illness. By doing this, we allow for correlation between the error terms of each equation. Thus, in this model we control by instrumental variable for the endogeneity of hospitals' volume activities, which is induced by differences in unobserved patient characteristics, measurement errors, and simultaneous correlation between hospital volume and outcomes.

We estimated this model using the '*PROC NLMIXED*' of SAS/STAT 9.4 software. This procedure fits nonlinear mixed models by maximizing an approximation of the likelihood integrated over the random effects using the Gaussian quadrature method. To illustrate the results, we also computed predicted patient outcomes and predicted probabilities of being treated with neoadjuvant chemotherapy according to different scenarios of organization of care, based on our parameter estimates.

### 3. RESULTS

#### 3.1. Black box models

In Table 4, the results from the logistic regression provide an insight of the correlation between hospital volume and outcomes, while results from the IV probit are indicative of the causal impact of hospital volume on outcomes.

Table 4: Standard logistic regression and IV Probit

	<i>Outcome</i>	
	Logistic regression	IV Probit
Volume	0.0379***	0.0108
Age	-0.0189*	-0.0129**
Prior cancer	0.4643	0.2953
Presence of ascites	-0.3018	-0.1820
<u>Histology:</u>		
- HGSC	0.2982	0.1988
- Other	Ref	Ref
- Unknown	1.7439***	1.0586***
<u>FIGO Stage:</u>		
- I	2.5158***	1.4741***
- II	2.0442***	1.2501***
- III	1.2584**	0.7550***
- IV	Ref	Ref
<u>Tumor Grade:</u>		
-1 or 2	Ref	Ref
- 3	0.1345	0.1160
- Unknown	-0.6573	-0.4671
Intercept	-0.7918	-0.2587
N	277	277
R squared	0.1326	NA
Log Likelihood	-164.6263	-1150.4281

Note: High-Grade Serous Carcinoma (HGSC); Low-Grade Serous Carcinoma (LGSC); Complete tumor resection (outcome); modality in reference (Ref); Not Applicable (NA). Significant at 1%, 5%, and 10% is indicated as \*\*\*, \*\*, and \*, respectively.

In the logistic regression, it can be seen that lower stages ( $p < 0.001$ ) and unknown histology of the tumor compared to other histological subgroups ( $p = 0.004$ ) were associated with higher likelihoods of complete tumor resection. Regarding our variable of interest, it can be seen that patients treated in higher volume hospitals were more likely to have a complete resection compared to patients treated in lower volume hospitals ( $p = 0.010$ ). This correlation between hospital volume and patient outcomes was lost in the IV Probit model when we controlled for the endogeneity of hospital volume ( $p = 0.612$ ).

### **3.2. Joint estimation of the full model**

Table 5 displays the results of the full model, with the four equations estimated jointly assuming correlation between the errors terms. From the volume equation, it can be seen that patients treated in higher volume hospitals were, on average, younger ( $p = 0.0091$ ) and more likely to have a HGSC than a different histological group ( $p = 0.0475$ ). Among our set of instruments, the function  $g(\cdot)$  of the distance appears to be highly correlated with hospital volume. Patients treated at their nearest hospital were less likely to be treated in a high volume hospital ( $p < 0.001$ ), and patients traveled longer distances to be treated in a high volume hospital ( $p = 0.0195$ ). As expected, higher volume hospitals tended to receive patients from a larger area.

Table 5: Full model with individual random effect

	<i>Log (Volume)</i>	<i>NACT</i>	<i>Log (TTS)</i>	<i>Outcome</i>
Volume		0.1321**	-0.04849***	0.03581***
Volume <sup>2</sup>		-0.00286	0.001163***	
NACT				1.4359***
Volume x NACT				-0.04952**
Age	-0.01029***	0.02708***	0.005257***	-0.01702**
Prior cancer	0.08901	0.4759*	-0.06767*	0.2395
Presence of ascites	0.1178	1.0340***	0.02555	-0.3005
Histology:				
- HGSC	0.2638**	0.6950**	-0.06294	0.01158
- Other	Ref	Ref	Ref	Ref
- Unknown	0.1077	1.5892***	-0.3584***	0.8053**
FIGO Stage:				
- I	Ref			Ref
- II	0.1044			-0.1510
- III	0.1603	Ref	Ref	-0.9188***
- IV	0.3676	0.4192	-0.02520	-1.7080***
Tumor Grade:				
- 1 or 2	Ref	Ref	Ref	Ref
- 3	0.1368	-0.02718	-0.01829	0.1909
- Unknown	-0.2169	-0.4684	-0.00774	-0.3862
Instruments:				
- Closest	-0.6197***			
- Log (Distance)	0.1319**			
- Population density	0.000067*			
- Median income	0.000020			
Constant	2.0452***	-4.7269***	-4.5265***	1.2395***
Gamma	-0.08318	0.7298***	-0.3746***	-0.09034
Log Likelihood	-1291.13			
AIC	2696.3			
Observations	277			

Note: High=Grade Serous Carcinoma (HGSC); Low-Grade Serous Carcinoma (LGSC); Neoadjuvant Chemotherapy (NACT); Complete tumor resection (outcome); modality in reference (Ref); Not Applicable (NA). Significant at 1%, 5%, and 10% is indicated as \*\*\*, \*\*, and \*, respectively.



In the NACT equation, older patients ( $p=0.0020$ ) and patients with ascites ( $p=0.0001$ ) were more likely to be treated with neoadjuvant chemotherapy rather than primary surgery, as well as being more likely to have an HGSC ( $p=0.0148$ ) or an unknown ( $p=0.0015$ ) histology compared to other histological subgroups. Our variable of interest shows that patients treated in higher volume hospitals were more likely to be treated with neoadjuvant chemotherapy rather than primary surgery ( $p=0.0483$ ).

In the TTS equation, conditionally on being treated with neoadjuvant chemotherapy, for older patients the time from the initiation of chemotherapy until surgery was longer ( $p=0.0001$ ), while for patients with an unknown histology this time was shorter compared to other histological subgroups ( $p<0.0001$ ). Our variable of interest shows that for patients treated in higher volume hospitals this time tended to be shorter ( $p<0.0001$ ), with a U-shaped effect ( $p=0.0003$ ).

In the outcome equation, it can be seen that older patients ( $p=0.0129$ ) and higher stage patients were less likely to be completely debulked after surgery ( $p<0.001$ ). Whereas patients with an unknown histology compared to other histological subgroups ( $p=0.0227$ ) and patients treated with neoadjuvant chemotherapy rather than primary surgery ( $p=0.0005$ ) were more likely to have no residual disease after surgery. Regarding our variables of interest, patients in primary surgery treated in higher volume hospitals were more likely to be fully debulked compared to patients who received the same treatment but in a lower volume hospital ( $p=0.0022$ ). While being treated in a higher volume hospital improved the outcome for patients in primary surgery, being treated with neoadjuvant chemotherapy reduced the difference in the likelihood of complete tumor resection according to hospital volume activities ( $p=0.0107$ ).

### **3.3. Predictions**

To further illustrate the implications of our findings, we simulated three scenarios using the parameter estimates of the full model:

*Scenario 1 - Decentralized care:* This scenario will be our reference point. It represents the ongoing organization of care whereby patients are treated at 74 different hospitals. Based on our parameter estimates, we predict what the rate of neoadjuvant chemotherapy use and the rate of complete tumor resection would be.

*Scenario 2 - Network formation:* In this scenario, we simulate an organization of care where first-line treatment decisions are discussed and coordinated by high volume hospitals, but where the hospital of treatment does not change. As in the descriptive statistics, we used a threshold of 10 cases per year to define a high volume hospital, which equates to comparing the ten hospitals with the highest volume to the other hospitals. We assume that treatment decisions of patients in low volume hospitals will be coordinated by the closest high volume center to the patients' residential municipalities. We then predict the rate of neoadjuvant chemotherapy use that would occur if the treatment decisions for patients in LVH were made by HVH. Based on this prediction, we also predict the rate of complete tumor resection that would occur conditionally on the fact that treatment decisions were managed by HVH, but where the care was still provided at the hospital chosen by the patient.

*Scenario 3 - Centralization of care:* In the third scenario, we assume that both the treatment decision and the treatment are performed at high volume hospitals. The predicted rate of neoadjuvant chemotherapy will be equivalent to that of scenario 2. However, the rate of

complete tumor resection will differ since we assume a complete centralization of care in this scenario, meaning that patients treated in low volume hospitals will be redirected to the nearest high volume hospital.

Table 6: Results of the predictions based on parameter estimates of the full model

	Predicted patient outcome for all stages			Predicted first-line treatment for advanced stages disease		
	CC-1 or CC-2	CC-0	Rate of CC-0	PDS	NACT	Rate of NACT
Scenario 1: Decentralized	118	175	59.7%	155	75	32.6%
Scenario 2: Network formation	100	193	65.9%	122	108	46.9%
Scenario 3: Centralization	93	200	68.3%	122	108	46.9%

Note: Neoadjuvant Chemotherapy (NACT); Primary Debulking Surgery (PDS); Complete tumor resection (CC-0); Incomplete tumor resection (CC-1 or CC-2). First-line treatment is predicted only for advanced stage patients, since primary surgery is the only treatment option for early stage.

The results of the simulations based on our parameter estimates are displayed in Table 6. It can be seen that the rate of neoadjuvant chemotherapy among advanced stage patients increased by 14.3% when the treatment decisions were made by high volume centers. The rate of complete tumor resection among all patients would increase by 6.2% if the patients were still treated in the hospital that they had chosen, and by 8.6% if the care was centralized at high volume centers.

## **4. DISCUSSION**

### **4.1. External validity**

In this study, we used data from three different regions of France. Figure 2 depicts the distribution of the hospital volume activities in these three regions. Out of all of the patients in first-line treatment for EOC in one of the three regions considered in 2012, the quartiles of the distribution were such that 77% were treated in hospitals with fewer than 13 cases per year, 53% in hospitals with fewer than 9 cases per year, and 29% with fewer than 5 cases per year. The health care market tended to be decentralized in each of the regions considered, despite the presence of high volume centers in each of them. The distribution of hospital volume activities we observed does not appear to be a specificity of the Basse Normandie, Bourgogne or the Rhone-Alpes regions. Indeed, there was one hospital treating gynecologic cancers for every 111,638 residents in Basse Normandie, one for every 154,845 residents in Bourgogne and one for every 113,174 residents in the Rhone-Alpes region in 2016 (source: National Institute of Statistical and Economic Information<sup>3</sup>, French National Authority of Health<sup>4</sup>). In comparison, there was one hospital treating gynecologic cancers for every 126,585 residents in the most populous region of France (i.e., Ile-de-France).

The results for patient characteristics from the joint estimation model are in line with the existing literature, thus supporting the notion that the results of our study can be extrapolated to a certain degree to other countries. Indeed, we found that higher volume hospitals treated the more

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<sup>3</sup> <https://www.insee.fr/fr/accueil>

<sup>4</sup> <https://scopesante.fr/>

severely ill patients. This result is consistent with the existing literature on the VOR for EOC patients in the USA (Bristow, Chang, Ziogas, Randall, & Anton-Culver, 2014; Cliby et al., 2015). We also found that the more severely ill patients and the patients treated in higher volume hospitals were more likely to be treated with neoadjuvant chemotherapy rather than primary surgery as first-line treatment. These results are consistent with a recent observational study using a similar methodology on a cohort of 62,727 patients diagnosed between 2003 and 2011 in the USA (Leiserowitz, Lin, Tergas, Cliby, & Bristow, 2017). The association that we found between the patient characteristics and the outcomes is also in line with the existing literature (Bois et al., 2009; Ji et al., 2008). The hospital volume - outcome relationship that we identified for patients in primary surgery has also been widely reported in the literature (Cowan et al., 2016). Our result on the positive impact of neoadjuvant chemotherapy compared to primary surgery is in line with a meta-analysis on four randomized controlled trials comparing these two treatments options (Yang et al., 2017).

#### **4.2. Validity and reliability of the instruments**

The robustness of our empirical strategy greatly depends on the choice of the instruments. An instrument has to be tightly correlated with the endogenous regressor (reliability), and to be uncorrelated with the error term of the instrumented equation (validity). With valid and reliable instruments, instrumental variables allow for estimation of the Local Average Treatment Effect (LATE). In the setting of the VOR, IV has been used in several studies to account for the simultaneity bias that occurs between volume and outcome, and for possible omitted variables

(Gaynor et al., 2005; Corinna Hentschker & Mennicken, 2017; Kahn et al., 2009; Tsai, Votruba, Bridges, & Cebul, 2006). For instrument hospital volume activities, they used the number of potential patients and other hospitals in a defined area by using the geographical location of patients and hospitals. In our study, we used a patient-level database, which provides detailed information of the patients' characteristics. Therefore, we had to find an instrument that could predict the likelihood of a patient being treated in a higher volume hospital, rather than instruments to predict hospital volume activities directly. We used a function of the distance from the patients' municipalities to the hospitals as our principal instrument. The assumption here is that higher volume hospitals will receive patients from a much larger area compared to lower volume hospitals, and therefore that patients will travel much longer distances to be treated at a higher volume hospital. We are confident about this assumption since the data in Table 5 shows that patients treated at their nearest hospital were more likely to be treated in a lower volume hospital ( $p < 0.001$ ), and that the log of the distance was positively associated with the hospital volume ( $p = 0.0195$ ). Higher volume settings are often located in or near big cities. To take into account that patients living in more populated areas will have greater access to these higher volume facilities, we included the population density of the patients' municipalities as an instrument. There could also be inequalities in access to quality care for less wealthy patients who could not afford the expense incurred by a greater distance to the hospital. To take this into account, we included the median income at the municipality level, assuming that patients living in more wealthy municipalities have greater access to higher volume settings that are further away from their place of residence. However, we could not identify a significant effect of median income, and we only found a weak association of hospital volume with the population density

( $p=0.0666$ ). This could be due to a lack of statistical power due to the fact that we used an aggregate measure of wealth instead of an individual one. Alternatively, additional health insurance could cover for extra fees incurred by longer distances, resulting in no inequality in access to higher volume hospitals according to patients' income.

Based on the results presented in Table 5, we are confident of the reliability of our set of instruments. We are also confident of their validity, since it is very unlikely that patients chose to live in a certain area according to the overall quality of the hospitals in that area.

#### **4.3. Why do higher volume hospitals use neoadjuvant chemotherapy more often than primary surgery?**

Unlike the black box model, the joint estimation of the four equations gives detailed information on the way patients were treated according to the volume activity of the hospital where they received treatment. We found that the higher volume hospitals were more likely to treat patients with neoadjuvant chemotherapy than by primary surgery (Table 5). The use of neoadjuvant chemotherapy as first-line treatment for EOC patients is a recent phenomenon, and is not yet established as a standard alternative to primary surgery. One reason from this difference in treatment assignment according to hospital volume activities could be due to a faster diffusion of innovation in higher volume hospitals. It has been reported that the diffusion of other types of innovations also tends to be faster in higher volume hospitals (Callea, Cavallo, Tarricone, & Torbica, 2017).

We also identified differences in the time from the initiation of chemotherapy until surgery for patients who were treated with neoadjuvant chemotherapy (Table 5). Indeed, higher volume hospitals tended to have a shorter duration (i.e., TTS) compared to lower volume hospitals. This result could have two distinct implications. It is possible that patients treated in higher volume hospitals received fewer cycles of chemotherapy on average. Alternatively, a shorter duration in higher volume hospitals could also be the result of shorter waiting times between the end of neoadjuvant chemotherapy and the surgery. Ultimately, both interpretations are likely to be related to the waiting times. The clinical guidelines for the number of cycles of neoadjuvant chemotherapy advocates that the use of 3 to 4 cycles is the appropriate way to treat advanced ovarian carcinoma (Altman et al., 2017; Xu, Deng, Lv, & Chen, 2016). For the patients considered in this study, the number of cycles varied from a minimum of 3 to a maximum of 10 cycles. The shorter duration underlined in our model should therefore not be interpreted as higher volume hospitals providing undertreatment. Thus, higher numbers of neoadjuvant cycles could also be related to waiting times and interpreted as a way to make patients wait for their surgery.

#### **4.4. Does the VOR only apply to patients treated with PDS?**

While higher volume hospitals tended more often to use neoadjuvant chemotherapy rather than primary surgery compared to lower volume hospitals, it appears that the difference in outcomes according to hospital volume activities decreased for patients treated with neoadjuvant chemotherapy (Table 5). This is why we did not find that there was an impact of hospital volume on outcomes in the black box model, where patients were pooled irrespective of the treatment



that they received (Table 4). The joint estimation and the information on treatments allowed us to unravel this heterogeneous impact, while we would have concluded that volume and outcome are independent in the black box model.

The heterogeneous impact of hospital volume according to the treatment received stems from a difference in the complexity of the procedure. The aim of neoadjuvant chemotherapy as first-line treatment is to avoid a surgical procedure that is too aggressive for the most severely ill patients. Thus, for this subgroup of patients, the use of neoadjuvant chemotherapy reduces the complexity of the surgery compared to a primary surgery. This reduction in the complexity of the surgical procedure could in part explain why we observed less or even no difference in outcomes according to hospitals volume activities for patients treated with neoadjuvant chemotherapy while we observed strong differences for patients in primary surgery. A remarkable result is that lower volume hospitals tended to benefit more from the use of neoadjuvant chemotherapy compared to higher volume hospitals, although they actually use it less. What is even more striking with this finding is that clinicians in higher volume hospitals are assumed to benefit from a learning effect due to the number of surgical procedures that they perform each year. They thereby develop greater skills and could hence be more able to perform a complex surgery compared to a less trained clinician at a lower volume hospital, although our data indicates that the clinicians in lower volume hospitals were, on average, more likely to perform complex surgery rather than use neoadjuvant to reduce its complexity.

#### **4.5. Policy implications for the organization of care**

Centralized care at high volume hospitals was the scenario that led to the highest average patient outcome (Table 6), and it has often been recommended in the literature (Cowan et al., 2016). However, several barriers, such as the likely increase in patient travel distances, have prevented such a reform of the organization of care from being applied. Indeed, in our scenario, centralized care at the nearest high volume center would increase the average distance travelled by patients from 39 kilometers to 66 kilometers. Moreover, centralized care at the nearest high volume hospital requires that patients are no longer given the option of choosing their preferred provider. Thus, in health systems where patients have the option of choosing their hospital (e.g., France, the United Kingdom, and the United States), the impact of centralization of care on distance could be even greater if patients do not choose to be treated at their nearest high volume hospital. Furthermore, changing the number of provider alternatives available to patients will also affect the demand drivers by increasing the weight given to distance in the demand function. Since hospitals are expected to be responsive to patient demands, increasing the importance of distance will lessen the importance of other aspect of the demand function. The current literature on the determinants of patient choices shows that quality of care, the distance to the hospital, waiting times, and other hospital amenities are the main factors taken into account by patients when making this choice (Baker, Bundorf, & Kessler, 2016; Beckert & Kelly, 2017; Gaynor, Propper, & Seiler, 2016; Gravelle, Santos, Siciliani, & Goudie, 2012; Victoor, Delnoij, Friele, & Rademakers, 2012). Thus, the decrease in options available to patients could lessen the providers' incentives to provide high quality care and to limit waiting times. An intermediate solution between centralized and decentralized care could be to make lower volume hospitals benefit

from the expertise of higher volume hospitals when making treatment decisions. This would have no impact on the distance travelled by patients and it would also reduce inequalities in access to specialized care. Indeed, with cooperation between low volume hospitals and high volume hospitals in regard to making important decisions as to how to treat patients, patients in low volume hospitals will benefit from the expertise of expert centers. This organization of care already exist in France for rare cancers (Bréchet, Chantôme, Pauporté, & Henry, 2015). For rare cancers, professional networks have been set up by the French National Institute for Cancer, and these are often defined at the regional level. Such a network typically comprises an expert center and 10 to 30 non-expert centers. The role of the expert centers in these networks is to confirm the diagnosis by a second examination of the medical files and to organize multidisciplinary consultation meetings (RCP) at the regional or national level. Ovarian cancer has not yet benefited from such an organization of care, as it is not considered to be a rare cancer. However, our findings support the notion that EOC patients would benefit from such an organization of care compared to the ongoing one.

More generally, an organization of care with cooperation between expert centers and low volume hospitals could improve patient outcomes for any complex disease that requires complex decisions to be made by the treating physicians. By contrast, for less complex diseases or when there is only a single treatment option, this type of organization of care would be less suitable. In this case, centralized care at high volume settings would be preferable in order to reduce the difference in outcomes according to hospitals volume activities.

## **5. DECLARATIONS**

*Ethics approval:* The study was conducted in accordance with the ethical principles for medical research involving human subjects developed in the Declaration of Helsinki by the World Medical Association (WMA). The study received approval in France from the National Ethics Committee (N°909226, and 16.628) and the National Committee for Protection of Personal Data (N°09-203, derogation N°913466). Although consent for participation is usually required, we requested derogation from the French National Committee for Protection of Personal Data (CNIL) in light of the very low survival rates for this pathology. The derogation was accepted, and therefore, the need for participant consent was waived.

*Availability of data and materials:* The dataset analyzed during the current study is not publicly available due to the risk of the participants being identified. Additional quotes and examples that will support the findings can be provided upon request.

*Competing interests:* The authors declare that they have no competing interests.

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*Author contributions:* MH made a substantial contribution to the literature searches, analysis and interpretation of the data, as well as drafting of the manuscript. IRC, LP, and XJ made a substantial contribution to the acquisition, analysis, and interpretation of the data, as well as critically revising the manuscript. All of the authors read and approved the final manuscript.

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