



Volume-outcome relationship in health, inequalities in access to care and referral of patients for specialized care

Marius Huguet

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UNIVERSITÉ DE LYON - ECOLE DOCTORALE DE SCIENCES ECONOMIQUES ET
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VOLUME-OUTCOME RELATIONSHIP IN HEALTH,
INEQUALITIES IN ACCESS TO CARE AND REFERRAL
OF PATIENTS FOR SPECIALIZED CARE

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University Lumière Lyon 2 is not going to give any approbation or disapprobation about the thoughts expressed in this dissertation. They are only the author's ones and need to be considered such as.

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List of Abbreviations

AFT	Accelerated Failure Time
AIC	Akaike Information Criterion
AKME	Adjusted Kaplan Meier Estimator
ATIH	Agence Technique de l'Information sur l'Hospitalisation
ATT	Average Treatment Effect on the Treated
BRCA	Human Breast Cancer Gene Mutation
CCAM	Common Classification of Medical Acts
CIA	Conditional Independence Assumption
DREES	Directorate for Research Studies Evaluation and Statistics
DRG	Diagnosis Related Group
EMS	Medical Evaluation and Sarcomas
EOC	Epithelial Ovarian Cancer
FIGO	Fédération Internationale des Gynécologues Obstétriciens
FRANCIM	Réseau français des registres de cancer
GP	General Practitioner
HAS	French National Authority of Health
HR	Hazard Ratio
HGSC	High-Grade Serous Carcinoma
HHI	Herfindahl-Hirschman-Index
HVH	High-Volume Hospital
ICD-10	International Classification of Disease
IIA	Independence from Irrelevant Alternatives
INSEE	National Institute for Statistics and Economic Studies
IPW	Inverse Probability Weighting
LATE	Local Average Treatment Effect
LDD	Long Duration Disease
LGSC	Low-Grade Serous Carcinoma
LVH	Low-Volume Hospital
NACT	Neoadjuvant Chemotherapy
OECD	Organisation for Economic Co-operation and Development
OS	Overall Survival
PDS	Primary Debulking Surgery
PFS	Progression-Free Survival
PMSI	Medical Information Systems Program
PP	Percentage Point
RCT	Randomized Controlled Trial
SAE	Statistique Annuelle des Etablissements
TTS	Time To Surgery
VOR	Volume Outcome Relationship
WHO	World Health Organization
2SLS	Two Stage Least Square
3C	Oncology Treatment-Coordinated center

General Introduction

0.1 The Learning Curve Theory: From Industrial Economics to Health Economics

In the 1930s, T. Wright shed light on an important stylized fact that will become the rationale of a wide spectrum of literature in the field of industrial economics (Wright (1936)). Wright observed an inverse relationship between the direct labor cost of producing an aircraft and the accumulated number of aircraft produced. Wright's seminal work (1936) has been formalized through the so-called *learning curve*, which is the relationship between the unit cost of producing an aircraft, which could be represented by the production time, according to the series already produced. Figure 1 provides an illustration of this stylized fact and depicts a hypothetical learning curve for producing a series of 40 aircraft, where the cost of the first aircraft is 50. Wright showed that the direct labor cost of producing an aircraft decreases with the accumulated number of aircraft already produced according to the function:

$$Y = aX^{-b}$$

Where Y is the labor cost per unit produced, X is the accumulated number of aircraft produced, a is the labor cost of producing the first aircraft, and b is the learning parameter that relates to the slope of the learning curve, in which the steeper the learning curve, the faster the learning process. Wright identified several mechanisms that could allow for a reduction in unit cost, such as the higher labor productivity of more experienced workers and scale economies on materials. This framework has then been largely applied to other industrial sectors, which most often led to the same relationship being observed (Asher and H. (1956); Hirsch (1952); Rapping (1965)).

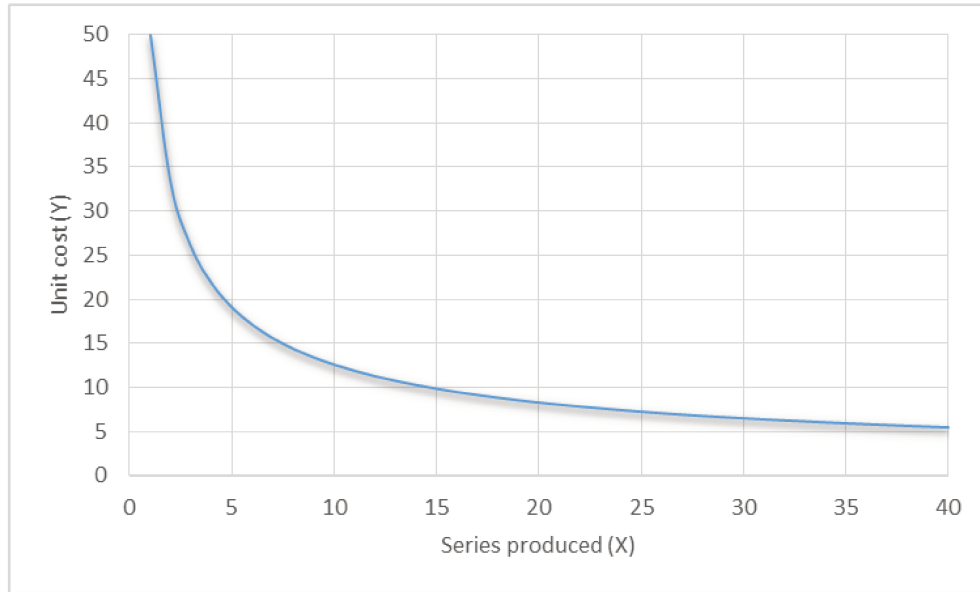


FIGURE 1: Hypothetical learning curve for the production of 40 aircraft series, with a learning parameter of 0.6

In the 1980s, the learning curve theory was applied to the healthcare sector (Luft et al. (1987); Flood et al. (1984); Lubitz et al. (1985); Luft et al. (1979)). The key concept that the direct labor cost of producing a product declines with its accumulated number produced has been translated to the specific case of carrying out surgeries for specific diseases in hospitals. In this context, the relationship between surgical volume and patient outcomes has been studied thoroughly. This literature has emerged based on the stylized fact that for several procedures, such as surgeries, patients treated in higher volume hospitals (i.e., hospitals that treated a higher number of patients) had better outcomes (e.g., lower mortality rate in hospital, lower readmission rates, etc.). This heterogeneity in patient outcomes according to hospital volume activities raises several crucial questions regarding the organization of the healthcare sector. Indeed, the industrial organization of the sector in most health systems is such that the healthcare market is competitive, where the demand side (i.e., patients) is free to choose its preferred provider and where the supply side (i.e., hospitals) may adjust their profile to attract more patients (Gaynor et al. (2015)). Broadly speaking, after being implemented for the first time in the US in the 1980s, payment systems that link hospital funding to activity have become the most common mode of hospital payment worldwide in most health systems over

the past decade (Busse et al. (2013); Fetter et al. (1980)). In France, an activity-based payment system called "T2A" has been in place since 2004/2005 (de Kervasdoué (1997)). This kind of payment system has been widely introduced based on the belief that it would incentivize hospitals to increase their efficiency in using their resources to provide care, since a fixed amount is paid for each diagnosis-related group (DRG). However, it has also been widely demonstrated in the literature that this kind of payment scheme could increase the risk of opportunistic/strategic behaviors from the providers, for instance by selecting patients on a DRG basis or shortening the length of the consultation or the hospital stay while increasing the number of visits/stays (de Kervasdoué (1997); Shleifer (1985)). Moreover, since the payment system is linked to hospital activities, providers are also inherently incentivized to increase their own activity, and thus have no incentive to cooperate with other providers (Or (2014)). This means that hospitals treating only a few patients each year for a specific condition or procedure have no direct incentive to refer these patients to a hospital with more experience in that treatment. Nevertheless, the fact that a substantial share of patients was still treated in low volume hospitals means that these patients chose to be treated in these hospitals in some cases. Why then, from a societal perspective, should we care about whether patients were treated in a high or low volume hospital, as long as they choose the provider that maximized their utility function? Patients are indeed free to pick the provider that best matches their preferences. However, several barriers could limit patient choice, such as the highly asymmetric information between patients and hospitals, a lack of available providers within a reasonable distance, etc. Moreover, for specialized care, patients need to be referred by their general practitioner (GP) in order to be fully reimbursed by the social security system. Assuming that GPs have arguably superior information on providers based on their experience and network, they play the role of the patient's agent in the decision-making process in order to reduce the risk of information asymmetry and adverse selection. Thus, because of their role as an intermediary between patients and hospitals, they may have some influence on the final decision made by patients. These barriers to patient freedom of choice and access to health-care lead to a market failure where the matching of patients and hospitals causes a suboptimal distribution of hospital volume activities. To prevent this market failure,

decision makers could act on the demand side of the market by limiting the barriers to patient freedom of choice and access in order to avoid referring patients to the lowest volume hospitals if they are assumed to be of lower quality. On the other hand, they could also intervene on the supply side of the market by reshaping the distribution of hospitals to avoid very low volume hospitals. Broadly speaking, if the quality of care for specific diseases or procedures is indeed a function of the accumulated number of patients treated each year, there will be a unique opportunity to substantially increase the overall quality of care through policies aimed at increasing hospital volume activities. From the decision maker's perspective, it is thus of primary interest to identify and verify whether a relationship between hospital volume and patient outcomes is indeed effective.

From the 1980s, this association has been empirically tested with several diseases and procedures. Nevertheless, an observed association between hospital volume and patient outcomes does not necessarily imply a causal impact. Luft et al. have proposed two hypotheses for how volume could correlate with outcomes (Luft et al. (1987)):

- *Practice-makes-perfect*: Hospitals and physicians treating more patients with the same condition will, on average, provide higher-quality care. Under this assumption, the quality of care is assumed to be a function of the accumulated experience of the healthcare provider and to benefit from organizational economies of scale.
- *Selective-referral*: Higher-quality providers are more attractive, and the referral system may channel more patients to hospitals providing higher-quality care. Under this assumption, the causation is reversed and runs from patient outcomes to hospital volume.

These two interpretations of the association between case volume and outcomes have totally different policy implications. Indeed, increasing hospital or physician

volume activity would increase the overall quality of care only under the *Practice-makes-perfect* hypothesis, when the causation runs from volume to outcome. Furthermore, even within the *practice-makes-perfect* hypothesis, there are different policy implications based whether the increase in quality is caused by static economies of scale or through a dynamic learning effect. If the relationship is mediated through static scale economy, today's volume would impact today's outcome only, while if the causation is mediated through a learning effect, today's volume would impact both today's and future outcomes. The volume-outcome relationship received particularly great interest for its strong policy implications. The *Practice-makes-perfect* hypothesis, if valid, could indeed provide an opportunity to substantially improve the efficiency of the healthcare sector by restructuring the supply side of the market. The more evident reorganization of healthcare provision most often recommended in the literature is the centralization of care (also called regionalization of care, concentration of care) (Cowan et al. (2016)). The key concept of the centralization of care is to withdraw the lowest volume provider (i.e., the provider that treated the smallest number of patients) from the market, and to reallocate patients treated in these hospitals to one of the remaining hospitals. Doing this avoids and prevents patients from being treated in hospitals that have less experience with that particular treatment. Moreover, the demand side of the market remains unchanged, while reducing the number of providers would naturally increase, on average, the number of patients treated in each of the remaining hospitals, and would therefore increase the overall quality of care under the *Practice-makes-perfect* hypothesis. Studies of the volume-outcome relationship are thus of primary interest to assess the potential impact of such reforms.

0.2 The Hospital Volume-Outcome Relationship (Chapter 1)

Two recent studies performed a systematic review of the volume-outcome relationship (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 et al. (2016); Pieper et al. (2013)). Most of the studies to date have found that higher volume hospitals have better outcomes for a wide range of

procedures and diseases (e.g., lower mortality rates). It is interesting to note that the volume effect is most often investigated and identified for diseases or procedures involving complex treatments, such as cancer care. For diseases requiring less complex care, the accumulated experience in performing that treatment is indeed less likely to play an important role in patient outcomes. However, the two mechanisms through which hospital volume could correlate with outcomes, namely the *Practice-makes-perfect* and the *Selective-referral* hypotheses, are likely to interact with each other. Thus, an observed correlation between hospital volume and patient outcomes does not necessarily imply a causal impact of volume on outcomes and it is of primary interest for policy making to identify which hypothesis dominates the volume outcome relationship. To that end, several estimation strategies have been employed in the literature to achieve a causal estimation. Several studies relied on an instrumental variable technique, and thus had to find an instrument that strongly predicts hospital volume, while being independent from patient outcomes. Most of the studies have instrumented hospital volume activities by the number of potential patients and other hospitals in a defined area (Gaynor et al. (2005); Hentschker and Mennicken (2018); Ho et al. (2007); Kahn et al. (2009)). The assumption made here is that higher volume hospitals will gain patients from a much larger area compared to lower volume hospitals, and that the patient's choice of their residential location is independent of whether there is a high-quality healthcare facility within a reasonable distance. This assumption of exogeneity of patient's distance to hospitals has also been exploited in another study, which addressed the reverse-causality bias by predicting hospital volumes based on a patient choice model (Rachet-Jacquet et al. (2019)). A recent study also proposed instrumentation of hospital volume by exploiting exogenous variation of hospital volume due to the creation or decommissioning of complete cancer clinics (Avdic et al. (2019b)). Using an instrumental variable strategy, most studies tend to confirm that the causation does indeed run from hospital volume to patient outcomes. A remarkable contribution to the study by Gaynor has been to distinguish the volume effect in a static scale economy effect from a dynamic learning-by-doing effect (Gaynor et al. (2005)). The volume effect seems to be induced by both static scale economy and dynamic learning-by-doing effect, although the static effect appears to be stronger. Other studies exploited panel data in order

to control for the unobserved patient heterogeneity and to identify this relationship (Ho et al. (2007); Kim et al. (2016); Ho and Hamilton (2000)). An interesting feature in the study by Ho et al. is that they modeled the consumer surplus and estimated the net volume effect after controlling for the impact of the decrease in market competition (Ho et al. (2007)). They still found a positive impact of volume, even after controlling for the reduction in market competition. Nevertheless, they showed that regionalization of care would increase consumer surplus only for diseases or procedures for which the volume effect is strong, while it could have a mixed effect for moderate volume effect.

The first chapter of this thesis intends to investigate the hospital volume-outcome relationship and estimate the potential gain in quality of care for first-line treatment of epithelial ovarian cancer (EOC). EOC is the eighth most common cancer for French women, with an incidence rate of 6 women for every 100,000 women/year in Central Europe¹. It remains the main cause of gynecological cancer deaths in industrialized countries, with an overall survival rate in France at five and ten years of 37% and 28%, respectively (Reseau FRANCIM (2010)). First-line treatment for EOC includes multiple treatment options that depend on the patient's condition and the clinician's decisions. Primary surgery has been the standard treatment for decades. It aims to remove all of the tumor (i.e., complete tumor resection). Neoadjuvant chemotherapy followed by surgery is a more recent treatment strategy for patients with advanced-stage EOC when they are found to have a low likelihood of complete tumor resection initially. The goal of chemotherapy is to reduce the size of the tumor before surgery in order to avoid a primary surgery that would be too aggressive for patients who are particularly ill (Qin et al. (2018)). EOC could be a particularly good candidate for the volume-outcome relationship, with substantive opportunity for learning-by-doing due to the complexity of the treatments and their impact on patient health. Moreover, the rather low incidence of this disease is likely to lead to very low hospital volume activities for a positive share of providers.

In this first chapter, we compare Progression-Free Survival (PFS) with first-line

¹Source: World Health Organization (<http://gco.iarc.fr/>)

therapy for EOC patients treated in high versus low volume hospitals in France. Several studies investigated the impact of the centralization of care for EOC patients in terms of volumes and patient outcomes (Aune et al. (2012); Bristow et al. (2010, 2014, 2015); Cowan et al. (2016); Ioka et al. (2004); Mercado et al. (2010); Phippen et al. (2013); Reade and Elit (2012); Vernooij et al. (2009); Woo et al. (2012)). They mostly found that patients are more likely to be optimally debulked in a high volume hospital or by a specialized provider. These studies have also shown that patients have better survival outcomes in high volume hospitals. However, most of these studies focused on advanced stage diseases, and none were carried out in France. In 2007, the French Cancer Institute set a minimum cut-off of 20 surgeries per year in order to receive authorization to treat gynecological cancers (Querleu (2008)). Below this volume of activity, a hospital is no longer authorized to treat patients with gynecological cancers. The aim of this reform was to avoid very low volume hospitals. However, this threshold takes into accounts all types of gynecological cancers, such as cervical, ovarian, vaginal, uterine, and vulvar cancers. Therefore, it is not clear whether the threshold has effectively concentrated care for EOC and thus whether findings from other countries are applicable to the French context. Moreover, the novelty of this study lies in part with the use of a longitudinal analysis with an extensive set of control variables to effectively measure and eliminate the strong selection bias on the observable between patients treated in high versus low volume hospitals. We used an exhaustive cohort² of 267 patients who underwent first-line treatment in 2012 in the Rhone-Alpes region of France. Using a very wide-ranging set of patient clinical characteristics (e.g., age, histology, tumor size, tumor grade, cancer history, neoadjuvant chemotherapy, and the presence of ascites), we used the Inverse Probability Weighting (IPW) method using the propensity score. The IPW method balances out the covariates of the two groups by weighting all patients in the database by the inverse of their propensity score. The propensity score is the conditional probability for a patient to be treated in a high volume hospital, conditionally on the observable characteristics. An Adjusted Kaplan-Meier Estimator (AKME), as proposed by Xie and Liu (Xie and Liu (2005)) and a univariate Cox model in the weighted sample, as described by Cole and Hernan (Cole and Hernán (2004)), were then applied in order

²Authorization: CNIL N°909226, CCTIRS N°09-203.

to determine the absolute and relative impact, respectively, of the concentration of care on the survival of EOC patients.

Our results indicate that being treated in a higher volume hospital increased the PFS of patients, compared to a lower volume hospital. More specifically, the probability of relapse (including death) was twice as high for patients treated in lower volume hospitals compared to patients treated in higher volume hospitals. The median PFS in high volume hospitals was 20 months, versus only 14.2 months in low volume hospitals. Despite the minimum volume threshold set in 2007 for gynecological cancers, we identified strong differences in hospital volumes and patient survival. Of all of the patients who had first-line treatment for EOC in the Rhone-Alpes region of France in 2012, 71% were treated in hospitals with fewer than 12 cases per year, 50% in hospitals with fewer than 8 cases per year, and 24% in hospitals with fewer than 5 cases per year. Moreover, high volume hospitals mostly treat advanced stage EOC, while it is clear that the concentration of care improves patient survival for both advanced and early EOC. Our findings thus indicate that there is a need for a specific minimum activity cut-off for ovarian cancer only.

0.3 What Is Hospital Volume a Proxy For? (Chapter 2)

What most volume-outcome studies lack is an in-depth look into what underlies the observed relationship. Volume alone is an imperfect correlate of quality. To devise volume-based policies, policy makers need to know what volume is a proxy for. Luft 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” (Luft (2017)). Does increasing hospital volume of any hospital increase its quality of care? What do higher volume hospitals do better than lower volume hospitals that could explain the wide difference in quality?

While there is very wide-ranging literature trying to identify the volume-outcome relationship, only a few studies have tried to disentangle this complex relationship

between hospital volumes and patient outcome. A study by Mesman et al. identified intermediate factors that could explain part of the observed VOR (Mesman et al. (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.). The study by Avdic et al. made a remarkable contribution by exploiting exogenous variation of hospital volume due to the creation or decommissioning of entire cancer clinics (Avdic et al. (2019b)). They 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 and they concluded that the effect of volume on outcomes is consistent with the learning-by-doing hypothesis, in which experience with treating highly heterogeneous patients plays a fundamental role in the learning process.

The relationship between hospital volume and outcomes is even more complicated to extricate when concerning diseases with multiple treatment options. Indeed, if there is a sole method for treating patients for a specific disease (e.g., a surgical procedure), a positive impact of hospital volume indicates that higher volume hospitals are more capable of performing the procedure considered. In this context, the learning-by-doing hypothesis could be sufficient to explain how and why patients treated in higher volume hospitals have better outcomes. However, for complex disease such as cancer, there are often multiple treatment alternatives (Panje et al. (2018)). In this case, how should one interpret a positive impact of hospital volume on patient outcomes? Are higher volume hospitals always providing higher quality care for all treatment options? And more importantly, is it the only explanation of the volume effect? These questions cannot be answered by only looking at differences in outcomes between patients treated in high and low volume hospitals, even if the analysis is replicated for all treatment options. With multiple treatment options, the positive impact of hospital volume could be due to variations in

clinicians' treatment choices. Thus, by investigating separately the volume relationship for all treatment options, the selection process during which clinicians choose their preferred treatment option to perform is ignored. Naturally, the choice of the best treatment option to care for a patient will be based on patient characteristics (e.g., specificity of the disease), likelihood of patient response to the treatment (e.g., chemotherapy responsiveness), and the patient's general state of health (Panje et al. (2018)). Nevertheless, the weight put on each attribute by clinicians in their decision-making process, as well as their assessments of patient characteristics, could substantially differ depending on their accumulated experience. To summarize, with multiple treatment options and where clinician decisions have major implications for patient outcomes, a volume-outcome relationship could be induced both by a learning effect that makes more experienced clinicians more able to perform a specific procedure, as well as by a learning effect that leads to variations in clinician decisions.

In terms of policy making, it is of primary interest to disentangle the volume-outcome relationship for diseases with multiple treatment options. In the literature, the centralization of care has often been presented as the only volume-based policy capable of increasing the quality of care. If clinician decisions do play an important role in the relationship, other volume-based policies could be applied that could offer alternatives to strict centralization. For instance, clinicians in higher volume hospitals could be incentivized to take part in the treatment decision process in lower volume hospitals. Under this policy, lower volume hospitals would still treat patients, but would have the opportunity to review their treatment decisions with more experienced clinicians in higher volume hospitals.

In the second chapter of this thesis, we provide empirical evidence of what underlies the volume-outcome relationship. The specific aim is to distinguish between a learning effect on the ability to perform a procedure and a learning effect on the ability to make the right treatment decisions in the causal impact of hospital volume on outcomes. The hypothesis tested in this chapter is that, conditionally

on 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. As in the first chapter, we study the case of ovarian cancer. EOC is characterized by a complex care pathway with multiple treatment options that depend on the patient's condition and the clinician's decisions, which makes it a good candidate to investigate how much of the volume effect is due to differences in treatment choices (i.e., care pathways). More specifically, we tested whether there are differences in the use of neoadjuvant chemotherapy according to hospital volume activities, and we examined whether this led to a heterogeneous effect with regard to the complexity of the treatment received. Deciding between initial debulking surgery or neoadjuvant chemotherapy is a real challenge and is not consensual in the decision-making process (Vergote et al. (2013)). Moreover, neoadjuvant chemotherapy is a treatment that is readily available for all hospitals and that does not involve expensive drugs. In this regard, the difference in the use of this treatment can be interpreted as a difference in the way clinicians decide on the optimal treatment to be prescribed, and not as a difference in terms of availability and access to the treatment for hospitals. 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.

Five French databases were used for this retrospective study. These comprised three clinical databases³ from clinical registries (n=355), the "Hospi Diag" public database of hospital characteristics, and open access datasets from the National Institute for Statistics and Economic Studies (INSEE). We jointly estimated a four-equation model, including an outcome equation and several equations that describe the process of selection into different care pathway groups. To control for endogenous volume, 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 with regard to how to treat patients, which contributes to the positive impact of hospital volume activities on patient outcomes. Our findings

³Authorization: CNIL N°909226, CCTIRS N°09-203.

thus confirm that clinician decisions play a role in the volume-outcome relationship. Our results provide an intermediate solution between centralized and decentralized care, which could consist of making lower volume hospitals benefit from the expertise of higher volume hospitals when making treatment decisions. Based on our parameter estimates, we found that the rate of complete tumor resection (i.e., no residual tumor after surgery) would increase by 15.5 percentage points with centralized care, and by 8.3 percentage points if treatment decisions were coordinated by high-volume centers compared to decentralized care. An interesting policy implication of this alternative organization of care is that patients would still be treated in their chosen hospital irrespective of whether it is a high volume hospital. However, first-line treatment decisions for patients treated in low volume hospitals would be discussed and coordinated by high volume hospitals. Compared to a centralization of care that is criticized for its impact on patient access to care, this alternative organization would have no impact on patient access to care.

0.4 Volume-Based Policies in Health (Chapter 3)

We found in chapter 2 that other volume-based policies, compared to centralization of care, could also provide a substantial increase in quality of care. Nevertheless, we also found that the centralization of care is the optimal organization of care to maximize patient outcomes. Worldwide, the centralization of complex care has moved to the center of the health policy debate as a unique opportunity to increase the quality of care through reorganization of the supply side of the market. In practice, only a few countries crossed the line to devise volume-based policies. In the US, incentives toward centralization have been put forward by the Leapfrog Group (a coalition of large healthcare purchasers representing collectively over 20 million people in the United States), which introduced minimum volume standards for eight procedures as part of their safety initiative. In 1995, surgeries for advanced stage ovarian cancer patients were centralized in one health region of Norway (Aune et al. (2012)). It defined a unique regional teaching hospital, which now performs all surgeries for advanced-stage ovarian cancer, while the seven non-teaching hospitals continue to perform these surgeries only for early-stage patients. Ten years after the

centralization was initiated, they showed a significant improvement in the overall quality of ovarian cancer care. Another example is the centralization of acute stroke care in England, where eight London Trusts were converted into Hyper Acute Stroke Units in 2010 (Friebel et al. (2018)). The aim was to discontinue acute stroke services in 22 London hospitals. However, the number of patients treated in the 22 London hospitals has declined only gradually, and the benefit to quality of care is still undetermined. Another type of volume-based policy in order to achieve centralization of care is the introduction of minimum volume standards (Morche et al. (2018)). The concept is to set a volume threshold for a specific disease or procedure, at which hospitals below the threshold will lose their authorization to treat these patients. The goal of this type of policy is still to centralize care in high volume hospitals. However, the decision of which provider to keep or to remove from the market is based on a volume threshold, instead of being chosen by the decision maker. As an illustration, a minimum volume threshold of 20 surgeries per year for ovarian cancer care was established in the Netherlands in 2012, which has been shown to successfully improve the quality of care (Timmermans et al. (2018)).

Why have so few countries moved toward a concentration of healthcare services, considering it has substantial potential for gain in quality? Centralizing care to high volume hospitals also raises important issues and questions about the potentially adverse consequences of the policy. Several barriers, such as the likely increase in patient travel distances, have indeed prevented such a reform in the organization of care from being implemented. A direct implication of the centralization of care for a specific procedure or disease is that the number of providers available on the market will decrease. Since the number of providers will be reduced while the demand will remain unchanged, a deterioration in patient access caused by the policy can be expected. Universal eligibility and the removal of financial barriers to healthcare are among the founding principles in most healthcare systems. Patient access to care has several components, such as the ability to pay (i.e., price component), but also the availability of healthcare personnel and facilities at a reasonable distance from patients' homes and accessibility by transportation (i.e., non-price component). In health systems where prices are set by the health authority (e.g. Germany, France,

the UK), prices do not vary from one provider to another and are reimbursed by the social security system. In this context, one can expect that centralized care to high volume hospitals would deteriorate patient access through its non-price component rather than through the ability of patients to pay for their healthcare. Conversely, in health systems where prices vary from one provider to another, and where care is not fully reimbursed, the centralization of care could deteriorate patient access through either an increase in the cost of care for patients or through a decrease in the availability of health facilities within a reasonable distance. Overall, the centralization of care launches a debate on the trade-off between increasing the quality of care and reducing patient access to care. Thus, it is of primary interest when drafting policy to have evidence of the potential increase in quality, as well as the potential decline in patient access to care if care were to be centralized.

To the best of our knowledge, only three studies have evaluated the impact of centralization of care on patient access.

- The impact of the centralization of care for ischemic heart disease and breast cancer on travel time has been simulated in the Kyoto Prefecture in Japan (Kobayashi et al. (2015)). Surprisingly, their main finding is that the centralization of care reduced inequalities in patient travel times. However, in the Japanese context, the centralization of care is achieved by centralizing care to designated regional core hospitals. In this structure, the impact of centralization of care on travel time strongly depends on how these regional core hospitals are chosen. Moreover, they assumed in their evaluation strategy that patients will choose to be treated in the closest high volume hospital after centralization, which might be a conservative assumption in health systems where patients have the option of choosing their hospital (e.g., France, the United Kingdom, and the United States).
- A German study has evaluated the impact of minimum volume standards for abdominal aortic aneurysm without rupture and hip fracture and found that minimum volumes do not compromise overall access to care (Hentschker and

Mennicken (2015)). They also assumed in this study that patients will choose to be treated in the nearest high volume hospital after centralization of care.

- The third study in the literature also deals with the German healthcare system, and focused on six conditions, which were governed by minimum volume regulations (Hentschker et al. (2018)). Here again, the simulation strategy relied on the strong assumption that patients will choose their closest hospital after centralization of care, and the results indicate a moderate impact of minimum volume thresholds on patient access.

Overall, studies in the existing literature ignored patient preferences in their evaluation strategy, even though patients are free to choose their healthcare provider in most developed countries (e.g., Germany, France, the United States, the United Kingdom). In this context, ignoring patient preferences is likely to underestimate the deterioration in patient access to care caused by a centralization of care. Indeed, patient preferences are likely to be an important driver of the impact of centralized care on patient access to care, since patients do consider several factors they care about when choosing where to be treated, rather than only basing their choice on the relative distance of each provider.

In addition to assessing the degree of deterioration in patient access, it is also of primary interest to evaluate how the burden of these policies will be distributed within the population. Inequalities in health and in access to healthcare is a major concern for the global society. There is ample evidence of disparities in the health status of different social groups in all countries – whether low, middle or high income (Beckfield and Olafsdottir (2013)). Strong inequalities in access to specialized care in favor of those who are wealthier have also been underlined in most OECD countries. These are largely due to spatial variation in the supply of healthcare to different social groups (Doorslaer et al. (2006)). These inequities have significant social and economic costs both for individuals and societies and are the focus of many policies. The impact of centralization of care on socioeconomic and spatial inequalities in access to care remains unclear. Its impact on spatial inequalities depends on whether low volume hospitals were located in areas already suffering from medical

desertification, which would thus increase the medical desertification in these areas if withdrawn from the market. Similarly, the burden of centralization of care on access to care could be unequal in terms of socioeconomic distribution if, for instance, poorer patients were treated in lower volume hospitals initially. Socioeconomic inequalities are even more unpredictable in health systems where prices are administered by the health authority (e.g., France, the United Kingdom, Germany), since prices do not vary from one provider to another and are reimbursed by the social security system. As part of the general interest in centralization, the French National Health Insurance published a report in 2018 with propositions for improving the efficiency of the French healthcare system. It has been put forward to increase the minimum volume threshold for breast cancer from 30 to 150 surgeries per year, and to set a specific volume threshold for ovarian cancer at 10 or 20 surgeries per year (French National Health Insurance (2018)).

In the third chapter of this thesis, we intend to evaluate the impact of the introduction of minimum volume standards for breast cancer and ovarian cancer and to assess the deterioration in patient access and impact on inequalities in access to care. To that end, we used an exhaustive nationwide administrative dataset⁴ (Medical Information Systems Program, PMSI) of 57,151 (4,001) patients who underwent surgical treatment for breast cancer (ovarian cancer) in mainland France in 2017. The PMSI is an exhaustive, nationwide database recording information about each hospital stay in France (Boudemaghe and Belhadj (2017)). To evaluate the impact of a minimum volume threshold on patient access, we elicit patient preferences based on observed choices before centralization of care and predict patient probabilities of hospital choice according to a revealed preferences framework. Then, we exploit these probabilities of patient choice to predict the flow of patients initially treated in a low volume hospital to one of the high volume hospitals. Assuming that adding or eliminating a hospital in the choice set will have no impact on the ratio of probabilities for the remaining hospitals (Independence from Irrelevant Alternatives (IIA)), and by adding the constraint that the probabilities sum to 1 over the remaining hospitals, it is possible to compute the probabilities of patient choice of a high volume

⁴Authorization: CNIL MR005, declaration N°2206880v0.

provider, after applying a volume threshold. For these patients, it is then possible to compute the expected distance as a sum of all combinations of patient-hospital distances weighted by the probabilities of patient choice. Then, to explore spatial inequalities, we investigate whether there are spatial variations in expected patient-hospital distances, expected square distances (i.e., to assume a higher degree of distance aversion), expected additional distances (i.e., only for reallocated patients), and the rate of patients affected by the policy. We evaluate socioeconomic inequalities through jointly investigating two mechanisms. Firstly, the likelihood of being affected by the policy, which could correlate patients' socioeconomic characteristics. Secondly, the variations in the degree of deterioration in patient access among the subgroup of patients affected by the policy according to socioeconomic characteristics. As a benchmark, we also use the evaluation strategy often used in the literature, which consists of assuming that patients will choose to be reallocated to their closest available hospital. By following this assumption, patients are no longer given the choice of their preferred provider and we thus predict a reallocation of patients to high volume hospitals that minimizes patient-hospital distances. In the analysis, breast and ovarian cancer are studied separately because they differ in several aspects. Breast cancer is the most frequent cancer among women, impacting 2.1 million women each year, while ovarian cancer is the eighth most common cancer among women with 300,000 new cases each year. Statistics from the Surveillance, Epidemiology, and End Results Program (SEER) indicate a five-year conditional relative survival of 93.2% for breast cancer against 69.9% for ovarian cancer for women of 65+ years old.

Our results indicate that the application of a minimum volume threshold in France will be very effective in centralizing care for breast cancer and ovarian cancer treatment. The median hospital volume activity post-centralization will be five times higher for breast cancer and four times higher for ovarian cancer compared to the hospital volume distribution observed initially, which would substantially increase the quality of care according to the *Practice-makes-perfect* hypothesis. As expected, our findings tend to indicate that patient access to hospital care for breast and ovarian cancer care would be substantially deteriorated by the policy. Breast

cancer (ovarian cancer) patients affected by the policy will have to travel on average 32.45 (38.89) kilometers further. In terms of patient population, it will affect 35.51% of breast cancer patients and 32.16% of ovarian cancer patients. What was more unpredictable is the impact of the policy on spatial and socioeconomic inequalities in access. We identified strong spatial inequalities in the share of patients affected by the policy among French departments. While less than 10% of the patients would have to be reallocated in some departments, and thus would incur an additional distance, the share exceeds 60% in the most affected departments. A striking result is the increase in spatial inequalities created by the policy, with departments that already have less access initially being more affected by the deterioration in patient access if care were centralized. Note that spatial inequalities are even stronger if a higher degree of distance aversion is assumed by putting more weight to longer distances. Our findings also indicate that the burden of the policy would be unequally distributed among different socioeconomic subgroups through the likelihood of being affected by the policy, as well as through variations in expected additional distance in favor of richer people who live in urban and less remote municipalities. In countries where patient choice of their preferred provider is effective, our findings underline the need to take into account patient preferences in order to have a complete picture of the impact of volume-based policies on patient access. Indeed, ignoring patient preferences drastically underestimates the deterioration in patient access, and thus leads to ignoring a major adverse consequence of such policies.

To summarize, a strict application of such volume thresholds would be unsustainable in terms of patient access. Our results have several implications in terms of policy making. For instance, instead of setting a volume threshold for the entire territory, policy makers could customize the volume threshold for areas where no hospitals would reach the national threshold within a reasonable distance, in order to adjust the volume threshold according to the density of hospitals. Alternatively, instead of reforming the supply side of the market, patients could be allowed to decide where they want to be treated.

0.5 Referral of Patients for Specialized Care (Chapter 4)

From a broader perspective, an understanding of the mechanism of patient referral to hospitals for specialized care is required to better understand whether there is a need to centralize care for complex care, such as breast cancer and ovarian cancer. Indeed, in most developed countries, patients have been offered a free choice of their preferred healthcare provider. Patient choice has been encouraged as a way to introduce competition between healthcare providers. Competition is expected to keep prices at a limit in health systems where prices are set by providers, and to incentivize providers to provide high-quality care in health systems where prices are administrated by a health authority (Gaynor et al. (2015)). Indeed, when prices do not vary from one provider to another, prices are excluded from the demand shifters, and providers are thus expected to compete on non-price components of the demand shifters, such as quality or waiting times. However, it should be noted that empirical evidence on non-price competition between providers is mixed, and it is not clear whether providers adjust their types according to demand elasticity (Moscelli et al. (2018); Longo et al. (2017); Lewis and Pflum (2017); Brekke et al. (2008)). In any case, patient choice plays a fundamental role in shaping the supply side of the market, since patient choices determine providers' sustainability and volume activities. In this context, under regulated price, and assuming the atomicity of the market, full information, and a fully unconstrained referral process, patients are expected to act as a rational consumer (i.e., utility maximizer) by choosing the provider that best matches their preferences.

Nevertheless, while patients have the right to choose the provider that best matches their preferences, several barriers could restrict their choice, such as information asymmetry, lack of providers within a reasonable distance, etc. (Victoor et al. (2016)). For specialized care, patients need to be referred by their general practitioner (GP) in most health systems in order to be reimbursed by the social security system. In this context, patient referrals could be defined as a two-stage decision process (Beckert (2018)). During the first stage, GPs preselect a subset of providers they deemed appropriate from all of the options. Then, during the second stage, patients will

choose their preferred providers among the preselected choice set. The aim of this two-stage decision-making process is to reduce information asymmetry, since GPs possess arguably superior information on alternative providers based on their experience and network. GPs thus have a central role in referring patients to hospitals and act as the patient's agent in the decision-making process. In this context, it is not clear whether patients are actively choosing their provider or if they instead defer to the decision by their GP, especially for complex care where information is likely to be even more asymmetric.

As part of the general interest in patient choice, several policies have been implemented in order to reduce the barriers that restrict freedom of choice. In 2006, a reform was implemented in the UK that mandated GPs to offer at least five alternative treatments when referring patients to a specialist. The aim was to increase patient choice through an increase in the size of the preselected choice set in order to offer a better opportunity for patients to find a hospital that best matches their preferences. A recent study employed a structural model of demand based on the natural experiment given by the 2006 reform, which explicitly models the selection process during which GPs preselect a subset of alternatives (Gaynor et al. (2016)). Results confirm the theoretical expectation that increasing the number of choices for patients makes them more responsive to clinical quality of care in health systems with regulated prices. Patients were treated in higher quality hospitals than they would have been without the reform, which has led to a decrease in overall mortality rates. However, it should be noted that the institutional setting for patient referral in the UK differs in many aspects from the current French institutional setting. Indeed, before 2006, choices were also constrained in the UK because GPs had strong incentives to refer patients to hospitals with which the local Primary Care Trust (PCT) had a contract. After the reform, contracts were abolished, but PCTs were given a fixed budget for the cost of care for the local population. In France, while GPs are assumed to preselect a subset of providers that includes several alternatives, they are not mandated to do so. In this aspect, the French institutional setting is similar to the one in the UK before the 2006 reform. Nevertheless, the French payment scheme is such that GPs have no financial incentives during the referral process. It should be noted that

since 2011, an additional remuneration based on public health objectives has been introduced for French GPs (*Rémunération sur Objectifs de santé publique*) (French National Health Insurance (2019)). This additional remuneration is intended to incentivize GPs based on three aspects: disease monitoring, prevention, and efficiency. However, patient referrals for specialized care is excluded from this additional remuneration, and GPs thus have no financial incentives during the referral process. It is therefore neither clear whether patient choice is fully constrained as in the UK before the 2006 reform, nor clear whether GPs act as imperfect agents for patients as after the 2006 reform in the UK. In a similar vein, in order to lessen information asymmetry, there have been several policies aimed at increasing patient access to objective quality information about healthcare providers, for instance through public websites that provide quality information in an easily understandable form (e.g., weisse-liste.de in Germany and scopesante.fr in France). However, evidence suggesting that patients rely on objective measures of quality is mixed, and patients tended not to use the additional information provided (Victoor et al. (2012); Gutacker et al. (2016); Avdic et al. (2019a); Baker et al. (2003); Varkevisser et al. (2012)).

In the existing literature, empirical studies focused mostly on hospital choice in the context of common surgical procedures, such as hip fractures and hip and knee replacements. These procedures are planned well in advance and are available in almost all hospitals. There is no need for a specific authorization from health authorities to perform these procedures. In this context, empirical findings showed that patient choice is effective, in the sense that patients often bypass the nearest provider to find a hospital that best matches their preferences (Beckert and Kelly (2016); Gravelle et al. (2012); Victoor et al. (2012); Gaynor et al. (2016); Moscelli et al. (2016); Beckert et al. (2012)). Findings suggest that the probability of a hospital being chosen increases with its measured quality, while it decreases with waiting times and distance. However, only a few studies have delved into the role of GPs in the referral process. In the US, there is a trend of integrating physician practices into hospitals, which has launched a debate about the effect of physician integration on the agency issue between physicians and patients (Baker et al. (2014)). Using data on Medicare beneficiaries, including the identity of their physician and data on the

identity of the owner of their physician's practice, hospital's ownership of a physician has indeed been shown to increase the probability that the physician's patients will choose the owning hospital (Baker et al. (2016)). Note that in most Western European countries (e.g., Germany, France, the UK) GPs are independent, in the sense that there is no integration into hospitals. Nevertheless, even in the absence of hospital integration, GPs have a central role in the referral process, since they do act as patient agents by preselecting a subset of providers based on their own utility function. Using UK administrative data on National Health Service inpatient admission, one study showed that ignoring the agency issue in the choice set formation leads to biases and inconsistencies (Beckert (2018)). Its findings support the notion that GPs act as imperfect agents for patients, since they also act as agents of the health authorities to contain costs. Conditionally on the preselected choice set, patients tended to base their choice on tangible hospital characteristics, such as distance, amenities and waiting times, while GPs preselection was driven by quality, and costs.

However, very little is known about patient preferences for cancer care. Cancer is a life-threatening disease that can be treated by only a subgroup of providers that received authorization from health authorities, which varies according to the respective type of cancer. In this context, information is highly asymmetric between patients and hospitals. Moreover, cancer treatments often include chemotherapy in the care pathways for patients. Chemotherapy treatment requires that the patient come back several times to the hospitals to receive the chemotherapy perfusion. These kinds of treatments could also decrease the likelihood for a patient to bypass the nearest hospital, since they will have to travel the distance to the hospital of treatment several times. Thus, in the context of cancer care, there might simultaneously be some uncertainty on the factors predicting patient choice and some uncertainty on the factors driving patient choice sets.

The fourth chapter of this thesis intends to evaluate whether patients are actively choosing their provider for complex care with highly asymmetric information, and to identify patient preferences for hospital choice with unobserved choice sets. We study the case of breast cancer, which is the most frequent cancer among

women, impacting 2.1 million women each year. We focus on first-line treatment for breast cancer, and particularly on hospital stays during which a debulking surgery was performed. We utilize hospital discharge data⁵ from the Medical Information Systems Program (PMSI), which comprehensively records hospital stays in French hospitals (Boudemaghe and Belhadj (2017)). We also used the French Hospital Survey (Statistique annuelle des établissements - SAE), managed by the Directorate for Research, Studies, Evaluation and Statistics (DREES), and the "e-Satis" survey of patient satisfaction managed by the French Authority for Health (HAS) in order to get details of characteristics and amenities at hospitals where breast cancer patients received treatment. Using a revealed preferences framework, the main methodological challenge in order to elicit patient preferences from observed patient-hospital allocation is that the true choice set (i.e., the preselected choice set) is unobserved to the econometrician. As a benchmark, we estimate a random coefficient logit model on the full choice set, which ignores the unobserved choice sets. For instance, ignoring unobserved choice sets does not take into account the GP preselection process. Nevertheless, it is still possible to identify factors (i.e., hospital characteristics) playing a role in the referral process. However, this specification does not allow patient choice sets to be unobserved. To that end, we used a novel approach proposed by Zhentong Lu, which allows the estimation of a multinomial choice model when choice sets are in fact unobserved, in order to distinguish patient preferences from GP preferences (Lu (2019)). This approach to dealing with unobserved choice sets is part of broader literature on methods based on conditional moment inequalities (Andrews and Shi (2013)). While the true choice set is unobserved, the concept is to set an upper bound and a lower bound of the true choice set. In this study, we defined the lower bound as choices made by other patients based on each patient's residential location. The assumption made here is that patients with the same condition and living close to each other are likely to benefit from a similar preselected choice set. This assumption relates the fact that GPs act as agents for patients but are assumed to have no idiosyncratic taste variations. To limit the number of choices, we restricted our sample to hospitals in a radius of 160 kilometers around each patient as the upper bound. The aim of this restriction is to avoid the most irrelevant alternatives, which might reflect

⁵Authorization: CNIL MR005, declaration N°2206880v0.

a wrong ZIP code in the data or patients having several residential locations and are thus excluded from the estimation. The bound in choice set can then be turned into a bound on choice probabilities, thanks to an important monotonicity property. Assuming that GPs are involved in the referral process only through the preselection of a subset of alternatives, this method makes it possible to derive patient preferences conditionally on the pre-selected choice set. Finally, we also evaluate the impact of the density of hospitals around patient residential locations on their preferences, and whether it could limit their choice.

We observe in our data strong variations in choices made by patients living very close to each other. These variations in choices are even more meaningful considering that our population of interest is composed of breast cancer patients who received the same treatment (i.e. surgical treatment) and is thus rather homogeneous. Assuming that patients and their GPs act as a single decision maker, we first estimate a random coefficient logit model in order to identify hospital characteristics affecting patient referral. By comparing studies that investigate patient preferences for more common surgical procedures, patient referrals for cancer care seems to differ by attributing more weight to the specialization profile and to hospital type, rather than to general quality indicators, such as hospital certification (Beckert and Kelly (2016); Gravelle et al. (2012); Victoor et al. (2012); Gaynor et al. (2016); Moscelli et al. (2016); Beckert et al. (2012)). Interestingly, the results of patient preferences conditionally on their preselected choice set differ substantially. Our findings indicate that breast cancer patients do consider several hospital attributes other than distance to rank providers preselected by their GP. Patients tend to defer to their GPs when it comes to hospital specialization profile and consider waiting times, general hospital quality indicators, and hospital type to make their choice. Nevertheless, we also identify strong inequalities in patient freedom of choice caused by the size of the choice set, which prevent patients who have few alternatives within a reasonable distance from ranking hospitals based on their quality. The distance to hospitals is found to be completely excluded from patient preferences, except for the most severely ill patients. Thus, only the most severely ill patients are found to be distance averse, in the sense that they prefer closer hospitals. Hospitals may be preselected based on their

relative location by GPs, and then chosen by patients based on their attributes and types. Overall, our findings bring new evidence on the possible role of GPs in the referral process, who may play a critical role by preselecting a subset of providers on the behalf of their patients.

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Chapter 1

The volume-outcome relationship for ovarian cancer care in France

Abstract

This article explores the relationship between hospital volume activities and the survival for Epithelial Ovarian Carcinoma (EOC) patients in France. We used an exhaustive cohort of 267 patients undergoing first-line therapy during 2012 in the Rhone-Alpes Region of France. We compared Progression-Free Survival for Epithelial Ovarian Carcinoma patients receiving first-line therapy in high- (i.e. ≥ 12 cases/year) vs. low-volume hospitals. To control for selection bias, multivariate analysis and propensity scores were used. An adjusted Kaplan-Meier estimator and a univariate Cox model weighted by the propensity score were applied. Our findings indicate that patients treated in the low-volume hospitals had a probability of relapse (including death) that was almost two times (i.e. 1.94) higher than for patients treated in the high-volume hospitals ($p < 0.001$). To the best of our knowledge, this is the first study conducted in this setting in France. As reported in other countries, there was a significant positive association between greater volume of hospital care for EOC and patient survival, despite the minimum volume threshold set in 2006 for gynaecologic cancers in France.

1.1 Introduction

While epithelial ovarian carcinoma (EOC) is known to be a serious disease, its impact is often underestimated due to its relatively low incidence and its high mortality rate. EOC remains the eighth most common cancer for women, with an incidence rate of 11 to 12 women for every 100 000 women/year. EOC remains the main cause of gynecological cancer deaths in industrialized countries, with a mortality rate in France of about 4/100 000 persons per year (Reseau FRANCIM (2010)). Indeed, survival estimates, based on the FRANCIM network registry data between 1989 and 2004, indicate an overall survival rate at 5 and 10 years of 37% and 28%, respectively. Relapse-free survival and overall survival of patients are related to the characteristics of the disease, the patient herself, and the disease management. The latter is based on surgery with a complete tumor resection, which can have a significant impact even on stage IV disease. Optimal debulking also has a positive impact on outcomes, but far less so than complete tumor resection. Surgical debulking has a positive impact on all histological subgroups. Nevertheless, mucinous carcinoma remains a strong independent prognostic factor for the disease (Du Bois et al. (2009)). Several retrospective studies have investigated the relationship between outcomes of ovarian cancer treatment and the type of care provider (Fung-Kee-Fung et al. (2015)). A higher quality of surgery when performed by gynecological oncologists in specialized hospitals (i.e. referral centers) and only small differences in chemotherapy regimens have been reported between the settings. Some studies have also investigated the impact of the centralization of care, in terms of volumes and patient outcomes (Aune et al. (2012); Bristow et al. (2010, 2014, 2015); Cowan et al. (2016); Ioka et al. (2004); Mercado et al. (2010); Phippen et al. (2013); Reade and Elit (2012); Vernooij et al. (2009); Woo et al. (2012)). Patients are more likely to be optimally debulked in a high-volume hospital or by a specialized provider. These studies have also shown that patients have better survival outcomes in high-volume hospitals. However, most of these studies focused on advanced stage disease, and none were carried out in France. The majority of patients with ovarian cancer do not receive care in specialized settings (Cowan et al. (2016)). Moreover, there is still substantial national debate about the necessity of centralization of care for ovarian cancer, with

major economic implications that need to be assessed.

As stipulated by the French ministerial order of 27 March 2007, French legislation requires a minimum hospital volume activity in order to receive authorization to treat gynecological cancers (Querleu (2008)). Thus, a hospital needs to perform more than 20 surgeries per year for gynecological cancers, such as cervical, ovarian, vaginal, uterine, and vulvar cancers, to receive authorization to treat patients with these specific diseases the following year. Patients are free to choose at which of the hospitals authorized to treat gynecological cancers they will be treated. Moreover, ovarian cancer is considered to be a Long Duration Disease (LDD) by the French social security system. Therefore, in this setting, 100% of the treatment costs are reimbursed by the government, based on the reference cost set by the social security system. However, patients may nonetheless incur additional fees, most often in private for-profit hospitals. For patients with a supplementary health insurance (already 95% of French residents were covered even before the reform of 2016) additional fees may be partially or fully reimbursed by their supplementary health insurance, depending on the type of policy that they have selected. The aim of this study was to compare Progression-Free Survival (PFS) with first-line therapy for EOC patients treated in high- versus low-volume hospitals in the Rhone-Alpes region of France in 2012. The novelty of this study lies in part with the use of a detailed set of patient characteristics in the analysis that allows for proper control of the strong selection bias between patients treated in high- versus low-volume hospitals.

1.2 Data

This retrospective study using a prospectively implemented database was conducted on an exhaustive cohort of patients treated in first-line during 2012 in the Rhone-Alpes Region of France¹. The database was constructed by the EMS team (Medical Evaluation and Sarcomas) from the Leon Berard cancer research center

¹With a population of 6 283 541 in 2011, the Rhone-Alpes region is the second most populous region of France. The region has several large cities; the three biggest being Lyon, Grenoble, and Saint-Etienne. The Rhone-Alpes region is located in the southeast of France, and it merged with the Auvergne region to form the Auvergne-Rhone-Alpes region in 2016. However, since patients in the database were treated in 2012, we will refer to the Rhone-Alpes region only, as it was delimited in 2012.

(Lyon, France). They established an exhaustive list of all patients newly diagnosed with ovarian cancer in the region using existing lists from oncology treatment - coordinated centers (3C), and from pathologists in the region. 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 in a hospital in the Rhone-Alpes region. The exclusion criteria were: non-epithelial disease, relapsed disease, less than 18 years of age, or patients living in the region who had undergone treatment in another region of France. Finally, Clinical Research Assistants from the EMS team collected the data at all of the included hospitals, two years after diagnosis period. For each patient, their age, cancer history (yes or no), presence of ascites (yes or no), histology (e.g. high-grade serous carcinoma, low-grade serous carcinoma, mucinous, endometrioid, clear-cell, or unknown), FIGO stage (I to IV), tumor grade (1 to 3), residual tumor (CC0: no residual; CC1 or CC2: microscopic or macroscopic residual), reoperated (yes or no), and the type of chemotherapy (e.g. neoadjuvant, adjuvant, both, or none) were recorded as well as the dates of progression and/or death or last contact.

1.3 Methods

Progression-Free Survival (PFS) was defined as the time elapsed between the diagnosis and disease progression (loco-regional or metastatic) or death from any cause. To determine whether the PFS was longer in high-volume hospitals (HVH), we needed to define a threshold based on the volume of activity of hospitals in the study. The upper quartile was chosen as the cut-off value for HVH where 25% of EOC patients in first-line treatment during the year 2012 are categorized as being treated in HVH versus 75% as being treated in Low-Volume Hospitals (LVH). As a sensitivity analysis, we also considered two other thresholds using the lower quartile and the median of the volume activity, in order to get two groups of patients treated as 75% in HVH - 25% in LVH and 50% treated in HVH - 50% in LVH, respectively. Investigation of whether there are differences in survival according to the volume activity of hospitals requires controlling for differences between the two groups

of patients (i.e. those treated in HVH vs. LVH). Indeed, without randomization, patients in high- and low-volume facilities may be different in regard to observed or unobserved factors that could affect outcomes (Austin (2014)). Since the database contained an abundance of patient characteristics, we relied on methods that adjust for observable selection bias (i.e. multivariate analysis and propensity score methods). In all statistical analysis, we relied on a 5% level of significance. Patients for whom the hospital for the first-line treatment or for which all of the characteristics were missing were excluded from the analysis.

1.3.1 Multivariate analysis

A common approach when dealing with confounding factors is to use multivariate regression (Johnson et al. (2009)). The principle was to regress the survival time on an indicator variable denoting HVH or LVH, and to control for prognostic factors such as age, histology, FIGO stage, grade, neoadjuvant chemotherapy, cancer history, and the presence of ascites. This specification was replicated for the three different thresholds that we used to define a HVH. In practice, we first ran a Cox proportional hazard model of the Progression-Free Survival (PFS) on the set of covariates, and we then tested whether the hazard was proportional or not by the Schoenfeld residual test and with a Log-Log plot (Schoenfeld (1980)). Then, if the proportional hazard assumption was upheld, the preferred model was a semiparametric Cox proportional hazard regression. If not, we resorted to a parametric determination with an Accelerated Failure Time (AFT) model. With the AFT model, we had to choose a parametric distribution of the hazard. A common practice was to at first determine a Generalized Gamma model which includes the Exponential ($k = \sigma = 1$), Weibull ($k = 1$), Lognormal ($k = 0$), and Gamma ($\sigma = 1$) distributions. It was then possible to test for these parameters in order to choose between these distributions by a likelihood ratio test. Multivariate analysis only allowed for determination of a relative effect, which could be seen as a conditional treatment effect: the average effect of being treated in a higher volume hospital at the individual level, as if a patient in a low-volume hospital was treated in a higher volume hospital. Propensity score methods had the advantage of allowing determination of both absolute and relative

treatment effects, as the CONSORT statement recommends evaluation of the treatment effect in an observational study (Austin (2014)).

1.3.2 Propensity score matching using inverse probability weighting

Propensity score methods were also applied to control for the selection bias and to determine both a relative and an absolute treatment effect. These two effects could be seen as marginal treatment effects in the sense that they corresponded to the difference in outcomes between the groups of patients in high- versus low-volume hospitals (Austin (2014)). By comparison, multivariate analysis allowed for evaluation of a conditional effect and not a marginal effect. In practice, we used Inverse Probability Weighting (IPW) using the propensity score. We used the standardized difference in means instead of the t-test to compare the baseline characteristics, as recommended by Austin (Austin (2014)) and Stuart (Stuart (2010)). The IPW method balances out the covariate of the two groups by weighting all patients in the data base by the inverse of their propensity score. The propensity score was the conditional probability for a patient to be treated in a high-volume hospital, conditionally to observables characteristics. We determined this probability by fitting a logit model of an indicator variable denoting high- or low-volume hospitals on age, histology, FIGO stage, grade, cancer history, neoadjuvant chemotherapy, and the presence of ascites. We excluded predictive variables of outcomes that may depend on patient choice and subsequent interventions from this model, and we only controlled for patient characteristics at the time of diagnosis (i.e. prior to the patients receiving their first-line treatment). Again, the determination of the weights was performed for each threshold of the hospital volume activities. We used the stabilized weights of the IPW proposed by Robins (Robins et al. (2000)). It should be note that T_i is the treatment variable, p_i the propensity score, and $f(T)$ the distribution of the treatment which was determined by a logit model without considering covariates. In order to determine the Average Treatment effect on the Treated (ATT), weights can be calculated with the formula in equation (1).

$$w_i^{ATT} = f(T) * [T_i + \frac{p_i(1-T_i)}{1-p_i}] \quad (1)$$

An Adjusted Kaplan-Meier Estimator (AKME), as proposed by Xie and Liu (Xie and Liu (2005)) and a univariate Cox model in the weighted sample, as described by Cole and Hernan (Cole and Hernán (2004)), were then applied in order to determine the absolute and relative impact, respectively, of the concentration of care on the survival of EOC patients. We used the robust variance estimator of Lin and Wei (Lin and Wei (1989)) for the weighted Cox model, to take into account the within matched set correlation due to the matching process. In order to test for a significant difference in survival curves for the two groups, we used the adjusted log rank test as proposed by Xie and Liu (Xie and Liu (2005)), to take into account that patients in high- and in low-volume hospitals are no longer independent after weighting using the IPW.

1.4 Results

1.4.1 Patient and hospital characteristics

In 2012, 267 patients were identified with an EOC in the Rhone-Alpes region, although only 231 (87%) were used in the modeling due to missing data. Patients were treated in 55 different hospitals across the entire region, including 51 low-volume hospitals (i.e. volume < 12 cases/year) and 4 high-volume hospitals. The median volume activity by hospital for the HVH was 19.5 (from 12 to 27) patients treated for EOC per year, versus 3 (from 1 to 10) for the LVH. Figure 1.1 depicts the distribution of hospital volume activities. In this figure, each bar represents a specific hospital. The distribution varied among the hospitals, from a minimum of one patient to a maximum of 27 patients in 2012.

Thirteen of the 55 facilities had treated only one patient in 2012 (24%), and twenty-four had treated no more than two patients (40%). The higher volume hospitals were either university hospitals, cancer centers, or private hospitals. Only 78 patients (37%) in a first-line setting were treated in a high-volume hospital. Of the 231 total subjects, 131 patients relapsed and 89 patients died (with or without having relapsed) during the follow-up. Table 1.1 lists the patient characteristics, comparing patients treated in high- versus low-volume hospitals. At baseline (i.e. before

matching), the higher volume hospitals tended to treat a higher proportion of grade 3 tumor patients ($p = 0.006$) and a lower proportion of grade 1 tumor patients ($p = 0.019$), compared to lower volume hospitals. The HVH also tended to treat a lower proportion of stage I patients ($p = 0.026$), and a higher proportion of stage III patients ($p = 0.046$). It can be seen that 81% of the patients treated in the HVH were Grade 3 versus only 63% of the patients treated in the LVH. There was a significantly higher proportion of patients with no residual tumor (CC0) ($p < 0.001$) and a significantly lower proportion of reoperation ($p < 0.001$) in higher volume hospitals. Patients in lower volume hospitals were more often treated with a post-surgery chemotherapy only ($p = 0.047$), while patients in higher volume hospitals were more likely to be treated with both a neoadjuvant and a post-surgery chemotherapy ($p < 0.001$). These differences in the use of chemotherapy are only from a descriptive point of view, and do not take into account that the HVH were treating patients with a higher tumor stage and grade.

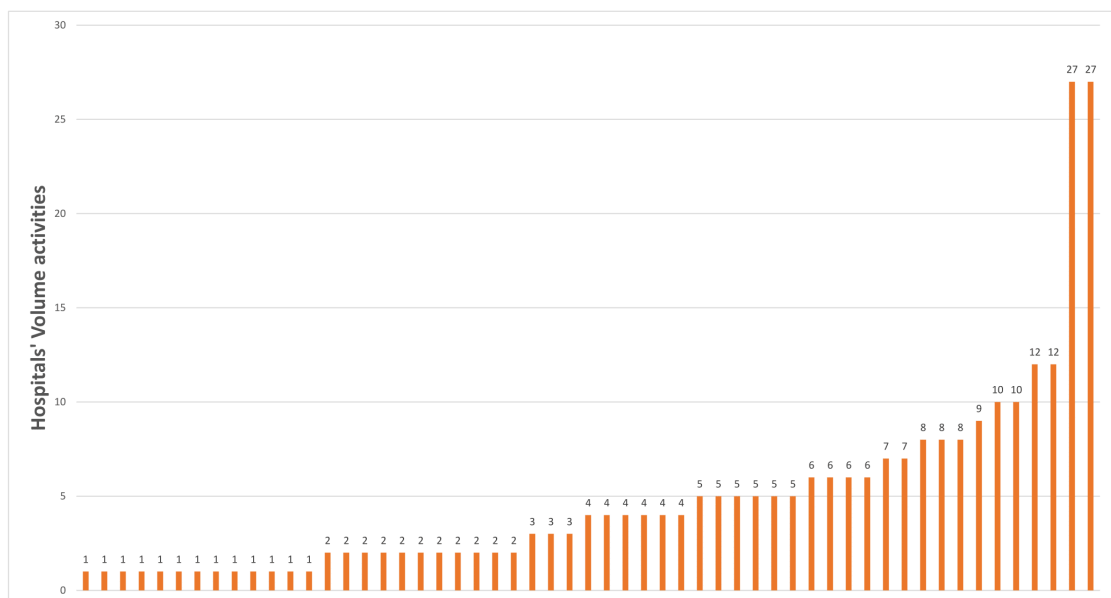


FIGURE 1.1: Distribution of annual hospital volume activities

TABLE 1.1: Patient characteristics at baseline (threshold of 12 patients)

	LVH (n=78 patients)	HVH (n=189 patients)	P-value	%bias
Age	63.78	66.10	0.193	17.9
Cancer history	0.14	0.17	0.622	6.6
Ascites	0.60	0.69	0.148	19.7
Histology:				
- HGSC	0.20	0.62	0.142	20.4
- LGSC	0.06	0.04	0.443	-11.0
- Mucinous	0.10	0.03	0.048	-30.2
- Endometrioid	0.14	0.13	0.867	-2.3
- Clear cell	0.06	0.04	0.421	-11.4
- Unknown	0.11	0.15	0.447	10.2
FIGO Stage:				
- I	0.25	0.13	0.026	-31.8
- II	0.05	0.08	0.438	10.1
- III	0.56	0.69	0.046	27.5
- IV	0.14	0.10	0.458	-10.3
Tumor Grade:				
- 1	0.16	0.05	0.019	-35.8
- 2	0.20	0.14	0.216	-18.0
- 3	0.63	0.81	0.006	40.3
Chemotherapy:				
- Neoadjuvant only	0.17	0.12	0.228	-16.8
- Post-surgery only	0.47	0.33	0.047	-27.1
- Both	0.18	0.45	0.001	60.2
- None	0.18	0.10	0.115	-22.3
Reoperation	0.34	0.12	0.001	-54.1
No residual disease after debulking surgery	0.70	0.45	0.001	50.5
			Mean	24.3
			Median	20.1

Note: standardized difference of the mean (%bias); High-Grade Serous Carcinoma (HGSC); Low-Grade Serous Carcinoma (LGSC).

1.4.2 Multivariate analysis

The Schoenfeld residual test revealed that the null hypothesis of proportional hazard was not rejected ($p = 0.0630$), whereas the Log-Log plot of survival revealed a non-proportionality of the hazard (see Appendix 1 for more details on the Log-Log plot). Since the p-value of the Schoenfeld residual test was close to a 5% level of significance, and the two curves crossed each other in the Log-Log Plot (i.e. indicating non-proportionality), we concluded that the Cox model was not appropriate. Thus,

we resorted to a parametric determination of an AFT model. It appeared that the Weibull distribution provided the best fit for our data. We chose Weibull instead of Gompertz and Loglogistic, which are not a particular case of the generalized gamma, because the AFT model with a Weibull distribution minimized the Akaike Information Criterion (AIC). Table 1.2 shows that, on average, patients treated in higher volume hospitals had a longer PFS ($p = 0.023$) than patients in lower volume hospitals.

TABLE 1.2: A Weibull accelerated failure time models of PFS

	Threshold = 12	Threshold = 8	Threshold = 5
High-volume hospital	0.41***	0.33***	0.21
Age	-0.01**	-0.01**	-0.01**
Cancer history	-0.20	-0.24	-0.24
Ascites	-0.32**	-0.34**	-0.32**
Neoadjuvant chemotherapy	-0.30**	-0.29**	-0.26*
Histology:			
- HGSC	Ref	Ref	Ref
- LGSC	0.23	0.30	0.28
- Mucinous	0.14	0.16	0.14
- Endometrioid	0.15	0.26	0.27
- Clear cell	-0.01	-0.16	-0.11
- Unknown	-0.19	-0.16	-0.09
FIGO Stage:			
- I	Ref	Ref	Ref
- II	-0.42	-0.35	-0.34
- III	-0.58**	-0.58**	-0.59**
- IV	-0.82**	-0.79***	-0.85***
Tumor Grade:			
- 1	Ref	Ref	Ref
- 2	-0.03	-0.09	-0.09
- 3	-0.01	0.05	0.06
Intercept	4.77***	4.65***	4.60***

Note: modality in reference (Ref); High-Grade Serous Carcinoma (HGSC); Low-Grade Serous Carcinoma (LGSC). *, **, ***: significant at 10%, 5%, and 1%, respectively.

We also estimated the same model with two other hospital volume activities thresholds as a sensitivity analysis. The magnitude of the coefficient associated with being treated in a HVH decreased when we employed a threshold of 8 patients treated per year, but remained strongly significant (Table 1.2). Whereas when we used a threshold of 5 patients treated per year there was no longer a difference

in the PFS, on average, between patients treated in high- or low-volume hospitals.

1.4.3 Propensity score approach: matching using the inverse probability weighting (IPW)

Table 1.3 shows a good quality for the matching by IPW. Indeed, there was no significant difference for all covariates between the two groups, while there were significant differences prior to matching in terms of the stage, grade, and histology. The mean of the standardized mean differences was 7.3 for the matched sample (Table 1.3) compared to 20.4 for the unmatched sample.

TABLE 1.3: Characteristics of the patients after using IPW matching

	LVH (n=78)	HVH (n=189)	P-value	%bias
Age	67.56	65.81	0.568	-13.5
Cancer history	0.15	0.17	0.830	5.7
Ascites	0.69	0.67	0.920	-2.5
Neoadjuvant chemotherapy	0.52	0.57	0.712	9.6
Histology:				
- HGSC	0.65	0.59	0.642	-11.7
- LGSC	0.05	0.03	0.70	-8.2
- Mucinous	0.03	0.04	0.739	6.6
- Endometrioid	0.14	0.11	0.659	-10.6
- Clear cell	0.05	0.05	0.995	0.1
- Unknown	0.08	0.17	0.318	27.5
FIGO Stage:				
- I	0.15	0.15	0.920	2.3
- II	0.08	0.07	0.916	-2.9
- III	0.68	0.66	0.848	-4.7
- IV	0.09	0.11	0.793	6.3
Tumor Grade:				
- 1	0.06	0.05	0.717	-6.5
- 2	0.14	0.14	0.980	-0.6
- 3	0.80	0.82	0.823	5.1
			Mean	7.3
			Median	6.3

Note: standardized difference of the mean (%bias); High-Grade Serous Carcinoma (HGSC); number of patients (n); Low-Grade Serous Carcinoma (LGSC).

Matching using IPW allowed for determination of both the absolute treatment effect, with the AKME, and the relative reduction of an event occurring by the univariate weight Cox model. Table 1.2, based on the AKME, indicates that patients in high-volume hospitals had a significantly longer PFS ($p < 0.0011$) than patients in low-volume hospitals. For example, the median survival for the PFS was 20 months in the high-volume hospitals, versus 14.2 months in the low-volume hospitals.

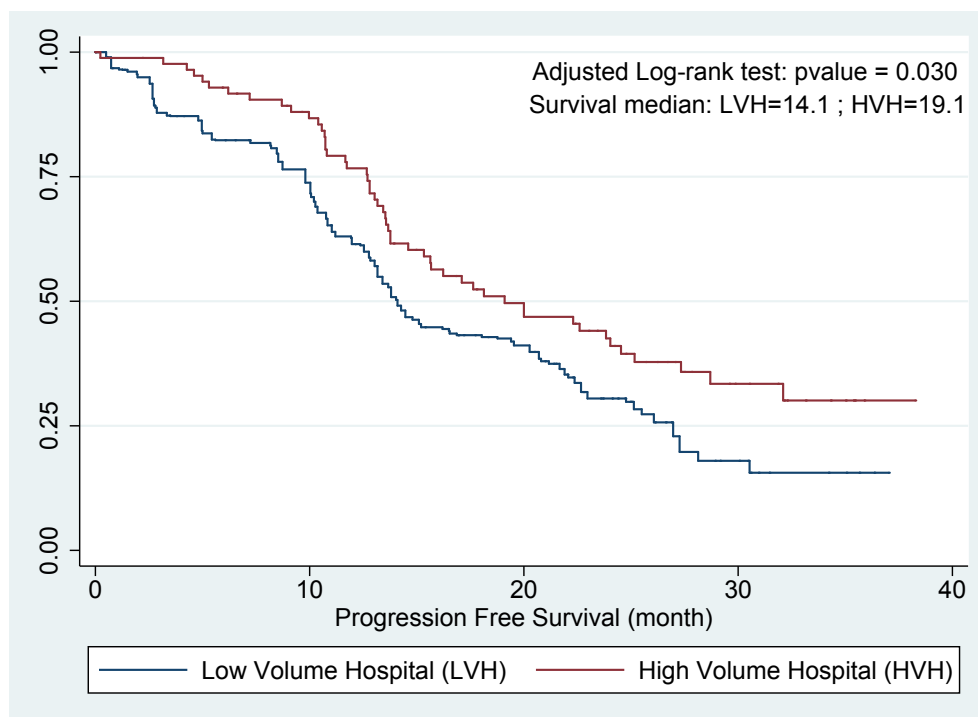


FIGURE 1.2: Adjusted Kaplan-Meier estimator of the Progression-Free Survival after weighing by the IPW

Furthermore, the univariate Cox model of the PFS, weighted by the inverse of the propensity score, revealed that the hazard ratio (HR) (i.e. the hazard or chance of events occurring in the treatment arm as a ratio of the hazard of the events occurring in the control arm) for treatment in a high-volume hospital was $HR = 0.52$ ($p < 0.001, 95\%CI : [0.35; 0.75]$). The Schoenfeld residual test revealed that the proportional hazard assumption was valid for the univariate weighted Cox model ($p = 0.1410$), and it confirms the robustness of the result. As a sensitivity analysis, we also ran the same analysis with a threshold of either 5 or 8 patients treated per year and per hospital. The univariate weighted Cox models revealed that the hazard ratio was $HR = 0.73$ ($p = 0.082$) with a threshold of 8, and $HR = 0.90$ ($p = 0.632$)

with a threshold of 5. Table 1.3, based on the AKME, indicates that there was no significant difference in survival between patients in high- and low-volume hospitals for both of the threshold of the sensitivity analysis.

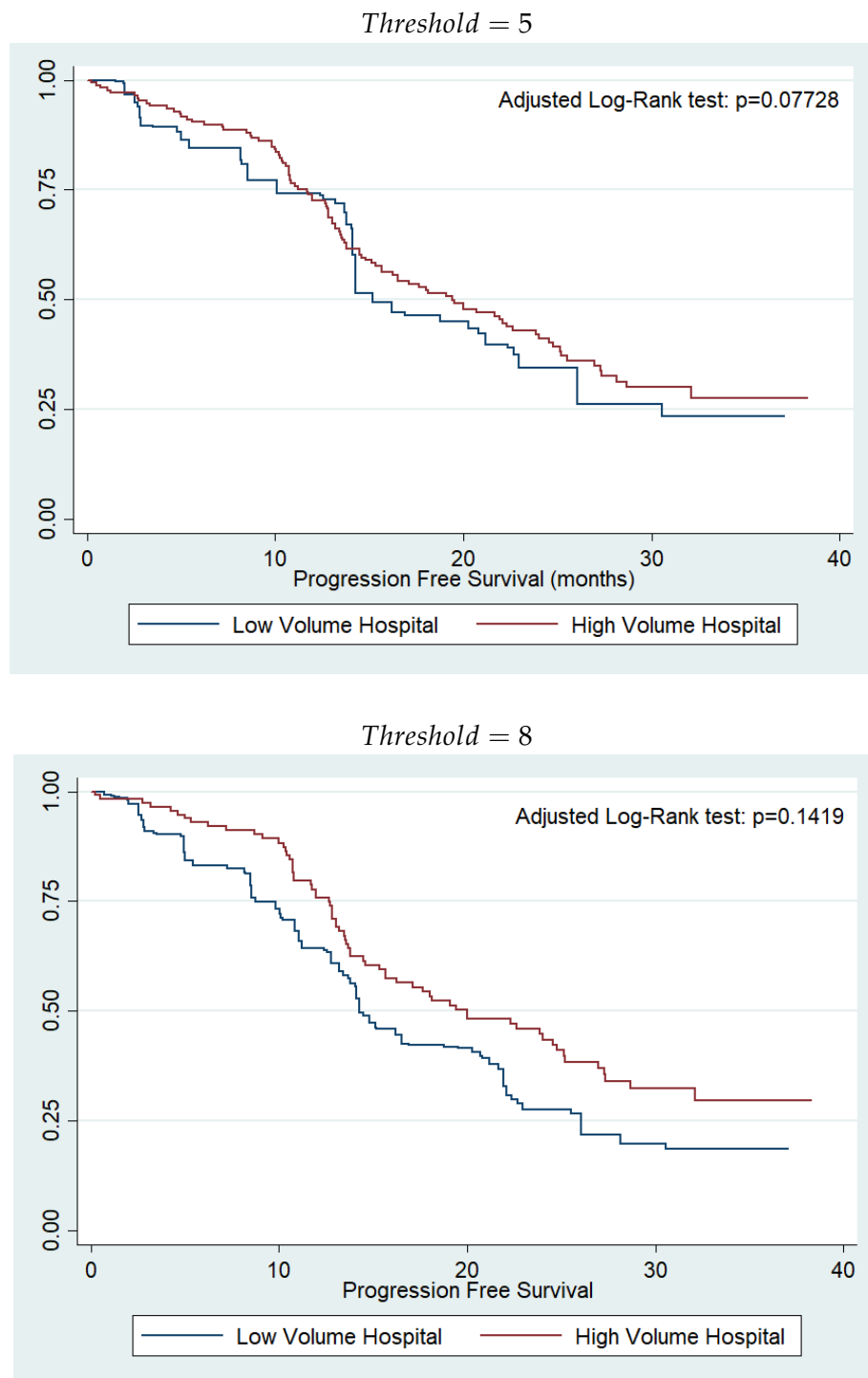


FIGURE 1.3: Sensitivity analysis: Adjusted Kaplan-Meier estimator of the Progression-Free Survival after weighing by the IPW with a threshold of either 5 or 8 patients treated per year and per hospital

1.5 Discussion

1.5.1 Definition of a high-volume hospital

In this study, we showed that being treated in a higher volume hospital increased the PFS of patients, compared to a lower volume hospital. More specifically, the probability of relapse (including death) was twice as high for patients treated in lower volume hospitals (i.e. 1.94 higher ($p < 0.001$) compared to patients treated in higher volume hospitals). Indeed, the median PFS in high-volume hospitals was 20 months, versus only 14.2 months in low-volume hospitals. Moreover, the higher proportion of complete tumor resections, and the lower proportion of reoperation (Table 1.1) support the notion that the quality of the first-line surgery appears to be better in high-volume hospitals, as reported previously studies (Vernooij et al. (2009); Ioka et al. (2004)). To define a high-volume hospital, different countries have employed different thresholds that are based on the prevalence of the disease (Aune et al. (2012); Bristow et al. (2010, 2014, 2015); Cowan et al. (2016); Ioka et al. (2004); Mercado et al. (2010); Phippen et al. (2013); Reade and Elit (2012); Vernooij et al. (2009); Woo et al. (2012)). For example, the mean volume of activity of high-volume hospitals in the study by Ioka et al. on a Japanese dataset was 8.8 patients, which may be considered to be low compared to what has been seen with studies in the USA (Ioka et al. (2004)). Yet it appears that in 2012, 93% of the hospitals had treated fewer than 12 patients in first-line treatment for EOC per year in the Rhone-Alps region of France, 82% had treated fewer than 8, and 60% had treated fewer than 5. We chose the upper quartile (12 patients) in the main analysis as the threshold, in order to obtain a share of 25% of patients treated in a HVH that is more in line with the threshold of 20 cases that is widely used in the USA, which yielded a distribution of 17.9% of patients treated in HVH in the study by Bristow et al. (Bristow et al. (2014)). We also considered two other thresholds, namely 5 and 8 patients per year, as a sensitivity analysis in order to cover all of the quartiles of the patient distribution. The sensitivity analysis showed that the results were mixed when we considered a threshold of 8 cases/year, and that there was no longer a volume-outcome effect with a threshold of 5 cases/year. Indeed, with a threshold of 8 cases/year, the

multivariate analysis revealed a positive impact of hospital volume activities on outcomes, whereas the propensity score analysis revealed no association at a 5% level of significance. Thus, the sensitivity analysis showed that the cut-off has to be restrictive enough in order to identify a volume outcome relationship for EOC.

Many countries already require a minimum level of activity for a hospital in order for it to be authorized to provide cancer treatments. In France, the minimum cut-off in order to receive authorization to treat gynecological cancers was defined by the French ministerial order of 27 March 2007 as 20 surgeries per year. Below this volume of activity, a hospital is no longer authorized to treat patients with gynecological cancers. This threshold, however, takes into accounts all of the various types of gynecologic cancers, such as cervical, ovarian, vaginal, uterine, and vulvar cancers. Our findings indicate that there is a need for a specific minimum activity cut-off for ovarian cancer only. Indeed, the overall threshold of 20 cases per year does not specify whether it refers to all gynecological cancers or ovarian cancer only. Out of all of the patients in first-line treatment for EOC in the Rhone-Alpes Region of France in 2012, 71% were treated in hospitals with fewer than 12 cases per year, 50% in hospitals with fewer than 8 cases per year, and 24% in hospitals with fewer than 5 cases per year. This distribution of hospital volume activities is not a specificity of the Rhone-Alpes region in France. Indeed, the public website² held by the French National Authority of Health (HAS) recorded that in the most populous region of France (i.e. Ile-de-France), 118 hospitals had authorization to treat gynecologic cancers in 2017, compared with 71 for the Rhone-Alpes region. With a population of 6 574 708 for the Rhone-Alpes region and of 12 142 802 for Ile-de-France in 2016 (source: National Institute of Statistical and Economic Information), there was one hospital treating gynecologic cancers for every 92 601 residents in the Rhone-Alpes region and one for every 102 905 residents in Ile-de-France. As the number of hospitals is similar between the two regions, the distribution of hospital volume activities is also likely to be similar.

²Website: <https://scopesante.fr>.

Our findings appear to support the use of a specific cut-off for ovarian cancer, and more research needs to be done for other rare cancers in order to verify whether a specific minimum activity cut-off is similarly required. Nevertheless, a threshold at the hospital level does not take into account the heterogeneity among the practitioners at any given hospital. A recent study has shown that the physician's volume of activity also positively correlates with survival, and that the combination of being treated in a high-volume hospital by a high-volume physician appears to be superior in terms of survival compared with other combinations of hospital and physician volumes of activity (Bristow et al. (2014)). More research needs to be done to develop a management program that takes into account the volume of activity at both the hospital and the physician level. Hospital participation in clinical trials has also been shown to improve EOC patient outcomes (Du Bois et al. (2005)). More research need to be done to properly understand what underlies the volume-outcome relationship.

1.5.2 Why should we use a counterfactual approach?

We used observational data, which allowed for a better external validity than randomized controlled trials (RCT) (Johnson et al. (2009)). However, in this context of observational data, which is often the case in retrospective studies analyzing the care pathway, the selection bias due to the sample heterogeneity must be taken into account (Johnson et al. (2009)). Indeed, a selection bias, or recruitment bias, could appear since participation in the treatment was not random - some types of patients had a higher probability of being treated than others. Several well-known methods can be used to correct for this issue, such as stratification or multivariate analysis, and more sophisticated methods are increasingly being used, such as matching using the propensity score or instrumental variable (Johnson et al. (2009)). In our case, patients treated in high- versus low-volume hospitals were not similar (Table 1.1). Thus, we expected selection bias to occur, which means that some types of patients were more likely to be treated in a high-volume hospital than others. The propensity score approach is based on less constrained assumptions than multivariate analysis (Austin (2013); Smith and Todd (2005)). Indeed, propensity scores and multivariate

analysis are based on the conditional independence assumption (CIA), which specifies that, conditional on observed covariates, patients were randomly treated in a high- or low-volume hospital. Based on the covariates recorded in our database, the CIA hypothesis assumes that two patients with the same age, cancer history, presence or not of ascites, histology, FIGO stage, neoadjuvant chemotherapy, and tumor grade will have similar outcomes (i.e. survival). However, multivariate analysis requires a stronger assumption about the distribution of the covariates and their relationship with relapse-free survival. In our case, we also had to choose a distribution of the hazard in order to fit a parametric AFT model of the relapse-free survival on a variable denoting treatment and on a set of covariates because the proportional hazard assumption was violated.

Therefore, the combination of a multivariate analysis and a matching method allowed us to determine both conditional and marginal effects of being treated in a high-volume hospital, and to prove the robustness of our findings. The conditional effect indicates that if a patient treated in a lower volume hospital was treated in a higher volume hospital, this would, on average, improve her progression-free survival ($p < 0.001$). Furthermore, the marginal treatment effect indicates that patients treated in higher volume hospitals had a probability of relapse (including death) that was nearly half that for patients treated in lower volume hospitals (1.94-fold difference, $p < 0.001$), and that the absolute difference in survival was significant ($p < 0.001$) (see Table 1.2). We have reason to be confident of the robustness of our result since both the parametric (AFT model) and the semi-parametric (propensity score) approach yielded similar results. With both methods, the type of chemotherapy was included as an indicator denoting one if the patient received a neoadjuvant chemotherapy; without differentiating for the use of neoadjuvant alone, in combination with adjuvant chemotherapy, the use of adjuvant chemotherapy alone, or no chemotherapy at all because this study sought to measure the impact of being treated in a HVH in first-line treatment. Adjuvant chemotherapy is not a first-line treatment, however, and could hence not be included as a prognostic factor. Neoadjuvant chemotherapy has been shown to decrease the Overall Survival (OS), meaning that it is linked to observed and unobserved patient characteristics that worsen

outcomes (Altman et al. (2017)). Thus, by controlling for it as a prognostic factor, we indirectly controlled for these observed and unobserved characteristics.

In the multivariate analysis, we used an AFT model instead of a semi-parametric Cox regression due to the non-proportionality of the hazard. We used the IPW matching as it was the method that best fit our data. Indeed, the IPW was the method with the lowest mean and median for the standardized difference of the mean, which indicates that this was the matching method that best balanced out the covariates between high- versus low-volume hospitals. Moreover, two simulation studies had shown that the IPW appears to perform better in determining the marginal hazard ratio of the treatment effect, compared with other matching methods (Austin (2013); Handouyahia et al. (2013)). It should be noted that the common support of the distribution of the propensity score is sufficient (see Appendix 2) to validate the overlap assumption. The mean standardized difference in the mean before matching was 20.4 versus 7.3 after matching using the IPW, which reveals a high quality of adjustment for the IPW matching. To our knowledge, this is the first study to use a propensity score approach in regard to the question of the concentration of care in ovarian cancer, while these methods have been widely used with other diseases (Hsu et al. (2016); Becker et al. (2015)).

1.5.3 Limitations

Our study is based on an exhaustive regional cohort. The external validity is therefore lower compared to a national cohort. Another limitation is that we could not properly compare our results with the existing literature since we used a different threshold than the one most often used in the literature in the USA (i.e. 20 cases). We also did not control for human Breast Cancer (BRCA) gene mutations, which are known to increase the probability of developing ovarian cancer (Antoniou et al. (2003)), co-morbidities, and being treated by a gynecological oncologist since this information was not in our database. It would have been interesting to assess the impact of the concentration of care in terms of overall survival (OS), but the OS data was not yet available.

1.6 Conclusion

As reported in other countries, the concentration of care for EOC has a significant positive impact on patient relapse-free survival. Indeed, the results indicate that in the Rhone-Alpes region of France patients treated in lower volume hospitals had a probability of relapse (including death) that was 1.94 times higher than for patients treated in higher volume hospitals. High-volume hospitals mostly treat advanced stage EOC, while it is clear that the concentration of care improves patient survival for both advanced and early EOC. More research needs to be done on monetary and non-monetary incentives for practitioners and patients in order to promote the centralization of care for EOC in France. The above limitations should, however, not undermine the main findings of this study. The high rates of progression and death suggest that there is a pressing need for improvements in regard to EOC treatments. The centralization of care in and of itself may provide only a marginal benefit to this patient population. More importantly, centralization should provide the best opportunity to quickly and safely introduce new treatments, and to evaluate and respond to ongoing population-level outcome results.

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Appendix A. Log-Log Plot

Appendix A displays the log-log survival curves (threshold of 12 cases), which are a transformation of the standard Kaplan Meier estimator. These curves can be used to test the proportional hazard assumption. Indeed, the hazard is proportional if the two curves look parallel, meaning that the hazard ratio is constant over time. In our case, the two curves doesn't looks parallel and even cross each other at the bottom right of the plot, meaning that the hazard is not proportional.

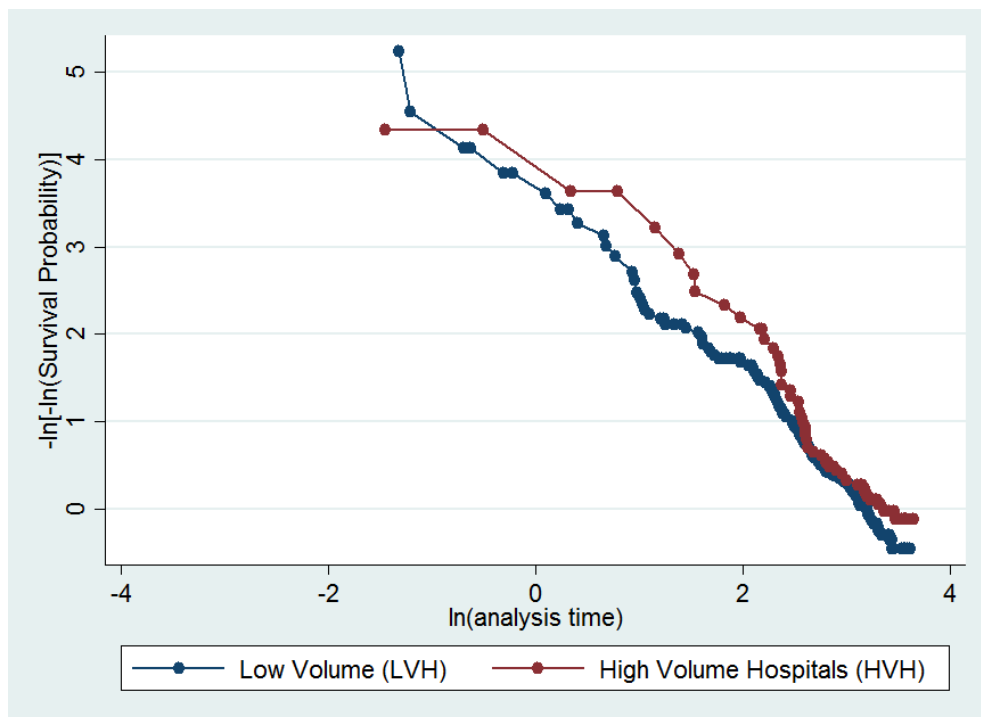


FIGURE 1.4: Log-Log progression free survival curves comparing LVH and HVH

Appendix B. Distribution of the propensity score

Appendix B displays the distribution of the propensity score for treated and untreated patients (threshold of 12 cases). The common support seems to be sufficient to allow for use of the matching method.

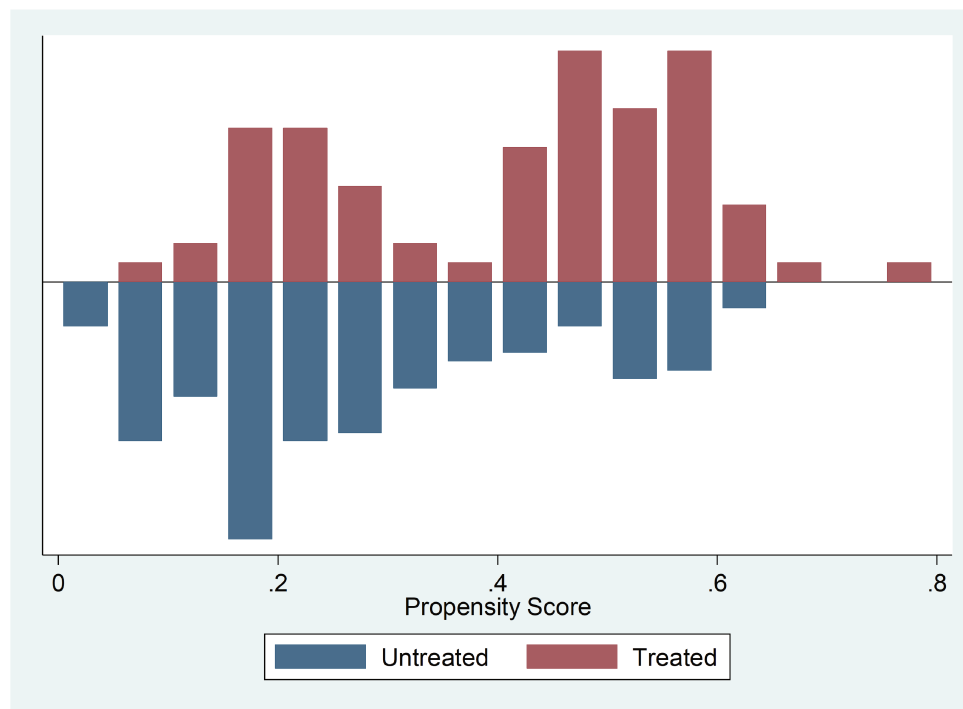


FIGURE 1.5: Common support of the distribution of the propensity score

Chapter 2

What underlies the observed hospital volume-outcome relationship?

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, 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 on patient outcomes by comparing treatment modalities for epithelial ovarian carcinoma patients. An exhaustive dataset of 355 patients in first-line treatment for EOC in 2012 in three regions of France was used. These regions account for 15% of the metropolitan French population. In the presence of endogeneity induced by a reverse causality between hospital volume and patient outcomes, we used an instrumental variable approach. Hospital volume of activity was instrumented by the distance from patients' homes to their hospital, the population density, and the median net income of patient municipalities. Based on our parameter estimates, we found that the rate of complete tumor resection would increase by 15.5 percentage points with centralized care, and by 8.3 percentage points if treatment decisions were coordinated by high-volume centers compared to decentralized care. 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.

2.1 Introduction

The Volume-Outcome Relationship (VOR hereafter) in health economics has been the subject of extensive investigation. To date, most of the studies have found that higher volume hospitals have better outcomes (e.g., lower mortality rates, longer progression-free survival) (Barker et al. (2010); Chowdhury et al. (2007); Cowan et al. (2016); Gaynor et al. (2005); Hentschker and Mennicken (2015, 2018); Kim et al. (2016)). 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 to explain how volume could correlate with outcomes (Luft et al. (1987)). The “practice-makes-perfect” hypothesis states that physicians and hospitals with a greater number of patients develop better skills through learning process, while the “selective-referral” hypothesis 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 of activities also makes hospital volume endogenous if they are correlated to patient outcomes. In the presence of endogenous hospital volume, instrumental variables allow estimation of a causal effect. To overcome these econometric issues, several studies have instrumented hospital volume of activities by the number of potential patients and other hospitals in a defined area (Gaynor et al. (2005); Hentschker and Mennicken (2018); Kahn et al. (2009)). What most volume-outcome studies lack, however, is delving into what underlies the observed or estimated relationship. To the best of our knowledge, the existing literature has focused mainly on identification of the causal impact of volume on outcomes. Our contribution to the literature is to determine the extent to which the learning process 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 to a better ability of clinicians to choose the optimal treatment, especially for complex diseases with multiple treatment options.

We study the case of Epithelial Ovarian Carcinoma, which is characterized by a complex care pathway and a relatively low incidence rate (6.0 per 100,000 women in central Europe) with multiple treatment options that depend on the patient's condition and the clinician's decisions. Although there has been extensive research on the VOR, few changes have been implemented in European countries regarding the organization of care (exceptions are a German pilot study (Keyver-Paik et al. (2016)), the centralization of ovarian cancer care in one health region in Norway (Aune et al. (2012)), and the centralization of acute stroke patients in London (Friebel et al. (2018))). For evaluating the VOR, we distinguish between a learning effect on the ability to perform a procedure and a learning effect on the ability to make the right decision. More specifically, we test whether there are differences in the use of neoadjuvant chemotherapy according to hospital volume of activities, and we examine whether they lead to a heterogeneous effect in regard to the complexity of the treatment received. Deciding between initial debulking surgery or neoadjuvant chemotherapy is a real challenge and there is no consensus regarding the correct decision-making process (Vergote et al. (2013)). Neoadjuvant chemotherapy is a treatment that is readily available for all hospitals and that does not involve expensive drugs. In this regard, the difference in the use of this treatment can be interpreted as a difference in the way clinicians decide the optimal treatment to be prescribed, and not as a difference in term of availability and access to the treatment for hospitals. To build volume-based policies, policymakers need to know what volume is a proxy for. Unraveling the process of learning and determining 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.

The remaining part of this paper is structured as follows: section 2 describes the data and the empirical strategy; section 3 presents the results, section 4 provides a discussion of the results and concludes. Section 5 outlines the limitations of this study.

2.2 Data and Methods

2.2.1 Data

Five French 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 clinical databases contained exhaustive datasets of patients in first-line treatment for EOC in 2012 in three regions of France (Calvados, Cote d’Or, and Rhone-Alps). These regions account for 15% of the metropolitan French population¹. 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, histology, the FIGO stage, and the tumor grade. 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 (Bristow et al. (2014)). Large differences in survival have been noted between different histological subgroup (Cliby et al. (2015)). 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 2.1 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) without first performing chemotherapy. Neoadjuvant chemotherapy followed by surgery is a more recent treatment strategy for patients with advanced-stage EOC when they are found to have a low likelihood of complete tumor resection initially, and the goal of chemotherapy is to reduce the size of the tumor before the surgery in order to avoid a primary surgery that would be too aggressive for patients who are particularly ill (Qin et al. (2018)). Deciding between initial debulking surgery or neoadjuvant chemotherapy is a real challenge

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

and is not consensual in the decision making process (Vergote et al. (2013)).

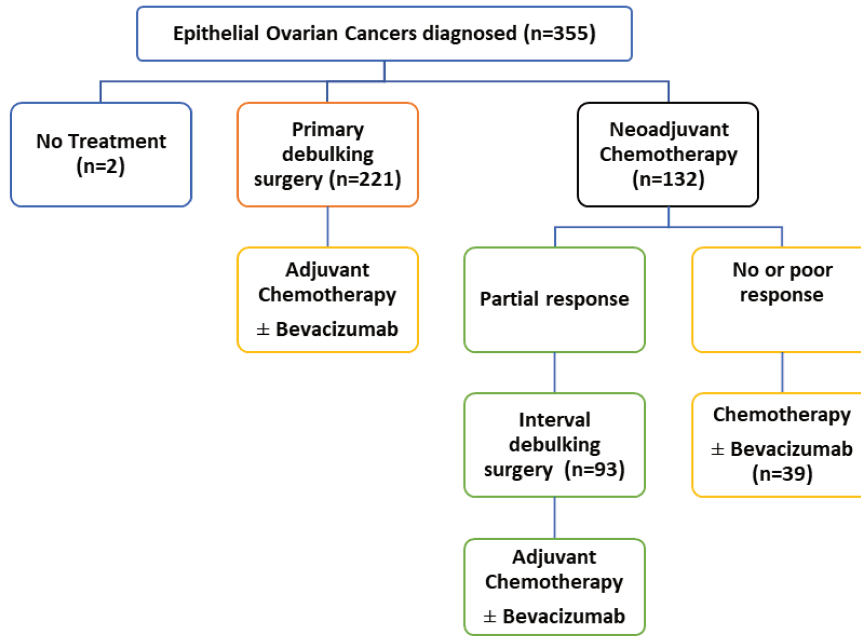


FIGURE 2.1: Care pathway of Epithelial Ovarian Cancer patients

Several hospital characteristics were taken into account², such as the share of the activity represented by oncology, the bed occupation rates in the surgery unit, the hospital's accreditation by the National Authority for Health (Giraud (2001)) and the Herfindahl-Hirschman Index³ (HHI). In order to estimate the causal impact of hospital volume on patient outcomes, we also need to find instruments that correlate hospital volume while being independent of patient outcomes. We computed the distance between each patient's residential postal code and the exact location of their hospital for first-line treatment. We also included information about the municipalities, 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 (Du Bois et al. (2005)). For EOC patients,

²The hospital characteristics were only used for descriptive statistics, except the Herfindahl-Hirschman Index, which was included in the econometric specification.

³We computed the market share of each hospital in terms of the volume of patients within a 50-kilometer radius of each hospital.

survival is strongly associated with the size of the residual disease after surgery (Chang et al. (2012)). 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.

2.2.2 Econometric specification

The main objective of this study was to separate the positive impact of hospital volume on patient outcomes, and to differentiate between a learning effect on the ability to perform a procedure and a learning effect on the ability to make the right decision. We investigate whether there is heterogeneity of care pathways given the patient characteristics according to hospital volume of activities, in order to assess whether more experienced clinicians tended to have a different appreciation of the best treatment to prescribe for a specific patient. We concomitantly investigated how this link could contribute to the positive impact of hospital volume on patient outcomes.

As a benchmark, we first simply estimated the causal impact of hospital volume on our outcome of interest (i.e., complete tumor resection). To do this, one needs to take into account that hospital volume is very likely to be correlated with the error term in an outcome model, which would bias the estimated coefficients. Indeed, the endogeneity of hospital volume in the VOR model is mainly due to the incomplete observation of the patient's state of illness: a part of the prognostic factors of EOC is likely omitted, as for the 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)). Other causes of endogeneity also warrant mention: the measurement errors related to the tumor staging - it has been shown that patients are more often properly staged at high-volume centers (Kumpulainen et al. (2006)) - and the well-known simultaneous relationship between hospital volume and outcomes. In the presence of endogeneity that is induced by observed and/or unobserved factors, a method to estimate a causal effect is the instrumental variable. The idea is to find instruments variables that are strongly correlated to the endogenous variable, but that are strictly exogenous (i.e., uncorrelated with the error term). As it

is commonplace in VOR studies, the hospital volume was instrumented by using a number of distance variables and we controlled for a set of patient characteristics that included age, a prior history of cancer, the presence of ascites, histology, the FIGO stage, and the tumor grade (Gaynor et al. (2005); Hentschker and Mennicken (2018); Kahn et al. (2009)). The full set of instruments were the logarithm of distance, an indicator for the closest hospital, the median net income in the patients' municipalities, and the population density of the patients' and the hospitals' municipalities. See section 4.1 for a discussion of the reliability of our set of instruments. The results of this first model, designated as the "black box model" are shown in Table 2.5 (Appendix A). It can be seen that in this specification we could not identify a causal impact of hospital volume on patient outcomes when we do not take into account the heterogeneity in the care pathway.

The black box model does not provide information about the process of learning that the relationship implies. In order to unravel this effect, we completed the original model by taking into account the care pathway decision and the care process. Thus, we now have several equations of interest (i.e., an outcome equation and several equations that describe the process of selection into different care pathway groups). To instrument hospital volume of activities in several equations, the typical approach would be to perform a 2SLS (i.e., two-stage least squares) estimation on each equation of interest. However, the power of such an estimation is limited by the available sample size. A natural way to model the endogenous hospital volume of activities in several equations (i.e., the care pathway and outcome) is to jointly link our equations of interest by allowing correlation between each error term (Vonesh and Chinchilli (1996)). To do this, one can assume a multivariate normal distribution of the error terms and estimate their covariance matrix by full-information maximum likelihood. However, for models with three or more equations, the cumulative normal densities of dimension three or higher must be computed (Genz and Carlo (2014)). We, in fact, used a more flexible approach that assumes that the error term in each equation includes a common random component in all of the equations and an independent idiosyncratic error term. The random component, which is assigned a parametric distribution, then has to be integrated into the likelihood function by

Gaussian quadrature. Finally, we jointly estimated the following model using the procedure NLMIXED in SAS® (Statistical Analysis Software):

$$\left\{ \begin{array}{l} \text{Log}(Vol_i) = \beta_1 X_i + \beta_2 Z_i + \beta_3 HHI_i + \gamma_1 \alpha_i + \epsilon_{1i} \\ NACT_i = \beta_4 Vol_i + \beta_5 Vol_i^2 + \beta_6 X_i + \beta_7 HHI_i + \gamma_2 \alpha_i + \epsilon_{2i} \\ \text{Log}(TTS_i) = \beta_8 Vol_i + \beta_9 Vol_i^2 + \beta_{10} X_i + \beta_{11} HHI_i + \gamma_3 \alpha_i + \epsilon_{3i} \\ Outcome_i = \beta_{12} Vol_i + \beta_{13} (Vol_NACT)_i + \beta_{14} NACT_i + \beta_{15} X_i \\ \quad \quad \quad + \beta_{16} HHI_i + \gamma_4 \alpha_i + \epsilon_{4i} \end{array} \right.$$

Where $i = 1, \dots, N$ are patient 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. HHI_i is the Herfindahl-Hirschmann index. The model is identified through our set of instruments Z_i for hospital volume, which are the same as for the black box model. We suppose for the idiosyncratic error terms $\epsilon_{1i}, \epsilon_{2i}, \epsilon_{4i} \sim IIN(0;1)$ and $\epsilon_{3i} \sim Weibull(\lambda; k)$. The individual's random terms (i.e., α_i), which is also assumed to be normally distributed, $\alpha_i \sim N(0;1)$ and independent of the idiosyncratic errors, represents the unobserved (to the econometrician) patient's state of illness. This term, which links all of the equations together, provides the main source of endogeneity of the hospitals' volume activities. $NACT_i$ relates the first-line treatment prescribed for patients (i.e., neoadjuvant chemotherapy or primary surgery). For patients treated with neoadjuvant chemotherapy, $\text{Log}(TTS_i)$ is the time between the first cycles of chemotherapy until the surgery. To reduce the skewness of the hospital volume distribution, we employed a log-transformation of the hospital volume when it was used as a dependent variable. We also used a quadratic function of the hospital volume when it was used as an independent variable, to allow for a non-linear impact of the hospital volume on the dependent variable.

After estimation, this model is used for simultaneous prediction of the patient outcomes and the probabilities of being treated with neoadjuvant chemotherapy according to different scenarios of the organization of care. As a robustness check, we also estimated our three equations of interest (i.e., $NACT$, $\text{Log}(TTS)$, and $Outcome$)

separately using a propensity score method, which is the other way of estimating a causal effect when selection is assumed to be only on observables factors. See Appendix B for the results and discussion of this alternative approach (Table 2.6, Table 2.7).

2.3 Results

2.3.1 Descriptive Statistics

In 2012, 355⁴ patients were identified in first-line treatment for EOC and they were treated in 74 different hospitals in the Calvados, Cote d'Or, and Rhone-Alpes region. The high number of hospitals compared to the low number of patients led to a mean hospital volume of activity of 4.8 patients treated in first-line per year and per hospital. A wide variation in the distribution is readily apparent in Figure 2.2, which depicts the number of hospitals for each volume activity and by region.

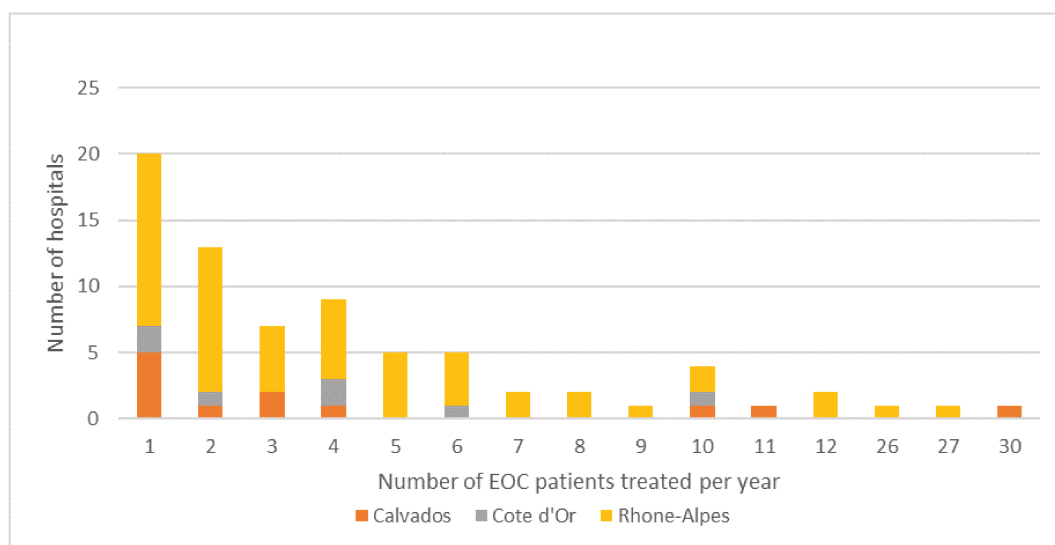


FIGURE 2.2: Distribution of hospital volume of activities

⁴Of the 355 patients recorded in the database, 41 patients did not undergo surgery. This could either be because they died before surgery, or because their health status precluded surgical treatment. Thus, throughout the entire care pathway, these 41 patients were treated only by chemotherapy. 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 as they only received palliative care. Finally, 20 of the 314 eligible patients were excluded due to missing data in regard to patient characteristics, outcomes, or instrument variables.

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 2.1. It can be seen that for about half of the patients there was 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 2.1: Share of patients that have a choice of N hospitals located within K kilometers from where they reside

	$N = 1$	$N = 2$	$N = 3$	$N = 4$	$N = 5$
$K = 10$	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

Note: Number of hospitals (N) ; Distance in kilometers (K).

Table 2.2 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. While the hospital characteristics differ according to hospital volume of activities, this is also the case for the patient characteristics (Table 2.8, Appendix C). Higher volume hospitals tended to treat the more severely ill patients and their patient intake was from a much larger area.

TABLE 2.2: Hospital characteristics

	Top 10 High-Volume Hospitals	Low-Volume Hospitals	P-value
Hospital volume of 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
Type of hospital (%)			0.000
- Private for profit	20	50	
- Private not for profit	10	6.45	
- Public	0	38.70	
- Teaching Hospital	70	4.85	
Accreditation (HAS)			0.732
- Accreditation	37.50	39.98	
- 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: French National Authority for Health (HAS). The differences were analyzed using the Student's t-test or the Chi square test.

2.3.2 Joint estimation of the full model

Table 2.3 displays the results of the full model, estimated jointly and integrated over the random-effects α_i . Our set of instruments well impacts the choice of hospital according to the volume: patients treated at their nearest hospital were less likely to be treated in a high-volume hospital ($p < 0.0001$) and as expected, higher volume hospitals tended to receive patients from a larger area. The population density around hospitals also increased the likelihood of being treated in a high-volume hospital ($p < 0.0001$).

TABLE 2.3: Full model with individual random effect

	Log(Volume)	NACT	Log(TTS)	Outcome
Volume		0.1776**	-0.0619***	0.0392***
Volume ²		-0.0039**	0.0016***	
Volume X NACT				-0.0449**
HHI	0.0001***	0.2656	-0.5855***	0.5549
Age	-0.0081**	0.0323***	0.0025	-0.0158**
Prior Cancer	0.0733	0.4834*	-0.0844*	0.1469
Presence of ascites	0.0485	1.0399***	0.0492	-0.3440
Histology				
- HGSC	0.2772**	0.7841***	-0.0401	-0.0214
- Other	Ref	Ref	Ref	Ref
- Unknown	0.1161	1.3856***	-0.2636***	0.5823*
FIGO Stage				
- I	Ref			Ref
- II	0.1546			-0.1220
- III	0.2014	Ref	Ref	-0.7611***
- Iv	0.3847*	0.4990	-0.0669	-1.6058***
Tumor Grade				
- 1 or 2	Ref	Ref	Ref	Ref
- 3	0.0864	-0.0337	-0.0827	0.1141
- Unknown	-0.2256	-0.1272	-0.1305	-0.3597
Instruments				
- Closest	-0.5450***			
- Log(Distance)	0.0527			
Population density	-0.0001*			
- Density around hospital	0.0001***			
- Median income	-0.0001			
Intercept	2.0824***	-5.4872***	-4.1430***	0.9480*
Gamma	0.1882*	-0.8914***	0.3683***	0.0218
Log Likelihood	-1377.1646			
AIC	2878.3			
Observations	294			

Note: High-Grade Serous Carcinoma (HGSC); Neoadjuvant Chemotherapy (NACT); Complete tumor resection (outcome); modality in reference (Ref); Herfindahl-Hirschman Index (HHI); Duration from the end of chemotherapy to surgery (TTS). Significant at 1%, 5%, and 10% is indicated as ***, **, and *, respectively.

In the treatment equation (NACT), 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 ($p = 0.0125$) with an inverted U-shaped effect ($p = 0.0500$). Furthermore, older patients, patients with ascites, HGSC or an unknown histology compared to other histological subgroups were more likely to be treated with neoadjuvant chemotherapy rather than primary surgery. In the duration equation (TTS), given a treatment with neoadjuvant chemotherapy, the time elapsed between the first chemotherapy and the surgery was shorter in higher volume hospitals ($p < 0.0001$), with a U-shaped effect⁵ ($p < 0.0001$). We also noticed that patients treated in hospitals with a higher HHI (i.e., less competitive areas) on average had a shorter time from the initiation of chemotherapy until surgery ($p < 0.0001$). In the outcome equation (i.e. complete tumor resection), patients treated with neoadjuvant chemotherapy rather than primary surgery ($p=0.0004$) 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 ($p = 0.0014$). 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 of activities ($p = 0.0165$). Other results: older patients and higher stage patients were less likely to be completely debulked after surgery.

2.3.3 Predictions

To further illustrate the implications of the market structure on patient outcomes and on clinicians' decisions, we simulated three scenarios reflecting different organization of care. After estimation, parameter estimates of the full model are used for simultaneous prediction of the patient outcomes and the probabilities of being treated with neoadjuvant chemotherapy according to different scenarios of the organization of care.

⁵Although the effect of volume was positive, it declined per unit of volume as the volume increased.

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.

Scenario 2 - Network formation: In this scenario, we predict 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 the treatment decisions of patients in low-volume hospitals will be coordinated by the closest high-volume center to the patients' residential municipalities.

Scenario 3 - Centralization of care: In the third scenario, we assume that both the treatment decision and the treatment are performed at the nearest high-volume hospitals.

TABLE 2.4: Results of the predictions based on parameter estimates of the full model

	Predicted patient outcome for all stages			Predicted treatment for advanced stages		
	CC-1 or CC-2	CC-0	Rate of CC-0	PDS	NACT	Rate of NACT
Scenario 1: Decentralized	133	170	56.1%	125	72	36.5%
Scenario 2: Network formation	108	195	64.4%	86	111	56.3%
Scenario 3: Centralization	86	217	71.6%	86	111	56.3%

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, as primary surgery is the only treatment option for early stage.

The results of the predictions based on our parameter estimates are displayed in Table 2.4. It can be seen that the rate of neoadjuvant chemotherapy among advanced stage patients increased by 19.8 percentage points (pp) when the treatment decisions were made by high-volume centers. The rate of complete tumor resection among all patients would increase by 8.3 pp if the patients were still treated in the hospital that they had chosen, and by 15.5 pp if the care was centralized at high-volume centers.

2.4 Discussion

2.4.1 Reliability of the instruments

To instrument the likelihood of a patient to being treated in a high-volume hospital, we used a function of the patient-hospital distance as our principal instrument. Distance has been widely used in the existing literature to instrument hospital volume of activities (Barker et al. (2010); Gaynor et al. (2005); Hentschker and Menicken (2018)). The assumption here is that higher volume hospitals will receive patients from a much larger area compared to lower volume hospitals. We are confident of this assumption since higher-volume hospitals were more often not the closest hospital to the patient's place of residence (Table 2.3). 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. Similarly, to take into account that hospitals located in more populated areas are more likely to have greater volume activities, we included the population density of the hospitals' municipalities. 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. 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 ($p = 0.0872$).

Based on the results presented in Table 2.3, we are confident of the reliability of our set of instruments since they appear to be good predictors of our endogenous variable (i.e., hospitals in more populated areas had greater hospital volume of activities ($p < 0.001$), as well as hospitals who caught patients in a broader area ($p < 0.001$). 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. The added value of our database is that it includes detailed information about the severity of the disease, which reinforced the validity of the distance as

instrument conditionally on these characteristics. It is not possible to perform a statistical test for the validity of the instrument in a non-linear model. We present some evidence that these instruments are likely to be valid in a linear model by estimating a linear probability model in a two-stage least square regression in order to perform a test of validity of the instrument. The Sargan ($p = 0.3645$) and the Basmann test ($p = 0.3886$) did not reject the null hypothesis according to which our instruments are uncorrelated with the outcome.

2.4.2 Why do higher volume hospitals use neoadjuvant chemotherapy more often than primary surgery?

Unlike the black box model, the joint estimation of the full model 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 2.3). Neoadjuvant chemotherapy is a treatment that is readily available for all hospitals that already have authorization to treat gynecological cancers (i.e., all of the hospitals included in this study), and it does not involve expensive drugs. In this setting, the difference in the use of this treatment can be interpreted as a difference in the way clinicians decide the optimal treatment to be prescribed, and not based on the availability and access to the treatment for hospitals.

We also identify differences in the time elapsed from the initiation of chemotherapy until surgery for patients who were treated with neoadjuvant chemotherapy (Table 2.3): higher volume hospitals tended to have a shorter duration (i.e., TTS). This result could have two distinct implications. It is possible that patients treated in higher volume hospitals received fewer cycles of chemotherapy on average, or alternatively be the result of shorter waiting times before surgery. Ultimately, both interpretations are likely to be related to the waiting times. The clinical guidelines for the number of cycles of neoadjuvant chemotherapy advocate that the use of 3 to 4 cycles is the appropriate way to treat advanced ovarian carcinoma (Altman et al. (2017)). 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.

2.4.3 Does the VOR only apply to patients treated with primary surgery?

While higher volume hospitals tended more often to use neoadjuvant chemotherapy rather than primary surgery, it appears that the difference in outcomes according to hospital volume of activities decreased for patients treated with neoadjuvant chemotherapy (Table 2.3). This could explain 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 (Appendix A). 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 indicate that

the clinicians in lower volume hospitals were, on average, more likely to perform complex surgery rather than use neoadjuvant to reduce its complexity.

2.4.4 External validity

The main limitation of this study is the sample size, which is low due to the disease characteristics and to the geographical area covered by this study. It would be interesting to replicate this study on an exhaustive cohort of patients at the national level. Such databases are difficult to construct since detailed information on the severity of the disease is required in order to properly control for selection bias, which is usually not available in nationwide administrative data. Since we used an exhaustive cohort at a subnational level, we missed patients living in the area covered by this study but who had decided to be treated in a hospital that was not in the area covered by this study, and this could have potentially led to a sample selection issue. However, using administrative data from the Medical Information Systems Program (PMSI), we found that this sample selection bias was negligible in our cohort, since only 3.64% of the patients living in the Calvados, Côte d'Or, and the Rhone-Alpes regions in 2017 chose to be treated in a hospital that was not in the area covered by this study. To assess the external validity, we also checked the consistency of our data and results on patient characteristics with the existing literature. Globally, the results are in line with the existing literature, thus supporting the notion that the results of our study can be extrapolated to a certain degree. Indeed, we found that higher volume hospitals treated the more severely ill patients. This result is consistent with the existing literature on the VOR for EOC patients in the USA (Bristow et al. (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 on a cohort of 62,727 patients in the USA (Leiserowitz et al. (2017)). The distribution of hospital volume of activities we observed does not appear to be a specificity of the Calvados, Cote d'Or, or the Rhone-Alpes regions. Indeed, there was one hospital treating gynecologic cancers for every 111,638 residents in Calvados, one for every 154,845 residents in Cote d'Or and one for every 113,174 residents in the Rhone-Alpes region

in 2016 (source: National Institute of Statistical and Economic Information , French National Authority of Health). 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).

Based on the parameter estimates of the joint estimation of the full model, we have predicted several scenarios of the organization of care. These predictions aim to provide an insight into the variation in the outcomes and the care pathways that would arise if patients were reallocated in other hospitals based on their volume of patients. The first goal of this study is to unravel the process of learning implied by the volume-outcome relationship rather than build a model with a high predictive power. Thus, we assumed that patients will choose to be treated in their closest high volume hospital. This assumption is conservative regarding the impact on patient access, but it should not undermine the variation in the quality of care and the care pathway highlighted in this study according to our three scenarios of organization of care. Finally, by using an instrumental variable approach, we estimate a local average treatment effect (LATE) for patients meeting our identification strategy. Thus, generalization of the results strongly depends on the reliability and validity of the instruments. As detailed in Appendix B, a robustness check shows that results based on the propensity score approach are globally consistent with those from the joint estimation of the full model. In other words, the LATE estimate is close to the Average Treatment Effect on the Treated (ATT), which supports the reliability of the instruments being representative of hospital volume of activities in our population of interest.

2.5 Conclusion

Centralized care at high-volume hospitals was the scenario that led to the highest average patient outcome (Table 2.4), and it has often been recommended in the literature (Aune et al. (2012); Avdic et al. (2019); Cowan et al. (2016); Friebe et al.

(2018)). 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 traveled by patients from 39 kilometers to 66 kilometers. The impact on the travel time for patients of the implementation of minimal volume standards in Germany has, however, been shown to be negligible when care is centralized to the nearest high-volume hospital (Hentschker and Mennicken (2015)). 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. 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. With this alternative organization of care, patients would still be treated in their chosen hospital irrespective of whether it is a high-volume hospital. However, first-line treatment decisions for patients treated in low-volume hospitals would be discussed and coordinated by high-volume hospitals. This would have no impact on the distance traveled 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. Our findings support the notion that EOC patients would benefit from such an organization of care compared to the ongoing one.

More research needs to be undertaken before our findings can be extended to other diseases, especially regarding the organization of care for other complex diseases which could have some common aspects with EOC. 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.

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Appendix A. Black box model

In the table below, the results from the black box model, which consist of a probit model with instrumented hospital volume, are indicative of the causal impact of hospital volume on outcomes. It can be seen that hospital volume and patient outcomes were independent when we controlled for the endogeneity of hospital volume if we do not take into account care pathways ($p=0.224$).

TABLE 2.5: Black box model

	Complete tumor resection
Intercept	-0.6483
Volume	0.0234
HHI	0.5832
Age	-0.0096
Prior Cancer	0.1623
Presence of ascites	-0.2435
Histology	
- HGSC	0.1512
- Other	Ref
- Unknown	0.7475**
FIGO Stage	
- I	1.3626***
- II	1.1339***
- III	0.8062***
- Iv	Ref
Tumor Grade	
- 1 or 2	Ref
- 3	0.0406
- Unknown	-0.3511
Instruments	YES
Log Likelihood	-1212.33
Observations	294

Note: High-Grade Serous Carcinoma (HGSC); modality in reference (Ref); Herfindahl-Hirschman Index (HHI). Significant at 1%, 5%, and 10% is indicated as ***, **, and *, respectively.

Appendix B. Robustness check using a propensity score approach

As a robustness check, we employed a propensity score approach. Use of a propensity score is an alternative approach to an instrumental variable to estimate a causal effect in the presence of selection bias, which is based on different theoretical assumptions regarding the selection process. These methods rely on the assumption that the selection into the treatment (i.e., the patient being treated in a high-volume hospital in our case) is made only through observable characteristics. While instrumental variables allow for estimation of a Local Average Treatment Effect (LATE), propensity score methods allow for estimation of the Average Treatment Effect on the Treated (ATT). Among the several methods based on the propensity score, we used the Inverse Probability Weighting (IPW) method, which is more suited for small samples compared to matching methods since it does not reduce the sample size.

The IPW method balances out the covariate of the two groups by weighting all of the patients in the database by the inverse of their propensity score. The propensity score is the conditional probability for a patient to be treated in a high-volume hospital, conditionally to observable characteristics. We determined this probability by fitting a logit model of an indicator variable denoting high- or low-volume hospitals on age, histology, FIGO stage, grade, cancer history, the presence of ascites, and the Herfindahl Hirschman Index (HHI). In order to define different groups and to fit the propensity score, we had to choose a threshold to define a high-volume hospital. Choosing a threshold is a constraining assumption, at least in the French health system, since no threshold has been officially defined. Thus, we used the same threshold as in Huguet et al. of 12 cases per year to define a high-volume hospital, which is the only study on the VOR for EOC patients in France (Huguet et al. (2018)). We excluded predictive variables of outcomes that may depend on patient choice and subsequent interventions from this model, and we only controlled for patient characteristics at the time of diagnosis (i.e., prior to the patients receiving their first-line treatment). We used the stabilized weights for the estimation of the

ATT, as proposed by Robins et al. (Robins et al. (2000)).

Table 2.6 displays the balance in covariates between patients in high- and in low-volume hospitals after being weighted by the IPW. It shows that there are no longer any differences between the two groups, thus indicating a good quality for the IPW approach. Table 2.7 displays the results of the main equations of interest estimated separately and weighted by the IPW. It can be seen that the results are fully consistent with those from the joint estimation of the full model, albeit with slightly larger standard errors (Table 2.3). The increase in the standard errors does not impact the significance of the results, except for the impact of being treated in a high-volume hospital on Log(TTS) ($p=0.355$). The concordance of the results from the joint estimation with instrumented hospital volume activities and the IPW (i.e., the LATE being close to the ATT) tends to support that the notion that our instruments are good predictors of the endogenous variable, and that the LATE estimate, to a certain extent, is representative of the impact on our population of interest.

TABLE 2.6: Quality of the weighting by the IPW

	High-Volume Hospitals	Low-Volume Hospitals	P-value
HHI	0.2217	0.2233	0.938
Age	61.12	60.15	0.728
Prior Cancer (%)	16.82	20.88	0.623
Presence of ascites (%)	71.03	71.02	0.999
Histology (%)			
- HGSC	62.62	66.95	0.679
- Other	22.43	23.42	0.913
- Unknown	14.95	9.63	0.478
FIGO Stage (%)			
- I	13.21	15.98	0.711
- II	6.61	7.75	0.835
- III	66.04	65.71	0.974
- Iv	14.15	9.99	0.573
Tumor Grade (%)			
- 1 or 2	23.36	24.04	0.942
- 3	71.03	74.82	0.698
- Unknown	5.61	1.14	0.330

Note: High-Grade Serous Carcinoma (HGSC); Herfindahl Hirschman Index (HHI).
The differences were analyzed using the Student's t-test.

TABLE 2.7: Results with inverse probability weighting

	NACT	Log(TTS)	Outcome
High-Volume Hospital (HVH)	0.882***	-0.075	1.388***
HVH x NACT			-1.409**
NACT			1.141**
Intercept	-1.130***	4.849***	-0.541**
Observations	294	81	294
Log Likelihood	-33.4		-34.61

Note: * $p < 0.1$, ** $p < 0.05$, *** $p < 0.01$. The three models are estimated separately. NACT and Outcome are logistic regression, and Log(TTS) is an ordinary linear regression.

Appendix C. Patient and municipality characteristics

TABLE 2.8: Patient and municipality characteristics

	High-Volume Hospitals	Low-Volume Hospitals	P-value
Distance to hospital (km)	42.92	36.21	0.414
Hospital chosen is the closest (%)	13.29	41.12	0.001
European Deprivation Index	3.21	2.82	0.414
Population density	1477.50	981.62	0.047
Median Income	20653	20593	0.857
Age	60.255	62.399	0.139
Prior Cancer (%)	15.19	15.46	0.944
Presence of ascites (%)	67.72	58.25	0.068
Primary inoperable (%)	45.57	31.12	0.005
Histology (%)			0.013
- HGSC	55.70	44.67	
- Other	23.42	38.06	
- Unknown	20.88	17.27	
FIGO Stage (%)			0.080
- I	17.99	30.09	
- II	5.89	5.61	
- III	60.64	52.55	
- Iv	15.48	11.75	
Tumor Grade (%)			0.007
- 1	6.96	17.77	
- 2	17.09	17.26	
- 3	61.39	46.70	
- Unknown	14.56	18.27	

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

Chapter 3

Centralization of Care and Inequalities in Access to Care

Abstract

Inequalities in health and in access to healthcare have significant social and economic costs both to individuals and societies, and are a target of many policies. In 2018, the French National Health Insurance proposed to increase the minimum volume threshold for breast cancer and to set a specific threshold for ovarian cancer in order to get an authorization to treat these patients. Using an exhaustive nationwide data set, the aim of this study is to evaluate the impact of the application of minimum volume thresholds for breast cancer and ovarian cancer in France on socioeconomic and spatial inequalities in patient access to care, taking into account patient preferences for their preferred provider. Our findings indicate that it would increase spatial inequalities and introduce socioeconomic inequalities in access to specialized care in terms of travel distance and will contribute to the medical desertification in rural areas that already have less access to non-specialized care. Our results underline that ignoring patient preferences when assessing the impact of such policies drastically underestimate the deterioration in patient access to care.

3.1 Introduction

Inequalities in health and in access to healthcare are a major concern for global society. There is ample evidence of disparities in the health status of different social groups in all countries – whether low-, middle- or high-income (Beckfield and Olafsdottir (2013)). Strong inequalities in access to specialized care in favor of richer people have also been underlined in most OECD countries, which are substantially influenced by spatial variation in the supply of healthcare for different social groups (Doorslaer et al. (2006)). These inequities have significant social and economic costs for both individuals and societies, and are the target of many policies.

Over the 21st century, increasing efforts have been made to improve the quality of care for complex and risky procedures. Worldwide, the centralization of complex care has moved to the center of the health policy debate as a unique opportunity to increase the quality of care through reorganization of the supply side of the market. In the US, incentives toward centralization have been put forward by the Leapfrog Group (a coalition of large healthcare purchasers representing collectively over 20 million people in the United States), which introduced minimum volume standards for eight procedures as part of their safety initiative. In Europe, a few countries made this jump and experimented with centralized practice, such as the centralization of surgeries for advanced ovarian cancer in Norway, the centralization of acute stroke care in London (UK), and the application of minimum volume standards for eight medical procedures in Germany¹ (Aune et al. (2012); Friebe et al. (2018); De Cruppé et al. (2015)). As part of the general interest in centralization, the French National Health Insurance published a report in 2018 with proposals to improve the efficiency of the French healthcare system. It has been put forward to increase the minimum volume threshold for breast cancer from 30 to 150 surgeries per year, and to set a specific volume threshold for ovarian cancer at 10 or 20 surgeries per year (French National Health Insurance (2018)). The application of minimum volume thresholds is intended to withdraw the lowest volume hospitals from the market based on the

¹Minimum volume thresholds have been set for eight medical procedures since 2004. However, ten years after their introduction, a study revealed that they have not been strictly applied and that centralized care has not been achieved in the intended way (De Cruppé et al. (2015)).

belief that increasing hospital volume activities would increase the quality of care. There have been hundreds of studies investigating the volume-outcome relationship in healthcare, and they indeed tend to confirm that higher volume hospitals tend to provide higher-quality care, especially for complex diseases such as cancer (Luft et al. (1987); Gaynor et al. (2005); Hentschker and Mennicken (2018); Cowan et al. (2016); Yen et al. (2017)).

However, the centralization of care sparks a debate on the trade-off between quality of care and patient access to care. Indeed, by centralizing care to high volume hospitals, the number of providers on the market would decrease more or less drastically depending on the volume threshold (i.e. the degree of centralization of care). Since the number of providers would be reduced while the demand would remain unchanged, a deterioration in patient access caused by this type of policy can be expected. Furthermore, in most developed countries, patients are free to choose their healthcare provider. In this context, patient preferences are likely to be an important driver of the impact of centralized care on patient access to care, since patients do consider several factors they care about when choosing where to be treated, rather than basing their choice on only the relative distance of each provider (Victoor et al. (2012); Beckert et al. (2012)). There is a lack of evidence on the impact of volume-based policies on patient access and, more importantly, on how they will be distributed among different socioeconomic subgroups and spatially within the country to fuel the debate. Indeed, although centralized care would obviously deteriorate patient access to care, its impact on socioeconomic and spatial inequalities remains unclear. Its impact on spatial inequalities depends on whether low volume hospitals were located in areas already suffering from medical desertification and would thus increase the medical desertification in these areas if withdrawn from the market. Similarly, the burden of centralized care in terms of access to care could be unequally distributed if, for instance, the poorer patients were treated in lower volume hospitals initially. The impact on socioeconomic inequalities is even more unpredictable in health systems where prices are set by the health authority (e.g., France, United Kingdom, Germany), where prices do not vary from one provider to another and are reimbursed by the social security system.

Using a nationwide database, the aim of this study is to evaluate the impact of the application of minimum volume thresholds for breast cancer and ovarian cancer in France on socioeconomic and spatial inequalities in patient access to care, based on a simulation approach. We use hospital discharge data from the Medical Information Systems Program (PMSI), which records comprehensively hospital stays in French hospitals (Boudemaghe and Belhadj (2017)). The completeness of the data allows us to compute volume activities in breast cancer and ovarian cancer hospitals as the number of patients treated respectively for breast and ovarian cancer in 2017 in each hospital. To evaluate the impact of a minimum volume threshold on patient access, the first stage is to predict how patients would reallocate when a portion of all hospitals is withdrawn from the market. To that end, we elicit patient preferences based on observed choices before the centralization of care and predict patient probabilities of hospital choice. After a transformation on the probabilities, we predict the flows of patients from hospitals withdrawn from the market to high volume hospitals. Then, to explore spatial inequalities, we investigate whether there are spatial variations in expected patient-hospital distances, expected square distances (i.e., to assume a higher degree of distance aversion), expected additional distances (i.e., only for reallocated patients), and rate of patients affected by the policy. We evaluate socioeconomic inequalities through jointly investigating two mechanisms. Firstly, the likelihood of being affected by the policy, which may correlate with patients' socioeconomic characteristics. Secondly, variations in the degree of deterioration in patient access among the subgroup of patients affected by the policy according to socioeconomic characteristics. As a benchmark, we also use the evaluation strategy often used in the literature, which consists of assuming that patients will choose to be reallocated to their closest available hospital (Kobayashi et al. (2015); Hentschker and Mennicken (2015); Hentschker et al. (2018)). By making this assumption, patients are no longer given the choice of their preferred provider and we thus predict a reallocation of patients to high volume hospitals that minimizes patient-hospital distances. In the analysis, breast and ovarian cancer are studied separately because they differ on several aspects. Breast cancer is the most frequent cancer among women, affecting 2.1 million women each year, while ovarian cancer is rather a rare disease with 300 000 new cases each year. Statistics from the Surveillance, Epidemiology,

and End Results Program (SEER)² indicate a five-year conditional relative survival of 93.2% for breast cancer against 69.9% for ovarian cancer for a 65+ year old woman.

To the best of our knowledge, there are only three studies in the existing literature on this topic, and none in the French context (Kobayashi et al. (2015); Hentschker and Mennicken (2015); Hentschker et al. (2018)). Overall, these studies found a moderate impact of centralized care on patient access to care. Nonetheless, they did not take into account patient preferences in their evaluation, and instead assume that patients will choose to be treated in the closest high volume hospital. Moreover, among these three studies, only one explored inequalities among the population. They evaluate the impact of the centralization of care for ischemic heart disease and breast cancer on travel time in the Kyoto Prefecture in Japan, and assess unequal spread of travel time using a Gini coefficient (Kobayashi et al. (2015)). Surprisingly, their main finding is that the centralization of care reduced inequalities in travel time for patients. However, in the Japanese context, the centralization of care is achieved by centralizing care to designated regional core hospitals, and thus does not rely on a minimum volume threshold. Therefore, the impact of centralization of care on travel time strongly depends on how these regional core hospitals are chosen. Among the two other studies, a German study has evaluated the impact of minimum volume standard for abdominal aortic aneurysm without rupture and hip fracture (Hentschker and Mennicken (2015)). The two procedures considered in that study did not require specific authorization of treatment, unlike cancer care, which means they can be performed in a lot more hospitals compared to cancer care. Therefore, the impact of the centralization of care for these two procedures cannot be directly extrapolated to cancer care.

Our contribution to the literature stems from several aspects. The key feature of this study is that we took into account patient preferences for their preferred provider in order to evaluate the impact of centralizing care. Conversely, studies in the existing literature instead assumed that patients would choose their closest hospital after centralization. In healthcare systems where patients are free to choose

²Source: <https://seer.cancer.gov/>.

their healthcare provider, ignoring patient preferences in the evaluation reverts to estimating the lowest boundary of the deterioration in patient access (i.e., patient-hospital allocations that minimize distances). This study also contributes to the literature by investigating socioeconomic and spatial inequalities in access that are caused by a centralization of care. To devise volume-based policy, policy makers are facing a trade-off between increasing the quality of care and worsening patient access. To fuel the debate, it is thus of primary interest to assess whether the burden in terms of patient access would be distributed unequally based on location and socioeconomics. Lastly, this is the first study evaluating the introduction of volume thresholds on patient access in France. To date, the French National Health Insurance has only made a proposed policy by publishing their annual report with proposals to improve the French healthcare system (French National Health Insurance (2018)). The French Minister of Health and Solidarity has also mandated the expertise of the French National Cancer Institute, which has recently published a report comparing two strategies to assess hospital volume activities for cancer care (French Cancer Institute (2019)). Therefore, our findings have obvious policy implications in the context of French healthcare.

Our findings indicate that the strict application of a volume threshold to centralized care would drastically deteriorate patient access to care. More importantly, the burden of the policy would worsen spatial inequalities in access to specialized care and be unequally distributed in favor of those who are wealthier, living in urban and less remote municipalities. Our findings also substantiate the need to take into account patient preferences so as to have a complete picture of the impact of volume-based policies on patient access, without which the deterioration in patient access is drastically undermined. To devise a volume-based policy, policy makers should take into account its variations of impact on patient access within different socioeconomic subgroups and spatially within the country and may need to adjust the threshold for the most affected areas. The remainder of this paper is structured as follows: section 2 describes the data; section 3 introduces our empirical strategy; section 4 presents the results; section 5 provides a discussion of the results, and section 6 gives the conclusion.

3.2 Data

In this study, we used three data sets in order to obtain detailed information on patient characteristics, hospital characteristics, and patient residential location characteristics for our two populations of interest. Firstly, we identified patients treated for breast cancer or ovarian cancer in France by using hospital discharge data from the Medical Information Systems Program (PMSI), managed by the government agency *Agence Technique de l'Information sur l'Hospitalisation* (ATIH). The PMSI is an exhaustive nationwide database that records information about each hospital stay in France (Boudemaghe and Belhadj (2017)). The inclusion criteria were being diagnosed for breast or ovarian cancer, surgically treated in a hospital in mainland France in 2017, and living in mainland France. More details about the inclusion criteria are provided in appendix A. For each patient, the information recorded included the FINESS number (a unique identifier for hospitals in France) for hospitals where the surgeries were performed, the exact location of hospitals, the residential location of patients (at municipality level), patients' length of stay at hospital, and the age of the patients. We also computed straight-line distance in kilometers between patients' residential municipalities and the exact location of all hospitals in mainland France³. Using the patient-hospital distances, we computed patient choice set size as the number of available hospitals (i.e., having an authorization to treat patient's cancer) within a radius of 50 km.

Secondly, we included hospital characteristics from the French Hospital Survey (Statistique annuelle des établissements - SAE), managed by the *Directorate for Research Studies Evaluation and Statistics* (DREES) in order to get detailed characteristics of hospitals in which breast cancer and ovarian cancer patients were treated. We included information about the type of hospital (public, private for profit, private not for profit), whether there is a department of oncology, the number of hospital stays

³Note that we computed straight-line distance to assess patient access to hospital care. A superior alternative would have been to compute travel distance over a road network or travel time by car, to take into account the variation in travel time between rural and urban areas. It is now possible to compute a high number of driving distances with some statistical software (e.g. Open Route Service API in R). However, we were limited to using SAS on an external server to access the data and doing the analysis as required by the French government agency ATIH, and thus could not export the data to compute the distances using R. Nevertheless, a study revealed negligible differences between straight-line distance and driving distance (Boscoe et al. (2012)).

in oncology, the number of surgical rooms, the bed occupation rate, and the number of employees for the prevention of nosocomial infection.

Lastly, we included aggregate information about patients' residential location from open access data sets, which are managed by the *National Institute of Statistics and Economic Studies* (INSEE). We obtained detailed information about the municipalities, such as the population size, median standard of living (in euro), number of drug stores, number of ambulances, and number of households having a car within each municipality in mainland France. We also obtained broader information on department characteristics, such as the number of emergency units and the number of short-stay hospitals within each department.

3.3 Methods

The aim of this study is to evaluate the impact of the application of minimum volume thresholds for breast cancer and ovarian cancer on socioeconomic and spatial inequalities in patient access to care in France. Our empirical strategy is composed of three steps.

(i) First, we will predict the expected hospital volume activities of the high volume hospitals (HVH), when a threshold k is applied. In this context, all hospitals below the threshold k (i.e. fewer than k patients treated per year in that hospital) will lose their authorization to treat the cancer considered (i.e. breast cancer, ovarian cancer or both). We will refer to patients who were treated in hospitals below the threshold as patients needing to be reallocated, in the sense that they will have to choose another hospital among the HVH hospitals in order to be treated. The volume activities of the remaining hospitals will increase on average, as the group of patients needing to be reallocated will have to choose a provider among the remaining ones. Thus, the expected hospital volume activity of a HVH hospital when a threshold of k is applied corresponds to its observed volume activity (i.e. number of patients treated in that hospital initially) plus the flow of patients who were treated

in a LVH hospital initially and chose to be treated in that HVH hospital.

As a benchmark, we follow the method used in the existing literature to assess patient flows (Hentschker et al. (2018); Hentschker and Mennicken (2015); Kobayashi et al. (2015)). Following this method, patients needing to be reallocated are assumed to have chosen to be treated in their nearest HVH hospital when threshold k is applied. This assumption is very conservative when assessing patient access to care, since it does not take into account patient preferences for hospital choice. Therefore, we also employed an alternative method that takes into account patient preferences in the prediction of patient flows from LVH to HVH hospitals. In this alternative method, patient flows are modeled in terms of probabilities. Thus, we define the expected hospital volume activity of a HVH hospital j when a threshold k is applied as:

$$E(\text{Volume}_j^k) = \text{Volume}_j + \sum_{i \in N^{LVH}} P_{ij}^* \quad (1)$$

Where Volume_j is the observed volume activity of hospital j initially and P_{ij}^* is the probability that patient i chooses to be treated in hospital j . Note that $\sum_{j \in HVH} P_{ij}^* = 1$, which ensures that the sum of the expected volume activities⁴ over all HVH hospitals, will correspond to the initial population size. The first challenge is to estimate the probabilities P_{ij}^* . Indeed, we cannot directly estimate these probabilities because we did not observe a choice among the HVH hospitals for patients needing to be reallocated, since they were treated in an LVH hospital initially. To overcome this issue, we estimated a Conditional Logit model in order to estimate the probabilities of hospital choice (i.e. probability that a patient i chooses to be treated in hospital j) over all hospitals, regardless of their volume activities (McFadden (1974)). Since the Conditional Logit is estimated on the full choice set: $\sum_{l=1}^J P_{il} = 1$.

$$P_{ij} = \frac{e^{\beta' H_{ij}}}{\sum_{l=1}^J e^{\beta' H_{il}}} \quad (2)$$

Where H_{ij} is a matrix of hospital-specific characteristics used as predictors of patient choice. We included the distance between patient's home and hospital location

⁴Expected hospital volume activities are continuous (while initial hospital volume was discrete), since we introduced a continuous probability to model the flows of patients.

as our main predictor of patient's hospital choice. The distance was included as a continuous variable (i.e. in kilometers), as a dummy variable indicating whether the hospital is the closest, and in interactions with the age of patients and their length of stay at hospital to allow for heterogeneous preferences for distance. Patient distance aversion might indeed vary according to age and the degree of illness (Victoor et al. (2012)). The full set of hospital-specific characteristics included the type of provider (i.e. public, private for profit, private not for profit), the specialization profile (e.g. an indicator indicating whether there is a unit specialized in oncology and the number of hospital stays in oncology), the number of surgical rooms, the bed occupation rates, and the number of employees for prevention of nosocomial infections. An important assumption of the Conditional Logit model is the Independence from Irrelevant Alternatives (IIA). This assumption implies that for any two hospitals j and k , the ratio of the Logit probabilities is:

$$\frac{P_{ij}}{P_{ik}} = \frac{e^{\beta' H_{ij}} / \sum_{l=1}^I e^{\beta' H_{il}}}{e^{\beta' H_{ik}} / \sum_{l=1}^I e^{\beta' H_{il}}} = \frac{e^{\beta' H_{ij}}}{e^{\beta' H_{ik}}} \quad (3)$$

It can be seen in equation (3) that this ratio does not depend on any hospitals other than j and k . Thus, adding or eliminating a hospital in the choice set will have no impact on the ratio of probabilities for the remaining hospitals. Based on the IIA property, after deleting all LVH hospitals from the choice set and by adding the constraint that the probabilities sum to 1 over the remaining hospitals, we can compute our probabilities of interest P_{ij}^* , needed to compute the expected hospital volume activities as described in equation (1).

(ii) The second step of our evaluation strategy is to determine the additional distance that patients treated in hospitals under the minimum thresholds will have to travel with the application of minimum volume thresholds. This additional distance is the difference between the patient-hospital distances post-centralization of care (i.e. when a threshold k is applied) and the patient-hospital distance observed initially. Obviously, only patients needing to be reallocated will encounter an additional distance. Following the benchmark method, it is possible to directly compute this additional distance, since the post-centralization of care hospital is assumed to

be the closest to patient residential location and is thus observed in the data. However, it is not as straightforward with the alternative method that takes into account patient preferences, since we do not know in which hospital a patient who needs to be reallocated will choose to be treated. Nevertheless, we know the probabilities P_{ij}^* associated with each of the remaining hospitals (i.e., HVH hospitals). Thus, it is possible to compute the expected additional distance patient i will have to travel as a sum of the additional distance from patient i to each hospital j weighted by the probabilities that this patient chooses to be treated in each of the HVH hospitals after centralization of care.

$$E(add_distance)_i = \sum_{j \in HVH} (Distance_{ij}^{Post} - Distance_i^{Init}) \times P_{ij}^* \times 1_{\{If\ i \in N^{LVH}\}} \quad (4)$$

Where $Distance_{ij}^{Post}$ is the distance between patient i and hospital j post centralization of care, $Distance_i^{Init}$ is the observed distance between patient i and the hospital chosen initially. Patient preferences are taken into account in the estimation of the expected additional distance through the probabilities P_{ij}^* . We expect the additional distance computed following the benchmark method to be lower than the estimation including patient preferences, since assuming patients will choose their closest hospital is likely to be a conservative assumption for a substantial share of patients.

(iii) Lastly, the third step of our empirical strategy is to investigate whether the implementation of minimum volume thresholds might introduce socioeconomic and spatial inequalities in access to hospital care. Our variables of interest are the expected additional distance as described in equation (4), and the total distance post-centralization (i.e., initial distance plus additional distance). We explore spatial inequalities first by mapping observed (i.e., before centralization) and simulated (i.e., post-centralization) hospital location and patient density per department individually for breast and ovarian cancer. Secondly, we map the observed and simulated average patient-hospital distance per department and for both conditions. These maps intend to give an overview of the geographical spread of additional distances caused by the implementation of minimum volume thresholds, and to investigate whether they increase inequalities in access to hospital care. There could also be

socioeconomic inequalities in access to care through a pattern in the spread of additional distances caused by minimum volume thresholds that could be correlated to patients' socioeconomic characteristics. A natural way to explore these inequalities could be to regress additional distances on a set of socioeconomic characteristics as independent variables. However, we observe additional distances only for patients needing to be reallocated. Thus, an Ordinary Least Squares regression will be biased and inconsistent since it ignores the selection process through which patients are selected into the group of patients needing to be reallocated (Greene (1981)). In order to jointly model the selection process (i.e. needing to be reallocated or not) and the expected additional distance conditionally on the selection process, we estimated a Type 2 Tobit model (Tobin (1958)).

$$Reallocate_i = \begin{cases} 1, & \text{if } y_1^* > 0 \\ 0, & \text{if } y_1^* \leq 0 \end{cases} \quad E(Add_distance)_i = \begin{cases} y_2^*, & \text{if } y_1^* > 0 \\ 0, & \text{if } y_1^* \leq 0 \end{cases}$$

Where $y_1^* = X_1' \beta_1 + \epsilon_1$; $y_2^* = X_2' \beta_2 + \epsilon_2$; and the error terms ϵ_1 and ϵ_2 are allowed to be correlated and assumed to follow a bi-variate normal distribution with co-variance matrix $\begin{pmatrix} 1 & \sigma_{12} \\ \sigma_{21} & \sigma_2^2 \end{pmatrix}$. The matrix of patient characteristics X_1' included age, length of stay, distance before centralization of care, patient choice set size before centralization, information about patients' residential municipalities (e.g. population, median standard of living, number of drug stores, number of ambulances, number of households having a car), and information about patients' residential departments (e.g. number of emergency units, number of short-stay hospitals). The matrix of patient characteristics X_2' included the same characteristics as in X_1' , exception made for patient age and length of stay. This exclusion restriction is required for identification purpose (see Appendix B for a discussion of the exclusion restriction).

In their report, the French National Health Insurance proposed a threshold of 150 cases per year for breast cancer and 10 cases per year for ovarian cancer (French National Health Insurance (2018)). To see the impact of the threshold chosen on patient access, we replicated the analysis for each threshold $k^{BC} = 2, 3, \dots, 160$ and

$k^{OC} = 2, 3, \dots, 30$. However, analysis of inequalities is performed only at $k^{BC} = 150$ and $k^{OC} = 10$.

3.4 Results

3.4.1 Descriptive statistics

We identified 57,151 (4,001) patients surgically treated for breast cancer (ovarian cancer) in mainland France in 2017 who were treated in 511 (461) hospitals. Among the 461 hospitals treating ovarian cancer patients through surgery in 2017, 386 (84%) also had an authorization to treat breast cancer patients. The distribution of hospital volume activities for breast cancer varied from a minimum of 1 to a maximum of 1,911, with a median of 59 patients treated in 2017 per hospital. For ovarian cancer, the much smaller number of patients compared to the slightly smaller number of hospitals led to a distribution of hospital volume activities significantly below that for breast cancer. Indeed, the distribution varied from a minimum of 1 to a maximum of 110, with a median of 5 patients treated for ovarian cancer in 2017.

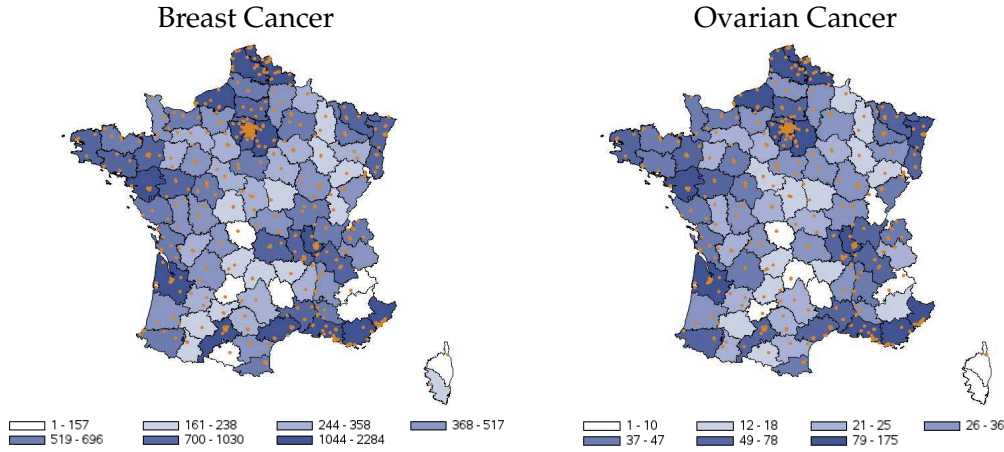


FIGURE 3.1: Patient density per department (blue grid) and geographical breakdown of hospitals (dots) before centralization of care

Figure 3.1 shows the geographical distribution of hospitals in mainland France for breast and ovarian cancer. It can be seen that the geographical coverage is rather similar for both conditions, which is not surprising considering that 84% of hospitals treating ovarian cancer patients also have an authorization to treat breast cancer

patients and cover the French territory relatively well. At the threshold proposed by the French National Health Insurance (i.e. $k^{BC} = 150$ and $k^{OC} = 10$), 401 hospitals (78.47%) among the 511 hospitals treating breast cancer patients, and 339 hospitals (73.54%) among the 461 hospitals treating ovarian cancer, would lose their authorization to treat the cancer concerned. Interestingly, among the 386 hospitals that treated both cancers in 2017, 237 hospitals (61.40%) would lose their authorization for both diseases at the same time. In terms of patient population, it would affect 35.51% of the breast cancer patients and 32.16% of ovarian cancer patients in 2017.

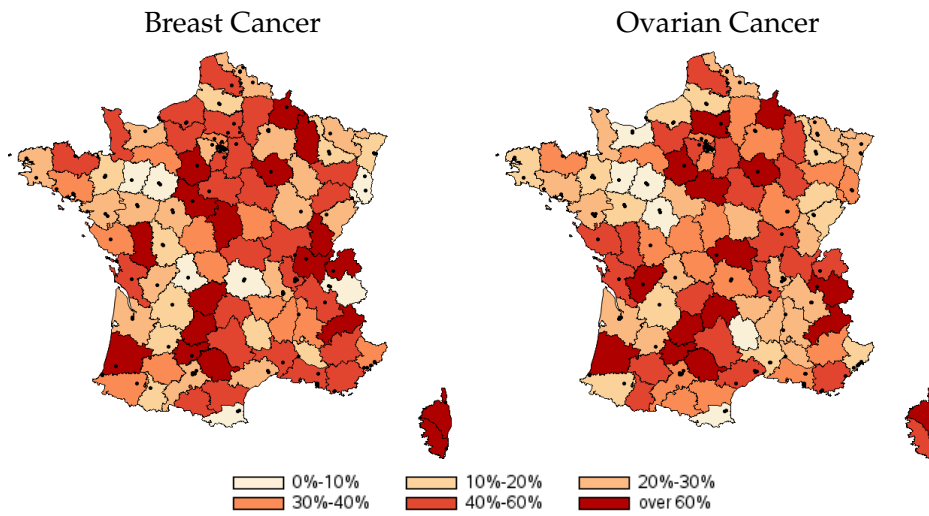


FIGURE 3.2: Rate of patients affected by the policy and geographical breakdown of hospitals after centralization of care

Figure 3.2 illustrates on a map the simulated geographical spread of hospitals if these thresholds were strictly applied. If there was a good geographical coverage before centralization of care (see Figure 3.1), it can be seen that several French departments would suffer from medical desertification if care were centralized. It is possible to identify broadly the same two areas for breast cancer and ovarian cancer that would suffer the most from the centralization of care, which are the center of France and the center south of France. It can also be seen on these maps that there is a wide variation in the rate of patients affected by the policy, in the sense that the initially chosen hospital would lose its authorization of treatment, by department. It is interesting to note that while we identify broadly the same two areas with no hospitals available for breast and ovarian cancer care, departments with the highest

rates of patients affected by the policy are not always consistent between ovarian and breast cancer.

TABLE 3.1: Patient, municipality, and department characteristics of reallocated ($R_i = 1$) and non-reallocated ($R_i = 0$) patients

	Breast Cancer			Ovarian Cancer		
	$R_i = 1$	$R_i = 0$	p	$R_i = 1$	$R_i = 0$	p
Age	63.20	60.75	0.0001	65.13	62.17	0.0001
Length of stay	2.82	2.08	0.0001	11.20	10.99	0.5110
Choice set size	20.64	24.08	0.0001	17.22	19.45	0.0088
Initial distance	17.74	30.93	0.0001	19.79	39.70	0.0001
Municipality characteristics:						
- Population	33639.7	45901.6	0.0001	35897.7	44635.6	0.0001
- Median standard of living (€)	21391.6	27726.5	0.0001	21324.5	21696.7	0.0043
- # of drug stores	12.60	16.46	0.0001	13.94	16.01	0.0309
- # of ambulances	3.26	3.79	0.0001	3.29	3.81	0.04023
- # of households having a car	0.8529	0.8438	0.0001	0.8498	0.8433	0.0501
Department characteristics:						
- # of emergency units	10.12	10.74	0.0001	9.86	10.68	0.0001
- # short stay hospitals	21.18	23.97	0.0001	20.35	24.09	0.0001
Frequency	18986	34472		1211	2554	
Share	35.51%	64.49%		32.16%	67.84%	

Note: number of (#) ; modality in reference (Ref) ; P-value (p).

We also observed in our data strong variations in patients and patient residential location characteristics (Table 3.1). Indeed, patients who would need to be reallocated are living in municipalities with a far lower population density, a lower median standard of living and in departments with less general healthcare facilities (e.g., drug stores, ambulances, emergency units, short-stay hospitals). It should also be noted that patients needing to be reallocated have on average a lower choice set size, meaning they are living in areas already with fewer hospitals available for their cancer care within 50 kilometers. Interestingly, the average patient-hospital distance observed initially is 17.74 (19.79) kilometers for patients who would be affected by the policy, compared to 30.93 (39.70) kilometers for patients already treated in a HVH hospital initially for breast (ovarian) cancer.

3.4.2 Probabilities of patients' hospital choice

Table 3.2 displays the results of the Conditional Logit model of patient hospital choice estimated across all hospitals, regardless of their volume activities. The results of this model will be used to predict the probabilities P_{ij}^* , required for our evaluation strategy. It can be seen that our set of hospital-specific characteristics are strong predictors of patient choice. Our main predictor, the distance between patient municipalities and hospitals, is as expected, strongly predicting patient choice. Patients were more likely to choose a hospital if it was the closest ($p < 0.001$), or closer ($p < 0.001$) to their home.

TABLE 3.2: Conditional Logit model of patient hospital choice on the full choice set

	Breast Cancer	Ovarian Cancer
Closest	0.6991***	0.8998***
Distance	-0.0293***	-0.0167***
Age x Distance	-0.0004***	-0.0004***
Length of stay x Distance	-0.0004***	0.0003***
Type of hospital		
- Public	Ref	Ref
- Private for profit	0.687***	0.2331***
- Private not for profit	0.8241***	0.4979***
Department of oncology	0.3241***	0.26***
# of hospital stays in oncology	0.0001***	0.0001***
# of surgical rooms	0.0173***	0.0273***
Bed occupational rate	0.0019***	0.0019***
# of employees for prevention of nosocomial infection	-0.0144***	0.0039
# patients	57151	4001
# observations	19166116	1202782
# hospitals	510	461
Log-Likelihood	-132733	-10337

Note: number of (#) ; modality in reference (Ref) ; significant at 1%, 5%, and 10% is indicated as ***, **, and *, respectively.

An interesting result is the heterogeneous impact of distance on the likelihood of hospital choice depending on patients' age and length of stay. Older patients tended to care more about distance when choosing where to be treated compared to younger patients ($p < 0.001$). Length of stay is used as a proxy for the severity of

the disease, with the assumption that the more severely ill patients will receive more intense treatment requiring longer hospital stays. Interestingly, the most severely ill breast cancer patients (i.e. longer length of stay) tended to care even more about distance compared to less severely ill patients ($p < 0.001$). Conversely, the most severely ill ovarian cancer patients tended to accept longer distance compared to less severely ill ovarian cancer patients ($p < 0.001$). Patients also tended to choose more often private for profit and most often private not for profit⁵ hospitals compared to public hospitals ($p < 0.001$), and hospitals specializing in oncology (i.e. having a department of oncology, with a higher number of hospital stays in oncology) ($p < 0.001$).

3.4.3 Expected hospital volume activities

Using the coefficient estimates of the Conditional Logit model, we estimated the individual probabilities P_{ij} that patient i chooses to be treated in hospital j . Then, as described in equation (1), we computed the expected hospital volume activities for each volume threshold $k^{BC} = 2, 3, \dots, 160$ and $k^{OC} = 2, 3, \dots, 30$. To illustrate the effectiveness of each volume threshold in centralized care, Figure 3.3 displays the minimum, first quartile, and mean hospital volume at each threshold for breast cancer and ovarian cancer separately.

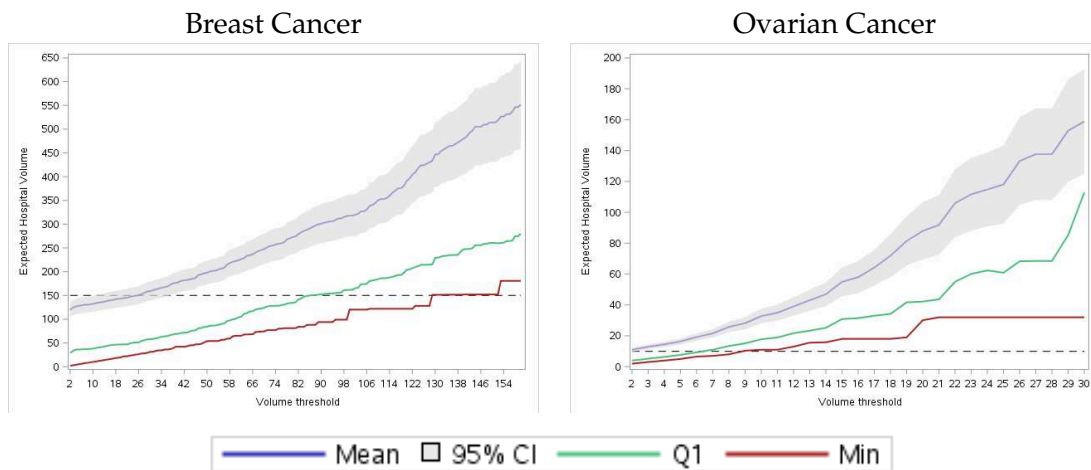


FIGURE 3.3: Expected hospital-volume activities when varying the volume threshold

⁵In France, private not for profit hospitals include a large coalition of Cancer Centers, named *Unicancer*, which is dedicated to cancer treatment.

Note that the uncertainty of the mean volume increases with the volume threshold, since the number of remaining hospitals (i.e. hospitals that will keep their authorization of treatment) decreases when the threshold increases. As anticipated, the average expected hospital volume increases more than linearly when the volume thresholds increase. It can be seen that at the thresholds set by the national insurance (i.e., $k^{BC} = 150$ for breast cancer and $k^{OC} = 10$ for ovarian cancer), the average expected hospital volume activity would reach 514.05 patients (32.77 patients) if care were centralized, while we initially observed an average volume of 112.53 (8.79) breast cancer (ovarian cancer) patients. As a benchmark, we also computed hospital volume post-centralization when patients are assumed to choose their closest provider for each volume threshold $k^{BC} = 2, 3, \dots, 160$ and $k^{OC} = 2, 3, \dots, 30$. Figure 3.6 in Appendix C displays the minimum, first quartile, and mean hospital volume at each threshold for breast cancer and ovarian cancer separately. It can be seen that using the benchmark method or our evaluation strategy led to a broadly consistent distribution of expected hospital volume.

3.4.4 Additional patient-hospital distance

An implication of minimum volume standard regulation is that patients who were treated in LVH hospitals (i.e. hospitals below the threshold) will have to be reallocated in one of the remaining hospitals after the application of a minimum volume threshold, and thus are likely to incur additional distances to be treated. As described in equation (4), we estimated the expected additional distance for each volume threshold $k^{BC} = 2, 3, \dots, 160$ and $k^{OC} = 2, 3, \dots, 30$ (Figure 3.4). In this figure, note that the uncertainty of the mean additional distance decreases with higher volume threshold, since the number of patients affected (i.e. for which we observe an additional distance) increases when the threshold increases, as illustrated by the green line. For breast cancer, a wide variation in the average additional distance when the volume threshold increases on the interval can be seen [2;30]. The uncertainty of average additional distance within this interval could be caused by the volume threshold already in place for breast cancer treatment at 30 surgeries per year in France. It can be seen that this threshold has not been strictly applied, since we still observe patients treated in hospitals below this threshold. Nevertheless, the number

of patients affected by the application of a minimum volume threshold remained low and tended to increase less than linearly on this interval, which could be an explanation of the wide uncertainty. Then, on the interval $[30; 160]$ a linear increasing trend of the average additional distance can be seen with the volume threshold ranging from 21 kilometers to 32 kilometers, and of the number of patients affected by the policy. For ovarian cancer, the mean additional distance is increasing almost linearly with the volume threshold ranging from 26 to 53 kilometers on the interval $[2; 30]$. Increasing the volume threshold translates into different degrees of centralized care, and the average additional distance patients initially treated in LVH hospitals will have to travel increases slightly with the volume threshold for breast cancer, and increases more significantly for ovarian cancer. Understandably, the number of patients affected by the application of the minimum volume threshold (i.e. in the sense that the initially chosen hospital will lose its authorization of treatment) drastically increases with the volume threshold, as illustrated by the green curve in Figure 3.4.

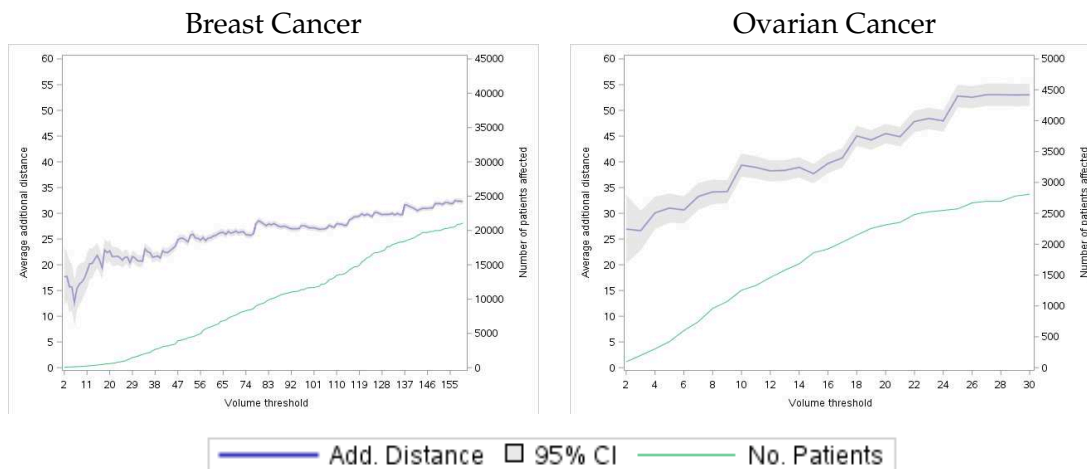


FIGURE 3.4: Average additional distance and number of patients affected when varying the volume threshold

As a benchmark, we also computed additional distance post-centralization when patients are assumed to have chosen their closest provider (Figure 3.7, Appendix C). As expected, redirecting patients to the closest available provider leads to a distribution of additional distances far below the one from our evaluation strategy that takes into account patient preferences. Ignoring patient preferences undermine additional distances and leads to additional distances below zero for low volume thresholds,

since not all patients were initially treated in their closest hospital.

3.4.5 Spatial inequalities

At the threshold required to reach the objective set by the French National Health Insurance (i.e. $k^{BC} = 150$ and $k^{OC} = 10$), patients will incur on average an additional distance of 32.45 kilometers for breast cancer and 38.89 kilometers for ovarian cancer to get to their hospital. To have an overview of the deterioration in patient access to hospital care caused by the volume threshold compared to the observed/initial situation, Figure 3.5 displays the average patient-hospital distance before centralization, the average expected distance post-centralization, and the average squared distance post-centralization per department. It can be seen that initially (i.e., maps on the top of Figure 3.5), patients living in departments in central France and in Corsica incurred longer distances compared to other French departments. A striking result is the increase in these spatial inequalities triggered by the introduction of a volume threshold. Indeed, it can be seen in the simulated maps (i.e., maps in the middle of Figure 3.5) that the distances post-centralization increase significantly for departments in central France, while remaining broadly constant for other departments. In other words, minimum volume standard tended to worsen spatial inequalities in access to hospital care for breast cancer and ovarian cancer by increasing patient-hospital distances more significantly in departments that already have the highest average distances. For both diseases, two departments in the center of France will particularly be affected, with an average post-centralization patient-hospital distance of over 125 kilometers.

Note also that the inequalities already in place before centralization, and the degree of deterioration in patient access post-centralization are stronger for ovarian cancer care compared to breast cancer care. The two maps on the bottom of Figure 3.5 display the average squared patient-hospital distance. By taking square distances, more weight is put on long distances when computing the average by department (i.e. higher patient distance aversion). Our approach to underline inequalities in distances is similar in many points to the approach of Shorrocks, which proposes

an index for measuring unemployment based on the well-known poverty index by Foster (Shorrocks (2009); Foster et al. (1984)).

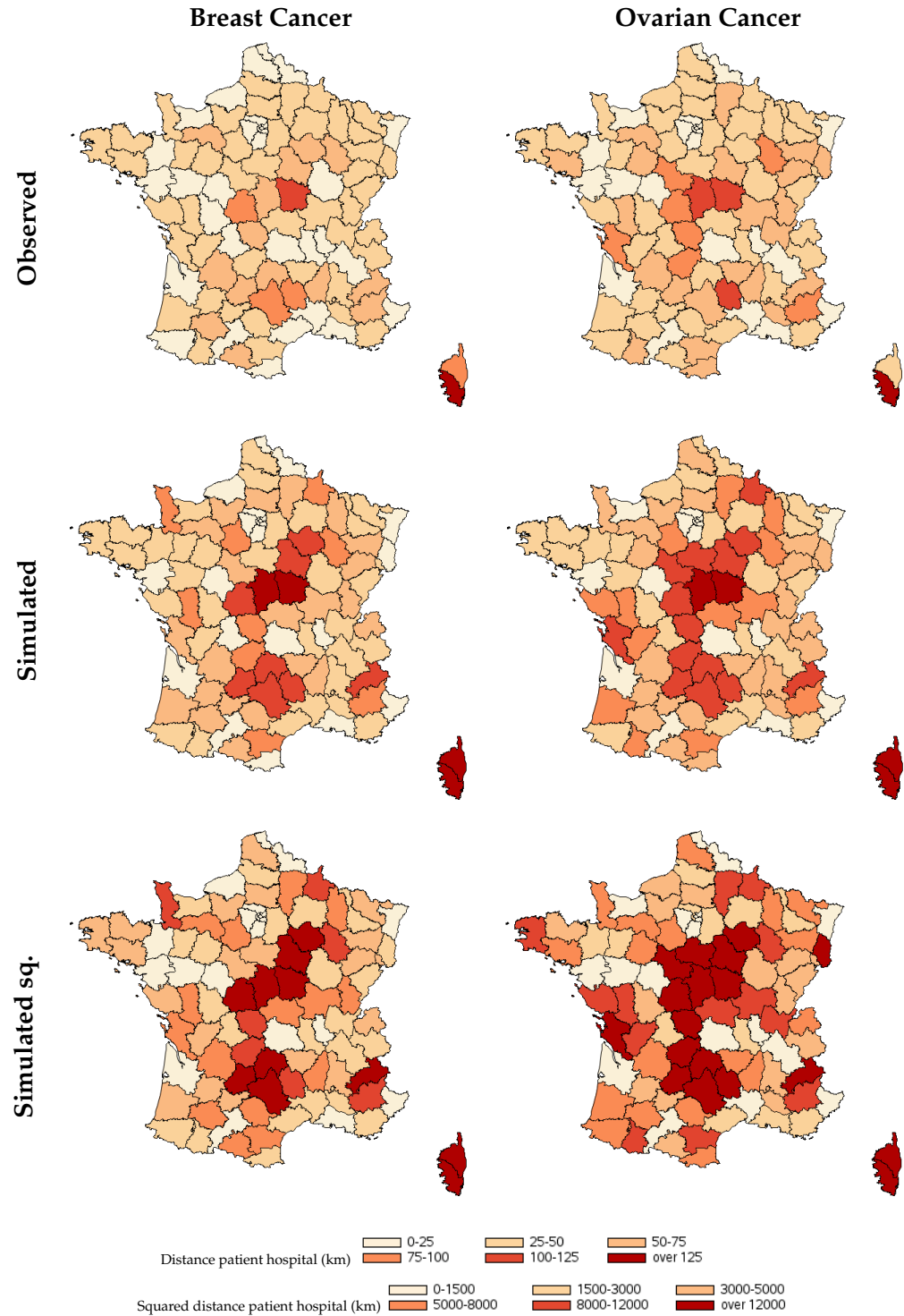


FIGURE 3.5: Average of the observed, simulated, and simulated squared (i.e., Simulated sq.) patient-hospital distance

Using a normative approach based on several axioms similar to those found in the literature on measuring poverty, this index is defined in terms of length of periods of unemployment at the power α , where α is a parameter reflecting aversion to long periods of unemployment. Thus, the Shorrocks index corresponds to the unemployment rate when $\alpha = 0$, the average length of unemployment period when $\alpha = 1$ and the average square length of unemployment period when $\alpha = 2$. Thus, our approach is similar in many points since the maps in Figure 3.2 display the rates of reallocation ($\alpha = 0$), the maps in the middle of Figure 3.5 the mean distance ($\alpha = 1$) and the maps on the bottom of Figure 3.5 the mean square distance ($\alpha = 2$). It can be seen that spatial inequalities across departments in square distances are even worse for both diseases, with even more differences between departments in the center of France compared to other locations.

3.4.6 Socioeconomic inequalities

So far, we have investigated whether the application of minimum volume thresholds would introduce spatial inequalities in access to hospital care in terms of average distances, and average additional patient-hospital distances. However, inequalities could also run through a correlation between patient characteristics (e.g. socioeconomic characteristics, municipality characteristics) and additional distances. To that end, we estimated a type 2 Tobit model for breast cancer and ovarian cancer patients separately (Table 3.3). It can be seen that for both cancers, older patients, patients living in departments with more emergency units and fewer short-stay hospitals, and patients living in less populated and poorer municipalities are more likely to be affected by the introduction of minimum volume thresholds, in the sense that they will need to be reallocated. Thus, in terms of probability of being affected by the policy (i.e., likelihood of seeing the hospital chosen for treatment withdrawn from the market), the most deprived and remote areas are more likely to be affected compared to patients living in richer and urban municipalities.

An interesting result is that patients who initially had a shorter distance to their hospital are also more likely to be affected by the policy ($p < 0.001$). Lower initial distances could either relate to patient distance aversion, but could also be caused by

a limited choice set when patients did not have the opportunity to choose other hospitals at a moderate distance from their home. Since we also controlled for the choice set size as an independent variable in the model, this result could be interpreted as the more distance-averse patients (i.e. patients who initially chose a closer hospital) being more likely to be affected by the policy. Patients not affected by the policy are those already treated in a HVH hospital initially. Our results agree with the idea that patients treated in HVH hospitals are less distance averse, and thus more able to accept longer distances in order to be treated in a HVH hospital. Furthermore, we identified a heterogeneous impact of the initial distance with patient choice set size of opposite sign for breast and ovarian cancer. Indeed, breast cancer patients with a lower initial distance were even more likely to be affected by the policy if they had a larger choice set, while the heterogeneous impact was reversed for ovarian cancer patients.

For breast cancer patients, the most severely ill patients (i.e., having a longer length of stay at hospital) were also more likely to be affected by the policy ($p < 0.001$). Although weakly significant, it is interesting to see that the severity of the disease included in the selection process had an effect of contrary sign for ovarian cancer, with the less severely ill ovarian cancer patients being more likely to be affected by the policy ($p = 0.0512$).

Conditional on the probability of being affected by the policy, it is interesting to see that for both cancers, patients living in municipalities with a lower population density, a lower median standard of living, a higher number of households having a car, and in departments with more emergency units and fewer short-stay hospitals were more likely to incur higher additional distances. A remarkable result is that the most deprived and remote areas are simultaneously more likely to be affected by the policy and more likely to incur longer additional distances among the subgroup of patients affected. Note that for both diseases, conditional on the probability of being affected by the policy, patients who were initially treated in closer hospital and patients who were offered fewer choices are naturally more likely to incur longer additional distances ($p < 0.001$).

TABLE 3.3: Type 2 Tobit model of the additional distance conditional on the selection process

	Breast Cancer		Ovarian Cancer	
	Reallocate	Additional Distance	Reallocate	Additional Distance
Intercept	-0.9950***	33.9206***	-0.3975	9.2633
Age	0.0667***		0.0832***	
Length of stay	0.1476***		-0.0346*	
Choice set size	-0.1636***	-12.7220***	-0.0226	-14.5533***
Initial distance	-0.6010***	-34.8827***	-0.4252***	-61.6213***
Choice set x init. distance	-0.3264***	-3.6715***	0.1114***	3.1679*
Municipality characteristics:				
- Population	-0.1954***	-22.9831***	-0.2641**	-25.4426***
- Median standard of living (€)	-0.0609***	-3.6664***	-0.0637**	-3.2621**
- # of drug stores	0.0125	16.4454***	0.1546	10.6403**
- # of ambulances	0.0443***	-3.1800***	0.0300	-0.9532
- # of households having a car	0.5649***	-17.5898***	-0.1871	-40.5477***
Department characteristics:				
- # of emergency units	0.1771***	1.8475***	0.2734***	10.7049***
- # short stay hospitals	-0.3067***	-15.1803***	-0.5122***	-30.5117***
Rho	-0.0482		0.8963***	
Sigma	28.4529***		40.4751***	
Observations	53458		3765	
Log-likelihood	-122686		-7850	

Note: number of (#) ; modality in reference (Ref) ; standardized variable (std) ; significant at 1%, 5%, and 10% is indicated as ***, **, and *, respectively.

3.5 Discussion

The centralization of care for complex procedures, such as surgeries in cancer care, is a major concern in health economics, and could offer an opportunity to substantially increase the quality of care through a reform of the organization of the supply side of the market. However, policy makers are facing a crucial trade-off between increasing the quality of care and decreasing patient access to care. As part of the general interest toward centralization, the French National Health Insurance proposed increasing the minimum volume threshold for breast cancer from 30 surgeries per year to 150 surgeries per year, and setting a specific threshold for ovarian cancer at 10 or 20 surgeries per year (French National Health Insurance (2018)). In

this study, we evaluate the impact of such a policy on patient access to care, and investigate how the burden of the policy would be distributed spatially and within socioeconomic subgroups.

Our findings tend to indicate that the application of minimum volume thresholds is very effective to achieve a centralization of care. The degree of centralization of care increases more than linearly with the volume threshold for both cancers (Figure 3.3). At the threshold proposed by the French National Health Insurance, the average expected hospital volume activity post-centralization will be four times higher for breast cancer and three times higher for ovarian cancer compared to the hospital volume distribution observed initially, which would substantially increase the quality of care. A question that still remains is what is the cost of this kind of centralized care in terms of patient access to hospital care? As illustrated in Figure 3.4, the average additional distance patients will have to travel increases almost linearly with the volume threshold applied. At these thresholds, breast cancer (ovarian cancer) patients affected by the policy will have to travel on average 32.45 (38.89) kilometers farther. In terms of patient population, it will affect 35.51% of breast cancer patients and 32.16% of ovarian cancer patients.

As expected, our findings tend to indicate that patient access to hospital care for breast and ovarian cancer care would be substantially reduced by the policy. What was more unpredictable was the impact of the policy on spatial and socioeconomic inequalities in access. We identified strong spatial inequalities in the share of patients affected by the policy among French departments (Figure 3.2). While less than 10% of the patients would have to be reallocated in some departments, and thus would incur an additional distance, the share exceeds 60% in the most affected departments. Similarly, while the average patient-hospital distance would be lower than 25 kilometers in some departments, the average distance could exceed 125 kilometers in the most affected departments (Figure 3.5). A striking result is that the centralization of care would increase existing spatial inequalities for the two diseases concerned in France. Indeed, some departments, especially in the center of France, have longer average distances compared to other departments. After centralization,

our results indicate that the average patient-hospital distances would drastically increase in these departments, while remaining broadly consistent elsewhere. In other words, the departments that would suffer the most from a centralization of care are those that already have less access to care. Note that spatial inequalities are even more significant if a higher degree of distance aversion is assumed by putting more weight to longer distances.

We identified substantial socioeconomic inequalities in the likelihood of being affected by the policy, as well as in variations in expected additional distance among socioeconomic subgroups (Table 3.3). Patients living in rural areas, with a lower standard of living, and who already have less access to non-specialized care are more likely to be affected by the policy, and also to incur longer additional distances. An interesting result is that patients who initially chose closer hospitals are more likely to be affected by the policy, depending on their choice set size (i.e. number of hospitals within 50 kilometers). In other words, distance-averse patients are more likely to be affected by the policy compared to less distance-averse patients. Similarly, older patients are more likely to be affected by the policy, while results from the Conditional Logit model indicate that they tended to attribute a more important weight to the distance in their preferences for hospital choice. The fact that more distance-averse patients would be more affected is a major concern in devising volume-based policies.

In the existing literature, it has been shown that the centralization of care in Germany and in Japan would have a moderate impact on patient access to hospital care (Hentschker et al. (2018); Hentschker and Mennicken (2015); Kobayashi et al. (2015)). In comparison, our results indicate that the introduction of minimum volume thresholds in France could drastically deteriorate patient access to specialized care, and that the burden of the policy will be unequally distributed in spatial and socioeconomic terms. Transportation costs would thus inherently either increase the out-of-pocket cost for patients or increase the expenses for the social security system if they were fully reimbursed. The divergence in this conclusion compared to the existing literature could stem from a differing evaluation strategy, the country or the

disease analyzed. In this study, we take into account the patients' choice of their provider based on their preferences in the evaluation strategy. Our evaluation strategy relates an implementation of a minimum volume threshold in a country where patients are free to choose their hospital, and is thus reflective of most healthcare systems, such as in the UK, USA, France, etc. In comparison, studies in the existing literature assumed that patients would be reallocated to their closest HVH hospital after the centralization of care (Kobayashi et al. (2015); Hentschker et al. (2018); Hentschker and Mennicken (2015)). For the purpose of comparison, we employed the same strategy as a benchmark. As expected, ignoring patient preferences substantially underestimates the deterioration in patient access. While we found an average additional distance of 32.45 km for breast cancer and 38.89 for ovarian cancer when patients preferences are taken into account, results using the benchmark evaluation strategy indicate an average additional distance of 18.9 km for breast cancer and 21.57 km for ovarian cancer. Thus, following the benchmark evaluation strategy we might also have concluded that the introduction of a minimum volume threshold would have a moderate impact on patient access. In fact, assuming patients will choose their closest hospital revert to estimating the lowest bound of the deterioration in patient access (i.e., patient-hospital allocations that minimize distances), or to assuming that distance is the only predictor of patient choice. Naturally, distance or travel time will be one of the most important factors in patient preferences, but other important factors are likely to be considered in the selection process as well. As an illustration, we observed in our data only 25.61% of breast cancer patients and 24.82% of ovarian cancer patients treated in the closest hospital to their home in 2017 in France. If the patient-hospital distance was the only predictor of patient choice, all patients would have been treated in their closest hospitals.

For that reason, we included in the Conditional Logit model variables we believed to be good predictors of patient choice (e.g. distance, hospital characteristics, heterogeneity with patient characteristics). It can be seen in Table 3.2 that these predictors are strongly significant, indicating that they are indeed good predictors. We have also performed further test of goodness of fit of our evaluation strategy as described in Appendix D. The Conditional Logit model shows a good predictive power

in predicting patient probabilities of hospital choice. As a robustness check, we were also able to replicate the observed distribution of hospital volume activities using the probabilities P_{ij}^* with an average error of less than one patients.

In this study, we evaluated the impact of a strict application of minimum volume thresholds on patient access. By retrieving from the market simultaneously hospitals not meeting the volume criteria, it does not allow the opportunity for LVH hospitals slightly below the threshold to get off the volume threshold thanks to patient flows from even lower volume hospitals. The decision maker could also choose to implement the minimum volume threshold progressively, until the distribution of hospital volume activities reached the desired level. In Appendix E, we determine in our data the minimum volume threshold that could be applied in order to still reach the goal that all hospitals post-centralization would have a volume activity higher than 150 for breast cancer and higher than 10 for ovarian cancer. Thanks to patient reallocation, we found that by reallocating patients treated in hospitals having a volume activity under 128 for breast cancer and under 9 for ovarian cancer, the remaining hospitals would all meet the volume criteria set by the French National Health Insurance. By doing this, 22 hospitals treating breast cancer and 21 hospitals treating ovarian cancer would be saved from closure. Naturally, we found a slightly lower degree of deterioration in patient access under these thresholds compared to the thresholds $k^{BC} = 150$ and $k^{OC} = 10$. However, it should be noted that the burden of the policy would still be unequally distributed through the same spatial and socioeconomic patterns. Understandably, the minimum thresholds we estimated for breast and ovarian cancer are not generalized out of our sample, and even less generalized to other countries. Nevertheless, they underline the importance of the dynamic of patient reallocation in devising volume-based policies.

3.6 Conclusion

Centralizing care to high volume hospitals is an opportunity to substantially improve the quality of care for diseases requiring complex procedures, such as surgeries in cancer care. However, policy makers are facing a trade-off between increasing the quality of care and decreasing patient access to care. In countries where patient choice of their preferred provider is effective, our findings underline the need to take into account patient preferences in order to have a complete picture of the impact of volume-based policies on patient access. Indeed, ignoring patient preferences drastically undermine the deterioration in patient access, and thus leads to ignoring a major adverse consequence of such policies. Furthermore, policy makers should pay particular attention to the impact of centralizing care on inequalities in access. Our findings do indeed indicate that the burden of the policy would be unequally distributed in spatial and socioeconomic terms in favor of those who are wealthier and living in urban areas with more access to other healthcare facilities. To conclude, our findings indicate that a strict application of such volume thresholds would be unsustainable in terms of patient access. To make the policy sustainable, policy makers could choose a lower volume threshold, which would reduce the adverse consequences on patient access but would also reduce the gain in quality of care. Alternatively, instead of setting a volume threshold for the entire territory, policy makers could customize the volume threshold for areas where no hospitals would reach the national threshold within a reasonable distance, in order to adjust the volume threshold according to the density of hospitals. Lastly, instead of reforming the supply side of the market, patients could be allowed to decide where they want to be treated. However, are patients treated in LVH hospitals aware that they could have better treatment in a HVH hospital that is farther away from their home? Policy makers would have to make sure that patients and their general practitioners have the opportunity to make an informed choice when choosing their preferred provider, and that there are no other barriers for accessing care in HVH hospitals.

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Appendix A. Inclusion Criteria

The PMSI database records information about all patients treated in a hospital in France, for all diseases and procedures. To identify our populations of interest (i.e. breast cancer and ovarian cancer patients who underwent treatment through surgery), we first included patients based on the World Health Organization (WHO) International Classification of Disease (ICD-10). The inclusion criteria were having an ICD-10 diagnosis code C56 (i.e. malignant neoplasm of ovary) or C50 (i.e. malignant neoplasm of breast). Among these patients, we excluded patients not surgically treated since our study investigated the centralization of care for patients who had surgical treatment. To do this, we used the complete list of Common Classification of Medical Acts (CCAM) codes corresponding to a surgical act for breast cancer or ovarian cancer. For ovarian cancer, we used a list of CCAM codes from a French study which had the same population of interest (Querleu et al. (2016)). For breast cancer, we used the list of CCAM codes published in a report of the French National Cancer Institute (French Cancer Institute (2013)).

Appendix B. Exclusion Restriction

There is a need to find variables that predict the selection process (i.e., initially being treated in an LVH hospital), while being independent of the outcome equation. In the literature, it has been shown for breast cancer and ovarian cancer care that older patients were indeed less likely to be treated in a high volume hospital (Bouche et al. (2008); Cowan et al. (2016)). There is a need to find variables that predict the selection process (i.e., initially being treated in an LVH hospital), while being independent of the outcome equation. In the literature, it has been shown for breast cancer and ovarian cancer care that older patients were indeed less likely to be treated in a high volume hospital (Victoor et al. (2012)). Thus, patient age is a good candidate for our exclusion restriction, since the literature tends to show it should be a good predictor of the probability of being treated in a high volume hospital (i.e., and thus to not be affected by the policy), while being totally independent of the additional distance post-centralization of care. Patient length of stay is also a good candidate since it is strictly orthogonal to additional distances, while it could predict, to some extent, the probability to be treated in a high volume hospital. For ovarian cancer care, it has been shown that the most severely ill patients were more likely to be treated in high volume hospitals (Cowan et al. (2016)). Conversely, for breast cancer care, earlier-stage patients have been found to be more likely to be treated in a high volume setting (Bouche et al. (2008)).

Appendix C. Benchmark Evaluation Strategy: Redirected to Closest Hospital

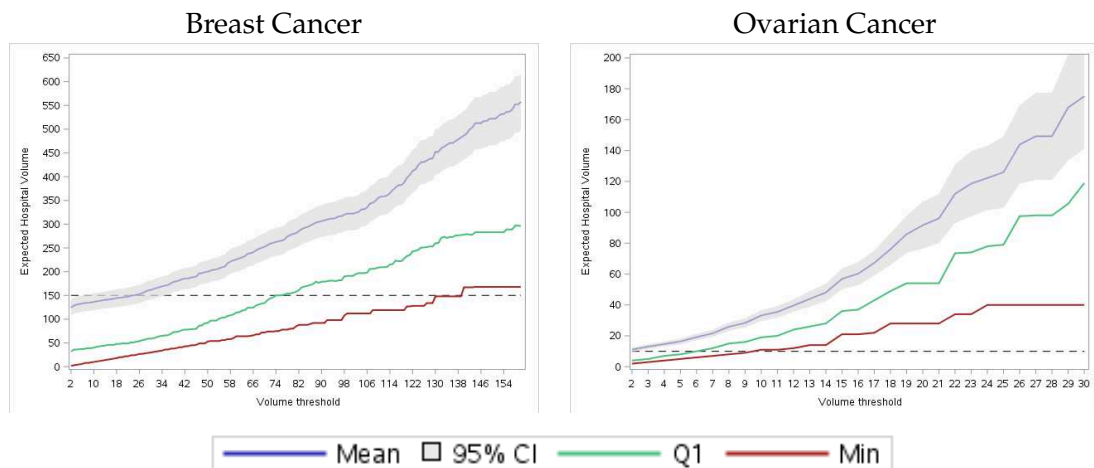


FIGURE 3.6: Benchmark simulation of expected hospital-volume activities when varying the volume threshold for breast cancer (left) and ovarian cancer (right)

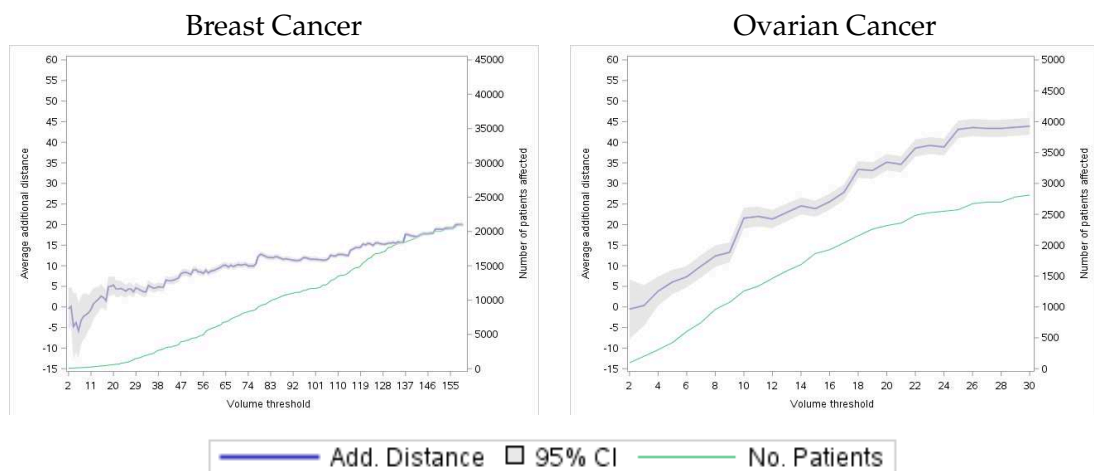


FIGURE 3.7: Benchmark simulation of expected additional distance when varying the volume- threshold

Appendix D. Predictive Power of the Conditional Logit Model

In our evaluation, we modeled patient flows from low volume hospitals to high volume hospitals in terms of probabilities. In this appendix, we present several robustness checks that test the predictive power of the Conditional Logit model in order to predict the probabilities P_{ij} that patient i chooses to be treated in hospital j . Testing the predictive power of such a model is not straightforward, and there is no fully satisfactory test. Indeed, the model estimates a continuous probability (P_{ij}), while our observed dependent variable is a discrete choice. Nevertheless, to compare the estimated probabilities for observed choices, it is still possible to look at the share of patients for whom their observed choice corresponds to their highest predicted probability or to one of the highest probabilities. To do this, we split the ovarian cancer sample and the breast cancer sample into a train sample (i.e. 70% of patients) and a test sample. We estimated the Conditional Logit model using the train sample for each cancer, and then predicted the out-sample probabilities P_{ij} using the test sample. The aim of doing predictions among a subsample unused in the estimation is to assess how the model has generalized to data unused in the estimation of the parameters, and thus to avoid over-fitting. To assess the out-sample predictive power of the model, we computed the share of patients for whom the highest estimated probability corresponds to the observed choice (i.e. the hospital chosen initially). We also computed this share for the top-five highest probabilities. It can be seen in Table 4 that for 29.86% (23.39%) of the test samples for breast cancer (ovarian cancer), the highest probability corresponds indeed to the observed choice. In other words, our model is able to predict in which hospital a new patient (i.e. who was not included in the estimation) will choose to be treated with 29.86% chance for breast cancer patients, and 23.39% for ovarian cancer patients. Since we used the predicted probabilities to compute expected hospital volume and expected additional distance, it is important that the highest probabilities correspond to observed choices. It can be seen that for 79.1% (73.18%) of breast cancer patients (ovarian cancer patients), the observed choice corresponds to an out-sample probability in the top 5 highest out-sample probabilities. It can be seen in Table 3.4 that the models performed as well for in-sample and out-sample predictions, which indicates that

we did not over-fit the data for our predictions, and that the parameter estimates of the Conditional Logit model are, to some extent, generalized.

TABLE 3.4: Share of observed choices corresponding to the top 5 highest probabilities

Rank	Breast cancer				Ovarian cancer			
	In-sample %	Out-sample %	In-sample %	Out-sample %	In-sample %	Out-sample %	In-sample %	Out-sample %
1 st	29.54	29.54	29.86	29.86	24.82	24.82	23.39	23.39
2 nd	24.31	53.85	24.20	54.06	18.95	43.76	19.97	43.36
3 rd	13.27	67.12	13.11	67.17	12.95	56.71	13.45	56.81
4 th	7.20	74.32	7.10	74.27	10.07	66.78	9.94	66.75
5 th	4.77	79.10	4.79	79.07	6.40	73.18	5.76	72.51

Note: percentage (%) ; cumulative percentage (Cum. %).

This robustness check is not fully satisfactory since we did not classify patients in HVH hospitals in our evaluation, but we rather relied on predicted probabilities. In order to test the predictive power of our evaluation strategy in estimating the expected hospital volume after centralization of care, we predicted hospital volume before centralization of care and compared them to observed hospital volume. It should be noted that this approach is valid only because hospital volume is not used as a predictor in the Conditional Logit model.

TABLE 3.5: Predicted versus observed hospital volume

	Breast cancer			Ovarian cancer		
	Observed (1)	Predicted (2)	Error (1)-(2)	Observed (1)	Predicted (2)	Error (1)-(2)
Mean	112.53	111.84	0.69	8.78	8.66	0.12
Std	174.22	153.99	114.54	12.68	10.37	8.68
Q1	23	55.34	-48.49	2	4.38	-3.47
Q2	59	76.91	-16.46	5	5.89	-0.93
Q3	129	116.59	33.90	10	8.73	2.26

Note: Standard deviation (std) ; lower quartile (Q1) ; median (Q2) ; upper quartile (Q3).

Table 3.5 shows that the mean predicted hospital volume (i.e. expected hospital volume, based on the probabilities P_{ij}) is 111.84 patients per year (8.66 patients per year) and that the observed mean hospital volume is 112.53 patients per year (8.78 patients per year) for breast cancer (ovarian cancer). Therefore, our model is

able to predict the mean hospital volume with an error of less than one patient for both cancers. However, our model does not completely translate the skewness of the observed hospital volume distribution, and therefore predicts a rather symmetric distribution of hospital volume. The skewness of the observed hospital volume distribution comes from the fact that there are many LVH hospitals and a few HVH hospitals, and the predictions tend to smooth that skewness.

Appendix E. Dynamic in Patient Reallocation

In Figure 3.3, it can be seen that the minimum volume threshold needing to be implemented in order to reach the objective set by the French National Health Insurance is $k_{min}^{BC} = 128$ for breast cancer and $k_{min}^{OC} = 9$ for ovarian cancer. At these thresholds, considering patient flows from hospitals losing their authorization to the remaining hospitals, our predictions indicate that all hospitals will treat at least 150 cases per year for breast cancer and 10 cases per year for ovarian cancer. Applying these thresholds will increase the median volume activity from 59 (5) patients treated per year initially for breast cancer (ovarian cancer) to 294.34 patients (19.66 patients). At the threshold, patients will incur on average an additional distance to get to their hospital of 30.07 kilometers away for breast cancer and 34.38 kilometers away for ovarian cancer. By applying these thresholds, 379 hospitals (74.2%) among the 511 hospitals treating breast cancer patients, and 318 hospitals (69%) among the 461 hospitals treating ovarian cancer will lose their authorization to treat the cancer concerned. Interestingly, among the 386 hospitals that treated both cancers in 2017, 211 hospitals (54.7%) will lose their authorization for both diseases at the same time. In terms of patient population, it will affect 29.8% of the breast cancer patients and 26.8% of ovarian cancer patients in 2017. Figure 3.8 and Figure 3.9 illustrate that the degree of deterioration in patient access is broadly stronger in most departments, but that its spatial distribution leads to similar spatial inequalities in access compared to the results in the main analysis (i.e., Figure 3.2 Figure 3.5). Note also that we observed broadly the same inequalities in the Tobit type 2 model (Table 3.6).

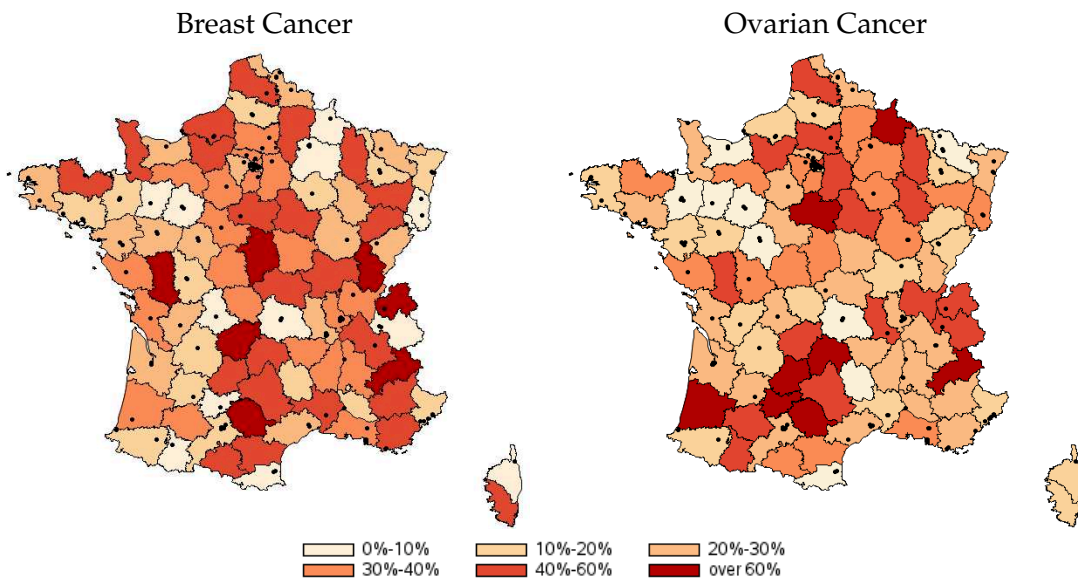


FIGURE 3.8: Rate of patients affected by the policy and geographical breakdown of hospitals after centralization of care at the thresholds $k_{min}^{BC} = 128$ and $k_{min}^{OC} = 9$

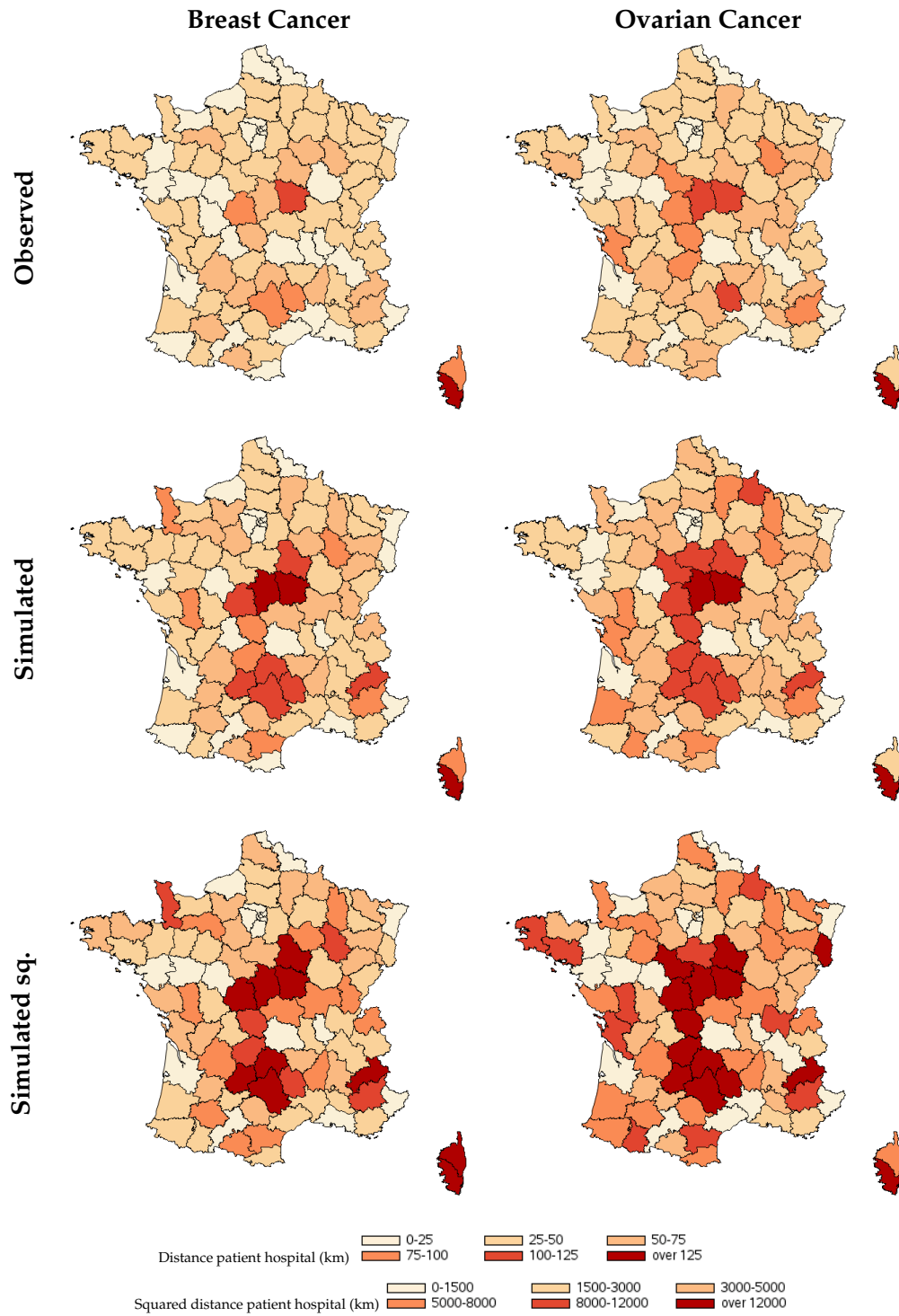


FIGURE 3.9: Average of the observed, simulated and simulated squared (i.e., Simulated sq.) patient-hospital distance at the thresholds $k_{min}^{BC} = 128$ and $k_{min}^{OC} = 9$

TABLE 3.6: Type 2 Tobit model of the additional distance conditional on the selection process at the thresholds $k_{min}^{BC} = 128$ and $k_{min}^{OC} = 9$

	Breast Cancer		Ovarian Cancer	
	Reallocate	Additional Distance	Reallocate	Additional Distance
Intercept	-0.7913***	37.2487***	-0.1774	11.4402
Age	0.0686***		0.0891***	
Length of stay	0.1454***		-0.0423**	
Choice set size	-0.1618***	-11.1484***	-0.0186	-13.6478***
Initial distance	-0.5722***	-35.2349***	-0.4046***	-59.1921***
Choice set x init. distance	-0.3062***	-0.3818	0.0918**	2.2304
Municipality characteristics:				
- Population	-0.2209***	-20.8396***	-0.1914*	-18.1233***
- Median standard of living (€)	-0.0576***	-2.9016***	-0.0433	-1.4269
- # of drug stores	0.0089	11.2306***	-0.0087	-1.2622
- # of ambulances	0.0482***	-1.6066***	0.0314	3.0589*
- # of households having a car	0.1625	-21.5675***	-0.6038	-45.3712***
Department characteristics:				
- # of emergency units	0.2044***	3.2232***	0.3289***	12.1203***
- # short stay hospitals	-0.2843***	-13.4769***	-0.5082***	-27.5513***
Rho	-0.1148*		0.8896***	
Sigma	22.7624***		36.9402***	
Observations	53458		3765	
Log-likelihood	-104942		-6802	

Note: number of (#) ; modality in reference (Ref) ; standardized variable (std) ; significant at 1%, 5%, and 10% is indicated as ***, **, and *, respectively.

Chapter 4

Patient preferences, referral process and access to specialized care.

Abstract

In most developed countries, patients have been encouraged to elect their preferred choice of health care provider. However, this is different for specialized care, where the patient's referral could be defined as a two-stage decision process and their options are pre-selected by their general practitioner (GP). In this study, we delve into the agency problem between patients and their GP in the referral process, and investigate whether patients are actively choosing their provider for cancer care. The French national hospital discharge database (PMSI - MCO 2017) has been used for investigation. We estimated a multinomial choice model when choice sets are in fact unobserved, in a revealed preferences framework. While the pre-selected choice set is unobserved, the concept is to set an upper bound and a lower bound of the true choice set. We study in the context of breast cancer with a focus on initial surgical treatment. Our results indicate that patients tend to defer their decision to their GP when it comes to the hospital specialization profile, and rather consider general hospital quality indicators and type as well as waiting times when making their decision. Hospital distance was found to be excluded from patient preferences and internalized during the GPs' pre-selection process. Our findings provide novel evidence that patients in French institutional settings are indeed taking part in the referral process for cancer care, which might be informative on the central role of GPs as the patient's agent.

4.1 Introduction

Understanding the referral process during which a patient chooses a health care provider is a major topic in health economics. In most developed countries, patient's choice of their preferred health care provider has been encouraged (Gaynor et al. (2015)). In the matching between patients and hospitals, information is highly asymmetric (i.e., especially for specialized care) (Arrow (1963); Choné and Ma (2011)). Patients may not have sufficient information about appropriate healthcare providers for their condition, and some hospital's attributes might be too complex for patients to understand (Gutacker et al. (2016); Faber et al. (2009)). Information asymmetry increases the risk of adverse selection. When patients lack information on provider's attributes they are less likely to make a choice which maximizes their utility. Moreover, gathering information about all providers can be costly when considering a large number of providers, and the large panel of alternatives can be demotivating for patients (Iyengar and Lepper (2000)). Hence, most health systems mandate patients to be addressed by their general practitioner (GP) for specialized care in order to be reimbursed by the social security system. In this context, patient referral could be defined as a two-stage decision process (Beckert (2018)). During the first stage, GPs pre-select a subset of providers they deemed appropriate from all alternatives. Then, during the second stage patients will choose their preferred provider among the pre-selected choice set. Thus, GPs have a central role in the referral of patients to hospitals. The role of GPs as patients agent is to reduce the risk of adverse selection. Indeed, GPs benefit from superior information on alternative providers, in particular by using their extended network and based on their accumulated experience.

Nevertheless, GPs act as imperfect agents for patients as they pre-select a subset of providers based on their own preferences rather than based on patients preferences (Beckert (2018)). Naturally, patients and GPs are likely to share a set of common attributes that they both care about in their utility function. It should be considered that GPs also assume the role of agent of health authorities since their decision may have an important impact on public health expenses (Brosig-Koch et al.

(2015)). Thus, there could be some attributes considered by patients only (e.g., hospital amenities) or by GPs only (e.g., technical quality indicators, public health expenses). Therefore in the presence of information asymmetry, it is not clear whether patients are actively choosing their provider or if they are deferring their decision to their GP. This is especially relevant for complex care where information is likely to be even more asymmetric, and the size of the pre-selected choice set could thus drastically constrain patient's choice. The extreme case would be a pre-selected choice set including a single provider, meaning that the choice was entirely made by the GP. The aim of this study is to evaluate whether or not patients are actively choosing their provider for complex care with highly asymmetric information, and to disentangle patient preferences from the pre-selection process. Using a nationwide database, we study the case of breast cancer which is the most frequent cancer among women, impacting 2.1 million women in the world each year. We focus on first line treatment for breast cancer, particularly on hospital stays during which a debulking surgery was performed. For this type of cancer in particular¹, patient preferences have major implications for their health as the outcome of the surgical act could vary significantly from one hospital to another, depending on their hospital volume activities (Yen et al. (2017)).

Several policies have been implemented in order to weaken the barriers obstructing the patient's freedom of choice (Victoor et al. (2016)). For example, in 2006 the UK set a reform which mandates GPs to offer at least five alternatives of providers when referring patients to a specialist. The aim was to give patients a greater opportunity to find a hospital that best matches their preferences by increasing the size of the pre-selected choice set. A recent study employed a structural model of demand based on the 2006 reform which explicitly models the selection process during which GPs pre-select a subset of alternatives (Gaynor et al. (2016)). Results support the theoretical expectation that increasing choices makes patients more responsive to the clinical

¹In France, hospitals are mandated to get a specific authorization of treatment to be allowed to perform breast cancer surgeries. Since 2007, the French Cancer Institute set a minimum volume threshold of 30 surgeries per year for breast cancer care below which hospitals wouldn't be empowered to care these patients.

quality of care in health systems where prices are excluded as demand shifters. Patients were treated in hospital of higher quality than they would have been treated without the reform, which has led to a decrease in overall mortality rates. There have been several policies aimed at increasing patient's access to objective quality information about health care providers to lessen information asymmetry. For example through public websites which provide quality information which is easy to understand (e.g., weisse-liste.de in Germany, scopesante.fr in France). Nevertheless, evidence that patients rely on objective quality information is mixed, with some patients tending not to use the additional information provided (Victoor et al. (2012); Gutacker et al. (2016); Avdic et al. (2019); Baker et al. (2003); Varkevisser et al. (2012); Faber et al. (2009)).

In the existing literature, a wide range of empirical studies have investigated the determinants of the patient's choice by assuming that GPs and their patients act as a single decision maker during the referral process. Empirical findings show that patients often bypass the nearest provider to find a hospital that best matches their preferences (Beckert and Kelly (2016); Gravelle et al. (2012); Victoor et al. (2012); Gaynor et al. (2016); Moscelli et al. (2016); Beckert et al. (2012)). Findings suggest that the probability of choosing a hospital increases with its measured quality and decreases with waiting times and distance. However, this literature assumed a fixed choice set and thus ignored the agency problem and the role of GPs in the referral process (Redelmeier and Shafir (1995)).

Only a few studies have delved into the agency problem and the role of GPs in the referral of patients to hospitals. In the US, there is a trend of integrating physician practices into hospitals, which has launched debates about the effect of such integration on the agency problem between physicians and patients (Baker et al. (2014)). Using data on Medicare beneficiaries, including the identity of their physician and of the owner of their physician's practice, the hospital's ownership of a physician has indeed been shown to increase the probability that the physician's patients will choose the owning hospital (Baker et al. (2016)). Note that in most western European countries (e.g., Germany, France, UK) GPs are independent in the sense

that there is no integration into hospitals. Nevertheless, even in the absence of hospital integration, GPs have a central role in the referral process by pre-selecting a subset of providers based on their own utility function. Using UK administrative data on National Health Service inpatient admission, a study showed that ignoring the pre-selection process (i.e., the choice set formation) leads to biases and inconsistencies (Beckert (2018)). Their findings support the notion that GPs act as imperfect agents for patients since they also act as agents for health authorities to contain costs. The main finding is that patients tended to base their choice on tangible hospital attributes such as amenities and waiting times, whereas GPs pre-selection was driven by distance, quality, and costs.

In this study, we exploit hospital discharge data from the Medical Information Systems Program (PMSI), which comprehensively records hospital stays in French hospitals (Boudemaghe and Belhadj (2017)). Using a revealed preferences framework, the main methodological challenge to disentangle patient preferences from observed patient-hospital allocation is that the true choice set (i.e., the pre-selected choice set) is unobserved by the econometrician. As a benchmark, we estimate a Random Coefficient Logit model which considers GPs and patients as a single decision maker and ignores the pre-selection process. By ignoring the agency problem, one can still identify factors (i.e., hospital attributes) playing a role in the referral process. However, this specification does not allow to disentangle patient preferences from the pre-selection process, which could be linked to GPs preferences. Regarding this issue we relied on an approach that allows the estimation of a multinomial choice model when choice sets are in fact unobserved (Lu (2019)). While the true choice set (i.e., the one pre-selected by the GP) is unobserved, the concept is to set an upper bound and a lower bound of the true choice set. In this study, we defined the lower bound as choices made by other patients around each patient's residential location. The assumption made here is that patients having the same condition, and which are living close to each other are likely to benefit from a similar pre-selected choice set. This assumption relates to the fact that GPs act as agent of patients, but are assumed to have no idiosyncratic taste variations. The bound on choice set can then be turned into a bound on choice probabilities, and the identification of the

bound estimator relies on a moment inequality approach, described in further detail in section 3. Assuming that GPs only intervene in the referral process through the pre-selection of a subset of alternatives, this method allows to elicit patient preferences conditionally on the pre-selected choice set. This study also investigates whether exogenous variation in the density of hospitals around patient's residential locations could lead to heterogeneous patients preferences. Accordingly, hospital attributes which concern patients in the patients choice model are interacted with a variable depicting the geographical disparities between patients in the number of alternatives within a reasonable distance.

This study contributes to the existing literature by building on several aspects. First, we provide evidence on patient preferences for cancer care providers. Indeed, very little is known about patient preferences for cancer care. Cancer is a life-threatening disease that can only be treated by a subgroup of providers which receive approbation from health authorities. Information in this context can be even more asymmetric between patients and hospitals. Cancer treatments often include a chemotherapy treatment, which requires the patient to return for each chemotherapy cycle, and could also decrease the likelihood for patients to bypass their nearest hospital. While patients seem to actively choose their provider for common procedures (e.g. hip and knee replacement), it is not clear whether it is also the case for cancer care. This study is the first empirical study that addresses this topic. We also contribute to the literature addressing the choice set formation, by considering that choice sets are in fact unobserved. Thus, we are able to disentangle the pre-selection process, which might reflect the GPs preferences, from patients' preferences.

Overall, we observe strong variation in the choices made by patients living in a really close area. Results from the benchmark estimation tend to indicate that in comparison with studies investigating patients' referral for more common surgical procedures, patients' referral for breast cancer surgeries seem to attribute more weight to the specialization profile and hospital type rather than to general quality

indicators. When factoring in unobserved choice sets, results show that the hospital specialization profile and distance were internalized in the pre-selection process, while patients rather consider waiting times, general hospital quality indicator and hospital type to make their final choice. We also identify strong inequalities in the patient's freedom of choice resulting from exogenous geographical disparities in provider density. This affect prevents patients from having alternatives within a reasonable distance to categorize hospitals based on their quality.

The remaining part of this paper is structured as follows: section 2 describes the data, section 3 describes the empirical strategy, section 4 presents the results, section 5 provides a discussion of the results and concludes.

4.2 Data

We used three data-sets in order to get detailed information on patient characteristics, and hospital attributes. We identified patients treated for breast cancer in France by using hospital discharge data from the PMSI, managed by the government agency named the *Agence Technique de l'Information sur l'Hospitalisation* (ATIH). The PMSI is an exhaustive, nationwide database for recording information about each hospital stay in France (Boudemaghe and Belhadj (2017)). The inclusion criteria were being diagnosed for breast cancer, surgically treated in a hospital in mainland France in 2017, and living in mainland France. More details about the inclusion criteria are provided in appendix A. Each patient's, information included the FINESS hospital number where the surgeries were performed (i.e. a unique identifier of hospitals in France), the exact location of hospitals, the residential location of patients (i.e. at the municipality level), the patient's length of stay at hospital, and the age of the patient. We also computed straight-line distance in kilometers between patients' residential municipalities and exact location of all hospitals in mainland France. The comprehensiveness of the data allows us to compute the geographical availability of providers for each patient, as the number of available hospitals (i.e., having an authorization to treat cancer) within 50-kilometer radius using the distances patient-hospital.

We included information from the French Hospital Survey (SAE), managed by the Directorate for Research Studies Evaluation and Statistics (DREES), in order to get detailed attributes of hospitals in which breast cancer patients were cared for (DREES (2017)). We included information about the type of hospital (i.e., public, private for profit, private not for profit), the degree of specialization in oncology (i.e., proportion of oncology cases relative to the total activity), and waiting times (i.e., bed occupation rate). Our measure of hospital quality is the accreditation level assigned by the French Authority for Health (HAS) (French National Authority for Health (2018); Keribin et al. (2018)). The accreditation level is decomposed in four levels: without recommendations (A), with recommendations (B), with reservations (C), conditional accreditation (D). Naturally, the accreditation process is informative about a rather general dimension² of the hospitals' quality, which is certainly not the most relevant one for cancer care. For example, the degree of specialization might be more important for patient outcomes in cancer care (Yen et al. (2017)). Still, the accreditation level is one of the few quality indicators that are easily accessible by patients online, so are likely to be taken into account during decision process.

To get information on hospitals amenities, we matched our data with the "e-Satis" survey of patients satisfactory managed by the HAS (Gloanec et al. (2018)). We used the score to relate to how patients rated their room during their hospital stay (i.e., room rate), that is computed by the HAS over all respondent regardless of their disease and adjusted for patient's health status.

4.3 Methods

Using the random utility framework, one can describe patient i indirect utility from choosing hospital j as (Marschak (1974); McFadden (1974)):

$$u_{ij} = \Theta_{ij} + \Gamma_{ij} + \epsilon_{ij} \quad \forall j \in J^a \subseteq J$$

²Under the current procedure (i.e., V2014), accreditation levels are determined based on a range of indicators such as the evaluation of clinical practices policy, quality & security improvement program, risk management, patient needs, pain management, patient file follow-up, drug management, end of life, infectious risk, complaints, operating room, etc.

Where Θ_{ij} represents the observed attributes of the utility, including the distance between patients and hospitals (measured as a continuous variable as well as a dummy indicating whether the hospital is the closest to a patient's residential location), hospital amenities (i.e., patient room rate), hospital quality (i.e., accreditation level), type of hospital (i.e., public, private for profit or private not for profit), degree of hospital specialization and waiting times (i.e., bed occupational rates). Γ_{ij} is the unobserved attributes to the econometrician (but still considered by patients) such as hospital quality (unobserved part), personal experience or feedback from social networks ; ϵ_{ij} is an idiosyncratic shock representing taste heterogeneity ; J^a is the choice set pre-selected by the GP (i.e., true choice set), and finally, J is the full choice set. We allow for heterogeneity in patient preferences on distance according to their age and length of stay (i.e., proxy for the severity of the disease) via interactions terms. Heterogeneous preferences regarding hospital quality and amenities according to the geographical availability of providers (i.e., number of hospitals within 50 kilometers around patient's residential location) is also allowed through interaction terms. While being an exogenous constraint on patient choice, the number of alternatives available within a reasonable distance could lead to heterogeneous preferences. Note that geographical availability of providers is discretized as a dummy indicating 1 if the number of available hospitals is over the median and zero otherwise, due to the bi-modal distribution of that variable. We also allowed for unobserved heterogeneity in patient preferences through random coefficients for preferences on waiting times, degree of specialization, and type of hospital. We allowed for random coefficients only for attributes that were not already interacting with a individual characteristics to contain the number of parameters to be estimated.

Mixed Logit model, also called Random Coefficient Logit model, has become the standard approach to model hospital choice (McFadden D and Train K (2000)). In fact, any Random utility model can be approximated by a Mixed Logit model with the appropriate econometric specification. The key feature of such models is to allow for different preferences by patients through random parameters that vary among patients. However, the problem of estimating such a model is that the true choice set (J^a) is unobserved. Indeed, while we observe the full choice set (J), the

pre-selected choice sets (J^a) that GPs present to patients are naturally unobserved. As a benchmark, we estimate parameters of the random utility model using a Mixed Logit model by assuming that J^a corresponds to all hospitals within 160 kilometers around a patient's residential location. We excluded providers located further away in order to avoid the most irrelevant alternatives³. By assuming a fixed and observed choice set, the Mixed Logit model considers the GPs and patients as a single decision maker in the sense that it ignores the role of the GPs to pre-select a subset of alternatives. The aim of this benchmark estimation is to identify factors (i.e., hospital attributes) playing a role in the referral of patients to hospitals.

Nevertheless, to disentangle patient preference, it is necessary to estimate the probability of patients choice based on their pre-selected choice set. There are different ways of dealing with unobserved choice sets in the existing literature. The same issue has been reported in marketing science studies, where products change rapidly in markets which make the assumption of full information unreliable (Goeree (2008); Mehta et al. (2003)). The decision process of a consumer in a large supermarket is similar to the decision process of a patient choosing a hospital, in the sense that consumers do not fully consider all of the available products when they have to make a choice, but rather consider a subset of alternatives (i.e. the one they are familiar with). To address this issue, marketing science studies have proposed different ways of modeling the process of choice set formation. To compensate for the the fact that we do not observe the true choice set, these studies model all possible choice sets and estimate a conditional choice probability on each of these choice sets. Then, the unconditional choice probability corresponds to the sum of each conditional choice probability times the probability that the choice set is the true choice set.

$$P(d_{ij} = 1|X_{ij}) = \sum_{I \in \mathcal{I}} P(d_{ij} = 1|X_{ij}, CS_i) \times P(CS_i = I)$$

³This restriction excludes 850 patients (i.e., 1.49% of the sample) that were treated in a hospital located at more than 160 kilometers from their residential location. These extreme values on distance might reflect a wrong postal code in the data, or patients having several residential locations, and are thus excluded from the estimation.

Where d_{ij} is equal to one if patient i chooses hospital j ; X_i are the explanatory variables ; CS_i is the true choice set ; I is one possible choice set⁴. Note that $d_{ij} = 1 \Leftrightarrow u_{ij} = \operatorname{argmax}_{k \in I} \{u_{ik}\}$. Subsequently, different methods have been proposed to model the probability that a choice set is the true choice set (i.e. $P(CS_i = I)$). While these methods are suitable when the number of alternatives is reasonable, they become computationally expensive with high numbers of alternatives since they require integration over the distribution of unobserved choice sets in the estimation process.

Instead of modeling the consideration set formation, a recent study proposed an alternative method to consider unobserved choice sets (Lu (2019)). The basic idea is to directly restrict the distribution support of consideration sets by using bounds on choice sets. The main assumption is that each consumer's true choice set (CS_i) is bounded by an upper (CS_i^{sup}) and a lower (CS_i^{sub}) bound, such that $CS_i^{sub} \subseteq CS_i \subseteq CS_i^{sup} \subseteq J$. Assuming that the assumption holds, one can transform bounds on choice sets into bounds on choice probabilities.

$$\underline{P}_{ij}(X_{ij}, \theta_0) \leq P(d_{ij} = 1 | X_{ij}) \leq \bar{P}_{ij}(X_{ij}, \theta_0) \quad (1)$$

Where $\bar{P}_{ij}(X_{ij}, \theta_0)$ is the choice probability in the lower bound, $P(d_{ij} = 1 | X_{ij})$ is the choice probability in the true choice set, $\underline{P}_{ij}(X_{ij}, \theta_0)$ is the choice probability in the upper bound, and θ_0 collectively represent the true parameters in the random utility model . The key to the transformation is a monotonicity property induced by the utility maximization in the random utility framework. The monotonicity property implies that if an alternative h is chosen from a choice set I , and h is also an element of the subset $I^{sub} \subseteq I$, then h must be chosen from I^{sub} . In other words, if an alternative is chosen by a patient in the larger choice set, the same patient will choose the same alternative in the smaller choice set. Based on this monotonicity property, one can then derive the bounds of choice probabilities on equation (1), since the probability of choosing the alternative h in a larger choice set is inevitably lower compared to the probability of choosing h in a smaller choice set. The parameters θ are then estimated

⁴ I corresponds to a combination of all alternatives (i.e., hospitals) that forms a possible choice set. If J is the number of alternatives, there is 2^J possible combination of alternatives, and thus 2^J possible choice sets I .

using a moment inequalities approach, where point identification is achieved based on two pairs of quantities. The first pair measures the change in probabilities at each bound when the parameter θ deviate from θ_0 :

$$\begin{aligned} R_{ij}^{sup}(\theta; \theta_0) &= \underline{P}_{ij}(X_{ij}, \theta) - \underline{P}_{ij}(X_{ij}, \theta_0) \\ R_{ij}^{sub}(\theta; \theta_0) &= \bar{P}_{ij}(X_{ij}, \theta_0) - \bar{P}_{ij}(X_{ij}, \theta) \end{aligned}$$

The second pair measures the location of the true choice probability between the probabilities at each bound:

$$\begin{aligned} \Delta_{ij}^{sup}(\theta_0) &= P(d_{ij} = 1|X_{ij}) - \underline{P}_{ij}(X_{ij}, \theta_0) \\ \Delta_{ij}^{sub}(\theta_0) &= \bar{P}_{ij}(X_{ij}, \theta_0) - P(d_{ij} = 1|X_{ij}) \end{aligned}$$

Then, θ_0 is point identified if there exists some j such that when θ deviate from θ_0 :

$$P(R_{ij}^{sup}(\theta; \theta_0) > \Delta_{ij}^{sup}(\theta_0) \text{ or } R_{ij}^{sub}(\theta; \theta_0) > \Delta_{ij}^{sub}(\theta_0)) > 0$$

Note that $R_{ij}^{sup}(\theta; \theta_0) > \Delta_{ij}^{sup}(\theta_0)$ implies that $\underline{P}_{ij}(X_{ij}, \theta) > P(d_{ij} = 1|X_{ij})$, and $R_{ij}^{sub}(\theta; \theta_0) > \Delta_{ij}^{sub}(\theta_0)$ implies that $\bar{P}_{ij}(X_{ij}, \theta) < P(d_{ij} = 1|X_{ij})$. Thus, the model is point identified if there exist some j such that the inequalities in probabilities in equation (1) is violated for a positive share of patients when θ deviate from their true value θ_0 . In other words, the identification relies on the concept that some patients will have their true choice set relatively close to the bounds, such that the moment inequality will be violated when θ deviate from their true value θ_0 . The estimation of the system of conditional moment inequalities is detailed elsewhere (Lu (2019)). The standard errors are obtained by bootstrap re-sampling (Efron (1979)).

This method requires setting up an upper and lower bound on choice set. The upper bound could be defined as the whole market, which is in our case all hospitals that have treated at least one patient (i.e. that has been chosen at least by one patient). To limit the number of choices, we restricted our sample to hospitals in a radius of 160 kilometers around each patient as the upper bound. The aim of this restriction is to avoid the most irrelevant alternatives, in the sense that they are located at more than 160 kilometers from patient's home, and to ease the computation of the moment inequality estimator that could become computationally expensive

with large data sets. The lower bound is more difficult to define, and important for identification. We defined the lower bound for a patient i as hospitals chosen by others patients living in a radius of 15 kilometers around their residential location, excluding their own choice. The assumption made here is that patients with the same condition, and whom are living close to each other, are likely to benefit from a similar pre-selected choice set. This assumption relates to the fact that GPs act as agents of patients, but are assumed to have no idiosyncratic taste variations. If this assumption holds, two patients with the same condition living in the same area should make their choice based on a similar pre-selected choice set, whether or not they were referred by the same GP. Then, if the number of patients living close to each other is sufficient, and there is some variation in the preferred hospital based on the same pre-selected choice set, taking choices made by other patients is an informative lower bound of the true choice set. Note that patients own choices would be part of CS_i^{sub} as long as at least another patient within 15 kilometers chooses the same hospital. The aim of this restriction is to avoid choice-based sampling (e.g., where patient own choice is included in CS_i^{sub} by definition), which could cause identification failure.

4.4 Results

4.4.1 Descriptive statistics

We identified 57,151 patients who were surgically treated for breast cancer in mainland France in 2017, and cared for in 511 hospitals. The final sample used in this study fell down to 33,101 patients, treated in 232 hospitals, due to missing data on the patient room rate. Indeed, the participation of hospitals to the patient's satisfactory survey "e-Satis" is not mandatory for all providers. This attrition means that patients treated in hospitals for which the patients room rate is missing are excluded from the sample, and thus that these hospitals are also excluded from the bounds on choice sets in the bound estimator for other patients in the sample. Nevertheless, the comprehensiveness of the initial data set based on all observations still allows us to compute the geographical density of providers around patients residential locations, and then to restrict our sample to non-missing data. To maintain consistency in the

analysis the following descriptive statistics are computed for the restricted sample with no missing data.

TABLE 4.1: Descriptive statistics on patients characteristics and hospitals attributes

	Mean	Std	Min	Max
Patients characteristics (n=33,101)				
Distance	26.36	29.85	0.09	159.89
Age	61.50	13.44	15	102
Geographical avail. of providers	18.76	25.79	1	95
Closest hospital	21.72%			
Type of hospital				
- Public	1.06%			
- Private for profit	58.8%			
- Private not for profit	40.14%			
Hospitals attributes (n=232)				
Room rate	73.27	4.62	59.05	85.64
Share of hospital stay in oncology	43.11	34.85	2.81	100
Bed occupational rate	58.80	30.43	18.19	297.21
Hospital accreditation level				
- A	42.67%			
- B	40.09%			
- C or D	17.24%			
Type of hospital				
- Public	1.30%			
- Private for profit	80.17%			
- Private not for profit	18.53%			

Note: Standard deviation (std) ; Score relating how patients rated their room during their hospital stay from the "e-Satis" survey (Room rate) ; Geographical availability of providers (Geographical avail. of providers). The accreditation level is decomposed in four levels: without recommendations (A), with recommendations (B), with reservations (C), conditional accreditation (D).

Table 4.1 describes patient characteristics and hospital attributes in 2017 of our sample for breast cancer treatment in France. Patients had to travel an average of 26 kilometers to their chosen hospital (Appendix B provides more details about the distribution of distances). There is wide variation in the specialization profile of hospitals, with an average of 43% in hospital stay in oncology per hospital, from a minimum of 3% to a maximum of 100%. The average bed occupation rate was 59%, with wide variation between hospitals from a minimum of 18% to a maximum

of 297%⁵. Regarding our quality indicator, among the 232 hospitals in our sample, 42% had the highest accreditation level, 40% the intermediate level (i.e., B) and 17% had a rather low accreditation level. A strong majority of hospitals in our sample are private for profit (i.e., 80%), while 19% are private not for profit and only 1% are public hospitals. However, when considering the market share of each hospital (the number of patients treated by each hospital type), it is interesting to see that the relative weight of each hospital type differs significantly. Indeed, among patients, 59% are treated in private for profit hospitals, 40% in private not for profit hospitals and 1% in public hospitals. On this aspect, public hospitals are underrepresented in our sample due to missing data on the patient's room rate. While we only observe 1% of patients treated in public hospitals in our sample, this share reaches 28.96% in the initial data set based on all observations. Yet, the market share by hospital types are still consistently ordered, with private for profit hospitals having a higher market share (40.22%), followed by private not for profit hospitals, (30.82%) and lastly by public hospitals.

TABLE 4.2: Share of patients (%) having at least h hospitals available in a radius of k kilometer

	h=1	h=2	h=3	h=4	h=5
k=10	60.7	46.8	34.9	27.6	23.1
k=20	82.4	68.5	51.9	40.6	35.1
k=30	93.4	84.3	69.2	55.4	47.4
k=40	97.9	92.8	84.9	72.7	63
k=50	99.3	97.2	93.9	86.9	78.7

Note: number of hospitals available (h); radius in kilometer (k).

Table 4.2 gives an insight into the number of providers around patient's residential locations. Patients seem to have the opportunity to make decisions about their preferred provider among several alternatives within a reasonable distance. Indeed, half (46.8%) of the patients had at least two alternatives within 10 kilometers, and 55.4% had at least 4 alternatives within 30 kilometers. Almost all patients (97.2%) had at least two alternatives within a radius of 50 kilometers.

⁵The bed occupation rate can actually exceed 100%, since it is computed for bed in surgery department only. Thus, a rate exceeding 100% indicates that a positive share of patients in surgery have used beds from other departments due to a congestion in the surgery unit.

To further illustrate the opportunity of alternatives for breast cancer patients seeking a provider for a surgical procedure, Figure 4.1 displays the cumulative density of the geographical availability of providers defined as the number of hospitals within 50 kilometer radius. There is an observable wide variation in geographical availability of providers among patients living in mainland France, which relates to strong inequalities in access to care induced by the allocation of patients and hospitals in the territory. The average number of hospitals available is 18.76 hospitals within 50 kilometers, with a median of 9, a minimum of 1 and a maximum of 95 hospitals in a given area. The plateau in the geographical availability of providers cumulative density is due to the bi-modal distribution of that variable (i.e., Appendix C displays the histogram of the geographical availability of providers, which also highlights the bi-modal distribution).

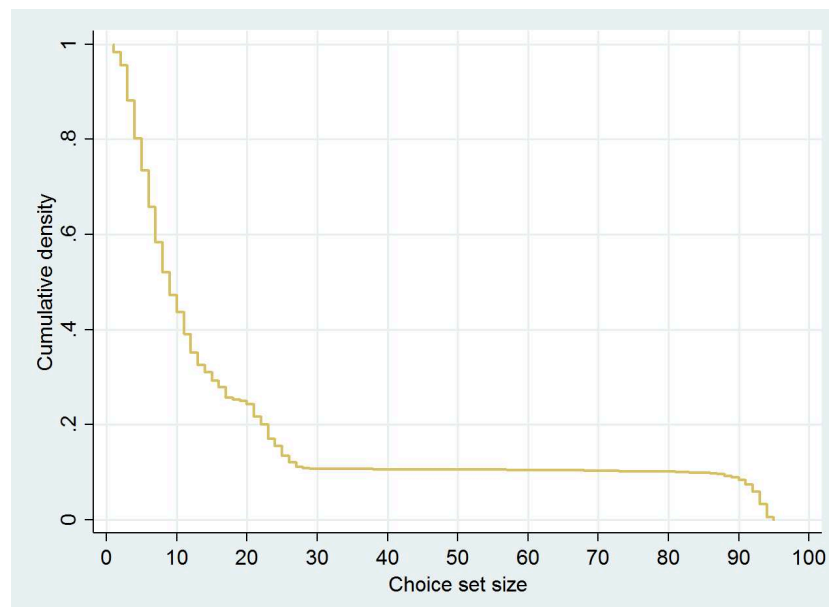


FIGURE 4.1: Cumulative density of patients geographical availability of providers

The fact that patients seem to have the opportunity of making a choice, in the sense that more than one hospital is located within a reasonable distance, does not necessarily imply that they would bypass their nearest provider. Table 4.3 displays the distribution of patients that chose their i^{th} closest provider. Note that only 26.05% of all patients chose to be treated in their closest hospital. From a descriptive point

of view, this thereby demonstrates that patients are making a choice among available providers, since they often bypass their nearest provider. Strikingly, the share of patients choosing their closest provider varies by patient age, length of stay, and geographical availability of providers. Indeed, the share of patients choosing their closest provider varied by age from 22.7% for the 1st quartile (i.e., younger patients) to 30.51% for the 4th quartile (i.e., older patients). Conversely, the share decreases with the geographical availability of providers quartile, from 35.48% for the 1st quartile (i.e., lower degree of freedom of choice) to 19.03% for the 4th quartile (i.e., higher degree of freedom of choice). From a descriptive point of view, this illustrates that older patients tended to be more distance-averse compared to younger patients and patients that had a higher degree of freedom of choice (i.e., a larger choice set) tended to bypass their nearest hospital more often.

TABLE 4.3: Share of patients (%) choosing the i^{th} closest hospital

	Hospital's rank in distance									
	i=1	i=2	i=3	i=4	i=5	i=6	i=7	i=8	i=9	i=10+
Age ($p < 0.001$)										
- Q1	22.77	16.93	11.64	7.24	5.25	4.46	2.98	2.35	1.92	24.46
- Q2	24.36	18.50	11.60	6.87	5.29	4.10	2.90	2.27	2.15	21.94
- Q3	26.00	19.42	12.14	6.88	5.10	4.07	2.62	2.50	1.92	19.35
- Q4	30.51	20.80	12.16	6.84	4.51	3.89	2.76	2.14	1.56	14.82
Geographical availability of providers ($p < 0.001$)										
- Q1	35.48	21.82	10.21	3.21	2.12	3.02	2.28	2.48	1.54	17.83
- Q2	30.24	22.50	15.30	7.76	4.76	3.22	2.05	1.16	0.68	12.32
- Q3	20.87	18.97	13.80	8.95	8.23	6.33	3.49	3.06	2.53	13.76
- Q4	19.03	13.09	7.46	7.22	4.44	3.80	3.32	2.67	2.81	36.15
Length of stay ($p < 0.001$)										
- Q1	22.33	16.97	11.68	7.53	6.05	5.11	2.85	2.56	2.11	22.81
- Q2	28.12	19.22	11.76	7.17	4.57	4.26	2.77	2.10	1.78	18.25
- Q3	26.19	28.33	11.57	6.83	4.42	3.47	3.10	2.36	1.93	21.80
- Q4	28.13	20.86	12.31	6.49	4.73	3.67	2.62	2.17	1.71	17.31
Total	26.05	18.97	11.90	6.96	5.02	4.12	2.81	2.31	1.88	19.98

Note: First, second, third and fourth quartile are respectively indicated as Q1, Q2, Q3 and Q4. Chi Square test of independence are perform for each patients characteristics. The total is computed for for our sample of 31,101 patients.

In the econometric specification of the bound estimator, we defined the lower bound of patient choice set as hospitals chosen by others patients living in a radius

of 15 kilometers within their residential location, excluding their own choice. Thus, only patients that have a lower bound choice set including at least two hospitals, and for which their observed choice is included in the lower bound choice set will contribute to the identification of the bound estimator⁶. Figure 4.2 displays the distribution of the lower bound choice set size. Wide variations in the distribution are present, which relates to either a variability in the density of patients within 15 kilometers of a patient, or variability in the choices made by patients living in the same area. The distribution varied from a minimum of 0 hospitals to a maximum of 41 hospitals, with a median of 5 hospitals included in the lower bound choice set. The rich variations tend to support that the definition of our lower bound is indeed informative to bound the true choice set. Among the 31,101 patients in our sample, 3,486 (11.21%) patients had less than two hospitals in their lower bound choice set. Among patients that had at least two hospitals in their lower bound choice set, 2,655 (8.97%) did not have their observed choice included in the set. Overall, among the 31,101 patients in our sample, 26,680 (86.69%) patients contribute to the identification of the parameters. In accordance, the distribution of the Upper bound choice set size is provided in appendix D (Figure 4.5).

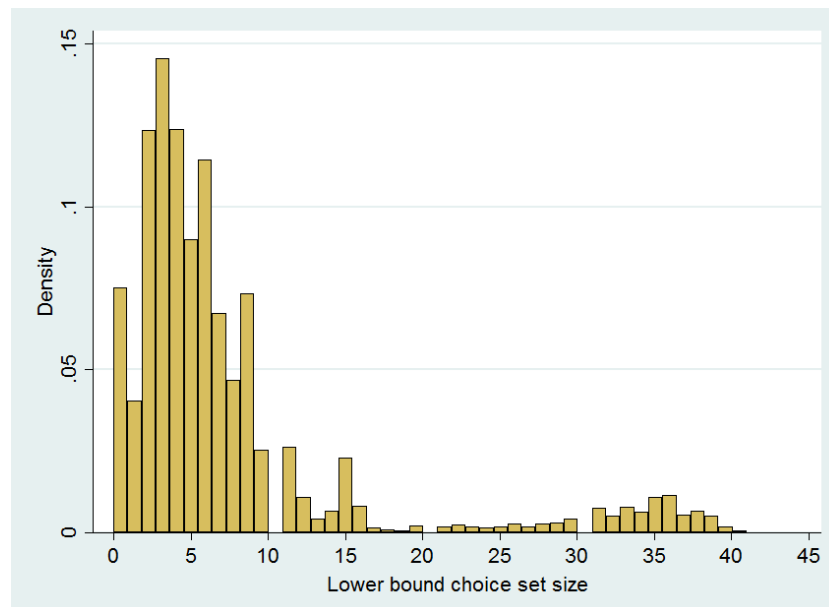


FIGURE 4.2: Histogram of the lower bound of patients choice set size in our identification strategy

⁶Otherwise one cannot compute the probability of hospital choice in the lower bound choice set.

4.4.2 Econometric results

Using a random coefficient Logit model and assuming that patients and their GPs act as one single decision maker, it is observed that the relative location of hospitals play an important role in the decision process (Table 4.4). Patients are indeed more likely to be treated in their closest hospital ($p < 0.001$), and in a hospital closer to their residential location ($p < 0.001$). We also identify heterogeneous effects of distance according to patients age and length of stay. The negative impact of distance tends to be stronger for older patients ($p < 0.001$) and the most severely ill patients ($p < 0.001$).

Patients could have preferences for hospitals that make efforts create an homely atmosphere and that provide a feeling of comfort. In our specification, this dimension of hospital amenities is assessed by the patient room rate, with a higher rate indicating a more comfortable room. Interestingly, patients with a lower geographical availability of providers⁷ tend to be referred more often to hospitals with highly comfortable rooms ($p < 0.001$), while having a larger choice set attenuates this effect ($p < 0.001$) such that a Wald test indicates that these patients are less likely to be referred to a hospital highly ranked for its room quality ($p < 0.001$).

We find mixed and heterogeneous results on the accreditation level, according to the exogenous constraint of patient's geographical availability of providers. Indeed, patients living in municipalities with less than 9 hospitals within 50 kilometers, and thus having limited options, are not more likely to be treated in a higher quality hospital. They are even more likely to be referred to a moderate (i.e. accreditation level B) ($p < 0.001$) or low quality (i.e. accreditation level C or D) ($p < 0.001$) hospital compared to a high quality hospital (i.e. accreditation level A)⁸. Interestingly, having a larger choice set (i.e., more than 9 hospitals within 50 kilometers) significantly

⁷While being continuous, the geographical availability of providers has been discretized as a dummy variable indicating 1 for a number of hospitals above the median (i.e., 9 hospitals within 50 kilometers), and 0 otherwise.

⁸A Wald test of equality between the coefficient associated to level B and level C of accreditation indicate that we cannot reject the null hypothesis of equality of the two coefficients ($p = 0.2271$). In other words, patients with limited options are both equally likely to be referred to a hospital with an accreditation level of B or C.

reduces the differences in the likelihood of a hospital to be chosen based on accreditation level B ($p < 0.001$) and C ($p = 0.001$), compared to level A. Nevertheless, a Wald test indicates that patients with a larger choice set are still overall less likely to be treated in hospitals with the highest accreditation level (i.e., accreditation level A) compared to a hospital with accreditation level B ($p < 0.001$) or accreditation level C or D ($p < 0.001$).

In our sample, breast cancer patients are also found to be more likely to be treated in a private not for profit hospital compared to a private for profit hospital (i.e., a Wald test of equality between the coefficient associated to private for profit and private not for profit hospitals indicate that we can reject the null hypothesis of equality of the two coefficients ($p < 0.0001$)). While preferences regarding private not for profit hospitals tend to be homogeneous ($p = 0.650$), we identify unobserved heterogeneity in preferences regarding private for profit hospitals ($p < 0.001$). The specialization profile as well as waiting times (i.e., bed occupation rate) also tends to be taken into account during the referral process, with a higher likelihood for a hospital to be chosen associated with more specialized hospitals ($p < 0.001$) and with less waiting times ($p < 0.001$). Note that while preferences regarding the specialization profile tend to be homogeneous ($p = 0.650$), we identify unobserved heterogeneity in preferences regarding waiting times ($p < 0.001$).

To assess robustness, we estimated the random coefficient Logit model on the full sample without missing data by excluding patients room rate which induced the missing values (see Appendix E.) While this robustness check does not completely waive the risk of selection bias, it supports the fact that patient preferences included in our sample (Table 4.4) are consistent with those of patients and hospitals in the full sample (Table 4.5). For example, patients are still more likely to be treated in a private not for profit hospital compared to a private for profit hospital.

TABLE 4.4: Parameter estimates from the Mixed Logit model, and of the bound estimator

	Mixed Logit		Bound estimator	
	Coef.	std coef.	Coef.	std coef.
Closest	0.8372***		-2.648	
Distance	-0.0419***		-0.0886	
Age x Distance	-0.0006***		0.0001	
Length of stay x Distance	-0.0012***		-0.0044***	
Patient room rate	0.0318***		-0.1182***	
Patient room rate x Geographical avail.	-0.0406***		-0.146***	
Hospital accreditation level				
- A	Ref		Ref	
- B	0.4341***		-1.9594***	
- C or D	0.3784***		0.3947**	
Geographical avail. x Hospital accreditation level				
- Geographical avail. x A	Ref		Ref	
- Geographical avail. x B	-0.3717***		-1.3485***	
- Geographical avail. x C or D	-0.1899***		-0.8613***	
Type of hospital				
- Public	Ref	Ref	Ref	Ref
- Private for profit	0.2495***	6.3252***	0.8931**	1.1646**
- Private not for profit	0.6667***	-0.0888	0.5193***	0.2066***
Share of hospital stay in oncology	2.1956***	0.7319	4.2555	-2.3541***
Bed occupational rate	-0.0028***	-0.0075***	-0.0150***	-0.0212***
# patients	33,101		33,101	
# observations	986,012		986,012	
Log-Likelihood	-52,124.912		n.a.	

Note: number of (#) ; modality in reference (Ref) ; significant at 1%, 5%, and 10% is indicated as ***, ** and * respectively ; not applicable (n.a.) ; coefficient (coef.) ; standard deviation of coefficient (std coef.) ; geographical availability of providers (Geographical avail.).

When solely assessing patient preferences in the bound estimator approach, the distance from patients to hospitals is no longer assuming an important role in the decision making process ($p = 0.2599$, Table 4.4). Indeed, distance seems to be considered during the pre-selection process, but not during the final patient's choice. Conversely, most severely ill patients still tend to prefer closer hospitals ($p < 0.0001$). We found no heterogeneity in preferences for distance according to patients age. Thus, the heterogeneity according to patients age underlined in the Mixed Logit seems unrelated to variation to distance aversion, but is actually a factor taken into account during the pre-selection process.

Patient preferences for the accreditation level identified by the bound estimator differ substantially from the results of the Mixed Logit where the pre-selection process is ignored. In the bound estimator, we identify a strong heterogeneity in patient preferences for high quality hospitals according to their geographical availability of providers. Patients having a restricted choice set (i.e., less than 9 hospitals within 50 kilometers) tend to prefer hospitals with accreditation level A compared to accreditation level B ($p = 0.0002$). Nonetheless, they often choose hospital with accreditation level C compared to level A ($p = 0.0110$). Interestingly, patients with a larger choice set (i.e., more than 9 hospitals within 50 kilometers), tend to put more weight on the quality of hospitals, such that they often choose higher quality care hospitals compared to lower quality care hospitals.

Contrary to the Mixed Logit results, we found with the bound estimator that patients tend to prefer private for profit hospitals compared to private not for profit hospitals (i.e., testing the linear constraint of equality between the coefficient associated to private for profit and private not for profit hospitals indicates that we can reject the null hypothesis of equality of the two coefficients ($p < 0.0001$)). Note that we also identify strong unobserved heterogeneity in patient preferences regarding the type of hospital.

While the degree of specialization played an important role in patient referral, and with no unobserved heterogeneity, our findings indicate no impact on the likelihood of patients choice conditionally on their pre-selected choice set. Nevertheless, note that we identify unobserved heterogeneity associated with this factor. Waiting times are also playing an important role in patients preferences ($p < 0.0001$), and were also found to determine patients referral.

4.5 Discussion

In this study, we investigate the extent to which patients are actively choosing their provider for breast cancer care, and investigate patient preferences, considering that choice sets are in fact unobserved. Descriptively, patients seem to have the

opportunity of choosing between several providers within a reasonable distance, however this is accompanied by an unequal distribution of providers in the country and thus unequal access (Table 4.2, Figure 4.1). An interesting descriptive indicator of the degree of patient choice could be the share of patients bypassing their closest provider. This could be indicative of the portion of patients that choose their provider not only based on their location or for which their GP did so. In our data, three quarters (74%) of patients bypassed their closest provider, and half (43%)⁹ of bypassed the three closest ones (Table 4.3). Interestingly, patients with more providers available near their residential location tend to bypass their closest provider more often. Considering that our population of interest is composed of breast cancer patients that received the same treatment, a remarkable descriptive evidence is that the median size of the lower bound choice set is 5 hospitals, which highlights strong variation in choices made by patients living really close to each other (Figure 4.2).

According to a revealed preferences framework, we exploit these variations in patients' choices to explore the mechanisms underlying the referral process of breast cancer patients. Assuming that patients and their GP act as a single decision maker, we first estimate a Mixed Logit model in order to identify hospital attributes affecting patient referral. Our results underline that patients were more often referred to a closer hospital, to private not for profit hospitals compared to private for profit hospitals, to hospitals more specialized in oncology, and to hospitals with shorter waiting times. Interestingly, patients are not more likely to be referred to hospitals with a higher accreditation level, and are even more likely to be referred to low or moderate accreditation levels when their choice set is constrained by the geographical density of providers around their residential location. In comparison with studies investigating patient referral for more common surgical procedures, patient referral for breast cancer surgeries seems to attribute more weight to the specialization profile and to hospital type rather than to general quality indicators such as hospital accreditation (Beckert and Kelly (2016); Gravelle et al. (2012); Victoor et al. (2012);

⁹By summing the first three column in the line total of Table 4.3 we obtained: $26.05 + 18.97 + 11.9 = 56.92\%$ patients treated in their closest, second closest or third closest hospital. In other words, $100 - 56.92 = 43.08\%$ bypassed their three closest providers.

Gaynor et al. (2016); Moscelli et al. (2016); Beckert et al. (2012)).

When considering unobserved choice sets by setting an upper and lower bound, our findings substantially differ from those of the Mixed Logit. In the bound estimator on the pre-selected choice set, patients are more likely to choose a hospital with a higher accreditation level if they benefited from a larger panel of hospitals around their residential location. Yet, this association disappears when patient choice is constrained by the number of available providers within a reasonable distance. Regarding hospital type, patients tend to prefer private for-profit hospitals compared to private not for profit hospitals, and lastly public hospitals. While our results underline a significant preference for shorter waiting times, we found no effect for the specialization profile. As stated before, the specialization profile might be more directly associated with patient outcomes compared to the accreditation level in the case of breast cancer surgeries (Yen et al. (2017)). Nevertheless, our results suggest that patients rely on rather general quality indicators such as the accreditation level for more common procedures, while the specialization profile tends to be internalized in the pre-selection process. Regarding hospital type, patients are more likely to be channeled to a private not for profit hospital compared to a private for profit hospital when considering the full choice set (i.e., Mixed Logit), while they conditionally prefer private for profit hospitals compared to private not for profit hospitals on their pre-selected choice set (i.e., bound estimator). This opposite result on hospital types depending on the choice set considered demonstrates the importance of considering unobserved choice set in the referral process. One possible explanation could be that GPs, as agents of health authorities, often tend to pre-select private not for profit hospitals compared to private for profit hospitals, while patients tend to prefer private for profit during the final stage of the decision process.

Our empirical strategy to disentangle patient preferences from the pre-selection of alternatives relies in part on the assumption that the role of GPs during the referral process is restricted to the pre-selection of a subset of providers during the first stage. If this assumption was violated, then the preferences identified conditionally on the pre-selected choice set could still be a combination of GPs and patient

preferences. Nevertheless, we are confident about the validity of this assumption in the French setting, where the patient's freedom of choice is at the core of the health system, and where GPs already have the opportunity to give more or less freedom to their patients in the decision process through the size of the pre-selected choice sets. Another potential limitation is that we lack information on the patient's room rate for some providers, which could lead to a risk of selection bias of the sample used in this study. This could lead to a potential issue of selection if the missing patients in the sample have different preferences compared to patients included in the sample. This attrition in the sample could also impact on patient choice sets, either in the random coefficient Logit or in the bound estimator. Hospitals dropped because of missing data were also removed from the choice sets (i.e., full, lower and upper bound choice sets), while these hospitals might have been considered in the decision process. This could thus restrict patient choice sets. However, the results of the random coefficient Logit model on the full sample, estimated by excluding the regressor creating missing values, are globally consistent with the results based on the sample with missing values (Table 4.5 in appendix E). In this study, we computed the geographical availability of providers as hospitals within 50 kilometers, the lower bound choice set as choices made by other patients within 15 kilometers and the upper bound choice set as hospitals within 160 kilometers. Unfortunately, it was not possible to perform a sensitivity analysis on these radius parameters because of the computation time of the bound estimator.

Overall, our findings substantiate the importance of considering choice sets when assessing patient preferences. The pattern through which unobserved choice sets influence our results might reflect the central role of GPs in the referral process. Regardless of the disease, the existing literature on the agency problem in patient referral process is scarce. While several studies have investigated patient referral by treating the GP and patient as a single decision maker, there are to the best of our knowledge, only two studies that examined unobserved choice sets in the identification of patient preferences, and both investigated the UK health system (Beckert (2018); Gaynor et al. (2016)). The institutional setting in the UK for patient referral differs in many aspects from the French one. First of all, GPs have to propose at least

five alternatives of providers to patients during the referral process, thanks to the 2006 reform in the UK. Gaynor et al exploited the natural experiment given by the 2006 reform and showed that after the reform, patients were treated in higher quality hospitals than they would have been prior to the reform (Gaynor et al. (2016)). Before 2006, choices were also restricted in the UK because GPs had strong incentives to refer patients to hospitals with which the local Primary Care Trust (PCT) had a contract with. After the reform, contracts were abolished, but PCTs were given a fixed budget for the cost of care for the local population. In this context, W. Beckert investigated whether GPs internalize these costs and consider the opportunity cost of referring a patients for other patients within the same PCT (Beckert (2018)). They found that GPs responded to indirect financial incentives in the referral process, which shed light on a potential conflict of interest. They showed that GPs act as imperfect agents of patients, and that patients defer the decision to their GP when it comes to hospital quality, and instead based their choice on tangible attributes such as distance, waiting times, and hospital amenities. In France, while GPs are assumed to pre-select a subset of providers including several alternatives, they are not mandated to do so. Therefore, on these grounds the French institutional setting is similar to the UK setting before the 2006 reform. In France, however, the payment scheme is such that GPs have no financial incentives during the referral process. It is not clear whether patient choice is fully restricted as was in the UK before the 2006 reform, or whether GPs act as an imperfect agent for patients as after the 2006 UK reform. Our findings extend those from Beckert by providing evidence to suggest that unobserved choice sets are also playing an important role in the French institutional setting, which might suggest that GPs act as an imperfect agent for patients even in the absence of financial incentives. GPs might also have non-financial incentives such as their reputation with patients, consultants, and, health administrators, whom also lead to a misalignment of incentives. Moreover, our findings provide novel evidence that patients are indeed participating in the referral process for cancer care in the French institutional setting (i.e., when GPs are not constrained during their pre-selection of providers but when they are also not mandated to pre-select several alternatives). Breast cancer patients consider several hospital attributes other than distance to sort providers pre-selected by their GP. Assuming that unobserved

choice sets are completely due to the GPs pre-selection process, and that GPs intervene only at this stage of the referral process, one possible interpretation of our findings could be that patients defer to their GPs when it comes to hospital specialization profiles, rather considering waiting times, hospital quality (i.e., for patients having a large choice set only) and hospital type to make their choice. Nevertheless, we also identify strong inequalities in patient's freedom of choice induced by the geographical availability of providers, which prevents patients from having sufficient alternatives within a reasonable distance to choose from hospitals based on their quality. In our study, hospital amenities as measured by patient room rate is not found to drive patient preferences. The distance to hospitals is also found to be completely excluded from patient preferences, except for the most severely ill patients. Thus, only the most severely ill patients are found to be distance averse, with a clear preference for closer hospitals. Hospitals are potentially pre-selected by the GPs based on their relative location, and then chosen by patients based on their attributes and types.

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Appendix A. Inclusion criteria

The PMSI database records information about all patients treated in a hospital in France, for all diseases or procedures. To identify our population of interest, we first included patients based on the World Health Organization (WHO) International Classification of Disease (ICD-10). The inclusion criteria were having an ICD-10 diagnosis code C50 (i.e. malignant neoplasm of breast). Among these patients, we excluded patients not surgically treated in order to focus our analysis on first line treatment choices. To do this, we used the complete list of Common Classification of Medical Acts (CCAM) codes published in a report of the French National Cancer Institute corresponding to a surgical act for breast cancer (French Cancer Institute (2013)).

Appendix B. Distribution of distances patients - hospitals

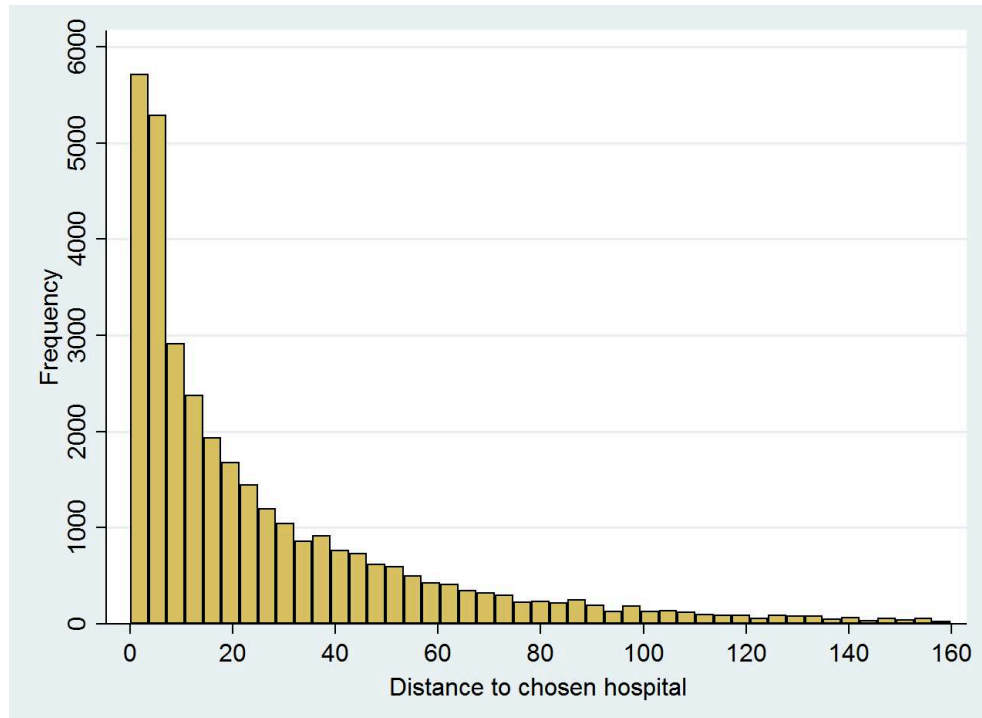


FIGURE 4.3: Distribution of distances patients-hospitals

Appendix C. Multi-modal distribution of geographical availability of providers

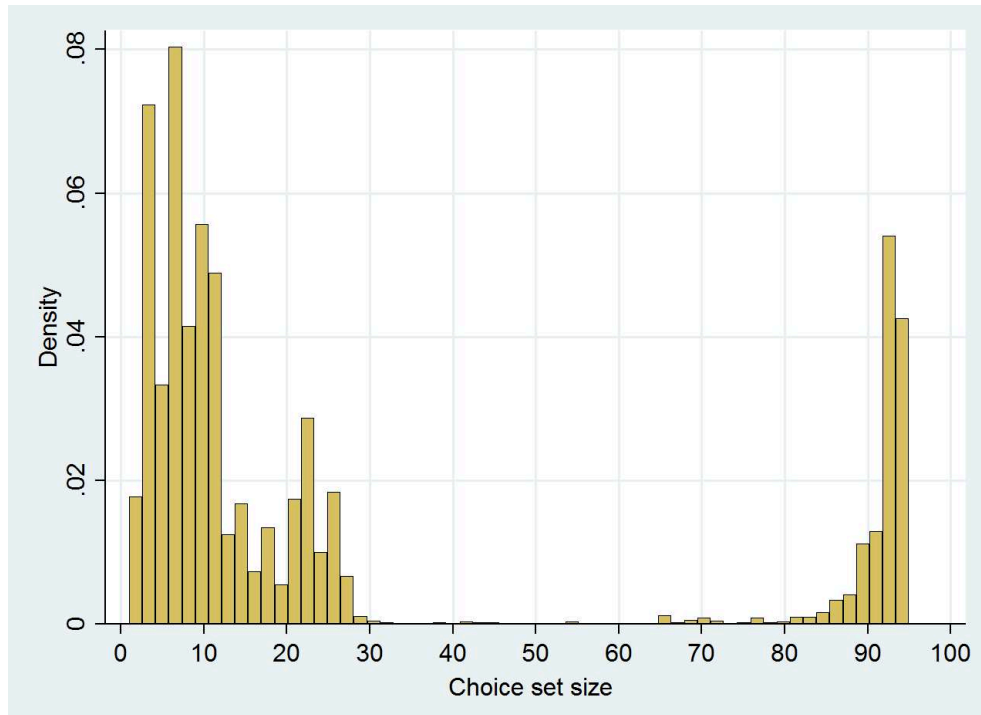


FIGURE 4.4: Histogram of patients geographical availability of providers

Appendix D. Histogram of the upper bound of patients choice set size

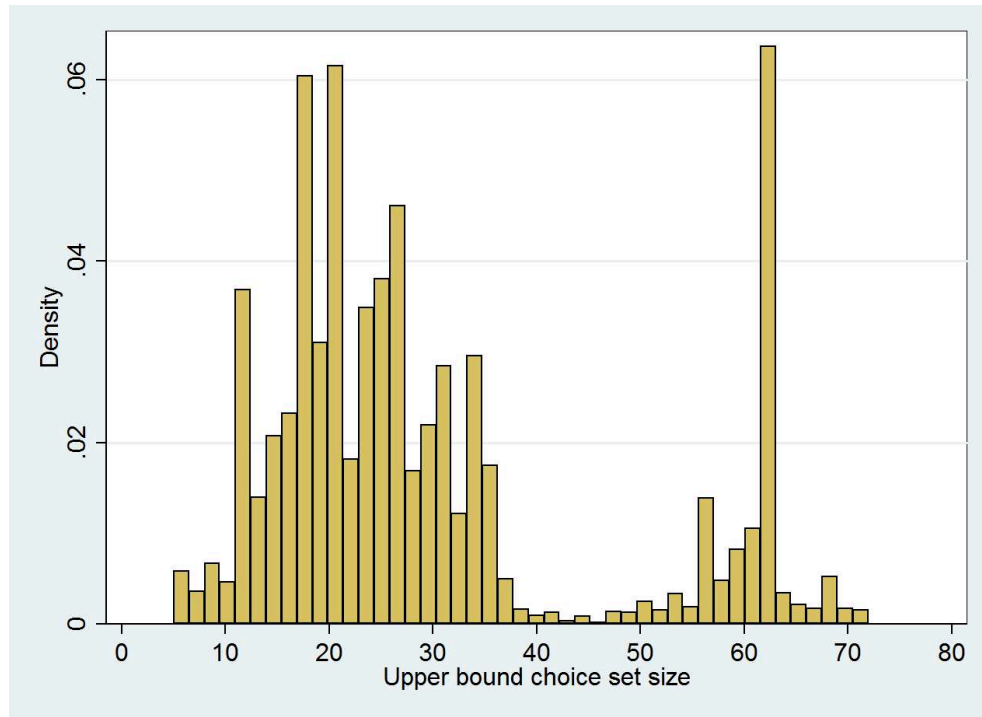


FIGURE 4.5: Histogram of the upper bound of patients choice set size, relating the number of providers within 160 kilometers

Appendix E. Benchmark estimation in the full sample without missing data

TABLE 4.5: Parameter estimates from the Mixed Logit model in the full sample without missing data, thus excluding the parameters on patients room rate

	Mixed Logit	
	Coef.	std coef.
Closest	0.6747***	
Distance	-0.0459***	
Age x Distance	-0.0005***	
Length of stay x Distance	-0.0004***	
Hospital accreditation level		
- A	Ref	
- B	0.1955***	
- C or D	0.0027	
Geographical avail. x Hospital accreditation level		
- Geographical avail. x A	Ref	
- Geographical avail. x B	-0.0169	
- Geographical avail. x C or D	-0.2829***	
Type of hospital		
- Public	Ref	Ref
- Private for profit	0.2387***	-2.8933***
- Private not for profit	0.3117***	5.8149***
Share of hospital stay in oncology	2.0512***	-0.6056***
Bed occupational rate	-0.0026***	-0.0023***
# patients	57,151	
# observations	3,860,303	
Log-Likelihood	-117,631.29	

Note: number of (#) ; modality in reference (Ref) ; significant at 1%, 5%, and 10% is indicated as ***, ** and * respectively ; coefficient (coef.) ; standard deviation of coefficient (std coef.) ; geographical availability of providers (Geographical avail.).

General Conclusion

This PhD dissertation contributes to the existing scientific literature on several aspects. Firstly, while the literature on the volume-outcome relationship for ovarian cancer care identified this relationship mostly in the US, our results provide evidence of such a relationship in the French health system for the first time. Despite the fact that the French National Cancer Institute set a minimum volume threshold of 20 surgeries for treatment of gynecological cancers in 2007, we still observe very low volume of activity for ovarian cancer care by a substantial proportion of providers. We draw attention to the need for a specific threshold for ovarian cancer in order to achieve a centralization of care for this condition, since care was still strongly decentralized under the implementation of the 2007 threshold, with a majority of patients treated in rather low volume hospitals. The sensitivity of our results to the volume-threshold also substantiated that the volume threshold must be strict enough in order to improve patients' outcomes significantly. Furthermore, our findings clearly indicate that the volume-outcome relationship is effective for both early and advanced stages, while most studies to date focused on advanced stage ovarian cancer patients.

Secondly, this thesis provides evidence that clinicians decisions play an important role in the causal impact of hospital volume on patient's outcomes for disease with multiple treatment options. While the literature digging into what underlies this relationship is scarce, this is the first study to evaluate what proportion of the volume-outcome relationship could be induced by variations in clinician's decision on which treatment path to follow. In terms of policy making, this could have major implications, offering new possibilities to design volume-based policies, such as by cooperation between high- and low-volume providers for making treatment decisions. Note that a centralization of care, where patients would all be treated in high

volume hospitals, is still the organization of care leading to the highest improvement in quality, in comparison with the current organization (i.e., decentralized care) and to one in which treatment decisions in low-volume hospitals could be coordinated by higher-volume providers. Nevertheless, the centralization of care also raises the issue of the inequalities in access to specialized care for patients.

Thirdly, this thesis brings new evidence on the plausible adverse consequences of volume-based policies, which are of primary interest for policy-making in order to have a complete picture of the impact of centralized of care. Our findings indicate that the burden of the policy might be spatially and socioeconomically unequally distributed, in such a way that strict application of these thresholds may be unsustainable in terms of patient access. To the best of our knowledge, only three studies have dealt with this topic, and none in the context of the French healthcare system. While other studies in the existing literature ignored patients' preferences for a particular provider in the evaluation of a centralization of care, and assumed that patients would chose to be treated in their closest available hospital post-centralization, we took into account patients preferences in our evaluation strategy. Our findings tend to support the notion that ignoring patients' preferences in the evaluation of a centralization of care on patients access leads to a drastic underestimation of the impact of centralization on patients' access to care. Thus, policy makers should pay particular attention to patients' preferences to evaluate the plausible deterioration in patients' access caused by centralization of care. Our contribution also lies in the analysis of spatial and socioeconomic inequalities in access caused by such policies. Analyzing the average impact on patients access of centralization of care, one might conclude that the effect would be strong but sustainable. However it becomes clear that a strict application of such a reform might be unsustainable when looking at how the burden is distributed spatially and socioeconomically. Apart from the issue of the inequalities in access, it is also of primary interest to better understand the referral process of patients to hospitals for specialized care, as it strongly determines hospitals' sustainability and volume activities.

Lastly, this PhD dissertation also contributes to the literature by providing evidence on patients' provider preferences for breast cancer surgeries, taking into account that choice sets are in fact unobserved. While it has been shown in the literature that patients seem to actively choose their provider for common procedures, it was not clear whether this is also the case for cancer care. The highly asymmetric information between patients and hospitals, and the fact that cancer is a life-threatening disease could constrain patients' choice. Regardless of the disease considered, this is also the first study to investigate patients' preferences in the French institutional setting using a revealed preferences framework. More importantly, this research contributes to the literature addressing the choice set formation, by taking into account that choice sets are in fact unobserved. While the true choice set is unobserved, we relied on a moment inequalities approach by bounding the true/unobserved choice set in order to approximate the probability of hospital choice conditionally on the true choice set. For specialized care, unobserved choice sets could be related to the role of GPs in the referral process. While several studies have investigated patients' referrals by assuming a fixed and observed choice set, and thus treated the GP and the patient as a single decision maker, the existing literature on the agency problem or on unobserved choice sets in patients referral is scarce. Our findings suggest that breast cancer patients do consider several hospital attributes other than distance to rank providers pre-selected by their GP. Our findings also substantiate the necessity to take into account unobserved choice sets, and support the notion that the distance and the hospital specialization profile might be internalized during the choice set formation (e.g., GPs pre-selection), while patients rather consider waiting times, hospital quality (i.e., for patients having a large choice set only) and hospital type to make their final decision.

This PhD dissertation also has several potential limitations. Firstly, an obvious limitation is the relatively small size of the samples used in chapters 1 and 2, which is due to the disease characteristics and to the geographical area covered. It would be interesting to replicate these studies on an exhaustive cohort of patients at the national level. There is also some uncertainty regarding the external validity of the

findings to other diseases and/or other countries. Indeed, in chapter 1 and chapter 2, we study the case of ovarian cancer care. It is likely that for other diseases sharing some common aspects with ovarian cancer (i.e., multiple treatment options, complex surgical act), the variations in clinician decisions and in quality of care according to hospitals volume activities might also apply. However, our results are not generalized outside of ovarian cancer care, and thus cannot necessarily be applied. While results from the third chapter are based on a nationwide data set, they might be less generalized to other countries since they strongly depend on the initial location of patients and hospitals within the territory. In comparison, results from chapter 4 are more generalized to other countries, at least for health systems sharing some common aspects with the French one (e.g., administrated price, two stages referral process). However, in the sample used in chapter 4, public hospitals might be underrepresented due to their participation rate in the patients' satisfactory survey "e-Satis". From a broader perspective, this PhD dissertation lacks information on clinicians and GPs. It would have been interesting to investigate whether the way the volume activity of a hospital is allocated among the clinicians could also lead to residual variations in quality of care or clinicians' treatment choices. In the same way, having information on GPs would have been interesting in order to formally elicit their preferences for the pre-selection of providers during the referral process of a patient for specialized care.

In summary, this PhD dissertation provides evidence supporting the notion that centralization of care is the organization of care that would maximize patient outcomes, but that a strict application of a volume threshold would be unsustainable in terms of patients' access to care. Where do we go from here? To make the centralization of care sustainable, policy makers will have to find solutions to reduce its impact on patients' access to care. To that end, the introduction of minimum volume thresholds could be associated with a policy of assistance and financial support for patients' transportation. In France, transportation costs are reimbursed up to 65%¹⁰ by the social security system only in cases that a patient's condition prevents them

¹⁰Source: French Nation Health Insurance (<https://www.ameli.fr/assure/remboursements/rembourse/frais-transport/frais-transport>).

from taking public or private transport. If care were centralized through the introduction of minimum volume thresholds, patient transportation would need to be fully reimbursed by the social security system in order not to financially penalize the poorer patients, who are already penalized through a higher likelihood of being affected by this kind of policy. Naturally, an increase in the rate of transportation cost reimbursement combined with longer distances to travel for a substantial proportion of the population would be costly for the social security system. In addition to transportation costs, policy makers could also choose a lower volume threshold in order to lessen the deterioration of patients' access. However, choosing a lower volume threshold would naturally lead to a lower degree of centralization of care, which would in turn impede the improvement in quality of care. Overall, choosing a lower volume threshold does not solve the issue of patients access to care, but rather reflects the degree of deterioration in access deemed acceptable in the trade-off between increasing patient outcomes and declining accessibility. Instead of choosing a lower volume threshold, an alternative option to reduce the deterioration in patients access could be to let the threshold vary between areas (e.g., departments, regions) according to the anticipated post-centralization density of hospitals within the area. Indeed, what makes a strict application of minimum volume threshold unsustainable for breast and ovarian cancer care in France is that a national threshold would be implemented for the entire territory, while patients and hospitals are not uniformly distributed within the country. Therefore, decision-makers could design several volume thresholds, specific to more rural and remote areas. It is important to note, however, that by allowing the threshold to vary within a country will, by definition, lead to a varying degree of centralization, which could consequently lead to a varying level of quality of care. Another perspective for volume-based policy-making could be to enhance cooperation between high and low volume providers. In this thesis, we showed that the expertise of high-volume providers in making treatment decisions plays an important role in the causal impact of hospital volume on patients' outcomes for ovarian cancer care. Therefore, policy makers could incentivize clinicians in high-volume hospitals to cooperate and help clinicians in low-volume hospitals to make complex treatment decisions. Nevertheless, our results are not generalized to other diseases, and there is therefore a need for future

research on other complex diseases with multiple treatment options. In terms of policy making, it should be noted that this would require changing or adapting the activity-based payment scheme in France, in order to allow for more cooperation between providers. From a broader perspective, instead of reforming the supply side of the market in order to withdraw the lowest volume providers, one could conceive the centralization of care as a goal to be reached from the demand side of the market. From this perspective, a less interventionist policy compared to the application of minimum volume thresholds could be to intervene on the referral process of patients to hospital, in order to reduce the share of referrals to the lowest volume providers. This type of intervention shares some attributes with the solution discussed earlier that consists of allowing for a heterogeneous volume threshold according to the geographical spread of high volume providers. Indeed, by reducing the barriers in access to high volume providers as a way to centralize care, patients and GPs would be given the opportunity to decide whether using a high volume provider is conceivable based on the relative location of high and low volume providers close to their homes. By giving the choice to patients, this allows the degree of centralization of care to be tailored to the levels of patients' distance aversion, and to take into account the heterogeneity of patients preferences.

However, from the decision-maker point of view, what can be done to increase the share of referrals to high volume providers? The referral process of patients to hospitals is a complex decision process involving multiple stakeholders, especially for specialized care. Studies in the literature have substantiated the central role of GPs in the referral of patients to hospitals for specialized care, which act as patients' agent in the decision process (Beckert (2018); Gaynor et al. (2016)). In this thesis, we underline the importance of taking into account unobserved choice sets to elicit patients' preferences for specialized care in France, which could also be related to the role of GPs in the referral process. Nevertheless, GPs and patients are not the only stakeholders likely to play a role in the referral process. Hospitals could also have some influence and/or display strategic behavior. For example, hospital's ownership of a physician has indeed been shown to increase the probability that the physician's patients will choose the owning hospital (Baker et al. (2016)). Depending on

the institutional setting, such as in the US, GPs decisions might also be influenced by insurers through direct financial incentives. It has been shown in the context of women giving birth in California that the trade-off faced by GPs between quality, price and patient preferences was indeed influenced by the capitation rates which incentivize GPs to lower costs (Ho and Pakes (2014)). Likewise, in the case of public insurance such as the Medicare program in the US, the variation between hospitals in reimbursement per hospital stay, and therefore the variation in spending, also raise the question of whether higher spending indeed increases patient outcomes or whether it is unnecessary because of moral hazard concerns. Taking patient selection into account, a study on Medicare beneficiaries provides evidence underlining a negative association between spending and mortality (Doyle et al. (2015)). Overall, more research needs to be done at the hospital level, since they might also be an important stakeholder in the referral process. Note that their role might strongly vary according to each national institutional setting. While we looked at the demand side of the market in this thesis, we did not explore the strategic behavior from the offer side (i.e., hospitals). For example, a crucial question that still remain is whether hospitals are indeed competing for patients, and whether they compete on quality in health systems where price are administrated. Indeed, evidence on non-price competition between hospitals are mixed (Moscelli et al. (2018); Longo et al. (2017); Lewis and Pflum (2017); Brekke et al. (2008)). Further research on this topic would be of primary interest to have a better understanding of whether hospitals are passive in the referral process, or whether they are part of strategic behavior by stakeholders.

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