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Association between hospital volume and outcomes in invasive ovarian cancer in Belgium: A population-based study

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ABSTRACT

Objectives: To study the association between hospital volume and outcomes in patients with invasive epithelial ovarian cancer (EOC).
Methods: This study included 3988 patients diagnosed with invasive EOC between 2014 and 2018, selected from the population-based database of the Belgian Cancer Registry (BCR), and coupled with health insurance and vital status data. The associations between hospital volume and observed survival since diagnosis were assessed with Cox proportional hazard models, while volume associations with 30-day post-operative mortality and complicated recovery were evaluated using logistic regression models.
Results: Treatment for EOC was very dispersed with half of the 100 centres treating fewer than six patients per year. The median survival of patients treated in centres with the highest-volume quartile was 2.5 years longer than in those with the lowest-volume quartile (4.2 years versus 1.7 years). When taking the case-mix of hospitals into account, patients treated in the lowest volume centres had a 47% higher hazard to die than patients treated in the highest volume centres (HR: 1.47, 95% CI: 1.11–1.93, p = 0.006) over the first five years after incidence. A similar association was found when focussing on the surgical volume of the hospitals and considering only operated patients with invasive EOC. Lastly, the 30-day post-operative mortality decreased significantly with increasing surgical volume.
Conclusions: The large dispersion of care and expertise within Belgium and the volume-outcome associations observed in this study support the implementation of the concentration of care for patients with invasive EOC in reference centres.

1. Introduction

Ovarian cancer has a poor prognosis associated with diagnosis at an advanced stage, which earned it the nickname of the “silent killer” [2]. In 2020, 808 new cases of invasive ovarian cancer were diagnosed in Belgium, with a World standardized incidence rate of 6.6/100 000 person years [3]. The 5-year relative survival proportion for people diagnosed in 2016–2020 was 45.6% (95% CI [43.3–47.8]), with the poorest survival observed for women 70 years and older (30.2% [26.9–33.5]) [3].

While the relation between volume and outcomes has been demonstrated for several cancer types in Belgium [4–8], the Belgian Health Care Knowledge Centre (KCE) recommended in 2014 to halt the high dispersion of care for patients with rare or complex cancers [9], by addressing them to reference centres, with a sufficient number of patients treated per year to maintain a high level of expertise. Such

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centralisation has been successfully implemented in several surrounding countries [10–15], demonstrating the benefit of treating ovarian cancer patients in high-volume specialised centres [15–24]. However, patients with ovarian cancer can still be treated in any acute care hospital in Belgium, without a required minimal caseload for hospitals or surgeons.

The aim of this study was to evaluate the association between hospital volume and outcomes in patients diagnosed with invasive epithelial ovarian cancer (EOC) between 2014 and 2018, in Belgium.

2. Material and methods

2.1. Data sources

The main data source was the Belgian Cancer Registry (BCR) database, which was linked with health insurance data obtained via the Intermutualistic Agency (IMA) [25] and vital status data obtained via the Crossroads Bank for Social Security, based on the National Number for Social Security. IMA data up to June 30, 2020 were used and the vital status was followed until December 1, 2021.

2.2. Study cohort

A total of 5934 tumours of the ovary, fallopian tube and primary peritoneum, invasive and borderline, newly diagnosed in 2014–2018 were identified in the BCR database. From this cohort, there were 4148 patients with an invasive EOC according to the RARECARENet definition of Epithelial Tumours of Ovary and Fallopian Tube ICD-O-3 topography and morphology codes (http://rarecarenet.istitutotumori.mi.it/). Patients with no link with the health insurance data, the same incidence date as the date of death, multiple invasive ovarian tumours registered during the study period, and those not assigned to a main (treatment) centre were excluded from the final study cohort (Appendix A).

2.3. Hospital allocation

Because not all patients are treated in one hospital, an algorithm had to be developed so that every patient could be assigned to the hospital that is estimated to have the highest impact on the outcome for the patient. Assigning the patient to one hospital was either done based on the centre of main treatment or the centre of main surgery.

Overall, 82.0% of patients received all treatments given (surgery and/or chemotherapy) in one centre; hence that centre was selected as 'centre of main treatment'. For patients who received surgery and (neo-) adjuvant chemotherapy in different centres (8.8%), the centre of surgery was selected as the centre of main treatment. As no oncological treatment was considered a valid treatment decision, patients without an oncological treatment (8.4%) were assigned to the centre of the oncological care program which reported the tumour to the BCR, if only one reported the case. Less than 1% of patients could not be assigned to a hospital.

When a patient underwent more than one surgical intervention in different hospitals, an allocation algorithm allowed to assign the patient to the hospital where the main surgery was performed [1]. In total, a centre of main surgery was defined for 99.5% of all operated patients.

The accuracy of the hospital allocation algorithm and the methodology used to identify diagnostic and therapeutic procedures were validated in eight Belgian hospitals. Overall, 99% of patients were correctly allocated to their main (treatment) centre.

2.4. Hospital volume

The treatment volume of each hospital was calculated as the number of newly diagnosed invasive EOC patients in the period 2014–2018 who received their main treatment in that particular hospital.

For the surgical volume only one surgical procedure (the main surgery) per patient was counted. Prior or additional surgeries or procedures for a recurrence were thus not taken into account.

2.5. Statistical analyses

The Kaplan–Meier method was used to estimate the overall survival probabilities [26]. The associations between observed survival after diagnosis and hospital main treatment volume and surgical volume, treated as a categorical (using the quartiles) and continuous variable, were assessed with Cox proportional hazard models. A plot of the Martingale residuals of the model containing all adjustment variables versus hospital volume was inspected to decide on the functional form of volume as a continuous predictor. Linear or piecewise linear associations, consisting of two intervals and both linear sections joined at the knot, versus volume were used. For the piecewise linear model, the knot giving the lowest Akaike Information Criterion was selected. The analyses were adjusted for potential confounders (i.e., age at diagnosis, anatomic site, WHO performance status, diabetes, cardiovascular comorbidity, respiratory comorbidity, inpatient bed days during year prior to incidence date, tumour stage, histological type (high-grade serous vs other), and presence of multiple tumours in 2004–2018) by adding them as covariates in the models. Potential interactions with volume were tested. Additionally, the clustering of patients into hospitals was accounted for by adding hospital as a random term to the model.

The 30-day post-operative mortality was calculated as the ratio of the patients who died within 30 days and the number of patients alive at time zero. Patients censored within the specified time interval were not considered in the denominator. The day of surgery was used as time zero. The association between hospital surgical volume and post-operative mortality was evaluated using logistic regression models adjusted for the same potential confounders using both a categorical (based on the quartiles) and continuous volume variable. Similarly, a plot of the deviance residuals of the model was used to construct the model and hospital was added as a random term to the logistic regression model.

The association between hospital surgical volume and 30-day post-operative complicated recovery was assessed using logistic regression models adjusted for the same covariates. Complicated recovery was defined as a hospitalisation for more than 30 days after surgery and readmission or death within 30 days after surgery.

Statistical analyses were performed with SAS 9.4 (SAS Institute, Cary, NC, USA). Figures were created with R version 4.0.5.

3. Results

3.1. Dispersion of care

Overall, 3988 patients with an invasive epithelial carcinoma of the ovary (87.5%), fallopian tube (8.9%) or peritoneum (3.6%) were included (Table 1).

Patients received their main treatment in 100 different centres. The median volume of a centre was 5.6 patients/year. A quarter of the centres treated fewer than 3 patients/year (Fig. 1a). The centres in the upper volume quartile treated 10 newly diagnosed patients yearly or more.

Surgery for invasive EOC was also very dispersed: 3123 patients were operated in 98 different centres. Half of the centres operated 4 or fewer patients/year and a quarter of the centres operated not more than two patients/year (Fig. 1b). The 25% largest hospitals operated 8 or more patients with invasive ovarian cancer per year. Only 5 hospitals operated more than 20 patients/year.

3.2. Hospital main treatment volume and survival

The 1, 2 and 5 year unadjusted observed survival probabilities increased from 60.1% to 83.2%, 47.0% to 70.6%, and 28.8% to 44.3%, respectively from the lowest to the highest main treatment volume

Table 1
– Patient and tumour characteristics at the time of diagnosis (N = 3988).

	N (%)
Anatomic site	
Ovary	3491 (87.5)
Fallopian tube	355 (8.9)
Primary peritoneum	142 (3.6)
Age at diagnosis (years)	
<50	391 (9.8)
50–59	683 (17.1)
60–69	1043 (26.2)
70–79	1096 (27.5)
80 +	775 (19.4)
WHO performance status	
0 – Asymptomatic	814 (20.4)
1 – Symptomatic but completely ambulatory	2250 (56.4)
2 – Symptomatic, < 50% in bed during the day	380 (9.5)
3 – Symptomatic, > 50% in bed, but not bedbound	115 (2.9)
4 – Bedbound	31 (0.8)
Missing	398 (10.0)
Diabetes	
Absent	3500 (87.8)
Present	488 (12.2)
Cardiovascular comorbidity	
Absent	1985 (49.8)
Present	2003 (50.2)
Respiratory comorbidity	
Absent	3661 (91.8)
Present	327 (8.2)
Previous inpatient bed days	
0–5 days	3241 (81.3)
> 5 days	747 (18.7)
Tumour stage	
I-IIA	846 (21.2)
IIB-IV	2760 (69.2)
Unknown	382 (9.6)
Histological entity	
High grade serous	2299 (57.6)
Other	1689 (42.4)
Multiple tumour (other than EOC)	
No	3521 (88.3)
Yes	467 (11.7)

EOC: epithelial ovarian cancer

quartile. The difference in median observed survival time between Q1 and Q4 was 2.5 years (Table 2). After adjustment, a 31–47% higher hazard to die of any cause in the two lowest volume quartiles was observed compared to the highest (Table 2).

When volume was considered as a continuous variable, the hazard to die of any cause decreased on average with 1.1% per additional patient assigned until a threshold of 9 patients yearly on average (≤9 patients: HR, 0.989; 95% CI, 0.984–0.993; p < 0.0001 vs. >9 patients: HR, 1.000; 95% CI, 0.999–1.001; p = 0.83, Fig. 2a).

3.3. Hospital surgical volume and survival

The unadjusted observed survival probabilities per surgical volume quartile show that the 1 and 2 year survival probabilities were 11% points higher in the highest hospital volume quartile compared to the lowest (91.6% vs. 80.1% for the 1-year survival and 79.4% vs. 68.1% for the 2-year survival). This difference was smaller at the 5-year survival time (Table 2).

Similar to what was shown with main treatment volume, results indicated a significant increased hazard to die of any cause in the lowest two hospital volume quartiles compared to the highest volume quartile

Table 2
– 5-year observed survival probabilities, median observed survival and adjusted HRs for observed survival (within 5 years after diagnosis) in patients with invasive epithelial ovarian cancer.

Characteristic	N patients	5-year observed survival (95% CI)	Median observed survival (years)	Adjusted HR (95% CI)*	p-value
Main treatment volume over 5 years					
≥50 patients (Q4)	2351	44.3 (42.2, 46.5)	4.2	1.00	
29–49 patients (Q3)	878	41.6 (38.1, 45.0)	3.5	1.06 (0.91, 1.24)	0.45
15–28 patients (Q2)	536	33.4 (29.3, 37.7)	2.5	1.31 (1.10, 1.56)	0.002
1–14 patients (Q1)	223	28.8 (22.9, 35.0)	1.7	1.47 (1.11, 1.93)	0.006
Surgical volume over 5 years**					
≥42 patients (Q4)	1883	51.8 (49.3, 54.2)	5.3	1.00	
22–41 patients (Q3)	735	52.5 (48.6, 56.3)	5.4	1.01 (0.87, 1.17)	0.91
11–21 patients (Q2)	354	46.8 (41.3, 52.2)	4.3	1.29 (1.08, 1.55)	0.006
1–10 patients (Q1)	151	47.7 (39.2, 55.8)	4.4	1.47 (1.14, 1.89)	0.003

* Adjusted for age at diagnosis, WHO performance status, comorbidities, previous inpatient bed days, histological entity (serous vs. non serous), tumour stage and single versus multiple tumours (i.e., other tumour than ovarian diagnosed from 2004 onwards). * * Patients who did not receive surgery from 1 month before to 9 months after incidence were excluded.

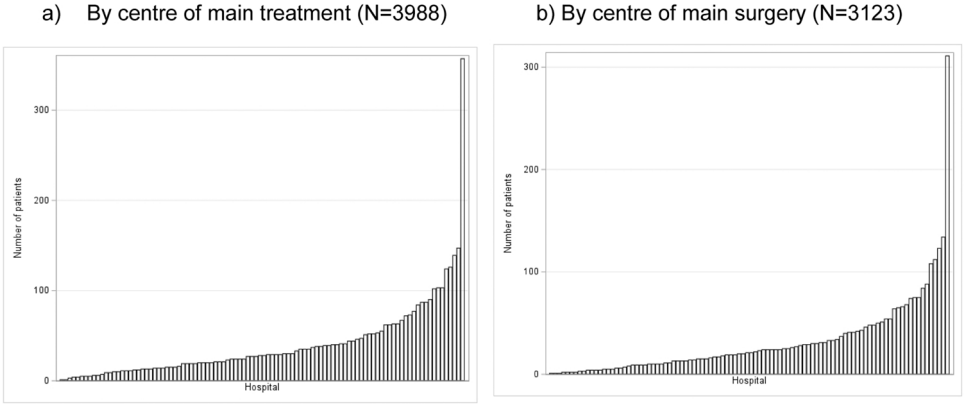

Fig. 1. – Distribution of patients with invasive epithelial ovarian cancer by hospital of main treatment over the 5-year study period.

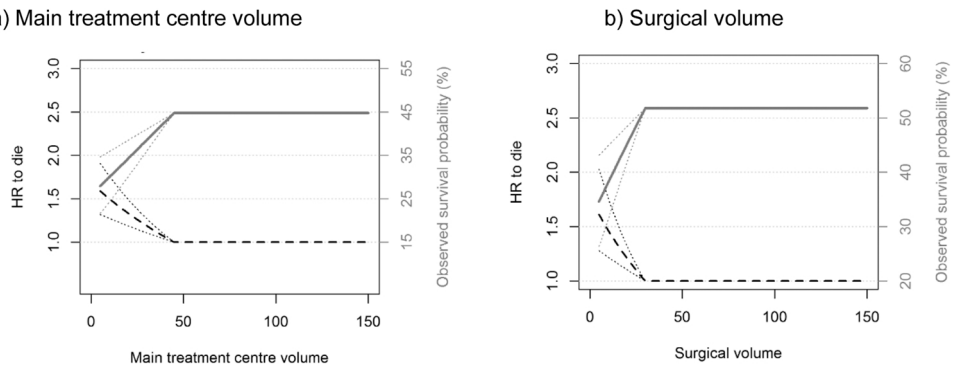

Fig. 2. – Association between hospital volume over the 5-year study period and observed survival at 5 years in patients with invasive epithelial ovarian cancer. Note: Hazard ratio of the association between surgical centre volume and 5 year observed survival is represented by the dashed black line (left axis) and the observed survival probability by the solid grey line (right axis). The hazard ratios are relative to a volume hospital > 30 patients/5 years (or 6 patients/year). The 95% confidence intervals are presented by dotted lines. Over the five year study period, 66 centres operated 6 or even fewer invasive ovarian cancer patients per year.

(Table 2).

When surgical volume was considered as a continuous variable, the hazard to die decreased on average with 1.9% per additionally operated patient ($p < 0.0001$). This volume-effect was observed among centres operating 6 patients or fewer per year (Fig. 2b).

3.4. Hospital surgical volume and mortality

The 30-day postoperative mortality was significantly higher in the lowest quartile compared to the highest quartile (i.e., 8.6%; 95% CI, 4.7–14.3% vs. 1.3%; 95% CI, 0.8–1.9%). After adjusting for case-mix variables, the difference between the two extreme quartiles was confirmed (OR, 4.78; 95% CI, 2.04–11.19; $p = 0.0003$ for Q1 vs Q4). When analysing surgical volume as a continuous variable, the odds to die in the 30 days after surgery decreased with 10.2% per additional operated patient up to a maximum of 4 patients/year (OR, 0.898; 95% CI, 0.849–0.951; $p = 0.0002$).

3.5. Hospital surgical volume and complicated recovery

Among women undergoing surgery for invasive EOC, 16.8% (95% CI, 15.5–18.2%) had a complicated postoperative recovery during the first 30 days after surgery. There was no association with surgical volume (OR, 1.18; 95% CI, 0.75–1.85; $p = 0.48$ for Q1 vs Q4).

4. Discussion

4.1. Hospital volume and outcomes

Our results demonstrated that in our country where half of the hospitals treat less than 6 patients per year, differences in survival probabilities between lower and higher volume centres exist; EOC patients who were treated in higher-volume centres had on average a 31–47% higher chance to survive than those who were treated in lower-volume centres. A positive volume-outcome relationship has already been demonstrated in several studies [15–24], while others did not find such association [27–30]. Some studies based their analyses on the overall number of patients treated annually per hospital [16–19,27,28,31–36], while others rely on the annual surgical volume [10,20–24,30,37–41], or on the annual chemotherapy volume [29,42]. In our study, survival probabilities were also significantly higher for patients operated in higher surgical volume centres.

In addition, several studies have shown a positive effect of the surgeon volume on survival [27,39,43–45], which could not be investigated in this study due to the lack of data at the surgeon level. This might have affected our results (dilution of the effect) if for instance, a surgeon operated patients in different hospitals.

The literature shows a high heterogeneity in the definition of "high-volume" across studies. Based on studies published by Bristow et al., [32,34,38] the minimal requirement of treating (or operating) 20 patients per year was often used as an arbitrary threshold in the literature and guidelines [10,17,19–21,23]. The updated European Society of Gynaecological Oncology (ESGO) guidelines further considered 20 surgeries for advanced stage invasive ovarian cancer performed per year per centre and per surgeon as the minimum required target, while 50 and 100 surgeries per year per centre were put forward as the intermediate and optimal targets, respectively.[46] While the results of our analyses provide strong evidence supporting the concentration of care for OC patients, the volumes achieved in Belgian hospitals are still far below these guidelines and those reported in surrounding countries. Thus, evidence from the literature, experiences from abroad and from clinical experts should be taken into account when defining minimum volumes for reference centres in our country.

A higher hospital volume also gives the possibility to the whole care team (including anaesthesiologists and nurses involved in the perioperative care as well as pathologists) to gain experience [47,48]. The importance of expert perioperative care is reflected in the inverse association between hospital volume and post-operative mortality. Similar to our study, other studies showed that higher-volume hospitals have a lower post-operative mortality, despite having the same level of post-operative complications [21,49]. Furthermore, a higher volume allows for efficient delivery of comprehensive care services necessary in reference centres, including for example a lymphoedema clinic, genetic counselling and advanced palliative care [9].

4.2. Dispersion of care and centralisation

Our results demonstrated a large dispersion of care and of expertise over the Belgian territory. However, centralisation of OC patients has already been implemented in several surrounding countries (e.g. the Netherlands, Sweden, England, Norway, France etc.), and many studies investigated the effect of centralisation and showed an improvement in adherence to guidelines and also in patient-outcomes [10–15].

In some countries such as Norway and England, the recommendations for centralised surgery started already in the nineties, which resulted in an improvement in survival of gynaecological cancer [14]. In the Netherlands, following a national consensus in 2011 and the recommendation of limiting cytoreduction surgery to institutions where a minimum of 20 cytoreductive surgeries are performed yearly, the number of hospitals performing this type of surgery decreased from 90 in 2004 to 34 in 2013, and the average annual caseload per hospital increased from 8 in 2004 to 28 in 2013. Improvements in optimal cytoreduction surgery and in 1-year overall survival probability were also observed [10]. In the western Swedish healthcare region, the

centralisation of surgery for advanced ovarian cancer introduced in 2011 was associated with an increase in complete cytoreduction, a shorter time interval between primary debulking surgery and adjuvant chemotherapy and improved 3-year relative survival [12,13]. In France, following the recommendations of the governmental "Plans Cancers" (2009–2013), in 2014, 41% of the operations with curative intent were performed in centres performing at least 20 operations annually, an increase of 6% from 2011 [50].

For 1131 patients, we found that the hospital where the first diagnostic imaging was performed differed from the main (treatment) centre. This is indicative of either an active referral by the medical team/hospital or a patient decision to seek a second opinion. Furthermore, if some of the smaller centres do not specifically refer their patients to a larger centre, but do discuss the treatment plan of their patients with larger expert centres, this may dilute the observed volume-outcome effect. However, even when adjusted for case-mix, a volume-outcome relationship remained, suggesting that current efforts to refer or discuss patients can still be much improved.

Thus, in line with these examples and with the KCE Report on the organisation of care for adults with a rare or complex cancer [9], this study supports the concentration of care for patients with invasive OC in reference centres. In Belgium, initiatives have been taken in 2019 to concentrate pancreatic and oesophageal surgery. Similar discussions are ongoing (or scheduled) regarding the concentration of care for other types of cancer, i.e. head and neck and ovary. Moreover, specific recommendations were formulated by the KCE experts and a multidisciplinary group of clinical experts in the field to achieve a comprehensive care pathway for ovarian cancer patients and suggesting how care should be organised between reference and peripheral centres [1,9]. For instance, while surgery for invasive ovarian cancer should always be carried out in reference centres, other parts of the care pathway, such as chemotherapy can be carried out in the peripheral centres, in consultation with the reference centre and the patient, as long as comprehensive oncological care and sufficient expertise/staff are available. In addition to volume, there are other important requirements for hospitals to meet in order to qualify as a reference centre (e.g. sufficient specialised staff; required facilities and equipment; specialised multidisciplinary oncological consultations with (para)medical experts with expertise in the management of EOC patients; patient centred care; specific requirements regarding expertise, experience and infrastructure; being involved in clinical research and other scientific activities) [9].

Finally, as part of this quality improvement process, all Belgian hospitals received an individual feedback report, with their hospital results benchmarked with the results of the other (blinded) hospitals. Each hospital can launch an individual initiative to improve the quality of care, drawing on the practices of centres that achieve better results.

4.3. Strengths and limitations

The main strengths of this study are the large coverage of the BCR database (more than 98% of all cancer cases in Belgium) and the validation of the methods in eight Belgian centres, representative of academic vs non-academic hospitals and the regional landscape. The methodology to retrieve diagnostic and therapeutic procedures including the algorithm for hospital allocation were validated to confirm the reliability of data and preliminary results.

While we were able to adjust for a large number of patient and tumour characteristics, several potential confounders could not be considered because they were not available in the database (e.g. residual disease after surgery, socio-economic status). Lastly, patient-reported data, such as quality of life and patient preferences (e.g. to pursue, to delay or to interrupt a treatment), were not available.

5. Conclusion

The current study confirms a positive volume-outcome association for both surgical and hospital treatment volume for patients with invasive EOC in Belgium, supporting the implementation of the centralisation of care for ovarian cancer. Although some patients may already be referred for their treatment, still, many hospitals treat very few patients per year. Based on the experiences from other countries, treating ovarian cancer patients in high-volume specialised centres appears as the best approach to guarantee quality of care and a higher probability to survive.

Author Contributions

All authors contributed to the conception and design of the study; HMP, CDG and GS analysed the data; data interpretation was performed by all authors; IS wrote the first draft of the manuscript. All authors contributed to manuscript revision, read and approved the submitted version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2023.113402.

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