ORIGINAL RESEARCH

Increased hospital case volume is associated with improved survival and quality of care for uterine corpus cancer in Belgium

Joren Vanbraband[a], Nancy Van Damme[b], Geert Silversmit[b], Anke De Geyndt[b], Alejandro Herreros-Pomares[a], Gauthier Bouche[c], Gerd Jacomen[d], Eric de Jonge[e], Frédéric Goffin[f], Hannelore Denys[g], Frédéric Amant[a,h,i,*]

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ABSTRACT

Objective: This study aimed to prospectively evaluate whether hospital case volume is positively associated with both the outcome and the quality of care of uterine corpus cancer in Belgium.

Methods: This was a prospective, observational, registration-based, real-world database study. Hospital case volume was categorized according to the total number of patients treated on average per year: low (<10/y), medium (10-19/y), and high (≥20/y). Adjusting for patient case mix and intra-hospital correlations, logistic and Cox proportional hazards regression were used to test for associations between hospital case volume and a multi-disciplinary set of process and outcome indicators. Sub-group analyses by recurrence risk were performed for overall survival and disease-free survival.

Results: In total, 4178 patients diagnosed with a primary cancer of the uterine corpus between 2012 and 2016 in Belgium were included. Compared with patients treated in high-volume hospitals, patients treated in low-volume hospitals were more likely to die of any cause within 5 years after diagnosis (adjusted hazard ratio 1.37, $p < .01$), as were patients treated in medium-volume hospitals (adjusted hazard ratio 1.18, $p < .05$). Similar results were observed in the sub-group analyses, but only among patients with high-intermediate-risk and high-risk disease. In contrast, hazards for disease-free survival did not differ by hospital case volume, neither in the total study population nor in the sub-group analyses by recurrence risk. Furthermore, analysis of the process indicators showed that patients treated in low- and medium-volume hospitals were less likely to receive multiple guideline-recommended procedures compared with those treated in high-volume hospitals, including minimally invasive surgery, surgical lymph node staging, staging omentectomy, and adjuvant chemotherapy.

Conclusions: On average, increased hospital case volume was positively associated with improved overall survival and quality of care, supporting centralization of uterine corpus cancer care into high-volume reference centers in Belgium.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Retrospective studies have suggested a positive association between hospital case volume and uterine corpus cancer outcomes. However, prospective evidence is lacking, and the mechanisms underlying this association remain largely undetermined.

WHAT THIS STUDY ADDS

This study provides prospective evidence that the outcome of uterine corpus cancer is better when treated in high-volume hospitals, especially for higher-risk and advanced-stage tumors. Furthermore, by taking advantage of our specific data collection to measure quality indicators, this study also shows that this positive volume-outcome relationship may be largely explained by differences in quality of care.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

These findings indicate that care for uterine corpus cancer should be centralized in high-volume reference centers, especially for high-intermediate-risk and high-risk patients.

Keywords:
Uterine Corpus Cancer; Endometrial Cancer; Hospital Case Volume; Patient Outcomes; Quality of Care; Quality Indicators; Hospital Volume-Outcome Relationship

INTRODUCTION

The global burden of uterine corpus cancer has increased dramatically over the past few decades, including a 132% increase in the number of cases and a 63% increase in the number of deaths between 1990 and 2019.[1] Thus, uterine corpus cancer is the most common gynecologic cancer in developed countries. Moreover, despite improvements in treatment and access to health care, the age-standardized mortality rate of uterine corpus cancer has also increased significantly between 1990 and 2019 in 91 countries and regions worldwide.[1] Additionally, a recent database analysis in

* ***Correspondence to*** *Dr Frédéric Amant, Unit of Gynecologic Oncology, Department of Oncology, KU Leuven, Campus Gasthuisberg, ON4 Herestraat 49, Box 1045, 3000 Leuven, Belgium; frederic.amant@uzleuven.be (F. Amant)*

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the United States showed that uterine corpus cancer is the only cancer site for which relative survival has decreased since 1975, demonstrating one of the fastest increases in cancer mortality.[2] While the underlying mechanisms are likely multi-factorial, these deteriorating trends in uterine corpus cancer survival and mortality may be largely attributable to persistent underfunding,[2] as well as ongoing disparities in diagnosis and treatment according to racial, socioeconomic, and hospital-related factors.[3]

To optimize clinical outcomes, it is crucial to have sufficient experience in all aspects of patient care. Hence, using volume of cases as a surrogate for experience, numerous studies have shown that patients with cancer have improved short- and long-term outcomes when they are treated by high-volume providers.[4,5] At the physician level, a higher caseload may translate directly to better clinical judgment and technical proficiency. Furthermore, at the hospital level, it may be associated with a broader range of specialist and technology-based services, better-equipped intensive care units, a better structure and organization of care, and other resources that may be less available in lower-volume hospitals.[4,5]

In the context of uterine corpus cancer, several population-based cohort studies have already provided statistical evidence that treatment of patients by high-volume providers is associated with lower morbidity and mortality, better health care resource utilization, and improved survival.[3,6-9] However, these studies were all retrospective and did not assess explanatory factors. Moreover, other retrospective data were either unable to demonstrate a statistically significant volume-outcome relationship[10,11] or showed mixed results.[12]

Hence, this study aimed to prospectively investigate whether increased hospital case volume is associated with improved survival for uterine corpus cancer in Belgium. Moreover, by taking advantage of our specific data collection to measure a multi-disciplinary set of process indicators, this study also aimed to assess whether such positive volume-outcome association could be largely explained by differences in quality of care.

METHODS

Study Design and Data Sources

This observational, registration-based, real-world database study used multiple data sources: (1) the study-specific EFFECT (EFFectiveness of Endometrial Cancer Treatment) database, a multi-center prospective observational database on uterine corpus cancer in Belgium; (2) the Belgian Cancer Registry (BCR) database, covering cancer registration data on all new cancer diagnoses in Belgium since 2004; (3) the InterMutualistic Agency database, including information on the medical procedures and pharmaceuticals reimbursed to the patient by the Belgian national health insurance; and (4) the Crossroads Bank for Social Security database, used to retrieve the patient's vital status. These data sources were deterministically coupled using the patient's unique national social security number. This study did not require approval from an ethics committee or institutional review board, as detailed in the Ethical Approval section.

The EFFECT Database

The EFFECT database is registration-based and contains clinical, pathologic, and treatment-related data on patients with uterine corpus cancer diagnosed in Belgium between January 2012 and December 2016. Specifically, by use of an online registration module, these data were registered by 60 Belgian hospitals on a prospective and voluntary basis. This was done by trained registration staff who received a study manual including (1) the rationale and objectives of the study; (2) an overview of the inclusion and exclusion criteria; (3) a full description and explanation of the study variables; and (4) detailed instructions on how to collect and register the data (Appendix A). To control data quality, both automated and manual validation procedures were performed to detect and remove errors and inconsistencies, and duplicate and missing information from the EFFECT database.

Quality Indicators

Forty-one quality indicators were used to measure quality of care and patient outcomes, comprising 38 process indicators and 3 outcome indicators.[13] Covering all steps of the care pathway, the process indicators each assessed one specific aspect of uterine corpus cancer treatment and measured quality of care as the percentage of patients receiving guideline-recommended treatment. The outcome indicators included post-operative mortality, observed survival, and disease-free survival. A full description of the quality indicators is included in Appendix B.

Hospital Case Volume

A hospital's case volume was based on the total number of patients who received their main treatment in that particular hospital during the study period 2012-2016. For this purpose, all patients diagnosed with uterine corpus cancer in Belgium in the 2012-2016 period were first retrieved from the BCR database. These patients were then assigned to their hospital of main treatment. In total, 67% of patients were treated in a single hospital, which was therefore designated as their hospital of main treatment. The other 33% were assigned using the following priority rules: hospital of (1) surgery; (2) chemotherapy; (3) radiotherapy; (4) endocrine therapy; (5) multi-disciplinary team meeting; (6) biopsy; or (7) diagnostic imaging. Finally, using the total number of patients treated on average per year, volume was categorized into low ($<$10/y), medium (10-19/y), and high ($\geq$20/y). These thresholds were determined arbitrarily on the basis of expert opinion and the need to have a balanced distribution of hospitals and patients, considering the Belgian context in which many hospitals treat only a low number of patients.

Patient and Tumor Characteristics

The patient and tumor characteristics available for analysis included age, World Health Organization performance status score, American Society of Anesthesiologists pre-operative risk score, co-morbidity index, number of inpatient bed days in the year before diagnosis, multiple tumor status, tumor FIGO (International Federation of Gynecology and Obstetrics) stage (clinical, pathologic, and combined stage), tumor histologic type, and tumor grade. A full description of these variables can be found in Appendix C.

Statistical Analyses

General Modeling Strategy

Process indicators and 90-day post-operative mortality were estimated as binary percentages with 95% confidence intervals (CIs), and survival probabilities were estimated using the Kaplan-

Meier method. To test for associations with hospital case volume, logistic regression was used for the process indicators and 90-day post-operative mortality, while Cox proportional hazards regression was used for observed survival and disease-free survival. Observed survival and disease-free survival were modeled over the 0- to 5-year and 0- to 3-year time period after diagnosis, respectively, with censoring of patients surviving beyond 5.05 years and 3.05 years, respectively. The event for observed survival was death from any cause. The event for disease-free survival was death from any cause or recurrence of uterine corpus cancer, whichever occurred first. Non-proportional hazards between the levels of categorical co-variates were assessed in a univariable manner and resolved using a piecewise proportional hazards model. All non-proportional hazard terms and second-order interactions were added to the Cox model, and non-significant terms were removed through backward elimination. Volume effects were estimated as adjusted odds ratios (aORs) and adjusted hazard ratios (aHRs) with 95% CIs. SAS 9.4 was used for all statistical analyses (SAS Institute). p-Values $<.05$ were considered statistically significant.

Case-Mix Adjustment, Intra-Hospital Correlations and Immortal Time Bias

To adjust for case-mix differences, patient and tumor characteristics were added to the regression models on the basis of clinical relevance and statistical significance (ie, univariable $p < .10$). Furthermore, intra-hospital correlations were taken into account by adding the hospital of main treatment as a random effect term to the models. Finally, immortal time bias was also adjusted for by adding surgery status as a time-varying co-variate to the Cox models.

Model Fit, Model Stability, and Missing Observations

Model fit was assessed using goodness-of-fit statistics and visual inspection of model residuals, including the Hosmer-Lemeshow goodness-of-fit test, the χ^2 test of the Pearson and deviance goodness-of-fit statistics, and the Schoenfeld and generalized Cox-Snell residuals. The presence of large standard errors on the model parameter estimates was used to identify potential model instability. Finally, to prevent over-fitting, we applied the rule of thumb that there should be at least 10 events and non-events available per model parameter. No imputation techniques were used to handle missing data. Instead, missing observations were included in the models as a separate category within their respective variables.

Sub-Group Analyses

Sub-group analyses by recurrence risk were performed for observed survival and disease-free survival. To this end, 3 risk groups were distinguished on the basis of FIGO stage, tumor grade, histologic type, and age (Appendix D).

In accordance with the journal's guidelines, we will provide our data for independent analysis by a team selected by the Editorial Team for the purposes of additional data analysis or for the reproducibility of this study in other centers if such is requested.

RESULTS

A total of 4178 patients with uterine corpus cancer were included in this study. These patients underwent their main treatment in 86 different hospitals: 555 patients were treated in 37 low-volume hospitals, 1402 patients in 29 medium-volume hospitals, and 2221 patients in 20 high-volume hospitals. Multiple patient and tumor characteristics varied significantly with hospital case volume (Appendices E and F).

Observed survival differences were identified according to hospital case volume. More precisely, after case-mix adjustment and compared with patients treated in high-volume hospitals, the hazard of death of any cause within 5 years after diagnosis was 18% higher for patients treated in medium-volume hospitals (aHR 1.18, 95% CI 1.00 to 1.38) and 37% higher for patients treated in low-volume hospitals (aHR 1.37, 95% CI 1.12 to 1.68) (Table 1; Fig. 1). Similar effects were found in the sub-group analyses, but only among high-intermediate-risk and high-risk patients (Table 1; Fig. 1). Finally, by splitting the follow-up period, it was also found that the observed survival benefit in high-volume hospitals was only present during the first 2.5 years after diagnosis. After 2.5 years, hazard estimates were no longer significantly different (Table 1).

Similarly, although case-mix adjustment could not be performed because of a low number of events, 90-day post-operative mortality was higher in low-volume hospitals than in high-volume hospitals (2.1% vs 0.8%, odds ratio 2.66, 95% CI 1.20 to 5.91) (Table S1). In contrast, hazards for 3-year disease-free survival did not differ by hospital case volume, neither in the total study population nor in the sub-group analyses by recurrence risk (Table S2).

Concerning diagnostic workup, a pre-operative biopsy of the primary tumor or metastasis was performed less often in low-volume hospitals than in high-volume hospitals among operated patients with endometrial carcinoma (aOR 0.51, 95% CI 0.29 to 0.92) (Table 2). In contrast, regardless of hospital case volume, $>$95% of all patients were discussed in a multi-disciplinary team meeting, and clinicopathologic risk factors were reported and available for treatment decision in $>$90% of patients, except extra-nodal extension and hormone-receptor status (Table S3).

Regarding surgical treatment and staging, the following procedures were performed less frequently in low-volume hospitals than in high-volume hospitals: (1) minimally invasive surgery (ie, traditional or robotic-assisted laparoscopy) among operated patients with clinical stage I endometrial carcinoma (aOR 0.15, 95% CI 0.05 to 0.50); (2) pelvic lymph node staging with or without para-aortic lymph node staging among patients with clinical stage I, high-grade endometrial carcinoma (aOR 0.40, 95% CI 0.16 to 1.00); and (3) omentectomy among patients with clinical stage I to II serous carcinoma, clear-cell carcinoma, or carcinosarcoma (aOR 0.21, 95% CI 0.06 to 0.72) (Table 2). The latter was also performed less often in medium-volume hospitals (aOR 0.36, 95% CI 0.16 to 0.82) (Table 2). No significant volume-associations were observed for the other indicators (Table S4).

Finally, regarding adjuvant treatment, 3 procedures were less frequently performed in low-volume hospitals than in high-volume hospitals: (1) adjuvant treatment within 60 days after surgery (aOR

Table 1 Five-Year Observed Survival Probabilities and Hazard Ratios by Average Annual Hospital Case Volume.

Average annual hospital case volume	Number of hospitals	Number of patients[a]	Unadjusted 5-year observed survival probability (95% CI)	aHR for 0-5 years after diagnosis (95% CI)[b]	aHR for 0-2.5 years after diagnosis (95% CI)[b]	aHR for 2.5-5 years after diagnosis (95% CI)[b]	Adjusted 5-year observed survival probability (95% CI)[b]
Total study population							
High volume	20	2214	72.7%	1.00	1.00	1.00	72.7%
(≥20 patients)			(70.8% to 74.5%)	(reference)	(reference)	(reference)	(reference)
Medium volume	29	1398	69.8%	1.18 (1.00 to 1.38)	1.19 (0.99 to 1.43)	1.16 (0.91 to 1.47)	68.7%
(10-19 patients)			(67.4% to 72.2%)	$p = .0496$	$p = .07$	$p = .23$	(63.1% to 73.7%)
Low volume	37	553	67.3%	1.37 (1.12 to 1.68)	1.61 (1.29 to 2.01)	0.86 (0.59 to 1.25)	65.6%
(<10 patients)			(63.2% to 71.0%)	$p < .01$	$p < .0001$	$p = .43$	(57.8% to 72.2%)
Low/low-intermediate risk							
High volume	18	925	90.1%	1.00	1.00	1.00	90.1%
(≥20 patients)			(88.0% to 91.9%)	(reference)	(reference)	(reference)	(reference)
Medium volume	26	589	90.9%	0.92 (0.65 to 1.32)	0.97 (0.66 to 1.43)	0.89 (0.60 to 1.30)	90.8%
(10-19 patients)			(88.3% to 93.0%)	$p = .67$	$p = .87$	$p = .54$	(86.8% to 93.7%)
Low volume	28	217	88.9%	1.16 (0.73 to 1.86)	1.56 (0.95 to 2.56)	0.80 (0.46 to 1.37)	88.8%
(<10 patients)			(83.9% to 92.4%)	$p = .52$	$p = .08$	$p = .41$	(82.0% to 93.2%)
High-intermediate risk							
High volume	19	331	82.1%	1.00	1.00	1.00	82.1%
(≥20 patients)			(77.6% to 85.9%)	(reference)	(reference)	(reference)	(reference)
Medium volume	25	218	74.0%	1.50 (1.02 to 2.21)	1.57 (1.04 to 2.36)	1.44 (0.95 to 2.17)	74.6%
(10-19 patients)			(67.5% to 79.3%)	$p = .04$	$p = .03$	$p = .08$	(64.3% to 82.4%)
Low volume	27	99	78.8%	1.54 (0.91 to 2.59)	2.03 (1.18 to 3.50)	1.04 (0.57 to 1.87)	75.9%
(<10 patients)			(69.3% to 85.6%)	$p = .11$	$p = .01$	$p = .91$	(61.6% to 85.5%)
High risk							
High volume	20	874	52.6%	1.00	1.00	1.00	52.6%
(≥20 patients)			(49.2% to 55.9%)	(reference)	(reference)	(reference)	(reference)
Medium volume	28	514	46.2%	1.20 (0.98 to 1.46)	1.23 (0.99 to 1.52)	1.12 (0.85 to 1.49)	46.5%
(10-19 patients)			(41.8% to 50.5%)	$p = .08$	$p = .06$	$p = .42$	(38.0% to 54.6%)
Low volume	32	204	42.2%	1.39 (1.09 to 1.78)	1.59 (1.23 to 2.06)	0.81 (0.53 to 1.26)	42.8%
(<10 patients)			(35.3% to 48.8%)	$p < .01$	$p < .001$	$p = .35$	(31.8% to 53.1%)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval.

[a] A total of 4165 patients were included in the analyses of 5-year observed survival (13 patients were excluded because of a survival time of 0).

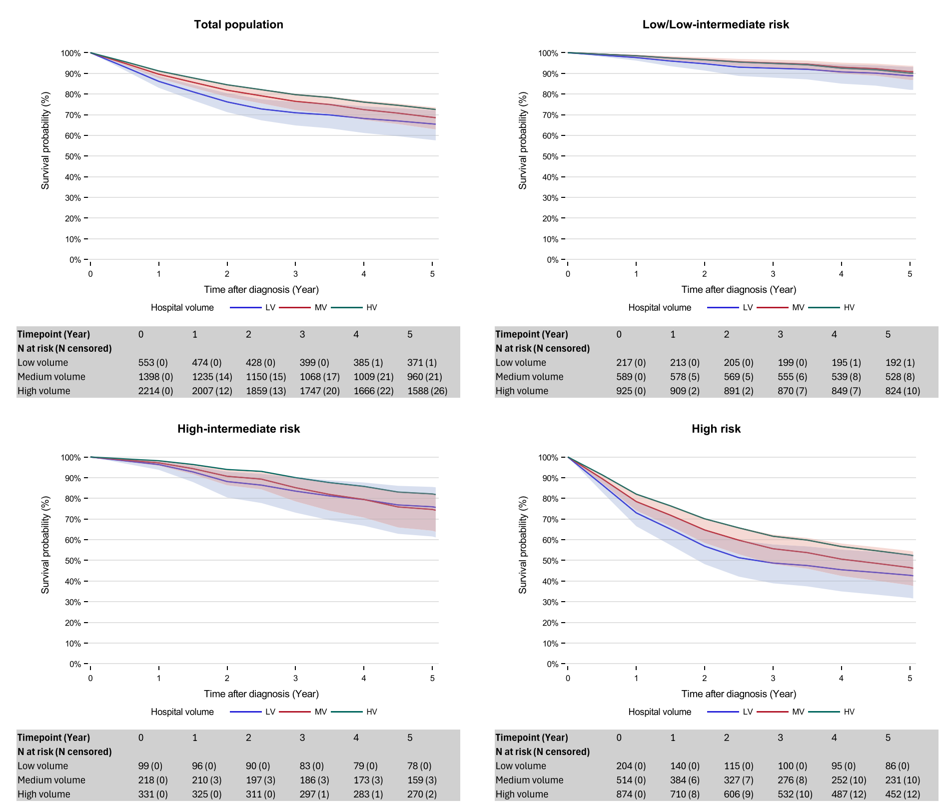
[b] Adjusted for case-mix differences (age group, World Health Organization score, American Society of Anesthesiologists score, co-morbidity index score, number of inpatient bed days in the year before cancer diagnosis, multiple tumor status, combined FIGO [International Federation of Gynecology and Obstetrics] stage, and histologic type) and intra-hospital correlations.

0.33, 95% CI 0.17 to 0.64); (2) 3-dimensional conformal radiation therapy or intensity-modulated radiation therapy (aOR 0.07, 95% CI 0.01 to 0.75); and (3) platinum-based chemotherapy (aOR 0.39, 95% CI 0.16 to 0.98) (Table 3). Furthermore, operated patients with locally advanced (pathologic stage III to IVA) endometrial carcinoma were less likely to receive adjuvant chemotherapy in medium-volume hospitals than in high-volume hospitals (aOR 0.46, 95% CI 0.21 to 0.99) (Table 3). The remaining indicators were not significantly associated with hospital case volume (Table S5).

DISCUSSION

Summary of Main Results

This study shows that outcomes of uterine corpus cancer are generally better in hospitals with a higher caseload. More precisely, increased hospital case volume was found to be associated with a lower risk of death of any cause within 5 years after diagnosis, especially for patients with high-intermediate-risk and high-risk disease. This 5-year survival benefit in high-volume hospitals was mainly driven by a lower risk of death during the first



Total population

Timepoint (Year)	0	1	2	3	4	5
N at risk (N censored)						
Low volume	553 (0)	474 (0)	428 (0)	399 (0)	385 (1)	371 (1)
Medium volume	1398 (0)	1235 (14)	1150 (15)	1068 (17)	1009 (21)	960 (21)
High volume	2214 (0)	2007 (12)	1859 (13)	1747 (20)	1666 (22)	1588 (26)

Low/Low-intermediate risk

Timepoint (Year)	0	1	2	3	4	5
N at risk (N censored)						
Low volume	217 (0)	213 (0)	205 (0)	199 (0)	195 (1)	192 (1)
Medium volume	589 (0)	578 (5)	569 (5)	555 (6)	539 (8)	528 (8)
High volume	925 (0)	909 (2)	891 (2)	870 (7)	849 (7)	824 (10)

High-intermediate risk

Timepoint (Year)	0	1	2	3	4	5
N at risk (N censored)						
Low volume	99 (0)	96 (0)	90 (0)	83 (0)	79 (0)	78 (0)
Medium volume	218 (0)	210 (3)	197 (3)	186 (3)	173 (3)	159 (3)
High volume	331 (0)	325 (0)	311 (0)	297 (1)	283 (1)	270 (2)

High risk

Timepoint (Year)	0	1	2	3	4	5
N at risk (N censored)						
Low volume	204 (0)	140 (0)	115 (0)	100 (0)	95 (0)	86 (0)
Medium volume	514 (0)	384 (6)	327 (7)	276 (8)	252 (10)	231 (10)
High volume	874 (0)	710 (8)	606 (9)	532 (10)	487 (12)	452 (12)

Figure 1 Adjusted observed survival probabilities until 5 years after diagnosis by hospital case volume for both the total study population and the recurrence risk groups. Using Kaplan-Meier estimates and adjusted hazard ratios obtained via Cox proportional hazards regression, adjusted observed survival probabilities were estimated over 0 to 5 years after diagnosis for both the total study population and the recurrence risk groups (ie, low/low-intermediate risk, high-intermediate risk, and high risk). Case-mix variables considered included age group, World Health Organization score, American Society of Anesthesiologists score, co-morbidity index score, number of inpatient bed days in the year before cancer diagnosis, multiple tumor status, combined FIGO (International Federation of Gynecology and Obstetrics) stage, and histologic type. Intra-hospital correlations were taken into account by adding the center of main treatment as a random effect term to the regression models. The bands around the survival curves represent the 95% confidence limits. HV, high volume; LV, low volume; MV, medium volume; N at risk, number of patients at risk; N censored, number of patients censored.

2.5 years after diagnosis and a lower risk of 90-day post-operative mortality.

Moreover, this study also shows that this positive volume-outcome relationship may be largely explained by disparities in quality of care given that patients treated in high-volume hospitals were more likely to receive several guideline-recommended procedures. These included pre-operative biopsy, minimally invasive surgery, surgical lymph node staging, omentectomy, adjuvant chemotherapy, and adjuvant treatment within 60 days after surgery.

Results in the Context of Published Literature

Since first described by Luft and colleagues[14] in 1979, many studies have examined the relationship between provider case volume and the outcomes of patients with cancer, including a number of systematic reviews and meta-analyses.[5,15-18] In line with our findings, these reviews have generally shown that increased case volume is positively associated with improved outcomes, especially for patients undergoing complex cancer surgery.[5,15-18] While the mechanisms underlying this association remain poorly understood, it could be largely explained by the fact that high-volume hospitals tend to be much larger facilities with a broader range of specialist and technology-based services, better-equipped intensive care units, an overall better structure and organization of care, and other resources that may be less available at smaller hospitals. Moreover, at the physician level, a higher caseload may translate directly into better clinical judgment and technical proficiency.[5,15-18] Accordingly, as recommended by the European Society of Gynaecological Oncology,[19,20] care in high-volume hospitals is probably more often delivered by a dedicated, multi-disciplinary team of specialists in the diagnosis and management of gynecologic cancers, which has been identified as an independent prognostic factor for improved treatment and survival.[21,22]

Our results are also consistent with retrospective cohort studies that specifically examined the volume-outcome relationship for endometrial cancer.[3,6-9] Seagle and colleagues[6] assessed overall survival disparities by hospital volume among 306,221 patients with endometrial cancer in the United States. After case-mix adjustment, increased annual treatment volume was associated with a significantly lower risk of all-cause death. Likewise, in a large National Cancer Database analysis, Fader and colleagues[3]

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Table 2 Process Indicators on Diagnostic Work-up and Surgical Treatment by Average Annual Hospital Case Volume.

Quality indicator	*n/N*	% (95% CI)	aOR (95% CI)[a]	*p*-Value[a]
Diagnostic work-up, pathology, and staging				
Proportion of operated patients with endometrial carcinoma who had a pre-operative biopsy of the primary tumor or metastasis				
High volume (≥20 patients)	1745/1956	89.2 (87.8 to 90.6)	1.00 (reference)	
Medium volume (10-19 patients)	1085/1241	87.4 (85.5 to 89.2)	0.74 (0.42 to 1.29)	.28
Low volume (<10 patients)	382/457	83.6 (79.9 to 86.9)	0.51 (0.29 to 0.92)	.03
Surgical treatment and staging				
Proportion of operated patients with clinical stage I endometrial carcinoma who had minimally invasive surgery (ie, traditional or robot-assisted laparoscopy)				
High volume (≥20 patients)	799/1140	70.1 (67.3 to 72.7)	1.00 (reference)	
Medium volume (10-19 patients)	472/789	59.8 (56.3 to 63.3)	0.64 (0.21 to 1.97)	.44
Low volume (<10 patients)	88/276	31.9 (26.4 to 37.7)	0.15 (0.05 to 0.50)	<.01
Proportion of patients with clinical stage I, high-grade endometrial carcinoma who had pelvic lymph node staging with or without para-aortic lymph node staging				
High volume (≥20 patients)	214/300	71.3 (65.9 to 76.4)	1.00 (reference)	
Medium volume (10-19 patients)	121/173	69.9 (62.5 to 76.7)	0.90 (0.44 to 1.85)	.78
Low volume (<10 patients)	28/53	52.8 (38.6 to 66.7)	0.40 (0.16 to 1.00)	<.05
Proportion of patients with low-risk endometrial carcinoma (ie, clinical stage IA, grade 1-2, endometrioid or mucinous) who had surgical lymph node staging				
High volume (≥20 patients)	87/264	33.0 (27.3 to 39.0)	1.00 (reference)	
Medium volume (10-19 patients)	44/162	27.2 (20.5 to 34.7)	0.69 (0.38 to 1.27)	.23
Low volume (<10 patients)	14/77	18.2 (10.3 to 28.6)	0.36 (0.16 to 0.79)	.01
Proportion of patients with clinical stage I-II serous carcinoma, clear-cell carcinoma, or carcinosarcoma who had omentectomy				
High volume (≥20 patients)	84/149	56.4 (48.0 to 64.5)	1.00 (reference)	
Medium volume (10-19 patients)	34/97	35.1 (25.6 to 45.4)	0.36 (0.16 to 0.82)	.02
Low volume (<10 patients)	6/31	19.4 (7.5 to 37.5)	0.21 (0.06 to 0.72)	.01
Proportion of operated patients with clinical stage I endometrial carcinoma who had total hysterectomy and bilateral salpingo-oophorectomy				
High volume (≥20 patients)	1095/1140	96.1 (94.8 to 97.1)	1.00 (reference)	
Medium volume (10-19 patients)	716/789	90.7 (88.5 to 92.7)	0.43 (0.25 to 0.75)	<.01
Low volume (<10 patients)	255/276	92.4 (88.6 to 95.2)	0.61 (0.30 to 1.25)	.18

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.
[a] Adjusted for case-mix and intra-hospital correlations. The following patient and tumor characteristics were available for case-mix adjustment: age group, World Health Organization score, American Society of Anesthesiologists score, co-morbidity index score, number of inpatient bed days in the year before cancer diagnosis, multiple tumor status, FIGO (International Federation of Gynecology and Obstetrics) stage, tumor histologic type, and tumor grade.

aimed to identify hospital-related differences in treatment and survival among 228,511 patients with endometrial cancer. Controlling for other factors, patients treated in low-volume hospitals (<5 cases per year) had significantly worse 5-year overall survival compared with patients treated in high-volume hospitals (≥30 cases per year). Among 6015 patients who had surgery for endometrial carcinoma, Wright and colleagues[9] found that peri-operative surgical complications, post-operative medical complications, and post-operative death were less likely for patients treated by high-volume surgeons (>30 procedures per year) than for those treated by low-volume surgeons (<15 procedures per year). Finally, 2 studies in Japan found very similar results for relative survival and overall survival.[7,8]

In contrast, several other retrospective cohort studies were either unable to demonstrate a statistically significant volume-outcome relationship[10,11] or found mixed results.[12] For instance, Becker and colleagues[10] studied the association between hospital volume and relative survival among 9133 patients who were surgically treated for endometrial carcinoma between 2005 and 2010 in the Netherlands. Adjusting for case mix, they found no differences in relative survival by hospital volume, neither in the total study population nor in the sub-group analyses of patients with high-risk endometrial carcinoma and of those undergoing complex surgery. However, in the Netherlands, surgeons from large referral centers frequently travel to perform operations in smaller regional centers. Additionally, regional centers often

Table 3 Process Indicators on Adjuvant Treatment by Average Annual Hospital Case Volume.

Quality indicator	*n/N*	% (95% CI)	aOR (95% CI)[a]	*p*-Value[a]
Adjuvant treatment				
Proportion of operated patients for whom adjuvant anti-cancer therapy, if performed, was started within 60 days after surgery				
High volume (≥20 patients)	512/615	83.3 (80.1 to 86.1)	1.00 (reference)	
Medium volume (10-19 patients)	275/357	77.0 (72.3 to 81.3)	0.68 (0.38 to 1.21)	.19
Low volume (<10 patients)	82/124	66.1 (57.1 to 74.4)	0.33 (0.17 to 0.64)	<.01
Proportion of operated patients who received adjuvant external beam radiation therapy for whom the radiation technique used was 3DCRT or IMRT				
High volume (≥20 patients)	127/210	60.5 (53.5 to 67.1)	1.00 (reference)	
Medium volume (10-19 patients)	77/124	62.1 (52.9 to 70.7)	0.62 (0.08 to 4.71)	.64
Low volume (<10 patients)	16/39	41.0 (25.6 to 57.9)	0.07 (0.01 to 0.75)	.03
Proportion of operated patients for whom adjuvant chemotherapy, if performed, was platinum-based				
High volume (≥20 patients)	309/330	93.6 (90.4 to 96.0)	1.00 (reference)	
Medium volume (10-19 patients)	114/127	89.8 (83.1 to 94.4)	0.67 (0.32 to 1.42)	.30
Low volume (<10 patients)	39/47	83.0 (69.2 to 92.4)	0.39 (0.16 to 0.98)	.04
Proportion of operated patients with locally advanced (pathologic stage III-IVA) endometrial carcinoma who had adjuvant chemotherapy				
High volume (≥20 patients)	184/258	71.3 (65.4 to 76.8)	1.00 (reference)	
Medium volume (10-19 patients)	61/119	51.3 (41.9 to 60.5)	0.46 (0.21 to 0.99)	<.05
Low volume (<10 patients)	25/42	59.5 (43.3 to 74.4)	0.44 (0.16 to 1.25)	.12

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy.
[a] Adjusted for case-mix and intra-hospital correlations. The following patient and tumor characteristics were available for case-mix adjustment: age group, World Health Organization score, American Society of Anesthesiologists score, co-morbidity index score, number of inpatient bed days in the year before cancer diagnosis, multiple tumor status, FIGO (International Federation of Gynecology and Obstetrics) stage, tumor histologic type, and tumor grade.

discuss their patients centrally with referral centers. This could largely diminish potential volume-outcome effects.

As shown in the sub-group analyses, we only found a statistically significant volume-outcome effect among patients with high-intermediate-risk and high-risk disease. Similarly, Fader and colleagues[3] observed a positive volume-outcome association only for patients with advanced-stage disease and not for patients with stage I disease. A possible explanation could be that high-volume hospitals are generally better-equipped to provide the complex and specialized care that is required by patients with higher-risk disease.

Indeed, we observed that patients treated in high-volume hospitals were more likely to receive multiple guideline-recommended procedures, such as minimally invasive surgery, surgical lymph node staging, omentectomy, and adjuvant chemotherapy. This is consistent with data from the United States,[23-27] also showing that lower-volume community-based and non-academic cancer centers less frequently perform minimally invasive surgery, surgical lymph node staging, omentectomy, and adjuvant chemotherapy for endometrial cancer compared with higher-volume academic and comprehensive cancer centers.

Strengths and Weaknesses

The EFFECT database was a major strength of this study, as its prospective and detailed data collection allowed us to measure a comprehensive and multi-disciplinary set of process and outcome indicators. Hence, this study was able to thoroughly investigate the relationship between hospital case volume and uterine corpus cancer survival in a large cohort of patients, including the identification of explanatory factors.

Nevertheless, the main limitations of this study are also related to the EFFECT database. First, the EFFECT database does not fully represent the Belgian population of uterine corpus cancer patients and hospitals, posing a risk of bias.[28] Second, given that the data presented pertain to the 2012-2016 period, this study might not provide the most contemporary information. However, as the organization of uterine corpus cancer care has not changed in Belgium in the past 2 decades, it can be assumed that the study's general conclusions remain valid today. Third, although many patient and tumor characteristics were available for case-mix adjustment, this study may have residual confounding. For instance, despite their well-known influence on access to health care and patient outcomes, we were unable to include race/ethnicity and socioeconomic status. Hospital factors, such as location and academic status, were also not included. Readers should take this into account when interpreting the results.

Implications for Practice and Future Research

In line with recommendations from the European Society of Gynaecological Oncology,[19,20] the results of this study further add to the evidence base that care for uterine corpus cancer should be centralized in reference centers with a sufficiently high caseload. Thus, centers with an insufficient caseload should refer their patients to specialized centers where treatment is performed by a multi-disciplinary and dedicated team of specialists to allow adequate diagnosis and surgical staging, as well as proper

tailoring of adjuvant treatment. Patients who are less likely to benefit from centralization are those who cannot undergo surgery or adjuvant treatment because of old age or poor performance status. This is consistent with an expert report of the Belgian Health Care Knowledge Centre regarding the preferred care model for cancers of the female genital system.[29] Future research should continue to focus on defining the most appropriate manner of achieving a comprehensive and centralized care pathway.

CONCLUSIONS

In this study, patients with uterine corpus cancer had improved overall survival when they were treated in hospitals with a higher annual caseload, where they were more likely to receive several guideline-recommended procedures. These included minimally invasive surgery, surgical lymph node staging, staging omentectomy, adjuvant platinum-based chemotherapy, and adjuvant treatment within 60 days after surgery. Hence, despite some limitations, this study supports the proposition that the care for uterine corpus cancer should be centralized in high-volume reference centers. In this regard, future research should continue to focus on defining the most adequate manner of achieving a comprehensive and centralized care pathway, including the most appropriate volume threshold.

Author Affiliations

[a]KU Leuven, Department of Oncology, Unit of Gynecologic Oncology, Leuven, Belgium
[b]Belgian Cancer Registry, Brussels, Belgium
[c]The Anticancer Fund, Meise, Belgium
[d]AZ Sint-Maarten, Laboratory of Pathological Anatomy, Mechelen, Belgium
[e]Ziekenhuis Oost-Limburg, Department of Obstetrics and Gynecology, Genk, Belgium
[f]CHU de Liège et Hôpital de La Citadelle, Department of Obstetrics and Gynecology, Liège, Belgium
[g]Ghent University Hospital, Department of Medical Oncology, Ghent, Belgium
[h]Netherlands Cancer Institute, Department of Surgery, Amsterdam, The Netherlands
[i]UZ Leuven, Department of Gynecologic Oncology, Leuven, Belgium

Ethical Approval Ethics committee approval was not necessary for this study. First, this study was performed within the legal framework of the Belgian Cancer Registry (BCR). More concretely, as outlined in article 138 of the Coordinated Belgian Law of May 10, 2015 (accessible online via: http://www.ejustice.just.fgov.be/cgi_loi/change_lg.pl?language=nl&la=N&cn=2015051006&table_name=wet), the BCR has a legal task to collect data on cancer, subject it to quality control, process and analyze it, encrypt and store it, report on it, make it accessible for research, and protect it. Second, this study does not fall under the Belgian Law of May 7, 2004 regarding experiments on human persons (art. 3, §2) (accessible online via: https://www.ejustice.just.fgov.be/cgi/article_body.pl?language=nl&caller=summary&pub_date=04-05-18&numac=2004022376).

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Author Contributions NVD, GB, GJ, EDJ, FG, HD, and FA were responsible for the conceptualization and design of the study. ADG was responsible for managing, maintaining, and making available the EFFECT database. JV and ADG were responsible for cleaning the EFFECT database. JV and GS were responsible for methods, software, and formal analysis. JV, NVD, GS, AHP, GB, GJ, EDJ, FG, HD, and FA were responsible for the critical appraisal and interpretation of data. JV was responsible for the drafting and editing of the manuscript. NVD, GS, AHP, GB, GJ, EDJ, FG, HD, and FA were responsible for the revising of the manuscript.

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Data Availability and Sharing The study data are not publicly available because of data confidentiality and ethical restrictions. However, data can be made available from the corresponding author upon reasonable request. More concretely, pseudonymized data can be provided within the secured environment of the Belgian Cancer Registry, after having been guaranteed that all applicable General Data Protection Regulations and safeguards are taken into account. These statements also apply to any additional data, documentation, or information related to the study.

Appendix A. Supplementary data Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijgc.2025.102849.

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