Endometrial Cancer – Long-Term Survival in Certified Cancer Centers and Non-Certified Hospitals

Comparative Analysis Based on a Large German Retrospective Cohort Study (WiZen)

Das Endometriumkarzinom – Langzeitüberleben in zertifizierten Krebszentren und nicht zertifizierten Krankenhäusern

Vergleichende Analyse basierend auf einer großen deutschen retrospektiven Kohortenstudie (WiZen)

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ABSTRACT

Introduction Endometrial cancer is the most common malignant tumor of the female genital organs. In Germany, treatment is provided in both cancer centers certified by the German Cancer Society (Deutsche Krebsgesellschaft, DKG) and in non-certified hospitals. This study investigated whether treatment in DKG-certified centers leads to improved overall survival of patients with endometrial cancer.

Materials and Methods Data from 11 legally independent German statutory health insurance (SHI) funds of the AOK were analyzed as well as data from four clinical cancer registries (CCR), resulting in inclusion of 30 102 AOK patients and 8190 registry patients with a diagnosis (incidental cases) of ICD-10-GM code C54 (malignant neoplasm of corpus uteri). For comparative survival analyses, multivariable Cox regressions and Kaplan–Meier analyses were used.

Results The Kaplan–Meier estimator for 5-year overall survival was 66.7 % for patients from certified centers and 65.0 % for patients from non-certified hospitals (using SHI data; CCR data: 63.4 % vs. 60.7 %). Cox regression adjusted for relevant confounders showed a hazard ratio (HR) of 0.93 (SHI data; 95 % CI 0.86–1.00; p = 0.050) and 0.935 (CCR data; 95 % CI 0.827–1.057; p = 0.281) for all-cause mortality. In a subgroup analysis (CCR), patients with International Union against Cancer Control (UICC) stage I had a significant survival benefit if treated in a certified center (HR 0.783; 95 % CI 0.620–0.987; p = 0.038).

Conclusion The study presented herein shows that patients with endometrial cancer treated in a certified cancer center tend to have better survival rates. This should be considered when selecting the treating hospital.

ZUSAMMENFASSUNG

Einleitung Das Endometriumkarzinom ist die häufigste maligne Erkrankung des Genitaltrakts bei der Frau. In Deutschland werden Patientinnen sowohl in Krebszentren, die von der Deutschen Krebsgesellschaft (DKG) zertifiziert sind, als auch in nicht zertifizierten Krankenhäusern behandelt. Untersucht wurde hier, ob eine Behandlung in einem DKG-zertifizierten Zentrum zu einem besseren Gesamtüberleben von Patientinnen mit Endometriumkarzinom führt.

Material und Methoden Die Daten von 11 unabhängigen gesetzlichen Krankenkassenversicherungen (GKV) der AOK wurden analysiert zusammen mit den Daten von 4 klinischen Krebsregistern (KKR). Insgesamt wurden 30 102 AOK-Patientinnen und 8190 Registerpatientinnen (Neuerkrankungsfälle) mit einer ICD-10-GM-Code C54-Diagnose (bösartige Neubildung des Corpus uteri) in die Studie aufgenommen. Die multivariable Cox-Regressionsanalyse sowie Kaplan-Meier-Analysen wurden für eine vergleichende Überlebensanalyse eingesetzt.

Ergebnisse Der Kaplan-Meier-Schätzer für das 5-Jahres-Gesamtüberleben betrug 66,7 % für in zertifizierten Zentren behandelte Patientinnen und 65,0 % für Patientinnen von nicht zertifizierten Krankenhäusern (basierend auf GKV-Daten; KKR-Daten: 63,4 % vs. 60,7 %). Nach Ausschaltung relevanter Störfaktoren wies die Cox Regression eine Hazard Ratio (HR) von 0,93 (GKV-Daten; 95 %-KI 0,86–1,00; p = 0,050) bzw. 0,935 (KKR-Daten; 95 %-KI 0,827–1,057; p = 0,281) für die Gesamtmortalität auf. Eine Untergruppenanalyse (KKR) zeigte, dass Patientinnen im Union for International Cancer Control-(UICC-)Stadium I einen deutlichen Überlebensvorteil aufwiesen, wenn sie in einem zertifizierten Zentrum behandelt wurden (HR 0,783; 95 %-KI 0,620–0,987; p = 0,038).

Schlussfolgerung Diese Studie zeigt, dass Patientinnen mit Endometriumkarzinom, die in einem zertifizierten Krebszentrum behandelt werden, tendenziell höhere Überlebensraten aufweisen. Dies sollte in die Wahl des behandelnden Krankenhauses einfließen.

Introduction

Endometrial cancer ranks as the sixth most prevalent cancer in women globally and the 15th most common cancer overall. In 2020, there were over 417 000 new cases of endometrial cancer reported worldwide [1]. According to the latest German national cancer report [2], around 10 860 cases of cancer of the uterine body (corpus or endometrial carcinoma) were newly diagnosed in 2020, with an average age at diagnosis of 67 years. Furthermore, malignant tumors of the uterine body represent the most common malignant disease of the female genital organs [3]. Fortunately, the incidence of endometrial cancer is decreasing slightly [3]; moreover, the prognosis is generally favorable [4, 5], as reflected by a relative 5-year survival rate of 78 % [3].

In Germany, specialized certified centers accredited by the German Cancer Society (Deutsche Krebsgesellschaft, DKG) focus on the complex treatment of endometrial cancer and other gynecological tumors. As of 2021, there were 182 certified gynecological cancer centers, with seven certification procedures in progress [6]. Despite the substantial number of certified centers, there is a notable lack of studies examining the impact of certification on patient outcomes. The specific question addressed by the current study was whether patients with endometrial cancer who have been treated in a DKG-certified center have an advantage in terms of survival and better treatment outcomes compared to patients of non-certified hospitals. This was analyzed in the context of the WiZen project, which investigated the effectiveness of healthcare in oncology centers [7]. The results of the WiZen study pertaining to endometrial cancer are presented in this publication.

Materials and Methods

Objective

The WiZen study, funded by the German Innovation Fund (grant number: 01VSF17020), was a comprehensive cohort study that assessed treatment and survival outcomes in both certified and non-certified centers across 11 cancer entities, including endometrial cancer [8]. WiZen was designed as a retrospective cohort study and carried out between July 1, 2018, and August 31, 2021. Four different institutions contributed to the WiZen study: the Center for Evidence-Based Healthcare (Zentrum für Evidenzbasierte Gesundheitsversorgung, ZEGV) of the Dresden University of Technology (TU Dresden), the Tumorzentrum Regensburg (TZR) with its clinical cancer registry, the Arbeitsgemeinschaft Deutscher Tumorzentren (ADT), and the AOK Research Institute (WIdO). Cooperation partners also participating were the DKG and the following cancer registries: Klinisches Krebsregister Dresden (KKRD), Klinisches Krebsregister Erfurt (KKRE), and Klinisches Krebsregister für Brandenburg und Berlin (KKRBB). Subject of the investigation were patients with 11 different cancer entities: breast cancer, colorectal cancer, cervical cancer, endometrial cancer, ovarian cancer, head and neck cancer, lung cancer, neurooncological tumors, pancreatic cancer, prostate cancer. Primary endpoint was overall survival (OS), with a comparison of outcomes between certified and non-certified hospitals as a central goal.

Data sources

Statutory health insurance (SHI) data

The AOK – Die Gesundheitskasse consists of 11 independent local healthcare funds in Germany, covering nearly one third of the German population [9]. For the WiZen study, the AOK Research Institute (WIdO) provided the following information for all AOK-insured persons who received treatment for the aforementioned cancer diseases between 2009 and 2017 (along with a preceding period of 3 years from 2006 to 2008 for identification of incident cases; a patient was only included as incident between 2009 and 2017 if there was no endometrial cancer diagnosis between 2006 and 2008, following the "Good practice of secondary data analysis" guideline [10]. For this reason, patients with a cancer diagnosis between 2006 and 2008 were excluded from the SHI-based analyses) [11]:

- International Classification of Diseases, German modification (ICD-10-GM) codes for all preexisting or current, oncological, non-oncological, outpatient, inpatient diseases;
- medical procedures (included in OPS codes, the German version of the International Classification of Procedures in Medicine, and EBM ["Einheitlicher Bewertungsmaßstab"], which is used as an encoding system for outpatient procedures);
- medical prescriptions (included in ATC codes);
- data concerning hospital admissions and discharges;
- state of insurance;
- demographic figures (age, sex, date of death).

Clinical cancer registry (CCR) data

A second dataset was provided by four large population-based clinical cancer registries (CCRs), whose catchment areas include four different regions in the south and east of Germany. These cancer registries are officially tasked with gathering data from all cancer patients within their jurisdiction. Their goal is to uncover possible shortcomings in diagnosis and treatment, as well as to monitor and enhance the quality of care. This dataset also covers the observation period from 2009 to 2017, and contains detailed information regarding the characteristics of a patients' tumor (date of diagnosis, histological subtype, UICC stage, and lymphatic and venous invasion), together with information about treatment and demographics (age, sex, date of death).

Hospital characteristics

From publicly available structured quality reports and DKG certification compilations, information concerning hospital caseload, academic status, ownership, and DKG certification status was obtained. These clinical characteristics were linked to the SHI and CCR data based on the hospital identification number. At times, the CCR data did not include a hospital identification number. However, cases from the center could still be recognized using a general "center treatment yes/no" variable indicating whether the patient received treatment at the center.

Inclusion and exclusion criteria

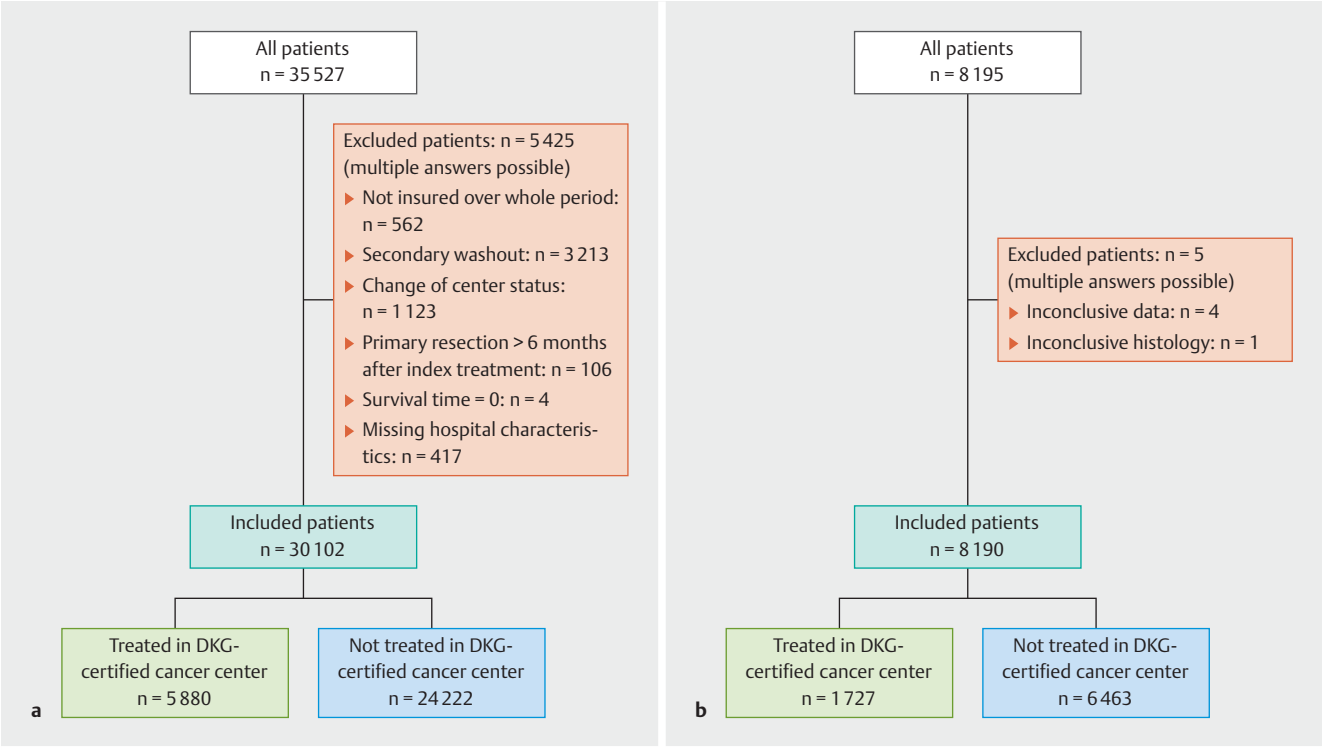
All findings discussed in this paper pertain to patients diagnosed with endometrial cancer, as classified under the ICD-10-GM code C54, which stands for malignant neoplasm of the corpus uteri. Furthermore, the following criteria had to be met to be included in either the SHI- or the CCR-based analyses: *a)* age at least 18 years at diagnosis; *b)* no previous diagnosis of endometrial cancer; *c)* adequate information regarding the certification status of the hospital.

Furthermore, the following criteria had to be met by the SHI data: *d)* a patient must have been insured by the AOK for the whole observation period and *e)* have at least one inpatient diagnosis related to the abovementioned diagnosis code.

For the SHI data, patients who had been treated in a hospital that became DKG-certified within 1 year before the first treatment (and because of that probably already reached or exceeded the quality standards necessary for certification despite being included in the analysis as members of the non-certified group) were excluded. With regard to the CCR dataset, only patients with histologic behavior code 3 (i.e., malignant) in the ICD-O3 morphology code were included.

Statistical analysis

Patients were classified as "certified cancer center patients" *a)* if the primary tumor resection was carried out in a certified cancer center (documented by the OPS code 5-68 ff [surgery corpus uteri], together with a primary inpatient diagnosis ICD-10-GM C54) or, if a primary resection is not documented, *b)* when the first endometrial cancer-specific treatment (documented by a primary inpatient diagnosis ICD-10-GM C54) had been performed in a certified endometrial cancer center. The entire hospital is considered certified if it includes a certified center, and, thus, as are all treatments within the hospital, regardless of whether they took



▶ **Fig. 1** Flow chart of inclusion and exclusion criteria. **a** SHI data, **b** CCR data.

place in the center or not. For this definition of a "center case" the rules of the certifying institutions DKG and OnkoZert were adopted, which assign a case to a center, when the decisive treatment decision and therapy is performed in the certified hospital.

OS was the primary outcome, recurrence-free survival (RFS) a secondary outcome (based on CCR data analyses only). The observation time for all included patients started at the date of index treatment (for SHI data; index treatment was defined as the first entity-specific inpatient treatment with a principal or secondary diagnosis of the respective entity [8]) or date of diagnosis (CCR data). The follow-up period was right-censored on December 31, 2017. The Kaplan–Meier method was applied to compare unadjusted survival rates between DKG-certified cancer centers and non-certified hospitals in the first 5 years after index treatment [12].

Multivariable Cox regression models were employed to account for the potential unbalanced distribution of important confounding variables. In the CCR analyses, one could feasibly adjust for age (categorized in groups), year of diagnosis, UICC stage, grading, and lymphatic and venous invasion. The following covariates were involved in the SHI-based analyses: age (categorized in groups), year of index treatment, distant metastasis, Elixhauser comorbidities (pertinent comorbidities chosen by a group of independent clinical experts, [13]), and hospital criteria (bed size categories, academic status, ownership). Treatment was purposely not included as an item of investigation (in the sense of a confounder) in this study, being presumably a strong explanatory variable for the benefit of center treatment. To consider a correlation between outcomes of patients who were treated in the same hospital for SHI data, a shared frailty term was also incorporated into the model [14].

All significance tests were two-sided with a significance level of 0.05. Depending on the analysis, either the p value and/or the upper and lower border of the 95% confidence interval (CI) are shown. IBM SPSS 25 (IBM SPSS Statistics for Windows, version 25.0; Armonk, NY, USA: IBM Corp.) was used for the CCR-based analyses, R version 3.6.3. was used for the SHI-based analyses (R Foundation for Statistical Computing, Vienna, Austria).

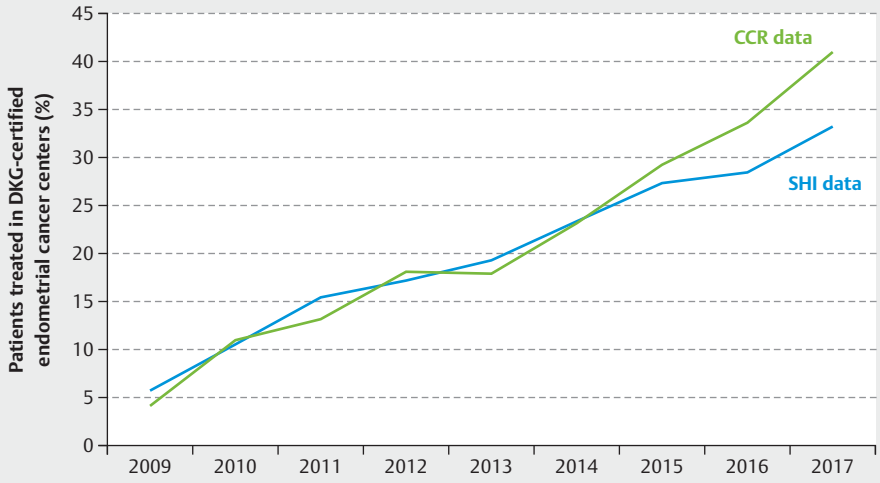
Data protection and ethics

At WIdO and the involved cancer registries, the data on DKG certification and patient, tumor, and hospital characteristics were pseudonymized. At ZEGV (SHI) and TZR (CCR), pseudonymized data were analyzed. The ethics commission of the TU Dresden approved the WiZen study (approval number: EK95022019). The study was also listed at ClinicalTrials.gov (identifier: NCT04334239). Data processing and analyses were done in accordance with the Declaration of Helsinki and the General Data Protection Regulation of the European Union.

Results

Inclusion process

The SHI dataset included 35 527 patients and the CCR dataset 8195 patients with an ICD-10-GM diagnosis C54 between 2009 and 2017. Upon implementing all inclusion and exclusion criteria, 30 102 patients (84.7%) from the SHI dataset and 8190 (99.9%) from CCRs could be included in the analyses (▶ **Fig. 1**).



▶ **Fig. 2** Share of patients treated in DKG-certified endometrial cancer centers over time.

Share of patients treated in DKG-certified cancer centers

The percentage of patients treated in a DKG-certified cancer center rose from 5.7% in 2009 to 33.1% in 2017 (SHI data). For the CCR data, a similar increase was observed: the share of center treatments was 4.1% in 2009 and increased to 40.9% in 2017 (▶ **Fig. 2**).

Description of collectives

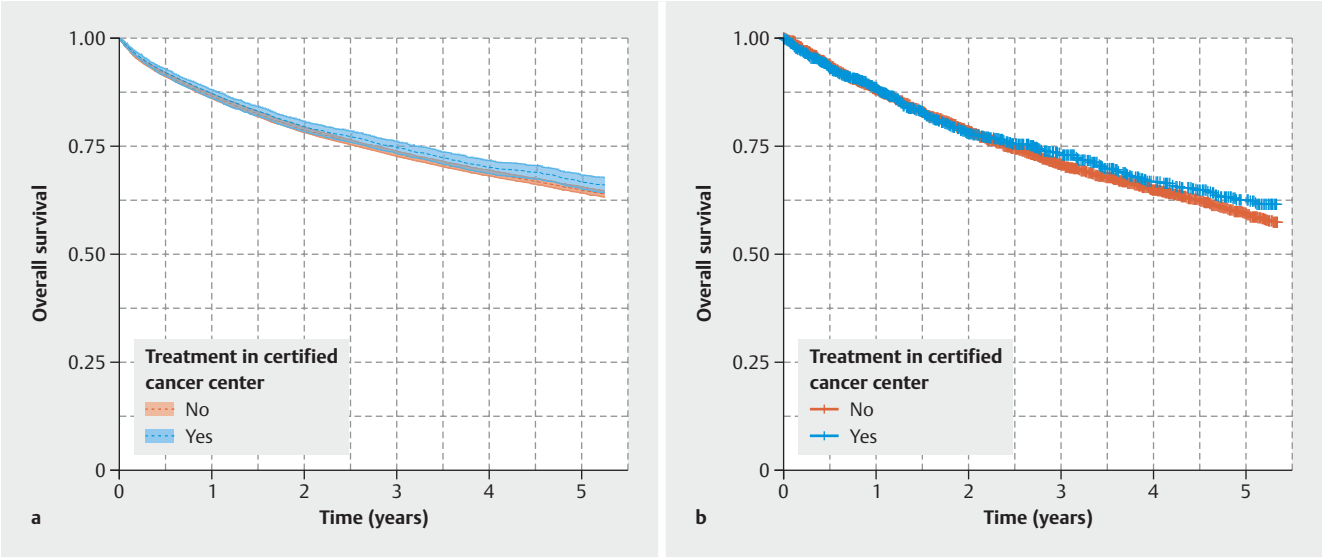
Within the SHI dataset, the median age of a patient treated in a certified center was 69 years (interquartile range [IQR] 60;77) compared to 72 years (IQR 62;79) in patients of non-certified hospitals. Within the CCR dataset, similar values are observed: the median age of a patient treated in a certified center was 68 years (IQR 59;76) compared to 70 years (IQR 61;77) among patients of non-certified hospitals. Concerning the distribution of age groups, the SHI data show that a higher share of younger patients were treated in certified centers (24.7%) compared to non-certified hospitals (19.7%). Correspondingly, more patients over the age of 80 years were treated in non-certified hospitals (22.1%) compared to certified centers (18.0%). In the CCR data, the same, albeit less distinct, tendency was observed (▶ **Table 1**).

More patients from certified than from non-certified hospitals had already developed distant metastases at the time of diagnosis (SHI data: 12.9% vs. 10.5%; CCR data: 8.9% vs. 5.9%; ▶ **Table 1**). Moreover, according to the CCR data, there were significantly fewer patients with UICC stage I/0 treated in certified hospitals than in non-certified hospitals (51% vs. 59.8%); in contrast, more UICC stage III and IV patients were treated in certified hospitals (12.3% vs. 9.1% and 8.0% vs. 5.9%, respectively; Online Supp. Table **S1**). Concerning grading, there was a tendency toward a higher classification in certified hospitals: grade 3/4 is seen in 28.1% of the patients in certified hospitals vs. 22.2% in patients of non-certified hospitals (CCR data; Online Supp. Table **S1**). In addition, lymphatic and venous invasion was seen more often among patients from certified centers.

Although the patient characteristics with regard to age and comorbidities did not differ significantly between certified centers

▶ **Table 1** Patient characteristics (SHI = statutory health insurance, CCR = clinical cancer registry).

Variable	Category	SHI data				CCR data			
		Treatment in DKG-certified centers				Treatment in DKG-certified centers			
		Yes		No		Yes		No	
		n	%	n	%	n	%	n	%
Age at diagnosis (years)	18–59	1450	24.7	4783	19.7	458	26.5	1513	23.4
	60–79	3370	57.3	14088	58.2	1033	59.8	3946	61.0
	80+	1059	18.0	5351	22.1	236	13.7	1004	15.5
Distant metastasis	Yes	759	12.9	2543	10.5	138	8.0	379	5.9
	Total	5879	100.0	24222	100.0	1727	100.0	6463	100.0



▶ **Fig. 3** Kaplan–Meier curves for overall survival according to center status. **a** SHI data, **b** CCR data.

▶ **Table 2** Hospital characteristics (SHI = statutory health insurance).

Variable	Category	Treatment in DKG-certified centers			
		Yes		No	
		n	%	n	%
Hospital beds	1–299	4	3.1	421	57.3
	300–499	34	26.2	206	28.0
	500–999	52	40.0	98	13.3
	1000+	40	30.8	10	1.4
Hospital ownership	Public	84	64.6	263	35.8
	Non-profit	37	28.5	316	43.0
	Private	9	6.9	156	21.2
Academic status	University hospital	20	15.4	7	1.0
	Teaching hospital	107	82.3	432	58.8
	Total	130	100.0	735	100.0

and non-certified hospitals, the differences that nevertheless did exist are taken into account in the adjustment for the estimation of the center effect (Online Supp Table **S2**).

In terms of SHI data, certified centers tended to be located in larger clinics (70.8% with ≥ 500 beds), while clinics without certification tended to be smaller (85.3% with < 500 beds). Hospitals with a certificate were also more often university hospitals (15.4%), whereas hospitals without a certificate were only rarely university hospitals (1.0%). They also differed in terms of their status as teaching hospitals and ownership (▶ **Table 2**).

Overall survival, Kaplan–Meier analyses

In the CCR data, the 5-year OS rate amounted to 63.4% (95% CI 59.6–67.1%) for treatment in a certified center, for treatment in a non-certified clinic it was 60.7% (95% CI 58.9–62.5%). However, the two Kaplan–Meier survival rates do not show a statistically significant difference (p = 0.196). The following results are seen with the SHI data: 5-year OS rate for all patients amounted to 66.7% (95% CI 65.2–68.3%) for treatment in a certified center, for treatment in a non-certified clinic it was 65.0% (95% CI 64.3–65.6%). The two Kaplan–Meier OS rates show a nearly statistically significant difference (p = 0.050; ▶ **Fig. 3**).

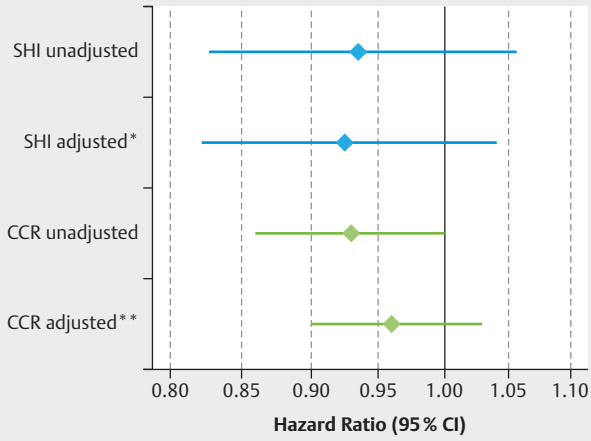
Overall survival, Cox regression analyses

For comparison of treatment in a DKG-certified center vs. in a non-certified hospital, the unadjusted hazard ratio (HR) over all patients for OS was 0.96 (95% CI 0.90–1.03; p = 0.236) obtained from the SHI data. After adjusting for age, year of index treatment, distant metastasis, Elixhauser comorbidities, and hospital characteristics, it dropped to 0.93 (95% CI 0.86–1.00; p = 0.038;

▶ **Fig. 4**). The detailed results for the adjusted multivariable Cox model can be seen in Online Supp. Table **S3**. Further sensitivity analyses were performed for bed classes (stratified): 0–299: HR 1.33 (1.01–1.75); 300–499: HR 0.80 (0.70–0.90); 500–999: HR 0.94 (0.83–1.07); 1000+: HR 0.99 (0.86–1.14; Online Supp. Table **S4a**). In addition, the duration of certification was taken into account: continuity of certification (ref: not certified): < 1 year: HR 0.92 (0.82–1.03), 1–< 2 years: HR 0.87 (0.77–0.99); 2–< 5 years: HR 0.95 (0.87–1.05), 5 or more years: HR 0.95 (0.82–1.09).

Analyzing the CCR data, the unadjusted HR over all patients for OS was 0.925 (95 % CI 0.822–1.041; p = 0.196) for treatment in certified centers. After adjusting for age, year of diagnosis, UICC stage, grade, and lymphatic and venous invasion, it increased to 0.935 (95 % CI 0.827–1.057; p = 0.281; ▶ **Fig. 4**; detailed results of the adjusted Cox model can be seen in Online Supp. Table **S5**). In the CCR-based subgroup analyses, only patients with UICC stage I showed significantly superior survival after treatment in a certified hospital (HR 0.783, 95 % CI 0.620–0.987; p = 0.038). No significant benefit could be observed in subgroups according to age at diagnosis and year of diagnosis (Online Supp. Table **S4b**).

With the CCR data it was also possible to analyze RFS. The adjusted HR for death or recurrence after treatment in a certified center amounted to 0.869 (95 % CI 0.738–1.022; p = 0.090; Online Supp. Table **S6**).



▶ **Fig. 4** Unadjusted and adjusted hazard ratios with 95 % CI for overall survival (SHI and CCR) following treatment in DKG-certified cancer centers compared to treatment in non-certified hospitals. * Adjusted for age, year of index treatment, distant metastasis, Elixhauser comorbidities, and hospital characteristics. ** Adjusted for age, year of diagnosis, UICC stage, grade, and lymphatic and venous invasion.

Discussion

The presented data are part of the WiZen study and are based on a large and representative collective of patients with endometrial cancer: 30 102 patients with endometrial cancer were evaluated from SHI data provided by the AOK and an additional 8190 patients from CCR data provided by four German cancer registries. The study explored whether DKG-certified centers provide a survival benefit compared to non-certified centers. Significant OS advantages were observed for endometrial cancer in SHI data, with a trend towards an advantage in CCR data. Furthermore, one can see a tendential advantage in RFS and, particularly pronounced, a statistically significant survival advantage in UICC stage I/0 (CCR data). Based on the results of the current study, treatment of endometrial cancer in certified centers is superior compared to treatment in non-certified hospitals. According to the study by Bierbaum et al. [15] the observed survival advantage of center treatment is equivalent to 156 deaths avoided 5 years post-diagnosis. The improvement of survival in stage I patients is notable, since the disease is mainly diagnosed in early stages. This may be due to differentiated use of multimodal treatment strategies in certified cancer centers.

The results of the WiZen study contribute to an ever-growing international evidence base on the topic of specialized treatment of endometrial cancer. As early as 2002, Münstedt et al. [16] described that the type of hospital (primary/secondary/tertiary/central care) in which endometrial cancer patients are treated is an important factor for the quality of reserved surgical treatment. This study from Germany refers to data from the GQH project, which recorded all diagnostic, surgical, and postoperative gynecological interventions in Hesse between 1997 and 2001. The authors state that experienced and specialized surgeons and hospitals are required for better treatment outcomes. As a result, their data seem to call for centralization. Since further work [17] indicates that longer survival is associated with appropriately specialized gynecologists, according to Münstedt et al. [16], gynecological tumor surgery should be reserved for specialized institutions and gynecologists. Thus, the results of Münstedt et al. are consistent with those of the present study, which indicate that treatment in certified centers is superior to that in non-certified centers.

A recent study by Piatek et al. [18] dealt with a similar question in Poland, namely whether endometrial or ovarian cancer is preferably treated or operated in a centralized or decentralized manner. In this context, a Polish paper was chosen for comparison because Poland is an important European neighbor of Germany and the decentralized structure is easily transferable to Germany, which is also rather decentralized. These authors examined patients treated in hospitals with different case numbers between 2017 and 2020. They concluded that patients with ovarian and endometrial cancer in Poland are mostly treated in a decentralized manner. Unfortunately, no survival data were available for these patients, so that the number of surgical cases cannot be used to draw any conclusions regarding prognosis. Further studies on prognosis and survival would be interesting to determine the role played by centralized and decentralized treatment of endometrial and ovarian cancer in Poland. This would be interesting in order to check whether decentralized treatments are just as inferior to centralized treatments as non-certified treatments are to certified treatments.

Similar observations have been made in studies on other types of cancer. For example, Jacob et al. [19] presented data on rectal cancer. They compared the treatment of patients suffering from

rectal cancer in periods before (2000–2008) and after (2009–2017) implementation of a certified cancer center. It could be shown that more quality goals could be achieved with the introduction of the certification, that the rate of anastomotic leaks improved, and that the 5-year recurrence rate declined. With regard to 5-year OS, an improvement in the patient group after certification was also observed compared to before certification.

Work by Völkel et al. [20, 21] shows that in Germany, treatment of colorectal cancer in certified centers is associated with significantly better survival rates. In 2019, certified and non-certified hospitals in the southern German region of Upper Palatinate were examined; in 2023, the surveys related to a cross-state project as part of the large-scale WiZen study [8]. Despite different examination conditions and study populations, both studies showed better outcomes for patients with colorectal cancer treated in certified clinics.

These results can also be reconciled with the trend shown in the present work: patients with endometrial cancer benefit from treatment in a certified center, albeit to a lesser extent than patients with colorectal cancer. The same can be seen in another publication from the WiZen study, due to breast cancer [22].

The WiZen project constitutes an extension of previous research on the impact of certification. It includes a very large patient cohort (more than 1 million patients with 11 tumor entities) from all over Germany, with a long observation period of 11 and a follow-up period of 5 years. This enabled a comprehensive longitudinal analysis of the implementation of the entire certification process. In addition, no patients with unfavorable characteristics such as advanced tumor stage or old age had to be excluded from the study collective [23, 24], so that the reported results are actually population-based "real-life" data.

Comparing the population characteristics (age, sex, and stage distribution) and survival rates reported in this article, similarity is given to the data in Germany's national epidemiological cancer report [2]. Consistent estimates can also be found in the reported results of the EUROCARE-5 study [25], which further emphasizes the validity and generalizability of the results reported herein. Even though data from only a single German health insurance company were available, this can still be regarded as very representative, since it covers about 30 % of all insured persons in Germany [9]. This limitation is not relevant to the CCR-based analyses, since the participating CCRs collect information on all patients with a cancer diagnosis who are registered in the respective service area. A notable advantage lies in merging two separate data sources, leading to enhanced information significance.

The current comprehensive analysis represents one of the most reliable available sources of real-world evidence on cancer center certification, given the limited availability of randomized controlled trials (RCTs) on the topic. The study design of an RCT is not feasible in this context (a variety of factors influence a patient's choice of hospital [26], and denying someone their liberty to select a hospital of their choice is considered highly unethical). For this reason, the present study design with independent standardized controlled prospective data collection in several CCRs and a large health insurance database appears to be most adequate. It was possible to incorporate a particularly large number of different patient- and tumor-associated factors into the multivariable analyses because data from different sources were available. Although not all confounders were available simultaneously for both data sources, the authors are convinced that they have taken the most important confounders into account in the analyses.

Generally, a conservative study design was chosen. Several factors might have contributed to attenuating the observed certification effect: if at least one hospital belonging to a consortium was DKG-certified, all patients treated in that consortium were considered center-treated. This could lead to an underestimation of the difference in survival between center patients and patients of non-certified hospitals. Moreover, it is possible that adjusting for the year of index treatment also reduced the observed certification effect, as the proportion of center treatments increased over time.

Another limitation is that although it was known whether patients were treated in certified centers or non-certified hospitals, no details regarding the treatments or how the treatments differed were available.

However, center treatment is a so-called complex intervention whose individual components are usually difficult or impossible to evaluate. In the study design, it was decided to evaluate the initial treatment (center vs. non-center) in order to delineate this complex intervention as clearly as possible. Adjusting for certain aspects of treatment (such as adjuvant therapy and tumor board adherence) would have led to a mediator bias of the certification effect of interest and therefore had to be excluded at all costs [27]. Otherwise, the certification effect would not have been estimated, but the effect of individual therapy components, which would have contradicted the project question. Of course, it would have been interesting to carry out a mediation analysis following the evaluation of the certification as an entire complex intervention in order to differentiate which therapy components led to the estimated therapy effect. However, performing these analyses was not part of the study protocol.

In the meantime, the treatment and classification of endometrial cancer has changed dramatically since the evaluation period, due to molecular classification and corresponding treatment approaches. Molecular subtyping (such as microsatellite instability [MSI] status, *TP53* mutation status, *POLE* mutation status) must be requested as soon as the diagnosis has been established. This is also reflected in the current International Federation of Gynecology and Obstetrics (FIGO) classification from 2023, which urgently requires molecular subtypes for risk assessment. The surgical procedure also depends on this risk classification, even though many practitioners now carry out sentinel node biopsy on all patients, which would not be necessary in the low-risk situation. Above all, adjuvant therapy depends on the risk classification.

For advanced or metastatic endometrial cancer there is a checkpoint inhibitor (CPI; dostarlimab; Ruby study [28]) approved in combination with carboplatin/paclitaxel and subsequent maintenance therapy for mismatch repair (MMR) deficiency. After platinum therapy, there has long been the option of a CPI monotherapy for MMR deficiency or of lenvatinib plus pembrolizumab also for microsatellite-stable (MSS) tumors. Immunotherapy was able to significantly extend survival in the studies [28 – 30].

Due to the increasing complexity, it can be assumed that the difference between treatment in a certified center versus a non-certified clinic has widened, as non-specialized treatment units may be less concerned with the innovations or not implement them promptly.

By looking at the differences seen in the case of a mix of DKG-certified centers and non-certified hospitals in the proportion of patients with distant metastases and stage I/0 disease, selective referral may be observed. In Germany, every patient has the freedom to select a hospital based on their preferences. Patients appear to prioritize factors such as shorter travel distances over a hospital's certification status. Our research aims to enlighten patients and referring physicians about the significance of certification, with the hope of fostering an increased preference for certified treatment centers in the future.

Conclusion

The presented results provide strong evidence that treatment of endometrial cancer in certified centers is likely beneficial for affected patients. While considerations regarding aspects such as longer journeys, particularly in rural areas, may arise, prioritizing the extended survival of patients should always take precedence. In addition, lower costs for the healthcare system are yet another advantage of centralized treatment (with an expansion of specialized care). It is essential to provide this information to both patients and physicians, enabling them to make well-informed, self-determined decisions.

Data Availability

The authors confirm that the data utilized in this study cannot be made available in the manuscript, the supplemental files, or in a public repository due to German data protection laws. Therefore, they are stored on a secure drive in the WIdO to facilitate replication of the results. Generally, access to data of statutory health insurance funds for research purposes is possible only under the conditions defined in German Social Law (SGB V § 287). Requests for data access can be sent as a formal proposal specifying the recipient and purpose of the data transfer to the appropriate data protection agency. Access to the data used in this study can only be provided to external parties under the conditions of the cooperation contract of this research project and after written approval by the sickness fund. For assistance in obtaining access to the data, please contact wido@wido.bv.aok.de

Supplementary Material

- Supp. Table **S1** Tumor characteristics according to treatment in DKG-certified centers yes vs. no (clinical cancer registry [CCR] data).
- Supp. Table **S2** Distribution of Elixhauser comorbidities (statutory health insurance [SHI] data).
- Supp. Table **S3** Full results for overall survival from adjusted multivariable Cox regression with shared frailty (statutory health insurance [SHI] data).
- Supp. Table **S4a** Unadjusted and adjusted hazard ratios with 95% CI for overall survival (statutory health insurance [SHI] data, subgroup analyses) following treatment in DKG-certified endometrial cancer centers.
- Supp. Table **S4b** Unadjusted and adjusted hazard ratios with 95% CI for overall survival (clinical cancer registry [CCR] data, subgroup analyses) following treatment in DKG-certified endometrial cancer centers.
- Supp. Table **S5** Full results for adjusted multivariable Cox regression for overall survival following treatment in DKG-certified endometrial cancer centers (clinical cancer registry [CCR] data).
- Supp. Table **S6** Unadjusted and adjusted hazard ratios with 95% CI for recurrence-free survival (clinical cancer registry [CCR] data) following treatment in DKG-certified endometrial cancer centers.

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Conflict of Interest

OS, VB, CB, and JS work in a university hospital with certified cancer centers, where MR also worked previously. They received grants from the Innovation Fund of the Federal Joint Committee when carrying out the study. Outside of the submitted work, JS received institutional grants for investigator-initiated research from the G-BA, the BMG, BMBF, the EU, the German Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He also took part in advisory board meetings as a paid consultant for Sanofi, Lilly, and the ALK. Outside of the submitted work, OS was a paid consultant for Novartis. He is also a member of the certification committee "Skin Cancer Centers" of the German Cancer Society and a member of the panel of experts for the project "Research into criteria to evaluate certificates and quality seals in accordance with Sec. 137a para. 3 sentence 2 No. 7 SGB V" for the Institute for Quality Assurance and Transparency in Healthcare (IQTIG). PW heads the DKG-certified Breast and Gynecological Cancer Center at the university hospital of the TU Dresden and is an additional member of the Board of Directors of NCT Dresden. PW receives institutional grants for investigator-initiated research from the DFG, Krebshilfe, Sächsische Aufbaubank (SAB), Gynäko-Onkologische Forschungsstiftung, Amgen, AstraZeneca, MSD, Novartis, Pfizer, Roche, Clovis, and GSK. PW receives honoraria as an advisory board member for Amgen, AstraZeneca, MSD, Novartis, Pfizer, Lilly, Roche, Teva, Eisai, Gilead, GSK, and Daiichi Sankyo. OO works in a certified breast cancer center, gynecological cancer center, and oncological center. OO is a member of the Executive Board of the German Cancer Society, head of the University Cancer Center Regensburg, and a member of the Board of Directors of CCC WERA. TL works in a certified breast and gynecological cancer center. TL has received honoraria (lectures/consultancy work/travel costs) from Novartis, Roche, Amgen, GSK, Pfizer, Gilead, Daiichi Sankyo, AstraZeneca, Lilly, Myriad, MSD, and Esai. TP is head of a DKG-certified breast and gynecological cancer center. St. Marien Amberg Medical Center is also an oncology center according to the criteria of the DKG. The other authors state that they have no conflict of interest.

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