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Impact of Epidural Anesthesia on the Outcome of Elderly Patients with Endometrial Cancer: Results of a Propensity Score-Matched Analysis

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Keywords

Epidural anesthesia · Endometrial cancer · Elderly · Outcome · Gynecologic oncology · Recurrence-free survival · Overall survival

Abstract

Introduction: Epidural anesthesia is a standard procedure to mitigate pain during surgery for endometrial cancer (EC). Little data exist about the influence of epidural anesthesia on the oncological outcome in elderly patients with EC. This retrospective study aimed to investigate potential correlations between epidural anesthesia and cancer recurrence in patients with EC. ***Methods:*** We screened the medical records of patients ≥60 years treated surgically for EC at the University Medical Center Mainz between January 2008 and December 2019. All women underwent general anesthesia (GA) alone or combined with epidural anesthesia (EGA). Cox regression, the Kaplan-Meier method and propensity score matching were used to analyze the prognostic influence of the anesthesiologic regime on survival. ***Results:*** A total of 152 women with EC were included. Twenty-nine patients (19.1%) formed the EGA cohort. The median time of follow-up (FU) was 31 months (interquartile range [IQR]: 8–67.5). The EGA cohort showed more in-hospital complications (27.6 vs. 8.9%; $p = 0.006$), especially thromboembolic events (3 vs. 0 events; $p = 0.006$), as well as a longer hospital stay (11 [IQR: 8–13] vs. 7 [IQR: 4–9] days; $p < 0.001$). Twenty-six patients (17.1%) developed a recurrence in the follow-up at a median of 13 months [IQR: 7.75–29.5]. Thirty-two patients died during FU (21.1%). The EGA cohort showed higher FIGO stages and a higher histological grading than the GA cohort. In the Kaplan-Meier analysis, EGA showed a significantly reduced 5-year recurrence-free survival (RFS) (36.5% vs. 72.6%, $p < 0.001$) and overall survival (OS) (58.6% vs. 79.9%, $p = 0.008$). However, in multivariate Cox regression analysis including FIGO stages and histological grading, EGA did not influence RFS (HR: 2.02; 95%-CI: [0.99–4.12], $p = 0.054$), and OS (HR: 1.03; 95%-CI: [0.40–2.66], $p = 0.951$). This was backed up by the propensity score- matched analysis for survival (RFS: $p = 0.604$, OS: $p = 0.86$). ***Conclusion:*** Considering risk factors, epidural anesthesia in combination with GA did not differ in recurrence-free and overall survival compared to GA. Prospective randomized trials are warranted in order to further evaluate this topic.

Introduction

Endometrial cancer (EC) is one of the most common gynecological malignancies in developed countries, accounting for 420,242 new cases worldwide in 2022 [1].

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Although most cases are diagnosed at an early stage, more than 90% of cases of EC occur in women older than 50 years of age [2], with a median age at diagnosis of 61 years [3]. The incidence and the associated mortality are currently rising, potentially due to various factors, including an increasing prevalence of obesity, diabetes and an aging population as well as the decreasing use of progestin-based postmenopausal hormone treatment. Therapy of EC comprises primary surgery in the early stages of the disease. Hereby, epidural anesthesia (EA) is a standard procedure to mitigate pain during surgery, especially for laparotomies. Currently, conclusive information is missing about how perioperative EA in surgical cancer treatment affects cancer recurrence and survival rates [4–6]. Regional analgesia, including neuroaxial analgesia via EA, is recommended in most intra-and postoperative Enhanced Recovery after Surgery (ERAS) protocols of abdominal surgery to perform opioid-sparing anesthesia and improve postoperative analgesia [7]. In general, ERAS in gynecologic oncology reduces the hospital length of stay, complications, and readmissions.

Perioperative EA is widely used in thoracic and abdominal surgeries for various solid neoplasms in order to reduce intraoperative opioids as well as anesthetics, minimize the stress response to surgery, and enhance postoperative pain relief and to lower postoperative in-hospital complications [8, 9]. The use of opioids is associated with an independent risk factor in the metastatic cascade of tumor cells, enabling them to circulate and spread [10].

Surgical resection remains the main curative mode to treat primary solid tumors without metastases. Nevertheless, extensive cancer surgery can create a microenvironment that favors spread of the tumor into the circulatory and lymphatic system. In particular, local pro-inflammatory and wound-healing responses caused by tissue damage during surgery have also been implicated in immunosuppression and in the patient's stress response, possibly triggering a high vulnerability of a patient to increased tumor progression [11, 12].

The precise role of epidural anesthesia in EC patients is still controversial. The aim of this retrospective study was therefore to elucidate how epidural anesthesia affects the oncological outcome in elderly EC patients undergoing surgery.

Methods

Study Population

Clinical records of patients ≥60 years with all stages of EC (based on the 2010 FIGO staging system) who underwent a primary oncological staging operation at the University Medical Center Mainz between January 2008 and December 2019, were screened. Standardized staging operations regardless of the surgical approach (traditional laparotomy or minimally invasive techniques such as laparoscopic or vaginal-assisted surgery) included a hysterectomy with bilateral salpingo-oophorectomy and, depending on the current tumor stage, with or without pelvic and para-aortic lymph node dissection. The surgical treatment was followed by adjuvant radiation or chemotherapy, when appropriated. The study comprised two groups, using either general anesthesia (GA) alone or combined general and epidural anesthesia (EGA). Ethical approval for use of routine patient data for research purposes was not required for this study in accordance with local/national guidelines.

Anesthetic Procedures

The epidural catheter was placed prior to the initiation of GA after obtaining the patient's informed consent, taking into account relative and absolute contraindications, especially abnormal coagulation factors. The GA group received 0.5 μg/kg sufentanil and 1.3–3.0 mg/kg propofol and 0.6 mg/kg rocuronium (rarely atracurium) for introduction. Anesthesia was maintained with approximately 2% volume of sevoflurane, a volatile anesthetic agent monitored using a minimal alveolar concentration (MAC) of 1 in the GA. MAC is defined as "the end-tidal concentration of inhaled anesthetic that ablates movement in response to surgical incision in 50 percent of a test population" [13, 14]. It essentially depends on the patient's age with a decrease of approximately 6% of MAC per decade [15]. GA was conducted as balanced or total intravenous anesthesia according to the standard operating procedures of the Department of Anesthesiology.

Intraoperative epidural anesthesia (EA) was provided by bolus application of bupivacaine 0.25% or more rarely ropivacaine 0.375% with or without the addition of epidural sufentanil according to the attending anesthetist. Lower MAC values were tolerated in the EGA group and controlled by electroencephalogram (EEG) monitoring (Bispectral Index BIS-module, Philips). All patients who received EGA were treated by patient-controlled EA consisting of bupivacaine 0.125% postoperatively. Epidural fentanyl (2 μg/mL) was added as long as the patients were supervised in intensive or intermediate care units, whereas bupivacaine 0.125% alone was used in the general ward. Patients who did not receive EGA or showed signs of insufficient EA received a patient-controlled intravenous anesthesia-device with piritramide. All EGA patients were supervised by a physician-based acute pain service affiliated to the Department of Anesthesiology as long as they received patient-controlled anesthesia.

Data Analysis

We examined hospital charts and records to gather general patient information. Long-term follow-up data were collected through telephone calls, written inquiries

to the patients or their physicians and by checking the available patient clinical records up to February 2021.

Patients' characteristics were expressed as a mean +/− standard deviation [SD] for parametric data or as a median with their interquartile range [IQR] for non-parametric data. Normal distribution was explored by Shapiro-Wilk test, followed either by Mann-Whitney U test if the variables were non-normally disturbed or independent-samples *t*-test for normally disturbed variables. Categorical variables were compared using the chi-square or Fisher's exact test.

We compared prognoses data in the two groups using the Kaplan-Meier estimator from survival analysis for the GA and EGA study cohort. Event times in months were the date of diagnosis which resulted in the date of definitive primary tumor resection up to death due to any cause (or recurrence) or the last follow-up (FU). Patients who were still alive (or without recurrence) and/or had incomplete data were censored.

Cancer recurrence comprised loco-regional lower abdominal recurrences and/or distant metastasis. Recurrence-free survival (RFS) included loco-regional lower abdominal recurrences and/or distant metastasis and death as an oncological event. The log-rank test was used to compare the curves.

Univariate and multivariate Cox regression analyses were also performed to compare the hazard ratio (HR) and 95%-confidence interval (95%-CI) for RFS and OS. Multivariate Cox regression analysis with backward logistic regression included all significant and clinical important variables from the univariate Cox regression analysis. In addition, a propensity score matching was calculated and patients were matched according to significant, as well as non-significant but clinically relevant characteristics found in the Cox regression.

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 27, propensity score matching and calculation of treatment effects were performed in RStudio based on R version 4.2.3 [16, 17]. All tests were two-sided and a p value of <0.05 was considered exploratory because no correction for multiple testing was performed. The manuscript was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [18].

Results

183 patients with EC were screened. 152 women met the inclusion criteria. Table 1 shows the characteristics of the study population. A total of 123 patients formed the GA group (80.9%), while 29 patients received EGA (19.1%). The mean age was 71 (+/−7.4) years, with a minimum age of 60 and a maximum age of 89 years. The two groups were comparable in relation to the demographic characteristics, see Table 1.

Concerning the comorbid conditions and their risk for mortality in longitudinal studies, we evaluated the Charlson-Comorbidity Index (CCI) for both cohorts [19]. The CCI did not show significant differences in the distribution of comorbidities among the groups. Most of the patients reached 3 or 4 points in the CCI, resulting in a predicted 10-year survival rate ranging between 53 and 77% [20].

Most patients (n = 123; 80.9%) were diagnosed in an early cancer stage and with endometrioid adenocarcinoma histological subtype. The EGA cohort comprised less endometrioid EC than the GA cohort (69.0% vs. 88.6%; p = 0.001). Furthermore, the EGA cohort showed significantly higher FIGO stages (p = 0.001) and histological gradings (p < 0.001).

With regard to the anesthetic parameter ASA Physical Status Classification System (ASA PS), no differences were recorded between the two groups (p = 0.305). Moreover, the majority of patients with EGA (n = 27; 93.1%) were operated via laparotomy compared to the GA cohort (n = 48; 39.0%) and thus following standard protocols. The EGA group had longer mean operating times than the GA cohort (192.6 min vs. 130.3 min; p < 0.001).

In addition, the EGA cohort had a significantly longer hospital stay than the GA cohort (11 [IQR: 8–13] vs. 7 [IQR: 4–9] days; p < 0.001). Furthermore, the EGA cohort had more in-hospital complications (27.6 vs. 8.9%; p = 0.006), especially more thromboembolic events (3 vs. 0 events; p = 0.006). The other perioperative complications including pulmonary events, wound infections and multiple organ failure were comparable. Surgical revisions were only observed in the GA cohort (n = 4 [3.3]; p = 0.425). The blood transfusion rate appeared to be slightly higher in the EGA group with 20.7% than in the GA cohort with 10.6% (p = 0.138).

Median time of FU was 31 months [IQR 8–67.5]. Overall, 26 patients (17.1%) developed a recurrence during the FU period, at a median of 13 months [IQR: 7.75–29.5]. Patients in the EGA cohort had more tumor recurrences (44.8 vs. 10.6%, p < 0.001) and died more often during follow-up (41.4 vs. 16.3%; p = 0.003), see Table 1.

In the univariable Cox regression analysis, EGA was associated with a significantly decreased RFS and OS (HR: 3.41; 95%-CI: [1.87–6.24]; p < 0.001 and HR: 2.54; 95%-CI: [1.24–5.20]; p = 0.011, respectively) (Table 2). In the multivariate analysis, adjusted for the conventional prognostic factors including mean BMI, mean age, FIGO stage, histological subtype and grading, ASA PS and surgical approach, there was no difference of EGA and GA detectable for RFS (HR: 2.02; 95%-CI: [0.99–4.12], p = 0.054), nor for OS (HR: 1.03; 95%-CI: [0.40–2.66],

Table 1. Clinical features of the study population

Parameter	Total, *n* = 152	EGA, *n* = 29	GA, *n* = 123
Demographic characteristics			***p* > 0.05**
Mean age, years	71.07 (±7.40)	70.72 (±6.77)	71.15 (±7.53)
Smoking status	13 (9.4)	2 (7.1)	11 (10.0)
Charlson-Comorbidity Index (CCI)			
0	0	0	0
1–2	36 (23.7)	5 (17.2)	31 (25.2)
3–4	72 (47.4)	15 (51.7)	57 (46.3)
≥5	44 (28.9)	9 (31.0)	35 (28.5)
Demographic characteristics			***p* = 0.03**
Mean BMI, kg/m^2	30.16 (±7.71)	27.92 (±7.26)	30.67 (±7.75)
Clinico-pathological tumor characteristics			
Tumor Stage (TNM – FIGO)			***p* = 0.001**
I	123 (80.9)	16 (55.2)	107 (87.0)
II	7 (4.6)	3 (10.3)	4 (3.3)
III	12 (7.9)	6 (20.7)	6 (4.9)
IV	10 (6.6)	4 (13.8)	6 (4.9)
Histological subtype			***p* = 0.008**
Endometrioid	129 (84.9)	20 (69.0)	109 (88.6)
Others	23 (15.1)	9 (31.0)	14 (11.4)
Histological grading			***p* < 0.001**
G1	74 (49.3)	8 (27.6)	66 (54.5)
G2	46 (30.7)	5 (17.2)	41 (33.9)
G3	30 (20.0)	16 (55.2)	14 (11.6)
Anesthetic and surgical characteristics			
ASA Classification			*p* = 0.305
I	4 (2.6)	1 (3.4)	3 (2.4)
II	59 (38.8)	7 (24.1)	52 (42.3)
III	88 (57.9)	21 (72.4)	67 (54.5)
IV	1 (0.7)	0	1 (0.8)
Surgical approach			***p* < 0.001**
Laparoscopic	57 (37.5)	2 (6.9)	55 (44.7)
Vaginal	20 (13.2)	0	20 (16.3)
Laparotomy	75 (49.3)	27 (93.1)	48 (39.0)
Operating time			***p* < 0.001**
Mean, min	142.2 (±82.4)	192.6 (±94.7)	130.3 (±74.8)
Length of hospital stay			***p* < 0.001**
Days (IQR)	7 (5–10)	11 (8–13)	7 (4–9)
Perioperative events			***p* = 0.006**
In-hospital complications	19 (12.5)	8 (27.6)	11 (8.9)
Thromboembolic	3 (2)	3 (10.3)	0
Perioperative events			*p* > 0.05
Transfusion rate	19 (12.5)	6 (20.7)	13 (10.6)
Pulmonary	5 (3.3)	1 (3.4)	4 (3.3)
Wound infection	8 (5.3)	3 (10.3)	5 (4.1)
Multiple organ failure	3 (2)	1 (3.4)	2 (1.6)
Surgical revision	4 (2.6)	0	4 (3.3)
Clinical Events			***p* ≤ 0.003**
Recurrence	26 (17.1)	13 (44.8)	13 (10.6)
Death (causes)	32 (21.1)	12 (41.4)	20 (16.3)
Endometrial Cancer	19 (12.5)	8 (27.6)	11 (8.9)
Therapy-related	1 (0.7)	1 (3.4)	0
Intercurrent disease	5 (3.3)	1 (3.4)	4 (3.3)
Other malignancies	2 (1.3)	0	2 (1.6)
Unknown	5 (3.3)	2 (6.9)	3 (2.4)

Values are given as *n* (% epidural) or mean (±SD). BMI, body mass index; CCI, Charlson-Comorbidity Index; G, histological Grading; GA, general anesthesia; EC, endometrial cancer; EGA, epidural general anesthesia; IQR, interquartile range; SD, standard deviation; TNM-FIGO, Tumor Staging System – International Federation of Gynecology and Obstetrics.

Table 2. Cox's proportional hazards model of selected parameters and relationship to recurrence-free and overall survival

	Univariate RFS			Multivariate RFS			Univariate OS			Multivariate OS		
	HR	[95% CI]	*p* value	HR	[95% CI]	*p* value	HR	[95% CI]	*p* value	HR	[95% CI]	*p* value
Demographic characteristics												
Mean age (lower vs. higher than average)	1.23	0.68–2.21	0.500				1.10	1.00–1.10	**0.036**	1.01	0.96–1.06	0.792
Mean BMI (lower vs. higher than average)	0.48	0.25–0.96	**0.038**	0.94	0.89–1.00	**0.049**	0.94	0.89–1.00	*0.052*	0.90	0.84–0.97	**0.007**
Smoking status (no smoker vs. smoker and former smoker)	1.32	0.47–3.7	0.604				0.93	0.22–3.91	0.917			
Clinical-pathological tumor parameters												
Tumor Stage – FIGO Local (stage I) vs. advanced (stages II-IV)	4.47	2.44–8.18	<**0.001**	2.51	1.21–5.23	**0.014**	4.81	2.38–9.73	<**0.001**	2.28	1.01–5.15	**0.046**
Histological subtype (endometrioid vs. others)	0.39	0.20–0.77	**0.006**	1.18	0.51–2.72	0.702	0.34	0.16–0.74	**0.007**	1.06	0.40–2.83	0.905
Histological grading (G1 vs. G2/G3)	2.43	1.26–4.67	**0.008**	1.45	0.68–3.08	0.336	3.60	1.54–8.41	**0.003**	2.49	0.99–6.29	*0.054*
Anesthesiologic and Surgical parameters												
ASA PS (ASA ≤2 vs. ASA >2)	2.44	1.26–4.76	**0.009**	2.86	1.40–5.84	**0.004**	3.33	1.43–7.72	**0.005**	4.86	1.96–12.03	<**0.001**
Epidural general anesthesia (GA vs. EGA)	3.41	1.87–6.24	<**0.001**	2.02	0.99–4.12	*0.054*	2.54	1.24–5.20	**0.011**	1.03	0.40–2.66	0.951
Surgical Approach (laparoscopic, vaginal vs. laparotomy)	2.10	1.10–3.96	0.024	1.31	0.61–2.79	0.487	2.02	0.95–4.31	*0.067*	1.47	0.62–3.46	0.381

Each factor was evaluated in a separate univariate Cox proportional hazards regression model, stratified by cohort (referent vs. variable X). HR, hazard ratio; [95% CI]: 95% confidence interval; TNM-FIGO, Tumor Staging System – International Federation of Gynecology and Obstetrics; ASA PS, American Society of Anesthesiologists Performance Status; GA, general anesthesia; EGA, epidural general anesthesia; bold written numbers, statistically significant *p* values <0.05; italic written numbers, clinically relevant *p* values <0.1.

$p = 0.951$). A higher FIGO stage, a higher BMI and a higher ASA PS (and a higher histological grading) correlated significantly associated with shorter RFS and OS, see Table 2.

Each factor was evaluated in a separate univariate Cox proportional hazards regression model, stratified by cohort (referent vs. variable X). This was backed up by a subgroup analysis, comprising only patients with laparotomy. Here, EGA was also not associated with a reduced RFS in patients with laparotomy (HR: 1.58; 95%-CI: [0.75–3.31], $p = 0.229$), when adjusted to multiple risk factors.

In the Kaplan-Meier analysis, the EGA group showed a significantly reduced 5-year RFS (36.5% vs. 72.6%, $p < 0.001$) and OS (58.6% vs. 79.9%, $p = 0.008$). However, this was refuted by the propensity score-matched analysis. The propensity score matching, performed for 149 patients, due to missing data in 3 cases, did not show a significant impact of EGA on RFS or OS (RFS: $p = 0.604$; OS: $p = 0.86$), when matched to FIGO stage, mean BMI, histological type, grading as well as surgical approaches, see Figure 1.

Discussion

In this study, EGA was not associated with a decreased RFS and OS in elderly women with EC after accounting for multiple previously established risk factors for this entity. It is noteworthy that the EGA group included significantly more patients with advanced EC (stage II–IV) than the GA group which might also adversely affect the RFS. This is underlined by the subgroup analysis in the EC cohort only operated

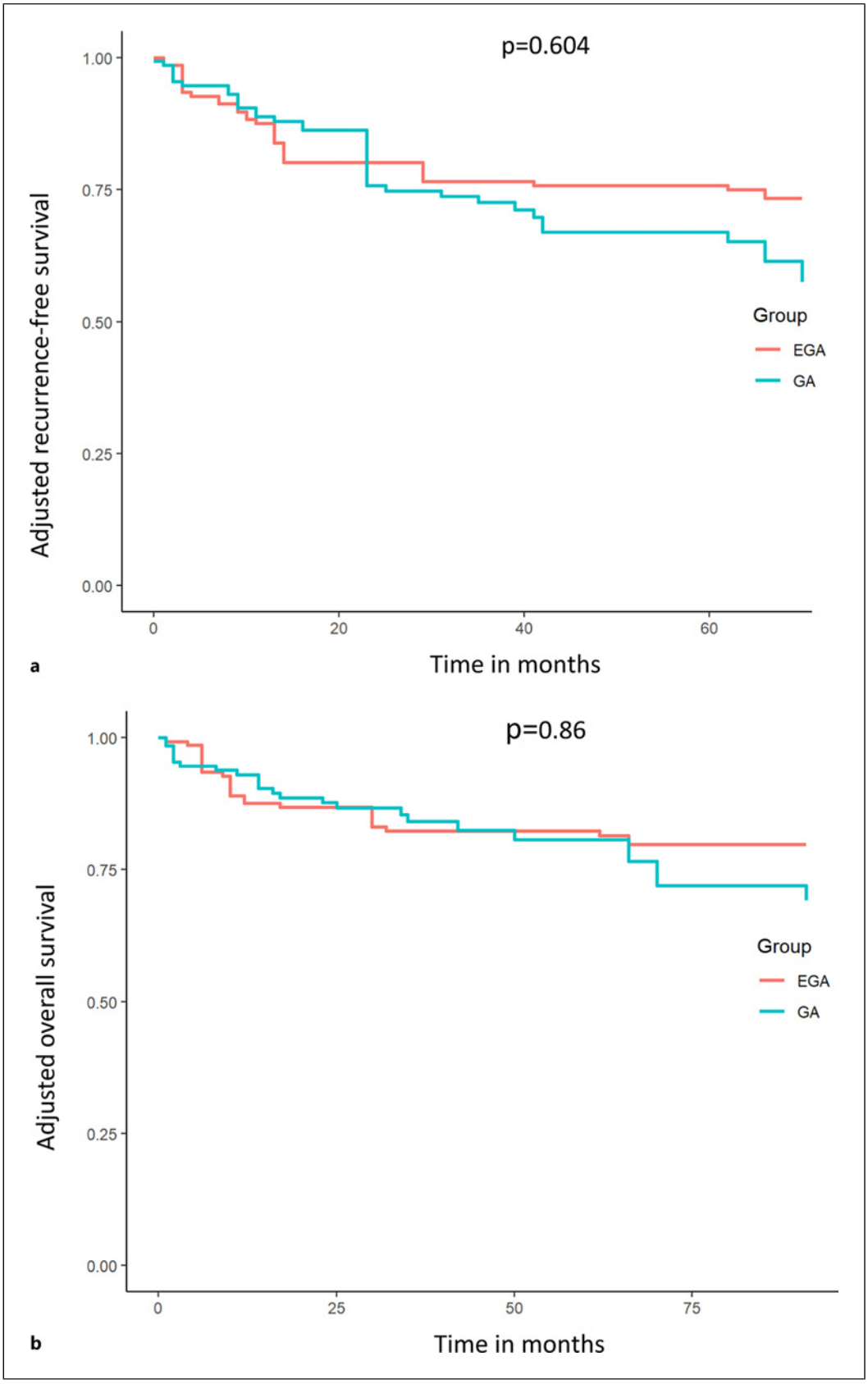

Fig. 1. Propensity score-matched survival estimates. **a** Adjusted recurrence-free survival: GA vs. EGA. **b** Adjusted overall survival: GA vs. EGA. GA, general anesthesia; EGA, epidural general anesthesia.

by laparotomy, in which EGA did not show a negative influence on RFS in multivariate analysis. In general, advanced-stage EC undergo open surgery with laparotomy and therefore require more often EGA for analgesia. Furthermore, the patients of the EGA group more frequently scored G3 tumor grading which might accelerate the tumor growth and spread. These factors might have therefore biased the effect of EGA in the univariate analysis. Local pro-inflammatory and wound-healing responses due to tissue damages might be implicated in modulating the patient's stress response and thus may generate a high vulnerability for tumor progression [11, 21].

A multicenter, prospective randomized trial comparing abdominal vs. laparoscopic hysterectomies could show in a subgroup analysis that EGA was associated with an increase in postoperative complications and length of hospital stay after abdominal hysterectomy in EC stage I, supporting our data. In this study of Belavy et al. [22] both groups differed in the pattern of analgesic use in the first 2 weeks after surgery. The authors speculated that the shorter transition to non-opioid analgesia in the GA group was the reason for the better outcome in this cohort. It is important to note that the patients were not randomized to the EGA or GA group. The operating time in this study was similar in both groups compared to our study, in which the patients of the EGA had longer operating times. The latter might negatively affect the surgical and oncological outcome due to a longer exposure to intraoperative opioids and anesthetics. Furthermore, longer operating times seem to be associated with increased postoperative complications in patients undergoing minimal-invasive surgery for endometrial cancer in general [23].

Another large database study including more than 2,035 patients receiving EGA at abdominal hysterectomy for gynecologic malignancies showed a higher 30-day complication rate among the EGA group as well as a longer hospital stay, retrospectively. The 30-day mortality was not affected in this analysis of the American College of Surgeons' National Surgical Quality Improvement Program database [24]. The increased complication rate could be due to the use of EGA in more complex surgical cases according to Ackroyd et al. [24] This might also be the reason for our increased in-hospital complication rate in the EGA group. In our study, patients in the EGA cohort had more thromboembolic events. A possible explanation could be reduced postoperative mobilization, resulting from longer open surgeries and an extended hospital stay compared to the GA cohort. The above mentioned large database study showed comparable rates of deep venous thromboembolism (GA: 0.9% vs. EGA: 1.5%) and pulmonary embolism (GA: 2% vs. EGA: 1.8%) in both cohorts. Nevertheless, a meta-analysis in 2014 showed a decrease in deep vein thrombosis thanks to EGA [25]. In addition, in our analysis, a major proportion of patients underwent open surgery for early stages of EC. Nowadays, minimal-invasive surgery has increasingly become the standard surgical procedure for patients with EC in Germany [26, 27]. Minimal-invasive surgery seems to be safer and more effective than open surgery [26, 28]. Furthermore, robotic-assisted surgery is also increasing. Consequently, our study could have reported higher rates of complications and surgical revisions compared to current standards. Moreover, EGA is predominantly used in open surgical techniques, which could influence its application in the evolving landscape of modern surgical practices.

In our study, a potential negative influence could not be reproduced in multivariate analysis for RFS and OS. Unlike other gynecological malignancies, EC usually has a good prognosis and a potential effect of perioperative epidural anesthesia treatment on OS might not be detectable due to short follow-ups.

Some published studies could link EGA to an improved PFS and sometimes also to an improved OS in big abdominal surgeries [21]. However, no obvious relationship between the improvement in prognosis of colorectal cancer comparing EGA to only GA could be detected in other studies [29, 30]. This is underlined by a randomized trial in 2011 which could not verify any influence of EGA on cancer-free survival in major abdominal surgery for cancer [31]. A recent study from 2021 that evaluated analgesia with EGA for major lung cancer surgery could not show improved RFS, OS, or cancer-specific survival compared with GA alone [32].

Only one study in a narrative review concerning the influence of perioperative anesthetic and analgesic interventions on oncological outcomes published in 2018 showed a negative effect of EGA compared to GA. This study demonstrated that the EGA cohort undergoing radical cystectomy had a worse RFS (HR: 1.67) and disease specific survival (HR: 1.53) compared to GA alone. The authors explained the effect due to the use of epidural sufentanil or due to the consecutively increased total morphine equivalents [33].

Moreover, previous findings in gynecological patients with ovarian cancer and EGA did not show a significant impact on progression-free survival (PFS) and OS [34]. Nevertheless, De Oliveira and colleagues showed an association of an intraoperative use of EA with an increased time to tumor recurrence after surgery in ovarian cancer patients in 2011 [35]. To sum up, the discrepant results observed in these cited studies on the impact of EA on oncological outcomes across various cancer types and tumor biologies underscore the challenges in comparing findings in this research field. It is difficult to conclusively rule out an effect on outcome related EA; however, the current overall consensus within the field of oncology anesthesia is that recent prospective trial data support the conclusion that EA does not influence cancer recurrence or overall survival [6, 31, 32, 36, 37].

Limitations

Study limitations arose due to the retrospective, non-randomized and single-center design of the study. We selected patients aged ≥60 years because this analysis was part of a retrospective study investigating frailty screenings in gynecologic oncology patients at the University Medical Center Mainz [38]. The global median age for newly diagnosed EC is currently 61 years [3], with a slightly higher mean average of 67 years in Germany in 2020 [39]. Consequently, the majority of EC patients were included. Nevertheless, expanding the study to include a younger patient population could potentially provide different clinical insights.

We acknowledge that we are unable to know the details of the epidural placement and the detailed perioperative use of medication. The enrollment period may have been sufficiently lengthy for surgical techniques and overall perioperative care within our organization to have undergone significant changes during that time.

In addition, the two cohorts were heterogenous, especially with regard to tumor stage and grading. There are also other limitations in this study besides the low cohort number. The inherent limitations involved in the definition of the term RFS should be considered. Only studies using the same definitions of the endpoints can really be compared. In addition, cancer recurrence was not systematically checked according to standardized protocols and, therefore, potentially biased. Furthermore, a staging according to the TCGA molecular subgroups was not available [40].

However, we performed a propensity score matching as an established, reliable method to reduce bias in observational studies. Moreover, to our knowledge, we present data of EGA and its influence on the oncological outcome in EC patients for the first time.

Conclusion

EGA is important in the advanced surgical treatment of oncological patients, including EC patients ≥60 years. Literature concerning the impact of EGA on the oncological outcome is inconsistent. We did not observe any statistically significant negative influence of EGA on RFS compared to GA in our elderly cohort when adjusted for multiple risk factors. Yet, generalizability is not possible due to the study limitations. Patients in the EGA cohort had a longer hospital stay and more in-hospital complications, especially thromboembolic events, possibly due to the higher use of EA during more complex, open surgeries. To further investigate the influence of EGA on the oncological outcome, prospective randomized trials are urgently needed in EC patients.

Statement of Ethics

The retrospective cohort study was conducted in accordance with the "Ethical principles for medical research involving human subjects" of the current version of the Declaration of Helsinki. Data collected for this study was obtained as a part of routine medical care in our department (reference No. 837.287.05(4945); Ethical Review Board of Rhineland-Palatinate). A particular ethical approval/written consent for this study was not required according to local guidelines.

Conflict of Interest Statement

The authors state that no relevant conflicts of interests are to declare. K.G. reports paid lectures by Clovis Oncology, AstraZeneca, Pharma Mar, MSD and Eisai not related to this trial. M.J.B. reports honoraria and expenses from Pharma Mar AG, Astra Zeneca, TesaroBio GmbH, GSK, Roche, Clovis Oncology and consultant activity to AstraZeneca, Clovis Oncology, Eisai, GSK, MSD, PharmaMar, Roche and Tesaro Bio GmbH. Furthermore, he has received research funding by AstraZeneca, Clovis Oncology, MSD, Eisai and Novartis. None were related to this study. E.-V.G. received personal fees from Edwards Lifesciences Services GmbH and Medtronic GmbH. None were related to this study. A.H. reports honoraria and expenses from AstraZeneca, Celgene, Leo Pharma, MedConcept GmbH, Med update GmbH, Medpublico GmbH, Pfizer, PharmaMar GmbH, Pierre Fabre Pharma GmbH, Roche Pharma AG, Tesaro Bio Germany GmbH as well as work as a consultant to MSD SHARP and DOHME GmbH, PharmaMar, Medpublico GmbH, Pierre Fabre Pharma GmbH, Roche Pharma AG and Tesaro Bio Germany GmbH. None were related to this study. Marc.S. reports personal fees from AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Lilly, MSD, Novartis, Pantarhei Bioscience, Pfizer, Pierre Fabre, Roche, and SeaGen, His institution has received research funding from AstraZeneca, BioNTech, Eisai, Genentech, German Breast Group, Novartis, Palleos, Pantarhei Bioscience, Pierre Fabre, and SeaGen. In addition, he has a patent for EP 2390370 B1 and a patent for EP 2951317 B1 issued. None were related to this study.

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Author Contributions

Design of the work: K.G., V.C.L., and M.J.B. Data acquisition: K.G. and M.J.B. Data analysis: V.C.L., K.G., Mark.S., M.W.S, R.H.,and M.J.B. Writing of paper: V.C.L., K.G., M.J.B, R.H., Mark.S., M.W.S., Marc.S., E.-V.G., A.H. and M.J.B. All authors critically and substantively revised the manuscript.

Data Availability Statement

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants but are available from the corresponding author V.C.L. upon reasonable request.

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