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ORIGINAL ARTICLE

Peri-operative and survival outcomes analysis of patients with endometrial cancer managed by three surgical approaches: a long-term Bulgarian experience

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Abstract

The study aim was to assess the peri-operative, oncologic, and survival outcomes for patients with endometrial cancer (EC) managed by abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), or robotic hysterectomy (RH) approaches at premier centers in Bulgaria. We analyzed histologically diagnosed EC cases operated via any of the three surgical methods during 2008–2019. Data analyses included patients and tumor characteristics, peri-operative outcomes, and disease status. We grouped FIGO stages I and II to represent early-stage EC and to investigate their survival. Kaplan–Meier and Cox regression analyses were performed to determine disease-free survival (DFS) and overall survival (OS). Consecutive 917 patients (AH = 466; LH = 60, RH = 391) formed the basis of study analyses. Most of demographics and tumor characteristics of the patients were comparable across the groups except few minor variations (e.g., LH/RH cases were younger, heavier, more stage IA, endometrioid, G1, low-risk group). LH and RH group cases had significantly lower operative time than AH ($p < 0.001$), shorter hospital length-of-stay ($p < 0.001$), higher post-operative Hgb ($p < 0.001$). RH cases had fewer blood transfusions than AH or LH ($p < 0.001$). Cox multivariate analyses indicate that OS was not influenced by the type of surgical approach. Despite the fact that the DFS in "early-stage" EC is significantly better in AH group than RH, the type of surgery (i.e., AH, LH, or RH) for "all stages" is insignificant factor for DFS. With our long-term experience, minimally invasive surgical approach resulted in superior peri-operative, oncologic, and survival outcomes. Specifically, RH is not only safe in terms of post-operative results, but also for mortality and oncologic rates.

Keywords Endometrial cancer · Abdominal vs. laparoscopic vs. robotic surgery · Peri-operative outcomes · Oncologic factors · Survival analysis · Bulgarian experience

Introduction

Globally, the second most common gynecologic malignancy is endometrial cancer (EC) [1]. Surgical treatment is considered to be the standard of care for this disease. In the past decades, total abdominal hysterectomy (AH) was the most common approach and considered to be a gold standard for surgical management of EC. Technological innovations and evolution in medicine, particularly in surgery, played integral part of the process for the treatment of malignant tumors. Such processes led to the development of minimally invasive surgical (MIS) approaches for EC in recent decades, i.e., total laparoscopic hysterectomy (LH) and robotic-assisted hysterectomy (RH). Nowadays, these three surgical approaches for the treatment of EC vary across the globe

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depending on the surgical skills and available resources at a given center.

The first reports of LH in women with histologically proven EC dates back to 1993, when Childers and colleagues published their experience in laparoscopic treatment of this cancer [2], and the first publications on RH began after nearly a decade [3]. Since the first US Food and Drug Administration (FDA) clearance of the da Vinci® robotic surgerical system (Intuitive Surgical, Inc., Sunnyvale, CA) for gynecologic indications in 2005, most of the limitations encountered during LH are being overcomed by RH due to wristed instruments, improved visualization, ergonomics and precision, including tremor filtering [4, 5]. The fact that MIS compared to AH led to reduction in morbidity in women with histologically proven EC has been confirmed by a number of randomized clinical trials [6–10].

Some specialized institutions provided early evidence that RH approach improves and enhances the use of MIS technologies [11–14], which has gathered speed ferociously. Within the MIS approaches, the RH approach seems to have advantages over purely LH such as increased accuracy, enhanced dexterity, shorter operative time, lower estimated blood loss (EBL), decreased hospital length-of-stay (LOS), complications rate, etc. The oncologic and survival outcomes comparing MIS and AH approaches are rather limited or ambiguous. Therefore, in this study, we sought to perform a retrospective study of over 10 year of our experience at two premier centers in Bulgaria to compare the peri-operative, oncologic, and survival outcomes for EC patients managed with three different surgical approaches.

Materials and methods

This study includes data from total hysterectomies performed in women with histologically proven EC using one of the three surgical approaches, i.e., AH, LH, or RH. It covers a period of more than 10 years, from 2008 to April 2019. All the surgeries were performed at two major centers of Bulgaria, viz., University Hospital "Saint Marina"—Pleven, and University Hospital "Dr. Georgi Stranski"—Pleven. We evaluated such key parameters as peri-operative, oncologic, and survival outcomes [i.e., disease-free survival (DFS) and overall survival (OS)]. The post-surgical follow-up consisted of regular visits at 1-month post-operatively, then every 3 months for 2 years, every 6 month up to 5 years, and annually thereafter.

Tumor characteristics include stage (TNM classification and FIGO classification) and histology (endometrioid, clear-cell, squamous cell and serous carcinoma and carcinosarcoma). Stage was derived from surgical pathology reports and patient epicrises. We grouped FIGO stages I and II to represent early-stage endometrial carcinoma and to investigate survival outcomes for this group. Based on the first joint European Society for Medical Oncology (ESMO), the European Society for Radiotherapy & Oncology (ESTRO), and the European Society of Gynaecological Oncology (ESGO) consensus conference on EC (December 2014, Milan, Italy; [15]) and the recommendations by Jørgensen et al. [16], we defined the following risk stratification groups: 'Low' (endometrioid adenocarcinoma FIGO IA G1-2); 'Intermediate' (endometrioid adenocarcinoma FIGO IB G1-2); 'High-intermediate' (endometrioid adenocarcinoma FIGO IA G3); 'High' (endometrioid adenocarcinoma FIGO IB G3; non-endometrioid FIGO I; FIGO II; FIGO III); 'Advanced' (FIGO IVA); and 'Metastatic' (FIGO IVB).

Our retrospective study of consecutive data collection was designated as quality assessment, quality improvement, and hypothesis-generating, and allowed by our Institutional Review Board (Research Ethics Commission), hence no separate patient consent was necessary.

Data were abstracted from patients' medical records (hard charts and electronic system), entered in an internally secured database, and processed with the statistical package IBM SPSS Statistics 25.0 and MedCalc Version 14.8.1 (Chicago, IL). A significance level at which the null hypothesis is rejected was $p < 0.05$. The following statistical methods were applied: χ^2, Fisher's exact test, Comparison of proportions, One-sample Kolmogorov–Smirnov, Shapiro–Wilk, test of Mann–Whitney, Kaplan–Meier Product Limit Estimation of the Survival Function, tests Log Rank, Breslow and Tarone-Ware, and Cox proportional hazards analyses.

Results

Peri-operative outcomes

This analysis included 917 consecutive patients (age 30–91 years) with EC who underwent hysterectomy procedures with one of the three surgical approaches during 2008–2019. The vital status of the patients was updated on July 9, 2019 (cut-off date). As shown in Table 1, there were following number of cases in different surgical groups: RH = 391 (42.6%), AH = 466 (50.8%), and LH = 60 (6.5%), respectively. The patient demographics and tumors characteristics are summarized and compared in Table 1. A relatively higher mean age was noted in AH (63.9 ± 9.59 years) and LH 63.73 ± 9.86 years) groups of EC patients as compared to those in RH group (61.98 ± 10.15 years), particularly in the older cases, i.e., age group ≥ 60 years. No significant difference was noted in the BMI, FIGO stage IB and II, pT1b and pT2, clear cell and serous histology cases when comparing for the three surgical groups of patients. Also, the size of the uterus [corresponding to 8 weeks of gestation (w.g.) and 12 w.g.], previous surgery (involving

Table 1 Demographics and tumor characteristics of patients with endometrial cancer treated with different surgical approaches

Characteristics	AH (Group 1)	LH (Group 2)	RH (Group 3)	*p* value between groups		
				1 vs. 2	1 vs. 3	2 vs. 3
Type of surgery						
n (%)	466 (50.8)	60 (6.5)	391 (42.6)			
Age (years)						
$\overline{X}$(SD)	63.90 (9.59)	63.73 (9.86)	61.98 (10.15)	0.971	**0.004**	0.196
Age group (years)						
n (%)						
30–39	5 (1.1)	0	8 (2.0)	0.906	0.427	0.566
40–49	22 (4.7)	4 (6.7)	32 (8.2)	0.721	0.050	0.866
50–59	107 (23.0)	16 (26.7)	103 (26.3)	0.635	0.299	0.927
≥ 60	332 (71.2)	40 (66.7)	248 (63.4)	0.569	0.018	0.726
BMI (kg/m^2)						
$\overline{X}$(SD)	29.32 (6.12)	27.98 (4.51)	33.20 (10.37)	0.586	0.165	0.257
Pre-operative hemoglobin (Hgb)						
$\overline{X}$(SD)	120.33 (16.23)	130.38 (15.18)	127.45 (13.37)	**< 0.001**	**< 0.001**	**0.029**
Pre-operative hematocrit (Hct)						
$\overline{X}$(SD)	34.92 (4.98)	38.22 (4.94)	37.11 (4.06)	**< 0.001**	**< 0.001**	**0.009**
Previous surgery						
n (%)						
None	24 (5.2)	0	9 (2.3)	0.138	**0.044**	0.490
1 Laparotomy	36 (7.7)	20 (33.3)	44 (11.3)	**< 0.001**	0.092	**< 0.001**
2 Laparotomies	6 (1.3)	3 (5.0)	6 (1.5)	0.122	0.965	0.187
≥ 3 Laparotomies	399 (85.8)	37 (61.7)	332 (84.9)	**< 0.001**	0.784	**< 0.001**
Size of uterus						
n (%)						
Normal	208 (44.6)	38 (63.3)	233 (59.6)	**0.001**	**< 0.001**	0.687
4 w.g	53 (11.4)	8 (13.3)	24 (6.1)	0.827	**0.001**	0.079
8 w.g	94 (20.2)	11 (18.3)	74 (18.9)	0.861	0.696	0.947
12 w.g	68 (14.6)	3 (5.0)	44 (11.3)	0.065	0.208	0.185
≥ 16 w.g	43 (9.2)	0	16 (4.1)	**0.028**	**0.005**	0.221
FIGO stage						
n (%)						
IA	96 (20.6)	28 (46.7)	165 (42.2)	**< 0.001**	**< 0.001**	0.606
IB	231 (49.6)	26 (43.3)	176 (45.0)	0.434	0.202	0.915
II	41 (8.8)	4 (6.7)	33 (8.4)	0.763	0.846	0.932
III	84 (18.0)	2 (3.3)	17 (4.3)	**0.007**	**< 0.001**	0.989
IV	14 (3.0)	0	0	0.351	**0.001**	–
pT stage						
n (%)						
pT1a	103 (22.1)	28 (46.7)	165 (42.2)	**< 0.001**	**< 0.001**	0.606
pT1b	240 (51.5)	26 (43.3)	178 (45.5)	0.290	0.093	0.858
pT2	50 (10.7)	4 (6.7)	36 (9.2)	0.462	0.539	0.696
pT3	65 (13.9)	2 (3.3)	12 (3.1)	0.034	**< 0.001**	0.752
pT4	8 (1.7)	0	0	0.649	**0.026**	–
Histology						
n (%)						
Endometrioid	390 (83.7)	57 (95.0)	365 (93.4)	**0.034**	**< 0.001**	0.851
Clear cell	25 (5.4)	0	12 (3.1)	0.128	0.140	0.340
Carcinosarcoma	40 (8.6)	1 (1.7)	11 (2.8)	0.106	**0.001**	0.950

Table 1 (continued)

Characteristics	AH (Group 1)	LH (Group 2)	RH (Group 3)	*p* value between groups		
				1 vs. 2	1 vs. 3	2 vs. 3
Squamous cell	5 (1.1)	0	0	0.906	0.102	–
Serous	6 (1.3)	2 (3.3)	3 (0.8)	0.529	0.708	0.294
Grade						
n (%)						
G1	166 (35.6)	29 (48.3)	191 (48.8)	0.076	**< 0.001**	0.947
G2	214 (45.9)	22 (36.7)	153 (39.1)	0.226	0.053	0.831
G3	86 (18.5)	9 (15.0)	47 (12.0)	0.628	**0.012**	0.656
Histopathological risk group						
n (%)						
Low	79 (17.0)	25 (41.7)	142 (36.3)	**< 0.001**	**< 0.001**	0.507
Intermediate	180 (38.6)	20 (33.3)	151 (38.6)	0.513	0.944	0.519
High-intermediate	7 (1.5)	2 (3.3)	10 (2.6)	0.628	0.368	0.907
High	126 (27.0)	12 (20.0)	76 (19.4)	0.315	**0.011**	0.948
Advanced	65 (13.9)	1 (1.7)	12 (3.1)	**0.013**	**< 0.001**	0.851
Metastatic	9 (1.9)	0	0	0.587	**0.016**	–
Other malignant tumor (concomitant)						
n (%)	12 (2.6)	1 (1.7)	6 (1.5)	0.985	0.379	0.654

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy, *BMI* Body mass index, *SD* Standard deviation, *Hgb* Hemoglobin, *Hct* Hematocrit, *w.g.* Weeks of gestation

two laparotomies), other malignant concomitant tumor, and intermediate- and high-intermediate histopathologic risk groups were not significant across the board (Table 1). A statistically significant difference was noted between the MIS group and the laparotomy group in terms of pre-operative hemoglobin (Hgb) and hematocrit (Hct) ($p < 0.001$).

Comparative analysis for the presence of previous surgery shows significant differences in all categories except "two laparotomies". The highest number of women (without previous surgery) was observed in the AH group, followed by RH and LH. Patients with one previous laparotomy have a significantly higher rate in the LH group (33.3%) than the other two groups, whose relative proportions did not differ statistically (RH = 11.3% and AH = 7.7%, $p = 0.092$). When analyzing "≥ 3 laparotomies", a significantly lower rate was observed in women operated by LH (61.7%) compared to those who cases underwent RH (84.9%) and AH (85.8%) group (Table 1). A notable difference among the three surgical groups was observed for all sizes of uterus except cases with 8 and 12 w.g. The largest uterine size (≥ 16 w.g.) represented a significantly higher rate in the AH group (9.2%) compared to other two groups (RH = 4.1% and LH = 0%, $p < 0.001$).

Considering the stage dependencies per the FIGO classification, 95.6% of RH patients and 96.7% of LH were of stage I and II (i.e., early-stage carcinoma), whereas AH patients were only 79% with this classification (Table 1). For stage III and IV, AH group of patients had significantly higher number of cases compared to the two MIS groups. As per the TNM classification, significantly higher rates in women with EC stages up to pT2 were noted in the MIS groups (AH = 96.9% and LH = 96.7%), where higher stages (pT3 and pT4) were significantly in higher proportion in the AH group (21%). Across the board, endometrioid carcinoma was the most common histology, and AH group also showed the prevalence of 8.3% carcinosarcoma cases compared to negligible cases in the MIS group ($p = 0.001$). Significantly differences in the G1 and G3 cases were noted among the groups ($p < 0.001$). Comparative analysis of histopathologic risk group revealed that low-risk patients were relatively more common in the MIS groups, whereas high-risk/advanced-risk patients were significantly more prevalent in the AH group (Table 1).

Table 2 summarizes a comparative assessment of peri-operative, surgical outcomes, and complication rates of EC patients managed with three surgical approaches. Mean operative time, hospital LOH, blood transfusion rates were significantly higher in the AH group as compared to the MIS groups. Lymph node retrieval was significantly lower in LH (33.3%) as compared to the RH (57.5%) and AH (56%) groups. Despite relatively lower number of mean nodes retrieved across the board, the mean node counts were significantly higher in the AH group as compared to the MIS groups ($p < 0.001$). Favorable peri-operative results with respect to post-operative hemoglobin (Hgb) and hematocrit (Hct) were noted in the MIS group compared to AH group of cases (Table 2). Intra- and post-operative complication

Table 2 Peri-operative, surgical outcomes, and complication rates of patients with endometrial cancer treated with different surgical approaches

Characteristics	AH (Group 1) ($n=432$)	LH (Group 2) ($n=59$)	RH (Group 3) ($n=374$)	p value between groups		
				1 vs. 2	1 vs. 3	2 vs. 3
Surgical/operative time (min)						
$\overline{X}$(SD)	115.35 (33.04)	81.44 (39.46)	93.37 (33.28)	**< 0.001**	**< 0.001**	**0.001**
Postoperative Hgb						
$\overline{X}$(SD)	113.10 (15.52)	121.25 (11.2)	118.77 (12.93)	**< 0.001**	**< 0.001**	**0.160**
Postoperative Hct						
$\overline{X}$(SD)	32.97 (4.9)	35.29 (4.9)	34.48 (3.9)	**0.005**	**< 0.001**	0.264
Lymphadenectomy						
n (%)	261 (56.0)	20 (33.3)	225 (57.5)	**0.001**	0.678	**0.001**
Number of lymph nodes (mean)						
$\overline{X}$(SD)	6.38 (7.99)	1.38 (2.78)	2.29 (4.28)	**< 0.001**	**< 0.001**	0.169
Hospital length-of-stay (days)						
$\overline{X}$(SD)	10.17 (2.43)	6.68 (2.92)	7.01 (2.56)	**< 0.001**	**< 0.001**	0.139
Blood transfusion						
n (%)	67 (14.4)	7 (11.7)	19 (4.9)	0.695	**< 0.001**	0.065
Intra-operative complications						
n (%)	9 (1.9)	0	5 (1.3)	0.607	0.591	1.000
Post-operative complications						
n (%)	24 (5.2)	3 (5.0)	10 (2.6)	1.000	0.055	0.395

p-values in bold represents significant

RH Robotic-assisted hysterectomy, *LH* Laparoscopic hysterectomy, *AH* Abdominal hysterectomy SD Standard deviation, *Hgb* Hemoglobin, *Hct* Hematocrit

rates were generally low across the board (< 7%) and did not significantly differ between the surgical approaches, and AH group showed relatively highest rate of operative complication. The types of intra- and post-operative complications for the three surgical groups are summarized in Table 3.

A comparative analysis of treatment showed that patients in AH group received significantly more frequent administration of post-operative adjuvant therapy (92.7%) and radiation therapy (91.6%) as compared to the MIS groups (87.7% and 87.7% cases for RH vs. 75% and 72.9% cases for LH, respectively; $p < 0.01$). Likewise, patients after laparotomy were administered significantly more post-operative chemotherapy [13.3% ($n=62$)] and hormone therapy [25.3% ($n=118$)] as compared to the RH group of patients [5.6% ($n=22$) chemotherapy and 9.2% ($n=36$) hormone therapy] ($p < 0.001$). The LH group of women did not show any statistical difference with other surgical group of cases in regard to chemotherapy and/or hormone therapy administration.

Oncologic outcomes

Vital status and cause of death are ascertained from the National Oncological Registry database and the oncologic/survival outcomes are described below:

1. Overall Survival for "All Stages" Endometrial Cancer

The mean follow-up time for women who underwent AH was significantly higher (4.75 ± 3.08, $p \leq 0.001$ years) than in the MIS group (LH = 3.68 ± 2.32 years and RH = 3.30 ± 2.0 years). Table 4A summarizes the results regarding patient's mortality. The cumulative incidence of all-cause death was statistically different in the AH vs. MIS group of patients ($p \leq 0.033$). The robotics and laparoscopy group of patients did not show significant difference in "all-cause" mortality. With respect to the "EC-specific death" and "other causes of death", no significant difference in mortality was observed between the three study groups (Table 4A). Significantly higher mean OS was noted for AH group of patients (10.24 years) as compared to RH group (8.36 years, $p=0.001$) and LH (8.02 years, $p=0.001$). The MIS group patients' OS was not significantly different. As shown in Fig. 1A, the Kaplan–Meier curve revealed a faster decline in the AH group. However, it ends later than the survival function for women operated by RH (with intermediate values in the LH group).

As shown in Table 5, Cox univariate and multivariate regressions were performed for OS that included known a priori risk factors for survival (type of surgery, tumor histology, grade, histopathological risk group, pT stage, pN stage,

Table 3 Identified intra- and post-operative complications in patients with endometrial cancer treated with, abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), and robotic-assisted hysterectomy (RH) procedures

	AH	LH	RH
Intra-operative complications, *n* (%)	9	0	5
Bladder injury	1 (11.1)	0	1 (20.0)
Small bowel injury	3 (33.3)	0	0
Cardiac arrest	0	0	1 (20.0)
Ureteral injury	1 (11.1)	0	0
Colon injury	0	0	1 (20.0)
Large vessel injury	1 (11.1)	0	0
Minor complications (bowel deserosation)	3 (33.3)		2 (40.0)
Post-operative complications, *n* (%)	24	3	10
Pulmonary embolism	1 (4.2)	0	1 (10.0)
Ileus	4 (16.7)	1 (33.3)	1 (10.0)
Vaginal cuff cellulitis	1 (4.2)	0	0
Post-operative hernia	1 (4.2)	0	1 (10.0)
Perforation of stomach ulcer	0	0	1 (10.0)
Acute renal failure	1 (4.2)	0	0
Urinary tract infection	0	1 (33.3)	0
Peritonitis	1 (4.2)	0	0
Arrhythmia	1 (4.2)	0	0
Deep-vein thrombosis with pulmonary embolism	1 (4.2)	0	0
Post-operative hemoperitoneum	1 (4.2)	0	0
Corpus alienum	0	0	1 (10.0)
Post-operative hemorrhagia with pulmonary embolism	0	0	1 (10.0)
Cardiac arrest	0	0	1 (10.0)
Hydronephrosis	1 (4.2)	0	0
Minor complications (wound infection, fever ≥ 38°, lymphedema)	11 (45.8)	1 (33.3)	3 (30.0)

FIGO stage, lymph node dissection, adjuvant radiation and/or chemotherapy, patient age, and other concomitant malignant tumor) as well as incidence of complications, blood transfusions and previous surgery, and size of the uterus. In univariate analysis model, all these factors (except lymphadenectomy) were risk factors that contributed significantly to lower the OS. Lack of influence was established for such parameters as "post-operative radiation" and "other concomitant malignant tumor" (Table 5). From multivariate analysis model, notable that the only significant risk factors remained age, incidence of complications, administration of post-operative chemotherapy, and histopathological risk group. Furthermore, Cox multivariate regression demonstrated that the type of surgical approach does not contribute to the patients' survival.

2. Overall Survival for "Early-Stage" Endometrial Cancer

The mean follow-up time for women who underwent AH was significantly higher (5.33 ± 2.89, $p \leq 0.001$ years) than in the MIS group (LH = 3.26 ± 2.11 years and RH = 3.80 ± 2.11 years). As shown in Table 4B, no significant difference in the mortality/survival incidence was noted for all-cause and/or EC-specific deaths in any of the three surgical approach groups. Also, Kaplan–Meier curve revealed that statistically no significant difference in the mean OS was noted between the surgical groups of "early-stage" cases (AH = 10.57 ± 0.26 years, LH = 8.03 ± 0.64 years, and RH = 8.47 ± 0.20 years; $p = 0.754$) (Fig. 1B).

Cox univariate and multivariate regressions were performed for the OS in patients with early-stage EC. As shown in Table 6, except lymphadenectomy, all the included risk factors for survival (such as older age, pT stage, tumor histology, grade, histopathological risk group, incidence of blood transfusions and complications, adjuvant chemotherapy, and larger uterine size) contributed significantly to decrease the OS in the univariate analysis model. Hazard ratio has the highest rates for such parameters as G3/G1 and histopathological risk group High/Low. No influence over survival rates was found in such parameters type of surgery, pN stage, post-operative radiation, and 'other concomitant malignant tumor'. When setting the key factors in the Cox Proportional-Hazards Model and using the Forward conditional procedure to determine the combined effect of the studied factors and eliminate the blurring ones between them, the following three indicators emerged significant: age, post-operative chemotherapy, and histopathological risk group (Table 6).

Table 4 **A** Patients' mortality in *"all stages"* of endometrial cancer patients managed with three surgical approaches. **B** Patients' mortality in ***"early stage"*** endometrial cancer patients managed with three surgical approaches

A.	AH ($n=466$) Group 1	LH ($n=60$) Group 2	RH ($n=391$) Group 3	*p* value between groups 1 vs. 2	1 vs. 3	2 vs. 3
Mortality Mean number of deaths, *n* (%)	140 (30)	10 (16.7)	67 (17.1)	**0.033**	**< 0.001**	1.000
Cause of death Mean number, *n* (%)						
Cancer-specific death	129 (27.7)	10 (16.7)	58 (14.8)	0.698	0.061	0.751
Other cause of death	11 (2.4)	0	9 (2.3)	0.541	0.657	0.468
Alive	326 (70)	50 (83.3)	324 (82.9)	**0.033**	**< 0.001**	1.000
B.	AH ($n=368$) Group 1	LH ($n=58$) Group 2	RH ($n=374$) Group 3	*p* value between Groups		
Mortality Mean number of deaths, *n* (%)	76 (20.7)	9 (15.5)	59 (15.8)	0.197		
Cause of death Mean number, *n* (%)				**1 vs. 2**	**1 vs. 3**	**2 vs. 3**
Cancer-specific death	68 (18.5)	9 (15.5)	52 (13.9)	0.813	0.631	0.700
Other cause of death	8 (2.2)	0	7 (1.9)	0.412	0.626	0.323
Alive	292 (79.3)	49 (84.5)	315 (84.2)	0.197		

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy

3. Disease-Free Survival for "All Stages" Endometrial Cancer

Mean follow-up time for EC patients in the AH arm was significantly longer [4.37 years (range 0.10–15.56); $p \leq 0.001$] than the MIS group [LH = 2.88 years (range 0.75–10.14) and RH = 3.27 years (range 0.20–9.96)]. A comparative analysis of the three surgical approaches by the number and type of recurrences, and by the mean times to their occurrence, is presented in Table 7A. The recurrence rates were: AH = 6.9%, LH = 6.7%, and RH = 5.4%, without any significant difference between the groups ($p = 0.657$). However, there is noticeable difference in the recurrence site between the groups (a significantly higher rate of local recurrences is observed in LH group compared to AH ($p = 0.003$), and no statistical significance was observed in the RH group compared to the other two surgical approaches. The relative share of distant metastasis was significantly higher in the AH group as compared to RH group ($p = 0.031$). No marked difference in the regional recurrence was noted between the three surgical groups. The site of relapse in the RH group was vaginal vault ($n = 5$), pelvis ($n = 8$), and distant metastasis ($n = 8$). In the LH group, three patients had a vault recurrence, none in the central pelvis, and one patient had distant recurrence of the disease. In the AH group, 2 patients were with local recurrence, 7 had a central pelvic relapse, 23 cases had distant metastasis. The mean time to recurrence did not differ significantly between the three groups (Table 7A). Kaplan–Meier curves also demonstrated this correlation with no significant differences in DFS between the investigated surgical groups (Fig. 1C). Thus, the type of hysterectomy/surgical approach has no effect on the DFS and cannot be considered a risk factor for recurrence.

A Cox Proportional Hazards Regression Analysis was performed to identify the factors influencing the relapse incidence and to evaluate their quantitative impact. As shown in Table 8, the following indicators were tested as potential factors: patient age, FIGO-, pT- and pN-stages, tumor histology, grade, histopathological risk group, lymph node dissection, uterine size, presence of complications, blood transfusions, adjuvant therapy, post-operative radiation or chemotherapy, and 'other concomitant malignant tumor'. The type of surgery (i.e., AH, LH, or RH) is insignificant factor for DFS in individual aspect as well as in the multivariate regression model. The only significant factors (in multivariate analysis) were FIGO stage and 'other concomitant malignant tumors' (Table 8).

4. Disease-free Survival for "Early-Stage" Endometrial Cancer

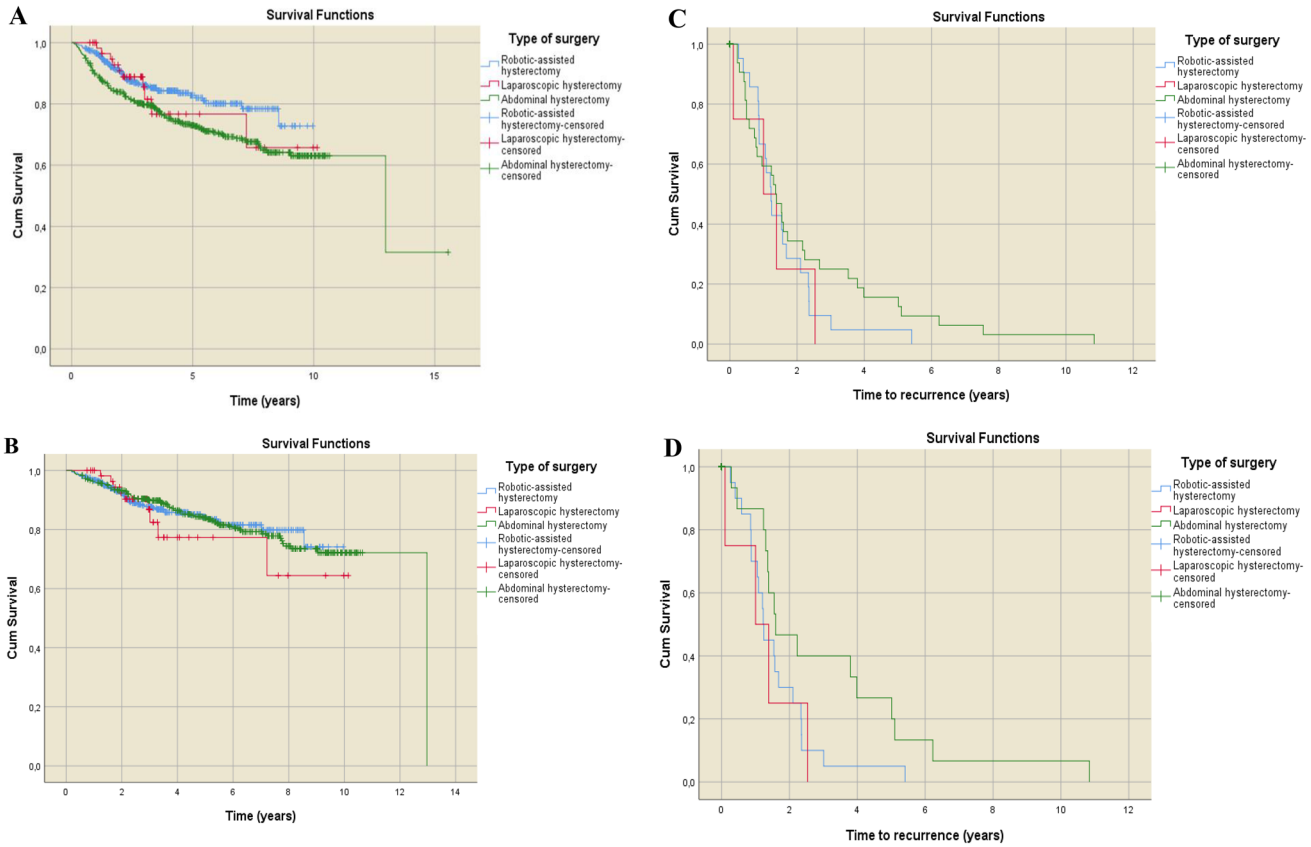

Fig. 1 Kaplan–Meier analyses curves for the cumulative (Cum) overall survival (OS) of patients with endometrial cancer: **A** "all stages", and **B** "early-stage". Kaplan–Meier analyses curves for the cumulative (Cum) progression-free survival (PFS) of patients with endometrial cancer: **C** "all stages", and **D** "early-stage"

Regarding early-stage (FIGO I + II) cases, a significant difference was observed between the mean follow-up times for AH = 5.06 years (range 0.21–12.97) as compared to the MIS groups [LH = 2.88 years (range 0.75–10.14) and RH = 3.39 years (range 0.20–9.96); $p \leq 0.001$].

A comparative analysis of the three surgical approaches by the number and localization of the relapses, as well as by mean time-to-recurrence is presented in Table 7B. Patients in the investigated groups did not differ statistically in the relative proportion of recurrences (AH = 4.1%, LH = 6.9%, and RH = 5.3%; $p = 0.549$) as well as in their number and type of recurrences. The LH group had noticeable lower mean time to relapse compared to AH group ($p = 0.029$). The recurrence mean time did not differ significantly between the AH vs. RH, and LH vs. RH surgical groups. Kaplan–Meier curves demonstrated this correlation in the cumulative DFS between the surgical groups (Fig. 1D). Thus, the type of hysterectomy (surgical approach) seems to have no impact on the DFS for early-stage EC patients and may not be considered a risk factor for relapse.

The results of the Cox regression analysis (crude and multivariate) for the DSF in "early-stage" EC patients are presented in Table 9. From the tested potential risk factors/indicators, a significant influence over DFS in individual terms were noted with 'other concomitant malignant tumor' and uterine size. When placing the significant risk factors in the Cox regression analysis and using the Backward conditional procedure, the same indicators remained significant. It is noteworthy that AH approach had significantly better DFS compared to RH in the crude (HR 0.483; $p = 0.049$) as well as in the multivariate analyses (HR 0.324; $p = 0.022$).

Discussion

In this study, we compared three surgical approaches (laparotomy, laparoscopic, and robotic) for peri-operative, oncologic, and survival outcomes of patients with endometrial cancer. We observed similar oncologic and better peri-operative outcomes in the MIS groups as compared to the open hysterectomy approach. Some of the early peer-reviewed publications, which demonstrated the capabilities of robotics

Table 5 Cox univariate and multivariate regressions performed for overall survival in *"all stages"* of patients with endometrial cancer

Factors	Comparison	Crude				Multivariate			
		HR	95% CI		*p* value	HR	95% CI		*p* value
			Lower	Upper			Lower	Upper	
Type of surgery	LH/RH	1.225	0.624	2.405	0.555				
	AH/RH	1.659	1.207	2.281	**0.002**				
Age (years)	Increasing with 1-year	1.059	1042	1.076	**< 0.001**	1.051	1.021	1.082	**0.001**
FIGO stage	II/IA + IB	1.998	1.270	3.142	**0.003**				
	IIIA + IIIB + IIIC/IA + IB	6.548	4.732	9.061	**< 0.001**				
	IVA + IVB/IA + IB	8.644	4.365	17.119	**< 0.001**				
pT stage	T2/T1a + T1b	2.023	1.328	3.082	**0.001**				
	T3a + T3b/T1a + T1b	8.422	5.994	11.833	**< 0.001**				
	T4a/T1a + T1b	6.750	2.746	16.593	**< 0.001**				
pN stage	N1/N0	8.138	5.026	13.177	**< 0.001**				
Histology	Non-endometrioid/Endometrioid	4.549	3.328	6.218	**< 0.001**				
Lymphadenectomy	Yes/No	0.764	0.653	0.894	**0.001**				
Complications	Yes/No	1.736	1.040	2.897	**0.035**	2.801	1.179	6.654	**0.020**
Blood transfusion	Yes/No	1.920	1.304	2.826	**0.001**				
Size of uterus	4 w.g./Normal	1.265	0.747	2.142	0.381				
	8 w.g./Normal	1.476	0.999	2.180	0.051				
	12 w.g./Normal	2.184	1.462	3.263	**< 0.001**				
	≥ 16 w.g./Normal	3.746	2.419	5.802	**< 0.001**				
Adjuvant therapy	Yes/No	1.850	1.031	3.319	**0.039**				
Post-operative radiotherapy	Yes/No	1.412	0.846	2.356	0.186				
Chemotherapy	Yes/No	4.125	2.924	5.820	**< 0.001**	3.478	2.018	5.995	**< 0.001**
Grade	G2/G1	1.571	1.101	2.240	**0.013**				
	G3/G1	5.375	3.718	7.771	**< 0.001**				
Other concomitant malignant tumor	Yes/No	1.651	0.679	4.015	0.269				
Hystopathological risk group	Intermediate/Low	1.249	0.733	2.129	0.413	1.084	0.304	3.869	0.901
	High-intermediate/Low	1.188	0.278	5.084	0.816	2.629	0.290	23.827	0.390
	High/Low	4.680	2.861	7.655	**< 0.001**	6.164	2.131	17.830	**0.001**
	Advanced/Low	10.823	6.379	18.362	**< 0.001**	20.011	6.918	57.885	**< 0.001**
	FIGO stage	13.901	5.205	37.129	**< 0.001**	7.660	1.320	44.435	**0.023**

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy, *HR* Hazard ratio, *CI* Confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *w.g.* Weeks of gestation

(although descriptive in nature), presented data similar to those of laparoscopic and open surgery approaches in terms of operative time, complications, and EBL rate [17, 18].

From clinical standpoint, in our study, the LOS and EBL outcomes are better in the MIS group, which are consistent with that observed by other early publication [19]. It is well established now that the robotic platform offers an increased precision, visualization, and dexterity, which leads to better peri-operative outcomes in this group. In our study, the shortest operative time is for the group of laparoscopic cases followed by the robotic and laparotomy cohorts, respectively. With early experience, Boggess et al. [19] reported data for the longest operative time for LH (213.4 min) compared to 191.2 min for RH, and shortest (146.5 min) for AH cases. Then after, Lim et al. [20] also published data demonstrating that laparoscopic hysterectomy in patients with EC is with the longest duration, followed by robotics, and laparotomy has the shortest operative time. Coronado et al. [21] published a shorter operative time for robotics compared to laparoscopy, but the shortest is for laparotomy, presumably, the main reason for these differing results could be found in the learning curve.

In contrast, we find no difference in the complications rate, which is rather similar to the publication by Lim et al. [20]. Boggess et al. [19] reported a statistically significantly lower rate of adverse events in the RH group compared to AH (5.9% vs. 29.7%, respectively, $p < 0.001$) These data were also supported by the publications of Gil-Moreno

Table 6 Cox univariate and multivariate regressions performed for overall survival in *"early-stage"* patients with endometrial cancer

Factors	Comparison	Crude				Multivariate			
		HR	95% CI		*p* value	HR	95% CI		*p* value
			Lower	Upper			Lower	Upper	
Type of surgery	LH/RH	1.307	0.641	2.666	0.461				
	AH/RH	1.017	0.700	1.476	0.931				
Age (years)	Increasing with 1-year	1.070	1.050	1.091	**< 0.001**	1.054	1.015	1.095	**0.007**
pT stage	T2/T1a + T1b	1.898	1.197	3.008	**0.006**				
pN stage	N1/N0	5.405	0.725	40.281	0.100				
Histology	Non-endometrioid/Endometrioid	3.509	2.290	5.377	**< 0.001**				
Lymphadenectomy	Yes/No	0.456	0.310	0.669	**< 0.001**				
Complications	Yes/No	2.348	1.346	4.097	**0.003**				
Blood transfusion	Yes/No	1.716	1.028	2.863	**0.039**				
Size of uterus	4 w.g./Normal	1.247	0.684	2.274	0.471				
	8 w.g./Normal	1.132	0.694	1.848	0.619				
	12 w.g./Normal	1.825	1.118	2.979	**0.016**				
	≥ 16 w.g./Normal	1.715	0.850	3.461	0.132				
Adjuvant therapy	Yes/No	1.926	0.941	3.943	0.073				
Post-operative radiotherapy	Yes/No	1.751	0.889	3.450	0.106				
Chemotherapy	Yes/No	2.583	1.478	4.513	**0.001**	5.260	2.218	12.477	**< 0.001**
Grade	G2/G1	1.553	1.017	2.371	**0.042**				
	G3/G1	4.937	3.119	7.815	**< 0.001**				
Other concomitant malignant tumor	Yes/No	1.451	0.461	4.565	0.524				
Hystopathological risk group	Intermediate/Low	1.182	0.692	2.017	0.541	0.930	0.260	3.332	0.911
	High-intermediate/Low	1.168	0.273	4.996	0.834	2.444	0.269	22.218	0.427
	High/Low	3.926	2.364	6.521	**< 0.001**	5.643	1.915	16.628	**0.002**

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy, *HR* Hazard ratio, *CI* Confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *w.g.* Weeks of gestation

Table 7 **A** Comparative analysis by the mean time to occurrence, number, and type of recurrences in *"all stages"* of patients with endometrial cancer who underwent hysterectomy procedures. **B** Comparative analysis by the mean time to occurrence, number, and type of recurrences in *"early-stages"* of patients with endometrial cancer who underwent hysterectomy procedures

	AH Group 1	LH Group 2	RH Group 3	*p* value between groups		
A.						
Recurrence, *n* (%)	32 (6.9)	4 (6.7)	21 (5.4)	0.657		
Type of recurrence, *n* (%)				1 vs. 2	1 vs. 3	2 vs. 3
Local	2 (6.3)	3 (75)	5 (23.8)	**0.003**	0.154	0.154
Regional	7 (21.9)	0	8 (38.1)	0.709	0.333	0.361
Distant	23 (71.9)	1 (25)	8 (38.1)	0.189	**0.031**	0.946
Recurrence mean time (months), ± SE	156.9 ± 9.99	106.73 ± 6.9	111.35 ± 1.93	0.539	0.981	0.667
B.						
Recurrence, *n* (%)	15 (4.1)	4 (6.9)	20 (5.3)	0.549		
Type of recurrence, *n* (%)				1 vs. 2	1 vs. 3	2 vs. 3
Local	1 (6.7)	3 (75)	5 (25)	**0.022**	0.333	0.175
Regional	4 (26.7)	0	7 (35)	0.636	0.876	0.422
Distant	10 (66.7)	1 (25)	8 (40)	0.352	**0.022**	1.000
Recurrence mean time (months), ± SE	148.84 ± 1.86	106.0 ± 7.2	111.52 ± 1.93	**0.029**	0.053	0.584

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy, *SE* Standard error

Table 8 Cox univariate and multivariate regressions performed for disease-free survival in *"all stages"* of patients with endometrial cancer

Factors	Comparison	Individual				Group			
		HR	95% CI		*p* value	HR	95% CI		*p* value
			Lower	Upper			Lower	Upper	
Type of surgery	LH/RA	1.179	0.403	3.449	0.764				
	AH/RH	0.737	0.415	1.309	0.298				
Age	Increasing with 1-year	1.037	1.001	1.073	**0.043**				
FIGO stage	II/IA + IB	0.529	0.153	1.831	0.314	6.071	0.708	52.094	0.100
	IIIA + IIIB + IIIC/IA + IB	1.828	0.984	3.396	0.056	44.263	2.096	934.908	**0.015**
	IVA + IVB/IA + IB	0.659	0.183	2.372	0.523	16.210	1.661	158.191	**0.017**
Other concomitant malignant tumor	Yes/No	7.99	1.71	37.38	**0.008**	32.458	4.476	235.381	**0.001**
pT stage	T2/T1a + T1b	0.64	0.23	1.84	0.410				
	T3a + T3b/T1a + T1b	2.09	1.07	4.08	**0.030**				
	T4a/T1a + T1b	5.11	1.13	23.15	**0.034**				
pN stage	N1/N0	3.70	1.41	9.74	**0.008**				
Histology	Non-endometrioid/Endometrioid	1.85	0.97	3.54	0.064				
Lymphadenectomy	Yes/No	1.453	0.842	2.506	0.179				
Complications	Yes/No	0.981	0.504	1.909	0.956				
Blood transfusion	Yes/No	0.740	0.289	1.891	0.529				
Size of uterus	4 w.g./Normal	0.851	0.346	2.092	0.726				
	8 w.g./Normal	0.531	0.243	1.157	0.111				
	12 w.g./Normal	0.968	0.473	1.981	0.930				
	≥ 16 w.g./Normal	0.362	0.127	1.030	0.057				
Adjuvant therapy	Yes/No	1.709	0.527	5.541	0.372				
Postoperative radiotherapy	Yes/No	1.690	0.521	5.482	0.382				
Chemotherapy	Yes/No	1.694	0.933	3.076	0.083				
Grade	G2/G1	2.351	1.086	5.090	**0.030**				
	G3/G1	2.412	1.067	5.453	**0.034**				
Hystopathological risk group	Intermediate/Low	0.595	0.242	1.459	0.256				
	High intermediate/Low	0.506	0.110	2.336	0.383				
	High/Low	0.932	0.429	2.028	0.859				
	Advanced/Low	1.347	0.559	3.249	0.507				
	Metastatic/Low	0.378	0.076	1.873	0.234				

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy; *RH* Robotic-assisted hysterectomy, *HR* Hazard ratio, *CI* Confidence interval, *FIGO* International Federation of Gynecology and Obstetrics, *w.g.* Weeks of gestation

et al. [22] and Seamon et al. [23]. Bell et al. [24] presented 110 cases of women with EC operated by one of the three methods, which contrast with our findings. Analogous to our current study, Bell et al. [24] reported less blood loss in MIS (166 mL for RH and 253 mL for LH, $p = 0.25$) compared to AH ($p = 0.01$), while their complication rate was the lowest in robotics (7.5%), compared to laparoscopy (20%), and open surgery (27.5%). Regarding lymph node retrieval, there was no difference between the three groups. In 2009, Seamon et al. [23] published a cohort study comparing robotic and laparoscopic hysterectomy data, demonstrating no difference in patient characteristics, lymph node counts, and complication rates, but lower rates of EBL, transfusions, and LOS in robotic group. Their results are comparable to those of other authors worldwide [19, 20, 25].

Our > 10-years' experience demonstrated better outcomes for the MIS compared to open surgery in terms of post-operative hemoglobin, blood transfusions, and LOS, with no difference in the complications rate. A number of groups have also reported similar outcomes, however, a lower intra- and post-operative complications rate in the MIS group [12, 26]. In contrast, Wright et al. [27] reported that robotics is with higher complications rate compared to laparoscopy (23.7% vs. 19.5%, respectively).

A systematic review and meta-analysis conducted by Gaia et al. [13], that included 1591 cases with endometrial cancer operated by one of the three methods, demonstrated

Table 9 Cox univariate and multivariate regressions performed for disease-free survival in "early-stage" of patients with endometrial cancer

Factors	Comparison	Individual				Group			
		HR	95% CI		*p* value	HR	95% CI		*p* value
			Lower	Upper			Lower	Upper	
Type of surgery	LH/RH	1.206	0.409	3.559	0.735	0.769	0.239	2.475	0.660
	AH/RH	0.483	0.234	0.997	**0.049**	0.324	0.127	0.823	**0.018**
Age	Increasing with 1-year	1.035	0.993	1.078	0.103				
Other concomitant malignant tumor	Yes/No	18.494	1.677	203.982	**0.017**	20.581	1.562	271.21	**0.022**
Histology	Non-endometrioid/Endometrioid	1.540	0.634	3.743	0.340				
Complications	Yes/No	1.040	0.500	2.161	0.917				
Blood transfusion	Yes/No	0.767	0.224	2.626	0.673				
Size of uterus	4 w.g./Normal	0.680	0.228	2.031	0.489	0.657	0.170	2.543	0.543
	8 w.g./Normal	0.495	0.187	1.312	0.157	0.266	0.087	0.816	0.021
	12 w.g./Normal	1.024	0.441	2.374	0.957	0.698	0.253	1.930	0.488
	≥ 16 w.g./Normal	0.088	0.011	0.730	0.024	0.167	0.018	1.533	0.114
Adjuvant therapy	Yes/No	1.498	0.356	6.305	0.582				
Post-operative radiotherapy	Yes/No	1.470	0.349	6.196	0.600				
Chemotherapy	Yes/No	1.555	0.674	3.586	0.300				
Grade	G2/G1	1.791	0.730	4.396	0.203				
	G3/ G1	1.957	0.771	4.973	0.158				
Hystopathological risk group	Intermediate/Low	0.573	0.231	1.420	0.229				
	High-intermediate/Low	0.475	0.103	2.199	0.341				
	High/Low	0.810	0.353	1.857	0.618				

p-values in bold represent significant

AH Abdominal hysterectomy, *LH* Laparoscopic hysterectomy, *RH* Robotic-assisted hysterectomy, *HR* Hazard ratio, *CI* Confidence interval, *w.g.* Weeks of gestation

statistically significant reduction in EBL for the RH, shorter LOS for RH and LH compared to AH, the lowest rates of blood transfusions in RH, and similar results in the three groups in terms of complications, whereas the operative time for robotics was similar to laparoscopy group but greater than laparotomy group. In a comparison of outcomes of robotic and open surgery, Subramaniam et al. [28] published results for significantly longer operative time for robotics, but improved results for this group in terms of EBL, LOS, blood transfusions rate and complications, without statistical difference between the two cohorts for the total lymph nodes obtained. While Venkat et al. [29] reported longer operative time for robotics than laparoscopy, same results as ours and Seror et al. [30] showed that the real operative time between both techniques is without any significant difference, but robotics takes a little extra time for preparation, etc.

The fact, that robotics is a safer alternative to the AH and LH approaches in offering improved peri-operative outcomes, is demonstrated not only by us but also by other international groups [9, 21, 31–34]. The widespread use of MIS in the treatment of EC is due to their shorter LOS and better peri-operative outcomes has previously been confirmed [35–37]. Furthermore, Ran et al. [34] published their meta-analysis which included 22 studies with 4420 patients who underwent robotic, laparoscopic or laparotomy procedures for EC, and pointed that robotics is superior to open surgery in terms of EBL, blood transfusions rate, LOS, and rate of complications, but inferior in regard to the operative time. Comparing to laparoscopy, the authors found robotic surgery superior in terms of EBL, but equal to it regarding operative time, transfusions rate, LOS, and complications rate [34]. These results are also consistent with other previous reports [38, 39].

Recently, Nayyar et al. [40] analyzed data from 150 patients who underwent robotic or laparotomic surgery for EC and concluded that RH approach leads to less blood transfusions, EBL, and complications, as well as to shorter LOS and lower operation time, with similar lymph node yields. Their data are in unison with other peer-reviewed publications [19, 41–43]. Another subsequent review and meta-analysis by Ind et al. [44], confirmed that the duration of robotic hysterectomy is without difference compared to laparoscopic one, but robotics is with lower LOS, EBL, and complications rate. Reduced operative time and EBL as well as shorter LOS for RH vs. LH were demonstrated by Corrado et al. [45] and Chan et al. [46]. Controversy, Maenpaa et al. [47] in their randomized control trial collated both

MIS techniques, which resulted in shorter operative time and similar EBL, LOS, and complication rates.

A recent meta-analysis, by Wang et al. [48], made a comparison of robotic surgery with laparoscopy and laparotomy in women with histologically proven EC, including 27 articles with a total of 6568 patients. The authors concluded that compared to the LH, the RH approach resulted in lower blood transfusions and complications rate, less EBL and shorter LOS, but had a longer operative time [48]. The study also concluded that compared to AH, the RH approach had less blood transfusions, complications and EBL, also shorter LOS, but had a longer operative time. Walker et al. [49] reported their GOG LAP-2 (a large, randomized trial, comparing laparoscopic to laparotomy approach in patients with EC), which demonstrated no difference between the groups in terms of oncologic outcomes, similar at 89.8% OS. Our results in this context are similar, except the OS, where we find better outcomes in AH compared to the RH, whereas LH did not differ to the other groups. Coronado et al. [21] published their retrospective review of 347 patients with EC and found no differences relative to OS or DFS among the three surgical groups. Before this study, there were previous experience published, which showed no difference in oncologic outcomes but only between laparoscopic and abdominal approaches for EC [25, 50, 51].

A retrospective chart review by Park et al. [52] included 936 patients with EC who underwent AH or RH procedures, in which robotics was associated with decreased complications and re-admission rates. The authors showed a 90.9% estimated 3-year DFS for RH and 78.3% for AH, and 89.1% estimated 5-year OS for RH and 79.5% for AH [52]. Similar to our current findings, the results from their multivariate analysis demonstrated that the type of surgical approach does not influence the DFS or OS. Analogic are also the results for robotics published by other groups over time [53–57]. Subsequent findings by other authors [37, 58, 59] are also similar who observed no significant difference in DFS and OS between the three surgical groups, which are comparable to our study observations. In contrast, recently, Song et al. [60] published their single-center retrospective study for 179 patients with EC, operated by either AH or RH, and found that robotics was associated with higher recurrence rate than laparotomy, while there was no difference in the 5-year OS between the groups.

One recent population-based prospective cohort study [16] analyzed oncologic outcomes and noted that AH was associated with higher mortality rate than LH and RH groups, without any significant survival difference between the two MIS approaches. Similar results were also previously reported by another group [61]. Accordingly, we consider MIS approach is oncologically safe, and with better peri-operative outcomes. Our oncologic data are also supported by Nayyar et al. [40], who also noted earlier that no significant difference in the DFS and OS between the robotics and open surgery groups.

Despite the large number of patients and the long-time period of the survey, there are some limitations in the present study that are likely to affect the statistical significance of the comparative analyses. The non-randomized retrospective nature of the study is a potential reason for some selection bias. Analyzing the OS for "all stages", the mean follow-up time is significantly longer (by about a year) in AH group as compared to the LH and RH groups. The results for "early stage" DFS demonstrate that the difference between AH and LH groups is more than 2 years and the difference between AH and RH groups is a little more than 1.5 years. This could be a possible explanation for the significant differences in the OS and DFS of patients who underwent AH compared to those in the RH and LH groups.

For the selection of different surgical methods, we have not used standardized criteria. This could explain the significant prevalence of patients in advanced stages (FIGO III and IV; pT3 and pT4), as well as high-risk/advanced-risk histopathological cases in the AH group. These circumstances are a predisposition for the higher rate of pre-operative radiotherapy/adjuvant therapy in these patient groups.

The non-standardized selection of surgical approach for hysterectomy and the surgeon's preferences obviously explains some of the differences in the patient demographics. Patients in the AH group were significantly older (AH 63.90 vs. RH 61.98 years; $p=0.004$), with lower pre-operative Hgb (AH 120.33 vs. LH 130.38 vs. RH 127.45 g/L; $p<0.05$) and Hct (AH 34.92 vs. LH 38.22 vs. RH-37.11%; $p<0.05$), with more than three previous laparotomies (AH 85.8% vs. LH 61.7%; $p=0.028$) and with large uterus (≥ 16 w.g.) (AH 9.2% vs. RH 4.1%; $p=0.005$). The differences in uterine size, for example, have its logical oncological explanation, as abdominal hysterectomy allows large uteruses to be removed without being morcellated.

Conclusion

This study performed a continuous and retrospective study of over 10 years of our experience at two premier centers in Bulgaria to compare the peri-operative, oncologic, and survival outcomes for EC patients managed with three different surgical approaches. We observed that compared to laparoscopic and laparotomy surgery, robotic-assisted surgery allows for an easier treatment of patients with EC due to overcoming the barriers of the other two types of hysterectomy procedures. The MIS (and robotics in particular) appears to be an effective and safe alternative to open surgery in the treatment of endometrial cancer, with better peri-operative and similar oncologic outcomes. Although

the multivariate analyses indicated that the DFS in "early-stage" EC is significantly better in AH group as compared to RH group, overall, the OS was not influenced by the type of surgical technique used, places MIS on the anterior front in the present as well as in the future.

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Author contributions STT: performed surgeries, co-conceived the study design and its implementation, data review and analyses, data interpretation, and manuscript writing, and take responsibility for the paper. GAG: performed surgeries, co-conceived the study design and its implementation, data review and analyses, data interpretation, manuscript writing, and take responsibility for the paper. DKK: assisted in surgeries, participated in data collection, management, analyses, interpretation (including quality control), statistical advice, created graphs and tables, and help writing the first draft. ADL: participated in data collection, analyses, interpretation, statistical advice, organization, and help in writing the draft. NHH: participated in data collection, analyses, interpretation, statistical advice, organization, and help in writing the draft. VDT: participated in data collection, analyses, interpretation, statistical advice, organization, and help in writing the draft. ZVG: participated in data collection, analyses, interpretation, statistical advice, organization, and help in writing the draft. SA: assisted in study design, scientific discussions, literature search, data interpretation and organization, help drafted the manuscript and submission process, and take responsibility for the paper.

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Declarations

Conflict of interest None of the authors has any potential financial or commercial conflict of interest associated with this original research manuscript.

Ethics approval This retrospective study was approved by the Research Ethics Commission of Medical University-Pleven, Bulgaria.

Consent to participate This retrospective study is classified as quality improvement and hypothesis generating, which is allowed by our Institutional Review Board (Research Ethics Commission) and no patient consent was required.

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