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Robotic Hysterectomy for Endometrial Cancer

ABSTRACT

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The author is currently a full-time PhD student at the Department of Obstetrics and Gynecology, Faculty of Medicine, Medical University – Pleven.

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The materials relevant to the dissertation defense are available on the website of MU – Pleven: www.mu-pleven.bg.

CONTENTS

List of used abbreviations

EC	endometrial cancer
AH	abdominal hysterectomy
MIS	minimally invasive surgery
LH	laparoscopic hysterectomy
RH	robotic hysterectomy
BMI	body mass index
OS	overall survival
DFS	disease-free survival

"Great things are never

done by one person;

they are done by a team of people."

Steven Paul Jobs

1. INTRODUCTION

Worldwide, endometrial cancer (EC) is the second most common malignant gynecological disease, and when diagnosed, surgical treatment is considered to be the preferable approach. In the past, abdominal hysterectomy (AH) was believed to stand as the "golden standard" for managing the disease. However, we are living in a rapidly developing world, where technological innovations in the medicine and surgery in particular are a compulsory part of the global evolution. This is a postulate for the establishment of new technologies and their integration in the process for operative treatment of malignant tumors. Laparoscopic and robotic systems, which underlie the minimally invasive surgical (MIS) approaches, are examples of this. Nowadays, EC surgeries are undertaken through laparotomy, laparoscopy and robotics, which is the newest approach. The first recorded evidence of laparoscopic hysterectomy (LH) for patients with histologically proven EC dates back to 1993, when Childers and Surwit publish their study, showing their experience in laparoscopic treatment of the malignant disease (27), and the first published data of robotic-assisted techniques of EC caused hysterectomy are from 2002 (38). Since its entry as a new possible approach for women with histologically proven EC, robotic assistance has been rapidly recognized as a preferable solution with several advantages over the "entirely laparoscopic" method: increased accuracy, enhanced dexterity, shorter operative time, lower estimated blood loss, decreased hospital length-of-stay, lower complications rate, etc. On the other hand, while there is abundant information about the perioperative results for the three surgical approaches, this is hardly the case with their oncological outcomes. The evident data to compare AH, LH and robotic hysterectomy (RH) regarding overall survival (OS) and disease-free survival is either limited or ambiguous.

2. OBJECTIVE AND TASKS

2.1. Objective

By comparing and analyzing the perioperative and oncological indicators for patients with endometrial cancer, treated with three approaches - robotic-assisted, laparoscopic and open surgery, to assess the clinical importance of the robotic hysterectomy and to determine its place in the modern gynecological surgery.

2.2. Tasks

1. **To analyze the perioperative outcomes for the three types of hysterectomy regarding main indicators of the patients – age, body mass index, previous surgeries, size of uterus and other concomitant malignant tumor.**

2. **To determine and analyze the main tumor characteristics – FIGO stage (2018) and pT-stage respectively, histological tumor variation (according to WHO), grade and histopathological risk group.**

3. **To examine the indicators "operative time", "lymph node dissection", "postoperative hospital length-of-stay" and "estimated blood loss" for the three types of hysterectomy.**

4. **To conduct a comparative analysis of the three types of surgery regarding intra- and postoperative complications and undertaken adjuvant therapies – radial, chemo- and hormone therapy.**

5. **To research and assess the overall survival and the factors that have impact on it for patients with endometrial cancer operated through the three approaches.**

6. **To research and assess the disease-free survival and the factors that have impact on it for patients with endometrial cancer operated through the three approaches.**

3. MATERIALS AND METHODS

3.1. Clinical contingent

The researched clinical contingent involves 917 patients wit histologically proven endometrial cancer who underwent robotic-assisted, laparoscopic or open hysterectomy at two major clinical centers of Bulgaria – the Clinic of Obstetrics and Gynecology at the University Hospital "Saint Marina", Pleven, and the Clinic of Obstetrics and Gynecology at the University Hospital "Dr. Georgi Stranski", Pleven, within a larger than a decade period of time – from January 2008 to April 2019. With significantly highest share (50.8%) are the patients with AH, followed by RH with 42.6% and LH with 6.5%, $p<0.05$ (fig. 1.).

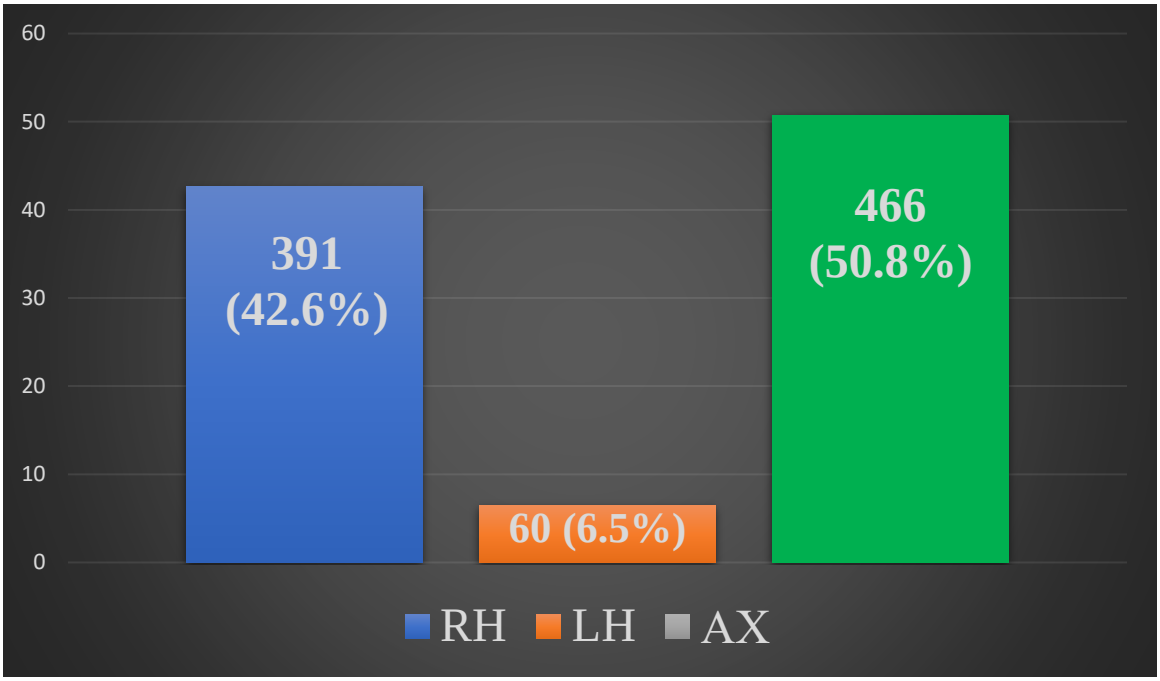

Figure 1. Frequency distribution of the patients according to the hysterectomy approach.

The postsurgical follow-up consisted of regular visits in the first month after the manipulation, then every three months for two years, every six months until the fifth year and annually thereafter. The FIGO and TNM stagings correspond with the 2018 classification (5) and the required data was derived from patient epicrises and postoperative histopathology reports. Histopathological risk groups were defined according to the FIGO stage and grade of the tumor and following the reports of ESGO, ESMO and ESTRO and the recommendations

of Jørgensen et al. (29, 77). Histopathological risk groups are introduced in figure 2. In addition, patients with FIGO I and II stages are grouped together, so as to represent the early-staged EC evidence regarding oncological outcomes. Vital status and cause of death data, OS and DFS resp., were ascertained from the National Oncological Registry database and were updated on 9 July, 2019.

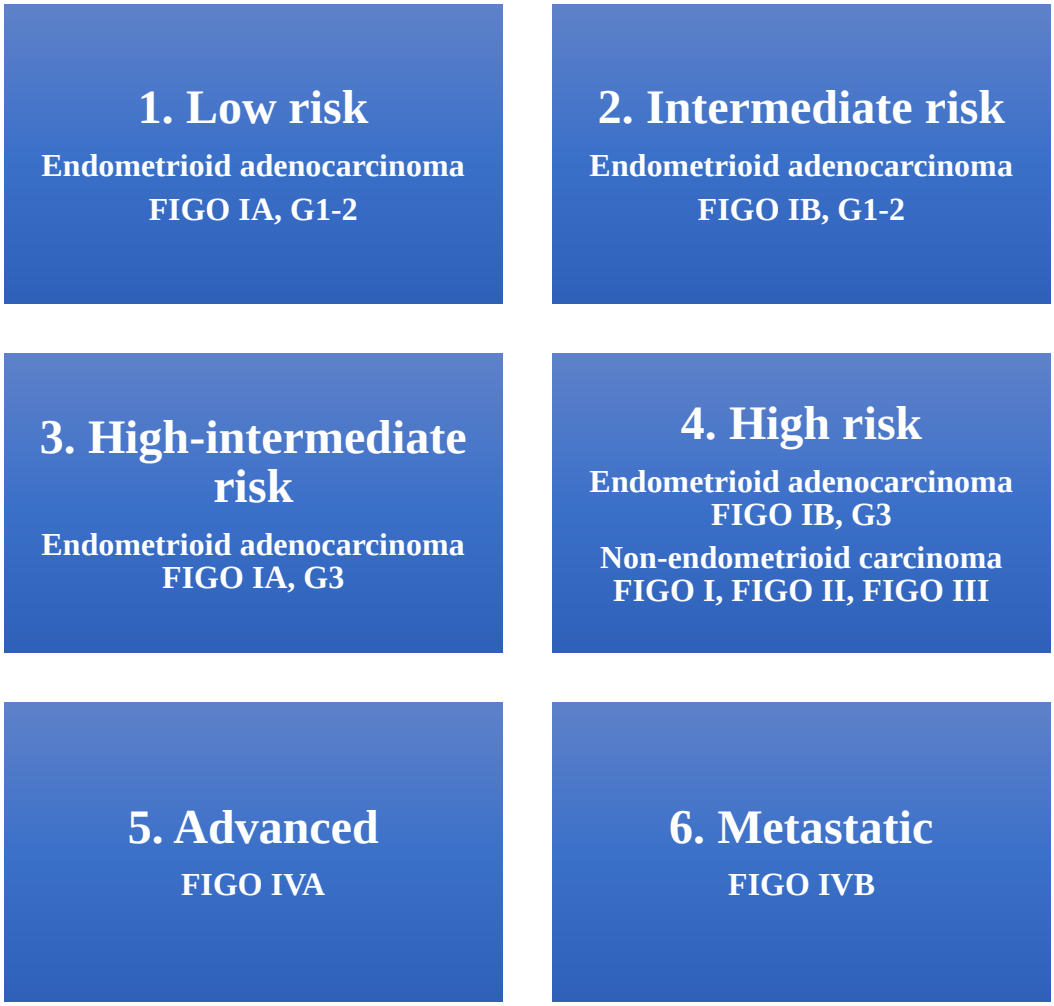

Figure 2. Types of risk groups for patients with EK according to FIGO stage and grade of the tumor.

3.2. Defining of the researched indicators

3.2.1. Main clinical indicators of the patients – age, body mass index, evidence of previous surgical interventions, size of uterus, and evidence of other concomitant malignant tumor.

3.2.2. Tumor characteristics – FIGO stage (2018), pT-stage resp., histological variation of the tumor (according to WHO), grade and histopathological risk group.

3.2.3. Mean operative time – for laparoscopies and laparotomies, it is defined as the time from the first section („incision time“) until the moment of stitching of the last trocar aperture/ applying the last sature onto the surgical wound („close time“); for robotic-assisted operations, it is defined as the time from the start of the “docking” until the stitching of the last trocar aperture.

3.2.4. Estimated blood loss – it is defined through the pre- and postsurgical hemoglobin and hematocrit rates and incidence of blood transfusions.

3.2.5. Hospital length-of-stay – the time (in days) from hospitalization to dehospitalization of the patient.

3.2.6. Lymph node status – performed lymph node dissection and number of removed lymph nodes.

3.2.7. Complications – intraoperative and postoperative.

3.2.8. Adjuvant therapy – postsurgical radial, chemo- and hormone therapy.

3.2.9. Overall survival.

3.2.10. Disease-free survival.

3.3. Surgical approaches

3.3.1. Types of performed surgeries

All 917 patients with histologically proven EC were treated with one of three hysterectomy approaches:

- Robotic-assisted hysterectomy;
- Laparoscopic hysterectomy;
- Open hysterectomy.

3.3.2. Equipment

For performing the minimally invasive trachelectomies for both groups was used laparoscopic equipment by the companies of Karl Storz and Olympus (figures 3. and 4.). The robotic-assisted interventions were performed with DaVinci X surgical system (figure 5.).

Figures 3 and 4. Systems for laparoscopic surgery.

Figure 5. System for robotic surgery DaVinci X.

3.4. Statistical methods

Data were entered and processed with the statistical package IBM SPSS Statistics 25.0 and MedCalc Version 14.8.1. A significance level at which the null hypothesis is rejected was $p<0.05$.

The following statistical methods were applied:

3.4.1. **Descriptive analysis** – the frequency distribution of the examined indicators, divided into researched groups, was presented in tabular form.

3.4.2. **Variation analysis** – for estimating the characteristics of the central tendency and the statistical dispersion.

3.4.3. **Graphical analysis** – for visualizing the received outcomes.

3.4.4. **Fisher's exact test $\chi 2$** for testing hypotheses of significant association between two categorical variables.

3.4.5. **Comparison of proportions.**

3.4.6. **Nonparametric one-sample Kolmogorov-Smirnov test and Shapiro-Wilk test** – for testing the normal distribution.

3.4.7. **Nonparametric Kruskal-Wallis test** – for comparing three or more independent groups.

3.4.8. **Nonparametric Mann-Whitney test** – for testing hypotheses of significant difference between two independent groups.

3.4.9. **Kaplan-Meier analysis –** for estimating the survival function of patient population.

3.4.10. **Nonparametric Log-Rank test** – for examining the difference between two independent groups.

3.4.11. **Breslow test** – for comparing the equality of the survival distribution.

3.4.12. **Tarone-Ware test** – comparing the equality of the survival distribution.

3.4.13. **Cox proportional hazards analysis** – for determining the cumulative distribution of the absolute probability.

4. OWN RESULTS AND DISCUSSION

4.1. ANALYSIS OF THE PERIOPERATIVE OUTCOMES FOR THE THREE TYPES OF HYSTERECTOMY REGARDING PATIENTS MAIN CLINICAL INDICATORS – AGE, BODY MASS INDEX, PREVIOUS SURGICAL INTERVENTIONS, SIZE OF UTERUS AND OTHER CONCOMITANT MALIGNANT TUMOR.

4.1.1. OWN RESULTS

Table 1. Comparative analysis of the perioperative outcomes for RH, LH and AH regarding main clinical indicators of the patients.

Characteristics		(1) RH	(2) LH	(3) AH	p-value		
					1-2	1-3	2-3
Age (years)	$\overline{X}$ (SD)	61,98 (10,15)	63,73 (9,86)	63,90 (9,59)	0,196	0,004	0,971
Age group (years)	n (%)						
30-39		8 (2,0)	0 (0,0)	5 (1,1)	0,566	0,427	0,906
40-49		32 (8,2)	4 (6,7)	22 (4,7)	0,866	0,050	0,721
50-59		103 (26,3)	16 (26,7)	107 (23,0)	0,927	0,299	0,635
≥60		248 (63,4)	40 (66,7)	332 (71,2)	0,726	0,018	0,569
BMI	$\overline{X}$ (SD)	33,20 (10,37)	27,98 (4,51)	29,32 (6,12)	0,257	0,165	0,586
Previous surgery	n (%)						
None		9 (2,3)	0 (0,0)	24 (5,2)	0,490	0,044	0,138
1 Laparotomy		44 (11,3)	20 (33,3)	36 (7,7)	<0,001	0,092	<0,001
2 Laparotomies		6 (1,5)	3 (5,0)	6 (1,3)	0,187	0,965	0,122
≥3 Laparotomies		332 (84,9)	37 (61,7)	399 (85,8)	<0,001	0,784	<0,001
Size of uterus	n (%)						
Normal		233 (59,6)	38 (63,3)	208 (44,6)	0,687	<0,001	0,001
m. l. I		24 (6,1)	8 (13,3)	53 (11,4)	0,079	0,001	0,827
m. l. II		74 (18,9)	11 (18,3)	94 (20,2)	0,947	0,696	0,861
m. l. III		44 (11,3)	3 (5,0)	68 (14,6)	0,185	0,208	0,065
≥ m. l. IV		16 (4,1)	0 (0,0)	43 (9,2)	0,221	0,005	0,028
Concomitant malignant tumor	n (%)	6 (1,5)	1 (1,7)	12 (2,6)	0,654	0,379	0,985

Table 1. shows that:

- The group of patients with open surgery has a relatively higher mean age rate compared to those who were treated with robotic-assisted technique, but not to the operated through laparoscopy, whose mean age is not statistically different from the rate of the other two groups;

- The comparative analysis of the patients with the three types of surgeries showed significant difference in the age group of ≥60 – the manipulated with laparotomy patients have higher percentage than those with robotic-assisted approach. In the group of 40-49-year olds, those two groups differ significantly in their p value (p=0.05), but the proportion there is reverse;

- The patients with the three types of surgery do not differ statistically in their BMI.

- The comparative analysis of the patients with one of the three surgeries showed significant differences in all "Previous surgeries" categories, with the exception of "2 laparotomies". Among the women who hadn't undergone operations before, the highest share have those managed with AH, followed by those with RH and LH, respectively. For the "1 laparotomy" category, patients from the group of laparoscopy have significantly higher percentage in comparison to the other two surgical approaches, whose shares do not statistically differ. For the patients with ≥3 previous laparotomies, those treated with laparoscopy have a considerably lower percentage compared to those with the other two types of surgery, whose shares do not statistically differ;

- Notable difference among the three surgical groups was observed for all sizes of uterus, except for m. l. II and m. l. III. Patients with normal uterine size represented a significantly lower rate in the AH group, whereas the other two surgery types have statistically equal relative proportions. For m. l. I patients, cases managed by robotic-assisted technique have considerably lower share than those with open surgery, but not compared to those managed by laparoscopy, whose relative proportion does not differ from those of the other two approaches. The largest uterine size (≥ m. l. IV) represented a significantly higher rate in the AH group, followed by those with RH and the women operated in the group of LH.

- No statistical contrasts were observed in the frequency distribution of the indicator "Concomitant malignant tumor".

4.1.2. DISCUSSION

The outcomes of our study aligns with the global data by confirming that EC is an age-dependent disease and its incidence increases within women in or beyond their sixth decade of life.

In medicine, patients' clinical characteristics are often determinant for the choice of certain surgical approaches. Our data show that RH is a preferable operative method for younger women compared to open surgery ($p=0.004$). No dependencies were revealed between the mean age of the patients with EC and the choice between conventional laparoscopy or AH, as well as between both minimally invasive techniques. In spite of that, the higher mean age of the patients who underwent laparotomy, in comparison to MIS, is noteworthy, with no remarkable difference between the groups. For the purposes of this study, we further divided the clinical contingent data into four age groups. Our data in the "≥ 60 years" reveal that AH is the main choice for hysterectomy for patients of advanced age, in comparison to RH, whereas robotic-assisted technique is preferred for younger women (age group "40-49 years"). With advancing age, classical open surgery increasingly becomes the favored option. Although there are deficient literature data to compare the three techniques by age of patients, the results of our research are commensurable to those of other authors (14, 108, 156, 170). The larger share of the worldwide studies has not drawn a connection between age and choice of surgical approach. Despite that, it is worth noting that a lot of them have only tested the correlations between two of the techniques rather than all three simultaneously (22, 44, 103, 144, 155, 156, 173).

Regarding BMI and presence of concomitant malignant tumor, we did not observe significant difference between the three operative methods. At the time of the study, there was no literature data of comparing RH, LH and AH by the presence of other concomitant tumor. When analyzing our results, the preference of robotics for patients with higher BMI is notable, however that data does not reach statistical significance. Similar results are given by Bell et al., as well as a number of other authors (14, 22, 71, 73, 94, 103, 129, 170, 173). Boggess et al. estimate a credibly higher BMI for RH compared to LH (32.9 vs. 29.0, $p=0.0008$), but the authors have not included open surgery in their study (17), with their results being supported by Seamon et al., BMI for RH vs. LH resp. 34 vs. 29, $p<0.001$ (144).

The major number of the patients in our study have previous surgeries. For our purposes, we divided the women into groups according to the presence and amount of preceding laparotomies. It is remarkable that, compared to AH, laparoscopy is not a desired approach for women with anamnestic data of higher numbers of previous operations. When observing the minimally invasive techniques, we could conclude that RH is preferred to LH for patients with preceding laparotomies. Comparing RH with AH, we did not find any difference in the choice of operative approach regarding the number of previous surgeries. Literature reveals exceptionally scanty information regarding this researched indicator. There is only one evident research to compare the three methods, with Manchana et al. noticing a prevailing number of patients with preceding laparotomies in the groups of RH and AH compared to LH, p=0.02 (108). Other authors collate both MIH approaches but do not estimate significant differences between the groups (22, 103). Nayyar et al., comparing RH and AH, express the standpoint that AH is the preferable technique for patients with previous laparotomies, resp. 13.3% vs. 28.0% for RH vs. AH, p=0.044 (120).

According to our results, the size of the uterus is an indicator with direct correlation for the choice of operative approach for hysterectomy. With the specifics of the minimally invasive techniques and the limited space for surgical access taken into account, it comes as no surprise that women with uterine size above 16 w.g. are preferably operated through open surgery ($p<0.001$), whilst MIS is a preferred approach for hysterectomy of uteri with smaller size ($p<0.001$). We did not find any difference in the preferences between RH and LH for the different uterine sizes, therefore it can be concluded that both minimally invasive techniques are equally applicable and appropriate for patients with EC. The majority of the publications lack to introduce data for comparison of all three operative methods in accordance to uterine size, with the few accessible literature data accounting the weight of uterus (in g) rather than its size. Two are the comparative analyses collating RH, LH and AH, where the authors do not estimate any of the three approaches as preferable regarding the uterine size (30, 71). Despite this, in their 12-year research from 2024, Ikebuchi et al. express the opinion that AH is preferentially undertaken for women with larger uterine size, with their data having no statistical significance, resp. 236.4 g for AH, 184.4 g for RH and 150.4 g for AH (71). Three studies compare the minimally invasive techniques for women with EC and discover no dependency between the tested indicator and the hysterectomy approach (22, 44, 103), whereas a retrospective analysis from 2024 r. determines that patients with larger uteri are preferably operated through laparoscopy in comparison to the robotic-assisted approach,

p=0.01 (173). Analogous to our conclusions, draw the data received by Subramaniam et al. They reveal that patients with larger uterine size are operated with predilection through laparotomy – 144.6 g in the RH group compared to 224.6 g in the AH group, p<0.001 (156).

4.2. ANALYSIS OF THE MAIN TUMOR CHARACTERISTICS FOR PATIENTS WITH ENDOMETRIAL CANCER OPERATED THROUGH ONE OF THE THREE HYSTERECTOMY APPROACHES – FIGO STAGE, pT STAGE, HISTOLOGICAL TYPE OF THE TUMOR, GRADE AND HISTOPATHOLOGICAL RISK GROUP.

4.2.1. OWN RESULTS

Table 2. Comparative analysis of the main tumor characteristics for patients with EC operated through RH, LH or AH.

Characteristics		(1) RH	(2) LH	(3) AH	p-value		
					1-2	1-3	2-3
FIGO stage	**n (%)**						
IA		165 (42,2)	28 (46,7)	96 (20,6)	0,606	<0,001	<0,001
IB		176 (45,0)	26 (43,3)	231 (49,6)	0,915	0,202	0,434
II		33 (8,4)	4 (6,7)	41 (8,8)	0,932	0,846	0,763
III		17 (4,3)	2 (3,3)	84 (18,0)	0,989	<0,001	0,007
IV		0 (0,0)	0 (0,0)	14 (3,0)	-	0,001	0,351
pT stage	**n (%)**						
T1a		165 (42,2)	28 (46,7)	103 (22,1)	0,606	<0,001	<0,001
T1b		178 (45,5)	26 (43,3)	240 (51,5)	0,858	0,093	0,290
T2		36 (9,2)	4 (6,7)	50 (10,7)	0,696	0,539	0,462
T3		12 (3,1)	2 (3,3)	65 (13,9)	0,752	<0,001	0,034
T4		0 (0,0)	0 (0,0)	8 (1,7)	-	0,026	0,649
Hystology	**n (%)**						
Endometrioid		365 (93,4)	57 (95,0)	390 (83,7)	0,851	<0,001	0,034
Clear cell		12 (3,1)	0 (0,0)	25 (5,4)	0,340	0,140	0,128
Carcinosarcoma		11 (2,8)	1 (1,7)	40 (8,6)	0,950	0,001	0,106
Squamous cell		0 (0,0)	0 (0,0)	5 (1,1)	-	0,102	0,906
Serous		3 (0,8)	2 (3,3)	6 (1,3)	0,294	0,708	0,529

Grade	**n (%)**						
G1		191 (48,8)	29 (48,3)	166 (35,6)	0,947	<0,001	0,076
G2		153 (39,1)	22 (36,7)	214 (45,9)	0,831	0,053	0,226
G3		47 (12,0)	9 (15,0)	86 (18,5)	0,656	0,012	0,628
Histopathological risk group	n (%)						
Low		142 (36,3)	25 (41,7)	79 (17,0)	0,507	<0,001	<0,001
Intermediate		151 (38,6)	20 (33,3)	180 (38,6)	0,519	0,944	0,513
High intermediate		10 (2,6)	2 (3,3)	7 (1,5)	0,907	0,368	0,628
High		76 (19,4)	12 (20,0)	126 (27,0)	0,948	0,011	0,315
Advanced		12 (3,1)	1 (1,7)	65 (13,9)	0,851	<0,001	0,013
Metastatic		0 (0,0)	0 (0,0)	9 (1,9)	-	0,016	0,587

Table 2. shows that:

- The comparative analysis of the patients with one of the three surgical approaches showed considerable differences in all FIGO stages with the exception of stages IB and II. Women with IA represent a significantly lower share of the AH group, whereas the other two surgery types have statistically equal relative proportions. Among the patients with stage III, those treated through open surgery are with a considerably higher percentage, whilst the other two operation approaches are represented with statistically equal relative proportions. Patients with stage IV who were operated through laparotomy are significantly more than those with robotic-assisted technique;

- Similar is the frequency distribution of pT stage – significant contrasts for all stages but T1b and T2. For T1a patients, the percentage of those managed by open surgery is considerably higher, whereas the other two surgeries are represented with statistically equal proportions. Among the women with T3 stage, significantly greater share have those treated within the group of AH, whereas the other two operations have statistically equal proportions. The patients with stage T4 managed by laparotomy are considerably more than those with RH;

- Considering the dependencies regarding histology of the tumor, significant differences were observed within the categories of endometriodic carcinoma and carcinosarcoma. Endometriodic carcinoma represents a significantly lower percentage among the operated

through open surgery patients, whilst the other two operations have statistically equal shares. Entirely reverse is the correlation among the women with histologically proven carcinosarcoma, where AH is considerably prevalent, whereas the other two surgery types are represented with equal statistical proportions;

- Regarding the indicator “Grade of tumor”, the G1 relative proportion of the patients managed with robotics is substantially greater than the share of those with laparotomy, however not when compared to that of the laparoscopy patients, whose proportion does not differ from those of the other two operation types. Among the patients with G2 and G3 grade are, there is a significantly higher percentage of women operated through AH than of those with RH, but not of those with LH, whose relative share is not different from those of the other two operations;

- The comparative analysis of the patients with one of the three surgeries showed significant differences in all of the histopathological risk groups, with the exception of „Intermediate“ и „High intermediate“. Among the women within the histopathological risk group “Low”, those treated with open hysterectomy have considerably lower percentage, whilst the other two surgeries are represented with statistically equal shares. For women in the histopathological group “High”, a greater percentage is noted for those operated through laparotomy compared to those treated with robotic-assisted technique, however not compared to those with laparoscopy, whose relative proportion equals those of the other two operative approaches. The percentage of patients with abdominal hysterectomy within the histopathological group “Advanced” is substantially higher, whilst the other two surgery types have statistically equal relative shares. Within the group with “Metastatic” histopathological risk, women with AH are significantly more than those in the RH group.

4.2.2. DISCUSSION

The choice of a certain operative approach seems to be directly dependent on the tumor characteristics of patients with malignant disease. The survival rate for women with EC is related to the characteristics of the tumor and the presence of metastatic cancer. Stage, grade, invasion depth and histological variation of the carcinoma are associated with the risk of extrauterine spread of the disease and impact the overall cancer survival prediction for the patients.

With account of the time interval covered by our study, the data used corresponds to the FIGO classification, 2018. According to it, the surgical staging of endometrioid cancer shall replace the clinical staging of the FIGO Committee of Gynecological Oncology (1988) and the further revised in 2009 staging. In the staging, which is in conformance with the rules of classification, we have included histopathological verification of grade and spread of the tumor (5).

Minimally invasive techniques are increasingly prominent in operative gynecology, including for patients with histologically proven EC. Our data confirms that, too. In order to receive a clearer understanding of the correlation between the choice of surgical approach and FIGO stage, we examined individually the obtained results for patients with early stage EC (FIGO I+II) and for those with advanced EC stages. Analogous comparison we made regarding pT stage. It is notable that the majority of women with EC, involved in our research, are in early stage, resp. 95.6% for RH, 96.7% for LH, and 79.0% for AH. The outcomes demonstrate a significantly larger number of performed minimally invasive surgeries for women with early stage of endometrial carcinoma compared to open surgery, $p<0.001$. In contrast to that subgroup, a preferable choice of operative treatment for patients with advanced and metastatic EC is AH. Open surgery for those patients is preferred to laparoscopy, as well as to robotics, with 21% AH, 4.3% RH и 3.3% LH resp., $p\leq0.001$ for RH vs. AH and $p=0.007$ for LH vs. AH. Similar observations and conclusions can be made about the distribution of the operative techniques with regards to pT stage. Our data is comparable to those of Boggess et al., Cardenas-Goicoechea et al., Park et al., as well as Eoh et al. (17, 22, 44, 129).

The grade of EC is connected to the prediction for the patients. Lower differentiation of the carcinoma is associated with a worse prediction, as well as expectation of a more complicated intraoperative finding. Our results demonstrate considerable preferences of RH compared to AH in the cases of G1 EC, resp. 48.8% vs. 35.6% for RH vs. AH, $p<0.001$. Our study reveals that for poorly differentiated EC (G3), open surgery is established as a desirable choice of operative treatment, in comparison to robotic-assisted technique, resp. 18.5% vs. 12.0% for AH vs. RH, $p=0.012$. In contrast to our outcomes, Subramaniam et al., as well as Coronado et al., did not discover any dependency between the choice of surgical method and tumor characteristics of the women (30, 156).

Our data, similarly to the available literature sources, confirm that the endometrioid EC is the histological variation with highest incidence, with a proportion of 93.4% of the RH, 95.00% of the LH and 83.7% of the AH cases. Statistically credibly larger number of the patients with

endometrioid endometrial carcinoma underwent one of the two types of MIS, $p \leq 0.034$. Notable difference in the preferred technique is also observed for the histological variation "carcinosarcoma". Out of 917 patients involved in our research, 52 women are represented with this histopathological tumor variation, with open surgery being the chosen operative approach, with respectively 2.8% for RH and 8.6% for AH, $p=0.001$. It is presumably the specific of the carcinosarcomas that determines the predilection of gynecologists for laparotomy.

The histopathological risk group of the patients is determinant for the prediction for them. To assess the correlation between histopathological risk and preferred operative method, we have divided the women with EC into 6 histopathological risk groups, in accordance to the reports of ESGO, ESMO and ESTRO and the recommendations of Jørgensen et al. (29, 77). For the women with low risk (endometrioid adenocarcinoma FIGO IA, G1-2), substantially larger part of the hysterectomies were performed with minimally invasive approach, with this correlation remaining valid for RH vs. AH ($p<0.001$), as well as for LH vs. AH ($p<0.001$). In contrast, open surgery is the predominant surgical technique for the groups with high (endometrioid adenocarcinoma FIGO IB, G3, and non-endometrioid FIGO I, FIGO II, FIGO III), advanced (FIGO IVA) and metastatic (FIGO IVB) risk cancer, $p \leq 0.016$.

There are rather few contemporary publications to analyze the three operative techniques regarding tumor indicators of women with EC. Eoh et al., as well as Yoon et al., cover in their comparative analyses the two minimally invasive approaches. They have not discovered any significant dependency between tumor characteristics and preference for RH or LH (44, 173). Two recent studies from 2024 r. collate RH, LH and AH with regards to the patients' tumor profile. The authors have not determined any difference in the tumor characteristics of the women with one of three surgical approaches and share the opinion that the method of hysterectomy is not dependent on that indicator (71, 73).

Based on the conducted analysis, we can establish the preferable histological profile of the patients for MIS, resp. RH – early stage of EC, with endometrioid histological variation and high differentiation (G1). AH is an appropriate choice for women with higher FIGO stage, poorer differentiation and more aggressive histological variation of EC. Similar conclusions draw Wright et al., as well as Manchana et al. (108, 168).

4.3. ANALYSIS OF THE PERIOPERATIVE RESULTS FOR THE THREE TYPES OF HYSTERECTOMY REGARDING THE INDICATORS "OPERATIVE TIME", "LYMPH NODE DISSECTION", "POSTOPERATIVE HOSPITAL LENGHT-OF-STAY" AND "ESTIMATED BLOOD LOSS" FOR THE THREE HYSTERECTOMY APPROACHES.

4.3.1. OWN RESULTS

Table 3. Comparative analysis of the three types of hysterectomy regarding main perioperative indicators.

Characteristics		(1) RH	(2) LH	(3) AH	p-value		
					1-2	1-3	2-3
Mean operative time (min.)	(SD)	93,37 (33,28)	81,44 (39,46)	115,35 (33,04)	0,001	<0,001	<0,001
Lymph node dissection	n (%)	225 (57,5)	20 (33,3)	261 (56,0)	0,001	0,678	0,001
Number of lymph nodes removed	(SD)	2,29 (4,28)	1,38 (2,78)	6,38 (7,99)	0,169	<0,001	<0,001
Hospital length of stay (days)	(SD)	7,01 (2,56)	6,68 (2,92)	10,17 (2,43)	0,139	<0,001	<0,001
Preoperative Hgb	SD)	127,45 (13,37)	130,38 (15,18)	120,33 (16,23)	0,029	<0,001	<0,001
Preoperative Hct	(SD)	37,11 (4,06)	38,22 (4,94)	34,92 (4,98)	0,009	<0,001	<0,001
Postoperative Hgb	(SD)	118,77 (12,93)	121,25 (11,20)	113,10 (15,52)	0,160	<0,001	<0,001
Postoperative Hct	(SD)	34,48 (3,90)	35,29 (4,90)	32,97 (4,90)	0,264	<0,001	0,005
Blood transfusion	n (%)	19 (4,9)	7 (11,7)	67 (14,4)	0,065	<0,001	0,695

Table 3. shows that:

- With significantly highest mean length of operative time (115.35 min.) are the patients operated through open surgery, followed by those with RH with 93.37 min., and LH with 81.44 min.;

- Patients that were laparoscopically operated have substantially smaller percentage of lymph node dissection than those who were treated with one of the two other techniques, which do not differ statistically in that indicator;

- Women operated through abdominal surgery have significantly higher rates of their mean number of removed lymph nodes compared to those who underwent one of the two minimally invasive methods, which do not differ statistically in that indicator;

- Patients with AH have considerably greater rates regarding the indicator “Hospital length-of-stay” by comparison with those managed with laparoscopy or robotic-assisted approach, which do not differ statistically in that indicator;

- With significantly highest preoperative hemoglobin and hematocrit are the women that underwent laparoscopy, followed by those with the robotic-assisted approach and laparotomy;

- Significantly lower rates of postoperative hemoglobin and hematocrit have the patients treated with open surgery, compared to those with undertaken LH and RH, which do not differ statistically in those two indicators;

- Patients who had laparotomy are with substantially higher percentage of blood transfusions in comparison to those of the LH group, which does not statistically differ from the other two surgical techniques.

4.3.2. Discussion

Analyzing the perioperative indicators of a certain surgical technique is the most objective means of estimating its advantages and disadvantages over other approaches. In this respect, operative time is among the most important factors. Blood loss is also one important indicator, which is most often associated with the operative time and postoperative hospital length-of-stay. Unlike the majority of authors, who account for blood loss in milliliters, we estimate it on the basis of pre- and postoperative hemoglobin and hematocrit rates, as well as with regard to the incidence of blood transfusions. Hospital length-of-stay is an indicator that provides valuable information of the time needed for postoperative recovery of the patients, which is also in close connection with their returning to a normal way of life. For assessment of the lymph status and the opportunities that the three surgical techniques provide, we compare the incidence of performing a lymphadenectomy within the three hysterectomy approaches, as well as the number of the removed lymph nodes in every technique.

In our study we observe better perioperative results in the MIS group compared to open surgery. The robotic-assisted approach and LH are characterized with credibly shorter mean operative time than AH, resp. 93.37 min. for RH, 81.44 min. for LH and 115.35 min. for AH, $p \leq 0.001$. From a clinical standpoint, in our study, the length-of-stay and estimated blood loss

outcomes are better in the MIS group, which corresponds with those of Bogges et al. in their 2008 research (17). It is well established now that the robotic platform offers an increased precision, visualization and dexterity, which leads to better perioperative outcomes in this group. Our observations show the shortest operative time to be for the group of laparoscopic cases followed by the robotic-assisted surgeries, which can presumably be referred to the lesser amount of lymph node dissections performed during the laparoscopies. Bogges et al. reported data for the longest operative time for LH – 213.4 min., compared to 191.2 min. for RH and, the shortest – 146.5 min. for AH cases. Coronado et al. report shorter operative time for RH compared to LH, but the shortest is for AH (30), which is also demonstrated in other articles related to the topic (14, 37, 58, 144). Possible reason for these differing results could be found in the learning curve.

Bell et al., in their 2008 study, presented 110 cases of women with endometrial carcinoma operated with one of the three methods. Their findings, in contrast to ours, reveal longer operative time for the group of RH compared to open surgery, with no difference only in comparison to the laparoscopic group, $p<0.0001$, $p=0.14$. Analogous to our current study, Bell et al. reported less blood loss in MIS (166 cc for RH and 253 cc for LH, $p=0.25$), compared to the laparotomic cases ($p=0.01$). Regarding lymph node retrieval, there was no difference between the three groups (14). In 2009, Seamon et al. published a cohort study comparing robotic and laparoscopic data for women with EC, demonstrating no difference in the number of removed lymph nodes but lower rates of estimated blood loss, incidence of transfusions and hospital stay after undergoing RH (144). Our research revealed better outcomes for MIS than after open surgery regarding postoperative hemoglobin, blood transfusions and length-of-stay. Other authors report similar results of their research (37).

A systematic review and meta-analysis conducted by Gaia et al., 2010, that included 1591 endometrial cancer cases operated with one of the three methods – robotic-assisted, laparoscopic and open, demonstrated statistically significant reduction in estimated blood loss for RH, shorter hospital length-of-stay after RH and LH and lower incidence of blood transfusions for RH. Their data, however, showed operative time for robotics similar to that for laparoscopy but greater than the rates in the open surgery group (53).

The analysis of the outcomes regarding the lymph node retrieval reveals a smaller number of performed lymphadenectomies during laparoscopy, whereas the respective results for robotic-assisted and open surgery are comparable. As for lymph node dissection, the opportunities

that robotized systems provide put robotic-assisted surgery in a prominent position compared to laparoscopy, which is also confirmed in our study.

In a comparison of the outcomes of RH and AH for treating endometrial cancer, Subramaniam et al. published results for significantly longer operative time for robotics but improve results for this group in terms of estimated blood loss, hospital stay and incidence of blood transfusions, without statistical difference between the two cohorts for the total lymph nodes obtained (156). While Venkat et al. reported longer operative time for robotics than laparoscopy – results that are analogous of ours, other authors state that no considerable difference is found for the real operative time between both techniques; however, the additional preparation time for RH has to be taken in account (130).

The fact that robotics is a safer alternative to the AH and LH approaches in offering improved preoperative outcomes is demonstrated not only by us but also by other authors in their studies (17, 30, 135, 156). In 2014 Ran et al. published their meta-analysis which included 22 studies with 4420 patients who underwent RH, LH or AH for EC. The authors pointed out that robotics is superior to open surgery in terms of estimated blood loss, blood transfusion incidence and hospital length-of-stay but inferior in regard to the operative time. Compared to laparoscopy, they found robotic surgery superior in terms of EBL but equal to it regarding the other tested indicators (135).

Nayyar et al., in 2019, analyzed data from 150 cases with RH or AH for treating EC and concluded that the RH approach, compared to AH, leads to shorter operative time, lower EBL, smaller number of blood transfusions, as well as shorter hospital stay after the surgery (120). Their data are in unison with other peer-reviewed publications (14, 17, 37, 53, 58).

Another subsequent review and meta-analysis – by Ind et al., 2017, confirmed that the duration of RH and LH is without difference, however robotics is with lower LOS and EBL (72). Reduced operative time and smaller blood loss, as well as shorter postoperative stay for RH compared to LH were also demonstrated by Corrado et al. and Chan et al. (26, 34).

A recent meta-analysis conducted by Wang et al., 2020, made a comparison of RH with LH and AH for women with histologically proven EC, including 27 articles with a total of 6568 patients. The authors concluded that, compared to LH, the RH approach resulted in lower rates of estimated blood loss and blood transfusion incidence, as well as hospital length of stay, but with longer operative time. Compared to AH, RH data gave the same results. While

our study noted a higher number of removed lymph nodes in the laparotomy group, Wang et al. found no significant differences between the three techniques (166).

Similarly to our outcomes, Corrado et al., as well as three recent studies, also support the fact that MIS is characterized with better perioperative results, incl. reduced operative time and EBL (32, 74, 84, 137). The advantages of RH for patients with histologically proven EC over the other two techniques are also reported by Liu et al. and Casarin et al. (25, 97). The findings of Ikebuchi et al. support our perioperative results by defining the robotic-assisted technique as a more appropriate and safe surgical approach for women with EC, in comparison to LH and AH (71).

Compared to laparoscopic and laparotomy surgery, robotic-assisted surgery allows a better treatment of patients with EC by overcoming the barriers of the other two types of hysterectomy procedures. Our data shows that MIS, and robotics in particular, is an effective and safe alternative to open surgery in the treatment of endometrial cancer, with better perioperative outcomes.

4.4. ANALYSIS OF THE THREE TYPES OF SURGERY REGARDING INTRA- AND POSTOPERATIVE COMPLICATIONS AND UNDERTAKEN ADJUVANT THERAPIES – RADIATION, CHEMO- AND HORMONE THERAPY.

4.4.1. OWN RESULTS

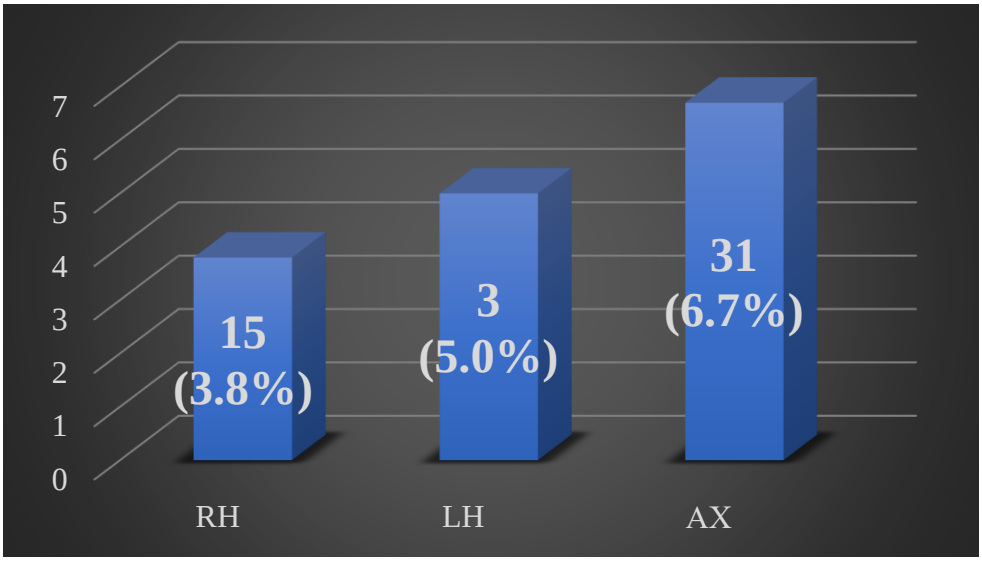

Figure 6. Comparative analysis of the mean number of complications for RH, LH and AH.

Table 4. Comparative analysis of the three types of surgery regarding the mean number of complications.

		(1) RH	(2) LH	(3) AH	p-value		
Complications					1-2	1-3	2-3
Mean number of complications	n (%)	15 (3,8)	3 (5,0)	31 (6,7)	0,720	0,093	0,785

Figure 6. and table 4. reveal significant differences between the three types of surgery regarding the mean number of complication occurrences.

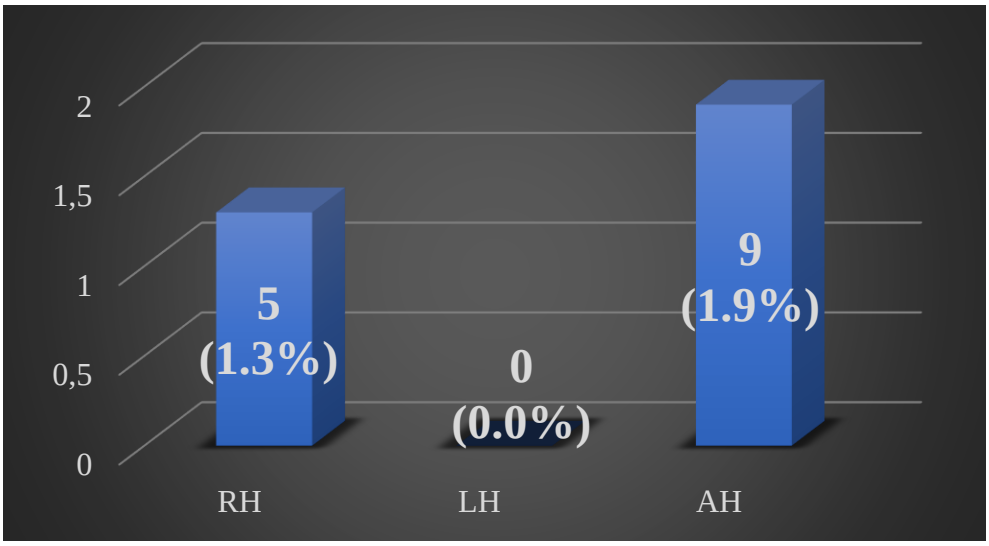

Figure 7. Comparative analysis of the number of intraoperative complications for RH, LH and AH.

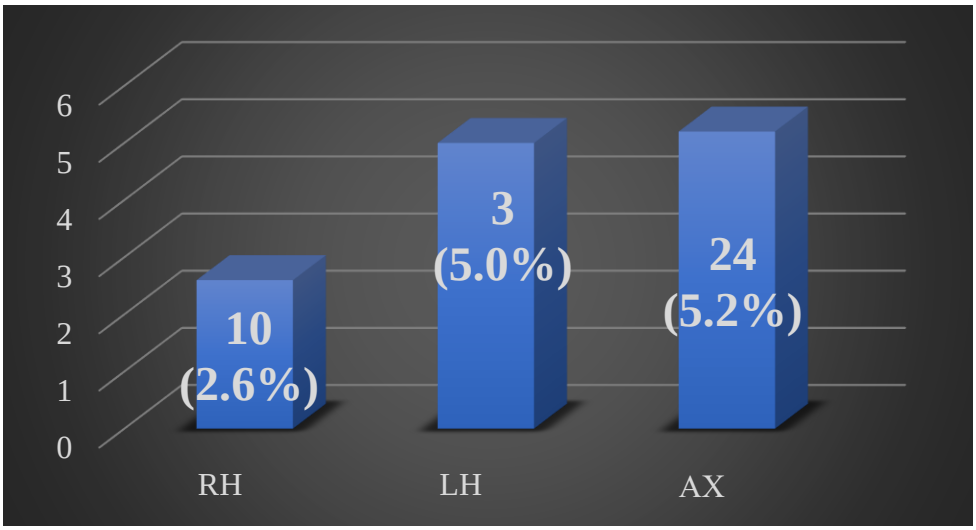

Figure 8. Comparative analysis of the number of postoperative complications for RH, LH and AH.

Table 5. Comparative analysis of the three types of surgery regarding the number of occurred intra- and postoperative complications.

		(1) RH	(2) LH	(3) AH	p-value		
Complications					1-2	1-3	2-3
Intraoperative complications	n (%)	5 (1,3)	0 (0,0)	9 (1,9)	1,000	0,591	0,607
Postoperative complications	n (%)	10 (2,6)	3 (5,0)	24 (5,2)	0,395	0,055	1,000

Figures 7. and 8. and table 5. reveal that there is not any significant difference between the three types of operations regarding the number of occurred intraoperative and postoperative complications.

Table 6. Comparative analysis of the types of intraoperative complications for RH, LH and AH.

Intraoperative complications		**(1) RH**	**(2) LH**	**(3) AH**	**p 1-2**	**P 1-3**	**p 2-3**
Types	**n (%)**						
Bladder injury		1 (33,3)	0 (0,0)	1 (16,7)	n.s.	n.s.	n.s.
Small bowel injury		0 (0,0)	0 (0,0)	3 (50,0)	n.s.	n.s.	n.s.

Cardiac arrest		1 (33,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Ureteral injury		0 (0,0)	0 (0,0)	1 (16,7)	n.s.	n.s.	n.s.
Colon injury		1 (33,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Large vessel injury		0 (0,0)	0 (0,0)	1 (16,7)	n.s.	n.s.	n.s.

Table 6 shows no significant difference between the three operative approaches in type of intraoperative complications.

Table 7. Comparative analysis of the types of postoperative complications for RH, LH and AH.

Postoperative complications		**(1) RH**	**(2) LH**	**(3) AH**	**p 1-2**	**p 1-3**	**p 2-3**
Types	**n (%)**						
Pulmonary embolism		1 (14,3)	0 (0,0)	1 (5,9)	n.s.	n.s.	n.s.
Ileus		1 (14,3)	1 (50,0)	4 (23,5)	n.s.	n.s.	n.s.
Vaginal cuff cellulitis		0 (0,0)	0 (0,0)	1 (11,8)	n.s.	n.s.	n.s.
Postoperative hernia		1 (14,3)	0 (0,0)	1 (11,8)	n.s.	n.s.	n.s.
Perforation of stomach ulcer		1 (14,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Acut renal failure		0 (0,0)	0 (0,0)	1 (5,9)	n.s.	n.s.	n.s.
Urinary tract infection		0 (0,0)	1 (50,0)	0 (0,0)	n.s.	n.s.	n.s.
Peritonitis		0 (0,0)	0 (0,0)	1 (5,9)	n.s.	n.s.	n.s.
Arrhythmia		0 (0,0)	0 (0,0)	1 (11,8)	n.s.	n.s.	n.s.
Deep-vein thrombosis with pulmonary embolism		0 (0,0)	0 (0,0)	1 (5,9)	n.s.	n.s.	n.s.
Postoperative hemoperitoneum		0 (0,0)	0 (0,0)	1 (11,8)	n.s.	n.s.	n.s.
Corpus alienum		1 (14,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Postoperative hemorrhagia with pulmonary embolism		1 (14,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Cardiac arrest		1 (14,3)	0 (0,0)	0 (0,0)	n.s.	n.s.	n.s.
Hydronephrosis		0 (0,0)	0 (0,0)	1 (5,9)	n.s.	n.s.	n.s.

Table 7. shows no significant difference between the three surgical techniques in type of postoperative complications.

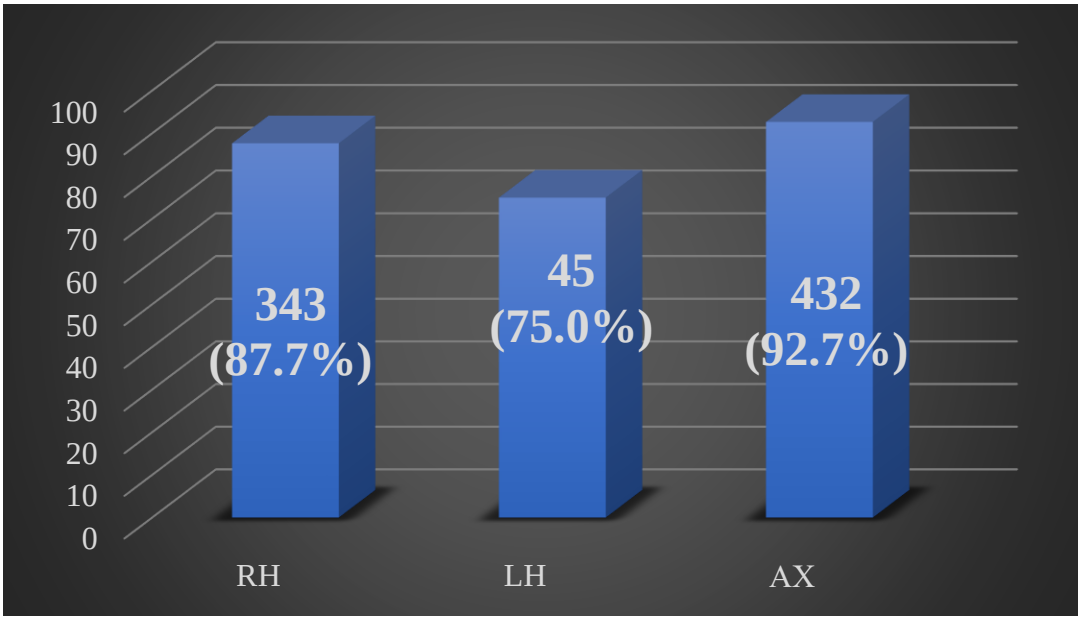

Figure 9. Frequency distribution of the undertaken adjuvant therapy for the three types of hysterectomy.

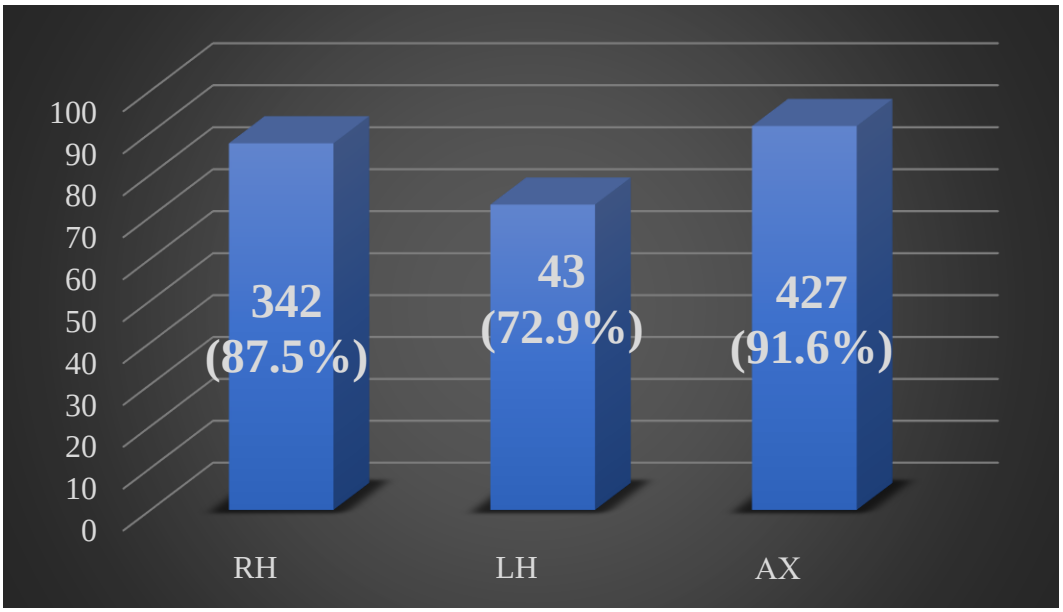

Figure 10. Frequency distribution of the undertaken postoperative radiation therapy for the three types of hysterectomy.

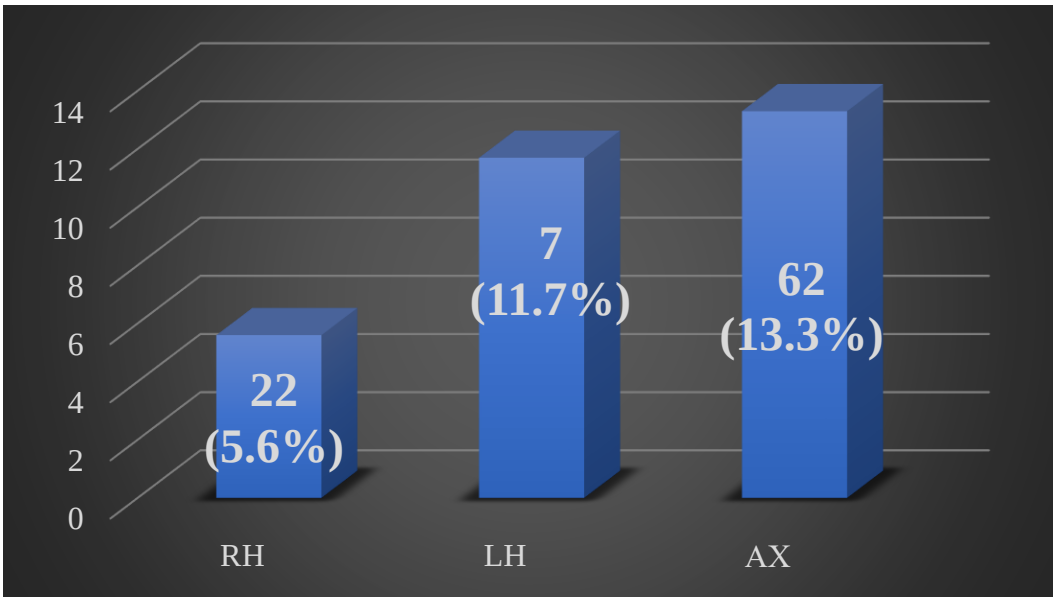

Figure 11. Frequency distribution of the undertaken postoperative chemotherapy for the three types of hysterectomy.

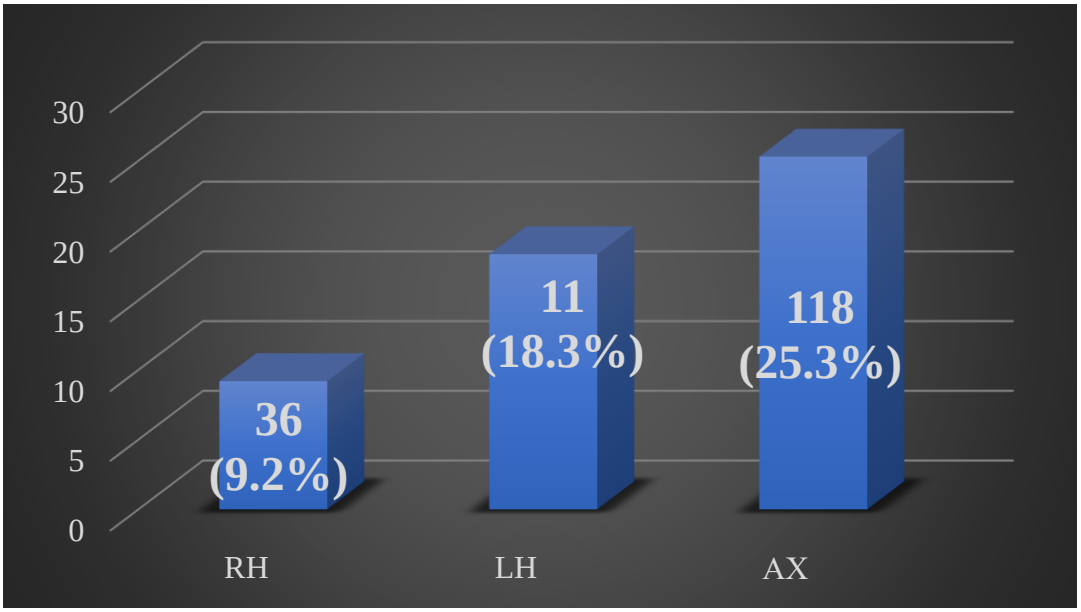

Figure 12. Frequency distribution of the undertaken hormone therapy for the three types of hysterectomy.

Table 8. Comparative analysis of the three types of hysterectomy regarding the undertaken adjuvant therapies.

		(1) RH	(2) LH	(3) AH	p-value		
Adjuvant therapy	n (%)	343 (87,7)	45 (75,0)	432 (92,7)	0,015	0,014	<0,001
Radiotherapy	n (%)	342 (87,5)	43 (72,9)	427 (91,6)	0,005	0,054	<0,001
Chemotherapy	n (%)	22 (5,6)	7 (11,7)	62 (13,3)	0,088	<0,001	0,841
Hormone therapy	n (%)	36 (9,2)	11 (18,3)	118 (25,3)	0,088	<0,001	0,268

The outcomes in figures 9., 10., 11. and 12 and table 8 reveal that:

- Patients in AH group received significantly more frequent administration of postoperative adjuvant therapy, followed by those with RH and LH.
- With significantly highest percentage of postoperative radiotherapy are the patients operated through open surgery, followed by those with robotic-assisted and laparoscopic surgery.
- Patients with laparotomy represent a considerably greater proportion of chemotherapy undertaken compared to those with RH, but not to those with laparoscopy, who do not differ statistically from the other two types of hysterectomy.
- Women with AH take up a substantially higher percentage of undertaken hormone therapy in comparison to the operated in the RH group, but not to those managed with LH, who do not statistically differ from those of the other two operations.

4.4.2. DISCUSSION

One of the leading indicators of the quality of a certain operative approach is the incidence of occurred complications during and after its performance. Complications serve as a mark for the applicability of a given operative technique, although their increased incidence might be associated with the surgeon's experience in a lot of cases.

In our study, we found no significant difference between the three operative methods in terms of incidence of complications, intra- or postoperative. It is albeit important to note that even without statistical significance, open surgery is characterized with a higher mean rate of undesired occurrences, which is also valid for the intra- and postsurgical complications. For AH we estimate 6.7% incidence of the mean number of complications, whereas in the RH and LH groups they are resp. 3.8% and 5.0%. When observing isolated cases of the different types of complications for MIS, the increased incidence of small bowel injuries during open hysterectomy could not remain unremarked, as well as the higher rate of accounted ileus in the same group. The systematic review by Gaia et al., 2010, supports our outcomes by reaching similar results between the three surgical techniques regarding the observed indicator (53).

In contrast with our study, where we found no difference in the incidence of complications, Bogges et al. report a statistically significant smaller number of complications for RH compared to AH - respectively 5.9% vs. 29.7%, $p<0.001$ (17). The data obtained by Bogges are also supported by Seamon et al. (144). Bell et al. report a lowest percentage of complications in the robotics group (7.5%) compared to the laparoscopies (20.0%) and open surgery (27.5%) (14). Other authors also establish lower incidence of the occurred intra- and postoperative complications in the group of MIS (37), with Ind et al. estimating priority for RH over LH regarding this indicator (72). Opposing the majority of evident scientific literature data, a research by Wright et al. demonstrates greater incidence of complications in the group of RH compared to LH – 23.7% vs. 19.5% (170).

More recent studies from the time period of 2019-2024, by comparing the three surgical approaches, establish the important advantages of robotic-assisted technique over LH and AH. отчитат значимите предимства на робот-асистираната техника пред ЛХ и АХ. Nayyar et al., in 2019, analyzed data taken from 150 cases of RH or AH for EC and found a decreased rate of complications for RH compared to AH, resp. 9.3% vs. 38.6%, $p<0.0001$ (120). A recent meta-analysis by Wang et al. compares RH with LH and AH for women with histologically proven EC within 27 articles with a total of 6568 patients. The authors conclude that, compared to LH, RH has lower incidence of the complication occurrences. When collating open surgery next to robotics, RH is further proved as the more appropriate choice of approach (166). The fact of robotic-assisted surgery being a safer procedure than AH is also supported by Raffone et al., who, in their systematic review and meta-analysis, assess a 2.5 times lower incidence of complications occurring after RH compared to AH. A

comparative analysis from 2024 defines the robotic-assisted surgery as safe and appropriate technique for women with EC, with a credibly decreased incidence of complications than LH and AH, resp. 16.7% for RH, 35% for LH and 40% for AH (71). Our data for absence of significant difference in the occurred intraoperative complications in the group of MIS are also supported by a Korean research of 2023. However, when comparing the postoperative complications, Eoh et al. discover advantages of RH over LH with resp. 7.7% vs. 13.8%, p=0.002 (44).

Our work determines considerably higher rates of adjuvant therapy performed after AH, compared to MIS. In the AH group we observe an incidence of 92.7% vs. 87.7% after RH and 75.0% after LH, $p \leq 0.014$. In terms of postoperative radiotherapy, a credibly larger number of patients are registered in the group of open surgery compared to that of laparoscopy ($p<0.001$). When observing the chemo- and hormone therapy, remarkable is the significantly greater incidence of their applying after AH than after RH ($p<0.001$). Possible explanation for these results is the considerably larger number of patients with advanced and metastatic EC in the open surgery group.

The data provided by the accessible literature sources to compare the three surgical approaches with regards to the applied adjuvant therapy are rather limited or ambiguous. Park et al. find no difference between RH and AH, with resp. 46% vs. 54%, p=0.08 (129). The fact that RH is a safe alternative for the patients with EC is also confirmed by Scalici et al. (142), as well as by the retrospective analyses of Manchana et al., who register no difference between the three operative methods in terms of applied adjuvant therapy (108). In contrast with our research, Wright et al. reported a higher proportion of the application of postoperative radiation therapy after MIS than after AH (34.3% after MIS vs. 31.3% after AH), with no difference in the incidence of conducted postoperative chemotherapy, p=0.81 (170). Regarding the indicator “adjuvant therapy”, as well as its subgroups, we have not estimated any difference between both minimally invasive techniques, which is supported by other authors (103, 170). Unlike us, an Indian study from 2019 registers a larger incidence of the application of adjuvant therapy after RH than after AH, resp. 44.0% vs. 38.6%, albeit with no statistical significance. When it comes to postoperative chemotherapy, both techniques are with comparable outcomes (120). A retrospective analysis from 2020 compares patients with RH and AH regarding the tested indicators and registers no difference between the two groups in the rate of postoperative radiotherapy, p=0.46. Nevertheless, it is important to note that their work covers a relatively small number of cases – 135 women in total (155).

4.5. ANALYSIS OF THE THREE TYPES OF SURGERY REGARDING THE OVERALL AND THE DISEASE-FREE SURVIVAL FOR THE PATIENTS WITH ENDOMETRIAL CANCER.

4.5.1. ANALYSIS OF THE THREE TYPES OF SURGERY REGARDING THE OVERALL SURVIVAL FOR PATIENTS IN ALL STAGES OF ENDOMETRIAL CANCER.

4.5.1.1. OWN RESULTS

The postsurgical follow-up was conducted through regular check-ups in the first month after the manipulation, then every three months for two years, every six months until the fifth year and annually thereafter. Vital status, resp. OS data were ascertained from the National Oncological Registry database and were updated on 9 July, 2019.

Table 9. Mean follow-up time for the three types of hysterectomy.

	RH **(n=391)**	LH **(n=60)**	AH **(n=466)**	**p-value**		
	1	2	3	1-2	1-3	2-3
Follow-up (days) $\overline{X}$ **(SD)**	1344,04 (847,75)	1204,37 (792,90)	1733,25 (1123,35)	0,283	<0,001	0,001
Follow-up **(**years**)** $\overline{X}$ **(SD)**	3,68 (2,32)	3,30 (2.00)	4,75 (3,08)			

Table 9. reveals that the mean follow-up time is significantly longest for the patients with AH compared to the length for the other two groups, which do not statistically differ in this indicator.

Table 10. Mortality and causes of death for the three types of hysterectomy.

	RH	LH	AH	p-value		
	1	2	3	1-2	1-3	2-3
Mortality n (%)	67 (17,1)	10 (16,7)	140 (30,0)	1,000	<0,001	0,033
Alive n (%)	324 (82,9)	50 (83,3)	326 (70,0)	1,000	<0,001	0,033
EC-specific death n (%)	58 (14,8)	10 (16,7)	129 (27,7)	0,751	0,061	0,698
Other cause of death n (%)	9 (2,3)	0 (0,0)	11 (2,4)	0,468	0,657	0,541

Table 10. shows that:

- Significantly highest rate of mean mortality have the patients with AH in comparison to those of the other two groups, which do not differ statistically in that indicator.
- Respectively, the AH patients have the lowest percentage in the indicator “Alive”, compared to the other two groups with no statistical differences there.
- With respect to the “EC-specific death” and “Other causes of death” categories was not observed considerable difference in mortality for the three researched groups.

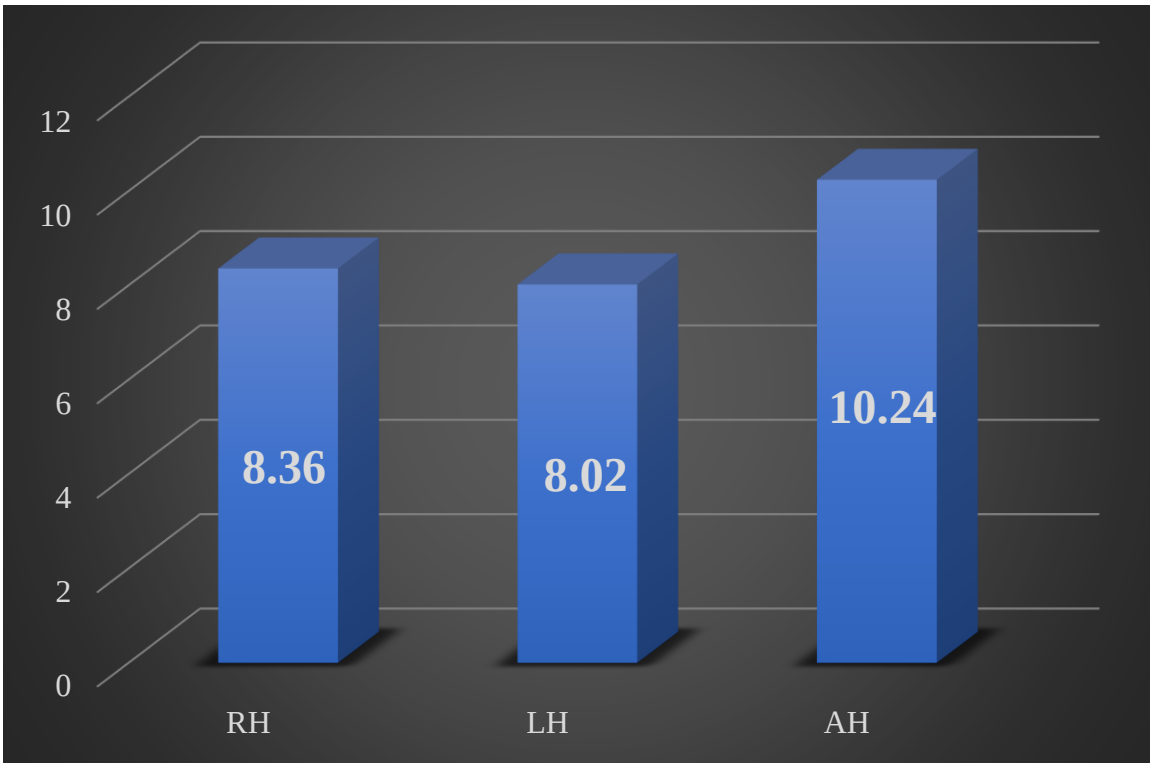

Figure 13. Overall survival for patients with EC after RH, LH and AH (in years).

Table 11. Mean OS for RH, LH and AH.

	RH (n=391)	LH (n=60)	AH (n=466)	p-value		
	1	2	3	1-2	1-3	2-3
Mean OS in days (Std. Error)	3052,47 (74,63)	2927,54 (223,67)	3738,94 (238,36)	0,638	0,001	0,343
Mean OS in months (Std. Error)	100.41 (2,45)	96.30 (7,36)	122.99 (7,84)			

The outcomes shown in figure 13. and table 11. reveal that the mean overall survival is substantially higher for patients who underwent AH compared to that for those with RH, while the survival rate of the LH group patients is not statistically different from that of the other two groups.

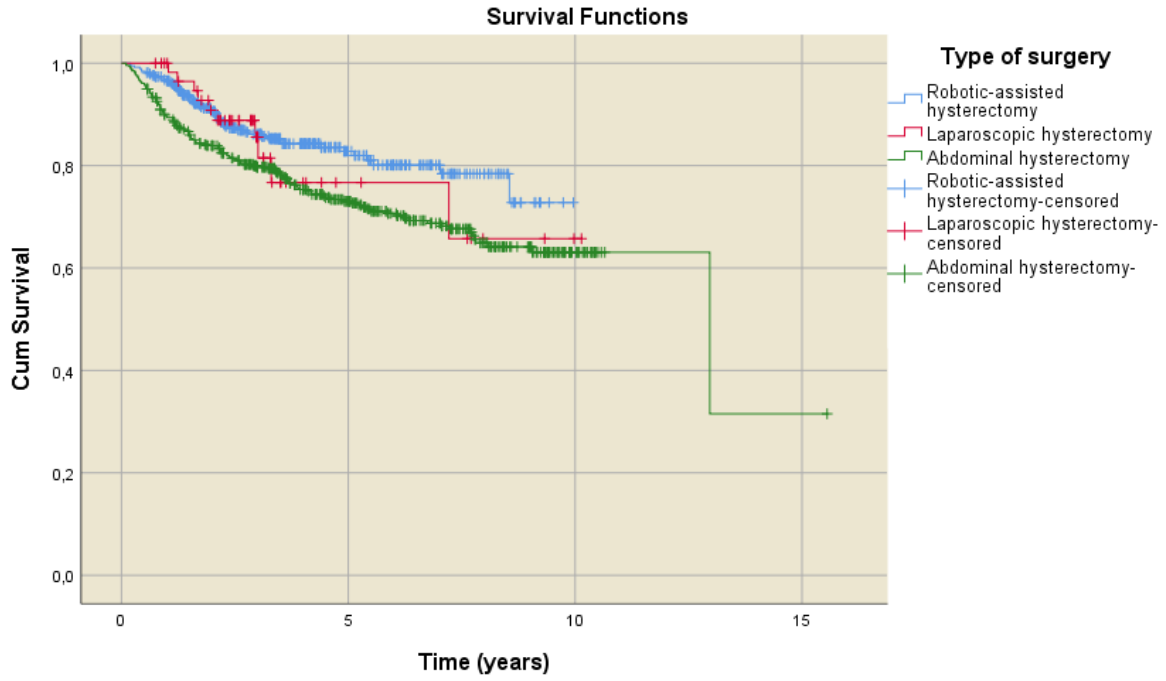

Figure 14. OS for the three types of hysterectomy presented with the Kaplan-Meier curve.

Figure 14. shows that the slowest decrease is observed at the survival function of patients who were operated through open surgery, whereas it is significantly faster for patients managed with robotic-assisted technique and has intermediate values in the LH group.

Table 12. HR and 95% CI of the analyzed factors for OS (Univariate and multivariate Cox regression analysis for the three types of hysterectomy).

Factors	Comparison	Crude				Multivariate			
		HR	95% CI		p	HR	95% CI		p
			Lower	Upper			Lower	Upper	
Type of surgery	ЛХ/РХ	1,225	0,624	2,405	0,555				
	АХ/РХ	1,659	1,207	2,281	0,002				
Age (years)	Increasing with 1 year	1,059	1,042	1,076	<0,001	1,051	1,021	1,082	0,001
FIGO stage	II / Carcinoma in situ+IA+IB	1,998	1,270	3,142	0,003				
	IIIA+IIIB+IIIC / Carcinoma in situ+IA+IB	6,548	4,732	9,061	<0,001				
	IVA+IVB / Carcinoma in situ+IA+IB	8,644	4,365	17,119	<0,001				
pT stage	T2 / Tis+T1a+T1b	2,023	1,328	3,082	0,001				
	T3a+T3b / Tis+T1a+T1b	8,422	5,994	11,833	<0,001				
	T4a / Tis+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				
Lymph node dissection	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	m. l. I / Normal	1,265	0,747	2,142	0,381				
	m. l. II/ Normal	1,476	0,999	2,180	0,051				
	m. l. III/ Normal	2,184	1,462	3,263	<0,001				
	≥ m. l. IV / Normal	3,746	2,419	5,802	<0,001				
Adjuvant therapy	Yes / No	1,850	1,031	3,319	0,039				
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				
Concomitant malignant tumor	Yes / No	1,651	0,679	4,015	0,269				
Histopathological 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

Table 12. illustrates the outcomes of the applied Cox regression analysis – univariate and multivariate.

In individual terms, the indicators “Type of surgery”, “Age”, “FIGO”, “pT stage”, “pN stage”, “Histology”, “”Lymph node dissection”, “Complications”, “Blood transfusion”, “Size of uterus”, “Adjuvant therapy”, “Chemotherapy”, “Grade” and “Histopathological risk group” all seem to significantly influence the overall survival. All factors except “Lymph node dissection” are considered risk factors, out of which HR has highest rates at “Histopathological risk group” (Metastatic/ Low, Advanced /Low) and FIGO stage (IVA+IVB/ Carcinoma in situ+IA+IB). No impact was observed regarding the indicators “Radiotherapy” and “Concomitant malignant tumor”.

After placing the significant risk factors in the Cox regression analysis and using the Forward conditional procedure, the following indicators remained: “Age”, “Complications”, “Chemotherapy” and “Histopathological risk group”.

4.5.2. ANALYSIS OF THE THREE TYPES OF SURGERIES REGARDING THE OVERALL SURVIVAL FOR PATIENTS IN EARLY STAGE OF ENDOMETRIAL CANCER.

4.5.2.1. OWN RESULTS

The postsurgical follow-up was carried out through regular check-ups on the first month after the manipulation, then every three months for two years, every six months until the fifth year and annually thereafter. Patients with FIGO I and II stages are grouped together, so as to represent the early-staged EC evidence regarding oncological outcomes. Vital status, resp. OS, were ascertained from the National Oncological Registry database and were updated on 9 July, 2019.

Table 13. Mean follow-up time for the three types of hysterectomy.

	RH (n=364)	LH (n=58)	AH (n=362)	p-value		
	1	2	3	1-2	1-3	2-3
Follow-up (days) $\overline{X}$ (SD)	1386,71 (849,00)	11190,86 (770,15)	1945,59 (1055,68)	0,106	<0,001	<0,001
Follow-up (years) $\overline{X}$ (SD)	3,80(2,11)	3,26 (2,11)	5,33 (2,89)			

Table 13. shows that the mean follow-up time is significantly longer within the patients with AH compared to that of those in the other two groups, which does not differ statistically regarding this indicator.

Table 14. Mortality and death causes for the three types of hysterectomy.

	RH (n=364)	LH (n=58)	AH (n=362)	p-value		
	1	2	3			
Mortality n (%)	59 (15,8)	9 (15,5)	76 (20,7)	0,197		
Cause of death n (%)				1-2	1-3	2-3
EC-specific death	52 (13,9)	9 (15,5)	68 (18,5)	0,700	0,631	0,813
Other cause of death	7 (1,9)	0 (0)	8 (2,2)	0,323	0,626	0,412
Alive	315 (84,2)	49 (84,5)	292 (79,3)	0,197		

Table 14. shows no significant difference between the three groups of patients regarding overall Mortality, EC-specific death, Other cause of death and Alive.

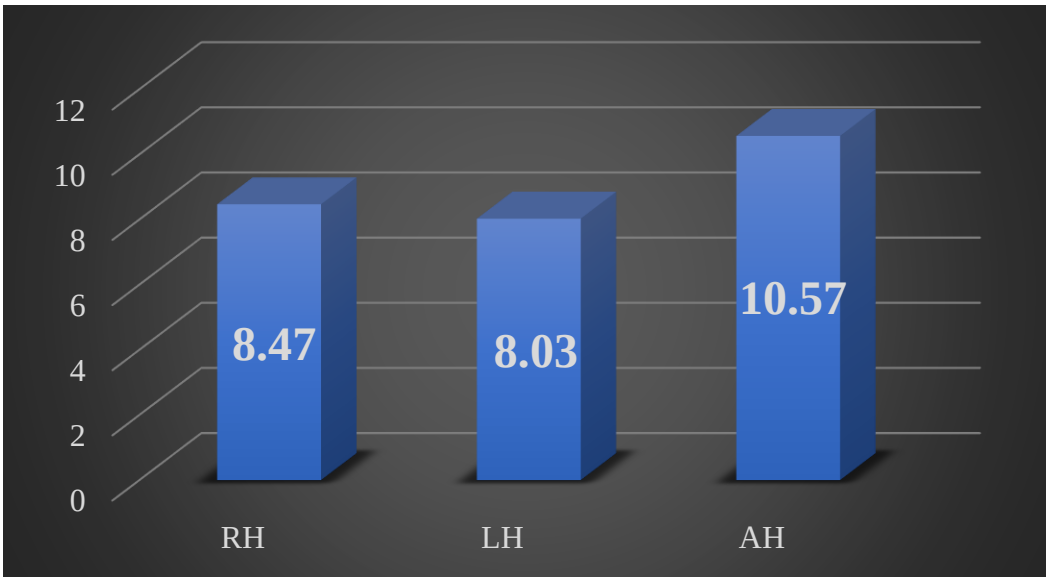

Figure 15. Overall survival for patients with early stage EC after RH, LH and AH (in years).

Table 15. Mean OS of women with early stage EC after RH, LH and AH.

	RH (n=364)	**LH (n=58)**	**AH (n=360)**	**p-value**		
	1	2	3	1-2	1-3	2-3
Mean OS in days (Std. Error)	3092,65 (74,05)	2934,69 (234,90)	3859,80 (95,61)		0,754	
Mean OS in months (Std. Error)	101,73 (2,44)	96,54 (7,73)	126,97 (3,15)			

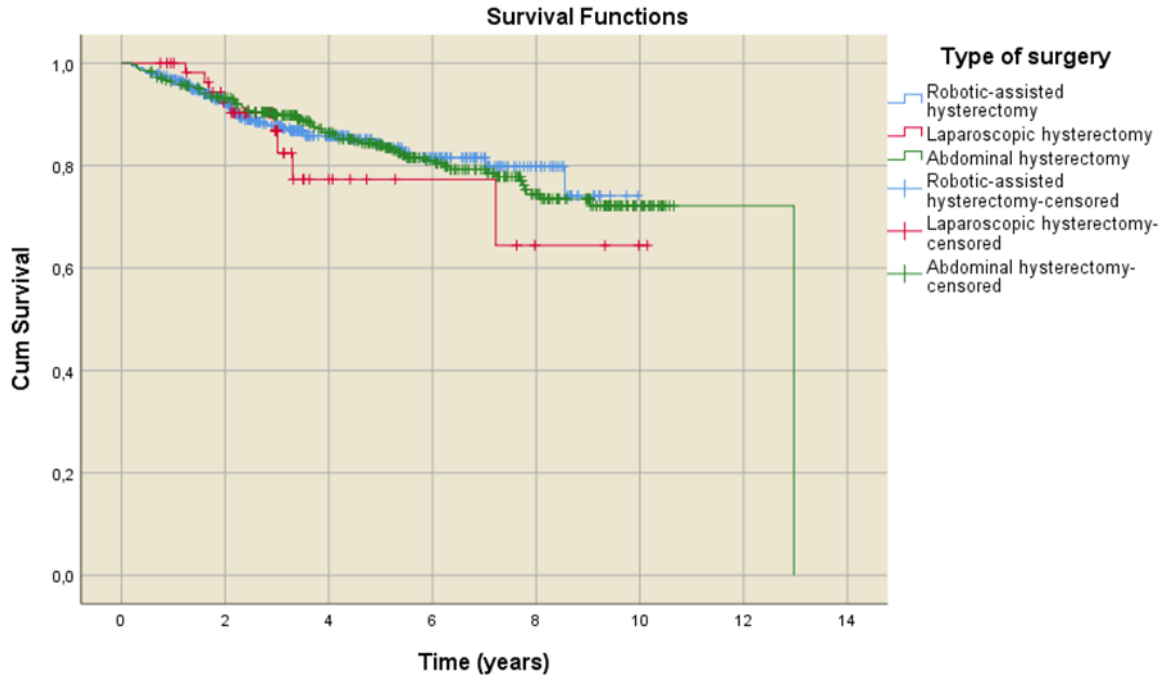

Figure 16. OS for early stage EC for the three types of hysterectomy, presented with the Kaplan-Meier curve.

The outcomes in figure 15. and 16. and table 15. show no significant difference between the mean overall survival of the patients, operated with the three approaches.

Table 16. HR and 95% CI of the analyzed factors for OS for patients with early stage EC (Cox univariate and multivariate regression analysis for the three types of hysterectomy).

Factors	Comparison	Crude				Multivariate			
		HR	95% CI		p	HR	95% CI		p
			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 / Tis+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				
Lymph node dissection	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	m. l. I / Normal	1,247	0,684	2,274	0,471				
	m. l. II/ Normal	1,132	0,694	1,848	0,619				
	m. l. III/ Normal	1,825	1,118	2,979	0,016				
	≥ m. l. IV / Normal	1,715	0,850	3,461	0,132				
Adjuvant therapy	Yes / No	1,926	0,941	3,943	0,073				
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				
Concomitant malignant tumor	Yes / No	1,451	0,461	4,565	0,524				
Histopathological 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

Table 16. illustrates the results of the conducted Cox regression analysis - univariate and multivariate.

In individual aspect, a significant impact on OS have the indicators “Age”, “pT stage”, “Histology”, “Lymph node dissection”, “Complications”, “Blood transfusion”, “Size of uterus”, “Chemotherapy”, “Grade of the tumor” and “Histopathological risk group”. Except for “Lymph node dissection”, all of the others are risk factors, with HR showing higher rates for “Grade” (G3 / G1) and “Histopathological risk group” (High / Low). No influence is registered regarding “Type of surgery”, “Radiotherapy” and “Concomitant malignant tumor”.

After placing the significant risk factors in the Cox regression analysis and using the Forward conditional procedure, the following indicators remained: “Age”, “Chemotherapy” and “Histopathological risk group”

4.5.3. ANALYSIS OF THE THREE TYPES OF SURGERY REGARDING THE DISEASE-FREE SURVIVAL FOR PATIENTS IN ALL STAGES OF ENDOMETRIAL CANCER.

4.5.3.1. OWN RESULTS

The postsurgical follow-up was carried out through regular check-ups on the first month after the manipulation, then every three months for two years, every six months until the fifth year and annually thereafter. Vital status, resp. DFS, were ascertained from the National Oncological Registry database and were updated on 9 July, 2019.

Table 17. Comparative analysis of the three types of surgery regarding the follow-up time.

	RH (n=388)	LH (n=60)	AH (n=465)	p-value		
	1	2	3	1-2	1-3	2-3
Follow-up (days) ***Median (Range)***	1196 (72-3638)	1053 (274-3704)	1596 (37-5682)	0,283	<0,001	0,001
Follow-up (years) ***Median (Range)***	3,27 (0,20-9,96)	2,88 (0,75-10,14)	4,37 (0,10-15,56)	0,283	<0,001	0,001

Table 17. shows that the mean follow-up time for the patients operated through open surgery is significantly longer than that for the women managed with one of the other two techniques, whose proportions regarding this indicator do not statistically differ.

Table 18. Comparative analysis of the three operations regarding type and number of recurrences, as well as the mean time to their occurrence.

	RH	LH	AH	p-value		
	1	2	3			
Recurrence n (%)	21 (5,4)	4 (6,7)	32 (6,9)	0,657		
Type of recurrence n (%)				1-2	1-3	2-3
Local	5 (23,8)	3 (75,0)	2 (6,3)	0,154	0,154	0,003
Regional	8 (38,1)	0 (0,0)	7 (21,9)	0,361	0,333	0,709
Distant	8 (38,1)	1 (25,0)	23 (71,9)	0,946	0,031	0,189
Recurrence mean time (days) (Std. error)	3389,07 (58,74)	3248,58 (209,91)	4775,63 (303,94)	0,667	0,981	0,539
Recurrence mean time (months) (Std. error)	111,35 (1,93)	106,73 (6,90)	156,90 (9,99)	0,667	0,981	0,539

Table 18. shows that:

- The three types of surgeries do not statistically differ in the relative proportion of recurrences, as well as the mean time to their occurrence.

- For local recurrences, the relative proportion of the patients who underwent laparoscopy is considerably larger than that of those operated through the robotic-assisted approach. The percentage of operated women in the group of RH is statistically equal to that of the other two groups.

- For regional recurrences, there is no statistically significant difference between the relative shares of the operated through the three methods patients.

- For distant recurrences, the relative proportion of the patients after AH is substantially larger than that of those with RH, but not than that of the women with LH. The percentage of the operated through laparoscopy is statistically equal to that of the operated through the other two techniques.

Table 19. Recurrence mean time (in years) for RH, LH and AH.

	RH	LH	AH	p-value
Recurrence mean time (Years) (Std. error)	1,56 (0,25)	1,26 (0,50)	2,24 (0,43)	0,472

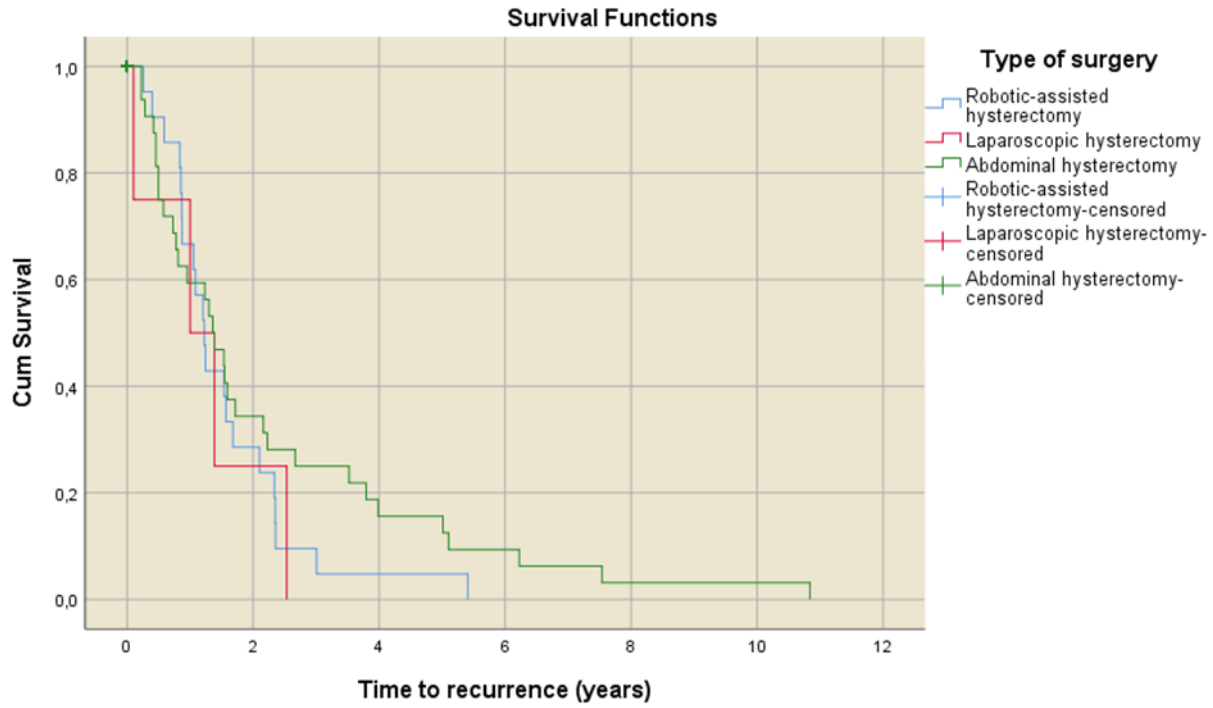

Figure 17. DFS for the three types of hysterectomy, presented with the Kaplan-Meier curve.

The outcomes of table 19. and figure 17. reveal no significant difference in the mean DFS of the patients operated through the three methods.

In order to determine the factors that influence a relapse incidence and to assess their quantitative impact, we conducted a Cox regression analysis. The following indicators were tested as potential factors: age, FIGO stage, pT stage, pN stage, histological stage, lymph node dissection, complications, blood transfusions, size of uterus, adjuvant therapy, radiotherapy, chemotherapy, grade, concomitant malignant tumor, and histopathological risk group. The outcomes are illustrated in table 20.

Table 20. HR and 95% CI of the analyzed factors for DFS (Cox univariate and multivariate regression analysis for the three types of hysterectomy).

Factors	Comparison	Crude				Multivariate			
		HR	95% CI		p	HR	95% CI		p
			Lower	Upper			Lower	Upper	
Type of surgery	LH / RH	1,179	0,403	3,449	0,764				
	AH / RH	0,737	0,415	1,309	0,298				
Age (years)	Increasing with one 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
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				
Lymph node dissection	Yes / No	1,453	0,842	2,506	0,179				
Complications	Yes / No	0,981	0,504	1,909	0,956				
Blood transfusions	Yes / No	0,740	0,289	1,891	0,529				

Size of uterus	m. l. I / Normal	0,851	0,346	2,092	0,726
	m. l. II / Normal	0,531	0,243	1,157	0,111
	m. l. III / Normal	0,968	0,473	1,981	0,930
	≥ m. l. IV / Normal	0,362	0,127	1,030	0,057
Adjuvant therapy	Yes / No	1,709	0,527	5,541	0,372
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
Histopathological 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

Table 20. shows, in individual aspect, that:

- Increase of age with one year also increases the risk of recurrence with approximately 44%.

- Compared to the lowest FIGO stages (Carcinoma in situ + IA + IB), the higher FIGO II and IVA+IVB stages have a protective character, whereas FIGO IIIA+IIIB+IIIC – risk, but HR have no statistical significance.

- The presence of concomitant malignant tumor is related to approximately 8 times higher risk of recurrence.

- Compared to the lowest pT stages (pTis+pT1a+pT1b), pT2 stage has a protective character (but HR has no statistical significance), pT3a+pT3b stages are related to approximately two times higher risk of relapse, and pT4a stage – with around 5 times higher risk.

- pN stage N1, compared to N0, is associated with around 3,7 times higher risk of recurrence.

- Regarding the histological variation of the tumor, non-endometrioid compared to endometrioid increases the relapse risk by around 85%.

- In terms of the presence of lymphadenectomy compared to its absence, the risk of recurrence is higher by around 45%.

- The occurrence of complications and the blood transfusion decreases the risk of recurrence within a few percentages but HR has no statistical significance.

- Compared to the normal, the other uterine sizes have a protective character but HR has no statistical significance.

- The presence of adjuvant therapy, as well as the subgroups of radiation and chemotherapy, increases by 70% the risk of relapse but HR has no statistical significance.

- Compared to G1, the higher tumor grades are related to approximately 2.4 higher risk of relapse.

- Compared to the histopathological risk group “Low”, the higher stages of “Intermediate”, “High intermediate”, “High” and “Metastatic” have a protective character, whereas the “Advanced” group – a risk character, but HR has no statistical significance.

In order to determine the combined effect of the found significant factors, we conducted a multivariate Cox regression analysis with the Forward: Conditional procedure. The received outcomes table 23.) show that:

- In the final model remain the factors “FIGO stage” and “Concomitant malignant tumor”.
- Compared to the lowest FIGO stages (Carcinoma in situ + IA + IB), FIGO stage II is associated with approximately 6 times higher risk of recurrence, FIGO stage IIIA+IIIB+IIIC – by around 44 times, and FIGO stage IVA+IVB – by 16 times.
- The presence of concomitant malignant tumor is related to approximately 32 times higher risk of relapse.

4.5.4. ANALYSIS OF THE THREE TYPES OF SURGERY REGARDING THE DISEASE-FREE SURVIVAL FOR PATIENTS IN EARLY STAGE OF ENDOMETRIAL CANCER.

4.5.4.1. OWN RESULTS

The postsurgical follow-up was carried out through regular check-ups on the first month after the manipulation, then every three months for two years, every six months until the fifth year and annually thereafter. Patients with FIGO I and II stages are grouped together, so as to represent the early-staged EC evidence regarding oncological outcomes. Vital status, resp. DFS, were ascertained from the National Oncological Registry database and were updated on 9 July, 2019.

Table 21. Comparative analysis of the three operations regarding follow-up time for patients with early stage of EC.

	RH (n=371)	LH (n=58)	AH (n=368)	p-value		
	1	2	3	1-2	1-3	2-3
Follow-up (years) ***Median (Range)***	3,39 (0,2,-9,96)	2,88 (0,75-10,14)	5,06 (0,21-12,97)	0,129	<0,001	<0,001
Follow-up (days) ***Median (Range)***	1237 (72-3638)	1053 (274-3704)	1848,5 (75-4737)	0,129	<0,001	<0,001

Table 21. reveals that the mean follow-up time is significantly longest for the patients with AH compared to that of those of the other two groups, which do not statistically differ in this indicator.

Table 22. Comparative analysis of the three operations regarding type and number of recurrences, as well as the mean time to their occurrence, for patients with early stage of EC.

	RH	LH	AH	p-value		
	1	2	3			
Recurrence n (%)	20 (5,3)	4 (6,9)	15 (4,1)	0,549		
Type of recurrence n (%)				1-2	1-3	2-3
Local	5 (25,0)	3 (75,0)	1 (6,7)	0,175	0,333	0,022
Regional	7 (35,0)	0 (0,0)	4 (26,7)	0,422	0,876	0,636
Distant	8 (40,0)	1 (25,0)	10 (66,7)	1,000	0,222	0,352
Recurrence mean time (days) (Std. error)	111.52 (1.93)	106.00 (7.20)	148.84 (1.86)	0,584	0,053	0,029
Recurrence mean time (months) (Std. error)	3394,49 (58,72)	3226,64 (219,22)	4530,42 (56,57)	0,584	0,053	0,029

Table 22. shows that:

- The three types of surgery have no statistical difference in the relative proportion of the occurred relapses.
- For the local recurrences, the relative share of the patients with LH is considerably larger than that of the women with AH, but not than that of those operated with robotic-assisted technique. The percentage of the patients after RH is statistically equal to those of the other two groups.
- For regional and distant recurrences, we found no statistically significant difference in the relative proportions of the occurred relapses within the three groups of patients.
- The mean recurrence time is significantly longer for the patients who underwent abdominal surgery than for those who were operated through laparoscopy, but not compared to the women from the robotics group, whose mean recurrence time is statistically equal to those managed by the other two techniques.

Table 23. Recurrence mean time (in years) for RH, LH and AH for patients with early stage EC.

	RH	LH	AH	p-value
Recurrence mean time (Years) (Std. error)	1,60 (0,26)	1,26 (0,50)	3,09 (0,73)	0,094

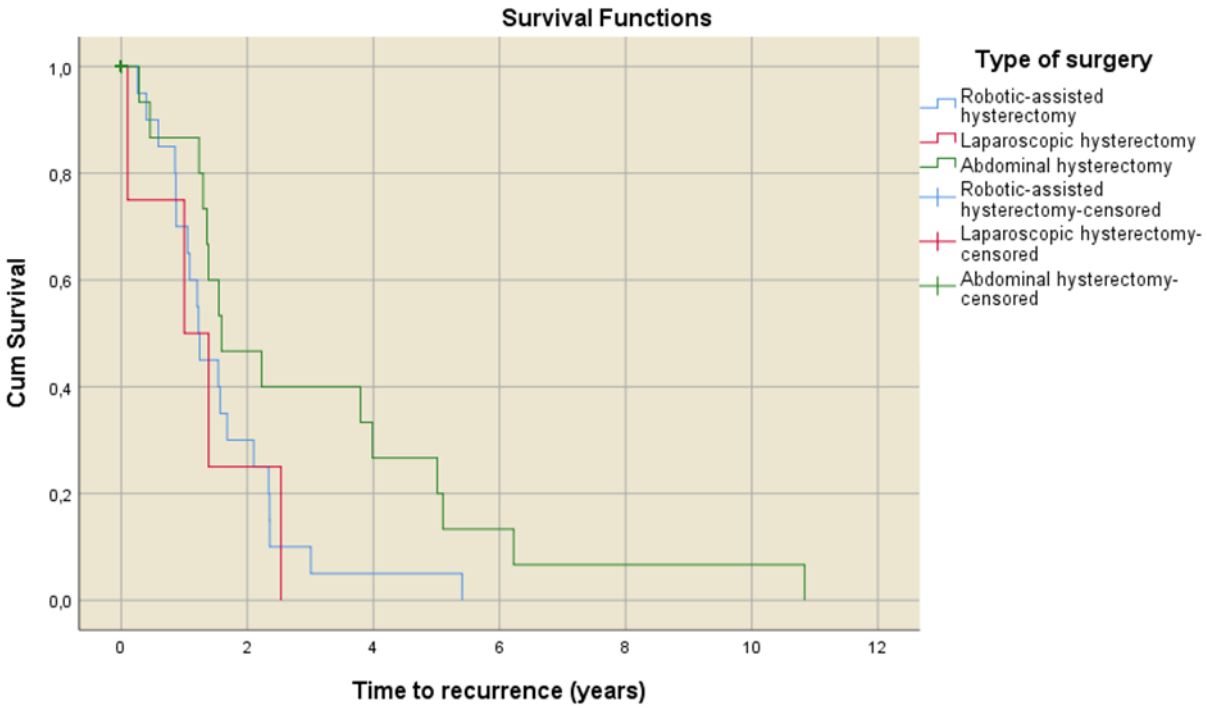

Figure 18. DFS for patients with an early stage of EC after RH, LH and AH, presented with the Kaplan-Meier curve.

The outcomes of table 23. and figure 18. show no significant difference in the mean DFS for patients with early stage of EC operated with one of the three approaches.

Table 24. HR and 95% CI of the analyzed factors for DFS for patients with early stage EC (Cox univariate and multivariate regression analysis for the three types of hysterectomy).

Factors	Comparison	Еднофакторен анализ				Многофакторен анализ			
		HR	95% CI		p	HR	95% CI		p
			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 (years)	Increasing with 1 year	1,035	0,993	1,078	0,103				
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				
Lymph node dissection	Yes / No	1,955	0,960	3,981	0,065	2,225	0,889	5,572	0,088
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	m. l. I / Normal	0,680	0,228	2,031	0,489	0,657	0,170	2,543	0,543
	m. l. II / Normal	0,495	0,187	1,312	0,157	0,266	0,087	0,816	0,021
	m. l. III / Normal	1,024	0,441	2,374	0,957	0,698	0,253	1,930	0,488
	≥ m. l. IV / 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				
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				

Histopathological 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

A Cox Proportional Hazards Regression Analysis was performed to identify the factors influencing the relapse incidence and to evaluate their quantitative impact. The outcomes are shown in Table 24. The following indicators were tested as potential factors: patient age, FIGO-, pT- and pN-stages, tumor histology, , histopathological risk group, lymph node dissection, presence of complications, blood transfusions, uterine size, adjuvant therapy, post-operative radiation or chemotherapy, grade, presence of other concomitant malignant tumor and histopathological risk group.

In individual aspect, type of surgery, presence or absence of concomitant malignant tumor, lymph node dissection and uterine size seem to have a significant effect on DFS of the patients.

When placing the significant risk factors in the Cox regression analysis and using the Backward conditional procedure, the same indicators remained.

4.5.5. DISCUSSION

The oncological outcomes of a certain surgical approach are determined with regards to the OS and DFS of the patients. By observing the above-mentioned indicators and with the aim of conducting a deeper topic analysis, we divided our results into two research groups – one that combines the patients' data for all stages of endometrial cancer, and another one, that focuses on the outcomes for women with early stage of EC.

OS is one indicator with a direct connection to the long term success of the operative techniques. By analyzing the results for all EC stages regarding mortality, we discover more desirable results after performed MIS compared to AH, with no significant difference in the cause of death. Our data reveals a substantially higher rate of mortality after AH compared to MIS, with this tendency remaining unchanged for RH, as well as LH. Despite the overall survival after AH being credibly higher when compared to the MIS group ($p=0.001$), observations show a more dynamic movement of the curve for open surgery, which indicates a larger number of deceased patients within the first follow-up years. In individual aspect, as well as after a conducted multivariate analysis, our results show that the choice of operative approach does not stand as a risk factor for the overall survival for the patients with EC, resp. the type of hysterectomy is not defining for OS. In terms of the early stage endometrial carcinoma, we establish no differences in mortality or cause of death for the researched

contingent, with substantially longer follow-up time for the women after undergoing open surgery. The applicability of MIS, as well as that of RH in particular, is also confirmed by the OS data, where we found no significant difference between the three surgical techniques (p=0.754). The outcomes of the Cox regression analysis (crude and multivariate) suggested no influence of the choice of hysterectomy type on the overall survival for the "early-stage" EC patients, which could determine the robotic-assisted approach as appropriate and safe for those patients.

DFS is a long term essential indicator for the effectiveness of a certain operative method, as well as for the patients' quality of life. By analyzing and collating the data after RH, LH and AH for women in all stages of EC, we observe no difference in the overall incidence of recurrence between the three groups (p=0.657), where the considerably larger rate of the repulses after undergoing LH compared to AH (resp. 75.0% after LH vs. 6.3% after AH, p=0.003) is noteworthy, as well as the credibly more distant recurrences after AH compared to RH (resp. 71.9% after AH vs. 38.1% after RH). Our data showing no statistically credible difference in DFS between the three researched methods of hysterectomy (p=0.472) are to support the statement that robotic-assisted technique is a safe and appropriate approach for treating histologically proven EC. The conducted univariate and multivariate Cox regression analysis aim to eliminate the blurring factors and to determine the effect of the remaining ones. With no influence on the type of surgery within both analyses registered, we consider RH for an appropriate approach of hysterectomy for patients with endometrial carcinoma. Similar results showed our analysis of the women with early stage of EC, with no significant difference in the incidence of recurrences between the three groups of operative techniques (p=0.549) but, once again, with significantly greater share of local repulses after LH compared to AH, resp. 75.0% after LH vs. 6.7% after AH, p=0.022. The safety of MIS, particularly of RH, for women with early EC, can be also noted in accordance with the outcomes for DFS, where no significant difference between the robotic-assisted approach, the laparoscopies and the open surgery (p=0.094) was found. Although the data analysis for early stage EC confirms the applicability and safety of RH, we should not omit the fact that the conducted Cox analysis – uni- and multivariate, reveals certain advantages of AH over RH, in spite of the values in individual aspect being limit (p=0.049).

Despite the large number of patients involved and the wide time 10-year period of time covered, the current research inevitably reached certain limitations that may influence the statistical significance of the comparative analyses. Our work is, in its nature, a

nonrandomized retrospective study, which could alone stand as a potential reason for certain statistical deviations with regards to the selection. When observing and analyzing OS for all stages of EC, we find a substantially longer mean follow-up time, by approximately a year, in the group of AH compared to RH and LH. Regarding DFS for women with early stage of EC, our results reveal a more then two-year difference between AH and LH, as well as a little over a year-and-a-half-difference between AH and RH. This seems to be a plausible explanation of the significant differences in OS and DFS for women after open surgery compared to those after one of the two minimally invasive techniques.

A considerable part of the accessible related literature presents summarized data for OS and DFS for patients with EC, with no separate analysis of the early endometrial carcinoma conducted. With the oncological outcomes of our 10-year experience taken into account, it can be concluded that MIS does not stand behind open surgery, neither for the OS indicator, nor for DFS. In 2006 Walker et al. published GOG LAP-2 – a major randomized study comparing the laparoscopic with the open approach for patients with EC (165). In it, no significant difference is registered between the two researched groups regarding oncological outcomes, with approximately 89.8% OS. Our findings are similar to theirs, with the exception of the indicator OS that within our research reaches a higher rate in the group of AH compared to RH, whereas LH does not significantly differ from the other two groups. In 2012 Coronado et al. published their retrospective work that covers 347 EC patients, with no contrasts in the rates of OS or DFS between the three surgical groups (30). There are earlier reports, issued prior to the abovementioned study, which also discovered no difference in the oncological results, however their scope is limited to comparing the laparoscopic and abdominal treatment for EC (22, 104, 105).

In 2012, Lau et al. published their oncological results for women with EC treated with robotic-assisted system, where they compare the received data with operated earlier patients with the same diagnosis but through laparoscopy or abdominal surgery. The authors find statistically credibly higher DFS in the group of RH (91). A retrospective study of Park et al. involving 936 women with EC that underwent one of both types of hysterectomy – RH or AH, compares survival function and recurrence incidence and determines RH as associated with decreased incidence of complications and repulses (129). The authors report 90.87% of 3-year DFS for RH and 78.30% for AH, as well as 89.14% 5-year OS for RH and 79.47% for AH. Correspondingly to our own results, the outcomes of their multivariate Cox regression analysis reveal that the choice of surgical method does not influence OS or DFS. Analogous

are the data for the group of RH by Brudie et al. (21), Kilgore et al. (82), as well as the outcomes of Magrina et al. (106), Cardenas-Goicoechea et al. (23) and Fader et al. (46). Similar data is likewise revealed by other authors (28, 32, 108), who also find no significant difference in OS and DFS between RH, LH and AH. The conclusions of the data obtained within their research are comparable to our study.

By contrast, in 2019 Song et al. published a single-center retrospective research involving 179 women with histologically verified EC who underwent RH or AH. Their results outline that robotics is connected to a higher percentage of repulses compared to open surgery, while no difference is found in the 5-year OS between the groups (155). Another report – a prospective cohort study from 2019, after analyzing the oncologic outcomes, noted that AH is associated with a higher mortality rate than LH and RH groups, without any significant survival difference between the two MIS approaches (77) – results confirmed by other works (139). Accordingly, we consider the MIS approach is oncologically safe, and with better perioperative outcomes. Our oncologic data are also supported by Nayyar et al., who also noted earlier no significant difference in the OS and DFS between the robotics and open surgery groups.

When collating the oncological outcomes after RH and after LH, only one comparative analysis notes the laparoscopic approach as advantageous over the robotic-assisted one regarding the 10-year OS and DFS (9). The majority of authors, similarly to our data, report the overall and the disease-free survival after RH and LH as comparable (44, 51, 60, 93, 173).

Unlike us, Fu et al. demonstrate in their meta-analysis a more favorable oncological outcomes after RH than after AH, and in the group of early stage EC, RH is with OS rates comparable to those within the laparoscopic approach data, but with lower DFS (51). The RECOURSE study from 2023 reported comparable OS and DFS after both MIS approaches but introduced longer OS after RH than after AH, with no significant difference regarding DFS (93). More favorable OS and DFS in the RH group, compared to LH and AH, are found by Eoh et al., with their data being statistically significant, $p<0.001$. Analogous to us, the authors recognize the essential advantages of robotics over the other two surgical methods and support their thesis with outcomes of a Cox regression analysis of the low risk, as well as the high risk groups of patients with EC (45).

The fact that the choice of operative approach of hysterectomy has no influence on OS and DFS, was not confirmed by Ishikawa et al., or from the results of the retrospective analysis of

Ikebuchi et al. from 2024. Similarly to our opinion, the authors determine the robot-assisted technique of hysterectomy as appropriate and applicable for women with EC, with comparable to LH and AH oncological outcomes (71, 73).

The evidence of the RH safety, not only in terms of perioperative outcomes but also with regards to mortality, suggest the practicality of this technique and encourages its application for treatment of women with histologically proven EC. Compared to laparoscopic and open surgery, robotics stands as a more appropriate approach 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 similar oncologic outcomes. The fact that neither OS nor DFS seem to be influenced by the type of surgical technique used places MIS on the anterior front in the present as well as in the future.

5. CONCLUSIONS

1. Compared to laparoscopic and open surgery, robotics serves as a more expedient approach for treating patients with endometrial cancer due to overcoming the barriers of the other two types of hysterectomy procedures.

2. Robotized hysterectomy is preferable for patients with significantly lower mean age, higher entry hemoglobin and hematocrit, normal uterine size, stages FIGO IA and pT1a, G1 and for the groups with low histopathological risk.

3. Open surgery is a method of choice for women of over 60-year age, with larger uterine size of m.l. II and ≥ m.l. IV, FIGO stage III and IV, resp. pT3 и pT4 stage, carcinosarcoma, G3, as well as for the histopathological groups of higher risk, advanced and metastatic EC.

4. Compared to MIS, open surgery is characterized with considerably longer operative time and hospital length-of-stay.

5. Minimally invasive techniques are with significantly better results in terms of estimated blood loss and incidence of blood transfusions.

6. Intra- and postoperative complications for the three types of hysterectomy are rare, and there is no evident relation between the registered complications and the type of surgery.

7. Open surgery, compared to robotic-assisted, is characterized with significantly larger incidence of adjuvant therapy.

8. Robotic-assisted hysterectomy for women with EC is a safe alternative of LH and AH that offers increased perioperative results.

9. The type of surgery has no statistically significant relation to the overall survival of the patients with EC.

10. The disease-free survival is not influenced by the hysterectomy approach for women with EC.

11. Minimally invasive hysterectomy, RH in particular, for patients with EC has high efficiency and is characterized with better perioperative and similar oncological outcomes.

6. CONTRIBUTIONS

6.1. SCIENTIFICALLY-THEORETICAL

1. For the first time in Bulgaria was conducted a multiaspect comparative analysis of the perioperative and oncological outcomes for patients with endometrial cancer operated through one of the three surgical approaches – robotic-assisted, laparoscopic and open hysterectomy.

6.2. SCIENTIFICALLY-PRACTICAL

1. A clinical-epidemiological research was conducted, involving 917 patients with endometrial cancer, operated in University Hospital "Saint Marina" - Pleven, and University Hospital "Dr. Georgi Stranski" - Pleven, within the period of time from 2008 to April 2019.
2. The patients' characteristics for the three surgical approaches were analyzed.
3. The correlations between tumor characteristics and hysterectomy approach for patients with endometrial cancer were introduced.
4. A comparative analysis of the perioperative indicators was conducted and the advantages of the minimally-invasive surgery for the treatment of women with histologically proven endometrial cancer were established.
5. The factors that influence the overall and disease-free survival for the three groups of patients were researched and analyzed.
6. On the basis of the clinical experience and the outcomes of the study, an optimized medical algorithm is possible for patients with histologically proven endometrial cancer.
7. Based on the outcomes of the clinical-epidemiological research, the place of the minimally invasive approaches, of the robotic-assisted hysterectomy in particular, in modern gynecological surgery for patients with endometrial cancer is defined.

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PARTICIPATION IN SCIENTIFIC RESEARCH PROJECTS:

1. Research Project: BG05M2OP001-1.002-0010 “Център за компетентност по персонализирана медицина, ЗД и телемедицина, роботизирана и минимално инвазивна хирургия“.