MEDICAL UNIVERSITY – PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY

Dr. Dimitar Georgiev Dimitrov

The Role of Indocyanine Green in the Assessment of the Regional Lymph Basin in Patients With Endometrial Carcinoma

ABSTRACT

Of a dissertation

To acquire a Doctor educational and scientific degree

Scientific supervisor: Prof. Dr. Nadezhda Hristova Hinkova, MD

Pleven 2026

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Research supervisor - Prof. Dr. Nadezhda Hristova Hinkova, MD

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The dissertation is written on 199 standard printed pages. The material is illustrated with 12 figures and 45 tables.

The literary sources used include 350 titles: 4 in Cyrillic and 346 in Latin.

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

Note: the numbering of the figures and tables does not correspond to that in the dissertation.

The dissertation was discussed and scheduled for public defense by an extended Departmental Council of the Department of Obstetrics and Gynecology, Faculty of Medicine, Medical University – Pleven, held on 24.06.2026.

The public defense of the dissertation will take place on September 9, 2026 at 3:00 p.m. in the Ambroise Pare Hall of MU - Pleven

Scientific Jury composed of:

Chairman:

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The materials for the defense have been published on the website of MU-Pleven (www.mu-pleven.bg) and are available to those interested in the Scientific Department of the Faculty of Medicine, MU-Pleven.

Contents

Abbreviations used:

EC –endometrial carcinoma

LN – lymph nodes

LD – lymph dissection

SLN – sentinel lymph nodes

SLND –sentinel lymph node biopsy

PLN –pelvic lymph nodes

PLD –pelvic lymph dissection

PALN –paraaortic lymph nodes

PALD –paraaortic lymph dissection

ICG – Indocyanine green

LVSI – lymphovascular invasion

I. Introduction

EC is the sixth most common cancer in women and the fifteenth most common cancer [105]. Approximately 420,000 cases of EC are diagnosed each year, accounting for 2.1% of all newly diagnosed cancers, and over 97,000 patients die from EC, accounting for approximately 1% of all cancer deaths [336]. Endometrial carcinoma is the second most common gynecologic malignancy after cervical carcinoma [336].

The incidence of EC has been increasing by approximately 1% per year in recent decades [16]. This is due to the lack of an accurate screening method and also to the increasing prevalence of risk factors such as obesity, diabetes mellitus, and hypertension in the population.

EC most commonly affects patients between the ages of 65 and 75 years. There is a trend toward a decrease in the mean age of those with histologically proven endometrial carcinoma [189]. Premenopausal patients account for between 14% and 20% of all patients with proven EC, and the percentage of patients under 40 years of age is relatively low – about 5% [6]. Young patients in most cases have a more favorable histological variant of the tumor, myometrial invasion is to a lesser extent, lymphovascular invasion is more often absent and, accordingly, they have a better prognosis [201].

In about 70% of patients, EC is diagnosed at an early stage [201]. The prognosis in these patients is good and the five-year survival rate is between 74% – 91%, but its rate drops significantly between 47% and 58% in patients in stage III of the disease and is extremely low (15%–17%) in those in stage IV [49, 186].

The assessment of regional LNs is of utmost importance for both staging and prognosis of EC. It is well known that EC metastasizes predominantly lymphogenously. Although the overall risk of pelvic and para-aortic lymph node metastases is low (9% and 6%, respectively), and in early, highly differentiated carcinomas it is reduced to 3% and 2%, respectively, this remains the most important prognostic factor due to the significantly reduced five-year survival rate [241]. The greater the number of metastatic LNs, the lower the five-year survival rate [60].

Currently, the therapeutic effect of lymp dissection and its volume are the subject of many discussions. It is also important to note that the more extensive it is, the greater the risk of intraoperative and postoperative complications. At the same time, magnetic resonance imaging has a sensitivity of about 25-29% and a success rate of about 83-90%, and positron emission tomography shows a sensitivity of about 53.3-60% and a success rate of about 97.8-98.7%, respectively, which makes them insufficiently accurate methods in terms of detecting metastatic LNs [279].

Evaluation of the regional lymph node basin in patients with endometrial carcinoma by performing a targeted biopsy of the lymph nodes could have more advantages than systemic LD [170]. It is the concept of SLN that allows, through special marking, to detect those LNs that first take up the drainage of the lymph from the primary tumor and subsequently be examined. If the histological status of the SLN reflects the general condition of the entire regional basin, then patients without metastases in them can be treated only with a sentinel biopsy instead of systemic PLD. This would lead to more precise diagnosis and staging, but also to a significant reduction in intraoperative and postoperative complications. Marking of the lymphatic pathways and the SLN also contributes to a more precise definition of the boundaries of the regional lymphatic basin in each patient.

The number of publications on this topic is constantly increasing and it remains to be seen whether SLN will become a standard approach in the treatment of EC.

II. Goal and objectives

1. Goal:

To investigate the feasibility and effectiveness of sentinel lymph node detection using the fluorescent method with Indocyanine green in patients with histologically verified endometrial carcinoma.

2. Objectives:

1. To determine the frequency and distribution of the risk factors associated with the development of endometrial carcinoma.
2. To identify prognostic factors associated with the presence of lymphatic metastases detected by sentinel lymph node biopsy after ICG administration.
3. To perform a comparative analysis of the diagnostic methods used in endometrial carcinoma in order to determine their effectiveness, informativeness, safety and practical applicability.
4. To analyze the perioperative and oncological outcomes in patients with endometrial carcinoma operated on using robotic surgery.
5. 5. To study and define the anatomical-topographic distribution of sentinel lymph nodes, as well as the frequency of their metastatic involvement after application of the fluorescent dye Indocyanine green.
6. To assess the validity of the fluorescence method in a quantitative aspect through the following criteria: sensitivity, specificity, negative and positive predictive value.

III. Material and methods

1. Studyied patients with EC included in the study

The study included 80 patients with EC treated at the Clinic of Obstetrics and Gynecology of the University Hospital “St. Marina: , Pleven, in the period from June 2020 to September 2023.

All patients had histologically proven EC after trial abrasion, separated trial abrasion or hysteroscopy.

The mean age of the patients was 58.04±10.46 years in the range between 28 and 78. All patients were studied prospectively.

Preoperative staging was performed after examination with a speculum, bimanual palpation and ultrasound examination by a gynecologist working in the clinic, as well as after conducting a preoperative imaging study (computed tomography or magnetic resonance imaging).

In preparing the patients for surgical treatment, the following routine consultations and examinations were performed: consultation with an internist, blood tests, chest X-ray and consultation with an anesthesiologist.

In all patients, the identification of the SLN was performed by intracervical injection of the fluorescent dye ICG and surgical intervention was performed on the uterus and LN in various volumes using the da Vinci X robotic system. All patients included in the study preoperatively signed informed consent for the dye used.

No patient was treated preoperatively for the underlying disease.

2. Methods used

2.1 Surgical method

2.1.1 Uterine surgery

The patients included in the study underwent robot-assisted total hysterectomy with adnexae and robot-assisted radical hysterectomy with adnexae.

Preparing the patient for robot-assisted surgery:

Prophylactic anticoagulant treatment was performed 12 hours preoperatively. The patient was placed in a lithotomy gynecological position. During induction of anesthesia, antibiotic prophylaxis was performed. After thorough disinfection of the anterior abdominal wall, internal genitalia, and vagina, an indwelling urethral catheter was placed. The abdominal cavity was insufflated with CO_2 to an intra-abdominal pressure of 14 mm Hg. To perform a surgical procedure using the da Vinci robotic system (Intuitive Surgical Inc., Sunnyvale, CA, USA), three working ports (8 mm) for the robotic system and two assistant ports (12 mm and 5 mm) were placed. The first of them (for the da Vinci Endoscope, 0 - Degree) was inserted along the midline approximately 20 cm above the symphysis (supraumbilically). The remaining trocars were placed under visual control. The trocars for the instruments of the robotic system were inserted in line with the first port, 6-10 cm to the left and to the right. A 12 mm assistant port is placed 7 cm lateral to the right port, and a second 5 mm assistant port is inserted 2 cm medial to the spina iliaca anterior superior after preliminary visualization of the a. epigastrica inferior dextra. The patient is then placed in the Trendelenburg position. In addition to the endoscope, which is installed on the second arm of the robotic system, Meryland Bipolar Forceps are placed in the first arm, and Monopolar Curved Scissors in the third arm. For suturing the vaginal chunk, the monopolar scissors are replaced with a Large Needle Driver.

Main stages in performing a robot-assisted total hysterectomy with adnexae:

1. Exploration of the abdomen and pelvis for the presence of metastases.
2. Coagulation and cutting of the round ligaments, lig. infundibulopelvicum bilateralis and of plica lata.
3. Opening the plica vesicouterina and dissection of the bladder to the level of the anterior vaginal fornix.

4. Coagulation and cutting of the uterine vascular bundle.
5. Coagulation and cutting of the parametria and sacrouterine ligaments.
6. Opening the anterior and posterior vaginal fornix.
7. Extirpation of the uterus and adnexa through the vagina.
8. Vaginal chunk restoration.

Main stages in performing robot-assisted radical hysterectomy with adnexae:

1. Exploration of the abdomen and pelvis for the presence of metastases.
2. Coagulation and transection of the lig. rotundum dextra and lig. infundibulopelvicum dextra.
3. Identification and dissection of the right ureter.
4. Development of the paravesical and pararectal fossae.
5. Dissection of the a. iliaca interna dextra and identification of the a. uterina dextra.
6. Division and clipping of a.uterina dextra and v. uterina superficialis dextra.
7. Mobilization of the bladder.
8. Tunneling of the right ureter and clipping of the v. uterina profunda dextra.
9. Parametriectomy on the right.
10. Identical steps on the left side of the uterus.
11. Development of the rectovaginal space.
12. Transection of the sacrouterine ligaments.
13. Colpotomy and extirpation of the uterus with the cervix and vaginal cuff, adnexa and lymph nodes.
14. Closure of the vaginal chunk with a continuous suture or Z-shaped sutures.

2.1.1 Lymph nodes surgery

The patients included in the study underwent LD in various volumes: SLNB, selective PLD or total PLD.

In all patients, after the injection of ICG into the cervix, the following stages were observed:

1. Identification of the lymphatic channels, SLN and the regional lymph basin.
2. Removal of SLN and sending for urgent histological examination.
3. In cases where metastases were demonstrated, the lymp dissection was extended.

In cases where SLN were not visualized, selective PLD was performed.

2.1.3 ICG injection technique

All 80 patients with EC were intraoperatively injected with ICG solution into the cervix. One vial from the manufacturer Verdye is 25 mg. It is pre-divided into five sterile smaller vials of 5 mg each. Immediately before each surgical intervention, one of these vials is diluted with 5 ml of sterile injection solution to achieve a concentration of 1 mg/ml. From the resulting ICG solution, we prepare 4 injections of 1 ml each (Fig. 1 and 2).

Figure 1. Fluorescent dye Indocyanine green

Figure 2. Injection solution of Indocyanine green

Stages of ICG injection:

1. After being brought into the operating room, the patient is placed in the gynecological position.
2. The patient is put under anesthesia and the anterior abdominal wall, external genitalia and vagina are disinfected.
3. The abdominal cavity is insufflated with carbon dioxide and after achieving the required pneumoperitoneum, the trocars are placed. (Figure 3).

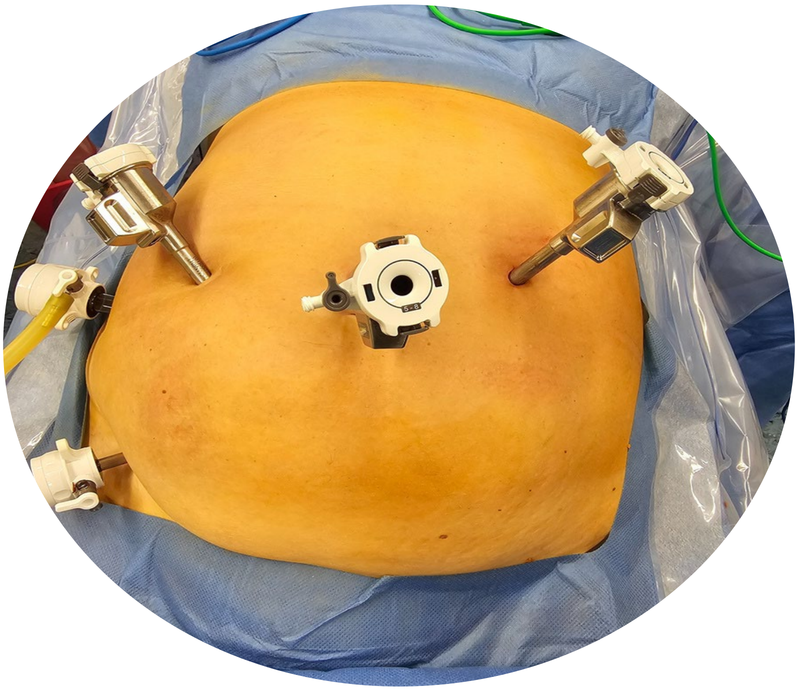

Figure 3. Positioning the trocars

4. The operating table is placed in Trendelenburg position.
5. The robotic system is docked (Figure 4).

Figure 4. da Vinci X robotic system

6. The fallopian tubes are coagulated.
7. Under visual control in PVCU at 3 and 9 o'clock, two of the prepared injections are injected. On each side, 1 ml is injected submucosally to a depth of 1-3 mm and another 1 ml is injected deep into the cervical stroma to a depth of 1-1.5 cm. (Fig. 5).

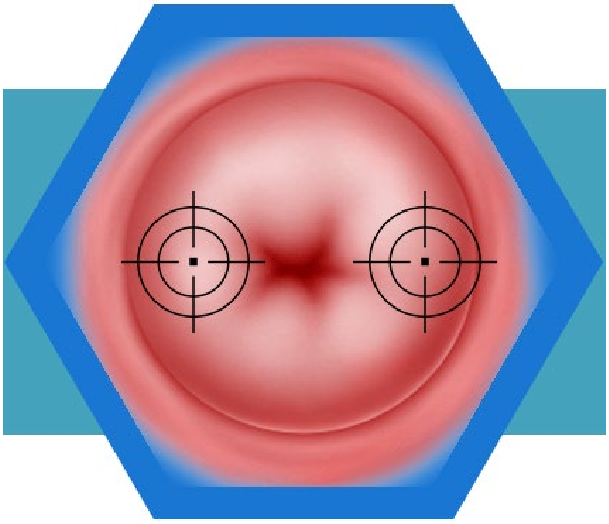

Figure 5. Indocyanine green injection site

8. After 10-15 minutes, the lymphatic channels are visualized and the sentinel lymph nodes are identified (Fig. 6).

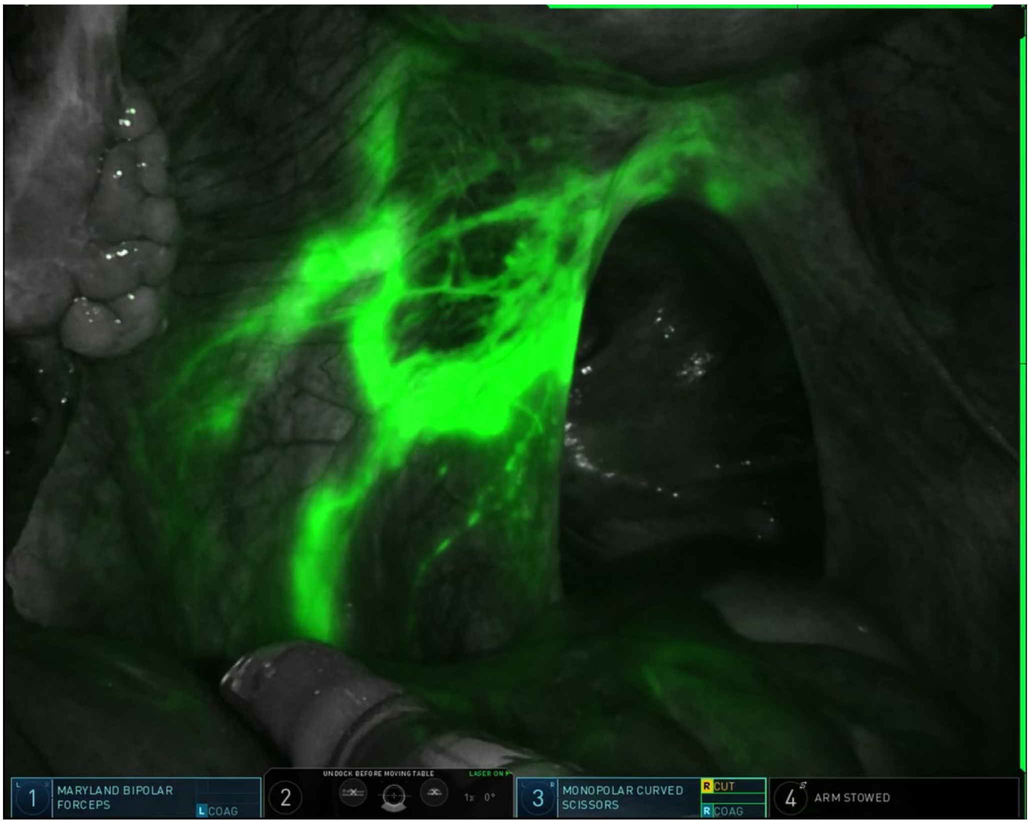

Figure 6. Upper and lower paracervical lymphatic channel (our material)

9. SLNs are dissected and sent for urgent histological examination (Fig. 7 & 8).

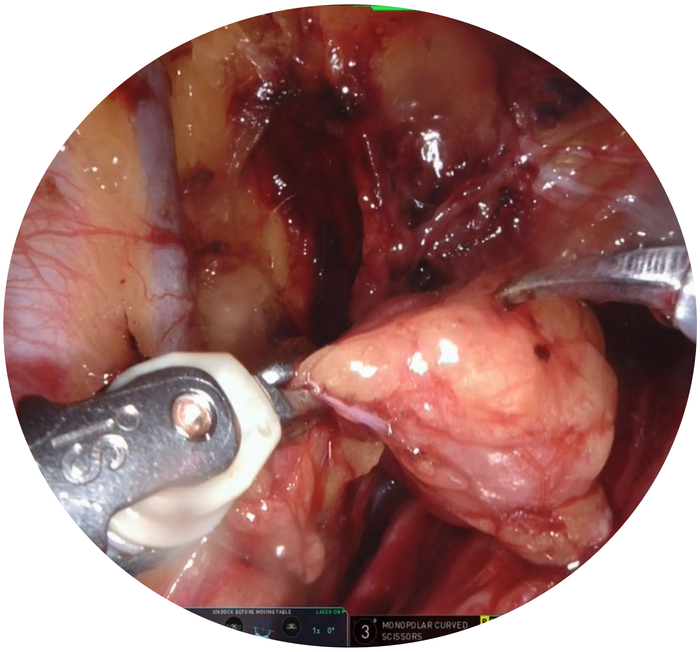

Figure 7. Sentinel lymph node (our material)

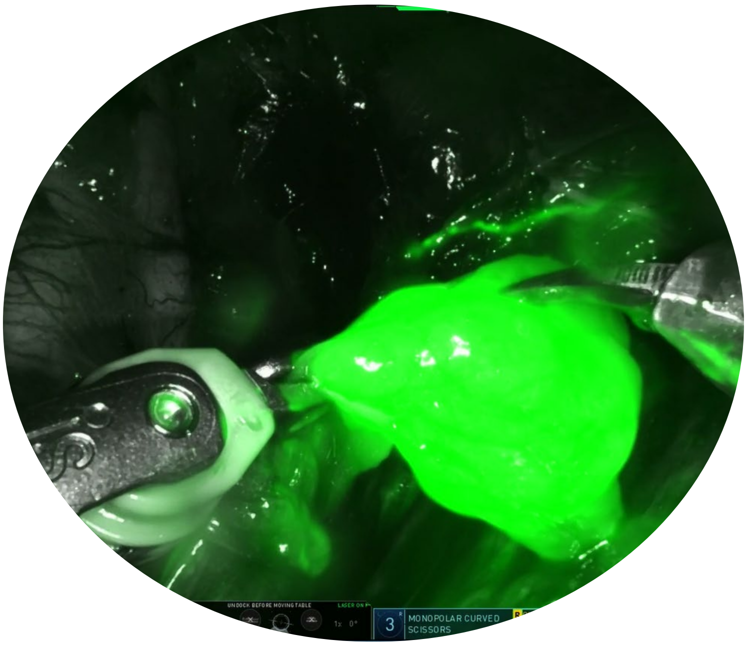

Figure 8. Sentinel lymph node after application of an infrared camera (our material)

10. In the time it takes to receive the result, the rest of the surgical intervention is performed.

11. When metastases are found in the lymphatic pathways, the lymph dissection is expanded.

2.2 Statistical methods

The data were entered and processed with the statistical packages IBM SPSS Statistics 25.0. and MedCalc Version 19.6.3. The significance level at which the null hypothesis is rejected was assumed to be $p<0.05$.

The following methods were applied:

1. ***Descriptive analysis*** – The frequency distribution of the considered features is presented in tabular form..

2. ***Variational analysis*** – to calculate estimates of central tendency and dispersion.

3. ***Graphic analysis*** – for visualization of the obtained results.

4. ***Fisher-Freeman-Halton exact test, Fisher's exact test и тест χ^2*** **—** for testing hypotheses about the existence of a relationship between categorical variables.

5. ***Comparing relative shares.***

6. ***Nonparametric Kolmogorov-Smirnov and Shapiro-Wilk tests*** – to check the distribution for normality.

7. ***Nonparametric Mann-Whitney test*** – to test hypotheses about the difference between two independent trials.

8. ***Nonparametric Wilcoxon test*** – to test hypotheses about the difference between two dependent trials.

9. ***Correlation analysis*** **–** for testing hypotheses about the existence of a relationship between two quantitative characteristics.

10. ***Kaplan-Meier method*** – to estimate the time until the occurrence of the studied event (Kaplan-Meier Product Limit Estimation of the Survival Function). The method is suitable for relatively small-scale studies. It follows a

group of **n** subjects with different times of inclusion in the study and fixes the time until the event occurs.

11. *Criteria for validation of screening tests*.

The following criteria are used to assess the ***validity*** of the screening (diagnostic) test [4]:

- Sensitivity;
- Specificity;
- Positive predictive value;
- Negative predictive value;
- Precision (% of correct answers).

IV. Results and discussion

1. Determining the frequency and distribution of risk factors associated with the development of endometrial carcinoma

1.1. Results

The study included 80 women treated at the Obstetrics and Gynecology Clinic of St. Marina University Hospital – Pleven. The average age of the patients was 58.04±10.46 years, ranging from 28 to 78. The largest number (37 or 46.3%) was in the age group 60+ years, followed by 50-59 years with 28 (35.0%), and the least (1 or 1.3%) – under 30 years (Fig. 9)

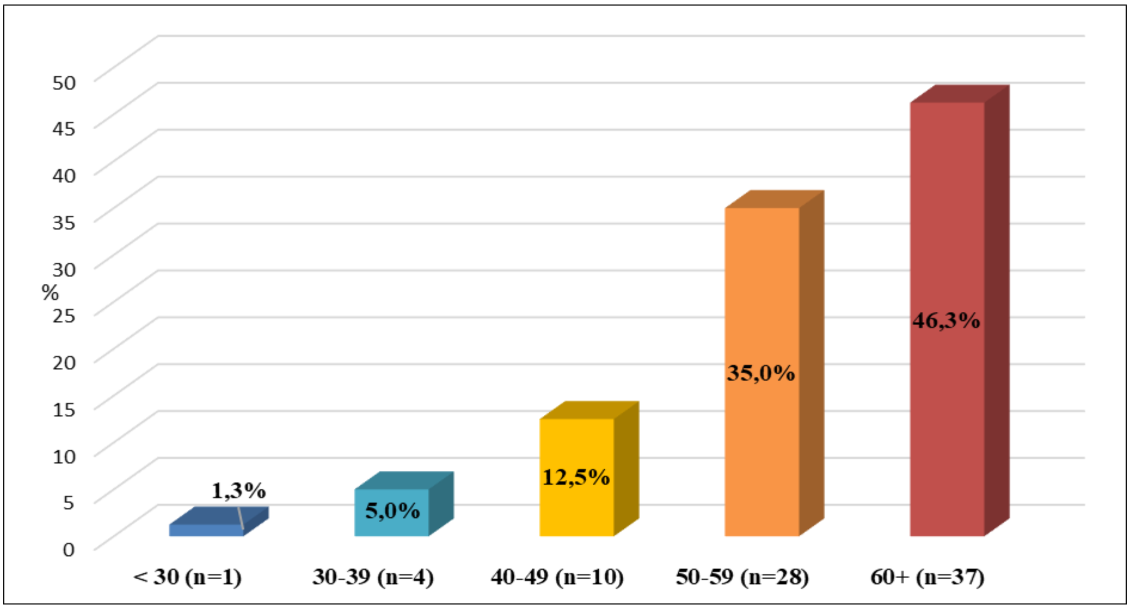

Figure 9. Distribution by age

Figure 10 shows that the frequency distribution of patients by BMI includes a small number of patients with subnormal values. Patients with normal and above-normal BMI values are approximately equal in number. The majority of patients are obese. The figure shows that the distribution of patients by BMI is significantly different from the normal.

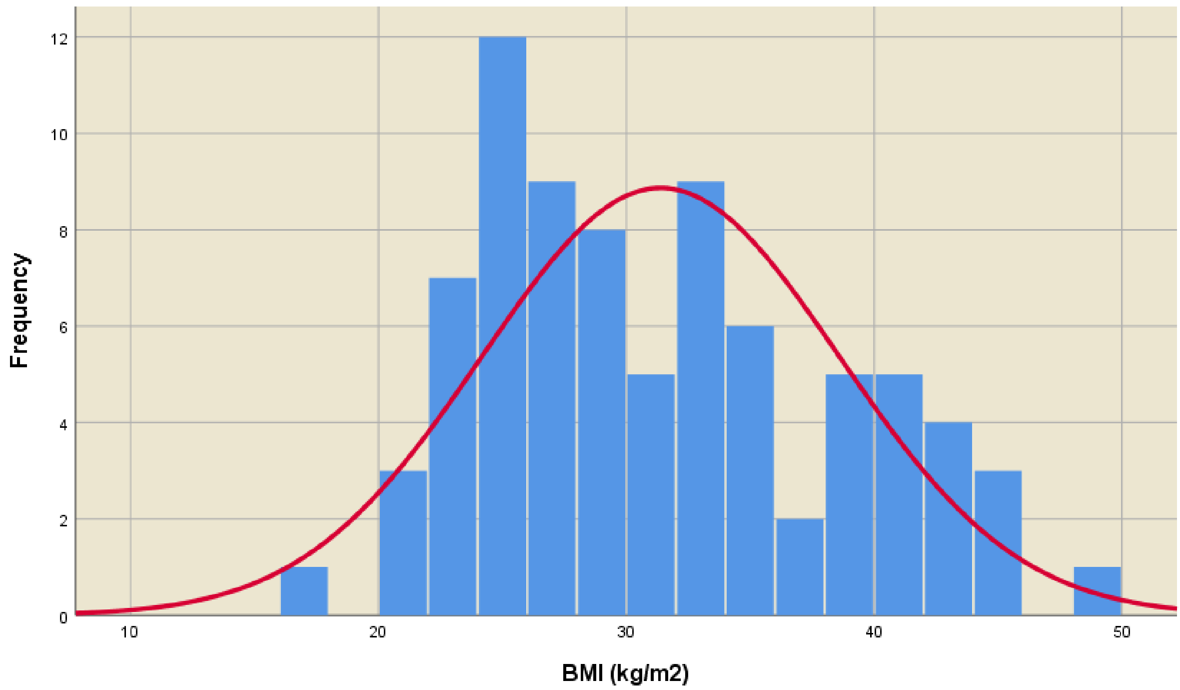

Figure 10. Frequency distribution of patients by BMI

(Kolmogorov-Smirnov p=0.030)

Regarding risk factors (Table 1), we can say that 29 (36.3%) of the patients had no such factors, while the remaining 51 had a total of 69 risk factors. The highest relative share (58.8%) was arterial hypertension, followed by diabetes with 15% and ovarian tumors (8.8%). The least (one patient or 1.3%) was the absence of pregnancy.

Table 1. Frequency distribution of risk factors

Risk Factors	**n**	**%**	**Sp**
Arterial hypertension	47	58.8	5.5
None	29	36.3	5.4
Diabetes	12	15.0	4.0
Ovarian tumors	7	8.8	3.2
Late menopause	2	2.5	1.7
Lack of pregnancy	1	1.3	1.2
Total	98	122.5*	

* The sum of the percentages exceeds 100 because some patients have more than one risk factor.

Table 2 shows that there is no significant correlation between the postoperative histological variant of the tumor and the risk factors indicator.

Table 2. Relation between postoperative histological variant of the tumor and risk factors (p=0.833)

Risk factors	Frequency	Postoperative histological variant of the tumor					
		Endometrioid adenocarcinoma	Mucinous adenocarcinoma	Clear cell carcinoma	Serous adenocarcinoma	Undifferentiated carcinoma	Mixed endometrioid and serous carcinoma
None	n	23	40	11	2	1	6
	%	79,3	85,1	91,7	100,0	100,0	85,7
Arterial hypertension	n	1	0	0	0	0	0
	%	3,4	0,0	0,0	0,0	0,0	0,0
Diabetes	n	1	1	0	0	0	0
	%	3,4	2,1	0,0	0,0	0,0	0,0
Ovarian tumors	n	2	3	0	0	0	1
	%	6,9	6,4	0,0	0,0	0,0	14,3

* Only those with up to one risk factor are included in the analysis.

Table 3 shows that the BMI of patients with visualized SLN is higher by about 3 units compared to that of patients without visualization. Unfortunately, the number of cases without visualization does not have the necessary statistical representativeness to conduct a statistically reliable comparative analysis.

Table 2. Relation between SLN visualization success rate and BMI

Visualization	Sentinel lymph nodes on the right			Sentinel lymph nodes on the left		
	n	$\overline{X}$	SD	n	$\overline{X}$	SD
No	6	28,44	7,79	7	28,96	6,65
Yes	74	31,62	7,15	73	31,61	7,25

* Category "No" does not have the necessary statistical representativeness to conduct a statistically reliable comparative analysis.

The results of Table 4 show that the age of patients with visualized SLN on the right is about a year and a half older than that of patients without visualization, while on the left it is about three and a half years younger. Unfortunately, the number of cases without visualization does not have the necessary statistical representativeness to conduct a statistically reliable comparative analysis.

Table 3. Relation between the success rate of sentinel lymph node visualization and patient age

Visualization	Sentinel lymph nodes on the right			Sentinel lymph nodes on the left		
	n	$\overline{X}$	SD	n	$\overline{X}$	SD
No	6	56,67	12,93	7	61,43	10,98
Yes	74	58,15	10,34	73	57,71	10,43

* Category "No" does not have the necessary statistical representativeness to conduct a statistically reliable comparative analysis.

The statistical analysis conducted (Table 5) did not establish a statistically significant correlation between the number of SLNs and BMI.

Table 5. Correlation analysis between sentinel lymph node count and BMI

Indicators	BMI
Number of sentinel lymph nodes on the right	-0,041
Number of sentinel lymph nodes on the left	0,049

* - p<0,05; ** - p<0,01; *** - p<0,001

1.2 Discussion

The genesis of EC is multifactorial and reflects the complex interaction between hormonal, metabolic, reproductive, genetic, and lifestyle determinants.

Age is one of the most important non-modifiable risk factors for the EC development. The study by Rodriguez et al. analyzed the trends in the incidence and age distribution of EC patients from 2000 to 2019 and demonstrated that in late-onset carcinomas, Caucasian women were most often represented in the age group 60–64 years, followed by the groups 55–59 and 65–69 years [263]. These data coincide with our results, which show that the largest number (37 or 46.3%) were from the age group 60+ years, followed by 50–59 years with 28 (35.0%).

Obesity is one of the most important modifiable risk factors for the development of EC and is mainly associated with estrogen-dependent endometrioid tumors. A prospective study by Reeves et al. showed that obese women have a 76% higher risk of EC compared to underweight or normal weight women, with waist-hip ratio being positively associated with the risk [260]. Our analysis also demonstrated the strong influence of obesity as a risk factor for the development of EC. We found that the majority of patients included in the study were obese.

Taylor et al. also reported that over half of the patients (53.0%) in their study were obese [307].
Another risk factor studied in our analysis is arterial hypertension. We showed that 58.8% of the patients included in the study had this diagnosis. Cooke et al. reported that postmenopausal women with EC had a higher prevalence of hypertension compared to women with benign uterine disease (54% vs. 25%) [68].
The relation between diabetes and EC has been confirmed by many studies. One of the most frequently cited is the meta-analysis by Friberg et al., which demonstrated that diabetes was statistically significantly associated with an increased risk of endometrial cancer (pooled RR 2.10; 95% CI 1.75–2.53) [101]. In our analysis, 15% of patients had diagnosed diabetes. Hooks et al. published similar data to ours, indicating that approximately 10–20% of women diagnosed with EC also have diabetes, although this proportion varied according to population characteristics [129].
Our analysis did not find a statistically significant relation between patients' BMI and SLN imaging due to the small number of cases without imaging. There was no association between body mass index and the number of visualized SLNs. Our results are consistent with those of Bedyńska et al., who reported an overall SLN detection rate of 84% and a bilateral detection rate - of 75%. The authors reported that there were no statistically significant differences in the overall or bilateral SLN detection rate according to BMI, surgical approach, or age [28]. Our results differ from those obtained by Andreika et al., who concluded that higher BMI showed a tendency towards unsuccessful mapping, but did not reach statistical significance (p = 0.06).

2. Identification of prognostic factors associated with the presence of lymphatic metastases detected by sentinel lymph node biopsy after ICG administration

2.1 Results

In our study, the endometrioid adenocarcinoma was with the highest relative proportion (82.5%), followed by serous adenocarcinoma with 7.5% and mixed endometrioid and serous carcinoma with 3.8%. The lowest percentage (1.3%) was mucinous adenocarcinoma. The total relative proportion of patients with non-endometrioid carcinoma was 17.5% (Table 6).

Table 6. Frequency distribution according to histological variant

Histologic result – postoperative	n	%	Sp
Endometrioid adenocarcinoma	66	82,5	4,2
Serous adenocarcinoma	6	7,5	2,9
Mixed endometrioid and serous carcinoma	3	3,8	2,1
Clear cell carcinoma	2	2,5	1,7
Undifferentiated carcinoma	2	2,5	1,7
Mucinous adenocarcinoma	1	1,3	1,2
Total	80	100,0	

In our study, we investigated the relation between postoperative histological variant of the tumor with myometrial invasion and lymphovascular invasion. The analysis did not reveal a statistically significant relationship between these indicators (Tables 7 and 8).

Table 7. Relationship between postoperative histological variant of the tumor and myometrial invasion (p=0.371)

Myometrial invasion	Frequency	Postoperative histological variant of the tumor					
		Endometrioid adenocarcinoma	Mucinous adenocarcinoma	Clear cell carcinoma	Serous adenocarcinoma	Undifferentiated carcinoma	Mixed endometrioid and serous carcinoma
Up to 50%	n	53	0	2	4	2	3
	%	80,3	0,0	100,0	66,7	100,0	100,0
Over 50%	n	13	1	0	2	0	0
	%	19,7	100,0	0,0	33,3	0,0	0,0

Table 8. Relationship between postoperative histological variant of the tumor and lymphovascular invasion (p=0.138)

Lymphovascular invasion	Frequency	Postoperative histological variant of the tumor					
		Endometrioid adenocarcinoma	Mucinous adenocarcinoma	Clear cell carcinoma	Serous adenocarcinoma	Undifferentiated carcinoma	Mixed endometrioid and serous carcinoma
No	n	53	1	2	4	0	3
	%	80,3	100,0	100,0	66,7	0,0	100,0
Yes	n	13	0	0	2	2	0
	%	19,7	0,0	0,0	33,3	100,0	0,0

In terms of tumor differentiation, both in the preoperative histological result and in the postoperative one, the highest percentage is well-differentiated carcinomas, followed by moderately differentiated ones, and lastly, poorly differentiated ones. Postoperatively, an increase in the relative proportion of G1 and a decrease in those of G2 and G3 are observed (Fig. 11).

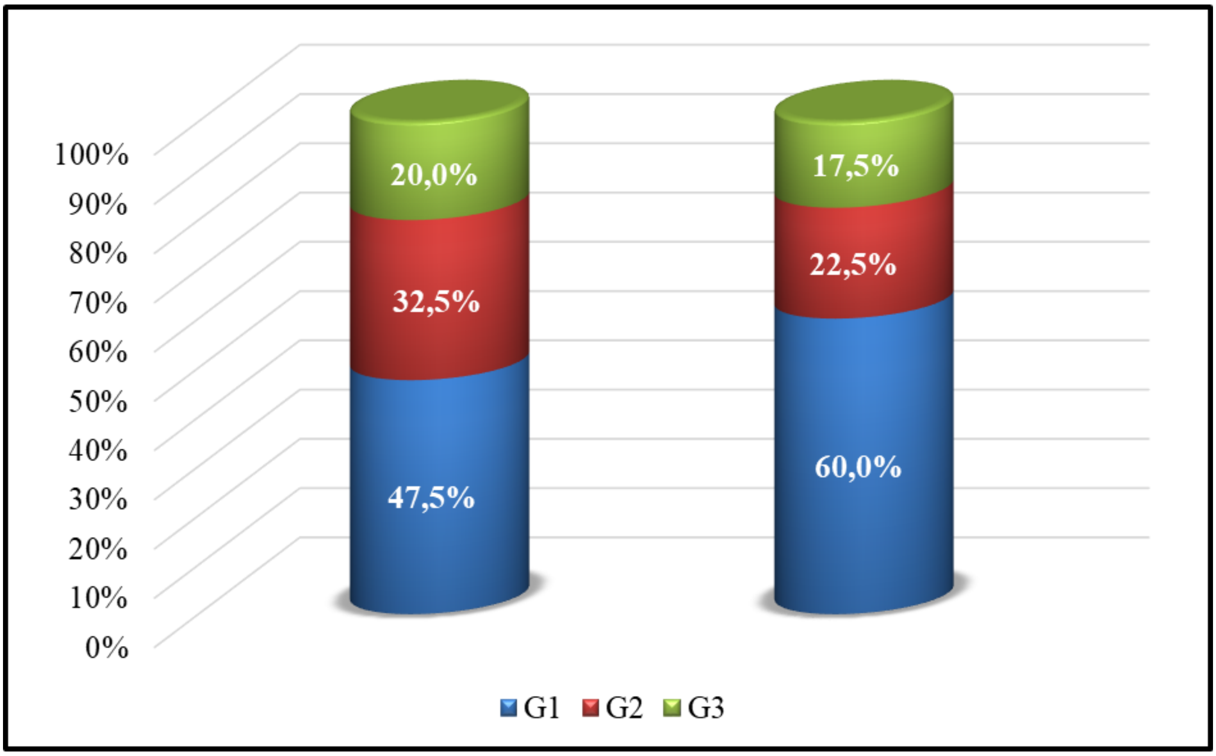

Figure 11. Frequency distribution of patients according to pre- and postoperative Grading

We also studied the relation between the degree of tumor differentiation and the indicators of myometrial invasion and LVSI. The analysis did not reveal a statistically significant relation between these criteria (Table 9).

Table 9. Relation between Grading and myometrial and lymphovascular invasion indicators

Indicator	Frequency	Grading		
		G1	G2	G3
Myometrial invasion (p=0.678)				
Up to 50%	n	39	13	12
	%	81,3	72,2	85,7
Over 50%	n	9	5	2
	%	18,8	27,8	14,3
Lymphovascular invasion (p=0.196)				
No	n	41	12	10
	%	85,4	66,7	71,4
Yes	n	7	6	4
	%	14,6	33,3	28,6

Table 10 shows the frequency distribution of patients according to the indicators of myometrial invasion, size, growth and localization of the tumor and LVSI. In most patients, myometrial invasion was up to 50%, and the tumor size was over 2 cm. Its growth was exophytic in 95% of cases and endophytic in only 5% of them. The carcinoma most often filled the entire uterine cavity (23.8%). Other frequent localizations were the posterior and anterior walls, as well as the left horn, respectively with 21.3%, 15% and 15%. The lesion was located least often along the left edge (2.5). The lymphovascular invasion was negative in 78.8% of cases.

Table 10. Frequency distribution of patients by the indicators: myometrial invasion, size, growth and localization of the tumor, lymphovascular invasion

Indicator	n	%	Sp
Myometrial invasion			
Up to 50%	64	80,0	4,5
Over 50%	16	20,0	4,5
Tumor size			
Up to 2 cm	29	36,3	5,4
Over 2 cm	51	63,8	5,4
Tumor growth			
Exophytic	76	95,0	2,4
Endophytic	4	5,0	2,4
Tumor localization			
The entire uterine cavity	19	23,8	4,8
Posterior wall	17	21,3	4,6
Anterior wall	12	15,0	4,0
Left horn	12	15,0	4,0
Right horn	9	11,3	3,5
Fundus uteri	5	6,3	2,7
Right edge	4	5,0	2,4
Left edge	2	2,5	1,7
Lymphovascular invasion			
No	63	78,8	4,6
Yes	17	21,3	4,6

No significant relation was found between myometrial invasion and lymphovascular space involvement (Table 11).

Table 11. Relationship between myometrial invasion and lymphovascular invasion

Indicators	Myometrial invasion			
	No		Yes	
	n	%	n	%
Lymphovascular invasion				
No	55	85,9	8	50,0
Yes	9	14,1	8	50,0

In our study, we also investigated the relation between tumor size and growth with lymphovascular invasion. It makes an impression that in all patients with lymphovascular space involvement, the lesion size was over 2 cm. The performed analysis did not reveal a statistically significant relation between tumor growth and LVSI (Table 12).

Table 12. Analysis of the relation between tumor size and growth, and lymphovascular invasion

Indicators	Lymphovascular invasion			
	No		Yes	
	n	%	n	%
Tumor size (p<0.001)				
Up to 2 cm	29	46,0	0	0,0
Over 2 cm	34	54,0	17	100,0
Tumor growth (p=0.573)				
Exophytic	59	93,7	17	100,0
Endophytic	4	6,3	0	0,0

Since our study covers the period from 06.2020 to 09.2023, all patients included in it were staged according to the FIGO staging system from 2009. The frequency distribution of patients shows that 63.7% of them were in stage IA, 15% were in stage IB, 12.5% - in stage II, 1.3% - in IIIA and 7.5% - in stage IIIC1 (Fig. 12).

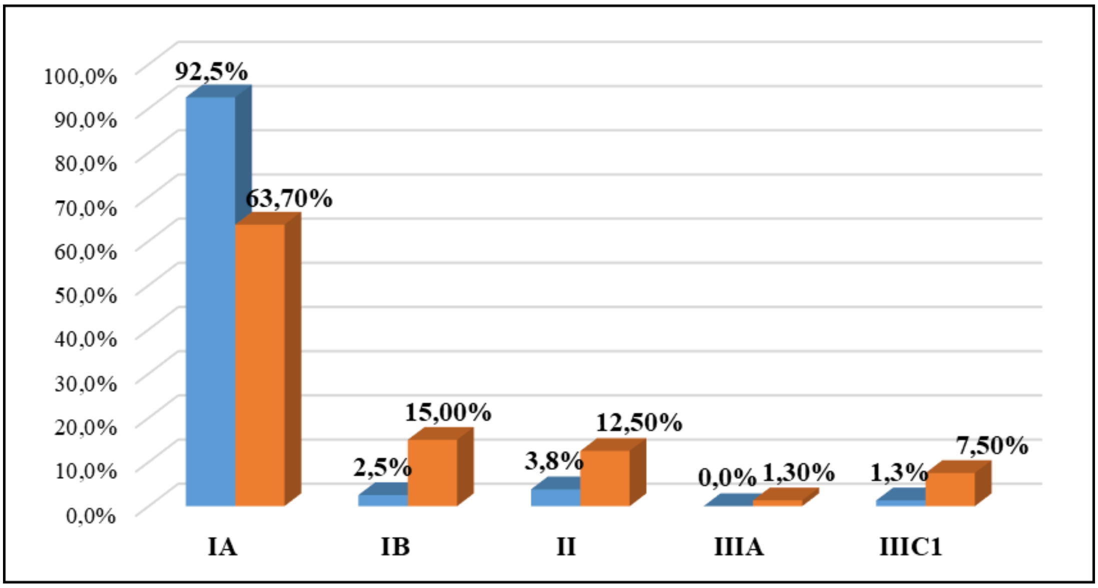

Figure 12. Frequency distribution of patients by preoperative and postoperative FIGO stage.

We conducted a statistical analysis to determine the relation between the histological variant of the tumor and lymph node metastases. The presence of the considered metastases is significantly higher in clear cell carcinoma, while in endometrioid adenocarcinoma the relative proportion of those without metastases is statistically significantly higher. In the remaining histological variants of the tumor, the difference between those with and without lymph node metastases is statistically insignificant (Table 13).

Table 13. Relation between the presence of metastases and the histological variant of the tumor

Histological variant of the tumor	**Lymph node metastases**				**P**
	No		Yes		
	n	%	n	%	
Endometrioid adenocarcinoma	63	85,1	3	50,0	**0,031**
Mucinous adenocarcinoma	1	1,4	0	0,0	0,772
Clear cell carcinoma	1	1,4	1	16,7	**0,023**
Serous adenocarcinoma	5	6,8	1	16,7	0,380
Undifferentiated carcinoma	2	2,7	0	0,0	0,685
Mixed endometrioid and serous carcinoma	2	2,7	1	16,7	0,084

The statistical analysis did not reveal a significant relation between tumor differentiation and the presence of LN metastases. (Table 14).

Table 14. Relation between presence of metastases and Grading

Postoperative Grading	Lymph node metastases				P
	No		Yes		
	n	%	n	%	
G1	45	60,8	3	50,0	0,512
G2	17	23,0	1	16,7	
G3	12	16,2	2	33,3	

The statistical analysis conducted did not establish a significant relation between the presence of metastases, myometrial and lymphovascular invasion (Table 15).

Table 15. Relation between the presence of metastases, myometrial and lymphovascular invasion

Indicator	Sentinel lymph node metastases				P
	No		Yes		
	n	%	n	%	
Myometrial invasion					
Up to 50%	57	80,3	5	83,3	1,000
Over 50%	14	19,7	1	16,7	
Lymphovascular invasion					
No	57	80,3	3	50,0	0,118
yes	14	19,7	3	50,0	

The relationship between tumor size and growth with LN metastases was also studied. In all patients with positive LN, the tumor size was over 2 cm, and its growth was exophytic. The analysis did not reveal a statistically significant relation between these indicators (Table 16).

Table 16. Analysis of the relation between tumor size and growth and lymph node metastases

Indicator	Lymph node metastases			
	No		Yes	
	n	%	n	%
Tumor size (p=0.082)				
Up to 2 cm	29	39,2	0	0,0
Over 2 cm	45	60,8	6	100,0
Tumor growth (p=1.000)				
Exophytic	70	94,6	6	100,0
Endophytic	4	5,4	0	0,0

2.2 Discussion

There is a wide variety of prognostic factors in EC. All of them may have different significance. EC in young patients has a significantly better outcome than in older patients. In patients over 63 years of age, the risk of recurrence is significantly higher, and survival is reduced. The poorer outcome in these patients is due to tumors with a more aggressive histological variant and poor differentiation [320]. Obesity significantly increases the risk of developing EC. In their study, Kamal et al. included 1,341 patients with EC and found that higher BMI caused the development of carcinoma in younger patients and led to the development of poorly differentiated tumors [148].

EC is divided into two subtypes. Type I is significantly more common (80%). It is characterized by well-differentiated tumors that mainly involve the uterine corpus. Type II is much less common, occurring in about 20% of cases, and is characterized by more aggressive, poorly differentiated tumors that involve the myometrium and lymphovascular space very early [320]. In our study, EC was type I in 66 (82.5%) of the patients and type II in 14 patients (17.5%). We investigated the relation between tumor histology and myometrial invasion and found no statistical significance. Not all histology variants show a linear relation between the depth of myometrial invasion and aggressiveness. Particular attention should be paid to poorly differentiated endometrioid carcinomas and non-endometrioid histologic variants. They may demonstrate extrauterine spread even with superficial myoinvasion, and the absence of deep invasion is not a guarantee of a favourable clinical outcome, especially in serous carcinoma. In endometrioid carcinomas, not only depth is decisive, but also the pattern of myometrial invasion plays an important role. The MELF pattern is characteristic of well-differentiated endometrioid carcinomas, but it often leads to LVSI and lymph node metastases [85, 95].

Although the highly differentiated and moderately differentiated carcinomas are defined as non-aggressive histologic variants, the presence of LVSI (mostly diffuse) significantly changes the probability of a favourable course. It increases the risk of LN metastases, local recurrence and reduces overall survival [137, 280]. Similar to myometrial invasion in poorly differentiated endometrioid carcinoma and non-endometrioid histological variants, the absence of LVSI does not rule out the possibility of an aggressive course of the disease.

Myometrial invasion is an independent prognostic factor. In our study, we did not find a significant relation between the degree of myometrial invasion and the involvement of the lymphovascular space. In a meta-analysis of 28,904 patients with EC, Wang et al. found that the risk of LVSI was higher with deeper myometrial invasion. They also reported that deep myometrial invasion was associated with lymphatic metastasis, disease recurrence, and reduced overall survival [332].

Our results show that there is a significant relation between tumor size and the presence of LVSI. This finding is supported by Oliver-Perez et al., who in their study of 327 patients found that the risk of lymphovascular involvement increased with tumor size >2 cm and tumor location in the lower uterine segment [228].

Lymph node status is extremely important for the correct staging of the disease and adequate subsequent treatment and is crucial for survival. Patients with stage I and II of the disease have a 5-year survival rate of between 80% and 91%. This rate drops dramatically when the tumor has spread to the lymph nodes and is between 44% and 52% [320]. Our study found that in 50% of patients with lymph node metastases, the lymphovascular space is involved, and in the remaining 50%, there is no LVSI. Dai et al. described that patients with metastatic LNs and positive LVSI were 3.8 times more likely to have LVSI than those with negative LVSI [74]. Jorge et al. reported that in stage I patients, a positive LVSI increased the risk of disease metastasis to regional LNs by 3 to 16 times [147]. In their study, Guntupalli et al. described that the risk of lymph node metastasis in a negative LVSI is 5% [115]. While Creasman et al. reported that involvement of the lymphovascular space increases the risk not only of PLN metastasis but also of PALN metastasis. PLN involvement was observed in 4.1% of patients and PALN involvement in a negative LVSI, but in a positive LVSI these rates were 37.5% and 23.8%, respectively [70]. Lucic et al. reported that the risk of lymph node metastasis in a positive LVSI increased with tumor differentiation. The lower the tumor differentiation, the higher the risk [187]. Zhang et al. described that the combination of deep myometrial invasion and lymphovascular space involvement significantly increases the risk of lymphogenous metastasis compared with positive LVSI alone [345].

3. Comparative analysis of diagnostic methods used in endometrial carcinoma in order to determine their effectiveness, informativeness, safety and practical applicability

3.1 Results

Three main methods were used for preoperative histological verification. These were trial abrasion , separated trial abrasion and hysteroscopy. Subsequently, 73 patients underwent robot-assisted total hysterectomy with adnexae and 7 patients underwent robot-assisted radical hysterectomy with adnexae and LND in different volumes. The most frequently used method for preoperative histological verification in the included subjects was trial abrasion (51.3%), followed by separated abrasion with 26.3%, and the least frequently used method was hysteroscopy (22.5%) (Table 17).

Table 17. Frequency distribution of histological verification methods

Histological verification method	**n**	**%**	**Sp**
Trial abrasion	41	51,3	5,6
Separated trial abrasion	21	26,3	4,9
Hysteroscopy	18	22,5	4,7
Total	80	100,0	

The conducted comparative analysis of the discrepancies of the methods for histological verification in the assessment of the preoperative and postoperative histological result showed that a statistically significantly higher percentage of discrepancies (19.5%) has the trial abrasion compared to the zero discrepancy of hysteroscopy (0.0%). The relative share of discrepancies of the separated trial abrasion is 14.3%. The study established a significant difference between the histological results obtained from trial abrasion and those obtained during the hysteroscopic examination **(p=0.046)** (Table 18).

Table 18. Comparative analysis of the discrepancies of the methods for histological verification in the assessment of the preoperative and postoperative histological result

Histological verification method	**Number tested**	**Number of discrepancies**	**% discrepancies**	**P**		
				1-2	1-3	2-3
1. Trial abrasion	41	8	19.5^{a}	0.615	**0.046**	0.099
2. Separated trial abrasion	21	3	14.3^{ac}			
3. Hysteroscopy	18	0	0.0^{bc}			

* The same letters on the vertical lines indicate the absence of a significant difference, and different letters indicate the presence of such one. (p<0.05).

A comparative analysis of the discrepancies of the methods for histological verification in the assessment of preoperative and postoperative Grading was performed. The results show that the highest percentage of discrepancies (43.9%) was found for trial abrasion , followed by separated trial abrasion with 28.6%, and the lowest (22.2%) – for hysteroscopy. The difference between the discrepancies of the three methods is not statistically significant (p>0.05) (Table 19).

Table 19. Comparative analysis of the discrepancies of the methods for histological verification in the assessment of preoperative and postoperative Grading

Histological verification method	Number tested	Number of discrepancies	% discrepancies	P		
				1-2	1-3	2-3
1. Trial abrasion	41	18	43,9[a]	0,246	0,116	0,652
2. Separated trial abrasion	21	6	28,6[a]			
3. Hysteroscopy	18	4	22,2[a]			

* - The same letters on the vertical lines indicate the absence of a significant difference, and different letters indicate the presence of such one (p<0,05).

In all patients, peritoneal lavage was aspirated for cytological examination. The cytological result was negative for tumor cells in 97.5% and positive in 2.5%. In all patients with a positive cytological result for tumor cells, the method for histological verification was a trial abrasion (Table 20).

Table 20. Distribution of patients by cytology

Cytology	n	%	Sp
Negative	**78**	**97,5**	**1,7**
Positive	**2**	**2,5**	**1,7**
Total	**80**	**100,0**	

3.2 Discussion

EC can be proved by a number of methods. Accurate and correct preoperative staging of EC is of key importance for subsequent management. The determination of the histological variant of the tumor, tumor differentiation, myometrial and cervical invasion are of utmost importance for its adequate treatment. One of the most commonly used methods is trial abrasion. It is a procedure that is performed blindly and in 60% of patients less than 50% of the area of the uterine cavity is cured, which makes targeted collection of material for histological examination difficult, and sometimes impossible [80]. Therefore, the risk of a false negative result after trial abrasion is significantly high, about 11% [92]. The hysteroscopy allows the examination of the cervical canal and the uterine cavity. It can also visualize small lesions and allow targeted biopsies.

Our study showed a 19.5% of discrepancy between the preoperative histological result after trial abrasion and the postoperative histological result, a 14.3% of discrepancy after separated trial abrasion, and zero discrepancy after hysteroscopy. Larson et al. described a discrepancy between the histological result after trial abrasion in 23% of 131 patients with EC [166]. Hsuan Su et al. reported that in 127 patients with EC who underwent trial abrasion , there was a discrepancy with the postoperative result in 12.6% (16 patients) [296]. Dokara-Friedrich et al. reported that of 139 patients with EC, 15.8% of Separated trial abrasion s showed a false-positive result for endocervical tumor invasion, and in another 11.5% the result was false-negative. Their results showed that the sensitivity of separated trial abrasion was 70.9% and its specificity was 73.8% [86]. Hsuan Su et al. reported that in 97.3% of patients with EC proven after hysteroscopy, there was a correspondence with the postoperative outcome, and the result did not coincide in only 2.6% of cases [296]. The results showed that the diagnosis of EC and histological evidence of its cervical invasion was much more accurate and reliable after hysteroscopy than after trial abrasion or separated trial abrasion.

The issue of dissemination of tumor cells through the fallopian tubes into the abdominal cavity after hysteroscopy in patients with EC is still debatable. Our study shows that in all patients who underwent hysteroscopy, peritoneal cytology was negative for tumor cells. It was positive in only 2.5% of patients, and the method of histological verification in them was trial abrasion. Zhu et al. reported that positive peritoneal cytology was observed in 5.6% of patients who underwent hysteroscopy and in 6.1% of patients who underwent trial abrasion [349]. In turn, Bradley et al. described that hysteroscopy increases the risk of dissemination of tumor cells into the abdominal cavity. A positive cytology result was found in 8.2% of patients who underwent hysteroscopy and 6.9% of patients after trial abrasion [46]. Egarter et al. demonstrated the conversion of negative cytology to positive after hysteroscopy during laparoscopy [91]. Dong et al. described in their meta-analysis of 3,364 patients that the hysteroscopy may increase the risk of tumor cells spreading through the fallopian tubes. The leading factor is not the stage of the disease, but the intrauterine pressure created during hysteroscopy. When it is above 80 mmHg, the risk is extremely high; it decreases at a pressure below 70 mmHg and is practically negligible at a pressure below 40 mmHg [87]. Zerbe et al. reported that prior tubal ligation does not prevent tumor cells from spreading into the abdominal cavity after hysteroscopy [344]. At the same time, dilation of the cervical canal and curettage of the uterine cavity in patients with abnormal genital bleeding may also increase the risk of tumor cells spreading into the abdominal cavity [277].

Sonoda et al. demonstrated that the use of a uterine manipulator during total laparoscopic hysterectomy significantly increased the risk of positive cytology in patients with EC compared with patients who underwent laparohysterectomy [289].

Performing diagnostic hysteroscopy, while adhering to safety principles such as low intrauterine pressure and short operative time, is a safe and reliable method for diagnosing EC. Thus, it allows both an accurate preoperative histological result and correct preoperative staging of the disease, with an extremely low risk of false-negative results and dissemination of tumor cells through the fallopian tubes into the abdominal cavity.

4. Analysis of perioperative and oncological outcomes in patients with endometrial carcinoma operated on using robotic surgery

4.1 Results

The average operative time in patients operated on using robotic surgery was 62.69±21.64 minutes in the interval between 35 and 120 minutes.

The performed statistical analysis (Table 21) did not find a significant correlation between operative time and BMI.

Проведеният статистически анализ (табл. 21) не установи наличие на сигнификантна корелация между оперативното време и BMI.

Table 21. Correlation analysis between operative time and BMI

Indicators	BMI
Operative time	0,059

* - $p<0,05$; ** - $p<0,01$; *** - $p<0,001$

The distribution of patients according to the indicator of previous operations showed that the largest relative share (66.3%) were patients with no previous operation, followed by those with one laparotomy (18.8%) and two laparotomies with 5.0%. With the smallest relative share (1.3%) is the trial abrasion (Table 22).

Table 22. Frequency distribution of previous operations

Previous operations	n	%	Sp
None	53	66,3	5,3
1 laparotomy	15	18,8	4,4
2 laparotomies	4	5,0	2,4
≥3 laparotomies	3	3,8	2,1
Laparoscopy	4	5,0	2,4
Trial abrasion	1	1,3	1,2
Total	80	100,0	

The analysis of the relation between operative time and previous operations shows that only two of the categories of the indicator of previous operations (“None” and “1 laparotomy”) have statistical representativeness. The difference between the operative time of these two categories is statistically insignificant (Table 23).

Table 23. Analysis of the relation between operative time and previous operations (p=0.824)

Previous operations	Operative time (minutes)		
	n	$\overline{X}$	SD
None	53	61,89	21,08
1 laparotomy	15	59,67	17,88
2 laparotomies	4*	63,75	39,02
≥3 laparotomies	3*	66,67	37,86
Laparoscopy	4*	73,75	13,15
Trial abrasion	1*	90,00	.

* The category is not included in the analysis due to lack of statistical representativeness.

In terms of uterine size, the patients with the largest relative share (66.3%) are those with normal size, followed by those with m. l. I and m. l. II (16.3% each), and the smallest percentage (1.3%) is m. l. III. (Table 24).

Table 24. Frequency distribution of uterine size

Uterine size	n	%	Sp
Normal	53	66,3	5,3
m. l. I	13	16,3	4,1
m. l. II	13	16,3	4,1
m. l. III	1	1,3	1,2
Total	80	100,0	

The average uterine weight was 93.20±19.92 grams in the range between 60 and 146, and the average blood loss was 38.88±22.99 ml in the range between 10 and 150. The correlation analysis (Table 25) did not establish a statistically significant relation between uterine weight and the amount of blood loss.

Table 25. Correlation analysis between uterine weight and blood loss

Indicators	Blood loss
Uterine weight	0.156

* - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$

The mean survival of patients, assuming that all deaths are counted, is 1,234.20 days with a 95% CI (1,185.73-1,282.67) or in years – 3.38 with a 95% CI (3.25-3.51) (Table 26). Assuming that only deaths from endometrial carcinoma are counted, the median survival is 1,258.14 days with a 95% CI (1,221.41-1,294.87) or in years – 3.44 with a 95% CI (3.34-3.55) (Table 27).

Table 26. Average patient survival, assuming all deaths are counted

Indicator	$\overline{X}$	Std. Err.	95% CI	
			Lower limit	Upper limit
Survival (days)	1,234.20	24.73	1,185.73	1,282.67
Survival (years)	3.38	0.07	3.25	3.51

Table 27. Average survival of patients, assuming only those who died from endometrial carcinoma are counted

Indicator	$\overline{X}$	Std. Err.	95% CI	
			Lower limit	Upper limit
Survival (days)	1,258.14	18.74	1,221.41	1,294.87
Survival (years)	3.44	0.05	3.34	3.55

The deceased patients accounted for 4 or 5% of the studied trial. The cause of death of two of them (2.5%) was related to the cancer in question, and of the other two – different from it (Tables 28 and 29).

Table 28. Distribution of living and deceased patients

Deceased patients	n	%	Sp
No	76	95,0	2,4
Yes	4	5,0	2,4
Total	80	100,0	

Table 29. Distribution of patients by cause of death

Deceased patients	n	%	Sp
Cancer specific dead	2	2,5	1,7
Other reason	2	2,5	1,7
The patient is alive	76	95,0	2,4
Total	80	100,0	

4.2 Discussion

Operative time is an important indicator in the evaluation of the different surgical interventions, as it reflects the technical complexity of the operation, as well as its applicability and effectiveness in real clinical practice. In our analysis, the mean operative time in patients operated on using robotic surgery was 62.69±21.64 minutes, ranging from 35 to 120 minutes. The data in the literature regarding operative time are very diverse, as the included studies differ in some indicators such as the type of LD (total PLD with or without PALD or SLNB), the inclusion of docking time, the type of hysterectomy (whether the study included radical hysterectomies) and the experience of the surgical teams in robotic surgery.

In our study, the mean operative time was shorter than that presented in the literature (62.69±21.64 minutes), which is why we decided to consider only the analyses using ICG. This is the study by Fierro et al., who described a mean operative time of 110 minutes in the range of 80–123.75 minutes [97], as well as the scientific work by Mereu et al., proving a mean operative time of 155 minutes (in the range of 112–175 minutes) [206]. Sinno et al. presented a total operative time of 88 minutes [285]. The values of operative time established in this study are comparable with those published in the literature, which supports the reproducibility and applicability of the method in the clinical practice.

In our study, the correlation analysis between operative time and BMI did not establish a significant relation. Fufuzono et al. did not find such a relation either ($p=0.31$), who described a mean operative time in patients with BMI <30 of 144 minutes, compared with 149 minutes in the group of patients with BMI ≥30 [102].

In our study, the average uterine weight was 93.20±19.92 grams, ranging from 60 to 146 grams. In the analysis of Abu-Rustum et al., it was 84 grams (range 54–220 grams) [8], and in that of Barlin et al., it was 155.8 grams (range 15–

1960 grams) [27]. Uterine size is an important indicator because it influences many factors, especially when it comes to minimally invasive surgery and oncological diseases. Such indicators include operative time, blood loss, hospital stay, and complications. In our analysis, the relation between uterine size and blood loss was studied. We found that the average blood loss was 38.88±22.99 ml, ranging from 10 to 150 ml. Similar results were shown by Casarin et al. – average blood loss 50 ml, and the authors compared it with the blood loss in a group of patients who underwent systemic PLD ($p < 0.001$) [56]. We performed a correlation analysis between uterine weight and blood loss, and the results rejected the presence of a statistically significant relation between the two indicators.

Analysis of overall survival is of utmost importance in the assessment of various oncological diseases, as it provides an objective assessment of the effectiveness of the treatment performed, while at the same time reflecting the combined effect of factors such as tumor biology, stage of the disease and specific characteristics of the patient. In patients with EC, surgical treatment is a very important factor that has an impact. In our analysis, the average survival of patients, provided that all deaths are taken into account, is 1,234.20 days with 95% CI (1,185.73-1,282.67) or in years – 3.38 with 95% CI (3.25-3.51). In the study by Kulhan et al., the reported mean overall survival was similar to that obtained in our study – 36.7 ± 13.4 months, which corresponds to approximately 3.1 ± 1.1 years [161]. Azam et al. described a longer mean overall survival – 65.6 months, due to the longer follow-up period of the patients [22]. Information on this indicator is limited in the literature, because in studies of robotic ICG-guided SLNB, survival is more often presented as 3-year or 5-year overall survival, rather than as mean overall survival. Togami et al. presented a 3-year overall survival of 98.9% [310], in the study by Zammarrelli et al. a lower 3-year overall survival – 72.1% [343] was described, and the data from the analysis by Nasioudis et al. presented intermediate results – 82.2% [222]. The majority of data in the literature present the 5-year overall survival, with the authors often comparing the group with SLNB and that with systemic LD. Such is the study by Ignatov et al., who presented a 5-year overall survival of 80.7% in the SLNB group and 77.0% in the systemic dissection group, without being able to prove statistical significance [133]. Garzon et al. also failed to prove such a result; in their analysis the 5-year overall survival in the first group was 90.9%, and in the second one – 81.9% [106]. From what has been said so far, it is clear that the assessment of overall survival remains essential in the evaluation of surgical treatment of EC, because it reflects the ultimate oncological safety of the chosen therapeutic approach. Although robotic surgery and SLNB offer clear perioperative advantages such as reduced surgical trauma, less blood loss, shorter hospital stay, and faster recovery, these advantages are only meaningful if they are achieved without compromising long-term survival. The literature data and our results are conclusive that this treatment approach is oncologically safe, while at the same time not compromising the quality of disease staging.

5. Study and definition of the anatomical-topographic distribution of sentinel lymph nodes and the frequency of their metastatic involvement after application of the fluorescent dye Indocyanine green

5.1 Results

Table 30 and 31 show the frequency distribution of patients according to the visualization of the SLN. It is noteworthy that the success rate of the methodology for identifying the SLN is high and is similar in both halves of the pelvis (right 92.5%, left – 91.3%). Bilateral visualization of the SLN also has a high relative share – 90%. In 6.3% of patients, the SLN was not identified bilaterally, and in 3.8% of them, it was detected only in one half of the pelvis.

Table 30. Frequency distribution of patients according to the visualization of the sentinel lymph nodes on the right and left

Visualization	Sentinel lymph nodes on the right			Sentinel lymph nodes on the left		
	n	%	Sp	n	%	Sp
No	6	7,5	2,9	7	8,8	3,2
Yes	74	92,5	2,9	73	91,3	3,2
Total	80	100,0		80	100,0	

Table 31. Frequency distribution of patients by sentinel lymph node visualization bilaterally

Visualization	Sentinel lymph nodes bilaterally		
	n	%	Sp
Without visualization bilaterally	5	6,3	2,7
Unilateral visualization	3	3,8	2,1
Bilateral visualization	72	90,0	3,4
Total	80	100,0	

We analyzed the localization of the detected SLNs for each of the two halves of the pelvis. **SLNs on the right** were identified most often between a. et v. iliaca externa (45.0%). In second place in frequency were the subvenous LNs (21.3%), followed by those along the course of *a. iliaca externa* (20.0%). The lowest percentage was reported in the group of presacral LNs – only 1.3%. In the case of **SLNs on the left**, the localization between a. et v. iliaca externa with the highest relative share (53.8%) was again between a. et v. iliaca externa, followed by subvenous LVs (20.0%) and LV along the course of a. iliaca externa with 15.0%. LNs were least frequently visualized in the group of common iliac LNs – 2.5% (Table 32).

Table 32. Frequency distribution of sentinel lymph nodes by level in the small pelvis

Sentinel lymph node localization	On the right			On the left		
	n	%	Sp	n	%	Sp
Lymph nodes along the course of a. iliaca externa	16	20,0	4,5	12	15,0	4,0
Lymph nodes between a. et v. iliaca externa	36	45,0	5,6	43	53,8	5,6
Subvenous lymph nodes	17	21,3	4,6	16	20,0	4,5
Lymph nodes along the course of a. iliaca interna and in fossa obturatoria	3	3,8	2,1	1	1,3	1,2
Common iliac	2	2,5	1,7	1	1,3	1,2
Presacral	1	1,3	1,2	0	0,0	

In **right-sided LNs identified between a. et v. iliaca externa**, mucinous adenocarcinoma and undifferentiated carcinoma have a statistically significantly higher relative share compared to mixed endometrioid and serous carcinoma, but not compared to the other variants, which do not differ statistically from each other.

In **right-sided LNs visualized in the group of common iliac LNs**, mucinous adenocarcinoma has a significantly higher relative share compared to endometrioid adenocarcinoma, serous adenocarcinoma and mixed endometrioid and serous carcinoma, but not compared to the other variants, which do not differ statistically from each other.

In the remaining right-sided LNs and all left-sided LNs, the difference between the relative shares of the postoperative histological variants of the tumor is statistically insignificant.

The conducted statistical analysis did not establish a significant relation between the histological variant of the tumor and the level of metastasis in the small pelvis.

No significant relation was found between tumor localization and SLN localization. The average number of LNs removed on the right was 0.49±1.76, on the left was 0.40±1.26, and bilaterally was 3.99±3.07 (Table 33).

Table 33. Average number of lymph nodes removed on the right, left and bilaterally

Localization	Number of lymph nodes		
	n	$\overline{X}$	SD
Right	80	0,49	1,76
Left	80	0,40	1,26
Bilaterally	80	3,99	3,07

The average number of removed SLNs on the right was 1.56±1.19, on the left was 1.54±0.98 and bilaterally was 3.10±1.77 (Table 34).

Table 34. Average number of sentinel lymph nodes on the right, left and bilaterally

Localization	Number of lymph nodes		
	n	$\overline{X}$	SD
Right	80	1,56	1,19
Left	80	1,54	0,98
Bilaterally	80	3,10	1,77

Table 35 shows the frequency distribution of patients with metastases in all removed LNs and in removed SLNs. It is noteworthy that in both groups positive LNs were detected in 6 (7.5%) patients.

Table 35. Distribution of patients according to the presence of lymph node metastases

Indicators	n	%	Sp
Lymph node metastases			
No	74	92,5	2,9
Yes	6	7,5	2,9
Sentinel lymph node metastases			
No	71	88,8	3,5
Yes	6	7,5	2,9
Unilaterally visualized sentinel lymph nodes	3	3,8	2,1

Table 36 presents the characteristics of the patients in whom positive SLNs were detected. In three of them, the histological variant of the tumor was highly differentiated endometrioid adenocarcinoma, and in the remaining three patients the carcinoma was serous – high grade, clear cell and mixed endometrioid and serous. In only one of the cases the myometrial invasion was over 50%, and involvement of the lymphovascular space was demonstrated in two of them. Metastatic LNs were detected in the left half of the pelvis in three patients, and in the right half – in two of them. False-negative LNs were detected in only one of the cases.

Table 36. Characteristics of patients with metastatic sentinel lymph nodes

Histological type of the tumour	Myometrial invasion	LVSI	Metastatic lymph nodes on the left side	Metastatic lymph nodes on the right side	False negative lymph nodes
1. Endometrioid adenocarcinoma G1	< 50 %	-	-	-	+
2. Endometrioid adenocarcinoma G1	< 50 %	+	+	-	-
3. Endometrioid adenocarcinoma G1	< 50 %	+	+	-	-
4. Serous carcinoma – high grade	> 50 %	-	+	-	-
5. Clear-cell carcinoma G3	< 50 %	-	-	+	-
6. Mixed endometrioid and serous carcinoma G2	< 50 %	-	-	+	-

5.2 Discussion

In our study, the success rate in detecting SLN after cervical ICG injection was 97%. SLNs were visualized in 92.5% of cases in the right half of the pelvis and in 91.3% in the left half of them, therefore the bilateral success rate of the method in our analysis was 90%. Similar results were obtained by Papadia et al. They reported an overall success rate in detecting SLN of 96% and an 88% bilateral success rate [237]. In another study of theirs, including 342 patients with early EC from 5 centers, the fluorescence method was compared with the combined approach with 99mTc-labeled colloids and blue dye. The dual method demonstrated a relatively similar overall success rate to ICG of 97.3% vs. 96.6%, but a significantly lower bilateral success rate of 73.5% vs. 84.1% [238]. Plante et al. also investigated the ability of ICG and fluorescence techniques to detect SLN, reporting an overall success rate of 96% and a bilateral success rate of 88% [249]. Lee et al. reported similar results after ICG application in 100 patients with EC – bilateral identification of SLN in 83%, in the right half of the pelvis – 91%, and in the left – 90% [170]. In another study, Cusimano et al. reprted an overall success rate of 97.4% (95% CI 93.6%–99.3%), a bilateral success rate of 77.6% (95% CI 70.2%–83.8%), and a unilateral success rate of 87.5% (95% CI 83.3%–91.0%) [72]. Eriksson et al. included 472 patients with EC in their study and compared the success rate of mapping the SLN after injection of ICG and blue dye. SLNs were visualized in 95% of patients who received ICG and in 81% of patients who received the colorimetric method. ICG demonstrated a bilateral success rate of 86% versus only 54% [94]. In a systematic review and meta-analysis, Bodurtha et al. included 4915 patients with EC from 55 studies. They found similar results in terms of bilateral identification of SLNs when comparing ICG with blue dye (75% versus 51%) [39]. In another prospective cohort study, Holloway et al. compared the bilateral success rate of the combination of Isosulfan blue with ICG and Isosulfan blue alone. The results showed an 83.9% detection rate of SLNs by the dual method compared to only 40% when blue dye was injected alone. The combination of dyes detected positive LNs in 21.1%, while the single use of Isosulfan blue detected metastatic LNs in 13.5% [126].

In our study, we investigated the localization of SLNs. The results obtained are identical for both halves of the pelvis. The most common localization is between the a. et v. iliaca externa (right 45%, left 53.8%), followed by the subvenous LNs (right 21.3%, left 20%) and LNs along the course of the a. iliaca externa (right – 20%, left – 15%). These results are also confirmed by Plante et al. They reported as the most common localization the group of external iliac LNs (usually on or below v.iliaca externa near the bifurcation) in 71.3% of cases, followed by obturator LNs – 17.8% and common iliac LNs – 5.7%. In their study, the least common location of LNs was found in the group of parametric LNs – 0.6% [249]. Holloway et al. also obtained identical results in their study, where they compared the combined method with Isosulfan blue and ICG with the application of Isosulfan blue alone. Again, the most common localization was the group of external iliac LNs with 52.4%, in second place in frequency were obturator LNs with 39.7% and in third place in frequency were internal iliac LNs – 4.9%. The least common SLN was identified in the group of parametric LNs – 0.2% [126]. In the study by Lee et al., the most common localization was reported as the group of obturator LNs with 46.1%, in second place in frequency was the external iliac region with 38.7% and in third place were internal iliac LNs with 7.4%. Again, parametric LNs were the least common localization with 1.4%. Similar to our study, the authors also did not find differences in the localization of SLN between the two halves of the pelvis [170]. In another study, Bizzarri et al. reported that the most common location of LNs was the external iliac group with 57.3%, followed by obturator LNs in 30.1% and internal iliac LNs in 6.3%. Paraaortic LNs were identified in 6 patients (1.1%), and in one of them (0.2%) these were the only LNs mapped. They compared LN mapping after ICG application during laparoscopic and robotic surgery and found no difference in either bilateral success rate or in the location of identified LNs [36]. In the multicenter prospective cohort study FIRES, 385 patients underwent SLNB after intracervical ICG application. In 293 (86%) of them, at least one LN was mapped. They were most frequently identified in the external iliac group (38%), followed by obturator LNs (25%), inframesenteric paraaortic LNs (14%), internal iliac LNs (10%), common iliac LNs (8%), presacral LNs (3%), infrarenal paraaortic LNs (1%) and parametric LNs (less than 1%) [266].

In our study, the mean number of LNs removed on the right was 1.56±1.19, on the left was 1.54±0.98 and 3.10±1.77 bilaterally. Lee et al. also obtained similar results, reporting that in their study the mean number of LNs removed on the right was 1.31, on the left was 1.20 and on average for each patient was about 2.54 [170]. Plante et al. reported that an average of 3 LNs were removed per case [249]. In another single-center prospective study, Ruiz et al. included 278 patients with EC. ICG was injected not only into the cervix but also into the uterine fundus. A total of 1,131 SLNs were visualized and removed, of which 712 were pelvic LNs and the remaining 419 were found in the paraaortic region [267]. In a systematic review and meta-analysis, Bodurtha et al., analyzing 55 studies, found that the mean number of SLNs mapped and removed per patient was 2.9 (95% CI 2.5-3.3) [39].

We identified positive LNs in 6 patients (7.5%). In 3 of them, the metastatic LN was found on the left, in 2 of them it was identified on the right, and in one patient the result was false negative. In a study by Plante et al., 22% of patients had metastatic LN. They also found a false negative result in only one patient [249]. Ruiz et al. investigated the detection of SLN with double injection of ICG into the uterine fundus and cervix. The detected cases with metastatic LN were 16.2%. In 9.4%, metastases were in the PLN, in 4.0% – in the PALN, and in 2.9%, metastases were found in both the PLN and PALN. A false negative result was reported in only one patient [267]. In another study, Holloway et al. performed a comparative analysis of two groups of patients with early EC. In one group, SLN mapping was performed with a combination of Isosulfan blue and ICG, and in the second group, lymphadenectomy was performed without visualization of SLN. In those patients where dye was used, significantly more metastases were demonstrated (30.3% vs. 14.7%). The SLN was the only metastatic site in 50% of cases. As in our study, a false negative result was reported in 1 patient. The authors found that SLN mapping significantly favoured the detection of metastases in them (OR=3.29, p<0.0001) [127].

6. Evaluation of the validity of the fluorescence method in quantitative terms using the following criteria: sensitivity, specificity, negative and positive predictive value

6.1 Results

Due to the lack of information from the gold standard (preoperative imaging) on the status of regional LNs, 3 patients dropped out of this part of the study.

Table 37 shows that according to the available data for 77 patients, the application of the fluorescence method for the detection of metastases in the SLN with the gold standard preoperative imaging (computed tomography or MRI) has both excellent values (over 90%) for three of the validation criteria – specificity, negative predictive value and precision, and very good (over 80%) sensitivity and positive predictive value. The false negative cases are only one (16.7%), and the false positives – 1.4%. The true positives are 83.3%, and the true negatives – 98.6% (Table 38)

Table 37. Values of the criteria for validation of the fluorescence method as a method for detecting metastases in sentinel LNs with gold standard preoperative imaging (computed tomography or MRI)

Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Precision (%)
83	99	83	99	97

Table 38. Frequency distribution of the presence of lymph node metastases according to the fluorescence method and preoperative imaging study

Lymph node metastases according to the fluorescence method	**Lymph node metastases according to preoperative imaging**				**Total**	
	No		Yes			
	n	%	N	%	n	%
No	70	98,6	1	16,7	71	92,2
Yes	1	1,4	5	83,3	6	7,8
Total	71	100,0	6	100,0	77	100,0

6.2 Discussion

When evaluating a diagnostic, screening, or classification method, it is essential not only to demonstrate the overall accuracy of the method, but also to analyze how the method performs in different clinically or analytically relevant error categories. Overall accuracy can be misleading, especially in cases of false positive or negative results. Therefore, sensitivity, specificity, positive predictive value, and negative predictive value are often used as complementary performance measures that provide more comprehensive assessment of the validity of the method. Taken together, these measures allow more detailed interpretation of the diagnostic method by distinguishing the ability to detect, the ability to exclude, and the practical reliability of positive and negative test results. Their combined use is particularly important in determining whether a method is suitable for application in a scientific research or clinical practice. To evaluate the use of ICG injection into the cervix for mapping of SLN, it is necessary to use diagnostic performance indicators (sensitivity, specificity, positive predictive value and negative predictive value), because the clinical value of this technique depends not only on whether SLN can be visualized, but also on whether the identified nodes will be the first to metastasize. SLN mapping aims to provide reliable information on lymphatic spread, while reducing the need for systemic LND and its associated morbidity. For this reason, information alone on the success rate of the technique alone is insufficient to determine whether the technique is oncologically safe and clinically applicable. Sensitivity reflects the ability of ICG-guided SLN mapping to correctly identify patients with metastases. A method with high sensitivity reduces the risk of false-negative results, which is of critical importance, since an undetected metastatic LN can lead to inaccurate staging, undertreatment, and poor prognosis. The negative predictive value indicates the probability that a patient with a negative sentinel lymph node does not actually have metastases. A high negative predictive value allows us to avoid performing systemic PLD when SLNs are negative. The specificity reflects the ability of the method to detect patients without metastases, while the positive predictive value indicates the probability that regional LNs will be positive if the SLN is metastatic. These indicators allow the method to be evaluated not only as a technique for visualizing lymphatic channels and nodes, but also as a diagnostic staging tool with an important role in planning treatment in these patients.

Rossi et al. reported the results of the FIRES study. In this prospective analysis, SLN mapping, followed by the golden standard – pelvic lymphadenectomy was performed in 340 patients. LN metastases were correctly identified in SLN in 35 of 36 patients, yielding sensitivity for detecting disease with positive LN of 97.2% (95% CI 85–100) and a negative predictive value of 99.6% (97.9–100) [266]. Since the patients in our study did not undergo systemic PLD, we used preoperative imaging as the gold standard. Our results showed a lower sensitivity of 83%, but a very similar negative predictive value of 99%.

Very similar results in terms of sensitivity (88.2%) and negative predictive value (97.3%) were obtained by Wang et al. [334]. In a systematic review with meta-analyses by Burg et al., including 2117 patients, the authors demonstrated that the diagnostic value of SLN mapping in patients with low- and intermediate-risk EC is excellent, with a negative predictive value of 100% (95% CI=98.8%–100%) and 99.2% (95% CI=97.9%–99.9%) in studies that also included poorly differentiated endometrioid tumors [52], results also very comparable to ours. Slightly better, but also similar, data were demonstrated in the analysis by Lee et al. – sensitivity 100% (95% CI: 59.04–100.00), specificity 99.52% (95% CI: 97.38–99.99), negative predictive value 100.00% and accuracy 99.54% [170]. Two other frequently cited studies are those of Plante et al. and Holloway et al. In the study by Plante et al., the sensitivity, specificity and negative predictive value were 93.3%, 100% and 98.7% [249], and in that of Holloway et al. they were 90%, 100% and 96%, respectively [128]. Bjørnholt et al. proved a sensitivity of the method of 86% and a negative predictive value of 96% [38]. Ruiz et al. injected the dye not only into the cervix but also into the fundus of the uterus and described a better sensitivity than ours – 94.44%, but similar specificity 100% and negative predictive value 97.83% [268]. Higher sensitivity of the method has been described by other authors: Persson et al. – 98% [247], Cusimano et al. – 96% (95% CI, 81%-100%) [72]. As it can be seen from the above, many studies do not report the positive predictive value. The reason for this is methodological: when SLN is positive, this is usually accepted as lymphatic metastasis, therefore, false positive results are rare or absent and very often the authors do not report them [207].

In conclusion, we can say that the use of these diagnostic indicators provides a more generalized assessment of the methodology, rather than just measuring the accuracy of detection, since it only reflects the technical success of the method. The added study of sensitivity, specificity, positive predictive value and negative predictive value determine whether the technique is diagnostically reliable and clinically relevant. The high and comparable values that we obtained in the analysis, which are comparable to those described in the literature, indicate that the injection of ICG into the cervix for the purpose of detecting SLN in patients with EC is a staging approach that can safely promote the implementation of less invasive and personalized therapeutic strategies.

V. Conclusions and contributions

Conclusions:

1. Age is confirmed as one of the main non-modifiable risk factors for the development of endometrial carcinoma, with the highest relative share of affected patients being found in the age group over 60 years, followed by the group of 50-59 years old.

2. The obtained data confirm the significant relation between obesity and endometrial carcinoma.
3. More than half of patients with endometrial carcinoma have established arterial hypertension, which confirms the frequent combination of the two conditions.
4. There is a significant relation between the tumor size and the presence of lymphovascular invasion, with all patients with lymphovascular space involvement having a lesion size of over 2 cm.
5. The presence of lymph node metastases is statistically significantly more common in patients with clear cell carcinoma and statistically significantly less common in patients with endometrioid carcinoma.
6. Hysteroscopy shows higher diagnostic accuracy and reliability in the detection of endometrial carcinoma and histological evidence of cervical invasion compared to trial abrasion and separated trial abrasion.
7. Robot-assisted hysterectomy, combined with sentinel lymph node biopsy and application of ICG as a fluorescent marker, is characterized by a favorable intraoperative profile, expressed in a relatively short operative duration and minimal intraoperative blood loss.
8. Robot-assisted surgical approach in combination with sentinel lymph node biopsy emerges as an oncologically safe treatment method, without compromising the quality, precision and reliability of disease staging.
9. Cervical injection of ICG provides a high overall success rate in the detection of sentinel lymph nodes.
10. The most common localization of sentinel lymph nodes is between a. et v. iliaca externa, followed by the subvenous and lymph nodes along the course of a. iliaca externa.
11. Sentinel lymph nodes are visualized most rarely in the group of common iliac lymph nodes and presacral lymph nodes.

12. The fluorescent method for detecting metastases in sentinel lymph nodes shows high diagnostic value, with excellent indicators of specificity – 99%, negative predictive value – 99% and precision – 97%, as well as very good values for sensitivity and positive predictive value – 83% and 83%, respectively.

Contributions:

1. Scientific-theoretical
   1.1. For the first time in Bulgaria, the role of Indocyanine green in the assessment of the regional lymph basin in patients with endometrial carcinoma has been studied.
2. Scientific and practical
   2.1. A clinical-epidemiological study was conducted, including 80 women with endometrial carcinoma, treated at the Clinic of Obstetrics and Gynecology of the University Hospital "St. Marina", Pleven, for the period from 06.2020 to 09.2023.
   2.2. The frequency and distribution of risk factors in patients with endometrial carcinoma have been determined.
   2.3. Prognostic factors and their influence on LN metastases have been identified.
   2.4. The most appropriate method for diagnosing endometrial carcinoma has been determined.
   2.5. Perioperative and oncological outcomes in patients with endometrial carcinoma were analyzed and the advantages of robotic surgery and sentinel lymph node biopsy were established.
   2.6. The success rate of sentinel lymph node mapping after ICG injection into the cervix was determined.

2.7. The localization of the detected SLNs for each of the two halves of the pelvis was analyzed.

2.8. The validity of the fluorescence method was assessed in a quantitative aspect using the following criteria – sensitivity, specificity, negative and positive predictive value.

Declaration of originality:

The author of this dissertation declares that all the data described are original and obtained as a result of his research work at the Medical University of Pleven and the University Hospital "St. Marina" - Pleven. The results, discussions and conclusions have not been borrowed from other sources without citation.

Declarant: Dr. Dimitar Georgiev Dimitrov

VI. PUBLICATIONS AND SCIENTIFIC COMMUNICATIONS RELATED TO THE DISSERTATION

PUBLICATIONS IN JOURNALS:

1. **Dimitrov D**, Hinkova N, Semova T, Gorcheva Z, Vasileva M, Petkova E (2024) Modern methods of diagnosis of endometrial carcinoma. Journal of Biomedical and Clinical Research 17(2): 197-204. https://doi.org/10.3897/jbcr.e138140

2. Hinkova N, Tsvetanova K, Totev T, Nikolova M, Semova T, **Dimitrov D**, Petkova E (2025) The diagnostic value of endometrial cytology in

diagnosing endometrial pathology. Journal of Biomedical and Clinical Research 18: 1-8. https://doi.org/10.3897/jbcr.e145118

3. Vasileva M, Prandzhev G, **Dimitrov D**, Gorcheva Z (2024) Current state of application of Artificial Intelligence in preoperative MRI assessment of endometrial cancer – a mini review. Series on Biomechanics 38(4): 127-132.
DOI: **10.7546/SB.17.04.2024**

SCIENTIFIC COMMUNICATIONS:

ABROAD:

1. Robotic sentinel lymph node detection with ICG in endometrial cancer patients - 17th SERGS Annual meeting, 05-07.06.2025, Pisa, Italy

IN BULGARIA:

1. The role of Indocyanine green in the assessment of the regional lymph basin in patients with endometrial carcinoma - XXV National Conference on Gynecological Oncology, 19-22.10.2023, Razlog
2. The diagnostic value of pipelle aspiration biopsy in the diagnosis of endometrial pathology - XXV National Conference on Gynecological Oncology, 19-22.10.2023, Razlog
3. Endometrial cytology - is it applicable in the screening of endometrial pathology - XXV National Conference on Gynecological Oncology, 19-22.10.2023, Razlog
4. The role of Indocyanine green in the assessment of the regional lymph basin in patients with endometrial carcinoma - First National Conference

of the Bulgarian Association for Minimally Invasive and Robotic Surgery (BAMIRS), Pleven, 2024

5. Endometrial pathology - risk factors for development - Public health: a look at the future, 27-28.09.2024, Plovdiv
6. The role of Indocyanine green for the assessment of the regional lymph basin in patients with endometrial carcinoma - XXVI National Conference on Gynecological Oncology, 17-20.10.2024, Razlog
7. Robotic sentinel lymph node detection with ICG in endometrial cancer patients - INTERNATIONAL SCIENTIFIC WORKSHOP ON SURFACE ENGINEERING FOR BIOMEDICAL APPLICATIONS - 17-21.03.2026, Borovets resort

PARTICIPATION IN RESEARCH PROJECTS:

1. Participation in research project No. 16/2023 on the topic: Role and place of endometrial cytology combined with sonography of the female reproductive system in the early diagnosis of precancerous and cancerous diseases of the endometrium.