MEDICAL UNIVERSITY – PLEVEN

FACULTY OF MEDICINE

DEPARTMENT OF OBSTETRICS AND GYNECOLOGY”

Dr. Teodora Krasimirova Semova

Place and role of modern minimally invasive approaches in the diagnosis and treatment of ovarian carcinoma

Dissertation Abstract

for the acquisition of an educational and scientific degree

"PhD"

Scientific supervisors:

Corresponding member Prof. Slavcho Tomov Tomov, MD, PhD

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The thesis is prepared on 397 standard printed pages. The material is illustrated with 63 figures and 67 tables.

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The author is a PhD student in part-time study 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 thesis.

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 thesis will take place on September 9, 2026 at 2:00 p.m. in the Ambroise Pare Hall of Medical University - Pleven.

Scientific jury composed of:

Chairperson:

Prof. Nadezhda Hristova Hinkova, MD, PhD

Members:

Acad. Grigor Angelov Gorchev, DSc, PhD
Prof. Yavor Dimitrov Kornovski, DSc, PhD
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Reserve members:
Assoc. Prof. Dobrinka Hristova Gincheva, MD, PhD
Assoc. Prof. Lachezar Stoyanov Tanchev, MD, PhD

The materials for the defense are 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, Medical University- Pleven.

CONTENTS:

Abbreviations used:

OC – ovarian carcinoma

OS – overall survival

MMR genes - mismatch DNA repair genes

NAC – neoadjuvant chemotherapy

ICS – interval cytoreductive surgery

PCS – primary cytoreductive surgery

SCS – secondary cytoreductive surgery

MIS – minimally invasive surgery

EC – endometrial carcinoma

CC – cervical cancer

EOC – epithelial ovarian carcinoma

WHO – World Health Organization

HGSC – high-grade serous carcinoma

LGSC – low-grade serous carcinoma

STIC – serous tubal intraepithelial carcinoma

OCCC – clear cell carcinoma

PFS – progression-free survival

DFS – disease-free survival

LS – laparoscopic surgery

OS– open surgery

RAS – robotic-assisted surgery

HRD – homologous recombination deficiency

I. INTRODUCTION

Globally, ovarian carcinoma (OC) ranks eighth among the most common cancers in women and eighteenth among all type of cancers (539). In addition to being one of the most common gynecological malignancies, OC is the most lethal gynecological neoplasm, with a 5-year overall survival (OS) rate of less than 45%. In 2022, the number of 324,398 new cases was diagnosed, with 206,839 deaths in the same year (539). According to data from the National Cancer Registry (2017), OC is seventh among the cancers that occur in women and sixth among the causes of death from malignant diseases in them. In Bulgaria, in 2017, 707 women were newly diagnosed with ovarian cancer (19.4/100,000), with 437 deaths (12.0/100,000) – data higher than the European average (603). According to Globocan forecasts, from 2022 to 2050, the number of women worldwide diagnosed with ovarian cancer will increase by over 55% to 503,448. The number of women who die from this disease each year is expected to increase to 350,956, an increase of almost 70% compared to 2022. This is due to the lack of an effective screening method, as well as the increasing frequency of certain risk factors such as obesity, metabolic syndrome and nulliparity (247).

Although the etiology of the disease is unclear and most cases are sporadic, the most significant risk factor is a family history of breast or ovarian cancer. The risk of developing invasive epithelial ovarian cancer is increased by approximately 50% in women who have a first-degree relative with ovarian cancer and by 10% in those who have a first-degree relative with breast cancer (561). Genetic predisposition is observed in about 15% of patients with ovarian cancer, and in 65–75% of cases it is associated with germline or somatic mutations in the BRCA1 and BRCA2 genes (317). Other inherited syndromes associated with OC include Lynch syndrome, Peutz-Jeghers syndrome, Cowden syndrome, Li-Fraumeni syndrome, and MUTYH-associated polyposis syndrome, due to mutations in the mismatch DNA repair (MMR) genes, STK11 and MUTYH (154,564,392,405).

The prognosis of patients with OC is directly related to the stage of the disease. Approximately 70% of patients are diagnosed at an advanced stage, with a 5-year OS of about 30%. In comparison, patients diagnosed at an early stage have a 5-year OS of 90% (268). Standard treatment for epithelial OC includes primary cytoreductive surgery aimed at optimal cytoreduction, followed by platinum-based chemotherapy. The size of the residual tumor after surgery is the main and independent prognostic factor for patient survival. In patients with poor general condition, significant comorbidity, and high perioperative risk, as well as in patients in whom complete cytoreduction could not be achieved due to disease spread, neoadjuvant chemotherapy (NC) is recommended to reduce tumor spread, followed by interval cytoreductive surgery (ICS) (316). Minimally invasive surgery (MIS), including traditional laparoscopic surgery and robotic-assisted surgery, is increasingly used in the surgical treatment of gynecological malignancies (97). As early as the early 1990s, pioneers in laparoscopic surgery used minimally invasive techniques in the treatment of gynecological malignancies, including laparoscopic staging in patients with early OC, primary cytoreductive surgery, and treatment of recurrence in selected patients (402). Since then, the role of MIS in the treatment of gynecological oncological diseases has been constantly increasing, and today it turned into the preferred method in the surgical treatment of early endometrial carcinoma (EC) and cervical carcinoma (CC). However, the important question of the role of MIS in the diagnosis and treatment of OC remains to be evaluated.

II. GOAL AND OBJECTIVES

1. Goal

To determine the place and role of minimally invasive surgery in the diagnosis, staging, and treatment of patients with ovarian cancer by analyzing perioperative and oncological outcomes.

2. Tasks

1. To investigate perioperative parameters: operative time, postoperative stay and blood loss, by conducting a comparative analysis between patients with early ovarian carcinoma operated on using minimally invasive and open surgery.
2. To study overall survival and disease-free survival in patients with early-stage ovarian cancer who underwent minimally invasive and open surgery.
3. To investigate the incidence of intraoperative capsule rupture and the factors contributing to its occurrence in patients with early ovarian cancer, and to determine its significance in terms of overall and disease-free survival.
4. To determine the role of diagnostic laparoscopy as a method for assessing tumor resectability in patients with advanced ovarian cancer.
5. To compare the perioperative and oncological outcomes in patients with primary cytoreductive surgery and interval cytoreductive surgery, as well as to analyze the presence and size of residual tumor.
6. To perform a comparative analysis of perioperative indicators: operative time, hospital stay, blood loss and postoperative complications in patients who underwent minimally invasive interval surgery and open interval surgery.
7. To study overall survival and disease-free survival in patients with interval cytoreductive surgery, comparing those operated on using minimally invasive surgery with those operated on using open surgery.

8. To determine the frequency of Carrier status for pathogenic variants in the BRCA1 and BRCA2 genes and the HRD frequency, and to determine their prognostic significance in patients with high-grade ovarian carcinoma.

III. MATERIAL AND METHODS

1. Clinical contingent – main characteristics

An ambispective clinical-epidemiological study was conducted, covering 268 patients with ovarian carcinoma, operated on at the University Hospital St. Marina – Pleven in the period January 2020 - June 2023. The average age of the participants was 57.43±11.98 years in the interval between 27 and 83.

Figure 1 shows that the largest proportion of participants (28.4%) belonged to the 60–69 years age group, followed by those aged 50–59 years (26.9%). The smallest proportion (1.1%) was observed in the age group under 30 years.

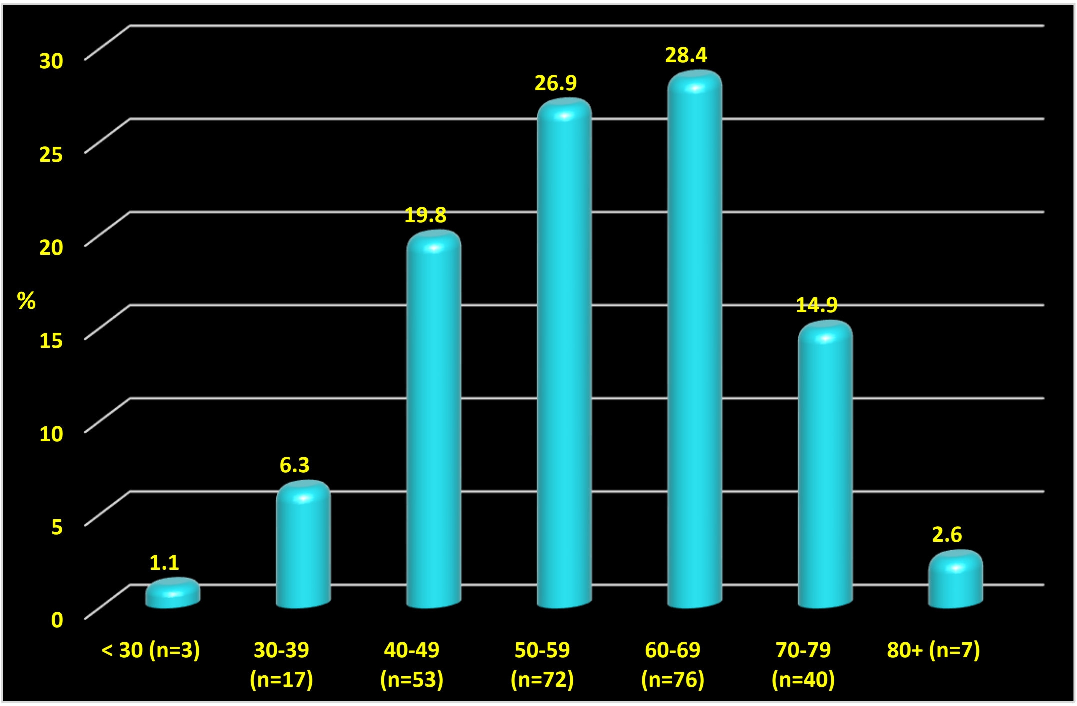


Figure 1: Distribution of the study participants by age group

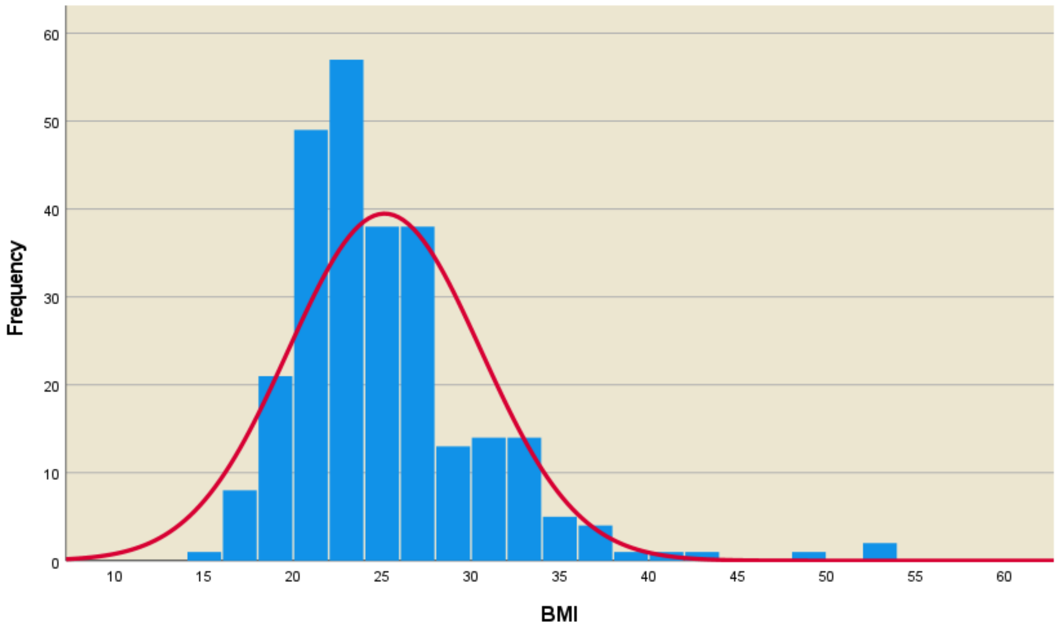


Figure 2: Distribution of patients in the study by BMI (Kolmogorov-Smirnov $p<0.001$)

Figure 2 shows that the distribution of BMI differs statistically significantly from a normal distribution, exhibiting a right-skewed pattern and a higher peak than the normal distribution curve within the range of normal BMI values.

2. Methods

2.1. Operational methods

Laparoscopic surgery

For diagnostic and operative laparoscopies, laparoscopic equipment from Karl Storz® and Olympus® was used. Two methods were used for CO2 insufflation – a closed method with a Veress needle and an open laparoscopic approach according to Hasson, which was the preferred method in patients with previous laparotomies, suspicion of existing adhesions or metastatic omentum.

Robot-assisted surgery

Robot-assisted interventions were performed with the DaVinci X® surgical system. The first step in performing the operations was to define the surgical workspace, which is the area in the patient that all instruments must reach in order to successfully complete the procedure. The next step was to define the target anatomy (the farthest point in the surgical workspace that must be reached during the operation). The incision for the endoscope port was made 10–20 cm from the target anatomy. In patients with previous midline laparotomies, an open Hasson approach was made at the site of the first working arm port. The working arm ports were placed in line 8 cm from the endoscope port. Two assistant ports were also placed next to the patient: a 10 mm port 8 cm lateral to the third working arm and a 5 mm port 8 cm distal to the first assistant port and 2 cm medial to the anterior superior iliac spine after visualization of the a. et v. Positioning and connection of the surgical robot to the patient ports was performed according to Intuitive Surgical requirements.

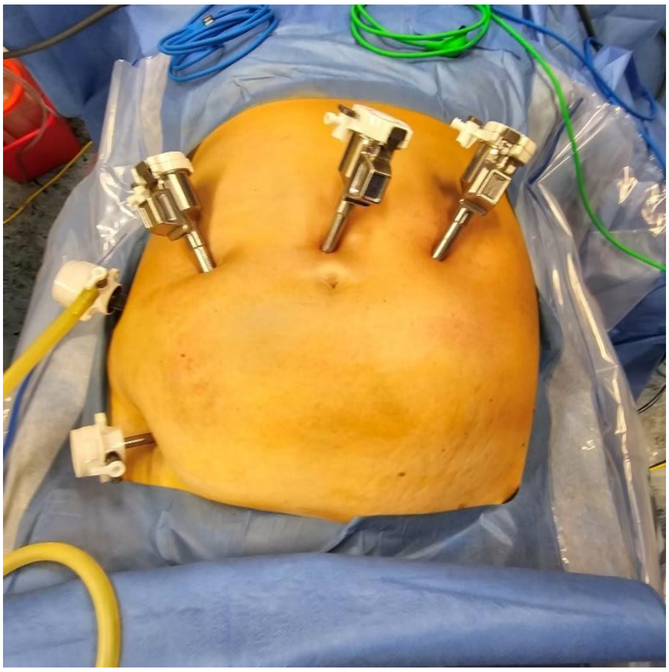


Figure 3: Placement of the trocars

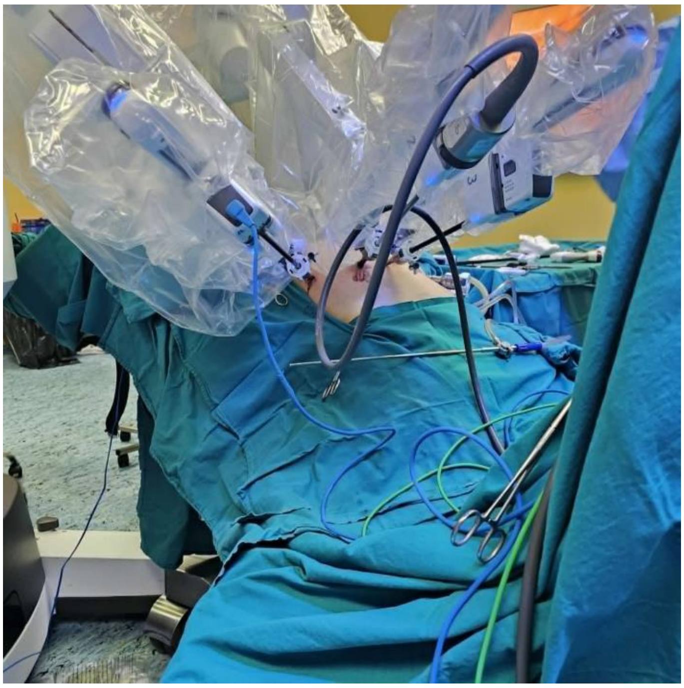


Figure 4: DaVinci X Robotic Surgery System ®.

2.2. Genetic research

For molecular genetic analysis for BRCA mutations and HRD, formalin-fixed, paraffin-embedded tumor tissue (FFPE material) was used. The next step involved selecting a tissue block containing a sufficient amount of invasive tumor tissue and assessing tumor cellularity, ensuring that the tumor cell content not being at least 30%. DNA extraction was performed from the selected tumor tissue using the QIAamp DNA Mini Kit / QIAamp-based methodology from QIAGEN, according to the manufacturer's recommendations. The standard approach includes deparaffinization, tissue lysis, DNA binding to the membrane, subsequent washing and elution of the purified DNA. This was followed by assessment of the quantity and quality of the isolated DNA and preparation of sequencing libraries according to the manufacturer's protocol using the AmoyDx® HRD Focus Panel NGS Panel. The analysis of BRCA1 and BRCA2 involves the identification of genetic variants, including single-nucleotide variants (SNVs) and small insertions and deletions (indels) within the coding regions and relevant exon–intron boundaries of both genes. HRD status was assessed by analyzing genomic instability markers, which were combined into a composite Genomic Scar Score (GSS).

2.3. Statistical methods

The data were entered and processed with the statistical packages IBM SPSS Statistics 27.0. and MedCalc Version 19.6.3. Microsoft Office Excel 2021 was also used for the figures. The significance level at which the null hypothesis is rejected was $p<0.05$.

The following methods were applied:

1. ***Descriptive analysis*** – The frequency distribution of the considered features is presented in tabular form.
2. ***Graphical analysis*** – for visualization of the obtained results.
3. ***Fisher-Freeman-Halton Exact Test, Fisher'exact test and test χ^2 –*** for testing hypotheses about the existence of a relationship between categorical variables.
4. ***Non-parametric Kolmogorov-Smirnov and Shapiro-Wilk tests*** – to check the distribution for normality.
5. ***Student's t-test*** – to test hypotheses about the difference between the arithmetic means of two independent samples.
6. ***Student's t-test*** – to test hypotheses about the difference between the arithmetic means of two dependent samples.
7. ***One-way analysis of variance (ANOVA)*** – for testing hypotheses about the influence of factors with more than two levels.
8. ***LSD coefficients*** – for testing hypotheses about differences between several independent samples.
9. ***Nonparametric Kruskal-Wallis test*** – for testing hypotheses about differences between several independent samples.

10. ***Nonparametric Mann–Whitney U test*** – to test hypotheses about the difference between two independent samples.
11. ***Nonparametric Wilcoxon tests*** – to test hypotheses about the difference between two dependent samples.
12. ***Kaplan-Meier method*** to estimate the time until the occurrence of the studied event (Kaplan-Meier Product Limit Estimation of the Survival Function).
13. ***Log Rank, Breslow, and Tarone-Ware tests*** to assess the influence of the studied factors on the occurrence of the analyzed event.
14. ***ROC curve analysis*** **–** for determining threshold values for quantitative variables.
15. ***Criteria for validation of screening tests*****.**

IV. OWN RESULTS AND DISCUSSION

1. Study of perioperative indicators: operative time, postoperative hospital stay and blood loss, by performing a comparative analysis between patients with early ovarian carcinoma operated on using minimally invasive surgery and open surgery.

1.1. OWN RESULTS

Fig. 5 shows that, with respect to the type of surgical intervention, open surgery accounted for the larger proportion (58.4%), while minimally invasive surgery represented 41.6% of the interventions. The latter, in turn, is divided into laparoscopic surgery (27.3%) and robotic surgery (14,3%).

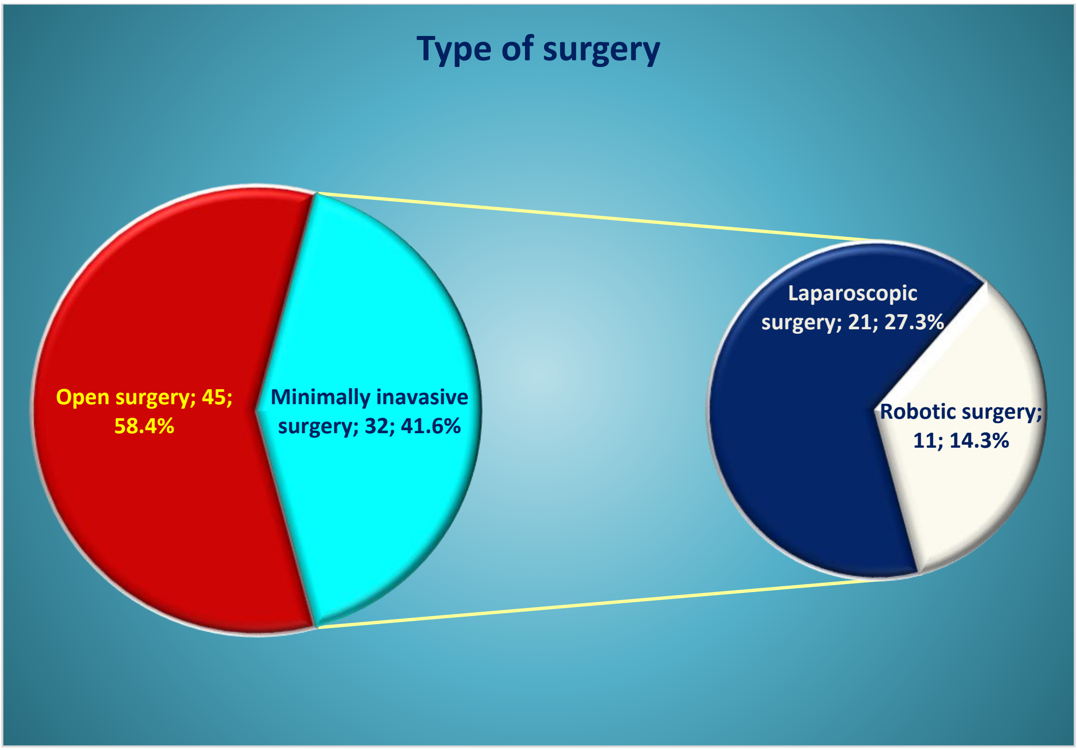


Figure 5: Distribution of patients with early-stage ovarian carcinoma according to the type of surgical intervention

The analysis of the relationship between the type of surgical intervention and the indicators of hospital stay, operative time during the operation and the dynamics of hemoglobin and hematocrit showed the presence of a statistically significant relationship, expressed in:

- Significantly higher mean values of the first two indicators in the open surgery group;
- In the dynamics of hemoglobin and hematocrit, the difference between the two groups according to the type of surgical intervention is statistically insignificant (Table1).

Table 1: Analysis of the relationship between the type of surgical intervention and the indicators of hospital stay and operative time during surgery, dynamics of hemoglobin and hematocrit

Indicator	Type of surgical intervention						P
	Minimally invasive surgery			Open surgery			
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Hospital stay during surgery (days)	32	3,88	0,98	45	7,62	1,99	**<0,001**
Operative time during surgery (minutes)	32	64,38	14,07	45	111,78	24,12	**<0,001**
Hb dynamics	32	-8,78	6,79	45	-10,04	9,71	0,504
Hct dynamics	32	-3,25	4,21	45	-3,36	3,24	0,339

The analysis of the relationship between the type of minimally invasive surgery and the indicators of hospital stay and operative time during the operation, dynamics of hemoglobin and hematocrit showed:

- A statistically significant difference was observed only for the first indicator, with patients who underwent robotic-assisted surgery demonstrating a significantly higher mean value (Table 2).

- Patients who underwent open surgery had a significantly longer mean operative time of 111.78 minutes. In comparison, the mean operative time among patients undergoing minimally invasive surgery was 64.38 minutes, including 61.67 minutes for laparoscopic surgery and 69.55 minutes for robotic-assisted surgery).
- Postoperative hospital stay was significantly longer among patients who underwent open surgery, with a mean duration of 7.62 days. In contrast,

patients who underwent minimally invasive surgery had a significantly shorter mean hospital stay of 3.88 days, comprising 3.29 days for laparoscopic surgery and 5.00 days for robotic-assisted surgery).

Table 2: Analysis of the relationship between the type of minimally invasive surgery and the indicators of hospital stay and operative time during surgery, dynamics of hemoglobin and hematocrit

Indicator	Type of minimally invasive surgery						P
	Laparoscopic			Robotic			
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Hospital stay during surgery (days)	21	3,29	0,64	11	5,00	0,00	**<0,001**
Operative time during surgery (minutes)	21	61,67	11,11	11	69,55	17,95	0,135
Hb dynamics	21	-9,62	7,35	11	-7,18	5,53	0,343
Hct dynamics	21	-4,00	4,92	11	-1,82	1,78	0,180

- Analysis of the relationship between the type of surgical intervention and the need for blood transfusion revealed a statistically significant association. Blood transfusions were significantly more frequent among patients who underwent open surgery compared with those who underwent minimally invasive surgery (Table 3). These findings suggest that the open surgical approach was associated with a greater requirement for perioperative blood transfusion).

Table 3: Analysis of the relationship between the type of surgical intervention and the blood transfusion indicator

Indicator	Type of surgical intervention				P
	Minimally invasive surgery		Open surgery		
	n	%	n	%	
Blood transfusion					**0,018**
No	32	100,0	37	82,2	
Yes	0	0,0	8	17,8	

1.2 DICUSSION

Although more than three decades have passed since Reich et al. (469) first reported laparoscopic staging of ovarian cancer, the efficacy, safety, and oncological safety of minimally invasive surgery in patients with early-stage ovarian cancer remain subjects of debate, with conflicting evidence and opinions. Comparison of perioperative outcomes among open, laparoscopic, and robotic surgery represents one of the most widely used and objective approaches for evaluating the advantages and disadvantages of these surgical modalities. Regarding operative time, the available evidence is inconsistent: some studies have reported significantly longer operative times for laparoscopic surgery (78, 190, 246, 310), whereas others have demonstrated statistically significantly shorter operative times in the laparoscopic group (425, 422, 427). These discrepancies likely reflect variations in surgical techniques and different experience of laparoscopic techniques among surgical teams (153). The results of our analysis show a significantly shorter operative time than described in the literature in both groups, and also demonstrate a statistically significant shorter operative time in the minimally invasive group compared to open surgery (64.38 min. compared to 111.78 min; p<0.001). Most studies define intraoperative blood loss as the volume of blood lost during surgery, expressed in millilitres (ml). This indicator does not reflect the clinical significance that the loss of a certain amount of blood has for the patient (295). In this regard, hematocrit is much more indicative and is used to assess acute and chronic blood loss. We use the dynamics of preoperative and postoperative hemoglobin and hematocrit for indirect assessment of intraoperative blood loss. The only study that examined the dynamics of hemoglobin preoperatively and postoperatively as a method of determining blood loss was that of Koo et al., who found a mean decrease in hemoglobin levels after surgery of 2.0 mg/dL in the laparoscopic group and 2.4 mg/dL in the open surgery group ($p=0.253$) (295). Our analysis also found no statistically significant difference in the dynamics of hemoglobin and hematocrit, although most studies that measure blood loss in ml find statistically significant less blood loss in the minimally invasive surgery group. Our results demonstrated that blood transfusion was required in 17.8% of patients who underwent open surgery, whereas none of the patients in the endoscopic surgery group required transfusion. Chen et al. also found a higher rate of blood transfusions in the open surgery group, but it was significantly higher (46.6%) than that observed in our study (74). Hospital stay is an important indicator because it reflects the degree of surgical trauma that a given surgical technique inflicts on the patient, represented by the time it takes for the individual to recover from this trauma. Our findings demonstrated a significantly shorter postoperative hospital stay in the endoscopic surgery group, with a mean duration of 3.88 days, compared with the open surgery group (7.62 days) ($p<0.001$). Our results are consistent with those of the majority of analyses (41,374,331,180) – a fact that has not only medical but also socioeconomic implications.

2. Study of overall survival and disease-free survival in patients with early-stage ovarian cancer undergoing minimally invasive and open surgery.

2.1. OWN RESULTS

Overall survival

The mean follow-up time was 39.69±10.73 months in the range of 14 to 63, and the mean OS was 61.39±0.92 months with a 95% CI of 59.59 to 63.19 months. Table 4 presents a survival analysis calculated using the Kaplan–Meier method. The following key findings are highlighted:

- Of the 77 patients, 3 (3.9%) died from the cancer under investigation, and one (1.3%) from other diseases;
- The highest mortality was observed between the 25th and 36th months – 2 cases or 66.7% of the total number of deaths during the follow-up period;
- Second place in mortality is occupied by the 13th - 24th month - one case or 33.3% of those who survived;
- During the first two years, one death (33.3%) occurred, while the remaining two deaths (66.7%) occurred during the third year;
- The first exit occurred at the 14th month;
- One-year survival is 100.0%, two-year – 98.7%, 3, 4, 5-year and 63-month – 95,9%;
- The maximum recorded survival was 63 months (just over 5 years).

Table 4: Kaplan-Meier overall survival table

Time (months)	Cumulative probability	Number of exits	Cumulative number of exits	Number of interrupted	Number remaining
0	1,000	0	0	0	77
12	1,000	0	0	0	77
14	0,987	1	1	0	76
24	0,987	0	1	1	75
36	0,959	2	3	33	40
48	0,959	0	3	21	19
60	0,959	0	3	16	3

63	0,959	0	3	3	0

As the next stage of the study, potential factors influencing the type of survival under investigation were analyzed. The Log-Rank, Breslow, and Tarone–Ware tests revealed no statistically significant differences ($p > 0.05$) in patient survival between the two types of surgical intervention (Table 5).

Table 5: Median survival and 95% confidence interval by type of surgical intervention

Type of surgical intervention	Number of events that occurred	Median survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
Minimally invasive surgery	2	60,58[a]	57,34	63,82
Open surgery	1	57,02[a]	55,13	58,92

Relapse-free survival

The mean follow-up time was 36.57±11.36 months, ranging from 7 to 62, and the mean recurrence-free survival was 54.63±1.88 months with a 95% CI of 50.94 to 58.31 months. Table 6 represents a table of recurrence-free survival calculated using the Kaplan-Meier method. The most significant findings are summarized as follows:

- According to the available data, 13 of the 77 patients (16.9%) experienced a relapse of the cancer under investigation;

➢ During the first year, 3 patients (23.1%) experienced relapse, while 4 patients (30.8%) relapsed in each of the second and third years. In the fourth year, the remaining 2 patients (15.4%) experienced relapse;

➢ The one-year recurrence-free survival rate is 96.1%, the two-year rate is 90.9%, the three-year rate is 85.3%, and the 4-, 5-year and 62-month rates are 90.9% and 90.9%, respectively– 79,4%;

➢ The first progression was registered at the 7th month;

➢ The maximum recorded recurrence-free survival is 62 months (just over 5 years).

Table 6: Kaplan-Meier recurrence-free survival table

Time (months)	Cumulative probability	Number of relapses	Cumulative number of relapses	Number of interrupted	Number remaining
0	1,000	0	0	0	77
7	0,987	1	1	0	76
12	0,961	2	3	0	74
24	0,909	4	7	0	70
36	0,853	4	11	30	36
48	0,794	2	13	21	13
60	0,794	0	13	11	2
62	0,794	0	13	2	0

As a subsequent stage of the study, potential factors influencing the survival outcome under investigation were analyzed. The Log-Rank, Breslow, and

Tarone–Ware tests demonstrated no statistically significant difference ($p > 0.05$) in progression-free survival between patients who underwent the two types of surgical intervention (Table 7).

Table 7: Median survival and 95% confidence interval by type of surgical intervention

Type of surgical intervention	Number of events that occurred	Median survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
Minimally invasive surgery	5	55,62[a]	50,43	60,80
Open surgery	8	46,33[a]	42,69	49,98

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

2.2. DISCUSSION

When comparing the two surgical procedures, any advantages in terms of perioperative outcomes and complication rates are of limited clinical significance if they are not accompanied by comparable oncological outcomes. In our study, the 5-year overall survival (OS) rate was 95.9%. In our study, the 5-year OS was 95.9%. These results are similar to those found in a multicenter observational retrospective study by Gallotta et al., who described a 5-year OS of 92.5% (175). Most authors did not find a significant difference between OS in the minimally invasive and open surgery groups. Lee et al. reported a 5-year overall survival of 91.3% in the laparoscopic group compared with 88.4% in the open surgery group ($p>0.05$) (310). Xiong et al. reported a slightly lower 5-year OS (86.7% vs. 86.8%), but also did not find a statistically significant difference ($p= 0.874$) (606). Our results support the literature data and also show a non-significant ($p>0.05$)

difference in patient survival between the two types of surgical intervention (minimally invasive and open surgery). We found one recurrence in the robotic surgery group and four in the laparoscopic group. There were 2 deaths in the laparoscopic group and none in the robotic-assisted surgery group. Statistical analysis of the data yielded results consistent with those reported in the literature, demonstrating no statistically significant difference between laparoscopic and robotic surgery with regard to oncological outcomes. DFS is the second oncological parameter that was studied in patients with early stage OC. It occurs earlier than OS, allowing for faster reporting of study results and more effective treatment evaluation (293). Hirose et al. studied 602 patients with early-stage ovarian cancer and described 70 relapses of the disease (11.6%) (239). In the analysis of Lenhard et al. this rate was 14.7% (314), and in our analysis it was 16.9%. In their analysis, Hirose et al. found that 41% of relapses occurred in the first year, 30% in the second, 4% in the third, 11% between the third and fifth years, and 13% after the fifth (239). In our study, the results were similar, with 3 (23.1%) progressions recorded in the first year, 4 (30.8%) patients in the second and third years, and the remaining two (15.4%) in the fourth year. Imterat et al. reported a 5-year DFS of 86% (256), similar to that reported by Gallotta et al. (84% (179). Upadhyay et al. reported a slightly lower 5-year DFS of 73% (567). In our analysis, this rate was 79.4%, a result similar to that reported in the literature. As has been demonstrated in most of the studies reviewed (41,180,27,175), our analysis also found no statistically significant difference in terms of DFS between the minimally invasive and open surgery groups, nor between the two subtypes of MIS. The interpretation of oncological outcomes is a key component in the comparative evaluation of the two surgical techniques, as it enables assessment not only of immediate operative outcomes but also of the long-term oncological efficacy and safety of each surgical approach. These findings support the oncological safety of the surgical intervention, which is an essential prerequisite for the broader adoption and widespread clinical application of the technique. However, the absence of randomized controlled trials, together with the low incidence of early-stage ovarian cancer, has resulted in a limited number of studies and considerable heterogeneity in the available evidence. These factors preclude the definitive establishment of minimally invasive surgical approaches as the gold standard for the surgical treatment of early-stage ovarian cancer.

3. To investigate the incidence of intraoperative capsule rupture and the factors associated with its occurrence in patients with early-stage ovarian carcinoma, and to assess its impact on overall survival and disease-free survival.

3.1. OWN RESULTS

Distribution of patients according to capsule rupture.

Figure 6 demonstrates that the vast majority of patients (81.8%) had no ovarian capsule rupture. Among patients with capsule rupture, the majority (14.3%) experienced an intraoperative rupture, whereas preoperative rupture was observed in only 3 patients (3.9%).

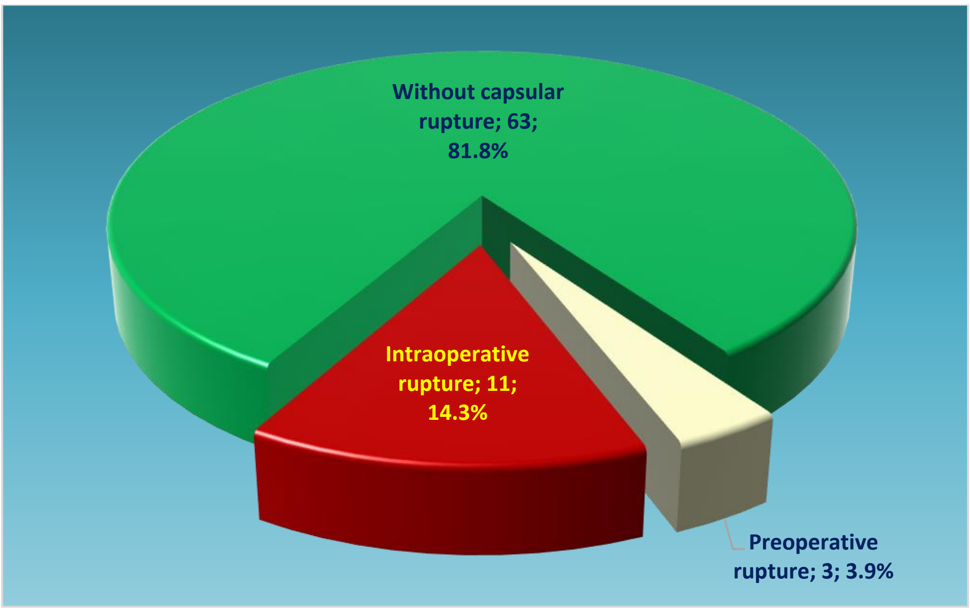


Figure 6: Frequency distribution of patients with capsule rupture

Relationship between capsule rupture and BMI.

The statistical analysis conducted revealed a significant correlation between capsule rupture and the patients' BMI, expressed in a higher average value for those with intraoperative rupture compared to those without (Table 8).

Table 8: Relationship between capsule rupture and BMI

Rupture of the capsule	BMI (kg/m^2)		
	n	$\overline{X}$	SD
No rupture	63	24,20[a]	4,32
Preoperative rupture ✦	3	23,32	4,32
Intraoperative rupture	11	27,46[b]	6,38

- Relationship between tumor size on the right and capsule rupture index.

Analysis of the relationship between right-sided tumor size and capsule rupture demonstrated a statistically significant association. In patients with intraoperative capsule rupture, tumors measuring 11–15 cm and >15 cm were significantly more frequent than those measuring ≤5 cm and 6–10 cm. The differences between the 11–15 cm and >15 cm groups, as well as between the ≤5 cm and 6–10 cm groups, were not statistically significant). In the case of preoperative rupture, the difference in the frequency distribution of the indicator of tumor size on the right is statistically insignifican;

Dependence between the type of surgical intervention and the indicators of capsule rupture.

The analysis of the relationship between the type of surgical intervention and the capsule rupture indicator found that there was no significant difference (Table 9).

Table 9: Analysis of the relationship between the type of surgical intervention and the indicator of capsule rupture

Indicator	Type of surgical intervention				P
	Minimally invasive surgery		Open surgery		
	n	%	n	%	
Rupture of the capsule					0,233
No	29	90,6	34	75,6	
Preoperative rupture	0	0,0	3	6,7	
Intraoperative rupture	3	9,4	8	17,8	

Dependence between the type of MIS and the indicators of capsule rupture and adhesions.

No statistically significant association was identified between the type of minimally invasive surgical approach and the occurrence of capsule rupture (Table 10).

Table 10: Analysis of the relationship between the type of minimally invasive surgery and the indicators of capsule rupture and the presence of adhesions

Indicator	Type of minimally invasive surgery				P
	Laparoscopic		Robotic		
	n	%	n	%	
Rupture of the capsule					1,000
No	19	90,5	10	90,9	
Preoperative rupture	0	0,0	0	0,0	
Intraoperative rupture	2	9,5	1	9,1	

Dependence between ruptures on the capsule and on adhesion.

Analysis of the association between the presence of adhesions and capsule rupture revealed a statistically significant relationship. In patients without adhesions, the proportion of cases without capsule rupture was significantly higher than the proportions of preoperative and intraoperative rupture. No statistically significant difference was observed between the rates of preoperative and intraoperative capsule rupture. In the case of adhesion to the colon and peritoneum of the cavum Douglasi, significantly higher percentages of the two types of rupture (indistinguishable between them) are observed compared to the absence of rupture. Regarding the number of adhesions, a statistically significant difference was observed only between the proportions of intraoperative capsule rupture and absence of rupture. In contrast, the proportion of preoperative rupture did not differ significantly from the other categories (table 11)

Table 11: Analysis of the relationship between the presence of adhesions and capsule rupture (p<0,001)

Presence of adhesions	**Чес-тота**	**Rupture of the capsule**			**Total**
		No	Preoperative	Intraoperative	
No	n	57	1	1	59
	%	90,5[a]	33,3[b]	9,1[b]	76,6
To the colon	n	0	1	4	5
	%	0,0[a]	33,3[b]	36,4[b]	6,5
To the uterus	n	2	0	0	2
	%	3,2[a]	0,0[a]	0,0[a]	2,6
To the contralateral ovary	n	1	0	0	1
	%	1,6[a]	0,0[a]	0,0[a]	1,3
Fossa ovarica	n	3	0	1	4

	%	4,8[a]	0,0[a]	9,1[a]	5,2
To the peritoneum of the cavum Douglasi	n	0	1	3	4
	%	0,0[a]	33,3[b]	27,3[b]	5,2
More than one of the above	n	0	0	2	2
	%	0,0[a]	0,0[ac]	18,2[bc]	2,6
Total	n	63	3	11	77
	%	100,0	100,0	100,0	100,0

* - The same letters on the horizontal lines mean no significant difference, and different letters mean the presence of such a difference. ($p<0,05$).

Significance of capsule rupture in terms of overall survival.

The results in Table 12 show that the studied event occurred only in those without rupture, therefore the median survival and 95% CI were calculated only for these patients.

Table 12: Median survival and 95% confidence interval according to the factor of capsule rupture

Rupture of the capsule	Number of events that occurred	Median survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
No	3	61,05	58,87	63,23
Preoperative	0	-	-	-
Intraoperative	0	-	-	-

Significance of capsule rupture in terms of disease-free survival.

The results presented in Table 13 show that the studied event occurred in all categories except among patients with preoperative capsule rupture. However, the difference in progression-free survival between the other two categories was not statistically significant.

Table 13: Median progression-free survival and 95% confidence interval by capsule rupture factor

Rupture of capsule	Number of events that occurred	Median progression-free survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
No	10	54,91[a]	50,85	58,97
Preoperative	0	-	-	-
Intraoperative	3	42,92[a]	34,87	50,97

3.2. DISCUSSION

Intraoperative rupture of the tumor capsule represents one of the principal concerns limiting the use of minimally invasive surgery in patients with suspicious adnexal masses. The available literature provides conflicting evidence regarding the factors associated with an increased risk of capsule rupture and the consequent potential for surgical upstaging. This motivated us to analyze this indicator in detail and compare the obtained data with those described in the literature. In general, capsule rupture is divided into spontaneous, occurring before surgical intervention, and intraoperative rupture, due to tumor manipulation during surgery. Dioun et al. reported a tumor capsule rupture frequency of 33.7% (118). In the study by Bakkum-Gamez et al. this proportion was 38% (24), and in that of Matsuo et al. – 22.5% (354). The results of our analysis are similar to those described, with an overall incidence of capsule rupture of 18.2%, with 14.3% occurring intraoperatively and only 3 patients (3.9%) occurring preoperatively. According to Ghirardi et al., higher body mass index increased the incidence of intraoperative tumor disruption ($p = 0.032$) (191). Our analysis also confirmed these results, finding a significant association ($p < 0.05$) with a higher mean score in those with intraoperative rupture compared with those without. We did not find any other observational cohort studies, case-control studies, or meta-analyses that specifically examined obesity or BMI as a risk factor for capsule rupture during surgical resection. In their observational retrospective study, Ghirardi et al. found that large diameter of the malignant formation ($p < .001$) and adhesions to the peritoneum of the ovarian fossa ($p = .007$) were independently associated with intraoperative capsule rupture (191). In our study, a statistically significant association was also observed between tumor size and the occurrence of capsule rupture ($p = .023$). In the presence of intraoperative rupture, the relative proportions of tumor size between 11 and 15 cm and over 15 cm (which did not differ statistically from each other) were statistically significantly higher than those with tumor size up to 5 cm and between 6 and 10 cm (which also did not differ statistically from each other). Many studies have compared the frequency of iatrogenic disruption of tumor integrity in patients operated on using minimally invasive and open surgery, but the data are contradictory. In our study, the analysis of the relationship between the type of surgical intervention (minimally invasive or open surgery) and the capsule rupture index found that there was no significant difference between the two groups ($p=0.233$). Gal et al. described a higher incidence of capsule rupture in the group of patients operated on by MIS compared with those operated on by OS when cystectomy was performed, but did not find such a difference between the two groups when the surgical intervention was adnexectomy (171). Our results differ from those obtained in the study by Ran et al., who demonstrated a higher incidence of intraoperative capsule rupture in patients with early stage OC operated on by laparoscopy compared with OS ($p=0.002$) (463), but coincide with those described by Heras et al., who also found no relationship between the type of surgery and capsule rupture (237). The relationship between capsule rupture and the presence of adhesions has been investigated in several studies, most of which demonstrate a relationship between the two indicators. In our study, the analysis of the relationship between the presence of adhesions and capsule rupture found that in the presence of adhesions, capsule rupture occurs significantly more often. Also, in adhesions to the colon and peritoneum of the cavum Douglasi, both types of rupture – preoperative and intraoperative – are observed in a statistically significantly higher percentage. In the study by Ghirardi et al. The authors stated that factors such as larger tumor diameter ($p < .001$), higher BMI ($p = .032$), certain ultrasound features ($p = .029$), adhesions to the colon (14% vs. 2.0%; $p = .003$), uterus (44% vs. 6.9%; $p < .001$), contralateral ovary (8.0% vs. 0%; $p = .004$), ovarian fossa (64% vs. 14.9%; $p < .001$), and peritoneum of the Douglas space (32% vs. 4.0%; $p < .001$) increased the incidence of tumor rupture. After conducting multivariate analysis, it was found that large tumor diameter ($p < .001$) and adhesions to the peritoneum of the ovarian fossa ($p = .007$) were independently associated with intraoperative capsule rupture and were included in the scoring system. (191).

Significance of capsule rupture in terms of oncological outcomes.

Some authors support the claim that capsule rupture worsens oncological outcomes in patients (428, 576, 521, 490, 377). In our study, conclusions regarding OS could not be drawn, since exit occurred in only 3 of the patients with early OC, and no capsule rupture was observed in all three. DFS data showed that disease progression was detected in a total of 13 patients – 3 with intraoperative capsule rupture and 10 with intact tumor capsule. Processing of the results showed that the difference in progression-free survival in these two categories was statistically insignificant. Despite the small number of cases, these data are supported by other studies that failed to demonstrate a relationship between capsule rupture and OS and DFS, the authors consider that this factor has limited prognostic significance. (24,466, 508, 204). The poorer prognosis observed in cases of capsule rupture may be explained by two principal mechanisms. The first explanation is that the rupture may lead to intraoperative dissemination of viable tumor cells during surgery. Second, occult tumor invasion of the capsule surface may predispose the tumor to intraoperative rupture at the affected site. Moreover, disruption of capsule integrity may complicate the pathological assessment of the specimen and make it difficult to distinguish pre-existing tumor invasion from changes resulting from intraoperative rupture (24).

4. Determining the role of diagnostic laparoscopy as a method for assessing tumor resectability in patients with advanced ovarian cancer.

4.1. OWN RESULTS

To evaluate the role of diagnostic laparoscopy in assessing tumor resectability, we compared the extent of residual tumor following primary cytoreductive surgery with that observed after diagnostic laparoscopy followed by primary cytoreductive surgery. Possible factors influencing overall survival were analyzed. Total protein, albumin, and residual tumor were tested. A significant threshold value was established only for albumin. For this purpose, the following validation criteria were applied::

- Satisfactory sensitivity (63%), poor specificity, positive predictive value and precision (57, 41 and 59% respectively); good negative predictive value (76%) (Table14).

The Log-Rank, Breslow, and Tarone–Ware tests demonstrated a statistically significant difference in survival ($p = 0.004$), with patients with serum albumin levels ≤37.75 having approximately 4 months shorter survival than those with higher albumin levels.

Table 14: Albumin threshold value for distinguishing between patients who died from ovarian cancer and those who remained alive at the end of follow-up, and the corresponding validation criteria for the screening test

Indicator	Threshold magnitude	Sensitivity	Specificity	Positive predictive value	Negative predictive value	% true answers
Albumin g/L	≤ 34,75	63	57	41	76	59

The applied Log Rank, Breslow and Tarone-Ware tests showed a significantly ($p<0.001$) higher survival of patients without residual tumor by about 36 months compared to those with tumors less than 1 cm in size and by about 39 months compared to those with ≥ 1 cm. No statistically significant difference in survival of patients with residual tumors of either size was found (Table 15).

Table 15: Median survival and 95% confidence interval according to residual tumor factor

Residual tumor	Number of events that occurred	Median survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
No	22	64,81[a]	62,00	67,62
Under 1 cm	24	28,95[b]	24,50	33,40
≥ 1 cm	21	25,41[b]	20,69	30,13

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

The statistical analysis conducted revealed a significant relationship between residual tumor and disease progression. The absence of residual tumor was characterized by a statistically significantly higher relative proportion of no progression, while its presence was characterized by a statistically significantly higher percentage of clinical progression (Table 16).

Table 16: Analysis of the relationship between residual tumor and the occurrence of progression (p<0,001)

Residual tumor	Frequency	Occurrence of relapse		Total
		No	Yes	
No	n	96	72	168
	%	98,0	52,9	71,8
There is under 1 cm.	n	1	34	35
	%	1,0	25,0	15,0
There is ≥ 1 cm.	n	1	30	31
	%	1,0	22,1	13,2
Total	n	98	136	234
	%	100,0	100,0	100,0

There is no statistically significant correlation between the operations total hysterectomy with adnexae or diagnostic laparoscopy with subsequent laparotomy and the indicators age, total protein, albumin, hospital stay during the operation and operative time, dynamics of hemoglobin and hematocrit pre- and postoperatively in patients in FIGO stages IIIC and IV. Among patients with different numbers of adhesions, a statistically significant difference was observed between the proportions of intraoperative capsule rupture and absence of rupture. However, the proportion of preoperative capsule rupture did not differ significantly from either of the other categories (Table 17). The dependence is expressed in a significantly higher relative proportion of the operation diagnostic laparoscopy with subsequent laparotomy in those without residual tumor and in a larger percentage of the operation total hysterectomy with adnexa in cases with residual tumor size ≥ 1 cm.

Table 17: Analysis of the relationship between FIGO stage IIIC–IV patients undergoing total hysterectomy with adnexectomy or diagnostic laparoscopy followed by laparotomy and the indicators of blood transfusion, residual tumor, and tumor localization

Indicator	Type of surgery				P
	Total hysterectomy with adnexae		Diagnostic laparoscopy with subsequent laparotomy		
	n	%	n	%	
Residual tumor					0,032
No	25	43,1	21	72,4	0,010
Under 1cm	13	22,4	4	13,8	0,343
≥ 1 cm	20	34,5	4	13,8	0,043

4.2. DISCUSSION

A number of studies (81,585,50,538) have investigated different diagnostic methods to determine the extent of carcinomatosis and predict the likelihood of achieving R0 resection during primary cytoreparative surgery. At present, the prevailing view is that laparoscopic assessment of disease extent, combined with preoperative CT, has the highest specificity in identifying patients who will achieve suboptimal cytoreductive results. For this reason, we aimed to compare the achieved type of resection in patients in whom primary cytoreductive surgery was preceded by diagnostic laparoscopy with those in whom direct radical surgery was performed. In patients with ovarian carcinoma, residual tumor after surgery is the most important prognostic factor. With the advent of a new therapeutic approach (neoadjuvant chemotherapy followed by interval surgery) after the publication of the results of two randomized trials, the EORTC and CHORUS (575), finding a reliable method to estimate the probability of achieving R0 resection has become of paramount importance. To confirm the significance of residual tumor after surgical treatment (primary cytoreparative surgery or interval cytoreparative surgery), we analyzed the possible factors influencing OS and PFS. We first examined quantitative features of OS and found a significant threshold value only for albumin. Dai et al. also found that low albumin at diagnosis was a statistically significant independent predictor of worse OS, even after removing factors such as the type of cytoreduction achieved, stage, and degree of tumor differentiation from the analysis (HR ~1.38, 95% CI 1.01-1.89) (107). In their analysis, Asher et al. concluded that patients with very low albumin (<25 g/L) had a median survival of ~4.8 months compared to ~43.2 months for those with albumin >35 g/L. Our statistical analyses showed a significantly ($p<0.001$) higher OS in patients without residual tumor, by about 36 months compared to those with tumors <1 cm and by about 39 months compared to those ≥1 cm. No statistically significant difference in survival was found for those with residual tumors of either size. Regarding PFS, the data showed a significantly ($p<0.001$) higher PFS in patients without residual tumor (by about 33 months compared to those with tumors <1 cm and by about 36 months compared to those with residual tumor ≥1 cm). This relationship has been demonstrated by many studies. In their analysis, Winter et al. showed that patients with stage IV OC and microscopic residual tumor had the best OS (median OS ~64 months) compared with those with residual tumor between 0.1-5.0 cm (median OS ~30 months), who also had a higher median OS than those with residual tumor >5 cm (median OS ~19 months) (601). As a next step in the analysis, we compared OS, PFS, and residual tumor in patients who underwent diagnostic laparoscopy, were deemed operable, and underwent laparotomy (29 patients) with those who proceeded directly to open surgery (58 patients). The aim of the analysis was to indirectly demonstrate that laparoscopy and the prediction of residual tumor after surgery lead to better oncological outcomes. The applied statistical analyses showed a non-significant ($p>0.05$) difference between the survival of patients from the two types of surgery, but found a significantly ($p<0.05$) higher PFS in patients in whom the surgery was started via diagnostic laparoscopy (by about 10 months) compared to those in whom it was directly switched to cytoreductive surgery. A statistically significant difference between the groups was also found for the presence and size of the residual tumor, expressed in a significantly higher relative proportion of diagnostic laparoscopy with subsequent laparotomy in those without residual tumor after surgery and in a higher percentage of directly performed PCS with residual tumor size ≥ 1 cm. Regarding the residual tumor, our data coincide with those obtained by Rutten et al., who also found a higher frequency of residual tumor over 1 cm in the group without prior laparoscopic evaluation. (487). In the study by Durdağ et al. of 93 patients who underwent preoperative laparoscopic evaluation, 77 underwent primary cytoreductive surgery. Complete cytoreduction was observed in 75.3% of cases, and optimal cytoreduction was achieved in 100% of patients. The authors reported that when diagnostic laparoscopy was used as a predictive method, no patient had suboptimal cytoreductive results (123). Our data confirm that diagnostic laparoscopy is a method that assists in the selection of a therapeutic approach, significantly reduces suboptimal cytoreductive results, which in turn leads to improved oncological outcomes in the group of patients in whom primary cytoreparative surgery was chosen as the therapeutic method.

5. Comparison of perioperative and oncological outcomes between patients undergoing primary and interval cytoreductive surgery, with analysis of the presence and extent of residual tumor.

5.1. OWN RESULTS

The results presented in Table 18 demonstrate statistically significant associations between the type of cytoreductive surgery (primary versus interval) and several clinical and perioperative parameters, namely age, total protein, albumin level, length of hospital stay, and operative time, as reflected by the following findings:

- Statistically significantly higher mean values of total protein and albumin in patients with interval surgery;
- Significantly greater mean hospital stay and operative time in patients with primary surgery;
- The differences between the two groups in terms of mean age and the preoperative-to-postoperative changes in hemoglobin and hematocrit levels were not statistically significant.

Table 18: Analysis of the relationship between the type of cytoreductive surgery and age, total protein, albumin, length of hospital stay, operative time, and preoperative-to-postoperative changes in hemoglobin and hematocrit levels

Indicator	**Type of cytoreductive surgery**						**P**
	PCS			ICS			
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Age (years)	87	59,61	11,34	60	57,55	9,73	0,264
Total protein (gL)	87	57,42	9,47	60	64,69	8,52	**<0,001**
Albumin (gL)	87	31,46	6,07	60	35,47	5,59	**<0,001**
Hospital stay during surgery (months)	87	9,05	3,27	60	6,65	1,91	**<0,001**

Operative time during surgery (minutes)	87	222,64	71,62	60	122,33	47,63	**<0,001**
Hb dynamics	87	-9,08	14,28	60	-5,10	13,91	0,176
Hct dynamics	87	-0,02	0,05	60	-0,02	0,03	0,714

Analysis of the association between the type of cytoreductive surgery and the presence and localization of residual tumor, histological tumor subtype, tumor grade, and FIGO stage revealed statistically significant relationships only for the presence and localization of residual tumor, as demonstrated by the following findings (Table 19):

- Significantly higher proportion of primary cytoreductive surgery in the presence of residual tumor size ≥ 1 cm;
- Significantly higher percentage of primary cytoreductive surgery in residual tumor localized to the peritoneum of the Douglas pouch, anterior rectal wall, and residual tumors with multiple localizations.

Analysis of the association between the type of cytoreductive surgery and intraoperative and early postoperative complications, as well as blood transfusion, revealed a statistically significant relationship only for blood transfusion. Blood transfusion was significantly more frequent among patients undergoing primary cytoreductive surgery (p=0,009).

Table 19: Analysis of the association between the type of cytoreductive surgery and the presence and extent of residual tumor

Indicator	Cytoreductive surgery				P
	Primary cytoreductive surgery		Interval cytoreductive surgery		
	n	%	n	%	
Residual tumor					0,013
No	46	52,9	39	65,0	0,146

Under 1 cm	17	19,5	16	26,7	0,305
≥ 1 cm	24	27,6	5	8,3	0,004

Median and OS by type of cytoreductive surgery (primary or interval) in patients with FIGO stage IIIC and IV.

The applied Log Rank, Breslow and Tarone-Ware tests assessed the difference ($p>0.05$) in the survival of patients from the considered groups with primary and interval surgery as insignificant (Table 20).

Table 20: Median survival and 95% confidence interval by type of cytoreductive surgery

Type of cytoreductive surgery	**Number of events that occurred**	**Median survival time* (months)**	**95% confidence interval**	
			Lower Bound	Upper Bound
Primary cytoreductive surgery	34	43,77[a]	39,22	48,32
Interval cytoreductive surgery	25	48,42[a]	41,60	55,23

PFS by type of cytoreductive surgery (primary or interval) in patients with FIGO stage IIIC and IV.

The Log-Rank, Breslow, and Tarone–Ware tests revealed no statistically significant difference ($p > 0.05$) in progression-free survival (PFS) between the groups under investigation (Table 21).

Table 21: Median recurrence-free survival and 95% confidence interval by cytoreductive surgery type

Type of cytoreductive surgery	**Number of events that occurred**	**Median survival time* (months)**	**95% confidence interval**	
			Lower Bound	Upper Bound
Primary cytoreductive surgery	65	22,97[a]	19,46	26,48

Interval cytoreductive surgery	49	26,73[a]	21,34	32,12

5.2 DISCUSSION

Despite advances in systemic therapy for OC, cytoreductive surgery remains a cornerstone of treatment, with the primary objective of achieving complete macroscopic tumor resection. Based on the timing of surgery in relation to systemic chemotherapy, cytoreductive surgery can be classified as either primary or interval cytoreductive surgery. In our study, the mean operative time was significantly longer in the primary cytoreductive surgery (PCS) group than in the interval cytoreductive surgery (ICS) group (222.64 vs. 122.33 minutes, respectively; $p < 0.001$). These findings are consistent with those reported by Markauskas et al., who observed a mean operative time of 210 minutes in the primary surgery group compared with 150 minutes in the interval surgery group ($p < 0.001$) (350). We also found a significantly shorter hospital stay in the ICS group, 6.65 days, compared with the hospital stay in the PCS group, which was 9.05 days ($p<0.001$). Ahmad et al. described a similar trend with a mean hospital stay in the PCS group of 8.11 days (SD 2.05) and in the ICS group of 7.69 days (SD 10.75)(6). To measure intraoperative blood loss, we examined the dynamics of hemoglobin and hematocrit pre- and postoperatively and found that it was statistically insignificant in both groups. These results differ from those found in most studies (350,625,195), which indicate greater blood loss in the primary surgery group. Supporting our findings is a meta-analysis of three studies (Fagotti 2016; Kehoe 2015; Vergote 2010) evaluating 1264 participants, describing little or no difference in the risk of bleeding with PCS or ICS (RR = 0.93, 95% CI 0.50 to 1.74; $I2 = 69\%$; low-certainty evidence). Another statistically significant association identified in our analysis was the higher mean levels of total protein and albumin among patients undergoing interval cytoreductive surgery (ICS) compared with those undergoing primary cytoreductive surgery (PCS) (p <

0.001). These findings are consistent with the results reported by Ghirardi et al., who demonstrated improved clinical outcomes in patients following 3–4 cycles of neoadjuvant chemotherapy of NACT: an increase in the incidence of ECOG = 0 (53.3% vs. 81.8%; $p < 0.001$) and mean serum albumin levels (3.0 g/dl vs. 4.0 g/dl; $p < 0.001$)(193). The most important outcomes, which are also the primary endpoints of most studies comparing PCS with ICS, are PFS and OS. Although there are variations in the results, in the majority of studies no statistically significant difference between the two groups was found. Vergote et al. demonstrated an OS of 29 months in patients undergoing PCS, compared with 30 months in patients treated with NACT and subsequent ICS. In the analysis of Onda et al. the described OS was 49.0 months in the PCS group and 44.3 months in the ICS group (412), and in the scientific study by Fagotti et al. - 41 months compared to 43. Our analysis shows similar results - median OS 43.77 months in the PCS group and 48.42 in the ICS group, with slightly better results observed for the median PFS indicator - 22.97 months in the PCS group and 26.73 months in ICS. When interpreting the available information, the latest published randomized clinical trial by Mahner et al. should also be taken into account, who also found no difference in median OS (54.3 months compared to 48.3), but described a statistically significant difference for the median PFS indicator (342). At this stage, it can only be stated with certainty that ICS is a possible alternative to PCS in cases where achieving R0 resection during PCS is impossible. In all other cases, primary cytoreductive surgery (PCS) remains the preferred approach and the current gold standard, with the primary surgical objective being complete macroscopic tumor resection and, consequently, the absence of visible residual disease.

6. Comparative analysis of perioperative indicators: operative time, hospital stay, blood loss and postoperative complications in patients who underwent minimally invasive interval surgery and open interval surgery.

6.1. OWN RESULTS

The analysis of the association between the type of interval cytoreductive surgery and patient age, total protein and albumin levels, length of hospital stay, operative time, and preoperative-to-postoperative changes in hemoglobin and hematocrit demonstrated the following findings (Table 22):

- The mean length of hospital stay and operative time were statistically significantly higher among patients undergoing open interval cytoreductive surgery.
- No statistically significant differences were observed between the two groups with respect to the mean values of the remaining parameters analyzed

Table 22: Analysis of the association between the type of interval cytoreductive surgery and patient age, total protein and albumin levels, length of hospital stay, operative time, and preoperative-to-postoperative changes in hemoglobin and hematocrit levels

Indicator	**Type of interval surgery**						**P**
	Minimally invasive			Open			
	n	$\overline{X}$	SD	n	$\overline{X}$	SD	
Age (years)	30	57,30	9,09	30	57,80	10,47	0,778
BMI (kg/m^2)	30	25,62	7,02	30	23,24	4,33	0,132
Total protein (gL)	30	64,40	9,38	30	64,99	7,72	0,793
Albumin (gL)	30	35,58	6,65	30	35,36	4,38	0,880
Hospital stay during surgery (days)	30	5,27	0,58	30	8,03	1,77	**<0,001**
Operative time during surgery (minutes)	30	96,50	31,24	30	148,17	47,53	**<0,001**
Hb dynamics	30	6,10	7,89	30	4,10	18,15	0,859
Hct dynamics	30	0,02	0,03	30	0,02	0,04	0,698

6.2. DISCUSSION

The introduction of neoadjuvant chemotherapy, which reduces tumor spread before surgery, has made it possible to use minimally invasive surgery in the treatment of advanced ovarian cancer. In order to improve perioperative parameters and thereby shorten the interval to the start of adjuvant chemotherapy, many studies have examined the feasibility and safety of minimally invasive interval surgery in selected patients over the past few decades (342). There are still no clear criteria to determine which patients are suitable for MIS. Available data in the literature show that minimally invasive ICS can be applied not only in patients with a complete but also in those with a partial response to the therapy (150). The results obtained in our study show that the average hospital stay in patients operated on by MIS is 5.27 days, and in those treated by OS, it is 8.03 days - a difference that is statistically significant ($p<0.001$). In a meta-analysis by Holzen et al., including 14 studies with more than 16,000 patients, a shorter operative time was also reported in the MIS group (3 days compared with 5 days; SMD −0.79, 95% CI [−1.06, −0.52], $p \leq 0.001$) (584). Statistical analysis of our data demonstrated that the mean operative time was significantly shorter in patients undergoing minimally invasive surgery (MIS) than in those undergoing open surgery (OS) (96.50 vs. 148.17 minutes, respectively; $p < 0.001$). In contrast, Brown et al., in a retrospective cohort study, reported a longer mean operative time in the MIS group compared with the OS group (171 compared with 150 minutes, $p = .007$) (57). Van Trappen et al. also found that the mean operative time was significantly longer in patients operated on by robot-assisted surgery compared with patients operated on by OS (159 minutes versus 105 minutes, $p=.0004$) (572). Although we found a twofold higher rate of blood transfusions in the OS group, these results did not reach statistical significance ($p=.299$). No such differences were found for the dynamics of preoperative and postoperative hemoglobin ($p=.859$) and hematocrit ($p=.698$). These results differ from those described by Brown et al., who found a statistically significant lower rate of blood transfusions (p=.006) in the MIS group (2% or 1/53) compared with OS (17% or 18/104). The authors also found significantly less blood loss in the MIS group (156 ml vs. 278 ml, p < 0,001)(57).

7. Comparison of overall survival and disease-free survival in patients undergoing interval cytoreductive surgery by minimally invasive versus open surgical approach

7.1. OWN RESULTS

Analysis of the association between the type of interval surgery and the presence and localization of residual tumor revealed no statistically significant differences between the minimally invasive and open surgery groups.

Average and overall survival of patients according to the type of interval surgery

The Log-Rank, Breslow, and Tarone–Ware tests demonstrated no statistically significant difference (p > 0.05) in overall survival between patients undergoing the two types of interval surgery (Table 23).

Table 23: Median survival and 95% confidence interval by type of interval surgery

Type of interval surgery	**Number of events that occurred**	**Median survival time* (months)**	**95% confidence interval**	
			Lower Bound	Upper Bound
Minimally invasive	12	49,08[a]	39,45	58,71
Open	13	40,72[a]	34,64	46,80

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

PFS according to the type of ICS

The Log-Rank, Breslow, and Tarone–Ware tests revealed no statistically significant difference ($p > 0.05$) in progression-free survival (PFS) between patients undergoing the two types of ICS (Table 24).

Table 24: Median progression-free survival and 95% confidence interval by type of interval surgery

Type of interval surgery	Number of events that occurred	Median survival time* (months)	95% confidence interval	
			Lower Bound	Upper Bound
Minimally invasive	22	29,41[a]	20,51	38,32
Open	27	22,53[a]	18,08	26,98

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

7.2. DISCUSSION

One of the most important prognostic factors regarding the survival of patients with OC is the cytoreductive status. For this reason, it has been considered in almost all research studies comparing oncological outcomes in patients operated on using minimally invasive or open ICS. In our study, no statistically significant difference was found in the type of cytoreduction achieved (complete, optimal and suboptimal), as well as in the localization of residual tumor between the two groups of studied patients. A large part of the literature data also supports these results. In the meta-analysis by Zeng et al. the authors demonstrated that the rate of achieving complete cytoreduction in the OS group was not statistically higher than in the control group (RR = 1.07; 95% CI = 0.93 to 1.23; heterogeneity: P = 0.098, I2 = 52.3%), and that there were no significant differences in the rate of optimal cytoreduction between the two groups of patients (RR = 1.08; 95% CI = 0.91 to 1.28; heterogeneity: P = 0.330, I2 = 12.6%) (620).

Statistical analysis revealed no statistically significant difference ($p > 0.05$) in overall survival between patients undergoing the two types of interval surgery. The median survival was 49.08 months in the minimally invasive surgery (MIS) group and 40.72 months in the open surgery (OS) group. Jorgensen et al. reported a similar median OS to that presented in our analysis - 46.7 months in the MIS group and 41 in the OS group [HR 0.86 (95%CI 0.79-0.94)], while demonstrating that the probability of 5-year survival was higher with MIS compared with laparotomy (38.3% vs. 34.8%, $p < 0.01$) (584). The results obtained in our study also showed a non-significant difference ($p>0.05$) in the PFS of patients with both types of interval surgery, with the median PFS in the MIS group being 29.41 months and that in the open ICS group being 22.53 months. Alletti et al. similarly reported that patients undergoing minimally invasive interval cytoreductive surgery (ICS) had significantly longer progression-free survival than those undergoing open surgery (OS). However, this difference did not remain statistically significant after adjustment for potential confounding factors in the multivariate analysis (217). Based on the findings discussed above, it can be concluded that one of the most important and yet unresolved issues concerning minimally invasive interval cytoreductive surgery (ICS) is the appropriate selection of patients who may benefit from a minimally invasive approach. Conte et al. created a nomogram to predict the success rate of minimally invasive ICS in patients with advanced ovarian cancer. After examining multiple factors, the authors considered that normalization of CA125, a surgeon with extensive experience in cytoreductive surgery for advanced ovarian cancer, the absence of an omental “cake,” and involvement of two or fewer peritoneal areas were predictors of the possibility of performing minimally invasive ICS (99). Given the guiding role of tumor markers and preoperative imaging, the final decision on the surgical approach is often made during laparoscopic abdominal examination. Considering the favorable perioperative outcomes and comparable oncological results observed in our analysis, we believe that, in the absence of increased surgical or oncological risk, patients in whom optimal cytoreduction can be achieved through a minimally invasive approach may appropriately undergo endoscopic surgery.

8. Assessment of BRCA1 and BRCA2 mutation prevalence and HRD status, and evaluation of their prognostic significance in patients with high-grade ovarian carcinoma.

8.1. OWN RESULTS

Fig. 7 shows that with regard to the BRCA mutation test:

- The largest relative share (60.8%) are the untested, followed by patients without mutations in the BRCA genes with 28,7%;
- Patients with a BRCA1 mutation accounted for 7.8% of the total study population, while those with a BRCA2 mutation represented the smallest proportion, at 2.6%.

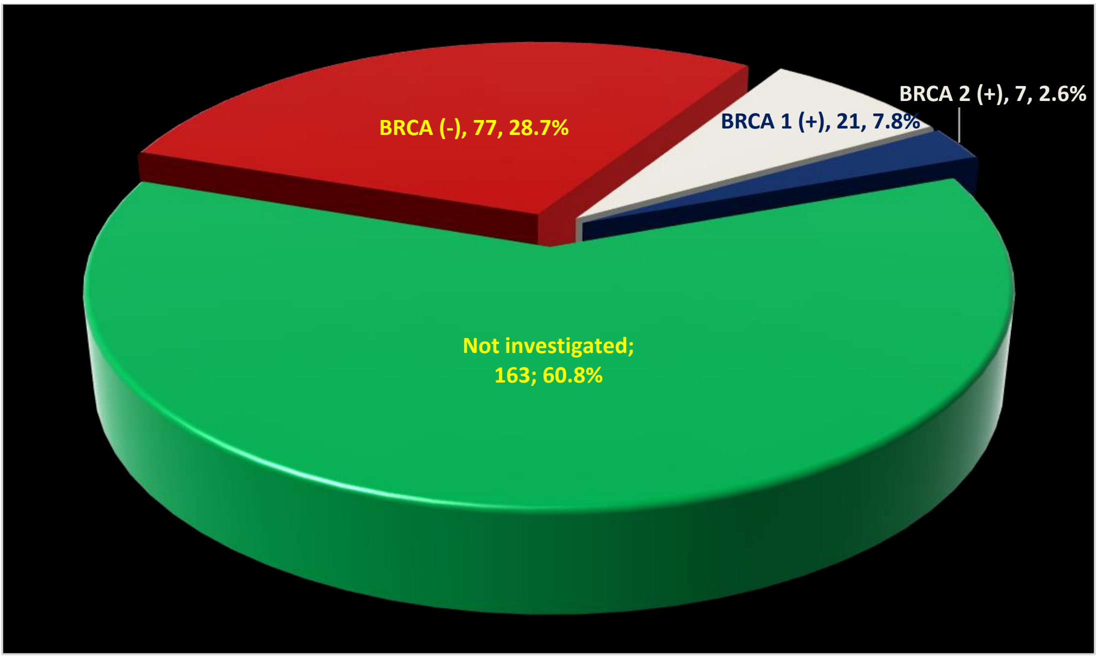


Figure 7. Distribution of patients according to BRCA mutation testing status

- Among all patients included in the study, 105 (39.2%) underwent testing for BRCA mutations. Of those tested, 21 patients (20.0%) were found to carry a BRCA1 mutation, while 7 patients (6.7%) carried a BRCA2 mutation.

According to the available data, the most frequently identified BRCA1 mutation was c.5266dup (p.Gln1756ProfsTer74), detected in 9 patients (3.4% of the total study population), with an overall allele frequency of 0.7869%. A total of 22 BRCA1 mutations were identified, whereas only seven BRCA2 mutations were detected, each occurring as a single case.

Analysis of the relationship between patients' BRCA status and age.

- Patients without BRCA gene mutations had a significantly higher mean age compared with both patients who had not undergone BRCA testing and those with a BRCA1 mutation. No statistically significant difference in mean age was observed between the untested patients and those with a BRCA1 mutation (Table 25).

Table 25: Relationship between BRCA mutations and age

BRCA mutations	Age (years)		
	n	$\overline{X}$	SD
No	163	56,19[a]	12,37
BRCA (-)	77	60,32[b]	11,11
BRCA 1 (+)	21	54,33[a]	10,64
BRCA 2 (+)✦	7	63,71	9,23

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

✦ - Not included in the analysis due to lack of statistical representativeness.

Relationship between BRCA status and OS

The Log Rank, Breslow and Tarone-Ware tests showed a non-significant ($p>0.05$) difference in OS of patients according to BRCA status.

Relationship between BRCA mutations and PFS

The applied Log Rank, Breslow and Tarone-Ware tests showed a non-significant ($p>0.05$) difference in PFS of patients according to BRCA status.

31 patients (11.6%) were examined for HRD. Of these, 15 or 5.6% had HRD, and 16 or 6.0% had no HRD (approximately equal proportion) (Fig. 8).

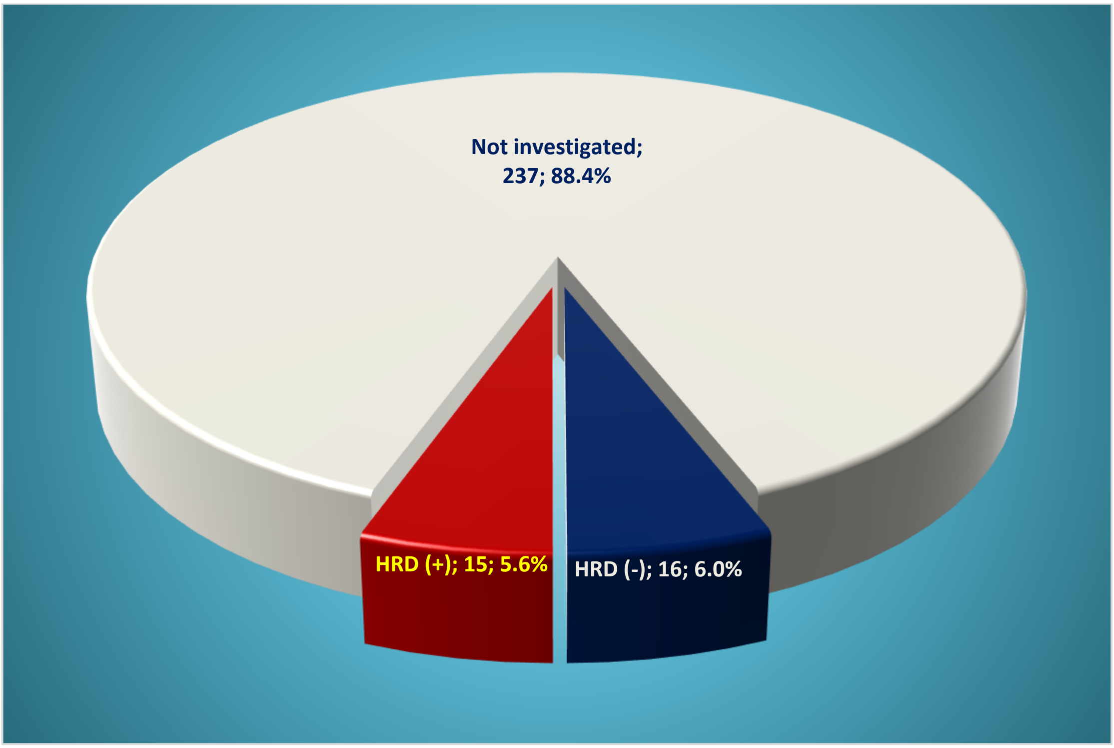


Figure 8: Frequency distribution of patients with homologous recombination deficiency

Ten or 66.7% of those positive for HRD are also positive for BRCA mutations.

8.2. DISCUSSION

Our analysis demonstrated a BRCA1 mutation rate of 20.0% and a BRCA2 mutation rate of 6.7%. Notably, all patients included in the analysis had histologically confirmed high-grade ovarian carcinomas. The study by Fumagalli et al. shows similar results to ours, as BRCA mutations in the tumor tissue of patients with OC were identified in 28.1% of cases (168). In the retrospective analysis by McCuaig et al. this percentage is 21.3% (361). However, the studies are unambiguous in the opinion that in patients with OC, cases with mutations in the BRCA1 genes prevail, compared to BRCA2. Peng et al. reported an overall frequency of pathogenic or likely pathogenic BRCA mutations of 26.6%, with BRCA1 and BRCA2 mutations accounting for 20.8% and 5.5%, respectively. Concurrent mutations in both BRCA1 and BRCA2 were identified in 0.3% of patients (434). According to our data, the most common mutation in the BRCA1 gene is c.5266dup,pGln1756ProfsTer74 – in 9 (3.4% of patients in the study sample) or 45.0% of cases with mutations in the BRCA1 gene. The c.5266dup mutation is also the most common in the study by Jasiewicz et al., accounting for over 50% of BRCA1 mutations (264). It is also the most common mutation in the analysis by Kluz et al. (289), considering that both refer to the Polish population. Other authors have also demonstrated that in patients with HGSC of Slavic origin, a high frequency of the mutation in the BRCA1 gene c.5266dupC (5382insC) is observed (334,371). The spectrum of mutations in BRCA1 and BRCA2 varies significantly between different populations. Regional and ethnic differences influence both the frequency and the type of mutations observed. For example, specific "founder" mutations such as c.5266dupC are common in Eastern European populations, while various recurrent variants predominate in Asian cohorts. Regarding BRCA2 pathogenic variants, a striking example of a founder mutation is observed in Iceland, where a single mutation in BRCA2 (999del5) explains practically all families with breast/ovarian cancer (554,133). Our study demonstrated a significantly higher mean age in patients without mutations in the BRCA genes compared to those with a mutation in the BRCA1 gene. A younger age at diagnosis of OC in patients with BRCA1 gene mutations has been confirmed by several studies. Cummings et al. reported a mean age of 53 years for BRCA1 variant carriers and 59 years for BRCA wild-type patients (105). In our study, the mean age of BRCA1 mutation carriers was 54.33 years and that of BRCA wild-type patients was 60.32 years. As a subsequent step in the analysis, we compared cytoreductive outcomes in patients with and without BRCA mutations and found no statistically significant difference between the two groups (p=0.367). Hyman et al. reported that complete cytoreduction was achieved in 84.1% of patients with BRCA mutations compared with 70.1% of patients with BRCA wild-type. However, after multivariate adjustment, the authors found that BRCA status was not independently associated with cytoreductive status. Given our results and the fact that the data in the literature supporting this thesis are more convincing, we believe that, although the prognostic value of BRCA status cannot be completely denied, it is more related to the response to platinum-based chemotherapy and the use of PARP inhibitors than to cytoreductive results after surgical treatment. Therefore, the next methodologically appropriate step in our study was to evaluate the association between BRCA mutation status and both overall survival and progression-free survival. Although patients with BRCA-positive tumors demonstrated longer overall survival (OS) than those with BRCA-negative tumors (58.51 vs. 40.13 months, respectively), as well as longer progression-free survival (PFS) (37.03 vs. 26.81 months, respectively), neither difference reached statistical significance (p>0.05). Lee et al. also found no statistically significant difference in oncological outcomes between the two groups (308). This was not demonstrated in the analysis of Kim et al. (284) and De Jong et al. (109). Homologous recombination is a critical DNA repair mechanism responsible for the accurate repair of DNA double-strand breaks. Tumors with HRD have a reduced ability to repair DNA damage induced by platinum agents and are particularly vulnerable to PARP inhibition through the mechanism of synthetic lethality. This makes HRD testing an important part of the modern therapeutic approach in OC, especially in advanced disease, where PARP inhibitors are indicated. Assessment of homologous recombination deficiency (HRD) in the patients included in the present study commenced in May 2020, with a total of 31 patients included in the analysis. Of these, 48.4% had homologous recombination deficiency. In the phase III PRIMA clinical trial conducted by González-Martín et al., 373 of the 733 randomized patients (50.9%).

V. CONCLUSIONS

Early stage of ovarian cancer:

- Operative time and postoperative hospital stay are statistically significantly shorter with the minimally invasive surgical approach compared to open surgery.
- Patients operated on through minimally invasive surgery are less likely to need blood transfusions.
- No significant difference was found in operative time and blood loss between patients operated on using laparoscopic and robotic surgery.
- No statistically significant difference in overall survival and disease-free survival was observed between the minimally invasive and open surgical approaches.
- There is no significant difference between laparoscopic and robotic surgery in terms of oncological outcomes overall survival and disease-free survival.
- LGSC and HGSC are the histological variants in which bilateral ovarian involvement is most commonly observed.
- Risk factors for capsule rupture in patients with early-stage ovarian cancer include obesity, tumor size greater than 10 cm, and the presence of adhesions.

- No association was found between the type of surgical approach—minimally invasive or open surgery—and the incidence of intraoperative tumor capsule rupture.

Advanced stage OC

- Low serum albumin levels at diagnosis of advanced ovarian cancer are a statistically significant independent predictor of poorer overall survival.
- Patients who achieve complete cytoreduction have statistically significantly better oncological outcomes than those with optimal or suboptimal cytoreduction.
- The inclusion of diagnostic laparoscopy in the triage of patients with advanced ovarian cancer reduces the cases with optimal and suboptimal cytoreductive results achieved.
- Interval cytoreductive surgery is associated with shorter operative times, reduced postoperative hospital stays, and higher serum albumin levels.
- Patients undergoing interval cytoreductive surgery have a significantly higher likelihood of achieving complete macroscopic (R0) resection compared with those undergoing primary cytoreductive surgery.
- No statistically significant differences in oncological outcomes were observed between patients undergoing primary and interval cytoreductive surgery, with regard to median overall survival and median progression-free survival.
- Minimally invasive interval cytoreductive surgery is associated with a significantly shorter mean postoperative hospital stay compared with open interval cytoreductive surgery.
- The incidence of perioperative complications does not differ significantly between patients undergoing minimally invasive cytoreductive surgery and those undergoing the open surgical approach.

- The rate of complete cytoreduction and the localization of residual tumor are not significantly influenced by the surgical approach, whether minimally invasive or open interval cytoreductive surgery.
- The type of interval cytoreductive surgery—minimally invasive or open—was not significantly associated with differences in overall survival or disease-free survival.
- In patients with ovarian cancer, cases with mutations in the BRCA1 genes predominate, compared to BRCA2.
- Among carriers of pathogenic variants in the BRCA1 genes in the Bulgarian population, the c variant has the highest frequency c.5266dupC, p.(Gln1756Profs*74).
- Mutations in BRCA2 exhibit greater variability both in terms of their distribution.
- Carrying a pathogenic variant in the BRCA1 gene is associated with an earlier age at diagnosis of ovarian cancer.
- HRD is found in a significant proportion of patients with OC, comprising approximately half of the studied population.

VI. CONTRIBUTIONS

1. Scientific-theoretical

- For the first time in Bulgaria, a systematic study of the frequency of BRCA1/2 mutations and HRD in patients with advanced high-grade ovarian cancer, as well as their association with basic clinicopathological characteristics, has been conducted.

2. Scientifically practical

- A clinical-epidemiological study was conducted, covering 268 patients with ovarian carcinoma, operated on at the University Hospital "St. Marina - Pleven" in the period 01.2020 - 04.2023.

- The dissertation systematizes the minimally invasive diagnostic and surgical interventions applicable to patients with early and advanced ovarian carcinoma, outlining their role in the diagnostic algorithm, assessment of resectability, and surgical treatment.
- A comparative analysis of the perioperative and oncological outcomes of laparoscopic and open surgical approaches in patients with early-stage ovarian carcinoma demonstrated significant perioperative advantages of laparoscopy, while no statistically significant differences in oncological outcomes were observed between the two groups.
- Factors associated with intraoperative tumor capsule rupture in patients with early-stage ovarian carcinoma were evaluated, and its impact on oncological outcomes was assessed.
- The role and significance of diagnostic laparoscopy within the triage algorithm for patients with advanced ovarian carcinoma were established, particularly for assessing tumor resectability, guiding the choice of primary treatment strategy, and optimizing subsequent therapeutic management.
- A comparative analysis of the perioperative and oncological outcomes of primary and interval cytoreductive surgery demonstrated certain perioperative advantages of interval surgery, while oncological outcomes were comparable between the two approaches.
- A comparative analysis of operative and oncological outcomes in patients undergoing open versus minimally invasive interval cytoreductive surgery demonstrated the safety, feasibility, and perioperative advantages of the minimally invasive approach in appropriately selected patients.

Declaration of originality:

The author of this dissertation declares that all data presented herein are original and were obtained through his research conducted at the Medical University of Pleven and University Hospital St. Marina – Pleven. The results, discussions, and conclusions are the author's own work and have not been reproduced or derived from other sources without appropriate citation.

Declarant: Dr. Teodora Krasimirova Semova

VII. PUBLICATIONS AND SCIENTIFIC COMMUNICATIONS RELATED TO THE DISSERTATION

PUBLICATIONS IN JOURNALS:

1. Semova T, Tomov S, Totev T, Dimitrov D, Gorcheva Z, Racheva V (2024) The role of minimally invasive surgery in the diagnosis and treatment of ovarian carcinoma. Journal of Biomedical and Clinical Research 17(2): 205-218. https://doi.org/10.3897/jbcr.e138141

2. T. Semova, D. Dimitrov, N. Hinkova, M. Vasileva, E. Petkova, Synchronous primary tumors of the endometrium and ovary: a retrospective single-center study. Bulgarian Medical Journal, 2024, 18(4), 42-50.

3. Racheva, V., I. Dekova, Z. Gorcheva, T. Semova, D. Dimitrov, E. Petkova "The Role of Albumin-To-Fibrinogen and Fibrinogen-To-Prealbumin Ratios in the Development of Ovarian Carcinoma" Acta Medica Bulgarica, vol. 52, no. 1, Sciendo, 2025, pp. 41-47. https://doi.org/10.2478/amb-2025-0006.

SCIENTIFIC COMMUNICATIONS:

ABROAD

1. Robotic interval debulking surgery for advanced epithelial ovarian cancer - 17th SERGS Annual meeting, 05-07.06.2025, Pisa, Italy

IN BULGARIA

1. Family history, clinical course and relapse-free period in patients tested for BRCA1 and BRCA2 mutations - XXIV National Conference on Gynecological Oncology, October 6 - 9, 2022, Hisarya

2. Surgical anatomy and types of surgical interventions in ovarian tumors - XXIV National Conference on Gynecological Oncology, October 6 - 9, 2022, Hisarya

3. Synchronous primary carcinomas of the ovary and endometrium – frequency, epidemiology, diagnostic criteria, prognosis. - 25th National Conference on Gynecological Oncology, October 19 - 22, 2023, Razlog

4. Place and role of minimally invasive approaches in the diagnosis and treatment of ovarian carcinoma - First National Conference of the Bulgarian Association for Minimally Invasive and Robotic Surgery (BAMIRS), 10-12.05.2024, Pleven

5. Surgical approach in patients with ovarian carcinoma and endometrial carcinoma - Second National Congress of the Bulgarian Association for Minimally Invasive and Robotic Surgery (BAMIRS), 19-21.06.2025, Pleven

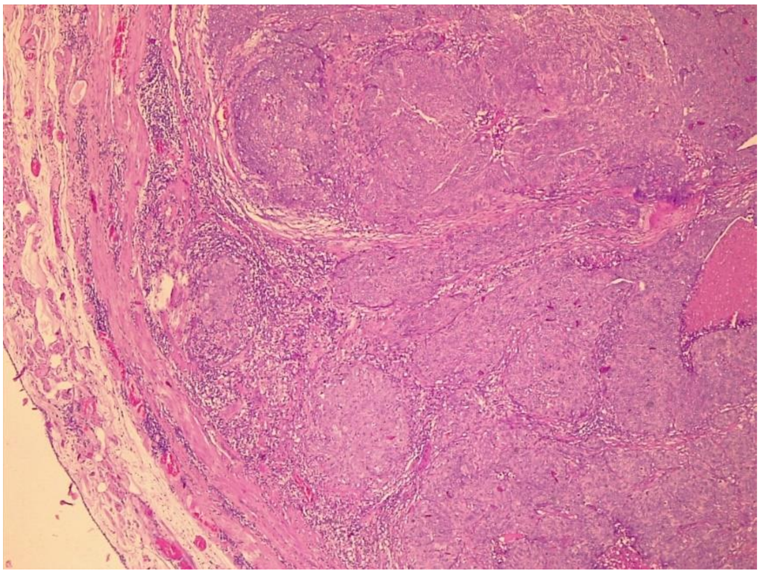
6. Intraoperative capsule rupture in patients with early stage ovarian carcinoma – risk factors and prognosis - 27th National Conference on Gynecological Oncology, 16 – 19.10. 2025, Razlog

7. Robotic interval debulking surgery for advanced epithelial ovarian cancer - INTERNATIONAL SCIENTIFIC WORKSHOP ON SURFACE ENGINEERING FOR BIOMEDICAL APPLICATIONS – 17-21.03.2026, Borovets

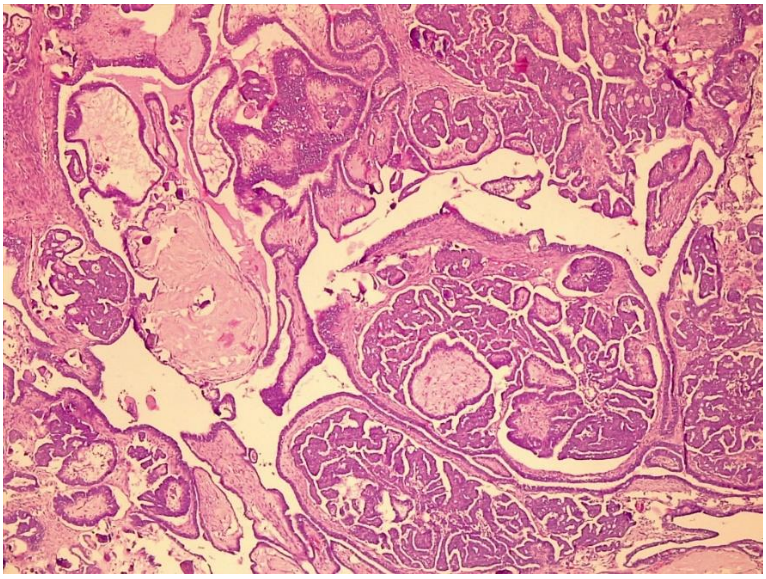
PARTICIPATION IN RESEARCH PROJECTS:

1. Participation in research project No. D9/2023 on the topic "Immunohistochemical study of the tumor suppressor gene ARID 1A in clear cell carcinoma of the ovary.

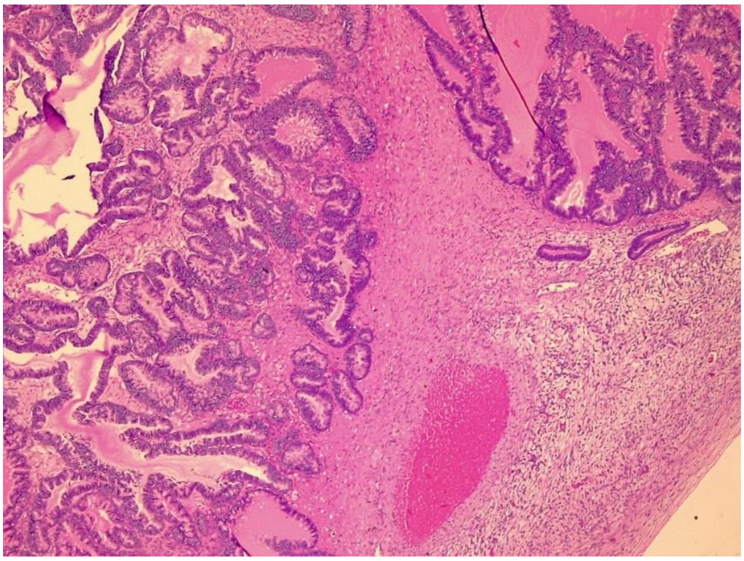
VIII. ANNEXES



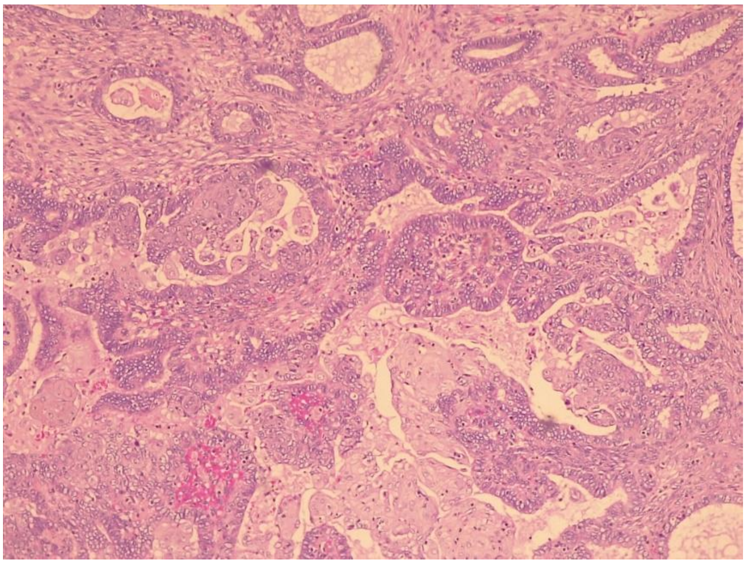
Appendix 1 – High-grade serous carcinoma



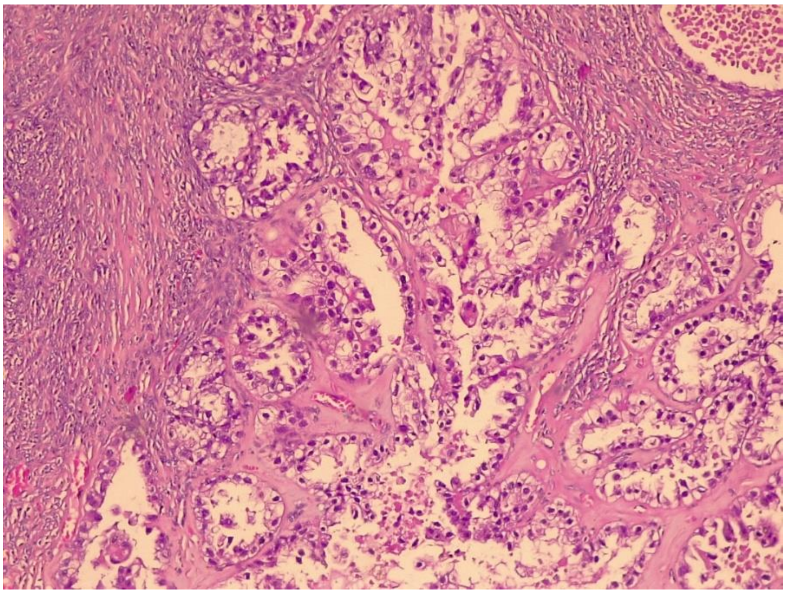
Appendix 2 – Low-grade serous carcinoma



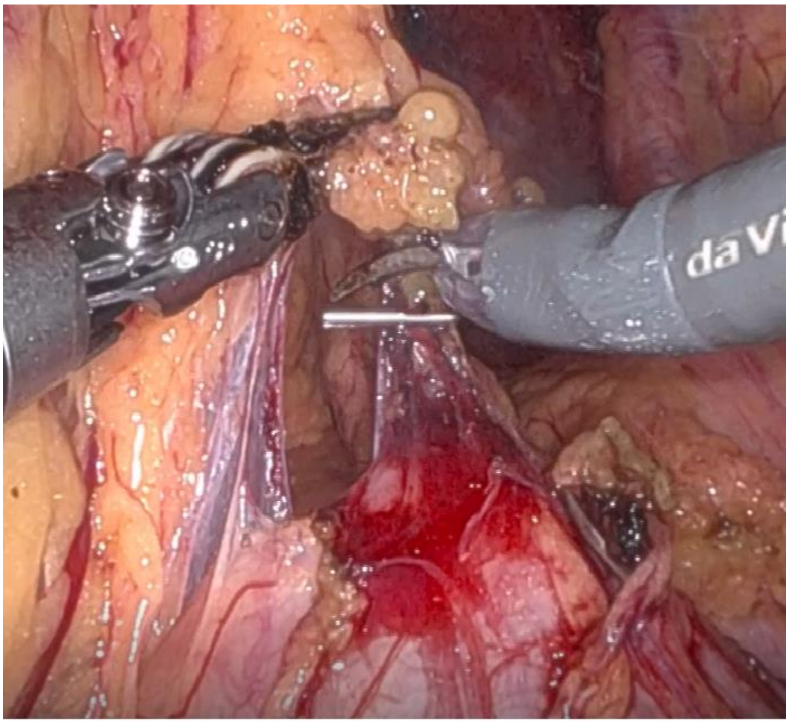
Appendix 3 – Mucinous carcinoma



Appendix 4 – Endometrioid carcinoma

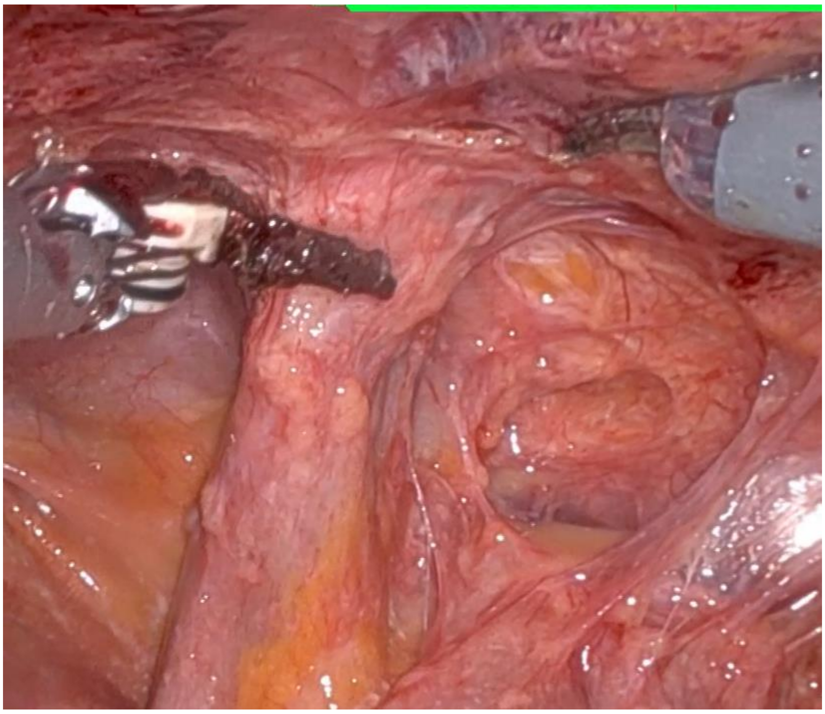


Appendix 5 – Clear cell carcinoma



Appendix 6 – Robot-assisted infracolic omentectomy (our material)

Appendix 7 – Laparoscopic excision of peritoneal metastasis (our material)



Appendix 8 – Adhesion syndrome after neoadjuvant chemotherapy (our material)