Medical university – Varna

Departement Obstetrics and Gynaecology

The abstract of the dissertation for the degree

Doctor of science

in speciality "Obstetrisc and Gynaecology"

of

Ass.prof. Dr. Elis Hyudaim Ismail, MD, Ph.D.

“Lympho vascular space involvement in patients with I FIGO stage endometrial endometroid carcinoma.”

Varna, 2019

Summary

In the USA, endometrial cancer is the most common gynecological practice, with 54,870 new cases diagnosed in 2015. This high prevalence is also evident in many other countries. Endometrial cancer is the 14th most common cancer in the world. In 2012, 320,000 new cases were diagnosed. There are several risk factors for this disease, some of which are obesity and old age. As the world faces an epidemic of obesity and an aging population, the number of cases is expected to increase. Therefore, the importance of determining appropriate treatment for women with uterine cancer is paramount for optimizing cancer outcomes, reducing costs and improving quality of life.

Surgical staging as a part of the treatment paradigm for endometrial cancer was first supported by the findings of large prospective surgical and pathological studies of endometrial cancer patients in clinical stage I and II conducted by the Gynecologic Oncology Group (GOG). Ectopic disease, including pelvic and para-aortic lymphatic metastases, is relatively common in this study. The risk of lymph node metastases is associated with the ultimate differentiation of the tumor and the depth of myometrial invasion, as established by the International Federation of Gynecology and Obstetrics (FIGO). The GOG study was the first to determine the incidence of pelvic and para-aortic lymphatic metastases.

Patients with tumors with different degrees of differentiation but limited in the endometrium or those with high-differentiation tumors entering less than the outer 1/3 of the myometrium have the lowest incidence of pelvic lymphatic metastasis (0-3 %); patients with invasion in the outer third of the myometrium have the highest percentage (11-34%). This is confirmed using the current FIGO staging system based on myometrial invasion less than or greater than 50%. These surgical findings led to a change in the staging system. In 1988, FIGO replaced an inaccurate clinical staging system with a more accurate surgical staging system, which was revised in 2009. The FIGO staging system continues to subdivide stage I disease based on the depth of myometrial invasion, and the disease affecting the lymph nodes is staged as a FIGO stage IIIC. However, in 2016, there is still no surgical standard for the care of women with endometrial cancer.

Uterine cancer is ranked fifth in the world among the most common malignancies in women. In 2008, 287,100 new cases of endometrial cancer were detected. In developed countries, uterine cancer ranks fourth and is among the most common malignancies in the female sex. In the United States, 43,470 new cases of endometrial cancer (EC) were diagnosed in 2010 and 7,950 deaths were reported (6). One of the major concerns for this disease is that its incidence has been relatively stable over the last decade and its mortality has doubled - 2,900 cases in 1987. Probably the reason for these statistics is multifactorial, but the reassessment of screening, diagnosis, staging and treatment are the mandatory processes that guide the overall management of this neoplasm. These reassessments are all the more important when considering that the EC staging and treatment algorithms are extremely variable and are usually based on institutional and individual medical philosophy, or both.

I. The aim of this study is

To present and assess the prognostic significance of tumor invasion in lymphatic and blood vessels in patients with endometrial endometroid carcinoma stage I according to FIGO.

II. Tasks

1. To determine the overall 5-year survival of patients from the study contingent.
2. Present disease-free 5-year survival to patients.
3. Determine the survival of patients with relapses after treatment.
4. To determine the localization of recurrences.
5. To establish the following histological parameters in the operated patients in the studied contingent: lympho-vascular invasion, depth of myometrial invasion above ½, G3 - differentiation of the tumor.
6. To determine the incidence of lymphatic metastases in patients with lymphoid dissection.
7. To determine the role of lymphatic dissection with respect to patient survival.
8. Determine the prognostic significance of postoperative radiation therapy for survival.
9. To determine by one-factor analysis the prognostic significance of adverse histological parameters: lympho-vascular invasion, MI above ½, G3.
10. To determine by prognostic analysis the prognostic significance of tumor invasion in lymphatic and blood vessels.

III. Materials and methods

1. Surgical method:

A) lymph node dissections:

- pelvic;
- paraaortic;

B) simple hysterectomy.

2. Histological examination and revision of operative preparations.

3. Radiation therapy.

4. Statistical methods.

5. Staging.

6. Follow up.

7. Data processing.

IV. Results

A retrospective clinical study was conducted for the period 2009-2014, involving 159 patients with endometrial cancer, treated and monitored at the Gynecology Clinic of St Anna - Varna AD and Oncology Center - Varna.

For a period of 6 years (01.01.2009 - 31.12.2014) 159 patients with endometrioid endometrial carcinoma in the first stage (data on patient epicrises) were operated at the Gynecology Clinic of St. Anna-Varna Hospital. . Patients have been diagnosed with prior abrasion testing or an accidental finding after hysterectomy for uterine prolapse.

All of these 159 patients were revised for post-operative preparations by two expert pathologists (working together).

As a result of the revision of the preparations, the diagnosis of endometrioid endometrial carcinoma in the first stage of FIGO was confirmed in 117 patients. The remaining 42/159 (26.42%) patients were different from the original diagnosis.

The study is retrospective.

As a result of the revision of the preparations, the diagnosis of endometrioid endometrial carcinoma in the first stage was confirmed in 117 patients. The remaining 42/159 (26.42%) patients were different from the original diagnosis. In 7/159 (4.40%) patients, revision of postoperative drugs showed adenomyosis, in 13/159 (8.18%) patients the post-trigeminal result was a lack of carcinoma (secretory endometrium or endometroid intraepithelial neoplasia without invasion), in 1 / 159 (0.67%) patient had glandular enometrial hyperplasia, 3/159 (1.87%) patients were diagnosed with carcinoma sarcoma, 15/159 (9.43%) patients were diagnosed with serous cancer, 1/159 (0.67%) patient with atypical hyperplasia, 1/159 (0.67%) patient with adenosquamous carcinoma and 1/159 (0.67%) patient

with squamous cell carcinoma of the mat of cancer. Due to a lack of criteria (first stage endometrioid endometrial carcinoma), 42/159 (26.42%) patients were dropped out for inclusion in the study (tabl. 1).

Table 1 – Dropped patients

Histopatological result	**Patients (n)**	**%**
Adenomiosis	7	4,40%
Lack of cancer	13	8,18%
Endometrial hyperplasia	1	0,67%
Carcinosarcomas	3	1,87%
Serous carcinoma	15	9,43%
Atypical hyperplasia	1	0,67%
Adenoscamous type	1	0,67%
Squamous cancer of the cervix	1	0,67%
Total	**42/159**	**26,42%**

The youngest patient diagnosed with endometrioid endometrial carcinoma was 41 years old, and the oldest was 86 years old. Patients in the group between 61-70 years have the highest relative share - 43 women (38.39%), followed by the age

group between 51-60 years, 26 women (23.21%), 23 (20.54%)) patients in the 71-80 age group, 17 (15.18%) in the 41-50 age group and 3 (2.68%) patients in the 81-90 age group.

The average age of the patients is 62 years (Fig. 1).

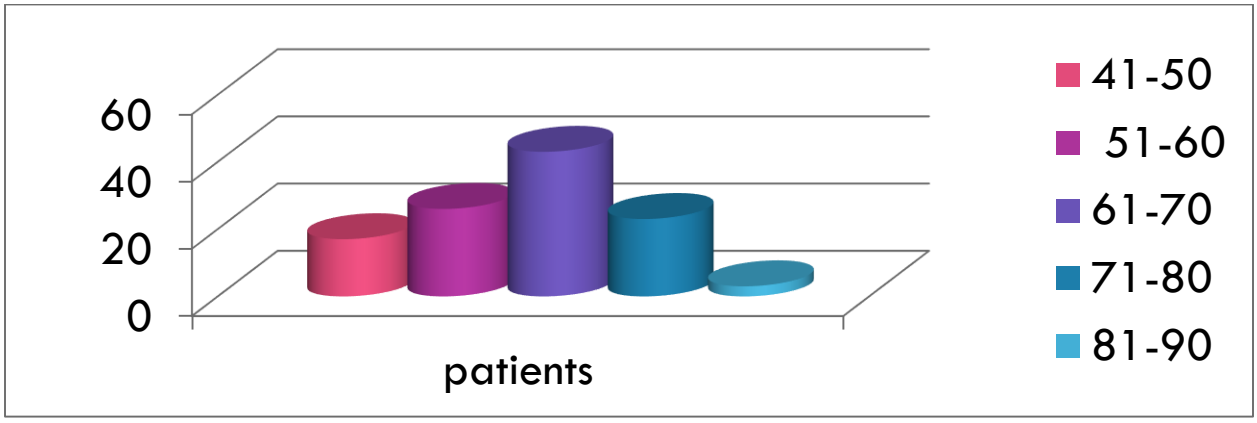

Figure 1 – Age of the patients

The remaining 117 patients were analyzed for the purpose and tasks of the thesis. The data from the personal files of the patients were kept, which are kept on Oncological hospital “Dr. Marko Markov" - Varna. Of the 117 patients in the first stage of endometrioid endometrial carcinoma, 27 have died and by March 2019, 90 patients are alive.

For 5 of the operated patients with the diagnosis of the first stage of endometrioid endometrial carcinoma no data were found in the system of the oncology hospital "Dr. Markov Markov" Varna, which was excluded from the study.

The total number of patients remaining after the revision of the postoperative drugs and the follow-up referral from the oncology center is 112.

IV. 1. Main clinical features

4.1.1. Grade:

After a revision of the postoperative preparations, 12/112 (10.71%) patients showed high tumor differentiation (G3), while the remaining 100 (89, 29%) patients had low to moderate tumor differentiation (fig. 2)

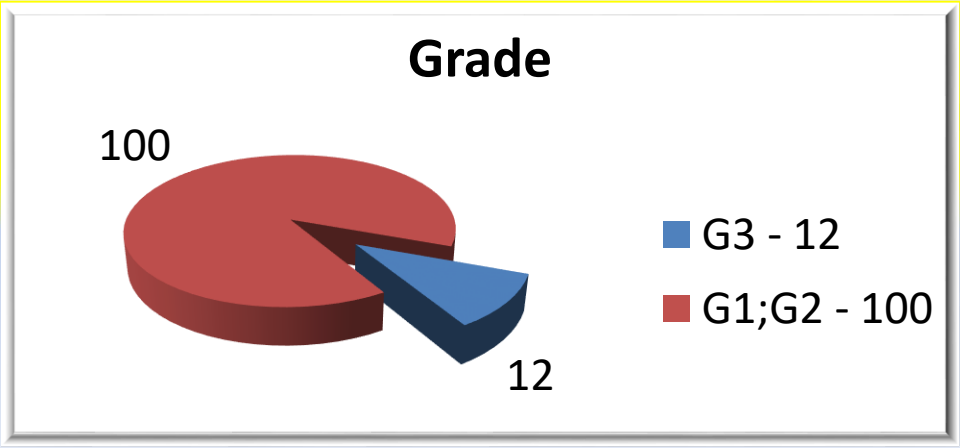

Figure 2 – Tumor grade

4.1.2. Myometrial invasion:

With the revision of the postoperative preparations, an evaluation of the invasion of the myometrium was evaluated, which was divided into tumor invasion of the myometrium below ½ and above ½. After analysis of the data, it was found that out of 112 patients, 35 (31.25%) had an invasion greater than ½ and 77 (68.75%) patients had a myometrial invasion less than ½ (tabl. 2) (fig. 3).

Table 2 – Myometrial invasion

Myometrial invasion	Patients (n) (%)
MI >1/2	35 (31,25%)
MI <1/2	77 (68,75%)

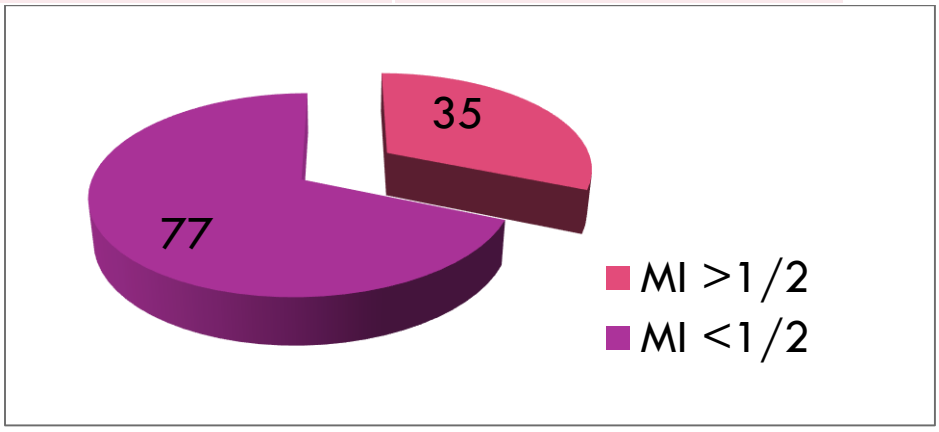

Figure - 3 Myometrial invasion of the patients

4.1.3. Lympho-vascular invasion:

The evaluation of LVSI in endometrial cancer is increasingly being promoted as a prognostic marker for recurrence. An LVSI evaluation was also performed in our clinical trial. Of 112 patients with endometrioid endometrial carcinoma in the first stage, 14 (12.50%) patients had LVSI and 98 (87.5%) had no LVSI (tabl. 3).

Table 3 – Lympho vascular space involvement

LVSI	Patients (n) (%)
LVSI (+)	14 (12,50%)
LVSI (-)	98 (87,5%)

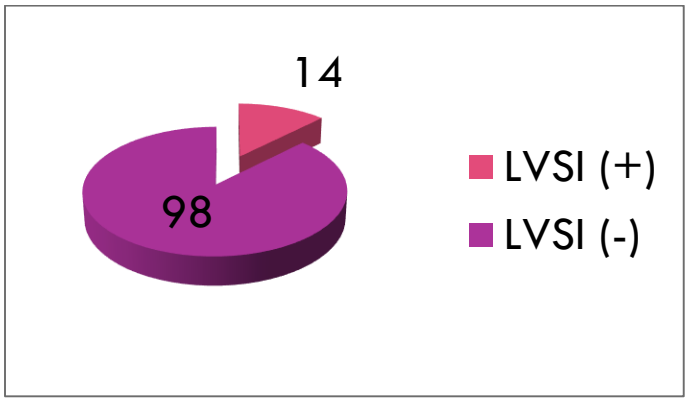

Figure 4 – patients with or without LVSI

Of 112 patients in the first stage of endometrial carcinoma, 14 (12.50%) had LVSI (Fig. 4).

4.1.4. Apllied treatment:

In addition to surgical treatment, 55 (49.11%) patients underwent postoperative radiotherapy and were not performed in 57 (50.89%) patients (tabl. 4).

Table 4 – Postoperative RT

Postoperative radiotherapy	Patients	%
PRT Yes	55	49,11%
PRT No	57	50,89%

IV.2. Overall survival of the studied patients.

Of the 112 patients with endometrioid endometrial carcinoma, 85 (75.89%) are alive and 27 (24.11%) have died (fig. 5).

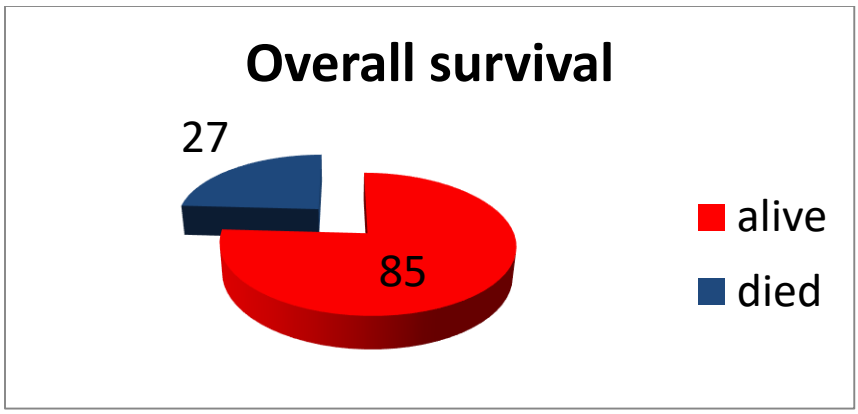

Figure 5 – Overall survival of the patients

The cause of death in 15/112 (13.4%) patients was not cancer.

In 12 patients, the cause of the death was cancer (tabl.5).

Table 5 – Overall survival

Died patients	**27 (100%)**
Oncological disease	12 (10,7%)
Other reason	15 (89,3%)

Table 6 – Progression of the disease

rogression of the disease	Patients (n)	(%)
)isease progression		
Recurrence or distant metastases		
БЩО 12		

Reccurence rates were 7/12 (58.33%), and the remaining 5/12 (41.67%) had disease progression leading to death. One in 12 patients (8.33%) had vaginal recurrence that was histologically proven, 1/12 (8.33%) patients had pelvic recurrence and 5/12 (41.67%) had distant metastases - black lungs and lungs. In 1 (8.33%) patients of the deceased there were liver metastases, in 1 (8.33%) the patient had lung metastasis and 2 (16.67%) of the patients had liver and liver metastases.

The patient with vaginal recurrence became ill on June 16, 2010 and was operated on in July of 2010. She did not undergo postoperative radiation therapy. In June 2013, it was proved by biopsy - adenopapillary carcinoma of the vagina of

endometrial origin. Radiation therapy was prescribed, in July 2013 the patient had no data on relapse. In January 2015 he again had data on vaginal recurrence, biopsy and histologically proven - moderately differentiated papillary adenocarcinoma. Chemotherapy was started and hormone therapy was later performed. The month of April 2015 the patient had CT data on the progression of the disease (vaginal recurrence - proven histologically: low-differentiated vaginal adenocarcinoma) and was prescribed palliative radiotherapy IMRI for a local relapse at a dose of OOD 40 Gy and DOD 2Gy, one month done brachytherapy with 7 Gy Ltd. and 7 Gy DOD. The patient's disease-free survival is 23 months. Survival after treatment for the first local recurrence is 60 months.

The patient with recurrence in the pelvis became ill in February 2011, underwent postoperative radiotherapy and in June 2012 had CT data on recurrence in the pelvis. The disease-free survival is 17 months. Surgical treatment was performed and the survival after treatment was 10 months.

One patient had liver metastasis. The patient became ill in July 2014 and liver metastasis was registered by PET / CT in May 2016. The patient's disease-free survival is 23 months. Chemotherapy for hepatic metastasis was initiated in June 2016 and the survival rate after treatment for recurrence is only 1 month.

Two of the deceased patients had lung metastases. One contracted the disease in June 2011, underwent postoperative radiotherapy and in December 2013 registered pulmonary metastasis. The disease-free survival is 29 months. Rested 1 month after registration of distant metastasis, no therapy for distant metastasis was performed. The second patient became ill in February 2011, underwent post-operative radiotherapy, and in December 2012 a distant lung metastasis was registered. The disease-free survival is 21 months. Three months later - died, no therapy was performed.

Two of the deceased patients had distant metastases to more than one organ. One fell ill in June 2011, underwent postoperative radiotherapy and in September 2011 had a disease progression - liver metastases, undergoing chemotherapy. In April 2013, a PET scan registered a distant metastasis (lung) and again underwent 6 courses of chemotherapy. The disease-free survival is 3 months. Survival after treatment for the first progression of the disease is 22 months. The second patient with more than one distant metastasis contracted the disease in February 2009. She underwent postoperative radiotherapy. February 2010 with CT data on lung metastases, chemotherapy was prescribed (2 courses with Epirubicin and Cisplatin conducted), which was incomplete due to toxicity and hormone therapy was initiated. December 2010 is a CT scan for liver metastases. The disease-free survival is 12 months and the survival rate after treatment for relapse is 18 months. The overall survival of the patients was 89.3%, the disease-free survival was 93.75%. The recurrence rate in the clinical group was 6.25% and the mortality rate was 10.70%.

The median follow-up time was 75.19 ± 28.94 months in the range of 1 to 122 months, and the mean overall survival was 111.83 ± 2.92 months at 95% CI 106.11 to 117.56 months.

The overall survival of the patients was 89.3%, the disease-free survival was 93.75%. The recurrence rate in the clinical group was 6.25% and the mortality rate was 10.70%.

The median follow-up time was 75.19 ± 28.94 months in the range of 1 to 122 months, and the mean overall survival was 111.83 ± 2.92 months at 95% CI 106.11 to 117.56 months.

Table 8 is a table of overall survival calculated by the Kaplan-Meier method. The more characteristic features of it are the following:

¬ Of 112 (89.3%) patients monitored for overall survival, 12 (10.7%) were excused from the disease under study and 100 dropped out of the follow-up for other reasons;

¬ The highest mortality rate was observed between the second and the third year - 7 cases or 58.3% of the total number of patients referred to at the time of follow-up at the time of follow-up;

Лe Second place in terms of lethality is the first year when 4 (33.3%) of the exits occurred;

¬ The minimum recorded overall survival was one month and the maximum was a little over 10 years;

96 One-year survival is 96.4%, 3-year - 90.1%, 5-year - 90.1%, and 10-year - 86.0%.

IV.3. Determining the role of lymph node dissection on overall survival.

As a next stage of the study, the probable factors that influenced the type of survival (lymphatic dissection and postoperative radiotherapy) were analyzed.

To this end, the Kaplan-Meier method was again applied and the impact assessment was performed with the purpose of the Log Rank, Breslow and Tarone-Ware tests.

Lymph node dissection was performed in 57 (50.89%) patients out of 112.

There were no lymphatic metastases in 54 (94.74%) patients with lymphoid dissection (Table 7). Only 3 (5.26%) had lymph node-positive metastases (tabl. 8).

Of the 85 living patients, lymphoid dissection was performed on 44 (51.76%) and of the 12 deceased patients, 10 (83.3%) had lymphoid dissection and 2 (16.7%) patients had no LD.

Table 7 – Lymph node dissection

Lymph node dissection	Patients (n)	
Yes		
No		

Table 8 – Lymph node metastases

Lymph node metastases	Patients (n)	%
Yes		
No		

Lymph dissection was performed in 5 (71.43%) patients in 7 with relapse. One (33.33%) of women with lymphatic metastases had a recurrence. Of the 7 women with recurrence, one had lymphatic metastases (14.3%). All three women with lymphatic metastases died, which is 25% of the 12 patients who died.

From the frequency analysis of the number of lymphatic metastases in patients with lymphoid dissection, it is clear that having a higher percentage (3.5%) of patients has more than 3, followed by those with 1 to 3 (1.8%). The majority (94.7%) were patients without lymphatic metastases.

The Kaplan-Meier survival analysis performed showed a lower average survival (by about 1 month) of those who had lymphoid dissection compared to those who did not have.

IV. 4. The role of postoperative radiation therapy on the overall survival of patients.

In addition to surgical treatment, some patients underwent adjuvant radiotherapy in the pelvis and upper 1/3 of the vagina at a dose of 5000 cGy and DOD 200 cGy. In the studied clinical contingent, 55 (49.11%) patients underwent postoperative radiotherapy and 57 (50.89%) patients did not receive adjuvant LT. Postoperative radiotherapy was performed in 8 (66.67%) / 12 of the patients with lethal outcome, and postoperative radiotherapy was not performed in 4/12 (33.33%). Of the 12 patients with excitus 5 (41.7%) had undergone postoperative radiotherapy and had a disease progression. Seven patients did not undergo postoperative radiotherapy and two of them relapsed. Of the relapsed patients, 5 had radiation therapy (71.43%) and 2 (28.57%) had no postoperative radiation therapy .

Postoperative radiotherapy was performed in 8 (66.67%) / 12 of the patients with lethal outcome, and postoperative radiotherapy was not performed in 4/12 (33.33%). Of the 12 patients with excitus 5 (41.7%) had undergone postoperative radiotherapy and had a disease progression. Seven patients did not undergo postoperative radiotherapy and two of them relapsed. Of the relapsed patients, 5 had radiation therapy (71.43%) and 2 (28.57%) had no postoperative radiation therapy (Table 9).

Table 9 – Died patients rate with PRT

Died patients with postoperative RT	Patients (%)
Yes	8 (66,67%)
No	4 (33,33%)
Total	**12 (100%)**

The Kaplan-Meier survival analysis performed showed a lower average survival (by about 1.5 months) of those who had postoperative radiation therapy than those who did not.

By March 2019, the number of living patients was 85/112 (75.89%).
Of these 85 women with endometrial cancer, 39 (45.88%) had postoperative radiotherapy and 46 (54.12%) did not.

IV. 5. The disease-free survival of the patients.

Of the 112 patients, 7 had a recurrence. They all died at the time of the study. The results of the frequency analysis of the localization of recurrences show that the highest percentage (4.5%) are distant metastases (liver, lung), followed by local recurrences (vaginal and pelvic recurrence) with 0.9% each. In the study sample, 7 (6.25%) of 112 patients relapsed and 105 patients (93.75%) had no recurrence (tabl 10 and 11).

Table 10 – Reccurence type

Patients (n)	Reccurence type	**%**
1	Vaginal reccurense	14,3%
1	Pelvic	14,3%
5	Distant metastases	71,4%
7	**Total**	**100%**

Table 11 – Type of reccurences

Patients (n)	Reccurense	**%**
1	Lung and Liver	14,3%
1	Liver and Lung	14,3%
2	Lung	28,6%
1	Pelvis	14,3%
1	Vagina	14,3%
1	Liver	14,3%
7	Total	100%

The median follow-up time was 73.93 ± 30.29 months, ranging from 1 to 122 months, and the median survival to relapse was 115.26 ± 2.47 months with a 95% CI of 110.42 to 120.10 months.

Of the 112 relapsed-free patients, 7 (6.25%) experienced relapses from the disease under study, and 105 dropped out of follow-up for other reasons;

- The highest incidence of recurrence was observed between 12-24 months - 4 cases or 57.1% of the total number of recurrences during the follow-up period of 7

patients;

- The minimum recorded relapse-free survival is 3 months and the maximum is 122 months;
- The 6-month survival rate is 99.1%, the one-year survival rate is 98.2%, the two-year survival rate is 94.4%, and the 3-year survival rate is 93.5%.

IV. 6. Survival of the patients with recurrence after treatment.

Of the 5 patients monitored for overall survival, 5 (100%) recovered from endometrial carcinoma after treatment;

The highest mortality rate was observed at the 26th month - 3 cases or 60% of the total number of patients who had been exposed at the time of follow-up at the time of follow-up;

The minimum recorded overall survival was 26 months and the maximum was 8.5 years;

One-year survival is 100%, 2-year - 100%, 3-year - 40%, 5-year - 20%, and 10-year - 0%.

Conclusions:

1. The overall and disease-free survival for stage I endometrial endometroid carcinoma is 89.3% and 93.75%, respectively.
2. The recurrence rate (local and distant) of the studied contingent is 6.25%.
3. Distant recurrences in parenchymal organs (liver, lung) account for 71% of the recurrence of the disease.
4. Over 50% of reccurence cases occur within the first 2 years and this should increase alertness in the follow-up of patients within the first 24 months after treatment.
5. Thorough staging with precision imaging (CT, contrast, MRI, or PET / CT) of the abdomen and lung before surgery is essential, especially in cases with adverse histological data (G3, LVSI).
6. Revision of histological preparations (second opinion) by an experienced (expert-pathologist) material from the diagnostic test abrasion will lead to selection of patients for more precise staging and therapeutic tactics.
7. Treatment of reccurence (local and distant) is unsuccessful, regardless of the therapeutic agents used (RT, CT, hormonal therapy) and efforts should be directed towards prevention of their occurrence.
8. In stage I EEC lymph node dissection does not have a staging role, except for increased palpation (clinical) and imaging methods. Lymph node dissection (pelvic and / or paraaortic) does not increase overall and disease-free survival.
9. Lymph node metastases have poor prognostic significance, regardless of the applied LT. The use of chemotherapy in these cases is appropriate.
10. LVSI patients have a 28-month average median survival to reccurence compared to the other patients.
11. A case of MI equal to and greater than ½ from the myometrium has a 12-month median survival to recurrence.

12. The tumor's with high grade factor (G3) has a strong negative effect on the median survival to relapse. Patients with this histological parameter experience 40 months less (10 times less) than others.
13. Postoperative RT (TGT) in the study contingent has no protective effect on overall and reccurence-free survival. Patients at increased risk (MI> 1/2-IB stage, G3, LVSI, LNM) should be combined with brachytherapy and / or chemotherapy.
14. LVSI and G3 are independent factors that reduce both overall and disease-free survival, whereas deep myometrial invasion alone does not affect these indicators.

Recommendations for the behavior of endometrial carcinoma
1. Revision of histological preparations of curettage material with accents: carcinoma, sarcoma, mixed tumor, hyperplasia, EIN; histologic type (endometroid, various components; nonendometroid-serous, clear - cell, adenosquamous), G3, LVSI.
2. All cases except pure endometrioid carcinoma, G1-2 without LVSI, are subject to expert imaging of the abdomen and lung (preferably PET / CT)
3. In the absence of distant or lymphatic metastases from imaging, the volume of surgical treatment is total hysterectomy with adnexa and exploration of the abdominal cavity and palpation of the retroperitoneal LV (pelvic and para-aortic). Lymph dissection is recommended only for increased LV.
4. Chemotherapy and brachytherapy are recommended postoperatively in the presence of LNM, LVSI, G3. TGT and brachytherapy are recommended in the presence of MI> 1/2, and in the absence of the abovementioned adverse factors observation or only vaginal brachytherapy.