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MODERN ASPECTS OF SURGICAL TREATMENT OF PATIENTS WITH ENDOMETRIAL CANCER (own experience)

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Ключові слова: *рак ендометрія, лапаротомія, лапароскопія, хірургічне втручання, лімфодисекція, тазова, парааортальна, ускладнення*

Ключевые слова: *рак эндометрия, лапаротомия, лапароскопия, хирургическое вмешательство, лимфодиссекция, тазовая, парааортальная, осложнения*

Abstract. Modern aspects of surgical treatment of patients with endometrial cancer (own experience). **Movchan O.M., Svintsitskyi V.S.** *In recent years, endometrial cancer has taken the lead among oncological processes of the female reproductive system. The high prevalence of this disease leads to disability of the working-age population, large socio-economic losses, which determines the relevance of this problem and the search for new methods of screening, diagnostics, optimal selection of treatment, thereby affecting the quality of future life. The choice of the method of treatment of patients depends on the following main factors: age, general condition, reproductive plans of the patient, histological type of tumor, degree of its differentiation, size, localization in the uterine cavity, prevalence of the*

tumor process. The main treatment for endometrial cancer is surgical treatment. The principles of surgical treatment consist in the individual selection of the volume of surgical intervention, adequate lymphadenectomy, prevention of recurrence and metastases. Lymph node dissection for cancer of the uterine body has always been a controversial issue. Lymphadenectomy is necessary to accurately establish the stage of endometrial cancer. In recent years, the discussion about laparoscopic lymph node dissection in comparison with open access, to what level lymphadenectomy should be performed, how many lymph nodes, frequency of complications, prognosis of patient survival, frequency of relapses has been developing. The article highlights own vision of the role of lymphadenectomy both in laparotomy and in laparoscopy, the importance of the volume of surgical intervention and complications for each type of treatment.

Реферат. Современные аспекты хирургического лечения больных раком эндометрия (собственный опыт). Мовчан О.М., Свинцицкий В.С. *Рак эндометрия в последние годы занимает ведущее место среди онкопроцессов женской репродуктивной системы. Высокая распространенность данного заболевания приводит к инвалидизации трудоспособного населения, крупным социально-экономическим затратам, что и обуславливает актуальность данной проблемы и поиска новых методов скрининга, диагностики, оптимального подбора лечения, что влияет на качество дальнейшей жизни. Выбор метода лечения пациенток зависит от следующих основных факторов: возраст, общее состояние, репродуктивные планы больной, гистологический тип опухоли, степень ее дифференциации, размеры, локализация в полости матки, распространенность опухолевого процесса. Основным методом лечения рака эндометрия является хирургическое лечение. Принципы хирургического лечения заключаются в индивидуальном подборе объема оперативного вмешательства, выполнении необходимого уровня лимфодиссекции для предупреждения рецидива и метастазов. Проведение лимфодиссекции при раке эндометрия всегда было спорным вопросом. Лимфаденэктомия необходима для точного установления стадии заболевания рака эндометрия. В последние годы дискуссия развивается по поводу лапароскопической лимфодиссекции по сравнению с открытым доступом: до какого уровня должна быть выполнена лимфаденэктомия, какое количество лимфоузлов, частота осложнений, прогноз выживаемости пациенток, частота рецидивов. В статье освещено свое видение роли лимфодиссекции как при лапаротомии, так и при лапароскопии, важность объема оперативного вмешательства и осложнения при каждом виде лечения.*

Endometrial cancer (EC) occupies a leading place in the structure of oncogynecological diseases and is characterized by an increase in both morbidity and mortality rates. According to global data, the number of newly diagnosed cases of the disease in Europe was almost 27.5% per 100,000 female population in 2019 [11].

In Ukraine, among the female population, the number of registered cases of the disease in 2019 is 12.2%, and compared to 2018 – 10.2% shows an increase in incidence by 2.0%, EC ranks first among cancer diseases of female genital organs and the third – after oncological processes of the mammary gland and melanoma [2].

Predominantly, EC is diagnosed in the early stages, in 80% at the 1st stage with a five-year survival rate of over 95%. However, survival rates are significantly lower in patients with regional spread or distant metastases – 68% and 17%, respectively [4].

The main method of treatment for stages I and II of EC is surgical, however, based on specific characteristics (age, concomitant pathology, type of tumor, degree of differentiation of the tumor, depth of invasion, according to additional methods of follow-up, presence of lymphovascular spread), the volume or extent of surgical intervention must be determined individually [7]. A complex surgical approach to EC includes: removal of the uterus, cervix, appendages, pelvic and para-aortic lymph nodes, as

well as examination of washings from the abdominal cavity and pelvis.

Metastasis to lymph nodes is the most common form of disease spread. Several studies have found that lymph node involvement is a strong predictor of survival, and its presence requires progression to III disease stage. In patients with EC, where more than half of the myometrium is invaded, metastatic pelvic and para-aortic lymph nodes can be expected in 34% and 23% of cases, respectively. The distribution of metastatic lymph nodes in patients with endometrial neoplasms is also important for the prognosis of the disease, relapses and patient survival. Despite the fact that pelvic and regional lymphadenectomy, recommended by the International Federation of Gynecology and Obstetrics (FIGO) as a component of establishing an accurate surgical diagnosis of EC, in which the para-aortic nodes are involved, includes a more advanced stage of the disease, than lesions of the pelvic nodes. The frequency of damage to lymph nodes increases with the depth of myometrial tumor invasion (T stage, in the TNM classification system). When determining pelvic (N – common, external and internal iliac) and/or paraaortic lymph nodes, the stage of the disease is classified as N1, and inguinal lymph nodes are considered stage M1 of the disease. The involvement of lateral nodes does not affect the classification of the disease. Several retrospective studies have suggested a correlation between the

number of involved lymph nodes excised and clinical outcome for patients with early-stage primary tumors (stage I or II). However, the number of histologically positive nodes is not decisive for the TNM or FIGO stage [3, 4].

Taking into account the peculiarities of lymph drainage, in high-risk patients with a high probability of regional metastases, according to the recommendations of ESMO, ESGO and ESTRO (European Society of Medical Oncology [ESMO], European Society of Radiotherapy and Oncology [ESTRO] and European Society of Gynecological Oncology [ESGO]) indicated pelvic and lumbar lymphodissection [8]. In patients with invasion of more than 1/2 of myometrial thickness and low risk, lymphadenectomy is indicated for study. In patients with stage II, a lymphadenectomy from the pelvic lymph nodes to the level of the renal arteries is recommended [9].

Despite the fact that pelvic and para-aortic lymphadenectomy is recommended by FIGO as part of establishing the exact stage of the disease, the impact on survival remains controversial [4]. According to the reports of a number of authors, in the absence of metastases, pelvic lymphodissection does not increase the survival rate of patients with EC, but increases the proportion of intra- and especially postoperative complications (lymphocyst formation).

The relevance of the study of this issue is obvious, since it is about a deterioration of the quality of life and a temporary loss of working

capacity in patients who are subject to extended panhysterectomy. However, the works of a similar plan are numerous, and studies on the comparative evaluation of the effectiveness of the surgical method, performed in different volumes for this disease, are clinically unfounded.

The purpose of the study is to evaluate the expediency of performing both pelvic and para-aortic lymph node dissection in uterine cancer depending on the stage of the disease, to share one's own experience, to analyze the indicators of the frequency of complications and patient survival.

MATERIALS AND METHODS OF RESEARCH

Retrospectively, database of the Department of Oncology and Gynecology of the National Cancer Institute (Kyiv, Ukraine) for the period 2010-2020 was analyzed.

Inclusion criteria: patients with EC, stage I-IV according to the FIGO classification with clinically significant lymph nodes who underwent systemic lymphodissection from the level of the renal vessels to the occipital fossa (Table 1). The staging system described below is the latest classification system revised and approved by the AJCC (American Joint Committee on Cancer), which became effective in July 2020 [6].

Exclusion criteria: sarcomas, recurrent cancer in the pelvis and para-aortic lymph nodes, combined cancer with other localizations.

Table 1

Classification of endometrial cancer (FIGO 2009)

Stage	Characteristics
I	The tumor is limited to the body of the uterus
IA	The tumor infiltrates <1/2 thickness of the myometrium
IB	The tumor infiltrates ≥1/2 thickness of the myometrium
II	The tumor spreads to the cervix, but does not go beyond the uterus
III	Local and/or regional spread of the tumor outside the uterus
IIIA	The tumor affects the serous lining of the uterus and/or appendages
IIIB	Vaginal lesions and/or parametria
IIIC	Metastases in the pelvis and/or para-aortic lymph nodes
IIIC1	Damage to the pelvic lymph nodes
IIIC2	Para-aortic lymph node involvement with/without pelvic lymph node involvement
IV	The tumor spreads to the bladder and/or colon mucosa and/or there are distant metastases
IVA	Tumor invasion of the bladder and/or colon mucosa
IVB	Distant metastases, including intra-abdominal and/or inguinal lymph nodes

All materials comply with the principles of bioethics set forth in the Helsinki Declaration "Ethical Principles of Medical Research Involving Humans" developed by the World Medical Association, the "General Declaration on Bioethics and Human Rights (UNESCO)", the Order of the Ministry of Health of Ukraine "On Approval of the Procedure of clinical trials of medicinal products and examination of materials of clinical trials and standard provisions on commissions on ethics" No. 690 dated 23.09.2009. This research complies with the fundamental ethical principles – complete confidentiality is ensured regarding information about the personal data of the participants and the amount of treatment performed, and the obtained results were used only for data research. The research program was approved by the bioethics commission of the National Cancer Institute of the Ministry of Health of Ukraine, and the work was approved by the local ethics committee. All patients were informed and consented to the study.

Primary treatment of patients with EC included complex surgical staging (total hysterectomy, bilateral salpingo-oophorectomy, lymphodissection of iliac and para-aortic lymph nodes, cytological examination of peritoneal washings).

Pelvic lymph node dissection typically included removal of lymph nodes from the distal half of the common iliac arteries, the anterior and medial part of the external iliac artery, and the vein below where the deep bypass iliac vein crosses the external iliac artery, as well as removal of fat around the n.obturatorius.

Dissection of paraaortic lymph nodes included removal of lymph nodes along the distal part of the inferior vena cava: from the level of the inferior mesenteric artery to the middle of the common iliac artery on the right and removal of lymphoid tissue between the aorta and the left part of the ureter, from the inferior mesenteric artery to the middle of the common iliac artery on the left. For a more accurate diagnosis, a histological examination of the surgically removed tumor specimen was performed. The following parameters were reflected in the pathomorphological report: histological type of tumor; degree of tumor differentiation; tumor size; depth of tumor invasion; the thickness of the myometrium in the place of the largest invasion of the tumor; tumor growth of the serous membrane of the uterine body; transition of the tumor to the cervix, ingrowth into the stroma of the cervix; the exit of the tumor in the parametrium; transition of the tumor to the vagina; the total number of removed and affected pelvic lymph nodes; the total number of removed and

affected lumbar lymph nodes; metastatic lesions of the ovaries, fallopian tubes.

The analysis of the types of hysterectomies was carried out in accordance with – Type I, II, III, IV – European Organization for Research and Treatment of Cancer (GCG-EORTC) 2007. In patients with clinically suspicious metastatic lymph nodes, systemic lymph node dissection was performed from the level of the iliac fossa (Pelvic lymphadenectomy - PLND) to the level of the renal vessels – Paraaortic lymph nodes (Paraaortic lymphadenectomy - PALND) (Table 3). Complications were assessed according to the classification of postoperative complications by P. Clavien and D. Dindo [8]. Standard methods of descriptive statistics were used for data processing; in particular, average values were calculated with their standard errors. Mathematical data analysis and verification of the results, in particular the calculation of the arithmetic mean and standard errors, were carried out on the basis of the "Statistica 6.0" software and on a personal computer using Microsoft Excel software packages (Microsoft Office 2010, licensed agreement (EULAID: O14_RTM_VL.1_RTM_RU) using the standard Student's t-test. The critical level of statistical significance is taken as $p < 0.05$ [1]. The results of the study show the main indicators of descriptive statistics with using generally accepted statistical criteria.

RESULTS AND DISCUSSION

In total, the results of treatment of 285 patients with I-IV stages of endometrioid cancer were analyzed. The average age of the patients involved in the study was 55 ± 5.7 years (from 25 to 82 years), while the largest number of patients was revealed at stage I of the disease – 74.5%. Endometrioid type of endometrial cancer is diagnosed in most cases – 89.0%.

In view of the relevance of the mentioned problem, during our own retrospective analysis, the evaluation was carried out taking into account the volume of surgical intervention and taking into account the stage of the disease, using the GCG-EORTC classification of 2007, which is presented in Table 2. The third stage was defined in patients with metastases both in the pelvic lymph nodes and in the ovary.

Starting from 2013 and during the last years, laparoscopic panhysterectomies are increasingly being used in the Department of Oncology and Gynecology of the National Cancer Institute in patients with stage 1 of EC. Laparoscopic access was included in the first type of surgical treatment.

On average, the duration of the surgical intervention in the department of oncology and

gynecology was: when removing the uterus with/without appendages – 1 hour 30 minutes ± 10 minutes, with PLND – 2 hours 10 min. ± 10 min., with PLND+PALND – 3 hours 20 min. ± 10 min. For laparoscopic panhysterectomy – 1 hour 10 min. ± 10 min. ($p < 0.05$).

Table 2

Data on the number and type of surgical intervention depending on clinical stage of disease (with laparoscopic access including)

Type of panhysterectomy	Stage of disease					
	AEH ¹	I	II	III	IV	Total
I type ² (n=)	11	114	6	7	15	153
Type II ³ (n=)	1	19	11	1	1	33
Type III ⁴ (n=)	0	18	12	8	3	41
Type IV ⁵ (n=)	0	0	0	1	1	2
Total (Σ=)	12	151	29	17	20	228

Notes: 1 – atypical endometrial hyperplasia; 2 – I type – extrafascial extirpation of the uterus; 3 – II type – modified radical extirpation of the uterus, including removal of the medial half of the cardinal and sacro-uterine ligaments; 4 – III type – radical extirpation of the uterus, involves the removal of most of the cardinal, sacro-uterine ligaments, the upper third of the vagina and pelvic lymph nodes; 5 – IV type – extended radical extirpation of the uterus, periurethral tissues are removed, resection of the upper vesical artery and $\frac{3}{4}$ of the vagina is performed.

The results of a retrospective study of Lin Li et al., published in 2020 also showed that the duration of surgery was longer ($p < 0.001$) in the group with paraaortic lymph node dissection, and the hospital stay was shorter ($p < 0.001$) in the group with type I of panhysterectomy than in the group with lymph node dissection [13].

The results of lymphodissection were compared. Determination of the level of removal of lymph nodes was carried out depending on the clinical stage, the degree of differentiation of the tumor and taking into account the data of research methods – ultrasound, MRI, CT with contrast, PET-CT.

Patients were divided into groups according to the volume of surgical intervention: without lymphadenectomy (PLND- / PALND-), with sampling of pelvic lymph nodes (PLND), systemic pelvic lymphadenectomy (PLND+ / PALND-) or combined pelvic and paraaortic lymphadenectomy (PLND+ / PALND+) (Table 3). Interventions with laparoscopic access are also included in these groups. During laparoscopy, sampling of pelvic lymph nodes was performed mainly in 6.7% of patients, 19.0% of such operations were performed in 2013-2020.

Table 3

Comparing number of surgeries depending on extent of surgical intervention: without/with lymph dissection depending on the level of lymph dissection

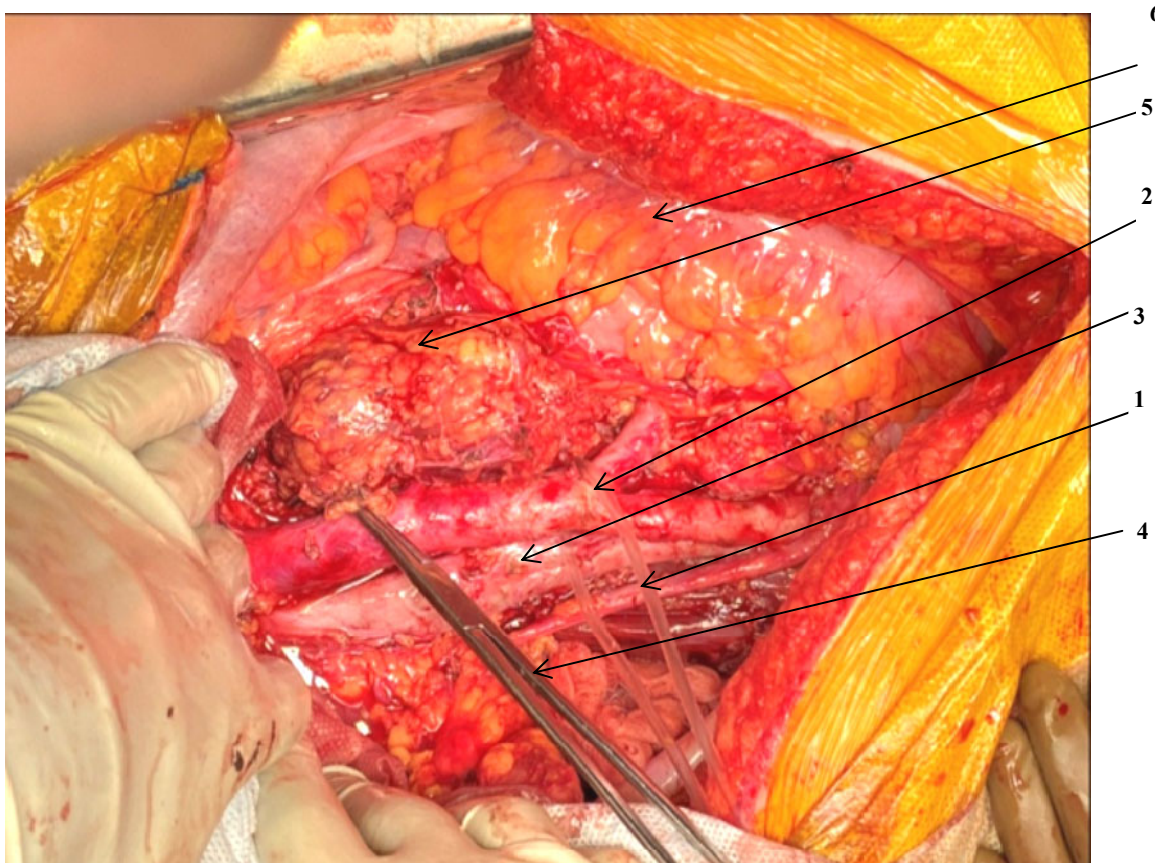
Extent of surgical intervention	Stage of disease					
	AEH ¹	I	II	III	IV	Total
Panhysterectomy without lymph dissection (n=)	11	114	6	7	15	153
Panhysterectomy with sampling of pelvic lymph nodes (n=)	1	28	3	3	2	37
Panhysterectomy with PLND ² (n=)	1	19	11	6	8	45
Panhysterectomy with PALND ³ (n=)	0	3	6	29	9	47
Total (Σ=)	13	164	26	45	34	282

Notes: 1 – atypical endometrial hyperplasia; 2 – pelvic lymph dissection; 3 – paraaortic lymph dissection.

The average number of lymph nodes removed during lymph node dissection was 7-11 of pelvic and 12-15 of paraaortic (Figs. 1 and 2). Based on the obtained data, metastases were found in 57.0% of pelvic lymph nodes at II-III stages, in 19.0% – in paraaortic lymph nodes at II-III stages ($p>0.05$), in 23.0% there were hyperplastic lymph nodes during sampling of pelvic lymph nodes, which was carried out mainly at the first stage of the disease. In 2 cases (0.01%), a metastasis was detected in sampling the pelvic lymph nodes on the left side, although according to additional research methods, no signs of damage were detected. During the laparoscopic biopsy of the

lymph nodes according to the results of the pathohistological examination, no metastases were detected.

When compared with the aforementioned study, the mean (\pm SD) number of lymph nodes was 20.9 (\pm 9.6) for laparoscopic access and 22 (\pm 11), $p=0.45$, for laparotomy. The difference in mean values was within -1.6 (95% CI -5.78 , 2.57). In 333 women who underwent surgery for EC: 121 underwent PLND+ / PALND- surgery, 166 underwent PLND+ / PALND+, and 46 – PLND- / PALND-. In 291 women, no difference in overall survival between PLND and PALND was found [13].

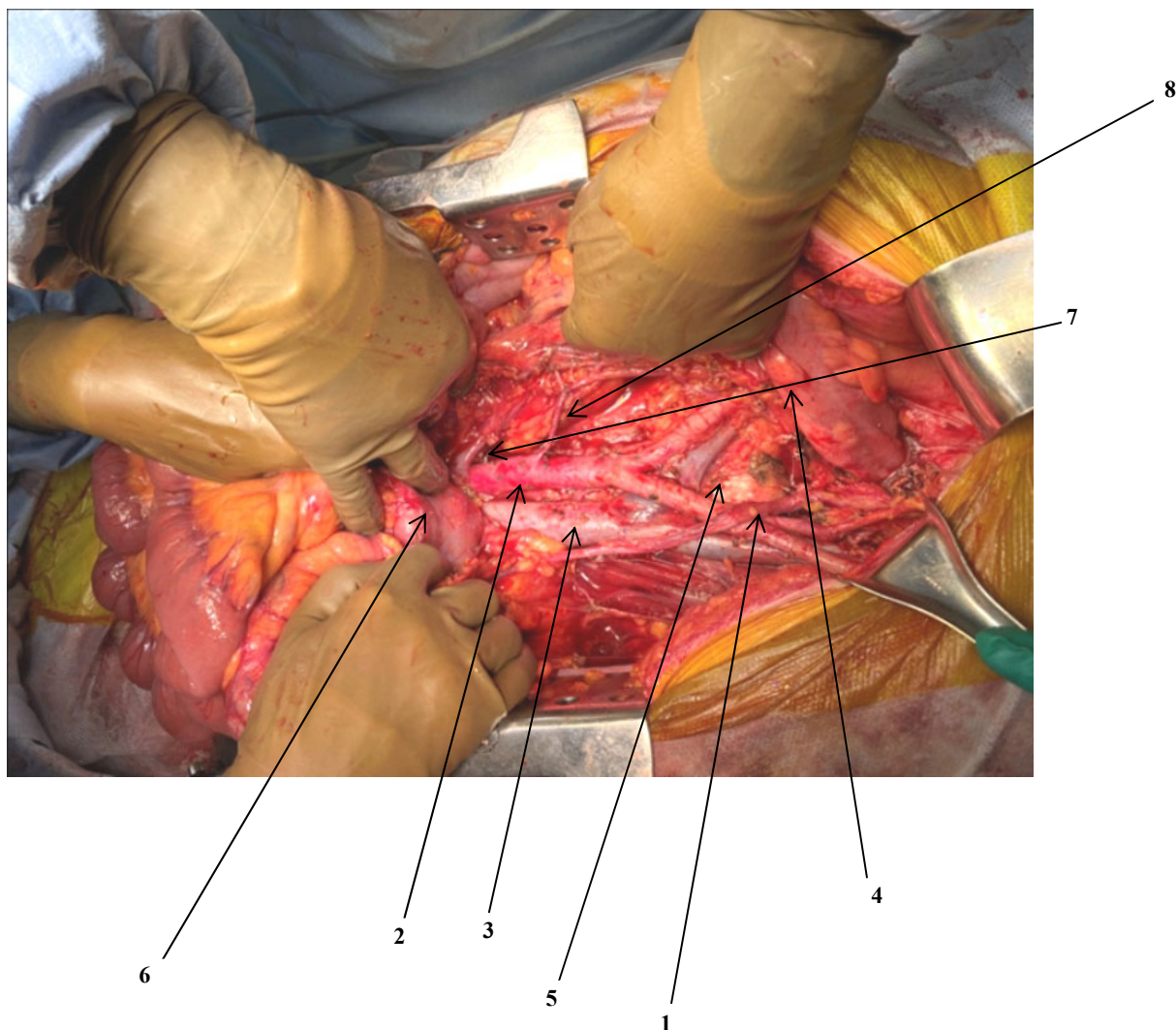


1 – right ureter; 2 – aorta with bifurcation on common iliac arteries; 3 – inferior vena cava; 4 – clamp; 5 – metastatic lymph node; 6 – loop of inferior sigmoid colon.

Fig. 1. Metastases in paraaortic lymph nodes

Relapses were found in patients with III-IV stages up to 1 year – 80%. Survival was better in patients who received radiation therapy or chemotherapy in the postoperative period. The best survival was in the group of patients with stage I – 80-90%. However, 15-20% of these patients had relapses in 3-5 years ($p>0.05$).

A retrospective analysis proved that patients who underwent complete dissection had a better prognosis than those who underwent selective lymph node dissection or none at all [9].



1 – ureter; 2 – aorta from the level of the renal arteries to the level of the bifurcation; 3 – inferior vena cava; 4 – loop of the descending colon; 5 – promontorium; 6 – duodenum; 7 – upper mesenteric artery; 8 – lower mesenteric artery.

Fig. 2. State after pelvic and paraaortic lymph dissection

Several studies have previously recommended risk assessment criteria for EC patients with lymph node metastases to check for tumor metastasis in patients who meet these criteria. These criteria are: endometrioid carcinoma, tumor of stage 1 or 2 of differentiation, <50% myometrial infiltration, no visible evidence during surgery, and the largest visible area does not exceed 2 cm. However, this assessment includes tumor pathology obtained after surgery with frozen sections [12]. Turkler S. et al. analyzed 257 patients with a low risk of lymph node metastasis and found that there was no difference in survival with low-risk lymphadenectomy compared to patients who did not undergo lymph node removal [15]. Bell J.G. et al. modified the Mayo criteria and included only patients who did not undergo lymph node dissection. They found that the 5-year overall

survival rate is 95.8%. Unfortunately, they relied only on pathomorphological results [6]. Kim M. et al. recently proposed a new standard of the Korean Gynecologic Oncology Group (KGOG), where the 3-year recurrence-free and 5-year survival rates were 98.6% and 98.6%, respectively [12]. However, clinical imaging for the diagnosis of myometrial invasion and lymph node size had a certain rate of misdiagnosis, especially with CT data.

Despite all the advantages of careful selection of patients, until now no randomized study has been conducted that would definitively determine the need for lymphodissection in stage I and II of EC. The results of previous studies do not have statistical reliability.

When performing surgical interventions, there is a high probability of the need for additional surgical

treatment, transfer of the patient to the intensive care unit (ICU) or the use of other treatment methods [8].

The following complications were analyzed: lymphocysts – in 50% of patients, 10% had postoperative complications (suppuration of wounds, separation of sutures during laparotomy, lymphorrhea), which corresponds to the first class of complications. Vascular ligation (arteries and veins) was performed in 0.1% of patients, relaparotomy and revision were performed in 4.8%, and in 0.1% of them – during laparoscopic interventions, which corresponds to the IIIb class of complications.

Compared with patients who underwent only pelvic lymphadenectomy, patients who underwent both pelvic and paraaortic lymphadenectomy had increased blood loss, a higher frequency of blood transfusion, hospital stay, and duration of anesthesia [13].

Complex surgical staging is associated with a certain risk. Potential complications include damage to blood vessels, nerves, lymphostasis. Lymphostasis worsens the quality of life of patients. The exact frequency of cases of lymphostasis is unknown, but the latest data indicate that 47% of patients suffer from it after lymphodissection [14]. At this time, a prospective GOG (Gynecologic Oncology Group) study is being conducted, which determines the real probability of lymphostasis. Performing lymphodissection can eliminate the need for additional radiation and related complications. Total lymphadenectomy can have a therapeutic effect due to the removal of hidden metastases that are not diagnosed. However, the prognostic value of routine lymphadenectomy of regional lymph nodes is still being discussed [10, 12, 14].

CONCLUSIONS

1. In most women, EC is detected at the first stage of the disease, and the probability of affecting the lymph nodes is about 5%.

2. It is obvious that lymphadenectomy affects the establishment of a more accurate diagnosis and the choice of treatment tactics, and the higher the level of lymphadenectomy, the greater the probability of clarifying the stage of the disease and improving the survival results.

3. When the volume of surgical intervention increases, the frequency of postoperative complications increases.

4. At this time, there is a need to develop more effective methods of detection and early diagnosis of uterine cancer, since the latest data do not support lymphadenectomy.

Contributors:

Movchan O.M. – methodology, software, formal analysis, research, writing the initial project, visualization;

Svintsitskyi V.S. – conceptualization, verification, resources, data curation, management, project administration, finding financial support, reviewing and editing.

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Conflict of interest. The authors declare no conflict of interest.

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