

THE STUDY DRUG PATHOMORPHISM AND IMMUNOHISTOCHEMICAL PARAMETERS OF TUMOR IN ENDOARTERIAL OF REGIONAL LONG-TERM CHEMOTHERAPY IN TREATMENT OF CERVICAL CANCER



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ABSTRACT

To improve the results of radiotherapy for cervical cancer used local and systemic radio-modification drugs.

Materials and methods: 1984 patients with locally advanced cervical cancer (2b - 3a stage), which at one stage of complex treatment by a course indo-arterial of regional long-term poly-chemotherapy (EARDPHT) mode: methotrexate - 50 mg/m², the first 12 hours, fluorouracil 1000 mg/m², over the next 12 hours and cisplatin - 100 mg/m², for 48 hours, 2 stage - surgical treatment in the volume expanding hysterectomy 3 type (modification of Wertheim - Meigs).

Results: The results of treatment of locally cervical cancer using VADRPHT, depending on the unilateral and bilateral tumor invasion in parametrial tissue showed that under unilateral lesion of parametrium results of treatment were higher than for the bilateral involvement of parametrium. Medical pathomorphosis in tumors of different severity was observed in 86.9% of patients, metastasis to regional lymph nodes were detected in 36% of operated patients, and also studied the degree of therapeutic pathomorphosis in lymph nodes. There was revealed that the complete regression of tumors, 5 - year survival rate is 98%, whereas in tumor regression of more than 50% of the original volume - 78.5%, with stabilization of tumor - no more than 58.4%.

Conclusion: The study of molecular-biological parameters of the tumor cells show the effectiveness of conducted neo-advent indo-arterial chemotherapy and play an important role in further treatment and prediction of disease.

UDC Code & KEYWORDS

■ 616-009 ■ CERVICAL CANCER ■ ENDOARTERIAL ■ CHEMOTHERAPY ■

INTRODUCTION

Currently, cervical cancer (CC) remains the most common malignant tumor of the female genital organs. Every year in the world according to IARC recorded up to 500.000 new cases of cervical cancer and deaths per year reaches more than half of patients. Most cases of locally cervical cancer are diagnosed in developing countries, where regular screening programs are not available. Detection of cervical cancer at early stages of treatment results is generally good. Nevertheless, according to many researchers, in some cases, there is rapid progression of tumor even identifying it at an early stage. In recent years the disease is detected increasingly young, reproductive age (64% of patients). To date, we know a lot of different factors influencing the survival of patients with cervical cancer, such as disease stage, presence of metastases in regional lymph nodes, etc. The number of prognostic factors for cervical cancer continues to be supplemented and corrected, with the view of some of them eventually reviewed.

The main role in the treatment of patients with cervical cancer is surgery and radiation therapy. Surgical treatment

is the main in the early stages of the disease (1a-1c), whereas radiation therapy - an independent method or in combination with surgery - is widely used in the treatment of locally CC (IV2 - IVa stage). Choosing a method of treatment of cervical cancer IV2 - IIa stage in Europe and the U.S. currently differs: In some clinics performed surgery followed by radiotherapy with or without chemotherapy, and some - only chemo-radiotherapy as a possible alternative to study the application stage, IV2 chemotherapy followed by radical surgery.

Choice of treatment of cervical cancer stage IIB is the subject of perennial debate among oncologists and gynecologists, ray of Physicians and Surgeons. According to the report of FIGO, the main method used in the treatment of cervical cancer stage II in 1996 - 1998 was radiation therapy, which was used in 65% of patients, 10% of patients used surgical treatment followed by radiotherapy, at 6% - Radiation Therapy followed by surgery and 5% of patients with chemo-radiotherapy. In stage III cervical cancer radiotherapy, as an independent method, was used in 75% of patients, 9% of patients received chemo-radiotherapy, and 2% underwent surgery followed by radiotherapy. Oncogynecology Petersburg School believes that the use of combined treatment of cervical cancer stage II is unduly limited and amounts to 3.3%.

The most frequent cause of death in patients with cervical cancer is a common progression in the pelvic area, the development of renal failure due to obstruction and compression of the urethra, approximately 4.4% of patients with cervical cancer are determined by common metastases to the lungs, spleen and brain.

Another controversy is the question of the effectiveness of radiotherapy in the presence of metastases in the pelvic lymph nodes. D. Dargent et. al. (2005) compared two groups of patients with cervical cancer stages IB2 - IV a, received radiation therapy: the first group was pelvic lymphadenectomy prior to radiotherapy, in the second - after its completion.

To improve the results of radiotherapy for cervical cancer used local and systemic radio-modification various drugs (Metronidazole, Courant, Allopurinol).

In some countries in Europe and Asia, especially Japan, for the treatment of patients with cervical cancer stage II b, applies in general radical hysterectomy with pelvic lymphadenectomy by the method of H. Okabayshi. The advantages of surgical method to radiation are the possibility of preserving ovarian function and elasticity of the vagina in young patients. In the planning of adjuvant radiotherapy can be performed transposition of the ovaries of the irradiated zone. During the operation, diagnosed spread beyond the uterus (metastases in the lymph nodes, invasion of parametrium or dissemination in the peritoneum), removal of large metastatic changes in adjuvant therapy. In addition, it is possible to remove the primary radio resistant tumors.

Quality of life in patients with cervical cancer was higher after combined treatment than after radiotherapy. Thus, the results of treatment of locally cervical cancer are improved with the use of chemo-therapy. However, there are not enough to be satisfactory. Dissatisfaction with the results of radiation and chemo treatments have caused attempts to complement these methods of surgical treatment, which can be seen on the literature of recent years devoted to the treatment of the local prevalence of cervical cancer devoted to treatment of the local prevalence of cervical cancer.

Studies have shown that cytostatics reinforce radiation-induced tumor cells at the expense of the mechanism of DNA repair, since the synchronization of tumor cells in the phase of the cell cycle, which are most sensitive to radiation exposure. It was also noted that cytostatics reduce the number of tumor cells in the resting phase, and contributes devitalization resistant to radiation therapy of cells in hypoxia. Revealed that the tumor is more chemo-sensitive before radiotherapy or surgery. In view of these, the decrease in tumor volume due to previous chemotherapy may increase the effectiveness of radiation therapy, or increase the possibility of surgical removal of the tumor with a significant reduction in the risk of intraoperative dissemination tumor cells.

JE Sardi, C. Sananes, A. Giaroli et al (1998) in a randomized controlled study investigated the possibility of chemotherapy before radiotherapy in the local prevalence of cervical cancer. 72 patients with cervical cancer stage II b in the first stage of treatment conducted 3 courses of chemotherapy according to the scheme PVB. The second phase was carried out concomitant radiotherapy. The control group consisted of 73 patients of cervical cancer stage II b, which was carried out concomitant radiation therapy in the same doses. Five-year survival rate in the main group of patients was 54% in the control group - 48%. In carrying out a radical hysterectomy for cervical cancer stage II b authors obtained the following results: five-year survival rate among 75 patients who underwent Wertheim operation as the first stage of treatment was 41%, resectability of the tumor - 56% among 76 patients who have surgery performed after 3 courses of chemotherapy, 5-year survival rates were 65%, resectability swell - 80 %.

Currently, the use of chemotherapy is increasingly used in locally advanced cervical cancer, which improves the immediate and remote results of treatment.

In the gynecological department of the National Cancer Center gained some experience in the treatment of cervical cancer patients, based on which are some of the most significant data of the medicinal pathomorphism and immunohistochemical parameters of tumor. The aim of our study was to evaluate the medicinal pathomorphism the application of chemotherapy in locally advanced cervical cancer (2b - 3a stage) and the identification of molecular-biological markers that would help at the stage of examination and treatment, cervical cancer patients to predict the effectiveness of preoperative chemotherapeutic effects on the tumor.

MATERIALS AND METHODS

In this work pathomorphological study of preoperative biopsy material and operating agents in 1984 patients with locally advanced cervical cancer (2b - 3a stage), which at one stage of complex treatment by a course indo-arterial of regional long-term poly-chemotherapy (EARDPHT) mode: methotrexate - 50 mg/m², the first 12 hours, fluorouracil 1000 mg/m², over the next 12 hours and cisplatin - 100 mg/m², for 48 hours, 2 stage - surgical treatment in the

volume expanding hysterectomy 3 type (modification of Wertheim - Meigs).

An integrated approach to the treatment of patients with high risk of progression can expect a significant improvement in survival rates. In high-risk group includes the progression of cervical cancer patients:

- With an area of the tumor equal to or more than 4 cm³;
- with metastases to regional lymph nodes;
- with metastases to distant lymph nodes;
- With metastases to the ovary;
- invasive tumors with more than 1 / 3 the thickness of the myometrium of the cervix uteri, with the presence of cancer emboli in a vessel
- with histologically unfavorable forms (adenocarcinoma, glandular-squamous, small cell, undifferentiated carcinoma).

Squamous cell keratinizing was diagnosed in 71 patients (84.6%), glandular - squamous - 3 (3,9%), adenocarcinoma in 10 (11,5%) of the diseased. Step treatment pathomorphism assessed by criteria pathomorphism tumor Lavnikovoy.

Immunohistochemical studies were performed on the material of paraffin blocks using a peroxidase method with antibodies to the oncoprotein p53, antibodies to COX-2, antibodies to RTEN. Set to determine the immunohistochemical expression of the oncoprotein p16 INK 4a. In all cases, as chromogen diaminobenzidine was used.

RESULTS

The effect of clinical stage of treatment outcome is undeniable. Involvement of the parameters in tumor process is an important prognostic factor. The results of treatment of locally cervical cancer using VADRPHT, depending on the unilateral and bilateral tumor invasion in parametrial tissue showed that under unilateral lesion of parametrial results of treatment were higher than for the bilateral involvement of parametrium. Medical pathomorphosis in tumors of different severity was observed in 86.9% of patients, metastasis to regional lymph nodes were detected in 36% of operated patients, and also studied the degree of therapeutic pathomorphosis in lymph nodes.

In squamous cell variant of therapeutic pathomorphosis 3-4 degrees in the tumor was diagnosed in 34.2%, in lymph nodes 50%, in adenocarcinoma pathomorphosis 2-3 degrees was observed in 33.3% and completely absent in the metastatic lymph nodes. When glandular-squamous form 2% of patients registered medical pathomorphosis 2-3 degrees in the tumor and metastatic lymph nodes, as well as in the squamous component of degree -3, -2 degree of glandular pathomorphosis in tumor and lymph nodes, while noting the direct dependence treatment pathomorphism in lymph nodes from a medical pathomorphism in tumors ($R > 0.5$) ($p < 0.05$)

Immunohistochemical study of 18 patients showed that the presence of expression of the oncoprotein p53 was combined with lower treatment pathomorphism, and conversely, the absence of p53 expression was accompanied by a pronounced treatment pathomorphism in the tumor. The higher the level of protein expression RTEN and the color intensity of the drug, the greater the effect of chemotherapy. Expression of protein p16 INK 4a was observed in all cases after treatment. With a high degree of therapeutic pathomorphism color intensity decreased sharply, and in cells with the most pronounced

dystrophic changes in staining was absent. In some cells were found complexes of tumor cells with marked nuclear expression of p16 INK 4a, which may subsequently be a source of local recurrence. The low level of expression of COX-2 showed a high degree of therapeutic pathomorphism, and conversely, high expression was observed at a low level of treatment pathomorphism.

The immediate results of therapy also had a significant impact on survival of patients with cervical cancer. Revealed that the complete regression of tumors, 5 - year survival rate is 98%, whereas in tumor regression of more than 50% of the original volume – 78.5%, with stabilization of tumor - no more than 58.4%.

This way, the use of neo-adjuvant EADRPHT in patients with locally advanced cervical cancer can get treatment pathomorphism in tumor grade 3-4 in 37.8% of cases in the lymph nodes in 46.2%, reflecting the positive impact of chemotherapy on the primary foci, regional metastases. The study of molecular-biological parameters of the tumor cells show the effectiveness of conducted neo-advent indo-arterial chemotherapy and play an important role in further treatment and prediction of disease.

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