OPTIMIZATION OF COMBINED RADIATION THERAPY OF THE CERVIX CANCER

Use of a new combination of known medical products - inhibitors of enzyme cyclooxygenase-2 (diclofenac, ketoprofen) with small doses cytostatics (methotrexate, 5-fluorouracil) as "nonconventional" radiosensibilizators for optimization of combined radial treatment of cervical cancer is offered. One hundred and twenty patients with cervix cancer were involved into research (average age - 52.5±3.3), mainly II stage of process (50.8±4.6%), morphologically - nonkeratinizing squamous cell carcinoma (65.0±4.4%). Frequency of full regress of a tumor in the basic groups has reached in 77.5±6.6% (1-basic group) and 82.5±6.0% (2-basic group) in comparison with a control group 70.0±7.2% (p<0.05). By results of the cytological research in cells the pathomorphosis of IV degree was recorded in 1-basic group - 60.0% (superficial smears) and 57.5% (a puncture biopsy), in 2-basic group - 85.0% (superficial smears) and 82.5% (a puncture biopsy) in comparison with the control - 55.0% (superficial smears and a puncture biopsy), p<0.05.

Keywords: Cervix cancer, cervical cancer, combined radial therapy, radiosensibilization, radiosensitization, inhibitors of enzyme cyclooxygenase-2 (COX-2), diclofenac, ketoprofen, cytostatics, methotrexate, 5-fluorouracil.

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Introduction

Radiation therapy (RT) is a leading method of treatment of the cervix cancer (CC) and frequently, in a combination to chemotherapy, appears unique at III-IV stages when operative treatment connection is infeasible (Ermakova, 2002; Thipgen, et al., 1994; Minagawa, et al., 1997). According to different authors, the five years’ survival rate among CC patients received an radiation as an independent method of treatment, makes up 42.0-64.2% at IIB stages, 23.0-44.4% - at III stage (Vishnevskaya et al., 2004; Granov and Vinokurov, 2002; Bohman, 2002; ESTRO, 2002). Not less than 40% of patients die the next years due to disease advancement after the termination of primary treatment (Vishnevskaya et al., 2004; Granov and Vinokurov, 2002; Bohman, 2002). Therefore increasing the treatment efficiency for patients with CC first of all is related to improving of radial therapy that assumes using innovative technical equipment, perfecting distribution of radiation doses in space and time, applying modifying impacts and combining the radial therapy with other methods of treatment. However, modernizing of physic technical equipment of radiotherapy leads to substantial increase of cost of treatment (Brahme, 2000), and use of the combined programs enlarges duration of therapy and can be regarded as the adverse factor (Coles et al., 2003; Perez et al., 1995), combined use of several factors of specific influence can lead to increase of frequency and gravity of collateral reactions, complications and, accordingly, to lower quality of a patients’ life (Tahmasebi et al., 2007).

Recently appreciable successes in radial therapy of CC are caused by achievements of clinical radiobiology. In the Kazakh Scientific Research Institute of Oncology and Radiology (KazNiiOiR), throughout many years studies of new approaches of the referred modeling of a radio sensitiveness of a tumor and normal tissues, including at patients with CC, have been carried out. Many foreign researchers study antitumor and preventive activity inhibitors of enzyme cyclooxygenase-2 (COX-2). It is known that tumoral cells actively develop enzyme COX-2, participating in synthesis of prostaglandins, and their hyper production brakes a cellular apoptosis, strengthens...
development of factors of growth and locally suppresses activity of immunocompetent cells. The neoangiogenesis also is COX-2-dependant mechanism that leads to a rough proliferation of a tumoral tissue and causes invasive growth. Active synthesis by tumor cells is connected with hyper expression COX-2 thromboxane A2, playing the important role in metastasis process and fixings of tumoral blood clots in healthy tissues (Brock et al., 1999; Gately et al., 2004; Grosch et al., 2006). Thus, the purpose of our research was increasing the efficiency of the combined radial therapy of the cervix cancer by a tumor radiosensibilization inhibitors of enzyme COX-2 (diclofenac, ketoprofen) in a combination with small doses cytostatics (methotrexate, 5-fluorouracil).

Materials and methods

120 patients with CC are included in clinical research (with histological verified diagnosis), were on treatment in 2006-2009 years in the department of brachytherapy of KazNiiOiR. Depending on treatment techniques all patients with CC were divided into three groups: the 1-basic group (n=40) - the patients who have received combined radiation therapy with radiosensibilization by local introduction (intratumoral) of a solution of diclofenac (3.0 ml, day after day, No5) and peroral reception of small doses of methotrexate (2.5 mg x 1 time/day, No25); the 2-basic group (n=40) - the patients who have received RT with radiosensibilization by local introduction (intratumoral) of small doses of 5-fluorouracil (250 mg, day after day, No5) and peroral reception of ketoprofen (50 mg x 2 times a day, No25); the control group (n=40) - the patients who have received RT by the standard scheme. For randomization of groups, “blind” selection of “envelopes” method (Dvojrin and Klimenkov, 1985) was used.

The intracavitary brachytherapy (BR) was carried out on gamma-therapeutic apparatus “Agat-VT” of high power of a dose (HDR) with a radioactive source 60Co by a technique “remote afterloading”. The external beam radiation therapy (EBRT) was spent on gamma-therapeutic apparatus “Teragam”, “Sirus” or linear accelerator “Clinac-600”. In studied groups, RT was carried out by using the same methods: in the beginning the EBRT of a small pelvis and zones of regional metastasis in the static or rotatory way to doses 20 Gy, further were connected sessions of BR by a doses 5 Gy at point A (8-10 x 5 Gy). EBRT are made between BR sessions of a small pelvis and zones of regional metastasis (with protective shielding of point A area, a bladder, and a rectum) by 2 Gy for point B to summarized doses of 40-44 Gy.

While estimating the treatment results, the ultrasonic and cytological data received in dynamics were taken into account (before treatment was considered, at 20Gy and after irradiation). The complex of Ultrasound (US) techniques consisted of two-dimensional ultrasonic in the B-regimen, tissue harmonic imaging, pre- and post-processing, amplitudes cystography, Ultrasound Image on 3D-technology, Colour Doppler Imaging (CDI) and Power Doppler (PD), referred fine needle puncture aspiration cytology with preliminary modeling of a line of carrying out of a needle. It is used Ultrasound equipment - “SDU-1200”, “Viking 2400” and “GE Logic 7”.

The cytological researches were spent on a program complex “Leica DMLS” (augmentation x400 and x1000) with marking of micropreparations by methods of Romanovsky-Gimza and Pappenheim. The smears taken from a surface of a tumor and puncture material, received were studied at referred fine needle aspiration cytology (under the US-control). Degree of a radial pathomorphosis of tumor cells has been defined according to morphological classification by Lavnikova (1976).

Results and discussion

The age of patients with CC (n=120) was in limits 27-80 years old (medians - 52.5±3.3 age). Of them the greatest share was made by women 40-49 years old (28.3±4.1%), and the least - by women to 29 years old (3.3±1.6%), p<0.05. II stage of CC (n=61) has been established in 50.8±4.6%, III stage (n=59) - in 49.2±4.4%. It is verified histologically in 65.0±4.4% non keratinizing squamous cell carcinoma and in 2.5±1.4% - adenocarcinoma (p<0.05). The mixed growth of a tumor has been noted in 52.5±7.9% (1st and the group 2-cores) and in 42.5±7.8% - in the control (p<0.05). The analysis of
the specified parameters on separate groups has shown presence basically of cervical cancer: in 1-basic group - at patients 40-49 (37.5±7.6%), mainly II stage of process (62.5±7.6%), and morphologically -non keratinizing squamous cell carcinoma (70.0±7.2%) and the mixed growth of a tumor (52.5±7.9%), p<0.05. In 2-basic group among the diseased the greatest share women 40-49 (35.0±7.5%), III stage of the CC (60.0±7.7%), non keratinizing squamous cell carcinoma have made a cancer (62.5±7.6%) and the mixed character of growth (52.5±7.9%), р<0.05. In control group high frequency of the CC was observed at patients 50-59 (32.5±7.4%), II stage of disease (60.0±7.7%), non keratinizing squamous cell carcinoma (62.5±7.6%) and the mixed type of growth (42.5±7.8%), p<0.05.

Efficiency of ways of a radiosensibilization was estimated on character of changes of US-parameters of the tumor observed in the course of treatment. So, in dynamics reduction of average volume of a tumor was observed: in 1-basic group - with 53.2±7.9cm³ to 29.7±7.2cm³ (20Gy) and 5.9±3.7cm³ (after RT); in 2-basic group - with 63.2±7.6cm³ to 28.1±7.1cm³ (20Gy) and 3.0±2.7cm³ (after RT); in the control - with 48.8±7.9cm³ to 31.5±7.3cm³ (20Gy) and 6.9±4.0cm³ (after RT), р<0.05. And, after the treatment end, more expressed reduction of volume of a tumor was observed in the basic groups at III stage of the CC: 1-basic group - with 94.7±3.5cm³ to 8.8±4.5cm³ (an efficiency index-10.8), 2-basic group - with 60.3±7.7cm³ to 2.5±2.5cm³ (an efficiency index - 24.1). In the control at II and III stages of the CC almost identical regress of a tumor became perceptible: II stage - reduction of a tumor with 41.8±7.7cm³ to 5.0±3.6cm³ (an efficiency index - 7.5), III stage - with 59.8±7.7cm³ to 7.9±4.3cm³ (an efficiency index - 7.6), p<0.05.

The greatest reduction in dynamics of primary volume parametrium an infiltrate was observed: in 1-basic group - with 12.2±5.2cm³ to 1.7±2.0cm³ (at a lesion on the right); in 2-basic group - with 11.8±5.1cm³ to 0.4±0.9cm³ (at a lesion on the right); in the control - with 11.4±5.0cm³ to 0.2±0.7cm³ (at a lesion at the left).

The positive effect of the radiosensibilization methods was characterized by reduction of US parameters of the sizes of hypoechoic (tumoral) formations of a cervical cancer, change of the cervical echostructure, occurrence of more accurate and equal contours of CC, reduction of infiltrative changes expression, and occurrence of set of hyperechoic including of the linear form (fibrosis). Reorganization of structure of a tumoral tissue also was characterized by change of a parity of a stroma and a parenchyma towards intensifying of damage of a parenchyma (one of the basic Ultrasound-criteria of sensitivity of a tumor to therapeutic influence). At 3D-techniques reconstruction of an intratumoral vascular network in dynamics depression of total of vessels was observed, their more correct branching, absence of randomness and intermittence of their course became perceptible. At use of regimen PD the treatment positive effect was characterized by reduction of quantity of visualized vessels with rising of the signal strength, expressing degree of fibrous changes and depression of degree of vascularization. The results of the treatment are presented below (Table 1).

### TABLE 1. RESULTS OF TREATMENT OF PATIENTS WITH CERVICAL CANCER IN DEPENDENCE FROM IRRADIATION TECHNIQUES

<table>
<thead>
<tr>
<th>Patients</th>
<th>Treatment Stages</th>
<th>Results of Treatment</th>
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<tbody>
<tr>
<td></td>
<td>20Gy</td>
<td></td>
</tr>
<tr>
<td>1-basic group</td>
<td>after RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (12.5±5.2%)</td>
<td>15 (37.5±7.6%)</td>
</tr>
<tr>
<td>2-basic group</td>
<td>after RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 (75.0±6.8%)</td>
<td>6 (15.0±5.6%)</td>
</tr>
<tr>
<td>Control group</td>
<td>after RT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>28 (70.0±7.2%)</td>
<td>5 (12.5±5.2%)</td>
</tr>
</tbody>
</table>
Results of the treatment at sick basic groups have appeared authentically better than indicators of the control group, and the frequency of the full effect of a tumor after beam therapy was 82.5±6.0% (2-basic group) and 77.5±6.6% (1-basic group), whereas in the control - 70.0±7.2% (p<0.05). In other words, application of radio modifiers on combined radial therapy at sick basic groups has raised number of cases of 75-100% resorption of tumors on 7.5% (1-basic group) and 12.5% (2-basic group). Whereas, in the control group, in 7.5% of cases signs of the further local progression of the disease were observed that it was not marked in basic groups.

Comparison of the given ultrasonic’s and cytology’s research has shown that the degree of regress of a tumor directly correlates with expression of therapeutic damage to tumor cells that is expressed in rising of percent of pathomorphosis III-IV of degree (both in superficial smears, and in fine needle aspiration cytology a material). So, in 1-basic group in the presence of full effect in 77.5% cases, in cells the pathomorphosis of IV degree (superficial smears - 60.0%, puncture biopsy - 57.5%) has been taped mainly. In 2-basic group full effect in 82.5% cases, and in cells also mainly a pathomorphosis of IV degree (superficial smears - 85.0%, a puncture biopsy - 82.5%). In control group these indicators have appeared lower than in basic groups. So, in the presence of full effect at 70.0% of patients IV degree of a pathomorphosis has been established only in 60.0% (superficial smears) and 57.5% (puncture biopsy).

Thus, according to the US echography, expression of changes of spatial characteristics of a tumor data (tumors volume, density, echo structure, character and degree of intraorganic blood supply, peak shifts of acoustic parameters, infiltrative and fibrous changes of tissues of a small basin) is characterized by corresponding degree of a destruction of cellular elements of the malignant tumor which found in cytograms.

**Conclusion**

The comparative multifactorial analysis has shown authentic improvement of direct results of radial treatment of patients with cervical cancer at a radiosensibilization of a tumor inhibitors COX-2 (diclofenac, ketoprofen) with small doses of cytostatics (methotrextate, 5-fluouracil). Frequency of full regress of a tumor in the basic groups has made 77.5±6.6% (1-basic group) and 82.5±6.0% (2-basic group), whereas in the control - 70.0±7.2% (p<0.05). By results of the cytological researches in cells the primary pathomorphosis of IV degree in 1-basic group - 60.0% (superficial smears) and 57.5% (a puncture biopsy), in 2-basic group - 85.0% (superficial smears) and 82.5% (a puncture biopsy), whereas in the control - 55.0% (superficial smears and a puncture biopsy), p<0.05 is taped. In other words, the higher the destruction degree in a tumoral tissue (on change of US parameters of a tumor) the higher is a damage rate of cellular elements of a malignant tumor especially expressed in cytograms.

Thus, the use of a new combination of the known drugs applied as nonconventional radiosensibilizators is one of ways of optimization of radial treatment of patients with cervix cancer.

**References**