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Research Article

IMPROVEMENT OF TRADITIONAL METHODS FOR THE TREATMENT OF ENDOMETRIAL CANCER USING NEOADJUVANT CHEMOTHERAPY AND METHODS FOR EFFECTIVENESS ASSESSMENT

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Djurakhon Gafurovna Saidkhodjaeva
Associate Professor, Department Of Faculty Hospital Surgery, Andijan State Medical Institute, Andijan, Uzbekistan

ABSTRACT

Malignant neoplasms of the organs of the reproductive system have the largest share in the structure of oncological morbidity in women - 37.3%, and genital tumors account for 17.3% of all malignant neoplasms. According to the International Agency for Research on Cancer (IARC), about 500,000 new cases of malignant neoplasms of the cervix, almost 320,000 cases of endometrial cancer and 240,000 cases of ovarian cancer are registered annually in the world. In our research r=the studied patients were divided into two groups. The main group consisted of 52 patients with IB2, IIB and IIIB stages of CEM who underwent neoadjuvant chemotherapy followed by radical surgery and/or chemoradiotherapy. Determination of the risk of adverse prognostic factors with careful dynamic monitoring of the tumor process is one of the main conditions for the use of multicomponent treatment of patients with REM. The technological basis of monitoring is the integration of MRI and ultrasound into diagnostic standards.

KEYWORDS

Malignant neoplasms, endometrial cancer, neoadjuvant chemotherapy, methods for effectiveness assessment.

INTRODUCTION

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Endometrial cancer (EM) is the most common malignant tumor in women, most often of reproductive age [4,5]. The prevalence of the disease depends on age, SEM are detected, according to various sources, in 25-50% of women under the age of 50 years [3]. Most often, fibroids are detected in women aged 30-35 years, the average age of tumor detection is 32-33 years, the peak incidence is 35-45 years. Recently, there has been an increase in the frequency of detection of fibroids in young women (up to 20-25 years old), which is apparently associated both with the hereditary nature of the disease (when the mother, close relatives also had this disease), and with the introduction of new , more advanced diagnostic methods, as well as increasing their availability [1, 4,].Even with endometrial cancer, which differs from other localizations in a less aggressive course, every fourth patient has regional or distant metastases by the time the tumor is detected.

In addition to an increase in the incidence and the number of patients with common forms of malignant neoplasms, there is a tendency for a shift in the peak of incidence towards a younger age. Decreased over the past 5 years (according to world statistics by 3-4%) mortality from malignant neoplasms can hardly be considered encouraging.

MATERIALS AND RESEARCH METHODS

The study was of a prospective-retrospective nature. The results of examination and treatment of 98 patients were analyzed. The criterion for inclusion in this study was a morphologically verified squamous SEM of stages IB2, IIB and IIIB. All patients underwent outpatient and inpatient treatment at AFSMCO for the period from 2017 to 2020.

The studied patients were divided into two groups. The main group consisted of 52 patients with IB2, IIB and IIIB stages of CEM who underwent neoadjuvant chemotherapy followed by radical surgery and/or chemoradiotherapy. The comparison group included 46 patients with CEM stages IB2, IIB and IIIB, who received only combined radiation therapy according to a radical program. In all the studied patients, the morphological structure of the tumor corresponded to squamous cell carcinoma - keratinizing (55.2%) and non-keratinizing (44.8%).

All patients underwent a comprehensive examination using general clinical, laboratory and radiological diagnostic methods.The general clinical study consisted of a detailed study of the premorbid background of patients, their general somatic and gynecological status. The general condition of the patients ("performance status") was assessed using the ECOG–WHO scale [275; 276].

All patients included in this study corresponded to 0 - 1 degree of this scale. The use of standard laboratory methods and radiodiagnosis (X-ray of the chest organs, ultrasound of the abdominal cavity, kidneys, sigmoidoscopy, cystoscopy) made it possible to obtain the necessary information about the presence of complications

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and concomitant diseases, as well as possible distant SEM metastasis. The results of these studies were used to determine the tactics of patient management, the need for corrective therapy before the start of special treatment, and the choice of anesthesia.

When examining the cervix in the mirrors and bimanual palpation examination, the shape, size, nature of the growth of neoplasms, involvement of the vaginal fornix, spread of parametria to the tissues were determined. To compare the results obtained, the volume of the cervical tumor was calculated using the formula V = A x B x C x 0.52 (ellipsoid volume formula), where A, B, C are the sizes of neoplasms, including parametric infiltrates, in three orthogonal planes.

In addition to standard laboratory and instrumental research methods, MRI and ultrasound were used before the start of special treatment and at all its stages. MRI was performed on a Toshiba ExcelartVantage 1.5 Tesla machine using the Magnevist contrast agent at a dose of 0.4 ml/kg of body weight. Due to the different intensity of the signal from the neoplasm and surrounding tissues, the visualization of the tumor focus was noted, its shape, the nature of the contours, and density were recorded.

Infiltration of paracervical tissues was established by the broken ring of the cervical stroma, the spread of tumor tissue beyond the cervix. The presence of enlarged lymph nodes and their size were noted. The sizes of cervical neoplasms, including infiltrates (if any), were recorded in three orthogonal planes, and the volume was calculated using the ellipsoid formula. Ultrasound was performed on an ESAOT Mylab 70 scanner. The following methods were used: two-dimensional echography in B-mode, 3D reconstruction in B-mode, EDC, color flow, 3D angiography. We used multifrequency, broadband sensors with the ability to collect volumetric information in automatic mode.For transvaginal examination, a microconvex volumetric ultrasound probe with a frequency of 3-9 MHz and a scanning depth of 28-159 mm was used. Ultrasound images were archived in one block in the hard disk memory of the ultrasonic scanner workstation, USB media, and thermal paper. Recording volumetric information in the archiving system and further viewing of statistical and dynamic echograms "VIDARInfoRad2.0" provided the possibility of a retrospective comparative analysis of the data obtained.

Examination of patients began with transabdominal ultrasound against the background of a filled bladder. The procedure was performed as standard in the supine position. After emptying the bladder, a transvaginal examination was performed. At the same time, the relative position of the pelvic organs, the state of the bladder, position, overall dimensions (length, width, anteroposterior), shape, contours and internal echostructure of the body and cervix were assessed; anterior-posterior size (Fig.1), contours and echostructure of the median uterine structures (M-echo), also determined the echostructure of regional lymph nodes.

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Figure 1. SEM of stage T2aN0M0. Vaginal variant (longitudinal scan).

The next step was ultrasound in three-dimensional B-mode. This method, thanks to the three-dimensional reconstruction of the obtained image, makes it possible to obtain a section of the studied organ in any desired plane [71], which plays an important role in determining the volume of the neoplasm [173] (Fig. 2).

Figure 2. 3D echogram (surface reconstruction mode). SEM stage T4 (bladder wall invasion)

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Next, the vascular structures of the cervical tumor were examined. In a qualitative assessment of intratumoral blood flow, the degree of vascularization, the location of vessels, their shape, uniformity, different calibers, discontinuity in the course, and distribution density were determined.

With the help of color doppler, an ultrasound image of the blood flow in the vessels was obtained by displaying the movement of erythrocytes. In the EDC mode, angle-independent images of vascular structures were obtained. The method, which is based on the analysis of the density of erythrocytes in a given volume, makes it possible to visualize vessels running at any angle and in any direction (Fig. 3).

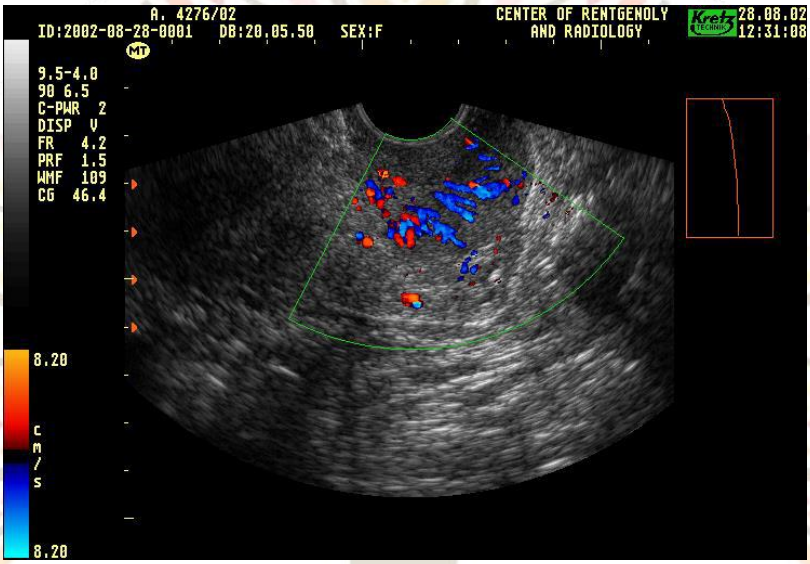

Figure 3 Doppler SEM of stage IB2 in CFM mode.

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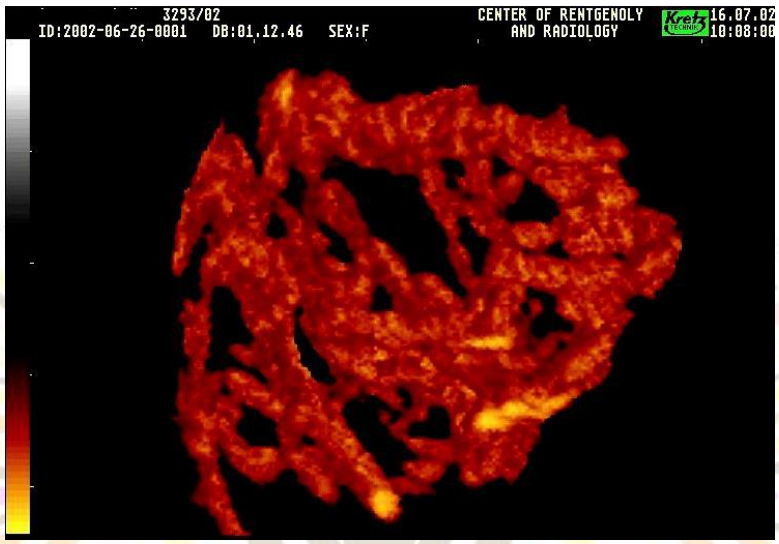

Figure 4. Doppler SEM stage IIA in the EDC mode.

3D Doppler ultrasound, as well as 3D reconstruction of sections obtained in the EDC mode, was used to obtain a spatial display of intratumoral blood flow (Fig.5).

Figure 5. Three-dimensional SEM angiogram stage III B (in EDC mode).

To assess the nature and speed of blood flow in the tumor vessels, the method of pulsed flow spectral Doppler was used. A control volume marker was placed at the blood flow study point, and all vessels were visualized, regardless of their course relative to the ultrasound beam. The resulting frequency shift was processed automatically, obtaining curves of blood flow velocities, which were used to calculate Doppler parameters and indices.

When analyzing the blood flow velocity, the following indicators were determined: the maximum systolic blood flow velocity (MCV), which reflects the highest velocity at the location point, the maximum end-diastolic blood flow velocity (DPV), which reflects the highest velocity at the end of diastole, the peripheral resistance index (resistance index - IR), which is the ratio of the difference between MSS and CDS to MSS. For the study of intratumoral blood flow, three color loci of different types were determined, which had the highest MCC and IR values, the lowest IR values, and the highest venous blood flow velocity.

Morphological studies were carried out in the pathological departments of the AFSMC.

RESULTS AND DISCUSSIONS

The studied patients were divided into three subgroups depending on the method of neoadjuvant chemotherapy. The dynamics of tumor size with its infiltrates was considered as an indicator of the effectiveness of cytostatic.

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Determination of the effectiveness of the effects of cytostatic was carried out 14 days after the end of their administration. A clinical study, MRI and ultrasound were used, the obtained data were compared with each other and, subsequently, with the results of a pathomorphological study of the surgical material.

Tolerability, the number of side effects of anticancer drugs were assessed, the diagnostic value of various methods of examining patients was studied in the formation of tactics for further management.

When using cytostatic, one of the complex problems is their systemic toxicity associated with a non-selective effect on tumor and healthy cells of the body. The emerging complications of chemotherapy can significantly impair the quality of life of patients, and early prevention and correction of side effects are a prerequisite for adequate treatment of patients.

In our study, 26 courses of systemic chemotherapy were performed, as well as 26 courses of combined chemotherapy with intravenous administration of paclitaxel and carboplatin with the addition of local intra-arterial infusion and embolization of tumor vessels.

Chemotherapy was accompanied by standard premedication and administration of antiemetogenic drugs. In all studied groups of patients, satisfactory tolerability of drug therapy was noted, the general condition of patients on the ECOG scale during treatment did not decrease by less than 1 point, the manifestation of side effects of cytostatics on the CTCAE toxicity scale did not exceed the second degree. Manifestations of gastrointestinal toxicity were noted in 15 patients treated using only intravenous cytostatics (57.9%) (n=26). Of these, grade I nausea on the CTC toxicity scale was noted in 8 patients (30.7%), grade II nausea in 6 (23.1%). Vomiting of I degree was noted in 7 patients (26.9%), II degree - in 1 case (3.8%).

In the subgroups of patients who received intra-arterial chemotherapy and embolization of tumor arteries (n=17), manifestations of gastrointestinal toxicity were noted in 9 (64.7%). Nausea I degree was observed in 9 patients (52.9%), II degree - in 7 (41.1%). In 3 patients of all subgroups, vomiting of the 1st degree (5.8%) was noted. We did not observe nausea and vomiting of III-IV degree among the studied patients of both groups.

Anemia, neutropenia and thrombocytopenia were noted in the studied patients in the analysis of hematological toxicity.

The initial anemia was in 21 studied patients with REM of both studied groups (21.4%). If necessary, patients underwent special hemostimulating treatment; by the time chemotherapy began, the hemoglobin level was at least 100 g/l.

Neutropenia I degree (not lower than 2.0x109/l) was established in 18 cases in patients in the group of intravenous administration of cytostatics and in 7 patients after intra-arterial administration. The level of neutrophils was restored without the use of hemostimulating therapy in all cases. The blood test was monitored

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5 days after the administration of cytostatic; if signs of neutropenia were detected, appropriate drugs were prescribed, which made it possible to carry out the planned treatment without violating the terms and volumes.

Thrombocytopenia of the 1st degree was established in 10 (10.2%) patients who received only intravenous administration of cytostatics, the level of platelets below 90x109/l was not observed, specific therapy was not required. Among patients subjected to intra-arterial chemotherapy, thrombocytopenia was not observed.

Nephrotoxicity was manifested in the form of a slight increase in blood creatinine levels. In 18 (18.3%) patients who received only intravenous chemotherapy, and in 6 patients (6.1%) from the intra-arterial chemotherapy group, the creatinine level increased to 120 mmol/l. These changes stopped without special treatment.

Thus, the introduction of anticancer drugs up to individually planned dosages was carried out in all patients with REM. In general, the treatment was well tolerated, there were slightly fewer manifestations of gastrointestinal and hematological toxicity with intra-arterial administration of chemotherapy drugs, but no statistically significant differences were found.

CONCLUSIONS

The highest incidence of endometrial cancer was found in the age group of 30-39 years with the largest number of patients in the reproductive period. The use of neoadjuvant chemotherapy in patients with CEM stages IB2 – IIIB made it possible to achieve complete tumor regression in 5.7% of cases, partial regression in 83.3%. Radical operations were performed in 91.9% of cases and determination of the risk of adverse prognostic factors with careful dynamic monitoring of the tumor process is one of the main conditions for the use of multicomponent treatment of patients with REM. The technological basis of monitoring is the integration of MRI and ultrasound into diagnostic standards.

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