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THE ROLE OF RADIATION THERAPY IN THE TREATMENT OF PATIENTS WITH THE VULVAR CANCER

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РОЛЬ ПРОМЕНЕВОЇ ТЕРАПІЇ В ЛІКУВАННІ ХВОРИХ НА РАК ВУЛЬВИ

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РОЛЬ ЛУЧЕВОЙ ТЕРАПИИ В ЛЕЧЕНИИ БОЛЬНЫХ РАКОМ ВУЛЬВЫ

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Summary/Резюме

Vulvar cancer is a rare malignant tumor, accounting for 3-8% of the total incidence of malignant tumors of the female reproductive system. However, in the structure of mortality, this pathology ranks fourth after cancer of the cervix, uterine body and ovaries and amounts to 18.2%. Features of the anatomical structure of the external genital organs of a woman with a developed system of blood and lymphatic vessels cause an aggressive course, a tendency to metastasis and rapid growth of a tumor of this localization. Prospects for the timely diagnosis of vulvar cancer and vaginal tumors are directly related to an increase in literacy and oncological alertness of staff in general medical institutions, in the implementation of which not only the detection of the disease in the early stages, but also work with women from risk groups to refer them to further examination and, if necessary, for treatment in a specialized institution. High mortality from these diseases is associated with the appeal of women at the late stages of the development of the oncological process, as well as with the insufficient effectiveness of the therapy, which necessitates the development of research in this area.

Key words: *vulvar cancer, x-ray therapy, chemotherapy.*

Рак вульви - рідкісна злоякісна пухлина, яка складає 3-8% від загальної захворюваності на злоякісні новоутворення жіночої репродуктивної системи. Однак в структурі смертності дана патологія займає четверте місце після раку шийки матки, тіла матки і яєчників і становить 18,2%. Особливості анатомічної будови зовнішніх статевих органів жінки з розвиненою системою кровоносних і лімфатичних судин зумовлюють агресивний перебіг, схильність до метастазування і стрімке зростання пухлини цієї локалізації. Перспективи своєчасної діагностики раку вульви і пухлин піхви безпосередньо пов'язані з підвищенням грамотності та онкологічною настороженістю персоналу в лікувально-профілактичних установах загального профілю,

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завдання яких не тільки виявлення захворювання на ранніх стадіях, а й робота з жінками з груп ризику, спрямована на направленні на дообстеження і, при необхідності, на лікування в спеціалізований заклад. Висока летальність від цих захворювань пов'язана зі звертанням жінок на пізніх стадіях розвитку онкологічного процесу, а також з недостатньою ефективністю проведеної терапії, що вимагає розвитку досліджень в цій області.

Ключові слова: рак вульви, променева терапія, хіміотерапія.

Рак вульвы - редкая злокачественная опухоль, составляющая 3-8% от общей заболеваемости злокачественными новообразованиями женской репродуктивной системы. Однако в структуре смертности данная патология занимает четвертое место после рака шейки матки, тела матки и яичников. составляет 18,2%. Особенности анатомического строения наружных половых органов женщины с развитой системой кровеносных и лимфатических сосудов обуславливают агрессивное течение, склонность к метастазированию и стремительный рост опухоли данной локализации. Перспективы своевременной диагностики рака вульвы и опухолей влагалища напрямую связаны с повышением грамотности и онкологической настороженностью персонала в лечебно-профилактических учреждениях общего профиля, задача которых не только выявление заболевания на ранних стадиях, но и работа с женщинами из групп риска по направлению на дообследование и, при необходимости, на лечение в специализированное учреждение. Высокая летальность от этих заболеваний связана с обращением женщин на поздних стадиях развития онкологического процесса, а также при недостаточной эффективности проводимой терапии, что требует развития исследований в этой области.

Ключевые слова: *рак вульвы, лучевая терапия, химиотерапия.*

The relevance of research

In the structure of morbidity and mortality among all malignant tumors of the female genital organs, vulvar cancer ranks fourth (3-8%), and in recent years the incidence of this pathology has a tendency to increase. Vulvar cancer is a malignant neoplasm that can occur in any part of a woman's external genitalia, but most often affects the labia majora or labia minora. Despite the simplicity and ease of diagnosis and the incidence of vulvar cancer in situ (stage 0) has more than doubled in the last 20 years, the incidence of invasive squamous cell carcinoma of the vulva remains stable and does not tend to decrease. To date, it is known that with timely detection (0, I and II stages) and treatment, the average 5-year survival of patients with vulvar cancer is approximately 70%. At the same time at patients with intact lymph nodes (0, I and II stages) this indicator makes about 90% whereas at involvement of lymph nodes in pathological process the 5-year survival rate decreases to 50%. The average age of patients with vulvar cancer at the time of detection of the disease is 68 years, the highest in comparison with other tumors of the reproductive system. In 2018 there were 24 new cases of vulvar cancer in Odessa region, including 30% of them that were at late stages. The index of 1-year lethality was 25% for the vulvar cancer in Odessa region.

Up to date, the five-year survival of patients with vulvar cancer, according to various authors, is from 23 to 60%, of which locally distributed forms does not exceed 30% five-year survival [2, 3, 9, 10]. In this regard, many aspects of the treatment of vulvar cancer still remain

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controversial. These include: the application of various methods of radiation therapy,the volume of surgery, the possibility of a combination of surgery,radiation and drug treatment.

Planning of the vulvar cancer treatment should take into account the specifics of blood supply to external genitalia, with an extremely elaborated network of lymphatic vessels, predisposing for a quite aggressive pace of development and the rapid nature of locally regional distribution with infiltration of the adjacent tissues, early metastasis to regional (inguinal and femoral) lymph nodes and multicentric growth.

The disease is common in the elderly who are characteristic for the reduction of functional and adaptive-compensatory capabilities of the organism, high frequency of comorbid diseases of various organs and systems and metabolic disorders with the development of skin and mucous membranes dystrophy. The above factors cause high recurrence rate, which ranges from 8% in stage I to 80% in stage IV of the diseases [1, 12, 14, 15].

Undoubtedly, in matters of determining the tactics of treatment as well as radiation therapy in vulvar cancer not only the methods of physical and clinical examination are important, but also the currently widely available non-invasive and minimally invasive diagnostic methods (ultrasound,computed tomography, magnetic resonance therapy). Data obtained from using these methods help to clarify the extent of the tumor process, assessment of the size of the primary focus, involvement of the anatomically related organs (urethra, anus, paraurethral tissue, pararectal tissue) and allow to diagnose regional and distant metastases, with the monitoring of the tumor process. Modern principles of treatment of vulvar cancer are strictly individual taking into account the peculiarities of the course of the malignant process in this area.Analyzing the data of various studies, N. Hacker (2012) suggested the main standpoints, determining the tactics of treatment of patients with vulvar cancer [15]:

- the volume of operation is determined individually;
- in the absence of multicentric tumor growth and precancerous diseases the vulva is preserved;
- in tumors not exceeding the diameter of 2 cm and the depth of invasion no more than 1 mm, inguinal lymphadenectomy is not performed;
- Pelvic lymphadenectomy is no longer a standard operation for vulvar cancer. At present its indications are very limited;
- inguinal lymphadenectomy and vulvectomy are performed from individual skin incisions which facilitates healing;
- in a peripheral localization of a tumor, which diameter does not exceed 2 cm and in the absence of metastases to the inguinal lymph nodes on the affected side, the contralateral inguinal lymph nodes are not removed;
- in the late stages, before surgery,the radiation therapy is performed. In some cases this helps to avoid exenteration of the pelvis. - in multiple metastases to inguinal lymphonodes postoperative radiation therapy is carried out, which reduces the risk of progression. However, despite the proposed standpoints, the role of radiation therapy in the treatment of this pathology is significant and ambiguous. Necessity and indisputability of the radiation therapy as a tool of combined treatment in the pre and / or postoperative radiation and as an independent radical course of treatment is attributed to many factors:
- the size of the primary focus and the depth of the invasion, localization of the tumor process;

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- histological structure of the tumor, its degree of differentiation;
- non-radical volume of the operation at the first stage (elements of tissue tumor along the edge of the resection);
- condition of the vagina, paravaginal and parauretral tissues, bladder;
- the condition of the inguinal, femoral and pelvic lymph nodes, their size and extent of damage.

Clinical experience shows that the use of combined therapy increases 5-year survival rate for 20% [4, 7, 24].Indicators of 5-year survival in combined treatment of stage II – III of the vulvar cancer for 58.7% [2, 7]. Overall cumulative 5-year patient survival ranges, according to different authors, from 31.7% [4, 9, 24]. Carrying out postoperative radiation therapy reduces the likelihood of disease progression and reduction of recurrences by 1,5 times [17].

As a radical independent method, radiation therapy is used in cases of absolute contraindications to surgery due to decompensated comorbidities or late stage, advanced forms of the main diseases, metastatic and recurrent forms of the disease. The localization of the vulvar tumor does not play the last role in determining the tactics of treatment. The close proximity to adjacent anatomical structures - urethra, vagina, anus or their involvement, sharply reduces the role of surgery, and accordingly causes an increase in the role of the radiation therapy. In addition, there observed a tendency in the recent decades for rejuvenation and diagnostics of the early forms of the vulvar cancer “in situ” , which encourages to search for new approaches in therapy of this pathology with the development of organ-preserving treatment methods that reduce psycho-emotional disorders and improve the quality of life especially in young people.

The starting point for the use of radiation therapy in vulvar cancer was X-Ray, which was used in the treatment of skin cancer. For a long time, near-focus radiotherapy, and subsequently, gamma teletherapy with classical dose fractionation was the traditional choice of radiation treatment of vulvar cancer [8, 6, 15, 22]. In radiation therapy of vulvar cancer it is fundamentally important to create an optimal dose distribution in the lesion site, ie strict individual planning, which is due to the anatomical features of the organ and different localization of the tumor process [16,18]. Modern radiotherapeutic technologies, alongside with the radiobiological achievements of recent years, give the chance to provide guarantees of quality of a radiation therapy in various treatment programs, to optimize radiation therapy options with different types and energies of ionizing radiation using tele-, intracavitary, intratissue and application methods of radiation [5,11, 19, 21].

The application of these methods stepwise or as a single option is determined by the general tactics of specific situation management with taking into account the stage of the disease,tumor localization, morphological structure,previous treatment and general somatic condition of the patient. Radical or combined radiation therapy assumes onemoment or consecutive exposure to radiation of the primary focus and areas of regional metastasis with achievement of complete carcinogenic effect. The tasks of the combined method of treatment are more diverse. Preoperative radiation therapy is aimed at: reducing the volume of the primary tumor process and, accordingly, the volume of surgery, which reduces the risk of postoperative complications, and most acceptable in people with local process (II-III stage of the disease). Postoperative radiation therapy is undeniable at doubtfully radical operations of the I – III stages disease, its role is to prevent and reduce the frequency of local and locore-

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gional recurrences of the disease. Goals and objectives of palliative and symptomatic radiation therapy for vulvar cancer are aimed at reducing manifestations of any symptoms (pain, bleeding), using gentle doses of ionizing radiation.

In conduction of the radiation therapy there should be taken into account the following:

- topographic data on the linear dimensions and the volume of the tumor process, the involvement of other organs and tissues, regional lymph nodes;
- instrumental and methodical equipment of the radiation therapy;
- determining the priorities of the remote or contact iadiation or their combination taking into account anatomical and topographic features of the tumor and surrounding tissues;
- the possibility and necessity of individualization of physico-dosimetric and radiobiological planning, using traditional and non-traditional methods of radiation (hypo-, hyper- and dynamic fractionation).
- the possibility of adjusting the plan of radiation therapy, taking into account the rate of regression of the tumor process;
- the place and role of various methods of radiation therapy in programs of combined, complex and radical concomitant radiation therapy.

Methods of the X-ray teletherapy.

X-ray therapy - the maximum dose is located on the the top of the skin, and 90% of the dose at the depth of about 2 cm. This method can be used when radiating minimally invasive forms of vulvar cancer. Gamma therapy - the maximum dose is shifted from the skin surface skin at the depth of 5 cm, which allows you to radiate infiltrative forms of the primary tumor and the regional zone metastasis.

Photon radiation - electron beams generated by betatron or linear accelerator with energy from 6 to 20 MeV and the range of particles in tissues up to 5-7 cm, 80% of the isodose is at a depth of 3–5 cm from the surface. alignment of radiation fields is possible with application of bonuses. The advantage of this type of radiation is the possibility of changing the energy of electrons and therefore a more optimal distribution over therapeutic isodose circuit. Dimensions of radiation fields at radiation teletherapy of the primary center, taking into account the volume of the tumor and of the used source of irradiation, make from 4–8 ·5–8 cm. At radiation of zones of regional metastasis the dimensions of the radiation fields are 8–10 · 10–12 cm. If it is necessary to radiate the iliac limph collectors, the following field sizes are used for radiation - 4–6 · 14–16 cm. Fractionation modes at remote irradiation of the primary center:

- classical fractionation of total boost dose (TBD) - 2.0 Gy,daily 5 fractions up to TBD - 40.0 Gy on the primary center and TBD - 60.0 Gy for areas of regional metastasis;
- hyperfractionation of single boost dose (SBD) 3.0–4.0 Gy with daytime breakdown after each 4-5 hours to SBD 39.0 Gy;
- dynamic fractionation taking into account the pace of tumor regression from day 1 to day 3 - SBD 4.0 Gr. From 4th day SBD 3.0 Gy with daily breakdown of 1.5 Gy · 2 times in a day TBD 33, 0 Gr [12].

Irradiation of areas of regional metastasis is carried out under traditional fractionation SBD 2.0 Gy · 5 times a week or hyperfractionation 3.0–4.0 Gy with breakdown of the daily dose to TBD 40.0–60.0 Gr depending on the presence or absence of metastatic lesions of regional lymph nodes. When performing only remote radiation therapy to the area of the

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primary focus, the TBD should be not less than 60.0 Gy. Due to the high radiosensitivity of external tissues genitals and the development of early radiation reactions, the implementation of the required total absorbed doses are achieved through the use of split courses irradiation. There should be no break in treatment exceeding 2-3 weeks. Contact irradiation of the primary or recurrent vulvar tumors involve the use of intratissue, intracavitary or application irradiation. For intracavitary and intratissue irradiation gamma-therapeutic hose devices are used on the principle of remote after loading, equipped with 60Co, 137Cs, 192Ir sources.

The advantage of these methods is the possibility of bringing directly to the tumor the center of high absorbed doses with rather homogeneous distribution on a therapeutic contour. Choice of intracavitary or intratissue technique depends on the location of the tumor, its length and volume [20, 23]. Single focal doses from intracavitary radiation therapy is 3.0–7.0 Gy in depth 0.5 cm from the surface at TBD 20.0–30.0 Gr. Conducting Intratissue radiation therapy involves the use of MUPIT template to implement introduction of needles in tissues with preservation of the set geometry, corresponding to the shape and volume of the tumor [10, 18]. Single and total focal doses from intratissue radiation therapy are calculated taking into account the activity and power of radiation sources. Depending on the volume of the irradiated surface the number of needles used is from 4 to 18 with length of active chain from 40 to 110 mm. Prolonged irradiation assumes summing up of the focal dose for one fraction (from 30.0 to 45.0 Gy) over irradiation time up to 25 hours. When using sources of high activity with short-term irradiation, the dose of 30.0–40.0 Gy is implemented in several fractions with a break up 5 to 7 days. The total focal dose atcontact therapy is determined by the method of treatment. In programs of combined or complex treatment it varies from 30.0 to 45.0 Gy. Radical course of contact radiation therapy requires implementation of the full carcinogenic dose to the primary tumor lesion (60.0–70.0 Gy).

In recent years researches it is the more commonly met works on system or local chemotherapy in vulvar cancer treatment programs [7, 14,16, 26]. Indications for chemotherapy are: common forms of vulvar cancer with a large length of the tumor process, absolute contraindications to surgical treatment, absence of therapeutic effect in radiation therapy.It is neoadjuvant chemotherapy that has received the widest practical application, aimed at reduction of linear sizes and volume of primary focus, affected lymph nodes and creation of the best conditions for conducting a combined or radical radiation therapy.

Cytostatic therapy in using the necessary number of courses of adequate selection of doses, keeping to the terms of introduction, allows to achieve increase in efficiency and quality of lives of patients. The morphological form of vulvar cancer is mainly represented by a squamous cell carcinoma that allows to recommend for systemic combination chemotherapy with the following drugs:

- 5-fluorouracil - 500 mg/m^2, 1st day;
- vincristine - 1.4 mg/m^2 intravenously, 1st day;
- bleomycin - 15 mg intramuscularly or intravenously,5 days in a row or - bleomycin - 10 mg/m^2 intramuscularly 2 times in a week, 2-3 weeks;
- methotrexate - 10 mg / m^2, oral administration, 2 times a week, 2- 3 weeks. The courses are repeated in 3 weeks (N.I. Perevodchikova,2000).

In patients with advanced or recurrent cancer of vulva, it is preferably to use the following schemes of polychemotherapy:

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- cisplatin 70–90 mg/m^2, intravenous infusion, with at a rate of infusion no more than 1 mg / min with pre- and posthydrationon on day 1, vinorelbine 25 mg/m^2 intravenously for 6–10 min on the 1st and 8th days;
- cisplatin 75 mg / m^2 intravenous infusion at a rate of no more than 1 mg / min with pre- and posthydration in the 1st day, fluorouracil 4 g/m^2 intravenously as a continuous infusion for 96 hours; - mitomycin C - 10 mg/m^2 intravenously for20–30 min on the 1st day, fluorouracil - 1 g / m2 intravenously 24-hour infusion starting 30 minutes after administration of mitomycin C on days 1, 2, and 3.

There are works that deserve certain attention, pointing at the advantage of endolymphaticpolychemotherapy in the treatment of vulvar cancer. Chemotherapeutic drugs are introduced into the lymphatic system of the lower limbs, which allows to bring high doses to primary tumor and metastatically altered lymph nodes. Use in the preoperative period of the endolymphatic administration of cyclophosphamide in a single dose of 100 mg or methotrexate in a single dose of 100 mg with intervals of 7 and 10 days followed by the subsequent radical surgery allows to achieve an overall 5-year survival up to 72.1%. In the literature there met reports on contact chemotherapy in patients with vulvar cancer by the method of dry-jet administration of chemotherapeutics under high pressure into the tumor tissue to a depth of 5 to 50 mm. Despite the use of large course doses of drugs (cyclophosphamide 6000-30000 mg, methotrexate up to 1000 mg, olivomycin 400–1000 mg, colchicine 40–12 mg), there were no noted severe manifestations of general toxic effect [14]. Clinical data on the use of chemotherapy with combined or radiation treatments in vulvar cancer has no standardized guidelines. In this regard, the use of new drugs is of high interest, in particular, use of taxane derivatives, lomustine, capicitabine in cases of prognostically unfavorable forms of vulvar cancer in various programs treatment. Thus, clinical and methodological principles of planning and implementation of modern surgical, radiation and chemotherapeutic treatment methods allow to carry out highly effective,organ-preserving treatment of vulvar cancer.

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ВПЛИВ КСАВРОНУ ТА РЕЗОНАНСНОЇ МАГНІТО-КВАНТОВОЇ ТЕРАПІЇ НА БІОЕЛЕКТРИЧНУ АКТИВНІСТЬ ГОЛОВНОГО МОЗКУ У ПАЦІЄНТІВ, КОТРІ ПЕРЕНЕСЛИ ГОСТРІ ПОРУШЕННЯ МОЗКОВОГО КРОВООБІГУ

Тещук В.Й., Тещук Н.В., Руських О.О.

ВЛИЯНИЕ КСАВРОНА И РЕЗОНАНСНОЙ МАГНИТО-КВАНТОВОЙ ТЕРАПИИ НА БИОЭЛЕКТРИЧЕСКУЮ АКТИВНОСТЬ МОЗГА У ПАЦИЕНТОВ, ПЕРЕНЕСШИХ ОСТРОЕ НАРУШЕНИЕ МОЗГОВОГО КРОВООБРАЩЕНИЯ

Тещук В.И., Тещук Н.В., Русских А.О.

EFFECT OF XAVRON AND RESONANCE MAGNETO-QUANTUM THERAPY ON BIOELECTRIC BRAIN ACTIVITY IN PATIENTS WITH ACUTE CEREBRAL CIRCULATION DISORDERS

Teshchuk V.J., Teshchuk N.V., Russkykh O.O.

Summary/Резюме

The article presents the results of a comprehensive analysis of the effect of the course complex application of Xavron and resonant magnetic quantum therapy (RMQT) on the bioelectrical activity of the brain (BEAB) in 33 patients who underwent acute cerebrovascular accident (ACVA) by ischemic type (IT) in the recovery period. Patients received RMQT sessions in combination with intravenous Xavron (20.0 ml per 200.0 ml