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MODERN CHEMORADIATION THERAPY TECHNIQUES IN THE TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER (LITERATURE REVIEW)

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ABSTRACT. Objective of the Study: To analyze literature data on the novel techniques of chemoradiation therapy for locally advanced cervical cancer.

Materials and Methods: The review comprises an analysis of articles submitted in the PubMed database.

Results: Image guidance in intracavitary radiation therapy allows for the individual optimization of dose distribution, enabling the maximum dose to be delivered to the target volume while minimizing radiation dose to organs at risk. Intracavitary radiation therapy is a decisive stage in treatment, where the local tumor volume in cervical cancer receives the maximum dose of exposure, equivalent to the total dose achieved from external beam conformal radiation therapy. Therefore, intracavitary radiation therapy is a major prognostic factor in the local control of cervical cancer.

Conclusion: It is expected that the use of 3D planning in intracavitary radiation therapy will expand in clinical practice in the near future and will be comparable in complexity to conformal radiation therapy technologies.

Keywords: Cervical cancer, conformal radiation therapy, intracavitary radiation therapy, intratissue radiation therapy.

СОВРЕМЕННЫЕ МЕТОДЫ ХИМИОЛУЧЕВОЙ ТЕРАПИИ МЕСТНО-РАСПРОСТРАНЁННОГО РАКА ШЕЙКИ МАТКИ (ОБЗОР ЛИТЕРАТУРЫ)

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АННОТАЦИЯ. Цель исследования. Провести систематизированный анализ современных научных данных, посвящённых инновационным технологиям химиолучевой терапии в лечении местно-распространённого рака шейки матки.

Материалы и методы. В обзор включены публикации, отобранные по ключевым словам в базе данных PubMed. Анализ осуществлялся с учётом

актуальности исследований, качества методологии и значимости полученных результатов для современной онкогинекологии.

Результаты. Использование методов визуального контроля при внутриполостной лучевой терапии обеспечивает высокую степень персонализации дозиметрических параметров, что позволяет максимизировать доставку терапевтической дозы в опухолевый очаг при одновременной минимизации радиационной нагрузки на органы риска. Внутриполостная брахитерапия является критически значимым компонентом комбинированного лечения, определяющим успех локального контроля заболевания. Суммарная очаговая доза, достигаемая на данном этапе, сопоставима или превосходит дозу, обеспечиваемую дистанционной конформной лучевой терапией, что подчёркивает её решающую роль в терапевтической стратегии.

Заключение. Ожидается, что дальнейшая интеграция трёхмерного планирования в практику внутриполостной брахитерапии усилит её клиническую эффективность и приблизит технологическую сложность процедуры к современным высокоточным методам дистанционной лучевой терапии. Данные тенденции подтверждают необходимость широкого внедрения 3D-визуализационных технологий в рутинную клиническую практику онкологических центров.

Ключевые слова: рак шейки матки; конформная лучевая терапия; внутриполостная брахитерапия; внутритканевая лучевая терапия; химиолучевое лечение.

Introduction. The high incidence and mortality rates of cervical cancer (CC) are alarming and represent a significant global health problem. The majority of newly diagnosed cases of cervical cancer in women occur in economically developing countries, where limited access to adequate treatment is due to poor availability of medical equipment and pharmaceutical supplies in healthcare institutions. As a result, mortality rates remain high. Consequently, treatment recommendations for cervical cancer, developed in economically advanced countries, are not adequately applicable in many developing countries.

It is known that the primary method for treating patients with locally advanced cervical cancer (LACC), where the tumor extends beyond the organ and shows signs of spread to adjacent tissue, vagina, pelvic lymph nodes, and abdominal cavity, is radical combined chemoradiation therapy. The improvement of computer technologies and imaging tools has fundamentally changed the strategy for both external beam radiation therapy (EBRT) and intracavitary radiation therapy (ICRT), allowing for the precise delivery of the prescribed dose to the target volume without exceeding the tolerance of critical organs.

With the advent of 3D planning for intracavitary radiation therapy, new challenges and opportunities arise for clinicians, which must be addressed and realized through a multidisciplinary approach.

1.1 External Beam Conformal Radiation Therapy. The main tasks of external beam radiation therapy (EBRT) are: targeting the primary tumor site and

the regions of regional metastasis, which consequently improve the technical conditions for intracavitary irradiation.

Currently, all methods of external beam radiation therapy can be conditionally divided as follows: conventional irradiation, conformal irradiation, intensity-modulated radiation therapy (IMRT), and image-guided radiation therapy (IGRT).

The main principle of conformal radiation therapy is to create a high dose at the target while minimizing the dose to surrounding normal organs and tissues as much as possible.

For 3D planning, the International Commission on Radiation Units and Measurements (ICRU) No. 50 and 62 introduced the concepts of therapeutic volumes, which are mandatory for use:

- GTV (Gross Tumor Volume): the determined tumor volume that requires the maximum therapeutic dose.
- CTV (Clinical Target Volume): the clinical target volume, including the GTV and the area of subclinical manifestations.
- PTV (Planning Target Volume): the planned target volume sufficient to irradiate the entire CTV with the required dose.
- OAR (Organ-at-Risk) and PRV (Planning Organ-at-Risk Volume): the planned volume of the organ at risk included in the therapeutic isodose contour [1, 2].

Optimal dose distribution should meet the following criteria:

- 95% of PTV should receive >90% of the planned dose.
- 120% of the planned dose can be received by <10% of PTV.
- 60% of the planned dose can be received by <5% of OAR.

The maximum dose occurs within PTV [3].

The general principles of volume and field boundary planning for external irradiation of the pelvis, including the regions of regional metastasis in cervical cancer, are well-known. The total dose during EBRT is 46-50 Gy with daily fractionation of 2 Gy, which is the standard in Russia. A similar dose should be applied to the para-aortic lymph nodes if affected. The American Brachytherapy Society has recommendations stating that in cases of para-aortic lymph node involvement, an additional dose in the form of a local boost should be given to achieve a total dose of 60-70 Gy [11]. To reduce local recurrences and distant metastasis, it is recommended to combine external radiation therapy with cisplatin-based chemotherapy at a dose of 40 mg/m², which remains the standard treatment today [4].

Thus, volumetric planning allows for more precise delineation of the boundaries between the clinical and planned target volumes, especially in cases of locally advanced cervical cancer with regional pelvic and para-aortic lymph node involvement. Several studies have been dedicated to investigating biological factors that influence the response to radiation in locally advanced cervical cancer, showing that conventional external irradiation of the entire pelvis with a total dose of 35-50 Gy (2 Gy per fraction) may not be sufficient. According to the literature,

approximately 50% of patients after such external radiation therapy have residual tumors of varying sizes, expressing oncogenic proteins associated with radioresistance [4,5].

Therefore, by the time intracavitary radiation therapy is performed after the completion of EBRT, the residual tumor consists of a pool of relatively radioresistant cells. Thus, the goal of external radiation therapy at the first stage of the radical combined treatment course for locally advanced cervical cancer is to achieve partial tumor regression, suppress tumor growth, reduce inflammation in surrounding tissues, and, consequently, create conditions for the administration of intracavitary radiation therapy.

A study conducted under the leadership of Kalash R. and colleagues (2018) noted that integrating PET/CT helps accurately identify patients at risk of recurrence and helps to identify patients with a worse distant prognosis. According to the presented data, incomplete responses after the intracavitary radiation therapy phase were observed in 20% of patients [6].

In studies by Malyapa R. et al. and Lin L. et al., the role of PET/CT in planning intracavitary radiation therapy sessions was evaluated, with authors reporting better target volume coverage without significantly increasing the dose to organs at risk.

1.2 Chemotherapy. External beam conformal radiation therapy, combined with chemotherapy and followed by intracavitary radiation therapy in the second stage of treatment, is the standard treatment for locally advanced cervical cancer (LACC). The total duration of the chemoradiation therapy course should not exceed 55 days.

A meta-analysis (Duenas-Gonzalez et al., 2003), based on 18 studies involving 3452 patients, showed that chemotherapy with cisplatin was used in 85% of patients, although chemotherapy regimens without platinum-based drugs were found to be equally effective (Vale et al., 2008). The results demonstrated an absolute improvement in 5-year survival rates by 6% (from 60% to 66%) and an 8% improvement in 5-year progression-free survival with conformal radiation therapy combined with chemotherapy, compared to conformal radiation therapy alone.

The total number of cisplatin administrations during chemoradiation therapy plays a significant role in the systemic control of patients with cervical cancer who have an unfavorable prognosis. In the EMBRACE study (2016), involving 753 cervical cancer patients, worse overall control was noted in patients with N+ disease who received fewer than 4 cycles of cisplatin-based chemotherapy, compared to those who received 5 or more cycles. At the 24-month follow-up, cervical cancer patients with N+ and stages III-IV demonstrated systemic control in 63% of cases with less than 4 cycles of chemotherapy, compared to 88% in those who received more than 5 cycles. At 3 and 5 years of follow-up, the survival rate without detectable metastases was 79% and 77%, respectively. These results align with those of Schmidt (2014), which showed that administering 5-6 cycles of

cisplatin-based chemotherapy can reduce the risk of distant metastasis, especially in patients with N+ and locally advanced cervical cancer (LACC) [7].

1.3 Intracavitary Radiation Therapy. Intracavitary radiation therapy for cervical cancer has profoundly influenced the development of various "systems" that attempted to combine empirical, systematic, and scientific approaches to treating cervical cancer.

With the advent of new technological approaches in radiation therapy methodology for cervical cancer, the GEC-ESTRO working group was formed in 2000. It consisted of doctors and medical physicists specializing in brachytherapy for oncological gynecological patients. Their initial goal was to describe new concepts and terms for unified terminology in the development of 3D intracavitary radiation therapy (ICRT) under visual control, focusing on MRI images, which are the preferred method of visualization. Additionally, the goal was to develop guidelines for dose-volume parameters in 3D ICRT. As a result, this allowed the development of a common language of definitions and led to improved information collection, analysis, and evaluation of patient treatment outcomes.

The general terminology and key concepts for implementing applicator systems under visual control were defined. Ultimately, after conducted studies, the GEC-ESTRO group identified the following volumes determined by MRI images:

- GTV (Gross Tumor Volume): This includes any visible and palpably detectable manifestation of disease at the time of intracavitary radiation therapy, as well as the "white" signal area defined by MRI images.
- HR-CTV (High-Risk Clinical Target Volume): This volume includes the previously defined GTV, the entire cervix, and all "gray zones" in the vagina, parametrium, uterine body, bladder, and rectum in T2-weighted MRI images. Gray zones are defined as tissues with intermediate signal intensity in the primary tumor spread area on T2-weighted MRI images.
- IR-CTV (Intermediate-Risk Clinical Target Volume): This is created by placing safety margins of 5-15 mm evenly from the HR-CTV, excluding adjacent normal structures (bladder, rectum, sigmoid colon) [8].

The planning target volume (PTV) is not added to the HR-CTV or IR-CTV, as the applicator is stabilized relative to the patient's anatomy, and therefore no additional margin is necessary. The HR-CTV volume is of the most importance, as this is the volume for which the treatment plan is optimized and doses are prescribed.

The GEC-ESTRO working group concluded that the use of this standard terminology could lead to the standardization of treatment across different centers.

The DVH parameters D90 and D100 were identified to assess target coverage. The D90 volume is less sensitive to small variations in target delineation than D100 and, therefore, is a more stable parameter for dose prescription. Instructions and worksheets developed at the University of Vienna for calculating EQD2 are available for online reading [9].

The American Brachytherapy Society (ABS) published its recommendations for intracavitary radiation therapy for cervical cancer in the high dose-rate (HDR)

range in 2000 and for low dose-rate (LDR) intracavitary radiation therapy for cervical cancer in 2002. These reports state that intraoperative orthogonal X-rays or fluoroscopy should be primarily used to verify the correct placement of the applicator. Correct applicator placement leads to improved overall and progression-free survival in patients with locally advanced cervical cancer. The applicator's movement and/or re-placement should occur before the positioning verification. The ABS updated their recommendations in 2012 in three parts.

When planning an ICRT session, the visualization of MRI/CT images is essential, with cross-sectional images having a slice thickness of 1 mm to 5 mm. For institutions using MRI for treatment planning, target volumes (GTV, HR-CTV, IR-CTV) should match those previously described in GEC-ESTRO recommendations. For institutions using CT-based planning, only HR-CTV is determined, which should include the entire cervix width, any parametric spread. The cranial size of the cervix should be extended by 1 cm towards the uterine vessels (if possible, intravenous contrast administration is recommended) or to where the cervix visually begins to widen. If the cervix cannot be adequately visualized on CT, the cranio-caudal height of the cervix should be taken as 3 cm.

The EMBRACE study (2015) recommends limiting doses to organs at risk but following the prescribed doses for ICRT as per the accepted traditions of specific clinics and general medical practice.

CT images for 3D planning allow for visualization of the primary cervical tumor, organs at risk, rectovaginal, and vesicovaginal septa. Early studies consistently showed that the maximum doses to the bladder, bladder neck, and rectum were higher when contouring was done based on CT images as compared to orthogonal radiographs.

For example, Kapp et al. studied 720 brachytherapy sessions for cervical cancer with an Iridium-192 HDR source and compared doses to the bladder and rectum obtained from contouring with orthogonal radiographs and CT images. They found that maximum doses to the bladder and rectum were, on average, 1.44 and 1.37 times higher when using CT images, respectively. The study emphasized the importance of evaluating doses across the entire volume of normal organs, not just the point of maximum dose.

Schoeppel et al. and Datta et al. (2006) compared doses to the bladder and rectum using orthogonal radiographs and CT scans and found that orthogonal radiographs significantly underestimated actual doses. Moreover, both studies showed that dose distribution relative to point A inadequately covered the cervix and/or tumor volume in all patients. Point A, as well as bladder and rectum points, weakly correlated with actual doses based on CT, although these studies did not attempt to correlate dosimetric data with clinical outcomes [10].

Conclusion. Thus, techniques based on the interpretation of 3D imaging in intracavitary radiation therapy (ICRT) require mastering several complex stages: knowledge of anatomy, pathology, 3D visualization, medical physics, biology, clinical experience, and the application of dose-volume histogram (DVH) parameters. Unfortunately, in Russia and the CIS countries, ICRT with 3D

planning based on CT/MRI images is insufficiently implemented. It is applied only in some clinics and often not to all patients or not at all. This is due to poor technical equipment and the lack of training centers for doctors and medical physicists.

Significant time is required for training and fully understanding the various aspects of these complex methods. However, it is expected that, in the near future, ICRT planned with 3D imaging will become more widely used in clinical practice and will be comparable in complexity to conformal radiation therapy technologies.

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