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## **MODERN APPROACHES OF CERVICAL CANCER RADIATION TREATMENT. LITERATURE REVIEW.**

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### **Abstract**

**Introduction:** Cervical cancer is one of the most common oncological diseases in the world, as well as one of the causes of death in the female population worldwide. The study and development of new areas of modern oncogynecology in locally advanced stages of cervical cancer is one of the ways to solve this urgent problem.

**Objective:** To present to the reader detailed overview of the epidemiological situation of cervical cancer, the evolution of radiation therapy from the beginning to the development of modern approaches to radiation treatment of cervical cancer, such as prophylactic irradiation of paraaortic lymph nodes.

**Materials:** The authors conducted a literature search of current approaches to radiation therapy for cervical cancer using the appropriate keywords in the search engine PubMed and Google Scholar, in the Scopus database, Web of Science, MedLine, The Cochrane Library, Global Health, CyberLeninka and to others.

**Conclusions:** Cervical cancer is a disease that has not lost its significance and has consistently high morbidity and mortality rates among all oncological diseases. Despite the successes achieved in the field of treatment, a number of promising areas remain that have not been fully studied in clinical trials. One of these areas is the prophylactic irradiation of paraaortic lymph nodes to improve patient outcomes, along with a reduction of the toxic effects associated with it, both in the short and long term.

**Key words:** *review, cervical cancer, radiation therapy, preventive radiation.*

### **Резюме**

## **СОВРЕМЕННЫЕ ПОДХОДЫ К ЛУЧЕВОЙ ТЕРАПИИ РАКА ШЕЙКИ МАТКИ. ОБЗОР ЛИТЕРАТУРЫ.**

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**Введение:** Рак шейки матки одно из самых распространенных онкологических заболеваний в мире, а также одна из причин смертности в женской популяции во всем мире. Изучение и разработка новых направлений современной онкогинекологии при местно-распространенных стадиях рака шейки матки является одним из путей решения данной актуальной проблемы.

**Цель:** Представить читателю подробный обзор эпидемиологической ситуации по раку шейки матки, эволюцию лучевой терапии от начала и до разработки современных подходов к лучевому лечению рака шейки матки, таких как профилактическое облучение парааортальных лимфатических узлов.

**Материалы:** Авторами был проведен поиск литературы о современных подходах к лучевому лечению рака шейки матки с использованием соответствующих ключевых слов, в поисковых системах PubMed и Google Scholar, в базах данных Scopus, Web of Science, MedLine, The Cochrane Library, Global Health, CyberLeninka и другим.

**Выводы:** Рак шейки матки является заболеванием, не утратившим своей значимости и имеющим стабильно высокие показатели заболеваемости и смертности среди всех онкологических заболеваний. Несмотря на успехи, достигнутые в сфере его лечения, остается ряд перспективных направлений, не до конца изученных в ходе клинических исследований. Одним из таких направлений является профилактическое облучение парааортальных лимфатических узлов для улучшения результатов лечения пациентов, наряду с уменьшением связанных с ним токсических эффектов, как в краткосрочной, так и в долгосрочной перспективах.

**Ключевые слова:** обзор, рак шейки матки, лучевая терапия, профилактическая лучевая терапия.

Түйіндеме

## **ЖАТЫР МОЙЫНЫ ОБЫРЫНЫҢ СӘУЛЕЛІК ЕМІНІҢ ЗАМАНАУИ ТӘСІЛДЕРІ. ӘДЕБИЕТТІК ШОЛУ.**

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**Кіріспе:** жатыр мойыны обыры әлемдегі ең кең таралған онкологиялық аурулардың бірі, сондай-ақ бүкіл әлемдегі әйелдер популяциясындағы өлім себептерінің бірі. Жатыр мойыны обырының жергілікті-таралған сатыларында қазіргі заманғы онкогинекологияның жаңа бағыттарын зерттеу және әзірлеу осы өзекті проблеманы шешудің бір жолы болып табылады.

**Мақсаты:** оқырмандарға жатырдың мойыны обырының эпидемиологиялық жағдайына егжей-тегжейлі шолу жасау, парааортальды лимфа түйіндерінің алдын алу сәулеленуі сияқты жатыр мойыны обырын сәулемен емдеу үшін заманауи тәсілдерді әзірлеу және басынан бастап сәулелік емнің эволюциясы.

**Материалдар:** авторлар тиісті негізгі сөздерді пайдалана отырып, жатыр мойыны обырын сәулелік емдеуге қазіргі заманғы тәсілдер туралы әдебиеттерді, PubMed және Google Scholar іздеу жүйелерінде, Scopus, Web of Science, MedLine, The Cochrane Library, Global Health, CyberLeninka және т.б. деректер базасында іздестіруді жүргізді.

**Қорытынды:** жатыр мойыны обыры өзінің маңыздылығын жоғалтпаған және барлық онкологиялық аурулар арасында аурушаңдық пен өлім-жітімнің тұрақты жоғары көрсеткіштері бар ауру болып табылады. Оны емдеу саласында қол жеткізілген жетістіктерге қарамастан, клиникалық зерттеулер барысында зерделенгендердің соңына дейін бірқатар болашақтағы бағыттар қалып отыр. Осындай бағыттардың бірі пациенттерді емдеу нәтижелерін жақсарту үшін парааортальды лимфа түйіндерінің алдын алу сәулеленуі болып табылады, қысқа мерзімді және ұзақ мерзімді болашақта онымен байланысты токсикалық әсерлерді азайтумен қатар.

**Түйінді сөздер:** шолу, жатыр мойыны обыры, сәулелік ем, профилактикалық сәулелік ем.

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**Introduction**

Cervical cancer is the fourth most common female oncological disease worldwide, accounting for 7.9% of all cancer cases. Accordingly, the first three places in the overall structure of cancer among women are breast cancer (25% of all cases), colorectal cancer (9.2% of all cases) and lung cancer (8.7% of all cases) [30]. It should be noted that these types of cancer localization are also the main causes of death: breast cancer accounts for 14.7% of all deaths, followed by lung cancer (13.8%), colorectal cancer (9.0%) and cancer cervix (7.5%) [6].

According to the IARC - International Agency for Research on Cancer, 528,000 new cases of cervical cancer and 266,000 deaths are reported annually in the world. This disease is most common among women from low- and middle-income countries per capita (about 70% of all cases), while India alone accounts for more than 1/5 of all new cases of the disease [10]. The incidence of cervical cancer is significant in different countries of the world: in 39 of 184 countries, this disease is the main localization of cancer among the female population, and in 45 countries cervical cancer takes a leading place in the structure of female mortality from cancer. These countries include sub-Saharan Africa (Mali, Guinea, Sierra Leone, Liberia, Ghana, Tanzania, Malawi, Mozambique, Zambia, Zimbabwe, Swaziland, Madagascar), countries of Southeast Asia (India, Myanmar, Laos, Thailand, Cambodia and Vietnam), as well as a number of countries in Central and South America [17]. At the same time, the lowest incidence and mortality rates for cervical cancer are found in Western Europe (Great Britain, France, Spain, Germany and Portugal), North America (Canada and the USA), Australia and New Zealand, as well as in the eastern Mediterranean countries (Greece and Italy) [2].

As for the Republic of Kazakhstan, back in 2008 the ratio of mortality to incidence of cervical cancer was 0.55, which corresponded to the level of the countries of the Central Asian region [11]. However, it should be noted that, starting from 2011, a number of activities are being systematically implemented in the country under the State program "Salamatty Kazakstan" and, subsequently, the "Densaulyk" program, which could not but affect the improvement of early diagnosis and timely treatment, and inevitably led to decrease in this indicator. According to Kaydarova D.R. et al., the ratio of mortality to morbidity in 2013 was 37.3, in 2014 - 39.2, in 2015 - 35.8, and in 2016 - already 37.2 [1].

According to 2012 data, a total of 9965 women were registered with cervical cancer, 1625 new cases were

registered, and 650 people died. A rather high proportion of the 3-4 stages of the disease was noted, which was 30%, according to the age composition, the majority of cases were in the cohort of 30-58 years old, and the annual mortality was 21.0% [12].

**The purpose** of the article is to conduct a detailed review of radiation therapy publications of the cervical cancer treatment, which includes the epidemiological situation of cervical cancer, the evolution of radiation therapy from the beginning to the development of such modern approaches to radiation treatment as prophylactic irradiation of paraaortic lymph nodes, which in general will make it possible to assess the role of the development of innovative directions in radiation therapy of the onco gynecological profile.

**Search strategy:** The search was conducted using the relevant keywords in the search engines PubMed and Google Scholar, in the databases Scopus, Web of Science, MedLine, the Cochrane Library, Global Health, CyberLeninka and others. The following keywords were used to conduct the search: cervical cancer, chemoradiotherapy irradiation of paraaortic lymph nodes, extended irradiation field. All sources used were selected in accordance with the basic context of the study. The preference was given to publications in international peer-reviewed scientific publications.

**Inclusion criteria** did not strictly set the criteria for inclusion of materials in the literature review, except for the use of materials in context and in expert analysis of the researcher.

**The exclusion criteria** were articles of low methodological quality that did not clearly describe the functions of the instrument and did not reflect its main significance.

**Results of research.****The development of radiation therapy as a method for the combined treatment of cervical cancer.**

The history of gynecological brachytherapy can be traced back to the discovery of the radioactivity phenomenon by Henri Becquerel in 1896, which contributed to the discovery of radium by Marie and Pierre Curie in 1898. For a long period of time, radium therapy has been the main form of brachytherapy, with the exception of the use of radon (a short-lived gaseous daughter product of half-life of radium). The first article on radium therapy in gynecological practice was published by Robert Abbe in

1905. In general, Abbe was the first to report the successful cure of cervical cancer with radium, which happened back in 1905 [29]. However, the first report on the use of interstitial brachytherapy appeared in the medical literature only in 1914.

The use of interstitial brachytherapy in gynecological practice has been quite limited for a long time, although Cade described in 1929 two approaches associated with intravaginal and intraperitoneal irradiation, an early form of intraoperative brachytherapy [3]. More than half a century after the first use of radium in gynecology, Ulrich Henschke first described a hand-held device for brachytherapy in the treatment of gynecological tumors in his 1964 work, followed by a 1966 publication on a remotely controlled brachytherapy device [9].

Thus, the basis of modern radiation therapy was described in literary sources before the end of the first decade of the twentieth century. Early experience with radiation therapy was associated with low (by current standards) effectiveness and a high frequency of toxic effects. Scientists still had to generalize experience and standard treatment regimens in order to develop technology (equipment design), improve initially non-existent radiation protection and set up production of radionuclides to replace radium, which could ultimately be used as miniature radioactive sources. In modern conditions, radiation therapy for cervical cancer is divided into external radiation therapy, brachytherapy and chemoradiotherapy. New developments are mainly aimed at increasing the level of tumor control and / or reducing treatment resistance. Innovative techniques such as modulated intensity radiation therapy (LTMI) have been introduced, which has reduced the toxic effects of the gastrointestinal tract and helps to selectively increase the dose of radiation therapy, while brachytherapy with visual control allows better radiation doses to be adapted to the size of the tumor [8].

Thus, the currently recommended approach to radiation therapy for cervical cancer consists of 3 elements: (1) external radiation therapy for the primary pelvic tumor and (if available) paraaortic lymph nodes (PALN) in a total dose of 45-50 Gy, (2) intracavitary brachytherapy and (3) chemoradiotherapy with cisplatin and weekly doses of 40 mg / m<sup>2</sup> [25]. This standard of treatment has been adapted based on a series of randomized controlled trials (RCTs), the first results of which were presented in 1999.

### **Cervical Cancer Treatment**

In accordance with modern concepts, the treatment of cervical cancer depends on its stage [5]. In addition to the stage, the choice of the treatment method depends on a number of other factors, such as the patient's age, the histological type of the tumor and the degree of its differentiation, the patient's desire to maintain fertility and overall health.

In general, patient survival and local disease control are better with unilateral, rather than bilateral, lesions of the parametrium. Studies of treatment outcomes in patients with IIIA and IIIB stages of cervical cancer show that survival depends on the prevalence of the disease, with unilateral involvement of the pelvic wall predicting a better result than bilateral, which, in turn, has a better prognosis than involvement of the lower third of the vagina [14]. These

studies also show progressive improvement in treatment outcomes and survival in parallel with a gradual increase in paracentral dose (point A) and the use of intracavitary radiation. The highest level of disease control can be achieved with doses at point A of more than 85 Gy [15].

Radiation therapy with concomitant chemotherapy are standard treatment options for cervical cancer in stage IIB, III and IVA of the disease. Moreover, the use of intracavitary radiation therapy and external radiation therapy to the pelvic region in combination with cisplatin chemotherapy or a combination of cisplatin / 5-fluorouracil (5-FU) are typical approaches to the treatment of this category of patients [4,13,18, 20-23, 27, 28]. Five randomized trials of phase III showed benefits in terms of improving the overall survival of patients with cisplatin-based chemotherapy concomitantly with radiation therapy [13,18,22,23,27,28], but one study that studied the same regimen, could not demonstrate any benefit [19]. In an attempt to improve the standard chemotherapy regimen, randomized study of the phase III was conducted that compared the simultaneous administration of gemcitabine with cisplatin and radiation therapy followed by adjuvant therapy with gemcitabine and cisplatin (the main group) with cisplatin combined with radiation therapy (the standard chemotherapy regimen) patients with stages IIB and IVA of cervical cancer. The primary endpoint of the study was survival without disease progression after 3 years of treatment. The study showed improved survival without disease progression after 3 years (main group 74.4%; 95% CI 68% -79.8% versus 65.0%; 95% CI 58.5% -70.7% in the control group). However, patients in the main group showed an increased risk of developing hematological and non-hematological toxic reactions of severity 3 and 4, as well as two cases of death, which may have been associated with the treatment.

Patients with mild para-aortic and pelvic lymph nodes lesions may undergo radiation therapy. Treatment with extended field radiation therapy in patients with unresected PALN leads to long-term disease control, provided that the lymph node is slightly affected. In the available literature, we were able to find only one study that showed an increase in the survival of patients who received preventive exposure to PALN. As a rule, toxic reactions during para-aortic irradiation are more pronounced than when irradiating only the pelvic lymph nodes, but, mainly, they are limited to patients who underwent previous surgery on the abdominal cavity [7].

### **Prophylactic irradiation of paraaortic lymph nodes in the treatment of cervical cancer**

Since the presence of metastases in regional lymph nodes is one of the most important prognostic factors for cervical cancer, prophylactic exposure to PALN is increasingly being used in modern oncology practice. For this purpose, wide field irradiation is most often used, which currently is the main approach [26].

One of the first studies in this area was an RCT performed by Rotman M et al., Which summarized a 10-year follow-up of patients with IB, IIA, and IIB stages of carcinoma according to the FIGO classification in terms of the effect of preventive exposure to PALN on tumor response and patient survival. This study included 367 women with primary cervical cancer and tumor size more

than 4 cm, which were randomized into two groups for standard irradiation of only the pelvic region, or for irradiation of the small pelvis and PALN. The overall 10-year survival rate was 44% for patients who received irradiation of only the small pelvis and 55% for patients who received irradiation of both the small pelvis and PALN ( $p = 0.02$ ). The cumulative mortality from cervical cancer was significantly higher in the group receiving only pelvic irradiation ( $p = 0.01$ ). Survival without relapse was the same in both groups, and survival after the first relapse was significantly higher in the group receiving PALN ( $p = 0.007$ ). However, this study also demonstrated a higher toxicity profile for preventive PALN exposure, which was 25% compared with the group that received only pelvic irradiation (8%). The cumulative incidence of toxic complications 4 and 5 degrees of severity after 10 years of treatment was 8% in the prophylactic irradiation PALN compared to only 4% in pelvic radiation group ( $p = 0.06$ ). Mortality from complications of radiation therapy was higher in the group receiving PALU irradiation, which was however statistically insignificant ( $p = 0.38$ ) [24].

Lee et al. Published a study evaluating 10 years of experience in preventive PALN irradiation using intensity-modulated radiation therapy in the treatment of locally advanced cervical cancer. The study included a total of 206 patients with cervical cancer of the IB2-IVA stages according to the FIGO classification. The average patient follow-up was 60 months (range 7–143 months). Five-year survival without relapse of the disease was 87.6% for the group receiving pelvic irradiation and 97.9% for the group receiving prophylactic PALN irradiation, which was statistically significant ( $p = 0.03$ ). At the same time, overall survival was 74.5% and 87.8% ( $p = 0.04$ ), respectively. In patients with III-IVA according to the FIGO classification or the presence of metastases in PALN, the 5-year survival rate without recurrence of the disease was 80.1% in the pelvic irradiation group and 96.4% in the PALN irradiation group ( $p = 0.02$ ), while overall survival was 58.1% and 83.5% ( $p = 0.012$ ), respectively. No toxic effects of severity  $\geq 4$  or treatment-related deaths were detected in this study. The manifestations of toxic effects of  $\geq 2$  degrees associated with the gastrointestinal tract and genitourinary system were insignificant in the group of patients who received prophylactic exposure to PALN ( $p = 0.09$  and  $p = 0.76$ , respectively). Grade 3 leukopenia developed in 38 (39.6%) patients in the PALN irradiation group and in 32 (29.2%) patients in the pelvic irradiation group ( $p = 0.14$ ). In the PALN irradiation group, there was a significant increase in the incidence of anemia of degree 3 severity ( $p = 0.049$ ). However, all cases of anemia were successfully controlled by conservative treatment. Thus, the authors come to the conclusion about the effectiveness of preventive exposure to PALN with an acceptable safety profile [16].

**Conclusions:** cervical cancer is a disease that has not lost its significance and has consistently high morbidity and mortality rates among all oncological diseases. Despite the successes achieved in the field of treatment, a number of promising areas remain that have not been fully studied in clinical trials. One of these areas is the prophylactic irradiation of paraaortic lymph nodes to improve patient

outcomes, along with a reduction of the toxic effects associated with it, both in the short and long term.

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