STATE ORGANIZATION «GRIGORIEV INSTITUTE FOR MEDICAL RADIOLOGY AND ONCOLOGY OF THE NATIONAL ACADEMY OF MEDICAL SCIENCES OF UKRAINE»

O.M. SUKHINA, L.YA. VASYLYEV, YE.B. RADZISHEVSKA, V.S. SUKHIN, K.V. NEMALTSOVA, N.O. ARTAMONOVA

CHEMORADIATION TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER: ONCOLOGICAL AND SOMATIC EFFECTS

Monograph

Kharkiv – 2025

UDC 618.146:616-006

ISBN 978-617-8036-03-4

Reviewers:

O.A. Mikhanovsky – Doctor of Medical Sciences, Professor, Head of the Department of Oncological Gynecology at the State Organization "Grygoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine".

V.P. Starenkyi – Doctor of Medical Sciences, Professor, Head of the Chair of Radiology and Radiation Medicine of the Ministry of Health of Ukraine.

Approved and recommended for publication by the Academic Council of the State Organization "Grygoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine" (Protocol No. 6, July 2025).

Authors:

Sukhina O.M., Vasylyev L.Ya., Radzishevska Ye.B., Sukhin V.S., Nemaltsova K.V., Artamonova N.O.

Chemoradiation treatment of locally advanced cervical cancer: oncological and somatic effects / O.M. Sukhina, L.Ya. Vasylyev, Ye.B. Radzishevska, V.S. Sukhin, K.V. Nemaltsova, N.O. Artamonova. – Kharkiv: State Organization "Grygoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine", 2025. – 76 p.

The monograph substantiates and presents the technology of individualized supportive care during chemoradiotherapy in patients with locally advanced cervical cancer, taking into consideration risk factors for disease prolongation (tumor-involved volume of cervix, parametric infiltration, SCC tumor marker expression level, platelet level) to increase the treatment efficacy by reducing the level of local recurrence and distant metastases, so as treatment toxicity.

The monograph is recommended as an educational item for physicians in training, oncologists and oncogynecologists, so as for medical university students of the IV level of accreditation, who have intendance for deepening knowledge in oncology and oncogynecology.

Table – 5, figures – 18, bibliography – 59 references.

UDC 618.146:616-006

ISBN 978-617-8036-03-4

CONTENT

FOREWORD

The relevance of this research direction is substantiated by the fact that cervical cancer ranks as the second most common malignant neoplasm of the female reproductive system worldwide. In the State Organization "Grygoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine" there have been developing early diagnostics methods, so as guidelines and schemes for effective treatment during a long-time [1,2].

The application of modern information technologies to arrays of archival data in scientific research allows for the identification of dependencies between the appearance of oncological consequences (OC) of the treatment of patients with locally advanced cervical cancer (metastatic or relapsed disease, appearance of secondary cancer) and the manifestations of radiation toxicity as an outcome of the radiation therapy. This can be achieved with minimal human resources by considering the clinical and biological characteristics of patients and the specific features of the chemoradiation treatment (CRT), which was administered. The dependencies, derived from this analysis, enable the development of proposals for adjusting anti-tumor therapy to provide individualized patient support, thereby increasing patient survival.

The monograph consists of such sections – introduction, three chapters, which contain results of proper investigation, practical recommendations and conclusions.

The first chapter is dedicated to review of the literature data, regarding the main approaches in evaluating the chemoradiation treatment outcomes in patients with locally advanced cervical cancer, as oncological, so as radiation consequences. There was analyzed the global experience in assessing and management of the side effects of chemotherapy, radiation therapy, and conservative treatment of patients with locally advanced cervical cancer (LACC).

The second chapter addresses the methodological approach, used by the authors in order to evaluate the risk factors for oncological consequences of the treatment and somatic effects. It was provided the characteristics for the technology of the patients' data accumulation, storage and data processing, as well as description of patient clinical indicators and follow-up data.

The third chapter focuses on the oncological and somatic effects of chemoradiation treatment of patients with LACC. This chapter evaluates the role of the tumor-associated marker SCC in the monitoring of treatment efficacy of the LACC patients. It was also provided characteristic features of the somatic effects of the treatment, so as predictive indicators for the future appearance of oncological consequences of the treatment, and survival assessment in patients with LACC, based on the actuarial calculations. Especial attention is given to the analysis of immediate radiation reaction (toxicity) and late radiation consequences of treatment.

Practical recommendations are provided, based on the data of the optimization of chemoradiation therapy in order to prevent the possible occurrence of late oncological consequences of the treatment of LACC patients.

The conclusions present summary of the latest literature data from the different institutions of the world and the main results of the studies, conducted at the SO "GRIGORIEV IMRO NAMS", regarding the treatment of patients with LACC concerning the identification of predictors and risks of appearance of the treatment-specific late outcomes, prognostic factors for patients' survival, the selection of the optimal treatment schemes for patients with LACC, in order to prevent the late outcomes of the antiblastome treatment.

INTRODUCTION

Despite of the fact, cervical cancer being a tumor of visual localization and could be easily diagnosed at routine examination, this pathology ranks second place in the overall structure of oncological morbidity and third place in mortality among gynecological oncological diseases.

According to modern data, the average incidence of cervical cancer is 9.0 cases per 100,000 people in highly developed countries and 17.8 cases per 100,000 people in developing countries. At the same time, the percentage of advanced disease (stages III–IV) remains consistently high [3]. The standard of treatment for such patients is de facto external beam radiation therapy and intracavitary irradiation (brachytherapy – BT), which is combined with chemotherapy (CT), based on cisplatin. The continuous improvement of radiation therapy (RT) methods has allowed for the establishment of the optimal radiation doses, particularly for zones, which are typical for regional metastasis, and has reduced the risk of radiation damage of the surrounding organs and normal tissues [4].

The quality of life of oncology patients, so as the objective tumor response on the treatment, is a determining criteria for the evaluation of effectiveness of the conservative therapy. Therefore, the search for methods to prevention of the radiation consequences of combined chemoradiotherapy (CRT) for LACC patients, so as settlement of the treatment scheme, are considered to be extremely actual and still stay as unresolved problem [5–7].

Unfortunately, a reverse trend is currently being observed in Ukraine: against the backdrop of active military actions, delayed visits for routine gynecological examination, and the forced intensification of the treatment process in case of diagnosis, the number of women with female genital tumors has rapidly increased. It is especially observed among young women (aged under 30 years old), – with a double fold increase in diagnosing, which makes the problem of improvement of early diagnostic and treatment of such conditions even more pressing.

The patterns, which presented in this monograph, are to be the identification of risk factors for local relapse and distant metastasis, so as the characteristics of patients survival in case of locally advanced cervical cancer. The study focuses on the detection of the risk period for the appearance of distant metastases and local recurrence. There were identifed new, previously unknown risk factors for appearance of late oncological consequences, immediate radiation reactions and late radiation outcomes, so as somatic complications, as well as methods for their prevention and management. The implementation of the results, obtained during the investigation, will contribute to the improvement of individualized patients support programs in case of locally advanced cervical cancer.

One of the potential strategy option for obtaining new knowledge is the analysis of previously processed (catamnestic) data on the course and outcomes of disease, using mathematical statistics and more advanced mathematical methods, such as Data Mining – the technology for finding the hidden knowledge [8].

CHAPTER 1: OUTCOMES OF CHEMORADIATION TREATMENT FOR LOCALLY ADVANCED CERVICAL CANCER

During the recent years, the incidence and mortality of LACC have been decreasing, yet it remains a serious social problem. This is mainly due to its prevalence in younger age groups and the relatively complex therapy, required for patients on late stages of disease. The treatment of cervical cancer patients at an early stage is primarily managed by oncogynecologists, while the conduction of modern RT, combined with systemic therapy, and sometimes in combination with immunotherapy, which are now considered as guidelines of treatment of LACC patients, requires the cooperative work of various specialists, such as gynecological oncologists, radiation and clinical oncologists, as well as engineers, dosimetrists, who take part in planning of the course of radiation. The indications for the neoadjuvant systemic therapy before the possible surgery or radical radiation therapy are more controversial [6]. This chapter reviews the current state of research on the occurrence of side-effects of chemotherapy, radiation therapy, or chemoradiation therapy.

1.1 Side Effects of Chemotherapy for Locally Advanced Cervical Cancer

In the 1990s, the platinum-based chemoradiation therapy became the standard treatment for patients with locally advanced cervical cancer. However, the anticipated increase in overall survival over a five-year period was only 6% in patients, who received chemoradiation therapy, compared with radiation therapy alone. Since the implementation of CRT, there have not been observed additional changes in the treatment results of patients with LACC, and approximately 30–40% of these patients do not achieve a complete response to CRT [7]. Therefore, alternative approaches in treatment are needed for improvement the treatment outcomes of these patients. One of such potential approach for treatment results improvement, according to the study results (V.S. Ivankova et al.) [6], can be neoadjuvant chemotherapy (NCT) with weekly administration of paclitaxel and carboplatin for 4–6 weeks as a dose-dense chemotherapy before CRT. A study of Soumarová R. et al. showed, that the overall response rate after NCT was 71%, in 61% of patients there was achieved a complete response by the end of the treatment [7]. Among the conclusions, based on results of the phase II study, conducted by Abd El Hamid DM et al., which study design was similar to the stidy, conducted by Soumarová R. et al., the most common side effects during NCT was hematological toxicity Grade 3 and 4, which was observed in 21% of patients. The overall patients survival at 9 and 12 months was 94% and 84%, respectively [9].

The identification of additional factors, which can influence on patient survival is closely investigated by the medical community and highlighted in scientific publications. Discussing the survival prognosis for cervical cancer patients with stage IVB, researchers (Yu W. et al.) have noted, that age, histology, tumor size (T stage), metastasis pattern and local relapse characteristics, scheme of CT and RT are to be independent prognostic parameters. Authors have developed and demonstrated a prognostic model for predicting the overall survival for patients with newly diagnosed distant metastatic LACC [10].

Chen Y. et al. announced, that peculiarities of recurrences in cervical cancer patients at an early stage can be useful as prognostic indicators. The authors studied the disease course and followed 1934 cervical cancer. In 167 patients, the recurrence was observed after radical hysterectomy, including pelvic lymphadenectomy and chemoradiation treatment. Recurrence types were classified into four groups: local, pelvic, distant only, and combined metastases. The relationship between these recurrence types and subsequent prognosis was also assessed [11]. According to the conclusions, the most common locations of recurrence were:

- lungs only (21.6%),
- central (21.0%),
- pelvic recurrences (17.4%),
- combined (40.0%).

The longest survival follow-up during the five-year observation was detected in patients with local recurrence (70.5%), in case of relapse in distant lymph nodes (58.4%), peritoneal recurrence (58.3%), and only as lung metastasis (36.8%). Late recurrence was detected in 28 patients (1.4%), who had a better prognosis, compared to those patients with early recurrence (in term up to 2 years). Based on these results, the authors conclude, that after therapy, conducted in case of central recurrence, distant lymph node metastatic relapse and peritoneal recurrences, there were achieved satisfactory results. However, patients in whom were detected early recurrence or those, with another recurrence localization, require more effective therapeutic strategies as initial treatment, in order to improve patients' survival.

Similar study results were published by Lindegaard J.C. et al. [12].

While studying the risk factors for pelvic and distant recurrences of LACC (stage IIB–IVA), authors [13] indicate, that the factors of risks of recurrence include a tumor size exceeding 6 cm and lymph nodes involvement. Similar conclusions are noted in publication [14], which points out that a tumor size, that not exceede 6.9 cm and concurrent chemoradiation therapy, as a primary treatment, are considered to be the favorable prognostic factors for patients with metastatic LACC. During the literature review, the authors of this publication have also noted, that clinical biomarkers for predicting survival outcomes in LACC patients have been studied quite extensively. The age of patients, their performance status, tumor size and lymph node status were reliably associated with recurrence-free survival.

The review content, dedicated to discussing various aspects of chemotherapy is quite substantial. For example, the study [15] examined the clinical outcomes of treatment of 120 patients with non-operabel LACC with different regimens of NCT. There was performed retrospective analysis of LACC patients, who underwent NCT, which included paclitaxel (Taxol) and cisplatin (Platinol) (TP regimen) or paclitaxel (Taxol) and lobaplatin (Lobaplatin) (TL regimen). The complete/partial response rate after treatment was 99.2%. Survival rates at one, three, and five years of follow-up were 99.2%, 82.5%, and 70.8%, respectively. In the TP and TL groups, three- and five-year survival were 85.5% and 65.5%, respectively, with no statistically significant differences. The five-year overall survival rates between patients with stage IIB and IIIB did not differ significantly (69.2% vs. 64.7%). In TP group there was observed more frequently gastrointestinal toxicity. Leukopenia, neutropenia, and thrombocytopenia were more common in the TL group. In general, there was not found any significant difference between the groups, concerning the toxicity manifestation – the frequency of anemia, enteritis, proctitis and cystitis. The authors concluded, that lobaplatin could be used as an alternative drug for patients with gastrointestinal complications, systemic reactions, or contraindications to cisplatin [16].

Similar conclusions were also presented in a study of Regalado Porras GO et al., in which authors analyzed the results of five randomized studies (cervical cancer patients with stages IIB-IVA). Their final conclusion is that, CT prolongs patient's survival compared to supportive care alone. Furthermore, polychemotherapy regimens are better than single-agent regimens. First-line therapy should be considered a combination of cisplatin and paclitaxel (paclitaxel 135 mg/m², 24 hr infusion with cisplatin 50 mg/m², 2 doses every 3 weeks). Other options include combinations of cisplatin with topotecan or gemcitabine (gemcitabine 1000 mg/m² on day 1 and 8 + cisplatin 50 mg/m² on day 1 every 3 weeks; or topotecan 0.75 mg/m² on days 1–3 + cisplatin 50 mg/m² on day 1 every 3 weeks) and the paclitaxel-topotecan doublet [17].

Thus, most studies focus on evaluating different treatment strategies, based on survival and recurrence rates. There is a lack of publications on a comprehensive analysis of the tpxicity of chemotherapy for locally advanced cervical cancer.

1.2 Radiation Toxicity in Patients with Locally Advanced Cervical Cancer

Radiation therapy has been successfully used in treatment of LACC patients for almost a century, because in 90% of case cervical cancer has squamous cell origin and, therefore, is highly sensitive to irradiation [18]. In case of early invasive cervical cancer it's indicated to perform radical surgery or external beam radiation therapy (EBRT), while for locally advanced tumors is applied combined radiation therapy (CRT) – a combination of EBRT and Brachytherapy. The increase of survival rate and local disease control have made CRT the standard of care for locally advanced cervical cancer patients [18–20].

According to meta-analyse data, conducted by Liu R. et al., 3D image-guided brachytherapy combined with EBRT demonstrates effective tumor control and an acceptable toxicity profile in women with locally cervical cancer. The local control of disease – appearance of vaginal recurrence, depends in the most part on the histological subtype and FIGO stage [21].

Depending on the source power brachytherapy can be of low dose rate (LDR), medium dose rate (MDR) and high dose rate (HDR) and can be used, depending on available equipment. Many investigators have concluded, that the LDR Brachytherapy is better than HDR BT, because recovery of the normal tissue after radiation treatment was higher. Nevertheless, the HDR-BT is prescribed quite widely. Thus, based on a review of numerous publications, the authors conclude, that because of the potential advantages HDR-BT, such as fix immobilization of patient during procedure, outpatient treatment, patients' convenience, precise source and applicator positioning, individualized radiation treatment planning and complete radiation protection for staff, HDR-BT should be considered as a standard treatment strategy for LACC instead of LDR-BT, especially in developing countries. The review contained the data of currently available advantages and showed, that the efficacy of HDR-BT was comparable to LDR-BT, based on survival-rate, as well as incidence of treatment-related complications in cervical cancer patients with clinical stages I–III. The authors recommend to implement HDR-BT for all patients with LACC.

J. Yang et al. consider, that the adverse effects of RT, which have influence on survival LACC patients, are currently less investigated. They present their results of analysis of a cohort of 44,602 patients. Especifically, the authors note a positive effect of RT on patients, who didn't undergo primary surgery, elderly age (≥ 45 years), advanced TNM stages (III–IV) or patients with a high tumor-involved volume of cervix (≥ 3 cm). However, they argue, that the influence of RT can be harmful for patients, whom was performed primary surgery, tumors diagnosed at a younger age (< 45 years), earlier TNM stages (I–II) of disease, or with a smaller tumor size (< 3 cm). In addition, external beam radiation therapy alone in most cases is less effective, compared to the combined RT and BT. As a conclusion, the authors state, that LACC patients have showed different reaction on the conducted RT. Survival rate for patients, who received both surgery and RT, is relatively low. In cohort of patients, whose treatment program was also consistent of RT, there should be considered clinical features, such as age, tumor size, and TNM stage of disease [22].

In the study, conducted Ayachi Z. et al. [23], there were discussed risk factors for RT complications and somatic consequences, which include hypertension and other disease of heart and vessels, inflammatory bowel disease, diabetes. As a cause of appearance of outcomes of radiation therapy, which was conducted for pelvis, there can be also previous abdominal surgery, which could cause the bowl adhesions, which can a factor of reduction of intestinal peristalsis even outside of the radiation field. An independent risk factor for developing RT complications is also smoking. It was also proved, that a body mass index higher than 30 kg/m², is a preventive factor during the RT for pelvic and abdominal regions, while a low body weight increases the risk of radiation toxicity. Thus, it is considered, that anatomical features can explain the different levels of complications, observed in patients, who were treated with the same RT regimens [20].

Treatment planning with RT optimization, due to application of adaptive RT (image-guided radiation therapy) can further reduce the risk of the gastrointestinal radiation toxicity. IMRT (intensive modulated radiation therapy) – is a highly conformal, advanced type of irradiation that applies multiple beams with dose modulation to conform to the tumor volume and minimize the dose overload on the surrounding healthy tissues. This technology requires complex treatment planning, which contributes significantly more time, than three-dimensional (3D) conformal RT (3D-CRT radiation planning) [24, 25].

1.3 The Impact of Conservative Treatment on Treatment Efficacy in patients with Locally Advanced Cervical Cancer

Chemotherapy for cervical neoplasms can be conducted alone or in combination with RT – chemo-radiation therapy. Thus, Agusti N. et al. have presented the results of a scientific search in PubMed and Cochrane Library for all recent cohort studies, related to different chemoradiation therapy regimens for LACC patients. The analysis concludes, that after the concurrent chemoradiation therapy the best treatment results were observed when using the doublet scheme of "Cisplatin + Docetaxel" and the highest five-year survival rate was detected in case of the combination of "Cisplatin + FU + Hydroxyurea". The lowest level of toxicity during the concurrent chemoradiation treatment was associated with the application of mono regimen of "Cisplatin" [26].

The non-randomized phase II study on safety and efficacy of capecitabine-enhanced brachytherapy in locally advanced cervical cancer has enrolled 118 patients with stage IB2–IVA. According to study design, after EBRT patients have obtained capecitabine, as radiosensitizer of brachytherapy. The main goal of investigation was the evaluation of tolerability of proposed treatment scheme, so as its influence on survival rate – both relapse – free (DFS), so as overall (OS). LACC patients have obtained EBRT (50 Gy in 25 fractions) and concurrent LDR-BT. During the follow-up of 1 year, the relapse-rate was 16.7% and there was detected one case of death. In conclusion, the concomitant application of capecitabine during BT was safety [27].

The Cochrane meta-analysis of chemoradiotherapy for cervical cancer is dedicated to a comparative analysis of results of CT and RT in LACC patients, based on 18 randomized controlled studies, conducted in various countries. The review results showed, that patients, who underwent CRT were more likely to have greater survival-rate, than those, who received RT alone. At five years follow-up, 66 of every 100 women, who received CRT were still alive, compared to 60 of every 100 women, who received only RT. Following patients after CRT, there was detected significantly lower recurrence-rate. Chemoradiation therapy was also effective in treatment of patients with a high-volume tumor, so as advanced disease cases. The authors confirmed the effectiveness of cisplatin, 5-fluorouracil and mitomycin-C, analyzing survival-rate of patients and inhibition of the oncological disease progression. Some short-term side effects were worse for women, who received chemoradiation therapy, but they were easily treated. Unfortunately, the information on the negative long-term effects of chemoradiation therapy was not provided [28].

M. Jemu et al. have presented their study results and discuss positive treatment outcomes for LACC patients concerning the overall survival-rate, when application the consolidating therapy. Patients received EBRT to the pelvic organs in fractions of 1.8 Gy daily 5 days a week up to a total dose of 50.4 Gy. After EBRT patients received HDR-BT in four fractions of 7.0 Gy, up to a total dose of 80 Gy to point A. Cisplatin (40 mg/m^2) was administered weekly during RT for at least five cycles. In recent years, consolidating CT has been used with two cycles of cisplatin 50 mg/m^2 and gemcitabine 1000 mg/m^2 [29].

A.N. Viswanathan et al. analyzed the effect of treatment and overall survival of LACC patients with stage IIB after CRT. Patients received CRT: EBRT of at least 45 Gy, two to four sessions of BT, and from one to six weekly cycles of concurrent cisplatin (40 mg/m^2, maximum – 60 mg/week). The average total dose at point A from RT and BT was 83 Gy, and the average treatment duration was 45 days. Weekly hemoglobin analyzes during the treatment have confirmed anemia, the mean value was 11.6 g/dl (range 8.8–

15.5). In total, one-third of patients received blood transfusions before or during CRT, and two-thirds of patients completed five or six cycles of weekly cisplatin administration with blood infusion. The reasons for prescription of fewer than five cycles of chemotherapy were neutropenia, renal failure, and side effects of chemotherapy. Patients, who have completed less than six cycles of chemotherapy, had the worst survival (55% vs. 76%). Thus, it was statistically proven, that in case of squamous cell carcinoma in LACC patients with stage IIB, those, who obtained non less, than six weekly infusions of cisplatin and a hemoglobin level > 10 g/dl, contribute better survival rate [30].

There was conducted multi-center randomized trial INTERLACE, in which have participated 32 medical centers in Brazil, India, Italy, Mexico, and the United Kingdom, which results were published in year 2024 (McCormack M. et al.). There was investigated treatment design of chemoradiation therapy with and without induction chemotherapy to determine if the induction chemotherapy improves progression-free and overall survival. At a median follow-up of 67 months, five-year progression-free survival was 72% in patients, whom was conducted induction CT and 64% in the CRT-only group, with a hazard ratio of 0.65 (95% CI 0.46–0.91, p = 0.013). Five-year overall survival was 80% in group of patients with induction CT and 72% in the CRT-only group, with a hazard ratio of 0.60 (95% CI 0.40–0.91, p = 0.015). Adverse events of Grade 3 or higher were reported in 147 of 250 (59%) patients, who obtained induction CT, compared to 120 of 250 (48%) patients in the CRT-only group [31].

The complications of radiation treatment in LACC patients have recently been a subject of serious discussion. A scientific review, conducted A. K. Gandhi et al., was dedicated to analyze of complications, which appeared after EBRT, mentions provocative factors for toxicity, which include anatomical peculiarities, concurrent CT or surgery. Although radiological consequences (side effects of radiation therapy), concerning the time of appearance are divided into immediate (acute) radiation reaction and late (42–90 days after treatment) radiation toxicity. Some late toxic effects are considered to be a continuation and further development of the same pathological process. Concurrent diseases and the dose of radiation can significantly increase the risk and severity of radiological consequences of radiation therapy [32].

Risk factors for gastrointestinal (GI) toxicity at RT include, in particular, previous conducted abdominal and pelvic surgery. The presence of an increased risk of small bowel obstruction is noted in patients, who received RT at a dose of > 50 Gy, as this can lead to an adhesive process that limits bowel displacement [32, 33]. In addition, patients with concurrent diseases, including previous pelvic inflammatory disease, vascular diseases on the background of diabetes and atherosclerosis, collagen vascular diseases, a history of smoking, or inflammatory bowel disease, may be at a greater risk for developing immediate (acute) radiation reactions as long-term effects.

In publication of Pechačová Z. et al. there was presented data, concerning side-effects and complications of pelvic RT. As the main immediate effects are presented diarrhea and cystitis, which are usually could be resolved on their own, and late radiation therapy consequences, which are presented as small and large bowel complications, genitourinary and vaginal complications. In 10% of patients, these complications are severe. The most frequent late consequences of RT is considered GI toxicity. The simultaneous application of radiation and chemotherapy can lead to more severe GI and acute hematological toxicity, that can be life-threatening for the patient (neutropenia – 16% vs. 8% and thrombocytopenia – 1.5% vs. 0.2%, in case of only RT without concurrent CT). Gastrointestinal toxicity of Grade 3–4 was observed in 9% of patients, who obtainned RT + CT and in 4% of patients after RT. Effective strategies in order to minimize or prevent GI toxicity include multiple fields RT to avoid significant dose non-uniformity, and full bladder to optimize the physical displacement of the small intestine [34].

A recently published results of randomized study, conducted Hallqvist D. et al., which evaluated toxicity and clinical outcomes in 44 LACC patients, who received EBRT to the entire pelvis or IMRT in dose of 50.4 Gy in 28 fractions with concurrent cisplatin 40 mg/m^2, followed by BT. Compared to 3D-CRT, IMRT was associated with a significantly low rate of immediate (acute) GI toxicity – Grade 2 and higher in 63.6% vs. 31.8% (p=0.034), and Grade 3 and higher in 27.3% vs. 4.5% (p=0.047). Furthermore, IMRT was associated with a low rate of late (chronic) GI toxicity (50% vs. 13.6%; p=0.011). The comparison of dosimetric data between two study groups demonstrated a significantly lower dose at IMRT to the rectum and small intestine, which likely explained these important clinical differences [35].

Significant reduction of the negative consequences of BT is facilitated by three-dimensional imaging, using computed tomography (CT) or magnetic resonance imaging (MRI), which allows the radiation source to be placed away from the critically important surrounding normal tissues [36]. In order to achieve the best effect, it is advisable to use a specialized CT and MR contouring atlas. The authors mentioned, that total dose, single dose, treatment duration, and volumes of the small and large intestine within the EBRT irradiation field are considered to be risk factors for GI toxicity after EBRT. Among the risk factors for genitourinary system toxicity, there were mentioned total obtained dose of irradiation, treatment duration and types of irradiation (EBRT, BT or their combination), so as previously conducted pelvic surgeries. However, the concurrent application of CT during the radiation treatment does not increase the risk of late bladder toxicity in LACC patients [36].

Large prospective study (Wang S.T et al.) has shown, that the hematological toxicity rate of Grade 3 and higher in case of cisplatin-based pelvic CRT in cervical cancer patients is approximately 20–25%. The extended field RT leads to irradiation of a larger part of the body mass and, consequently, can cause a higher level of hematological toxicity [37]. Hematological toxicity can cause in such patients the development of secondary infections, which could lead to the postponement CT and treatment interruptions, which could potentially jeopardize disease control. Moreover, in some patients with advanced disease, who require intensified treatment, hematological toxicity is a major obstacle for using intensified regimens of treatment, as in such a case, up to 72% of patients experience acute toxicity of Grade 3 and higher. One of the important advantages of IMRT, compared to traditional technology, is that, IMRT leads to less bone marrow irradiation overload and, accordingly, lower rate of hematological toxicity [37].

The study, conducted R. Singareddy et al., based on academic approaches of the evidence-based medicine (EM), using the ROC curve analysis for dosimetry parameters, states that the average bone marrow dose irradiation, exceeding 28.5 Gy, was significantly associated with bone marrow toxicity (sensitivity – 82.4%, specificity – 70.6%) [38].

In year 2020 WHO published a global strategy of cervical cancer management, as a public health problem, and presented a list of key areas for future work on the prevention and control of cervical cancer, which was supported by 194 countries worldwide [3].

CHAPTER 2: METHODOLOGICAL APPROACHES TO ASSESSING RISK FACTORS FOR ONCOLOGICAL AND SOMATIC EFFECTS

2.1 Characterization of the technology for data accumulation, storage, and processing

Currently, in EU countries, so as in Japan and USA, it is legally mandated that any new diagnostic or treatment method, before being applied into practical healthcare, must be appropriate investigated, according to the postulates of evidence-based medicine (EM). During the preparation of the study design, the following stages are identified: formulating the goal, planning, data collection, data preparation, data analysis, interpretation of results, presentation of results, and formulating conclusions, as well as publication of results [1, 2].

Clinics and research medical institutions generate and accumulate enormous volume of medical data. In addition to data recording, which contains all the steps of patients' treatment, this data contains implicit trends and statistical dependencies, that can be revealed during investigational analysis, followed the basic principles of EM. This data serve as a basis for obtaining new knowledge.

The data, presented below, is a result of a series of research studies, dedicated to the analysis of digitalized catamnestic data, in order to identify hidden trends and dependencies, using statistical analysis and Data Mining technology, based on the adherence to the principles of evidence-based medicine.

At the initial stage of the retrospective study, the authors have developed the infological model of a database, in order to accumulate the information about the course of disease, treatment of LACC patients and their outcomes. The range of indicators, stored in the database, chosen for analysis, was determined based on the analysis of experience of different research centers, so as including the authors' own experience [10, 17].

Among these indicators were constitutional-biological, biometric, and social characteristics of patients (including harmful habits, occupational and environmental hazards) [11], oncological heredity, gynecological history, treatment schemes and regimen, including the characteristics of its main steps, and treatment results [3, 13, 16, 25, 28]. Therapeutic effects and radiological consequences of radiation therapy were detailed described, based on the monitoring of clinical indicators [3, 16, 38].

For processing of catamnestic data there were applied technology of search for hidden knowledge «Data Mining» and methods of non-parametric statistics, implemented in program STATISTICA, SPSS and WizWhy: Mann–Whitney test (MWT), Chi-square criteria test and ROC curves characteristic. The data are then presented either as median and interquartile range, or as M (LQ; UQ), where M is the median, LQ is the lower quartile, and UQ is the upper quartile. During the analysis of patients survival, an important technology while analising the database is censoring variables. Censoring data is applied if the duration of follow-up observation and patients survival occur during a certain period of time. In such cases, the observations are called censored [39]. The advantage of censored data is that, the duration of observation can be different for each participant, and this can be taken into consideration during the analysis.

Data Mining can be characterized as the technology for discovering in databases previously unknown, non-trivial data, that is practically useful and available for obtaining new knowledge, and necessary for making decisions in various fields of activity, in which people are engaged [8].

New knowledge, obtained due Data Mining, is information, that must meet the following requirements:

- must be previously unknown and non-trivial;

− the knowledge must describe new connections between an object’s properties and its characteristics;

− it must predict the values of some features based on others.

Nowadays investigations, organized in medical enrichments are characterized by a high growth of the clinical information volume, accumulated as a result of a long-term patients observation. In this context, catamnestic data, which represent information, that reflects the patients’ health status, course of disease, complications, treatment efficacy and quality of life at long-term follow-up after therapy, is of particular value. Such data provides a unique opportunity for retrospective analysis and prognosing the treatment outcome. However, their volume, heterogeneity and complex structure require the application of specialized intellectual tools. The Data Mining technology is one of the most promising in this area. This approach allows for the automated detection of hidden patterns, interrelations and trends in large arrays of medical data, that cannot be found, using traditional methods of statistical analyze. The main advantages of Data Mining applying in catamnestic data analyze are the identification of hidden patterns in the disease course, finding groups of patients with similar dynamics of disease course, risks of complications or specific response to therapy. Based on long analyze of catamnestic data, it is possible to predict the probability of recurrence or the development of complications, to identify factors that have influence on treatment effectiveness, and to create personalized treatment protocols [8].

The use of large, representative, and multidimensional catamnestic datasets increases the statistical power of studies and the reliability of conclusions, promotes a deeper understanding of the long-term outcomes of treatment and contributes to the optimization of treatment strategies and its implementation of personalized medicine. Thus, the application of data mining technology in this context is not only appropriate, but also strategically important for the development of modern medical research.

In order to optimize the processing of the statistical data array, we have developed a reference-analytical system "Patient Database" (PD), which allows for the accumulation of medical information of any profile for its subsequent mathematical processing by any software.

The system meets the following requirements:

1) complete formalization of information, which assumes the absence of any descriptive information in the database. Non-numerical information is pre-formalized in the form of reference tables and is stored in the database exclusively as a link to the corresponding row of the reference table. Patient questionnaire data make the only exception.

2) a flexible structure allows for the addition of new types of studies and the modification of existing ones at any time without intervention in the program code.

3) high processing performance with no limitations on the volume of stored information.

4) the ability to select the information at any level. The software provides the ability to select information from the database, considering its completeness in accordance with the requirements for the stored data. The number of imposed conditions is not limited.

5) compatibility with existing software. The modern software market offers a large number of packages for statistical data processing and information visualization [1, 9, 10].

In order to determine the structure of prognostic parameters for LACC treatment efficacy, there was defined the infological model and was created a corresponding database [40–43]. The selection of study indicators for the analytical electronic database was based on the authors' own experience, results of an informational search and data of recent scientific publications [2, 44, 45].

The database includes a section "General Data", which after mandatory questions about last name, first name, patronymic, year of birth, height, body weight, Quetelet body mass index, blood groop and Rh factor, also covered information about profession, nationality, eye color, hair color and marital status. The presence of past surgical interventions on the small pelvis and blood transfusions before and during treatment was described separately.

The section "General Data" described harmful habits (alcohol consumption and smoking), as well as harmful occupational and environmental factors – radiation (doctors, nuclear power plant employees), paints, drug synthesis, contact with insecticides, nickel, chromium, lead, iron, arsenic, asbestos, car exhaust fumes, polymeric materials, working process of blast furnaces and printing houses.

The section "Heredity" provided the accumulation of information about family oncological history – which relatives had oncological diseases and their histological form.

Section "Gynecological History" provided information about menarche, cycle duration, number of pregnancies, abortions, duration of lactation, contraceptive use, menopausal status (premenopause / perimenopause), gynecological anamnesis (presence of fibroids, cervical erosion and other gynecological pathologies in the history).

The section "Epikrisis" reflects general characteristic of the treatment, covered the following questions:

- treatment regimen (neoadjuvant CT + EBRT + BT, or neoadjuvant CT + EBRT + BT + CT, or EBRT + BT + CT, or EBRT + BT, or EBRT or BT);
- treatment start date;
- treatment end date;

- radiation treatment start date;
- radiation treatment end date;
- date of appearance of recurrences/metastases;
- date of the last record in the medical history and an indicator regarding censored observation.

The block of oncological characteristics contained information about the stage disease, TNM staging, histology, grade of differentiation (G), form tumor growth (endophyte, exophyte, crater) and location of the infiltrate. From the diagnostic and examination data there was selected information about the echogenicity and tumor volume of the cervix.

There was analyzed the information about invasion (and if so) and its grade, as well as the presence of enlarged and/or affected lymph nodes, and whether there was lymphostasis of low extremities.

In order to optimize the mathematical processing of information there was partially duplicated previously obtained results of analysed data – if there was applied boost by radiation therapy, whether there was performed neoadjuvant or adjuvant CT, if there was detected relapsed or metastatic disease (time of appearance and its localization).

There was carefully processed the patients survival data, namely overall and recurrence-free survival at follow-up up to one year, two years, three years, five and more years.

Information about the concurrent somatic diseases in following categories was also accumulated:

- cardiovascular diseases,
- GIT diseases,
- gynecological diseases,
- diseases of the genitourinary and endocrine systems,
- blood disorders.

The most comprehensive was the section, which contains information, concerning radiation therapy (external beam and intracavitary) and chemotherapy.

The general parameters of the conducted EBRT included the course duration, type of equipment for radiation therapy, number of sessions (including boost), radiomodification (5-fluorouracil or cisplatin) and a comprehensive description of the total absorbed dose (total dose of irradiation):

- total dose;
- total dose to point A;
- total dose to point B;
- total dose to point A on the right side;
- total dose to point B on the right side;
- total dose to point A on the left side;
- total dose to point B on the left side.

The next section of "Database" contains data, which characterize the radiation fields for pelvis. Direct and oblique radiation fields for pelvis, iliac-gluteal and perineal fields, were characterized by the size of the fields and depth of the target, the number of irradiation sessions, including a boost, the value of the single dose (SD), SD to point A and to point B, as well as the same for the left and right sides of patient’s body. Additionally, it was noted whether chemomodification was applied. For the description of the irradiation of the para-aortic area, there were mentioned size and depth of the irradiations fields, the number of sessions of irradiation, including blocks, the number of simultaneous sessions of irradiation, conducted on the paraaortic and pelvic region, single dose value, and whether there has occurred simultaneously procedure with other radiation exposure were specified.

The general parameters of the conducted BT were the type of equipment (AGAT-V or MultiSourse), single dose to point A and to point B, total dose to point A and to point B.

The description of CT contained its nature (neoadjuvant, synchronous, or adjuvant) and the list of applied medications and its dosage.

The description of radiation consequences as early radiation reactions (in term up to three months) contains data on the appearance of leukopenia, anemia, lymphopenia, rectitis, colpitis, cystitis, enterocolitis, radioepitheliitis, and skin erythema of the radiations field. The description of late radiation complications included bladder ulceration, indurative changes in soft tissues, post-radiation soft tissue fibrosis, rectitis, colpitis, cystitis, enterocolitis, radioepitheliitis, cystolithiasis and skin pigmentation.

Similarly to the somatic diseases or disorders, which were diagnosed before the beginning of treatment, there were also monitored somatic diseases, that appeared at long-term follow-up after the end of special treatment.

Among with the clinical indicators before and after the treatment, there were also monitored levels of creatinine, urea, hemoglobin, platelets, erythrocyte sedimentation rate (ESR) and tumor marker SCC.

2.2 Characteristics of Patients and Observation Data

From the archive data in State Organization "Grigoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine" in order to make entry into the investigational electronic "Patients’ Database", there were selected medical case-histories of patients with LACC (stages IIB, III, IIIA, IIIB, IV, IVA, IVB), who underwent specialized treatment in clinic of the institute during the period of 1999–2022. The selection criteria were either an observation follow-up longer than one year or a documented disease manifestation within a follow-up up to one year. The end of observation was considered either the patient’s death or appearance of oncological consequences, or status «lost from follow-up for unknown reasons» (censored observations).

The study cohort included 213 cases of LACC, whose information was converted from paper medical histories into digital form and maximally enriched with information.

The age of the patients ranged from 26 to 78 years, with a median of 52 years and interquartile range of (44; 59) years.

The distribution of LACC patients by stage of disease is:

- Stage III – 138 (65%) patients,
- Stage IIB – 50 (24%) patients,
- Stage IV – 25 (11%) patients.

In order to reach the purpose of investigation, "Patients’ Database" should be adapted to the purpose of the study by creating a series of relational tables, whose structure allows for the reproduction of essence of the problem, which is under investigation. The semantic implementation of these objects is based on the detailed investigation of paper medical histories and the experience of physicians, who treat this patients’ cohort. The indicators (entities) to be accumulated in the future database were determined based on the analysis of more than 200 medical histories of LACC patients.

The grade of tumor spread was determined according to the FIGO classification, based on clinical examination data, including bimanual examination, data of ultrasound investigation of organs of the abdominal cavity and pelvic organs (providing sufficient information about the anatomical and morphological parameters of the primary tumor, pelvic and para-aortic lymph nodes, and the urinary system organs), cystoscopy, rectosigmoidoscopy, excretory urography/renoscintigraphy, pelvic MRI, CT of the pelvic, chest and abdominal cavity organs.

In order to monitoring the treatment efficacy there was conducted the dynamic follow-up with the ultrasound investigation of the tumor volume of the cervix, in conjunction with bimanual examinations. The aim of this examination is evaluation of decrease of the tumor size under the treatment. CT or MRI were conducted non-earlier than three months after the end of the treatment.

Analyzing the histologically data of tumor samples, there was defined the prevalence of squamous cell carcinoma without differentiation in 127 (60%) patients, and as type of tumor growth was most common endophytic form – in 159 (75%) patients.

About sixty percent of the observations (127 (59,6%) individuals) were censored, due to which the characteristics of overall survival were understated. The survival-rates were: for one-year – 100%; two-years – 93%; three-years – 73%; five-years – 55%; more than 5 years – 33%.

Similarly, the characteristics of recurrence-free survival are also understated. One-year survival is 100%; two-years – 77%; three-years – 62%; five-years – 50%; recurrence-free survival more than 5 years – 31%.

CHAPTER 3: ONCOLOGICAL AND SOMATIC EFFECTS OF CHEMORADIATION TREATMENT IN PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

3.1 The Role of the Tumor-Associated Marker SCC in Cervical Cancer Treatment Monitoring

It is well known, that one of the promising ways to assess the treatment efficacy, so as early diagnostic of relapsed disease of LACC is evaluation of the marker, associated with squamous cell tumors, – SCC (squamous cell carcinoma antigen) [46–48]. There was detected a direct correlation between the level of SCC expression and spread of the disease. It has been established, that the increased level of SCC expression at an early stage of LACC can indicate on the metastatic involvement of regional lymphatic nodes, where the number of SCC-positive cases reaches 91.7%. The increased level of SCC can serve as a risk factor for recurrence and indicates on the necessity for aggressive anti-tumor therapy and later on more thorough posttreatment follow-up of these patients, which has been confirmed by our long-term studies [49].

The greatest perspectives for the application of SCC in clinical practice are associated with LACC. Thus, in case of adeno-squamous LACC, the expression level of SCC exceeds the normal value in more than half of cases (56%), in case of cervical adenocarcinoma – in 21–25% of cases. At the same time, the diagnostic sensitivity of SCC for squamous cell LACC, according to data of different investigators, exceed 55–87% with a specificity of 90–91% [47, 48].

Therefore, considering the perspectives of application of the tumor-associated marker SCC for the optimization of further treatment and follow-up of LACC patients, a series of investigations, concerning informativeness and peculiarities of SCC marker application in LACC patients have been conducted at the SO "GRIGORIEV IMRO NAMS" since 2006 [46]. Some of study results are presented in tables (Tables 1–3).

Table 1. The value of SCC in LACC patients with different stages (FIGO) at primary diagnosis.

Stage	Number of patients (n=120)	Statistical Indicators, ng/ml					
		Mean, ng/ml	Std. Error	Std. Deviation	Median	Range min–max	P
I	27	1.49	0.38	1.98	0.64	0.18–7.30	$p_{I,\ II}$ = 0,002 $p_{II,\ III}$ = 0,107 $p_{III,\ IV}$ = 0,047
II	43	5.30	0.96	6.3	3.10	0.36–26.10	
III	40	7.84	1.62	11.31	4.35	0.43–70.00	
IV	10	14.50	1.89	9.8	14.90	0.20–30.60	

According to the data, presented in Table 1, the average statistical level of SCC values shows a clear dependence on the stage of LACC, even at early stage of the disease. The average of SCC value in patients with stage II is significantly higher (3.6 times), than in cervical cancer patients with stage I (p=0.002). At the same time, the upper limit of the value in patients with stage II was 26.1 ng/ml compared to 7.3 ng/ml in those with stage I.

In cervical cancer patients with advanced stage of the disease, higher SCC values were detected. Thus, in cervical cancer patients with stage III, there was noted a tendency to the increase of the average SCC value, approximately in 1.5 times, compared to stage II cervical cancer patients (p=0.107), although the upper limit of the marker, recorded in this group of patients, was the maximum among all examined patients and exceeded 70.0 ng/ml.

In cervical cancer patients with stage IV (LACC stage IV), the average SCC values were the highest, statistically significantly exceeding the analogous values in cervical cancer patients with stage III in 1.85 times (p=0.047), but the upper limit was lower, than in those with stage III and exceeded 30.6 ng/ml.

It’s worth to note, in patients with early-stage disease, there were no great differences between the SCC values. Only in 7 of 27 patients there were detected elevated SCC values – 1.7 ÷ 7.3 ng/ml.

In cervical cancer patients stage II, there were noted sharper individual fluctuations in SCC values – from lower, than discriminant (1.5 ng/ml) to very high values (up to 70.0 ng/ml).

Significant differences between the maximum of SCC values in cervical cancer patients stages III and IV may be related to the different tumor volume, as it is known, that at stage IV, the tumor volume of cervix may be smaller, but with presence of distant metastases.

Overall, the analysis of this data shows that the average SCC value consistently increased with the progression of the process, and statistical average of SCC values at different stages of LACC patients differed significantly from each other, with the exception of stages II and III.

During the individual analysis of SCC values, there were identified 3 intervals of SCC values within its fluctuations – normal (up to 1.5 ng/ml), elevated (1.5–8.0 ng/ml), and high (> 8.0 ng/ml) values (Table 2) [51, 52].

Table 2. Frequency and degree of SCC value increase in cervical cancer patients at different stages (FIGO), (%).

Stage	Number of patients (n=120)	SCC values in blood serum, ng/ml					
		Normal ≤ 1.5		Elevated 1.5–8.0		High > 8.0	
		n	%±m%	n	%±m%	n	%±m%
I	27	20	74.1±8.6	7	25.9±8.6	–	–
II	43	14	32.6±7.2	21	48.8±7.7	8	18.6±6.9
III	40	11	27.5±7.2	22	55.0±8.0	7	17.5±7.1
IV	10	3	30.0±15.3	1	10.0±10.0	6	60.0±16.3

Based on the data, presented in table, we can conclude, that the vast majority of cervical cancer patients with advanced stage, because of widespread tumor (stages III–IV) had elevated and high levels of SCC values. The frequency of SCC-positive cases (elevated of high SCC value) in cervical cancer patients stage I was (25.9±8.6)% (7 out of 27 cases), at stages III and IV there were (72.0±6.4)% (36 out of 50 cases). High SCC values (>8.0 ng/ml) were either not recorded at an early stages of disease (stage I) or were noted in rare cases (18.6 ± 6.9)% in cervical cancer patients stage II. At the same time, in the group of patients with stage IV, very high SCC values were recorded in 6 of 10 examined patients (60.0±16.3)%.

Thus, the stage-dependence of this marker was established not only by comparing the average SCC values in clinical groups of cervical cancer patients with different stages of disease, but also by analyzing the frequency of SCC-positive cases.

Determining the SCC value can be informative for clarifying the stage of cervical cancer disease, in order to avoid the underestimating, the spread of disease (TNM stage). This is supported by the results of a retrospective comparative analysis of SCC values at primary diagnostic, after surgery and obtaining the pathomorphological conclusion, concerning the status of regional lymph nodes.

Therefore, there was conducted comparative analysis of SCC values at the time of initial examination of these patients and diagnosing of recurrence in order to find a possible correlation (Table 3).

Table 3. Level of SCC value in blood serum in cervical cancer patients with recurrent disease.

Time of analysis	Number of patients with elevated SCC value		Statistical indicators, ng/ml					
	Abs.	%±m%	Mean, ng/ml	Std. Error	Std. Dev.	Median, ng/ml	Range min–max	P
Initial value before the treatment	22	91.7±5.8	8.96	2.26	5.81	7.85	0.20–26.7	0.048
Time of recurrence	18	75.0±9.0	13.21	3.46	9.32	10.5	0.16–65.0	

Analyzing the data, contained in Table 3, the average level of SCC values in patients with relapsed disease cervical cancer was significantly elevated (up to 13.21±1.46 ng/ml), overcoming the discriminant level in approximately of 9 times. In these patients, during the initial diagnosis of primary cervical cancer, the average level of SCC values was also significantly higher, than the normal values (8.96±1.22) ng/ml, although, less than at the time of detected recurrence ($p<0.05$).

A particularly interesting finding from the Data mining analysis was the "favorable" range for the SCC antigen level in patients with a survival period longer than 5 years. According to reference norms, it should be <1.5 ng/ml (at time of the investigation the SCC cut-off level, provided by labor was < 1,5 нг/мл). However, in the analyzed cohort of patients, who survived beyond the five-year interval, and in whom there was not detected oncological consequences during the last check-up, the SCC value level range was 0.3−9.1 ng/ml. This dependence was observed in 48 (77%) patients and was an exception in four individuals (7%). This suggests that the SCC value interval of 0.3–9.1 ng/ml is favorable for the prognosis of patients' survival without oncological consequences, the level of value of this tumor-specific marker higher, than 9.1 ng/ml, can be a factor for appearance of oncological consequences.

Thus, the obtained study results confirm the presence of stage-specificity of the tumor marker SCC in cervical cancer patients. This fact is also supported with our data, that in case of disease progression, there was documented the increase of both SCC value and the frequency of SCC-positive cases.

The direct correlation between the SCC value level and the spread of cervical cancer disease allows to recommend it for clinical application for assessment of treatment efficacy. It has also been established, that determining of the SCC value is appropriate for prognosing of possible recurrences of cervical cancer.

We have shown, that a high level of SCC value at primary diagnosis correlate directly with the recurrences-rate in the long-term follow-up, especially in patients with advanced stage of cervical cancer. In these patients, a high level of SCC value should raise vigilance, regarding disease recurrence and indicate the need for comprehensive antiblastome treatment and more precise follow-up.

Therefore, determining the SCC tumor marker is advisable both as a part of diagnostic in primary cervical cancer patients and for monitoring the treatment efficacy, as well as at follow-up, in order to early detection of disease recurrences.

3.2 Predictive indicators for future oncological consequences

During the study there were identified a number of indicators, that have predictive value regarding the appearance or absence of future oncological consequences (OC). The first indicator with a predictive value is the tumor-involved volume of the cervix (TVC), which, if conditionally represented as a cylinder (Figure 1), was calculated by the formula for the volume of a cylinder $V = \pi r^2 h$, where V – volume in mm^3; $\pi = 3.14$; r – radius in mm; h – length in mm.

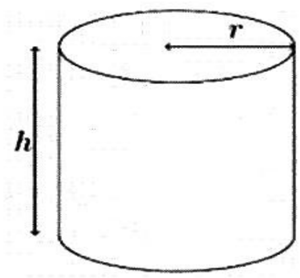

Figure 1. Conditional representation of the cervix for calculating its tumor volume

The presence or absence of OC was statistically dependent on tumor volume of the cervix (MWT, p=0.0209) (Figure 2).

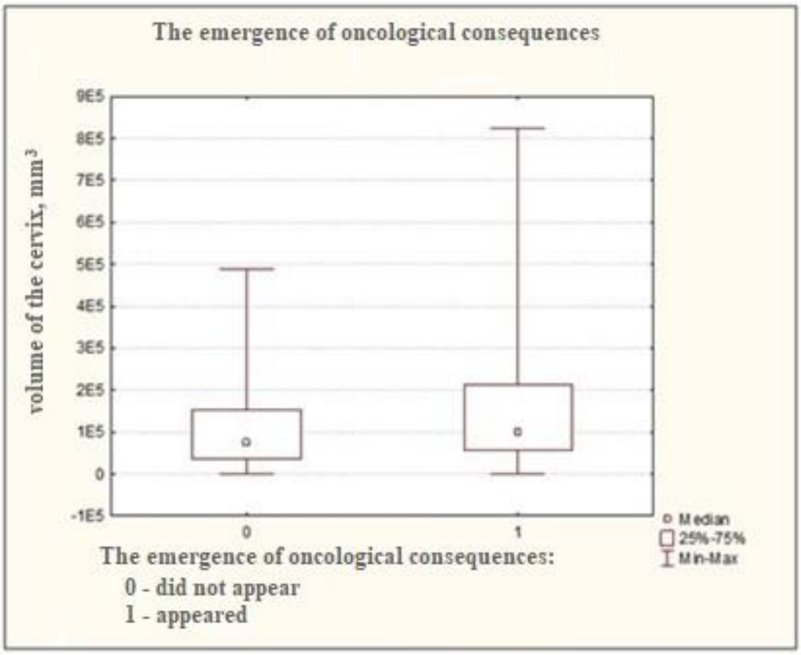

Figure 2. Dependence of the presence or absence of OC on the tumor volume of the cervix

In patients without OC, the TVC values were 76,612 (35,473; 153,098) mm³; in patients with OC these values were 100,396 (56,704; 211,328) mm³.

As the study samples cohort contained censored observations, the revealed dependence was additionally checked while distributing patients into subgroups, based on signs of recurrence-free survival ("yes" or "no") at follow-up of three years, five years and more than five years. The statistical significance of the dependence of survival on TVC was actual for three and five years. For recurrence-free survival for more than five years, the dependence did not manifest itself due to the reduction of the number of individuals without OC.

In order to specify the level, that separates the presence/absence of the risk for OC (cut-off), based on the TVC values, there was additionally applied statistical analyze of ROC curves. Using the ROC curve analyze, the test sensitivity and complementary value of the specificity have tendency to one. As more curved is the ROC curve, so as the test's prediction is more precise. The indicator of this property is the area under the curve: for the test with a zero degree of prediction its value is 0.5; for cases with a maximum degree of prediction its value is 1. For the tested hypothesis the area under the curve was 0.632 (Figure 3).

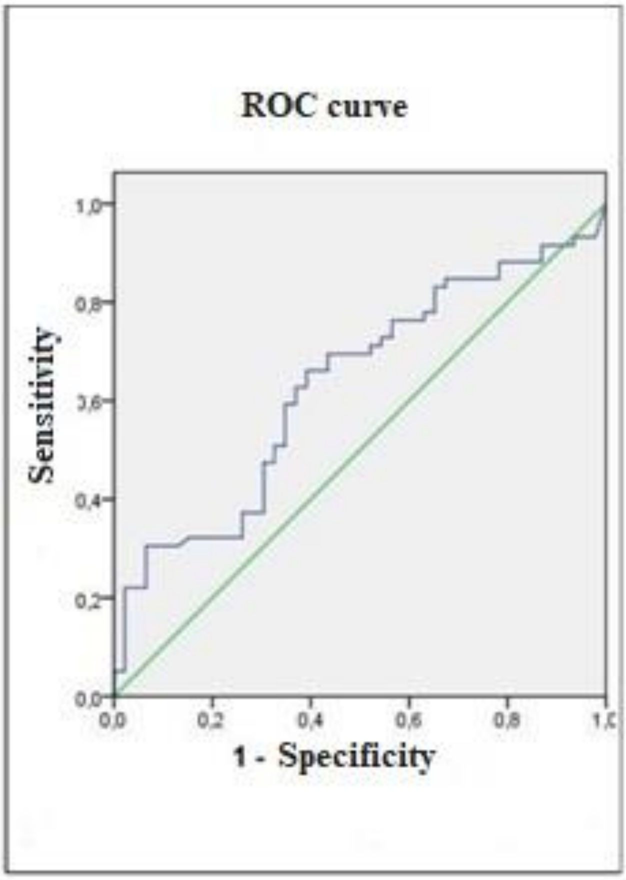

Figure 3. ROC curve of the "specificity-sensitivity" dependence for the test of OC prediction, based on the TVC values

Analysis of the obtained descriptive statistics and ROC curve coordinates allowed the determination of a cut-off for TVC at the level of 56,000 mm³ – exceeding of this level is a risk factor for appearance of OC in future. At the same time the test sensitivity is 76% with specificity of 56%.

The second statistically significant indicator with predictive properties (MWT, p=0.0083) was the platelet level at the beginning of treatment (Figure 4).

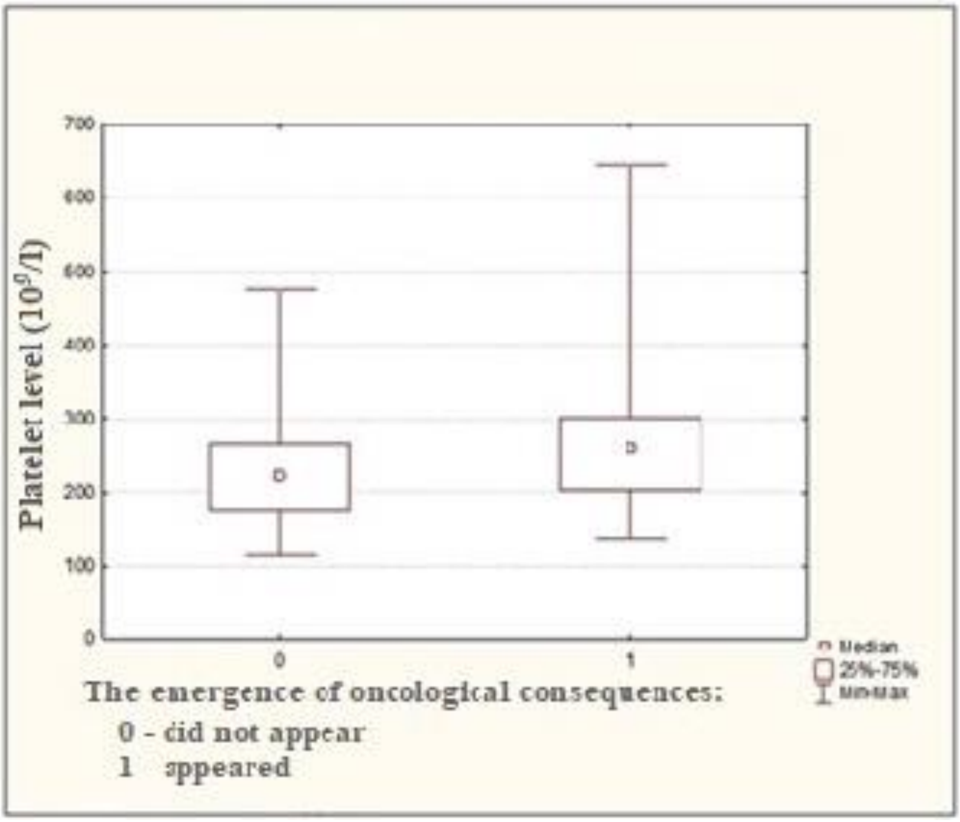

Figure 4. Dependence of the appearance or absence of OC on the platelet level (10^9/l) at the beginning of the treatment

In patients without OC, the platelets level at the beginning of treatment was 221 (175; 264) x 10^9/l; in patients with OC, it was 260 (204; 301) x 10^9/l.

The statistical significance of the dependence of recurrence-free survival on the platelets level at the beginning of treatment was actual for three-year and five-year survival. For the recurrence-free survival of more than five years, the dependence manifested itself as a trend.

The area under ROC curve (Figure 5) was 0.655, with a cut-off for platelets level at the beginning of treatment of 200 x 10^9/l – exceeding this level is a risk factor for the appearance of OC in future. The test sensitivity is 75% with specificity of 58%.

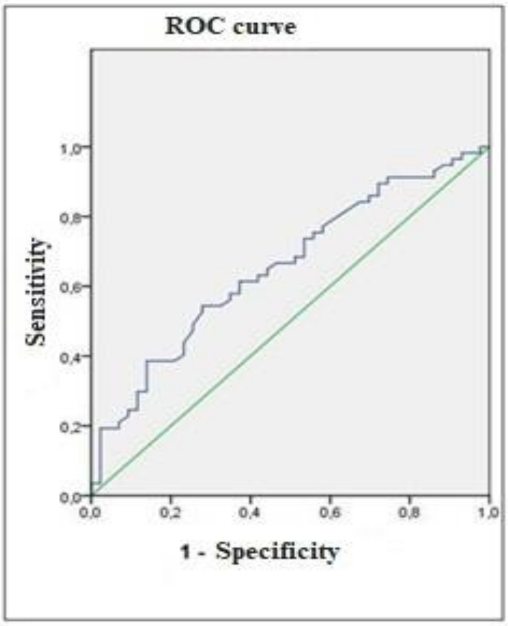

Figure 5. ROC curve for "specificity-sensitivity" dependence, based on the platelets level at the beginning of treatment

An additional, as a third prognostic factor, based on the determination of the platelets level was the relative dynamics of platelets between the beginning and end of the treatment, calculated by the formula:

dV = (V start – V end)/V start × 100%, where

V start – is the value at the beginning of treatment,

V end – is the value at the end of treatment.

In patients, in whom there can be detected OC in the future, the value was 23.2 (-1.2; 42.2), and without future OC – 17.1 (-9.3; 29.3) (Figure 6).

For patients with a tendency for decreasing of platelets level during the treatment period for more, than 30%, there is a risk of OC appearance in the future (Figure 6).

Thus, a platelets level at the beginning of treatment, exceeding 204 x 10^9/l, as well as a sharp decrease of this value at the end of treatment (more than 30%), are considered to be unfavorable prognostic factors.

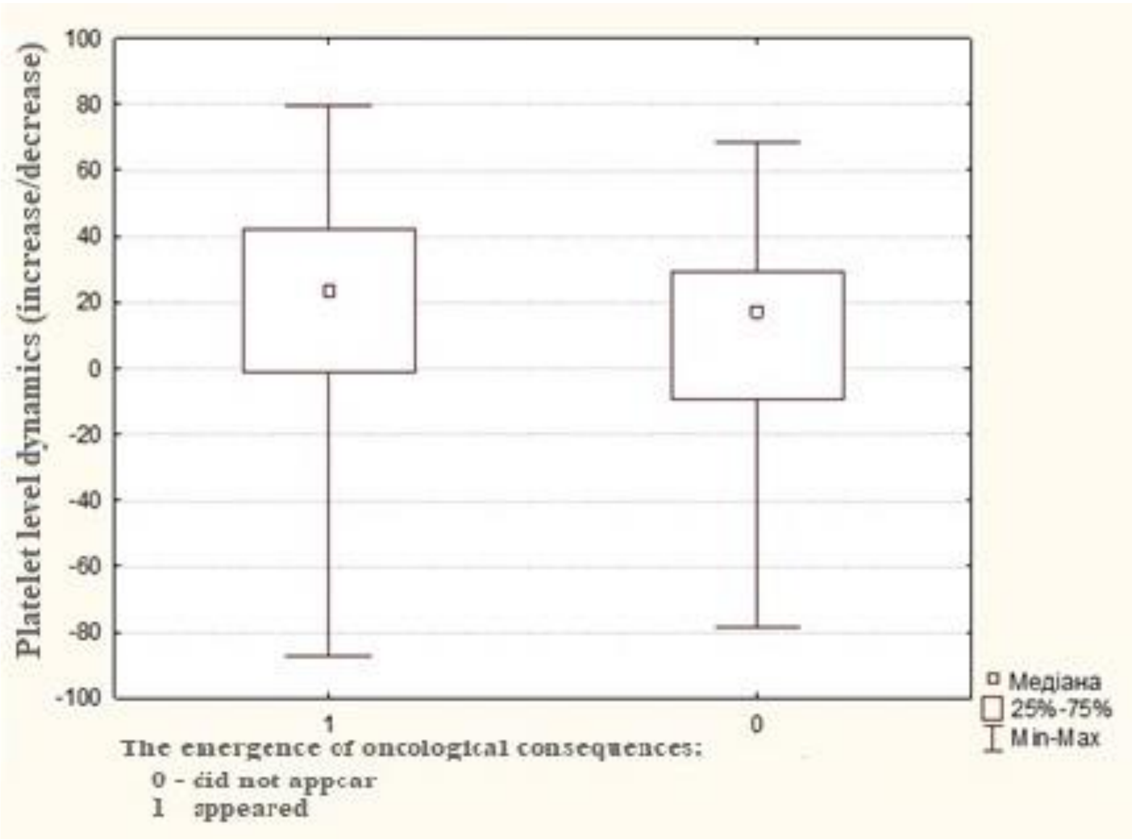

Figure 6. Dependence of the OC appearance on the relative dynamics of platelets between the beginning and end of the treatment

Regarding the obtained dependencies, there was presented in year 2022 by Canadian researchers data, which shows correlation between the increased platelet count and the occurrence of lung, ovarian, esophageal, colon, kidney, pancreatic and other GI tumors [53]. The goal of their study was to investigate the types of cancer, associated with an increased platelet count in relation to time of the cancer diagnosis. There were enrolled 8917187 residents of Ontario. Platelets levels were divided by clinical thresholds: thrombocytopenia (< 150 x 10^9/l), normal level (150–450 x 10^9/l) and thrombocytosis (> 450 x 10^9/l). The average platelets count in the last blood test was higher among cancer patients, than in group of comparison (245.7 x 10^9/l vs. 237.0 x 10^9/l). Patients, in whom were diagnosed solid tumors, were more likely to have an increased platelets count in comparison to the group without cancer, 44 344 (19.5%) vs. 65,626 (9.6%). It is worth to note, the platelets level in all patients remained within the normal range. Similar results were obtained in our investigation.

As addition to indicators with predictive value, concerning OC in the future, we have also applied the sign of the localization of pelvic infiltration: OC appears in 60% of cases with localization of infiltration in both parametria spaces and in 50% of cases with localization of infiltration of parametria only on the right side.

The application of modern information technologies to a digitized dataset of catamnestic records from patients with cervical cancer enabled the identification of several non-trivial correlations of high clinical relevance. These findings hold substantial value for preventing the development of distant cancerous and somatic effects, as well as for refining and optimizing treatment algorithms.

Specifically, statistical analysis demonstrated that the following factors are significantly associated with an increased risk of adverse oncological consequences: an initial tumor-involved cervical volume exceeding **60,000 mm³**; a tumor-specific marker **SCC level greater than 9.1 ng/mL**; **erythrocyte sedimentation rate (ESR)** at time of the end of the treatment above **16 mm/h**; **baseline platelet count** exceeding **204×10^9/L**; **platelet level decrease** during treatment of more than **30%**; and **bilateral** or **right-sided parametria infiltration**.

3.3 Analysis of immediate radiological consequences

While literature search, there can be found some publications [54–56] that emphasize the factors, influencing the development of radiation therapy consequences after pelvic irradiation, particularly in patients with LACC. A detailed publications review, concerning various radiation reactions and complications, related to RT, indicates that for these issues have been given a very particular attention, concerning both diagnostic and treatment [55]. Based on the time of occurrence, there were defined two types of radiation consequences: early radiation reactions and late radiation damages. The development of early radiation reactions can be observed during the RT or within the first three months after its completion. In this case, the radiosensitive and well-regenerating tissues are always affected, which can subsequently relative easily recover [56]. The clinical experience, accumulated by specialists in this field, has led to opinion, that late local radiation complications, which arise as a result of deep histochemical and histological changes, have a tendency to progress. Despite significant advances in RT, radiation-induced complications are still quite common in LACC patients.

According to the literature data, due to the high sensitivity of lymphocytes to irradiation influence, there can be often occurred a radiation-induced lymphopenia (RIL) after RT [57, 58].

According to the *Common Terminology Criteria for Adverse Events* (CTCAE; version 5), there are four grades of radiation-induced lymphopenia (RIL; G1–G4): Grade 1 – <1000–800 cells/μL; Grade 2 – 500–800 cells/μL, with a minimum decrease of 20%; Grade 3 – 200–500 cells/μL, with a minimum decrease of 50%; and Grade 4 – < 200 cells/μL, with a minimum decrease of 80% [59].

Due to the negative impact of radiotherapy (RT) on the immune system, a reduction in immune defense function has been observed in patients, which may contribute to the development of adverse events and negatively affect overall survival across various disease types, as demonstrated in experimental studies. Compared with other solid tumors, patients with locally advanced cervical cancer (LACC) exhibit a higher incidence of Grade 3 RIL (58%, range 53%–61%) [57]. Among patients with LACC, who have completed a full course of pelvic radiotherapy, the incidence of Grade 4 RIL may reach 33,1%, which substantially influences the overall survival. Although the absolute lymphocyte count typically returns gradually to normal levels after treatment. LACC patients in such cases may require up to five years in order to recover to their pretreatment values.

Thus, the efficacy of external beam radiotherapy (EBRT) and chemotherapy (CT) in patients with locally advanced cervical cancer (LACC) was evaluated at different treatment stages — during therapy, immediately after completion, and throughout the subsequent 60-month follow-up period. Analysis of early radiation-related complications demonstrated that the most common adverse effects included leukopenia (52%), radioepithelitis (30%), anemia (23%), cystitis (22%), enterocolitis (18%), lymphopenia (12%), radiation dermatitis (4%) (table 4.).

Table 4. Characteristics of early complications of chemoradiation treatment.

Type of Complication	Number of cases	Percentage, %
Leukopenia	111	52
Radioepitheliitis	64	30
Anemia	49	23
Cystitis	47	22
Enterocolitis	38	18
Lymphopenia	25	12
Radiation Epidermitis	9	4

Regarding leukopenia, as a factor of negative treatment outcomes, there was found the dependence between the appearance of leukopenia and the total dose to point B. As seen on Figure 7, the risks of leukopenia can increase, if the total dose to point B exceeds 41 Gy (MWT, p=0.004371).

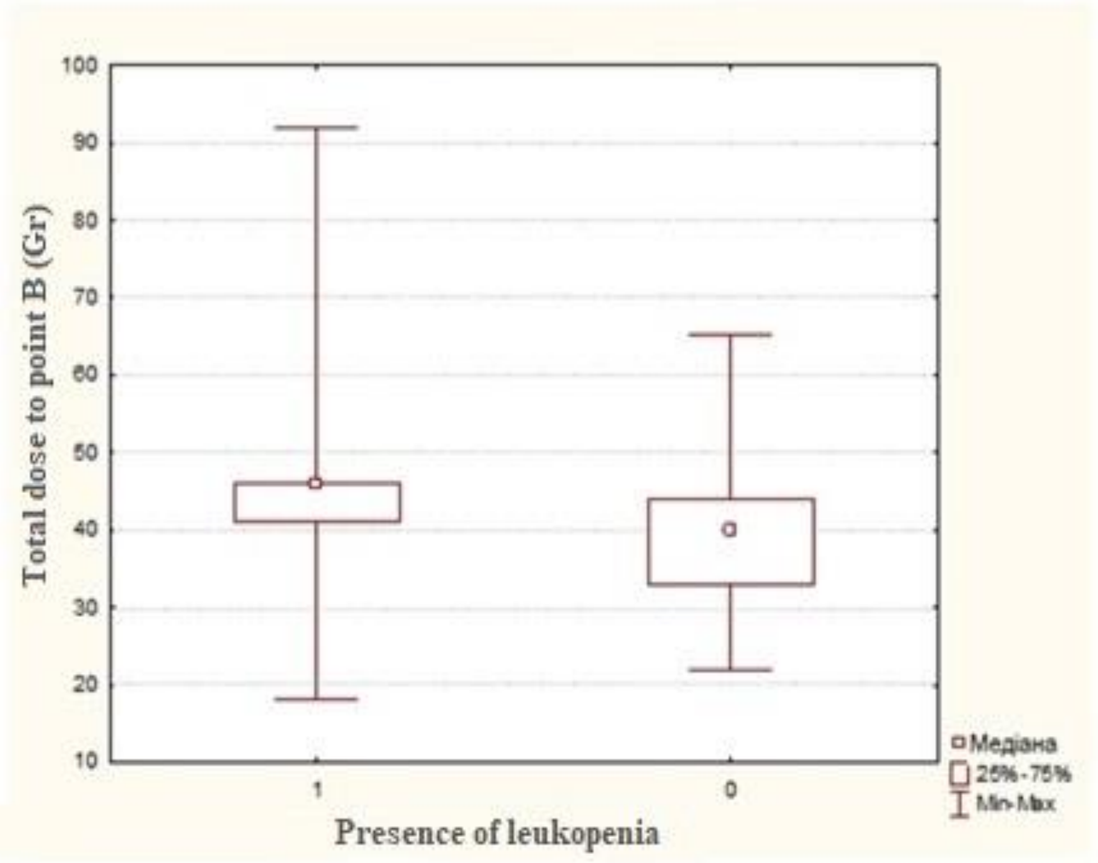

Figure 7. Dependence between the appearance of leukopenia, as an immediate treatment consequence, and the total dose to point B.

According to our data, the pre-treatment tumor-involved cervical volume (TVC) serves as a prognostic indicator. It was determined, that a tumor volume threshold of 139,000 mm³ and values, exceeding this level are associated with an increased likelihood of developing radioepithelitis of the vagina and cervix (Figure 8). This observation may be explained by the necessity of administering a higher dose of local irradiation, required in order to achieve the complete tumor response.

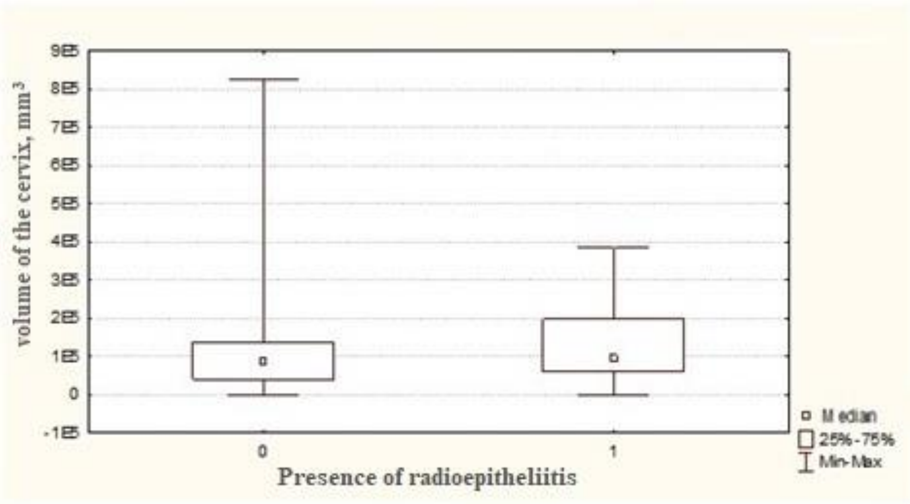

Figure 8. Dependence of the appearance of radioepitheliitis and tumor-involved cervical volume before the treatment

In addition, it is statistically significant, that a uterine cavum *length*, greater than 57 mm, can be an unfavorable factor for the appearance of **anemia** (MWT, p=0.029682). This may be related to the increase of the local dose of irradiation (Figure 9).

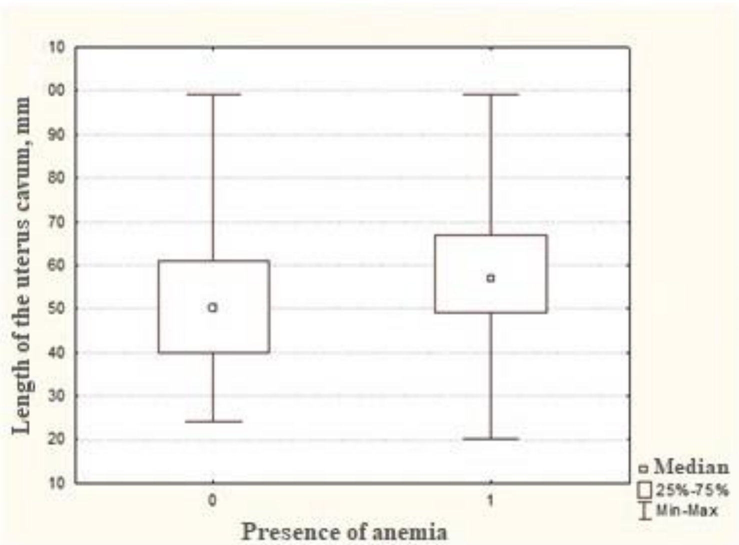

Figure 9. Dependence of the appearance of anemia and length of the uterus cavum during CCRT

The appearance of radiation induced **cystitis** is directly related to the patient's body weight: exceeding a threshold of 82 kg can be a statistically significant risk factor (MWT, p=0.014271) (Figure 10).

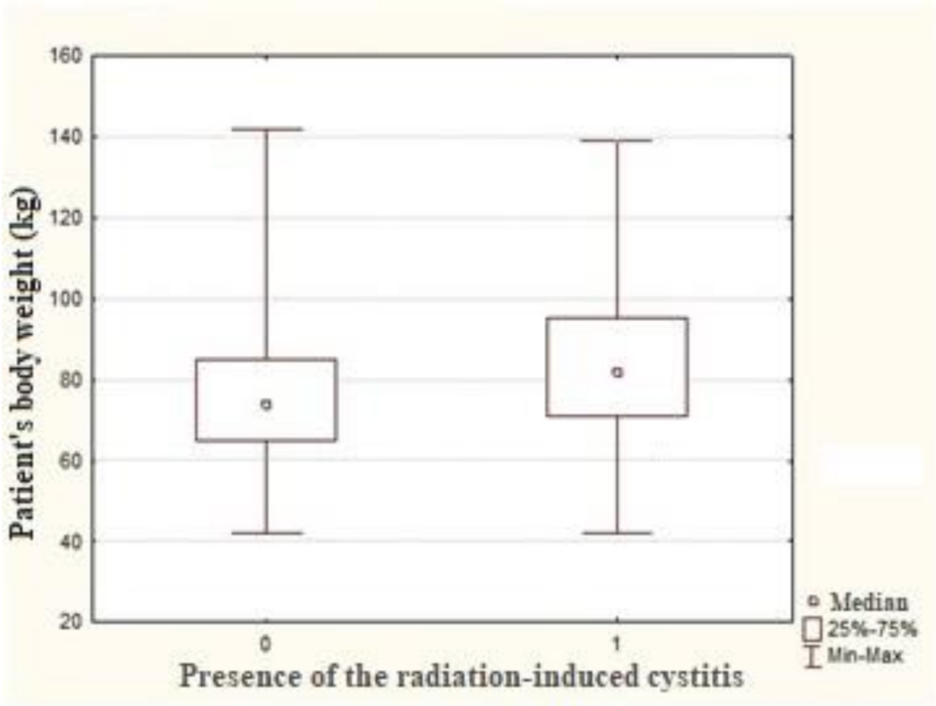

Figure 10. Dependence of the radiation-induced cystitis and patient's body weight during CCRT

Consequently, the **radiation field depth** in such cases exceeds **12.5 cm**.

The available data also allows for certain conclusions regarding the occurrence of **enterocolitis** as an early manifestation of radiation-induced toxicity. During radiotherapy, most cases were observed in the group of patients, who received EBRT using a **Co-60 (ROKUS-AM)** (51%, n = 18), compared with those, who were treated with a **linear accelerator** (43%, n = 15) (**χ^2 test**, p = 0.01731). However, in all cases, enterocolitis was limited to **Grade 1–2 toxicity**.

3.4 Assessment of Long-Term Radiological consequences

According to the data from leading international oncology clinics, the incidence of early radiation-induced catarrhal and fibrinous epithelial reactions in vagina, rectum, and urinary bladder, following radical radiotherapy for patients with locally advanced cervical cancer (LACC) can occur in **10% to 80%**.

Radiation damages of the pelvic organs – primarily **rectum** and **urinary bladder,** constitute the main component of **late radiation damages** in this patients population, and in the most part can determine their subsequent quality of life. Reported occurrence-rate of late radiation complications of the urinary bladder and rectum vary considerably across studies, ranging from **5–10%** to **45–50%**.

Specifically, **infiltrative-ulcerative rectitis** occurs in **1.5–5.9%** of cases, **ulcerative cystitis** in **0–2.8%**, **rectovaginal fistulas** in **1.9%**, and **necrosis of the cervix and vaginal walls** in **5.3–5.7%** of patients, depending on the **total obtained dose of radiation** and **regimens** of **fractionation, applied in the treatment program**. Mortality-rate, associated with radiation-induced damages ranges from **0.4% to 4%** [6].

Analysis of late radiation consequences of radiation therapy revealed an **inverse relationship** with oncological consequences (OC). Thus, patients, in whom was developed **radiation-induced cervical epitheliitis,** demonstrated a lower incidence of adverse oncological consuquences, compared with those, who did not experience late radiation complications. And on contrary, in case of absence of such complications, the oncological consequences rate was significantly higher.

Among **56 patients, in** whom were observed late **radiation-induced cervical epitheliitis**, in **41 (69%)** of them were no evidence of OC, while in **15 (31%) patients** exhibited such OC. This association was **statistically significant** (**χ^2 test, p = 0.0014**).

In total, **late radiation injury** of radiotherapy was observed in **108 (51%) patients.** The corresponding nosological spectrum is presented in **Table 5**.

Table 5. Late radiological consequences of radiation treatment of LACC patients.

Type of complication	Number of cases	Percentage of total (213 individuals), %
Radiation necrosis of the cervix	16	7.5
Colpitis	18	8.5
Radioepitheliitis of the Cervix	56	**26.3**
Telangiectasia	10	4.7
Rectitis	16	7.5
Gastroenterocolitis	2	0.9
Enterocolitis	6	2.8
Colitis	10	4.7
Skin pigmentation	6	2.8
Indurative changes of pelvic soft tissues	6	2.8
Fibrosis of the anterior abdominal wall soft tissues	32	**15.0**
Bladder ulceration	16	7.5
Cystitis	56	**26.3**
Fibrosis of the bladder walls	6	2.8
Leukopenia	2	0.9
Parametritis	2	0.9
Post-radiation plexopathy	2	0.9

Analyzing data of Table 5, we have concluded, that the most frequent long-term radiological consequences of the radiation treatment were:

- cystitis (26.3%),
- radioepitheliitis of the cervix (26.3%),
- soft tissues fibrosis of the anterior abdominal wall of radiation field (15%).

In order to eliminate the potential influence of the age factor on the identified associations, the age difference between the onset of the treatment and the time of appearance of long-term radiological complications was evaluated. No significant differences were observed (Figure 11).

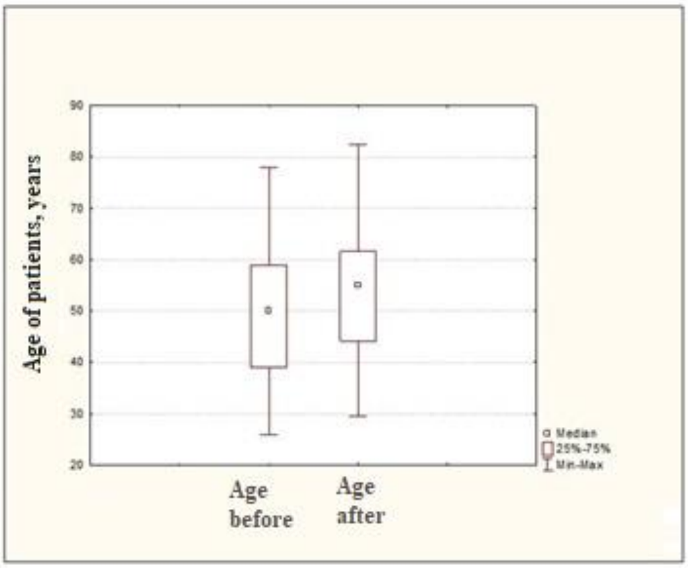

Figure 11. Age of patients before the treatment and during the long-term follow-up

Analyzing the data, presented in on Fig.11, there were not observed any significant differences.

3.5 Somatic consequences of the treatment of LACC patients

The analysis of the somatic consequences during the *long-term follow-up after the* treatment was conducted, considering the background of mandatory monitoring of the influence of the age factor. Among the cardiovascular and respiratory systems diseases in LACC patients, there were observed statistically significant increase of cases of atherosclerosis (from 2.8% to 7%), pulmonary emphysema (from 0.5% to 3%) and encephalopathy (from 3.8% to 11%) (Figure 12).

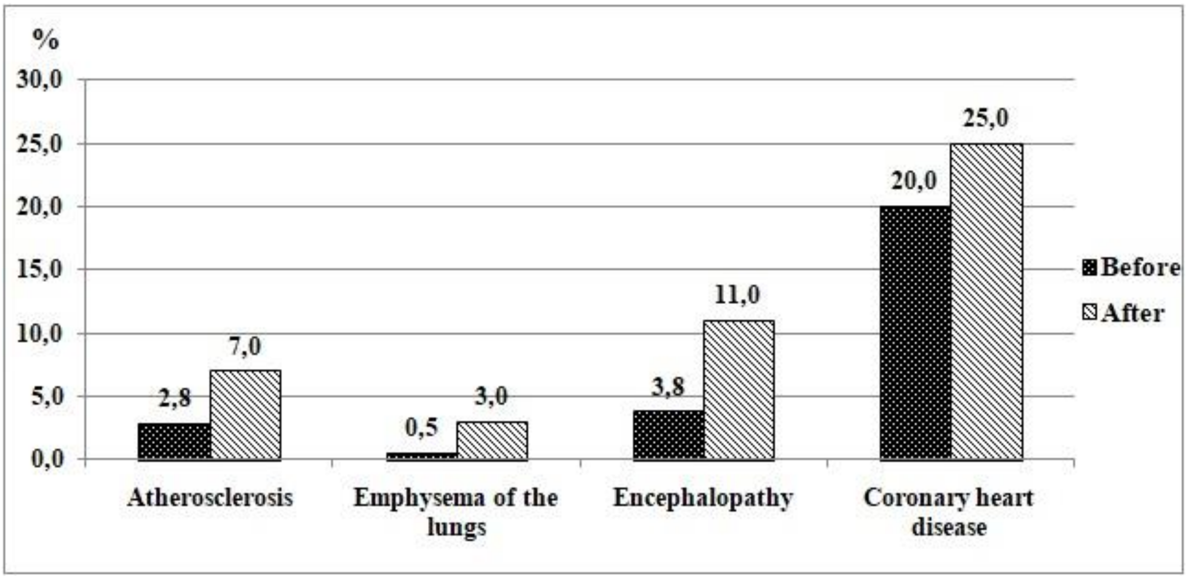

Figure 12. Level of somatic consequences in LACC patients at long-term follow-up after treatment

Although there was statistically not confirmed, a possible increase of the incidence -rate of ischemic heart disease from 20% to 25%was observed, which may also be attributed to the age-related factor.

Among the urinary system disease as side-effects of radiation therapy, there was observed the increase **of the incidence-rate of** cystitis, chronic renal failure, cases of urolithiasis, kidney inflammatory diseases, but these phenomena did not have statistical significance on the available cohort sample size (Figure 13).

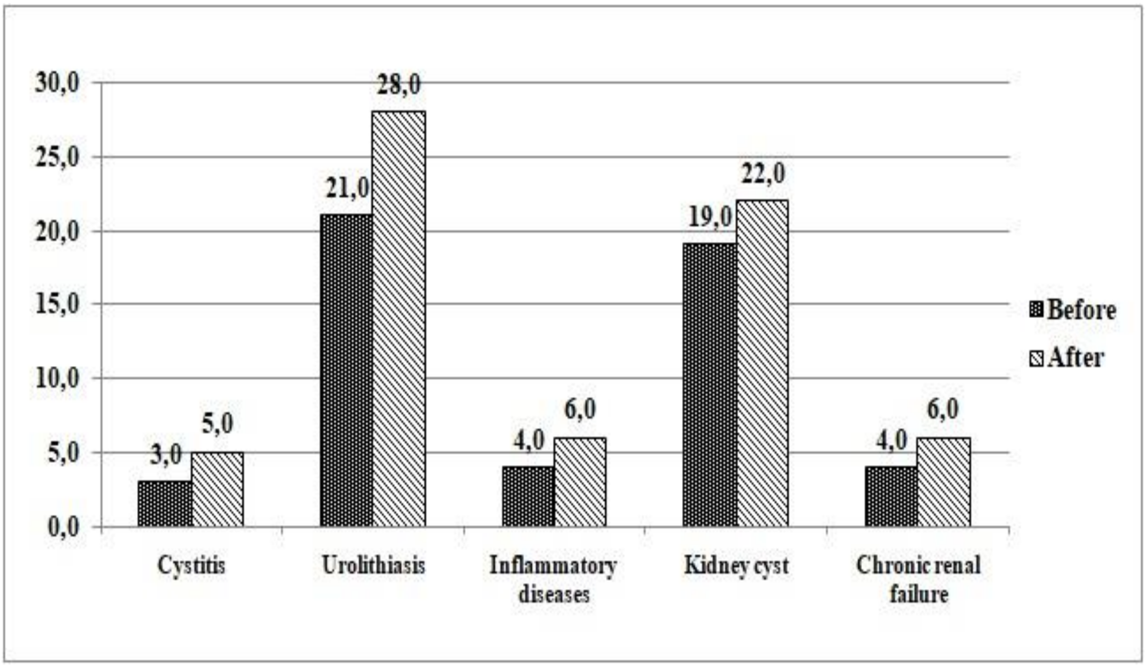

Figure 13. Incidence-rate of urinary system disease before and after treatment of LACC patients

Among gastrointestinal tract morbidity, as GI-toxicity of radiation consequence, a statistically significant increase of morbidity-rate, related to liver (from 27% to 43%) and gallbladder (from 27% to 38%) is noteworthy. An increase in the number of pathologies of the pancreas and large intestine is probable, although not statistically confirmed (Figure 14).

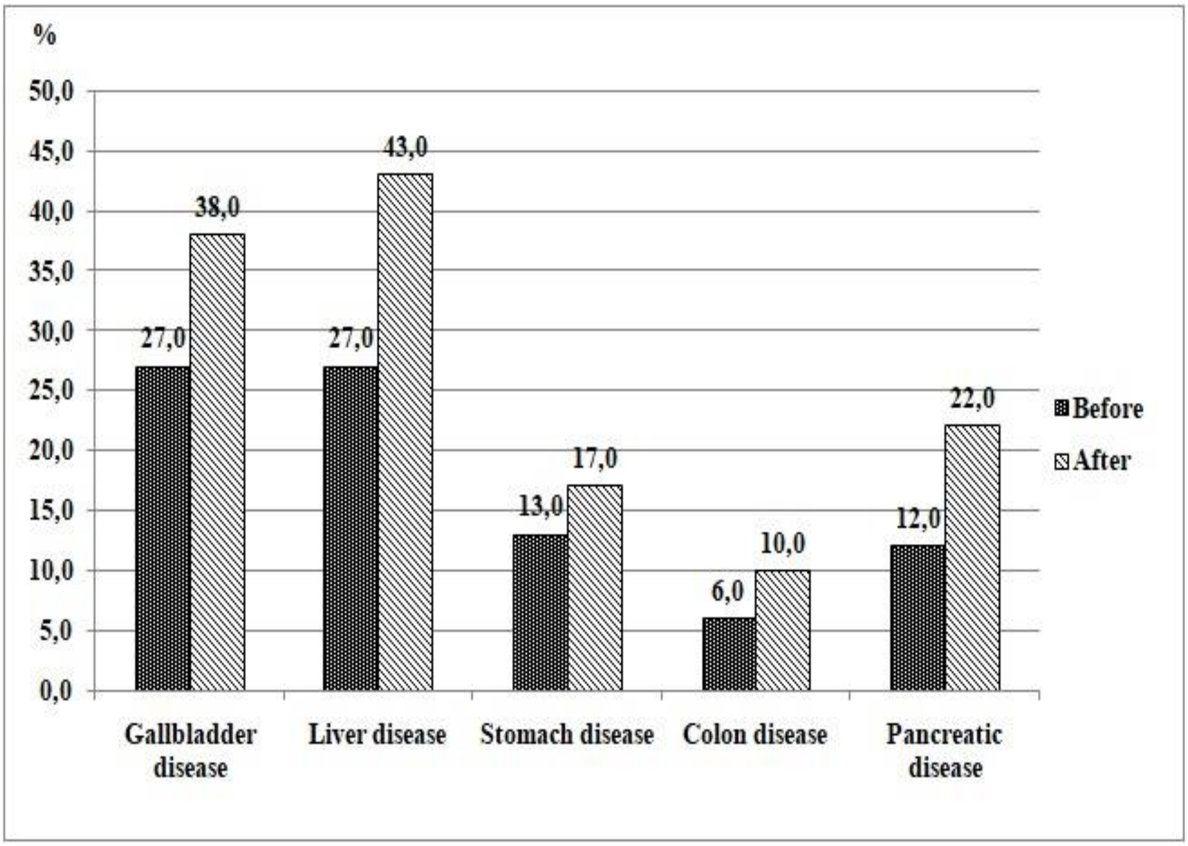

Figure 14. Increase of gastrointestinal tract morbidity, as GI-toxicity of radiation consequence in LACC patients

3.6 Assessment of patients survival, based on actuarial calculations

Researchers assess the effectiveness of LACC patients treatment, using various methods.

Analysis of survival after CRT, using the Kaplan-Meier method, showed that the maximum observation follow-up was 24.4 years (293 months); the median survival was 8.4 years (101 months). The survival curve is presented on Figure 15.

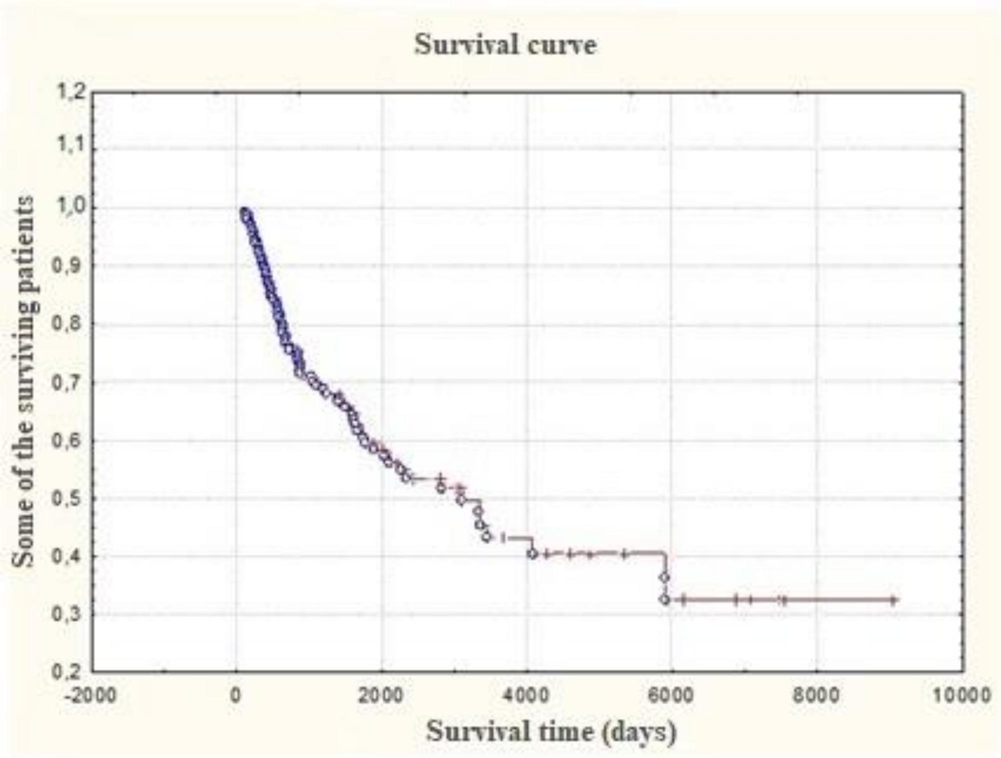

Figure 15. Survival of LACC patients, estimated by Kaplan–Meier method

Analysis of the graphical data indicates that the median overall survival, defined as the time point, at which 50% of the cohort remained alive, was approximately 3,800 days (10.4 years).

Another essential parameter, characterizing disease course is the failure rate or hazard function. Conceptually, the hazard function represents the instantaneous risk of death at a given time point during the next follow-up period, conditional the patient was alive at the beginning of that interval (Figure 16).

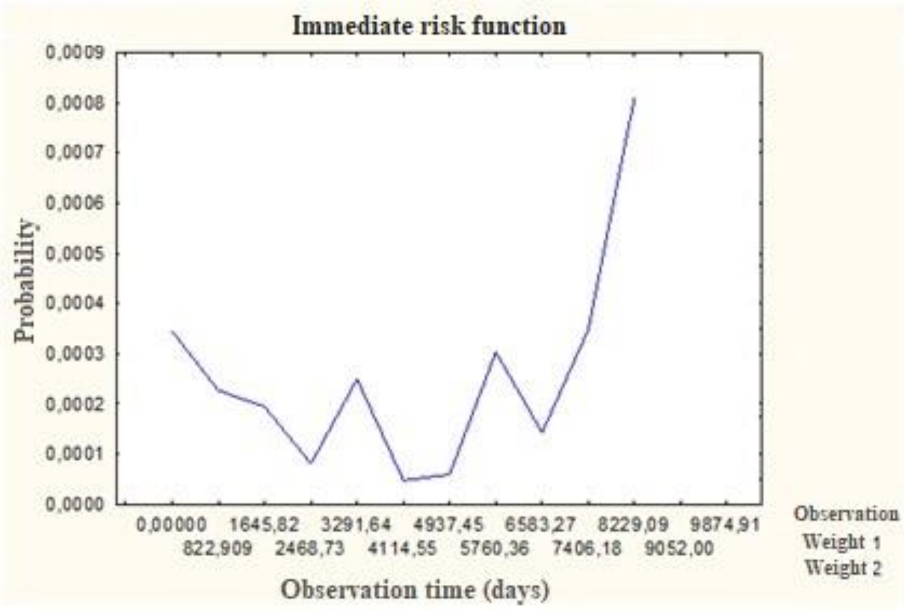

Figure 16. Immediate risk function for the overall survival of LACC patients

The risks of fatal consequences of the treatment initially decrease during 6.8 years (81 months), then increase to the peak at time point of 9 years (108 months).

A second period of increasing risk begins at 11.2 years (135 months), reaching a second peak at 15.8 years (189 months). A potential tertiary increase of risk may occur around 18 years; however, the most recent documented fatal event in the cohort was observed at 16 years. Thus, the peaks of elevated risk for death after treatment of LACC patients are determined at 9 years and 15.8 years, with a possible additional increase beyond 18 years of follow-up

A slightly different situation is observed, regarding the risks of recurrence (Figures 17, 18).

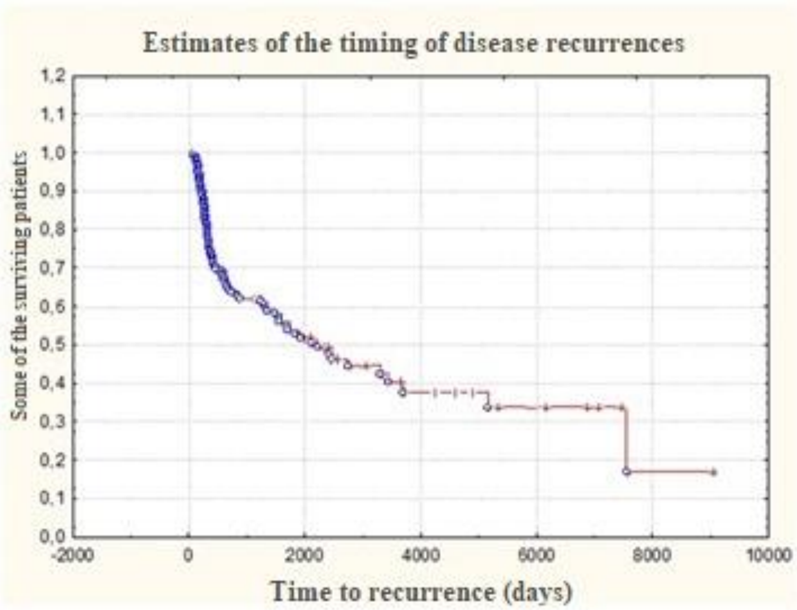

Figure 17. Kaplan–Meier estimates of the timing of disease recurrences in LACC patients

The timing of recurrences was 5.9 (1; 17.5) years. The first case occurred after 3 months and the last one – after 21 years.

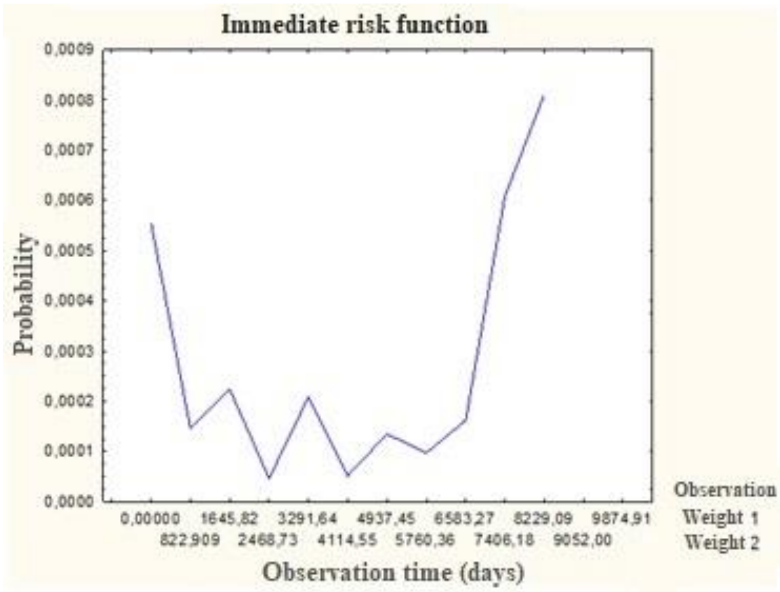

Figure 18. The function of immediate risk of recurrence in LACC patients

Analyzing the risks of recurrence, it was estimated, their decrease is observed from the beginning of treatment to a period of 2.3 years (27 months). The peaks of maximum risks are estimated at time-point of follow-up of **4.5 years** (54 months), **9 years** (108 months), **13.5 years** (162 months), and possibly at time-point of 18 years (216 months).

The identified risk periods for the appearance of late recurrences should be considered as mandatory control points during post-treatment monitoring.

Thus, a physician should consider that the mandatory time-points of active post-treatment monitoring are follow-up of the 5th, 9th, 14th, 16th, and 18th years after the special treatment.

3.7 Comparison of treatment outcomes, depending on type of equipment for conduction of radiation therapy

Analyzing the treatment outcomes, depending on type of equipment for conduction of radiotherapy, there was concluded, the general parameters of the BT were the type of equipment (HDR or LDR), **single dose** at point A and point B, total dose at point A and point B.

External beam radiation therapy was conducted with CO60 – LDR equipment (ROKUS-AM) in a classical fractionation regimen: SD of 2 Gy up to the total dose 20 Gy on the opposite open fields, after that fields were diverging at 3 cm from the center and EBRT was continued to the total dose at point A/B up to 30/44–46 Gy with or without chemomodification of cisplatin 40 mg/m² weekly.

Since year 2018, at our Institution EBRT has started to be performed using linear accelerator Clinac-600 (HDR). Single dose was similar to those, delivered with the ROKUS-AM equipment, up to the total dose of 46 Gy at point A/B with open fields.

After the completion of EBRT, a course of BT was conducted by LDR equipment (AGAT-V) twice a week with a SD at point A/B = 5/1.25 Gy up to total dose at point A/B bilaterally of 50–55/12.5–13.75 Gy (10–11 sessions). Since 2018, BT has been performed by HDR equipment (MultiSourse), with a single dose of 5/1.25 Gy at point A/B twice a week up to total dose at point A/B of 30/7.5 Gy (6 sessions). During the course of combined CRT, patients received total dose at point A/B of 76–80/57–60 Gy. After the completion of BT, in case of residual infiltrate or metastatic enlarged lymph nodes, based on data of the initial CT or MRI examination, a boost EBRT was added with the total dose at point B up to 60–62 Gy.

The study was conducted on a cohort observations from 1998–2021, which provided an opportunity to analyze and compare the results of different treatment strategies. Thus, comparing results of combined radiation treatment, using LDR and HDR units for BT, it was found that in case of LDR, the tumor progression was occurred after 3 months, with a maximum term of 173 months (14 years), while in case of HDR, the tumor progression was observed even during the first month after treatment with a maximum term of 20 months (1.7 years).

Thus, in case of LDR brachytherapy, tumor progression occurred in 20% of patients, and metastases disease was detected in 33%. In case of HDR BT, tumor progression occurred in 14%, and metastases in 17%. All results are statistically significant (CCT, $p<0.01$). That is, the application of a more powerful radiation therapy contributes to a decrease in local recurrence, but time to its diagnose is shorter.

This finding is a crucial contradictory observation. While the more powerful HDR machine improves overall survival (lower total recurrence rate), it seems to select for more aggressive, radio-resistant tumor cells that reappear more quickly. This means that while a successful treatment is more likely, the failures that do occur are more dangerous and require even faster detection and intervention. This suggests that the post-treatment monitoring schedule should be adjusted based on the specific equipment used for treatment.

PRACTICAL RECOMMENDATIONS

Based on the data, obtained in this study, several measures are recommended to reduce the likelihood of late oncological consequences, following the treatment of LACC patients:

1. At the initiation of specialized treatment for LACC, it is essential to document the dimensions of the tumor-affected cervix, using diagnostic imaging and to calculate the tumor volume, according to the appropriate formula $V = \pi r2h$, де V – volume (мм^3), $\pi = 3{,}14$, r – radius (мм), h – length (мм) at conditionally presented as a cylinder, and calculation or relative platelets dynamics according to formula dV = (V start – V end)/V start × 100%, where V start – is the value at the beginning of treatment, V end – is the value at the end of treatment.

2. If the tumor volume of the affected cervix (TVC) before the treatment exceeds 60,000 mm^3, or if the infiltrative process involves both parametrium regions or is localized on the right side, the patient should undergo neoadjuvant polychemotherapy, consisting of three to six cycles.

3. If the level of the tumor-specific marker SCC exceeds 9.1 ng/mL, the patient likewise requires neoadjuvant polychemotherapy, administered in three to six cycles.

4. If the platelet count at the beginning of treatment exceeds 204 × 10^9/L and/or if the relative changes in platelet level exceeds 30%, the patient should undergo adjuvant polychemotherapy in three to six cycles.

5. Physician should also consider the potential disease progression and ensure an active follow-up examination at time-point of 5th, 9th, 14th, and 16th years after completion of specialized treatment, irrespective of standard follow-up intervals. At each surveillance time-point, assessment should include measurement of the SCC tumor marker, complete blood count,

oncogynecological examination and either CT imaging of three anatomical regions or MRI of the pelvis.

Analysis of early complications, associated with chemoradiation therapy, demonstrated that the most common adverse events include leukopenia, anemia, lymphopenia, radiation-induced epithelial injury of the vagina and cervix, cystitis and enterocolitis.

For minimization of the occurrence of early radiation-induced reactions during the chemoradiation therapy, it is recommended that:

1. To prevent the development of leukopenia if the total dose of irradiation to point B exceeds 41 Gy, patient requires close monitoring of leukocyte levels with appropriate therapeutic intervention as indicated.

2. For reduction of the risk of radiation-induced epithelial injury, if the pre-treatment cervical tumor-involved volume exceeds 139,000 mm^3 and/or the uterine cavity length is greater than 57 mm, the initiation of intracavitary irradiation should be accompanied by local ointment-based treatment of the vagina and cervix.

3. For the management of existing anemia, whose severity is, according to our estimations, particularly pronounced in LACC patients with a uterine cavity length greater than 57 mm, is required oral iron supplementation. In severe cases, hemotransfusion should be performed in accordance to the clinical guidelines for anemia correction.

4. For the risk reduce of the post-radiation cystitis, especially in patients with a body weight exceeding 82 kg, there should be performed prior to the initiation of radiation therapy the urine analysis, obtained via catheterization (to exclude inflammatory changes, attributable to contamination by vaginal secretions). In case of abnormalities, there should be prescribed anti-inflammatory therapy with uroseptics for 7–10-day, according to established protocols for the treatment of urinary tract inflammatory disease. Following

completion of the radiation therapy course, non-pharmacological supportive management is advisable to prevent the development of cystitis.

For prevention of the development of late somatic consequences after antiblastic therapy, such as vascular atherosclerosis, pulmonary emphysema and the gallbladder and liver disorders, the implementation of combined supportive care during the treatment is recommended and essential.

In addition, it is advisable to inform patients about the importance to attend of medical care providers in case of appearance of first signs. Patients should also be counseled, that there may be occurred also conditions, such as ischemic heart disease, cystitis, chronic renal insufficiency, urolithiasis, urinary tract inflammatory diseases, and gastrointestinal disorders, including those affecting the colon and pancreas, may occur independently of the antiblastic therapy.

This monograph also demonstrates how the application of Data Mining technologies and methods of mathematical statistical analysis enable the identification of risk factors for the development of late oncological consequences, based on digitized clinical data of patients with locally advanced cervical cancer. The occurrence of early radiation reactions, so as late radiation-induced injuries, and long-term somatic disorders, underscores the need to recommend strategies for their prevention and management, as well as the importance of implementing additional measures to improve individualized patient-support programs.

CONCLUSIONS

1. Risk factors for the appearance of cancer-specific late treatment consequences in the future due to our estimations, are volume of the tumor-involved part of cervix before the treatment of more than 60,000 mm^3, SCC level of more than 9.1 ng/ml, a platelets count at the beginning of treatment of more than 204 x 10^9/l, a relative change in platelet level of more than 30%, and infiltrate localization in both parametria or on the right side. A favorable prognostic factor for survival without oncological consequences is a level of tumor-specific marker SCC in the interval of 1.5–9.1 ng/ml.

2. The mandatory control time-points of the patient's condition after chemoradiation treatment and its subsequent monitoring (risk of late recurrences and metastases) are the fifth year, the ninth year, the fourteenth year, the sixteenth year and eighteenth year.

3. The most frequent late radiological consequence after radiation therapy are cystitis, radioepitheliitis of the cervix, soft tissue fibrosis of the anterior abdominal wall. The most frequent immediate reactions after radiation therapy are leukopenia (with a total dose at point B above 41 Gy), radioepitheliitis (with a tumor-involved cervical volume exceeding 139,000 mm^3), anemia, cystitis, enterocolitis (in case EBRT was delivered with LDR equipment or linear accelerator (HDR-equipment)), lymphopenia and radiation epidermitis of the radiations fields.

4. The application of HDR brachytherapy contributes to decrease of local recurrence, but at the same time, the disease recurrence manifests in shorter time frames.

5. During the long-term follow-up of LACC patients after chemoradiation treatment, there was observed an increased level of cases of atherosclerosis, pulmonary emphysema, encephalopathy and liver disorders.

REFERENCES

1. Ye. B Radzishevska, O. M. Sukhina, L. Ya. Vasilyev et al. Risk factors of local recurrence and distant metastasis and manifestations of toxicity during chemoradiation treatment of cervical cancer patients Ukr. J. Radiol. Oncol. 2023. Vol. 31, No. 2. P. 175−189. DOI: https://doi.org/10.46879/ukroj.2.2023. 175-189.

2. Radzishevska YevB, Sukhina OM, Vasylyev LYa, et al. Risk factors for local and distant metastasis and survival characteristics of patients with locally advanced cervical cancer, revealed on the basis of analysis of historical data for the period 1998–2021 Ukr journ radiol oncol. 2024;32(1):44–55. DOI: https://doi.org/10.46879/ukroj.1.2024.44-55.

3. Radzishevska YevB, Sukhina OM, Vasylyev LYa, Sukhin VS, Nemaltsova KV, Kulinich GV, Solodovnikova OO. Treatment strategy and clinical characteristics f patients with cervical cancer as prognostic parameters of survival Ukr. Journ. Radiol. Oncol. 2022;30(3):65–78. DOI:https://doi.org/10.46879/ukroj.3.2022.65-78.

4. R. Liu, X. Wang, J. Tian, Yang K, Wang J, Jiang L, Hao XY. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer Cochrane Database Syst. Rev. 2014.10. Art.No.: CD007563. DOI: 10.1002/14651858.CD007563.pub3 .

5. Ivankova VS, Domina EA, Khrulenko TV, Makovetska LI, Baranovska LM, Glavin OA. Prediction of radiation complications by determining the blood oxidation processes in cervical cancer patients under chemoradiotherapy. Ukr. Journ. Radiol. oncol. 2024;32(1):56–69. DOI: https://doi.org/10.46879/ukroj.1.2024.56-69.

6. V.S. Ivankova, G.N. Shevchenko, T.V. Khrulenko, L.M. et al. Possible toxic complication of conservative treatment of advance forms of cervical

cancer and their prevention Clin. oncol. 2011. 1(1). 95–100. Access mode: https://www.clinicaloncology.com.ua/wp/wp-content/uploads/2011/05/95-100.pdf

7. Soumarová R. Current complex treatment for cervical cancer Klin Onkol. 2025. 38(3). 185-191. DOI: https://doi.org/10.48095/ccko2025185.

8. Abd El Hamid D.M., Riad A.Y., Mosalam N.A., Ahmed S.H. Phase II Study to Evaluate the Safety and Efficacy of Neoadjuvant Chemotherapy with Weekly Paclitaxel and Carboplatin Followed by Radical Chemoradiation in Locally Advanced Cervical Cancer in Egyptian Population Asian Pac J Cancer Prev. 2025. 26(4). P. 1459–1468. DOI: 10.31557/APJCP.2025.26.4.1459

9. W. Yu, L. Huang, Z. Zhong et al. Nomogram-based risk classification system predicting the overall survival of patients with newly diagnosed stage ivb cervix uteri carcinoma Front. Med. 2021. 8. 693567–69. DOI: https://doi.org/10.3389/fmed.2021.693567.

10. Y. Chen, Y. Zhu, J. Wu Prognosis of early stage cervical cancer according to patterns of recurrence Cancer Manag. Res. 2021. 13. 8131–8136. – DOI: https://doi.org/10.2147/CMAR.S314384.

11. Lindegaard JC, Petric P, Tan LT, Hoskin P, Schmid MP, Jürgenliemk-Schulz I, Mahantshetty U, Kirisits C, Pötter R. Are we making progress in curing advanced cervical cancer-again? Int J Gynecol Cancer. 2024 34(12):1940-1945. DOI: https://doi.org/10.1136/ijgc-2024-005572.

12. A. C. M. Queiroz, V. Fabri, H. Mantoan, Sanches SM, Guimares APG et al. Risk factors for pelvic and distant recurrence in locally advanced cervical cancer Eur. J. Obstet. Gynec. Reprod. Biol. 2019. l. 235. 6–12. DOI: https://doi.org/10.1016/j.ejogrb.2019.01.028.S. Hattori, N. Yoshikawa, K. Mogi, Yoshida K, Yoshihara M, et al. Significance of concurrent chemoradiotherapy as primary treatment in patients with metastatic cervical cancer Curr. Oncol. 2021. 28, № 3. 1663–1672. – DOI: https://doi.org/10.3390/curroncol28030155.

13. R. Liu, X. Wang, J. Tian, Yang K, Wang J et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer Cochrane Database Syst. Rev. 2014. 10. Art.N.: CD007563. – DOI: https://doi.org/10.1002/14651858.CD007563.pub3.

14. X. Tian, F. Yang, F. Li, Ran L, Chang J, et al. A comparison of different schemes of neoadjuvant chemotherapy followed by concurrent chemotherapy and radiotherapy for locally advanced cervical cancer: a retrospective study Cancer Manag. Res. 2021. 13. 8307–8316. DOI: https://doi.org/10.2147/CMAR.S328309.

15. R. Porras GO, Ch. Noguedo J, Poitevin CHason A. Chemotherapy and molecular therapy in cervical cancer. Rep. Pract. Oncol. Radiother. 2018. 23, №6. 533–539. DOI: https://doi.org/10.1016/j.rpor.2018.09.002.

16. Li M, Wu X, Liu X, Wen M. Effects of intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) on survival benefits and poor prognostic factors in patients with cervical cancer Biomed Eng Online. 2025 24(1):96. DOI: https://doi.org/10.1186/s12938-025-01433-1.

17. Pleyers C. La curiethérapie: un atout majeur dans le traitement du cancer du col de l’utérus localement avancé [Article in French. Brachytherapy: a crucial part of locally advanced cervical cancer treatment]. Rev Med Liege. 2024;79(S1):40-44.

18. Agusti N, Viveros-Carreño D, Melamed A, Pareja R, Kanbergs A, Wu CF, Nitecki R, Colbert L, Rauh-Hain JA. Adjuvant external beam radiotherapy combined with brachytherapy for intermediate-risk cervical cancer. Int J Gynecol Cancer. 2024;34(8):1149-1155. DOI: https://doi.org/10.1136/ijgc-2024-005570.

19. R. Liu, X. Wang, J. Tian et al. High dose rate versus low dose rate intracavity brachytherapy for locally advanced uterine cervix cancer Cochrane Database Syst. Rev. 2014. 10. CD007563. – DOI: 10.1002/14651858.CD007563.pub3.

20. Yang J., Cai H., Xiao Z. X., Wang H., Yang P. Effect of radiotherapy on the survival of cervical cancer patients: An analysis based on SEER database. Medicine (Baltimore). – 2019;98(30):e16421. DOI: https://doi.org/10.1097/MD.0000000000016421.

21. Ayachi Z., Gabro A., Camprodon G., Chopra S., Maingon P., Chargari C. Transformative clinical trials in gynaecologic radiation oncology in 2023-2024: Shaping modern treatment practices Cancer Radiother. 2024 Dec;28(8):719-726. DOI: https://doi.org/10.1016/j.canrad.2024.10.002.

22. Pohanková D., Sirák I., Hodek M. et al. Pattern of pelvic recurrence in MRI-only adaptive brachytherapy for locally advanced cervical cancer Brachytherapy. 2025; 24(1) 11-17. DOI: https://doi.org/10.1016/j.brachy.2024.10.012.

23. Z. Z. Fu, K. Li et al. Efficacy and toxicity of different concurrent chemoradiotherapy regimens in the treatment of advanced cervical cancer: A network meta-analysis Medicine (Baltimore). 2017;96(2): e5853. DOI: https://doi.org/10.1097/MD.0000000000005853.

24. Agusti N., Viveros-Carreño D., Melamed A. et al. Adjuvant external beam radiotherapy combined with brachytherapy for intermediate-risk cervical cancer Int J Gynecol Cancer. 2024;34(8):1149-1155. DOI: https://doi.org/10.1136/ijgc-2024-005570/.

25. Homaei Shandiz F, Arastouei S, Hosseini S. et al. Capecitabine-enhanced brachytherapy in locally advanced cervical cancer: a phase ii non-randomized trial on safety and efficacy Cancer Invest. 2025;43(4):244-256. DOI: https://doi.org/10.1080/07357907.2025.2493238.

26. Chemoradiotherapy for Cervical Cancer Meta-analysis Collaboration (CCCMAC). Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: individual patient data meta-analysis Cochrane Database Syst. Rev. 2010. 1 . CD008285. DOI: 10.1002/14651858. CD008285.

27. Tumour and treatment factors influencing the outcome of chemo-radiation in stage IIB cervical cancer: a single institution experience / M. Jemu, L. Wijk, M. Parker, G. Jones S. Afr. J. Gynaecol. Oncol. 2018; 10(1):5–10. DOI: https://doi.org/10.1080/20742835.2018.1441694.

28. Viswanathan A.N., Lee L.J., Eswara J.R. et al. Complications of pelvic radiation in patients treated for gynecologic malignancies // Cancer. – 2014. – Vol. 120, № 24. – P. 3870–3883. – DOI: https://doi.org/10.1002/cncr.28849.

29. McCormack M, Eminowicz G, Gallardo D. et al. Induction chemotherapy followed by standard chemoradiotherapy versus standard chemoradiotherapy alone in patients with locally advanced cervical cancer (GCIG INTERLACE): an international, multicentre, randomised phase 3 trial Lancet. 2024. 404(1046. 1525-1535. DOI: https://doi.org/10.1016/S0140-6736(24)01438-7.

30. study Gandhi A.K., Sharma D.N., Rath G.K., Julka P.K. et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized Int. J. Radiat. Oncol. Biol. Phys. 2013. 87, № 3. 542–548. DOI: https://doi.org/10.1016/j.ijrobp.2013.06.2059.

31. Palagudi M., Para S., Golla N., Meduri K.C., Duvvuri S.P. et al. Adverse effects of cancer treatment in patients with cervical cancer. Cureus J. med Sci. 2024;16(2):e54106. DOI: https://doi.org/10.7759/cureus.54106.

32. Pechačová Z., Lohynská R., Weitoschová Z., Zikan M., Dubova O. et al. Chemoradiotherapy in the treatment of cervical cancer - a single institution retrospective review (article in Czech) Klin Onkol. 2022;35(2):139-149. DOI: https://doi.org/10.48095/ccko2022139.

33. Hallqvist D, Kormann C, Pigorsch S, Kiechle M, Combs SE, Habermehl D.B one marrow toxicity in patients with locally advanced cervical cancer undergoing multimodal treatment with VMAT/IMRT: are there dosimetric

predictors for toxicity? Eur J Med Res. 2024; 29(1) :445-453. DOI: https://doi.org/ 10.1186/s40001-024-02041-w.

34. Huang Z, Yao W, Zhong Z, Yang G, Liu J, Gu H, Huang J. Chemotherapy alone versus chemotherapy plus 125-I brachytherapy for the second-line treatment of locally recurrent cervical cancer after/with radical treatment: A propensity score analysis Heliyon. 2024. 10(2). e24666. DOI: https://doi.org/ 10.1016/j.heliyon.2024.e24666.

35. Wang S.T., Ma G.F., Xiao C.L., Shi T.y., Xiang L.B. et al. Concurrent cisplatin chemotherapy with intensity-modulated radiotherapy followed by consolidation chemotherapy in early-stage cervical cancer patients with high-risk factors after radical hysterectomy J Obstet Gynaecol Res. 2025. 51(6). e16346. DOI: https://doi.org/10.1111/jog.16346.

36. Singareddy R., Bajwa H.K. , Reddy M.M., Raju A.K. Dosimetric predictors of acute bone marrow toxicity in carcinoma cervix - experience from a tertiary cancer centre in India Rep. Pract. Oncol. Radiother. 2021. Vol. 26, № 2. 259–265. DOI: https://doi.org/10.5603/RPOR.a2021.0039.

37. Radzishevska Ye.B., Sukhina O.M., Vasylyev L.Ya., Sukhin V.S., Nemaltsova K.V., Solodovnikova O.O. An infographic model of a database for conducting an analytical study of the long-term consequences of cervical cancer treatment. Ukr Rad Oncol Journ. 2023. 31, № 1. 83-92. DOI: https://doi.org/10.46879/ukroj.1.2023.83-92.

38. Ental, H., Aavik, H. M., Lubi, K., & Plešs, N. (2021). Estonian Cervical Cancer Screening–an opportunity that should not be missed. Road project report.

39. Cohen P.A., Jhingran A., Oaknin A., Denny L. Cervical cancer. Lancet. 2019. Vol. 393. P. 169–182. DOI: https://doi.org/10.1016/S0140-6736(18)32470-X.

40. Li H., Wu X., Cheng X. Advances in diagnosis and treatment of metastatic cervical cancer. Journal of gynecologic oncology. 2016. Vol. 27. e43. DOI: https://doi.org/10.3802/jgo.2016.27.e43.

41. Radzishevska, Y., Sukhina O., Vasylyev, L., Sukhin, V. et al. Determination of risk factors for the occurrence of recurrences, metastases, and somatic complications after treatment of locally advanced cervical cancer using modern information technologies. Ukr Rad Oncol Journ. 2024. . 32, № 4. C. 478–490. DOI: https://doi.org/10.46879/ukroj.4.2024.478-490.

42. Schmid, M. P., Lindegaard, J. C., Mahantshetty, U. et al. Risk Factors for Local Failure Following Chemoradiation and Magnetic Resonance Image-Guided Brachytherapy in Locally Advanced Cervical Cancer: Results From the EMBRACE-I Study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 2023 41(10), 1933–1942. https://doi.org/10.1200/JCO.22.01096

43. Sukhina O., Mihanovskiy O., Sukhin V.,Hertman V., Krugova I.. Application of tumor marker SCCA in prognosis of lymphatic nodes involvement in patients with cervical cancer. Ukr rad Journ. 2006. XIV.2;162-165.

44. Vorobyova L., Honcharuk I. Clinical significance of tumor marker SCC value in cervical cancer patients. J Clin Oncol. 2011.3(3); 42–45. https://www.clinicaloncology.com.ua/wp/wp-content/uploads/2011/09/42-45.pdf

45. Yoo JG, Kim SI, Yeo SG, Park DC. Usefulness of short-term imaging and squamous cell carcinoma antigen to early predict response to concurrent chemoradiotherapy in patients with cervical cancer Cancer Control. 2022; 29:10732748221074530. DOI: https://doi.org/10.1177/10732748221074530.

46. Shi L, Liu Y, Li J, Kou J, Ouyang Y, Chen F, Huang X, Huo L, Huang L, Cao X. Establishment of a risk stratification model based on the combination of post-treatment serum squamous cell carcinoma antigen levels and FIGO stage of cervical cancer for treatment and surveillance decision-making J

Cancer Res Clin Oncol. 2023;149(9):5999-6007. DOI: https://doi.org/10.1007/s00432-022-04558-1.

47. Huang XD, Huo LQ, Luo YS, Chen K, Li JY, Shi L, Huang L, Cao XP, Ou-Yang Y, Chen FP. Clinical utility of pretreatment serum squamous cell carcinoma antigen for prognostication and decision-making in patients with early-stage cervical cancer Ther Adv Med Oncol. 2023 15:17588359231165974. DOI: https://doi.org/10.1177/17588359231165974.

48. Sukhin V.S. Tumor marker SCCA in the monitoring of treatment of cervical cancer Oncology. – 2009 11:1:50-54. https://nasplib.isofts.kiev.ua/handle/123456789/11985.

49. Sukhin V. Feasibility of using marker SCCA in locally advanced cervical cancer. Neoplasms. 2013.(11). 48-52.

50. Giannakeas V, Kotsopoulos J, Cheung MC, Rosella L, Brooks JD, Lipscombe L, Akbari MR, Austin PC, Narod S.A. Analysis of platelet count and new cancer diagnosis over a 10-year period JAMA Netw Open. 2022 4;5(1):e2141633. DOI: https://doi.org/10.1001/jamanetworkopen.2021.41633.

51. Ye X, Zhou J, Guo S, Lou P, Ma R, Guo J. The undervalued acute leukopenia induced by radiotherapy in cervical cancer Curr Radiopharm. 2023 16(1):50-56. DOI: https://doi.org/10.2174/1874471015666221010141250.

52. Neu M, Wöhrl CM, Walter R, Balagiannis N, Poettgen C, Käsmann L, Stuschke M, Dannecker C, Stüben G, Kahl KH. Multimodal chemoradiotherapy including interstitial brachytherapy enhances outcomes in FIGO stage IVA cervical cancer: a focus on tumor control and quality of life Strahlenther Onkol. 2025: **201**, 1018–1030. DOI: https://doi.org/10.1007/s00066-025-02407-x.

53. Dumanskyi Yu.V., Domina E.A., Stoliarova O.Yu., Makovetska L.I Post-radiation complications as a factor in predicting the effectiveness of treatment of uterine and cervical cacner. Oncology. 2024: 26;3: 165–171. DOI: https://doi.org/10.15407/oncology.2024.03.165.

54. Li Y, Liu A, Wang X, Guo L, Li Y, Liu D, Liu X, Li Z, Li M. The role of lymphocyte recovery index in prognosis prediction for locally advanced cervical cancer with radiation-induced lymphopenia Cancer Med. 2025;14(4):e70638. DOI: https://doi.org/10.1002/cam4.70638.

55. Prades-Sagarra E, Yaromina A, Dubois LJ. Understanding the impact of radiation-induced lymphopenia: Preclinical and clinical research perspectives. Clin Transl Radiat Oncol. 2024; 49:100852. DOI: https://doi.org/10.1016/j.ctro.2024.100852.

56. de Kermenguy F. et al. Radio-induced lymphopenia in the era of anti-cancer immunotherapy. /de Kermenguy F, Meziani L, Mondini M, Clémenson C, Morel D, Deutsch E, Robert C. Int Rev Cell Mol Biol. - 2023;378:1–30. DOI: https://doi: 10.1016/bs.ircmb.2023.03.002.

57. Li Y, Liu A, Wang X, Guo L, Li Y, Liu D, Liu X, Li Z, Li M. The role of lymphocyte recovery index in prognosis prediction for locally advanced cervical cancer with radiation-induced lymphopenia Cancer Med. 2025;14(4):e70638. DOI: https://doi.org/10.1002/cam4.70638.

58. Prades-Sagarra E, Yaromina A, Dubois LJ. Understanding the impact of radiation-induced lymphopenia: Preclinical and clinical research perspectives. Clin Transl Radiat Oncol. 2024 Sep 6;49:100852. DOI: https://doi.org/10.1016/j.ctro.2024.100852.

59. de Kermenguy F, Meziani L, Mondini M, Clémenson C, Morel D, Deutsch E, Robert C. Radio-induced lymphopenia in the era of anti-cancer immunotherapy. Int Rev Cell Mol Biol. 2023;378:1–30. DOI: https://doi: 10.1016/bs.ircmb.2023.03.002.

ABBREVIATIONS

- **PD** – Patient Database
- **BT** – Brachytherapy
- **EM** – Evidence-Based Medicine
- **EBRT** – External Beam Radiation Therapy
- **KWT** – Kruskal–Wallis Test
- **MWT** – Mann–Whitney Test
- **CT** – Computed Tomography
- **CCST** – Pearson Chi-Square Test
- **LACC** – Locally Advanced Cervical Cancer
- **MRI** – Magnetic Resonance Imaging
- **MT** – Median Test
- **NCT** – Neoadjuvant Chemotherapy
- **OC** – Oncological consequences
- **TVC** –Tumor-involved Volume of Cervix
- **RT** – Radiation Therapy
- **CRT** – Combined Radiation Therapy
- **RIL** – Radiation-Induced Lymphopenia
- **SD** – Single Dose
- **CC** – Cervical Cancer
- **CT** – Chemotherapy
- **CRT** – Chemoradiation Therapy
- **GIT** – Gastrointestinal Tract
- **ESR** – Erythrocyte Sedimentation Rate
- **HDR** – High Dose Rate
- **IMRT** – Image-Guided Radiation Therapy (Intensity-Modulated Radiation Therapy)
- **LDR** – Low Dose Rate
- **MDR** – Medium Dose Rate
- **SCC** – Squamous Cell Carcinoma Antigen
- **TD –** Total dose
- **TL** – Chemotherapy regimen including paclitaxel (Taxol) and lobaplatin (Lobaplatin)
- **TP** – Chemotherapy regimen including paclitaxel (Taxol) and cisplatin (Platinol)
- **3D-CRT** – 3D Conformal Radiation Therapy

Scientific publication

O.M. SUKHINA, L.YA. VASYLYEV, YE.B. RADZISHEVSKA,
V.S. SUKHIN, K.V. NEMALTSOVA, N.O. ARTAMONOVA

CHEMORADIATION TREATMENT OF LOCALLY ADVANCED CERVICAL CANCER: ONCOLOGICAL AND SOMATIC EFFECTS

Monograph

Executive editor: T.H. Zolotarova
Literary editor: T.I. Kobzar
Desktop publishing (layout): P.S. Zaika

Publisher

State Organization "Grygoriev Institute for Medical Radiology and Oncology of the National Academy of Medical Sciences of Ukraine".

Publishing activity certificate No. 7115, series DK dated July 28, 2020

Підп. до друку 24.04.2025	Формат 60×84 1/16	Спосіб друку – цифровий
Умов. Друк.-арк. 9,9	Облік вид. арк. 8,9	Тираж 500 прим.
Зам. № 1/11		

Надруковано у друкарні «ПромАРТ»

61002, Харків, вул. Григорія Сковороди, 82

Тел.: (057) 725-50-74

2025 р.