

ABSTRACT

of the dissertation work of Almagul Zhabagina
on “Optimization of radiation therapy in locally advanced stages of cervical
cancer” for the degree of PhD in the specialty 6D110100 – Medicine

Relevance of the research subject. Right now, cervical cancer (CC) is the leading cause of morbidity and mortality. With 604,000 new cases and 342,000 deaths globally in 2020, cervical cancer is the fourth most often diagnosed malignancy and the fourth main cause of cancer death in women [Sung H. et al, 2021].

The Republic of Kazakhstan likewise has persistently high rates of CC incidence and mortality. CC is the fourth most common malignant tumor in women in Kazakhstan. The analysis of the incidence of malignancies at the national and regional levels reveals a rise in the prevalence of this malignancy in women. There were 15,265 new cases and 6,382 cancer-related fatalities throughout the course of the ten-year period. Additionally, there is a trend toward "rejuvenation," which affects women who are of reproductive age generally and is a significant social issue [Kaidarova D.R. et al., 2017].

The improvement of public health is the primary goal of the "Strategic Plan of the Ministry of Health of the Republic of Kazakhstan for 2017–2021 years." One goal is to increase the effectiveness of the healthcare system by creating new techniques for malignant tumor diagnosis and treatment [Strategic Plan of MH of RK for 2017-2021]. The use of progressive methods of diagnosis and treatment to battle malignant tumors is given special emphasis in the Decree of the Government of the RK dated June 29, 2018 No. 395 on approval of the Comprehensive Plan to Combat Cancer in the RK for 2018–2022. Despite advancements in diagnostic techniques and therapeutic technology, one-year death rates from C are significant and reached 12.7% in 2018. This indicates the detection of CC in neglected stages and the quality of treatment [Kaidarova D.R.; Shalgumbaeva G.M., 2018]. The standard treatment for locally advanced cervical cancer is combined chemotherapy and pelvic irradiation, which is based on the results of several randomized trials showing a 10-15% survival advantage and a 30-40% reduction in the rate of local and distant recurrence [Vale C. et al,2018; Rose P.G. et al,2017; Whitney C.W., et al, 2015]. An international group of oncologists and gynecologists reported that the incidence of PALN metastases depends on stage and is 5% in stage I, 16% in stage II, and 25% in stage III cancers. Patients with locally advanced cervical cancer have paraaortic node micrometastases in 17-37% of cases at the time of diagnosis [Chantalat E., et al 2015]. In addition, after receiving combined pelvic chemoradiotherapy, 15-25% of patients develop metastasis to para-aortic lymph nodes (PALN) during long-term follow-up [Vale C. et al,2018; Rose P.G. et al,2017]. Since metastases to the PALN are the most important prognostic sign of survival. Radiation therapy with an expanded radiation field or prophylactic PALN irradiation is an alternative treatment, allowing the expansion of the standard radiation field and capturing the area of PALN not detected by imaging prior to treatment. However, most of the data supporting the clinical benefit of prophylactic

PALN irradiation have come from patients receiving radiation therapy alone before the era of concomitant platinum-based chemoradiation therapy.

The Republic of Kazakhstan has not yet conducted any studies on the application of prophylactic PALN irradiation, which makes this issue pertinent. In order to maintain a high quality of life, extend life expectancy, and achieve positive results in CC patients, our work investigates the potential for using new alternative methods aimed at optimizing radiation therapy by preventive irradiation of para-aortic lymph nodes as well as improving treatment outcomes by implementing PALN method in a comprehensive treatment program. Given the aforementioned requirements, combined chemoradiotherapy for the treatment of CC is in need of improvement because the overall survival rates are not sufficient.

The **aim of this dissertation research** is to improve the effectiveness of radiation therapy for locally advanced stages of cervical cancer by preventive irradiation of para-aortic lymph nodes.

Research Objectives. The following tasks were defined in order to achieve the set aim:

1. To analyze the incidence and mortality rates due to cervical cancer in the East Kazakhstan region and the Republic of Kazakhstan for a period of 10 years.
2. To conduct a comparative toxicity estimation of the developed method of prophylactic irradiation of para-aortic lymph nodes and the standard chemoradiotherapy of cervical cancer.
3. To evaluate the effectiveness of the developed method of prophylactic irradiation of para-aortic lymph nodes and standard chemoradiotherapy of cervical cancer.
4. To carry out a comparative assessment of quality of life in patients with cervical cancer using the adapted module questionnaire for cervical cancer EORTC QLQ CX-24.

Research Methods.

The current research was conducted as part of Semey Medical University's "Grant funding of scientific research," agreement No. 26 from May 23, 2018, and is one of several components of the non-reciprocal international multicenter research Forum for Nuclear Cooperation in Asia (FNCA).

This scientific work is carried out according to the established program of dissertation research in stages:

Current theories regarding the epidemiology, diagnosis, and treatment approaches for cervical cancer were examined as part of the first stage of the dissertation work. Diagnostic imaging methods to assess the prognostic value of para-aortic lymph nodes in cervical cancer were also examined, as was the role of preventive radiation exposure of para-aortic lymph nodes in the treatment of cervical cancer. An in-depth review of 183 literary sources was performed as part of the literature review. When writing the section "literature review" such information databases were used as: Medline, Cochrane Library, Google Academy, Web of Science, Elsevier, e-library, Cyberleninka, Trip Database, Research Gate, regulatory

documents, the clinical protocol “Cervical cancer” of the Republican Center for Health Development of the Ministry of Health of the Republic of Kazakhstan were studied in details.

Analysis of incidence and mortality of cervical cancer in the Republic of Kazakhstan and East Kazakhstan region for the period of 10 years (from 2010 to 2019) was carried out during the second stage of research work. The main sources of information were the data of official statistics for the period from 2010 to 2019 on cases of cervical cancer, which were based on the reporting forms of oncological institutions of the Republic of Kazakhstan on the fact of establishment of oncological disease.

The third stage of the present dissertation study consisted of the study of age, sociodemographic, clinical and morphological data of 75 patients with cervical cancer.

Study design: controlled longitudinal clinical trial.

Inclusion criteria were:

- Patients with a verified diagnosis of cervical squamous cell carcinoma.
- IIB or IIIB stages of the tumor process according to the International Classification FIGO.

- there were no enlarged para-aortic lymph nodes.
- size of pelvic lymph nodes exceeded 1 cm.
- without prior chemotherapy or radiation therapy.

According to the exclusion criteria, patients with the following conditions were not included in this study:

- comorbidities, severe severity;
- pregnancy, regardless of gestational age;
- period of breastfeeding;
- if the patient refused to sign an informed consent to participate in a scientific study.

The task of this stage of the dissertation research was to study the toxicity and effectiveness of the developed method in comparison with the traditional method of chemoradiotherapy. The present study included 75 patients who formed the following groups:

- Control group - 49 patients underwent chemoradiotherapy in the standard mode, i.e., remote radiation therapy of the small pelvis, lymph drainage zones, intracavitary radiation therapy with the introduction of a central applicator and two ovoid applicators, chemotherapy with cisplatin.

- The main group - 26 patients underwent chemoradiotherapy, as well as prophylactic irradiation of the zone of para- aortic lymph nodes. PALN RT was performed 3-4 weeks after the start of ESWL of the pelvic organs.

Both groups received chemotherapy. Cisplatin at a dose of 40 mg/m² was administered weekly once a week before radiation therapy for 2 hours.

Based on the worldwide scale - General criteria for toxicity of the US National Cancer Institute (NCI/CTCAE), markers of acute hematological and non-hematological toxicity were evaluated. The worldwide categorization system RTOG/EORTC was used to determine the severity of late toxic responses. After

three months from the start of treatment, late radiation damage happens. Leukocytes, neutrophils, hemoglobin, and platelets were identified as hematological and non-hematological indications of toxicity as part of the study of the safety profile of chemoradiotherapy (nausea, vomiting, anorexia, diarrhea, colitis, rectal bleeding, pain, cystitis, dermatitis, fever, creatinine). Depending on the level of these indicators, in accordance with NCI / CTCAE, the degree of hematological toxicity, non-hematological toxicity of each patient of the control and main groups of the scientific study was determined.

The next section of the work was a study of the quality of life associated with health in patients with cervical cancer. All patients in the study were surveyed using the questionnaire of the European Organization for Research and Treatment of Cancer - EORTC QLQ-C30, version 3.0 with the addition of an adapted questionnaire for patients with cervical cancer - EORTC QLQ-CX24 in the state language. General quality of life scales, 5 functional scales, 3 symptomatic scales (weakness, nausea/vomiting and pain), 6 single items make up the 30 questions of the EORTC QLQ-C30 questionnaire. Each item was rated by the patient on a scale of 1 to 4. The exceptions were two questions about general health status, which were rated on a scale of 1 to 7. The QLQ-CX24 module includes 24 questions, 4 functional scales and 5 symptomatic scales (symptoms, lymphostasis, peripheral neuropathy, menopausal symptoms, sexual disorder). Each item was evaluated by the patient on a scale from 1 to 4, each patient's response was entered into the created Excel spreadsheet, where, using a special formula, points were calculated for each item on the scale from 1 to 100. High values symptomatic scales show the severity symptoms/problems. High scores on functional scales reflect a high/healthy level of functioning.

The main provisions for defense:

1. CC has high rates of morbidity and mortality in the Republic of Kazakhstan and East Kazakhstan region, with a prevalence of II-III stages of the disease, requiring chemoradiotherapy.

2. The results of early and late toxicity after the developed method are comparable with the results of the traditional irradiation method.

3. The method of prophylactic irradiation of paraaortic lymph nodes during chemoradiotherapy in patients with cervical cancer improves overall survival rates, progression-free survival rates.

four. Prophylactic irradiation of the para- aortic lymph nodes during chemoradiotherapy does not lead to a deterioration in the quality of life in patients with cervical cancer.

5. The use of an adapted questionnaire module for cervical cancer EORTC - CX 24 is an effective tool for assessing the quality of life in patients with cervical cancer.

Description of the main results of the study:

1. CC in the Republic of Kazakhstan and East Kazakhstan occupies the second place in terms of incidence after breast cancer in the structure of malignant

neoplasms in women. Over a 10-year period (2010-2019), standardized incidence and mortality rates from cervical cancer in Kazakhstan were 18.8 ‰ (95% CI: 17.9-19.7) and 7.0‰ (95% CI: 6.5-7.6), respectively, EKO in terms of cervical cancer incidence among all regions ranks third with 22.0 ‰ (95% CI: 20.90-23.1), and fourth in terms of mortality, which is 8.2‰ (95% CI: 6.20-10.6). The distribution of patients with cervical cancer by stages demonstrates the prevalence of stages that most often need combination therapy, in the Republic of Kazakhstan - II - III stages - 57.2%.

2. Based on the results of a comparative analysis of hematological and non-hematological toxicity, it was found that hematological toxicity in the two studied groups of patients with cervical cancer was comparable in terms of the comparative safety profile ($p = 0.003$). According to the results of non-hematological toxicity, the indicators in the main group were lower than in the control group. Thus, cystitis II, III degree were observed in 11.5% of patients of the main group, 28.6% in the control group ($p=0.013$). Chronic proctitis II, III degree was detected less frequently in the main group than in the control group, 11.5% and 24.5% and ($p=0.02$). In addition, grade IV proctitis in the form of a rectovaginal fistula was not detected in the main group, in contrast to the control group - 4.1% ($p=0.02$). Thus, the combination of CRT with PALN irradiation had a higher comparative safety profile.

3. A comparative analysis of survival rates revealed an improvement in the overall two-year survival rate in the main group of prophylactic PALN exposure ($p= 0.000$). According to the results of one-year progression-free survival, depending on the method of treatment, an advantage in the main group of 88.5% was also revealed compared to the control group of 83.7% ($p=0.046$). When comparing two-year progression-free survival in the main group of prophylactic irradiations of PAL with CRT, this indicator was 76.9%, while in the control group the indicator was lower and amounted to 71.4% ($p=0.05$). These results of a comparative evaluation of the effectiveness of two types of therapy confirm the advantage of the developed and implemented method of prophylactic radiation therapy of para-aortic lymph nodes in cervical cancer.

4. As a result of a comparative analysis of the quality of life in patients with cervical cancer, the overall indicators of quality of life, reflecting the general state of health and quality of life of patients, were higher in the group of chemoradiation therapy with prophylactic irradiation with PALN (52.7 vs. 42.7 $p<0.006$). There were no significant differences in the assessment of functional scales, such as physical cognitive, emotional, social functioning, as well as indicators on individual scales of symptoms in both comparison groups, all differences were statistically significant ($p <0.05$). Use of the adapted EORTC questionnaire QLQ CX -24, for the study of QoL of patients, it is effective in developing an individual treatment strategy, correcting disorders in the psychological sphere in patients with cervical cancer.

Substantiation of the novelty and importance of the obtained results.

Scientific novelty

First:

- studied the incidence and mortality rates from cervical cancer from 2010 to 2019 years in East Kazakhstan and Kazakhstan.

- substantiated and proposed a method of prophylactic irradiation of para- aortic lymph nodes during chemoradiotherapy for cervical cancer. (Certificate of state registration of rights to the object of copyright No. 2846 of the Ministry of Justice of the Republic of Kazakhstan).

- a comparative assessment of the results of the treatment of cervical cancer of the traditional chemoradiation method with the author's method of prophylactic PALN irradiation was carried out.

- for the first time, the quality of life was assessed in patients with cervical cancer using an adapted module-questionnaire for cervical cancer EORTC - CX 24 treated with the traditional chemoradio method in comparison with the proposed method of prophylactic irradiation PALN (Certificate of state registration of rights to the object of copyright No. 2968 MJ RK).

Practical significance

In clinical practice, the newly established technique of prophylactic para-aortic lymph node radiation during chemotherapy and radiation therapy in cervical cancer patients demonstrated high efficacy, increasing overall survival and progression-free survival.

For cervical cancer that is locally progressed, this approach is preferred.

Oncologists can evaluate quality of life and apply the results in a cervical cancer medical rehabilitation strategy by using the EORTC-CX24 Cervical Cancer Questionnaire module.

Practical recommendations:

1. It is necessary to recommend a method of prophylactic irradiation of para-aortic lymph nodes in locally advanced stages of cervical cancer for implementation in clinical practice in accordance with existing regulations and procedures.
2. The introduction into clinical practice of the method of prophylactic irradiation of PALN during chemoradiotherapy of cervical cancer has improved indicators of overall and progression-free survival, which is the rationale for the wider use of this technique in the Republic of Kazakhstan.
3. It is necessary to assess the quality of life associated with health in order to develop programs for the rehabilitation and psychological care of patients with cervical cancer.

Thus, the proposed method, based on prophylactic irradiation of para- aortic lymph nodes is an important tool for assessing the validity of scientific novelty, the importance and significance of the results obtained in a practical aspect.

Implementation of the research results:

- "Method of preventive radiation therapy of paraaortic lymph nodes in cervical cancer (certificate of state registration of rights to the object of copyright No. 2846 dated September 10, 2018).

- " EORTC QLQ- CX 24" (certificate of state registration of rights to the object of copyright No. 2968 dated September 27, 2018).

- Training manual in three languages "Advanced Interventional Technologies in the Treatment of Cervical Cancer" (copyright certificate No. 4409 dated 07/02/2019).

- The created video lecture on the topic of the dissertation in Kazakh, Russian is available for students of Semey Medical University, active link <https://youtu.be/lp6HrtAuibk>

The main results of the dissertation are used in the educational process at the Department of Clinical Oncology and Nuclear Medicine of the Semey Medical University in the training of undergraduates, doctoral students and oncologists and advanced training courses.

Compliance with the directions of development of science or government programs. Corresponds according to the Comprehensive plan for the fight against oncological diseases in the Republic of Kazakhstan for 2018 - 2022 (Decree of the Government of the Republic of Kazakhstan dated June 29, 2018 No. 395).

Description of the contribution of the doctoral student to the preparation of each publication. The author made a personal contribution to the writing of each publication, the collection and processing of primary material, the design of the article in accordance with the requirements of the journals, business correspondence with the journals.

The materials of the author's research were published in 9 publications, including 4 publications in the materials of international and republican scientific and practical conferences. 1 article - in the Iranian Journal of Public Health, which has an impact factor of 1.225 according to the Thomson ISI Web of Science database. 4 articles were published in scientific publications recommended by the Committee for Control in the Sphere of Education and Science of the Republic of Kazakhstan.

The main provisions of the dissertation were reported on:

International scientific-practical conference of young scientists "Science and Health", dedicated to Professor Musinov D.R., Semey, November 18, 2016

- XIII International Scientific and Practical Conference "Ecology. Radiation. Health", Semey, August 28-29, 2017

- Russian scientific and practical conference with international participation " Personalized approaches to the prevention, diagnosis and treatment of malignant neoplasms ", Barnaul, June 14-15, 2018

- FNCA FY2018 Workshop on Radiation Oncology, Dhaka, Bangladesh, 4-7 November 2018 y.

- Republican scientific and practical conference "Modern trends in the development of clinical and radiation oncology. Multidisciplinary approaches", Semey, May 22, 2019

- VII Congress of oncologists and radiologists of the Republic of Kazakhstan, Nur-Sultan, October 17-18, 2019.

- ESMO Asia 2019 Congress, Singapore, 22-24 November 2019.

- Russian scientific and practical conference with international participation "Modern advances in the diagnosis, surgical, radiation and drug treatment of malignant tumors", Barnaul, June 10-11, 2020

Scope and structure of the dissertation

The dissertation is presented on 106 pages of a computer set, consists of an introduction, literature review, description of materials and research methods, 2 sections of own research, conclusion and practical recommendations, 5 appendices, a list of used literary sources, including 182 titles. The dissertation contains 18 tables, 44 figures.