Original article

Preliminary analysis of early and late radiation responses in 3D image-guided brachytherapy for cervical cancer

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Abstract: *Rationale* – The use of 3D image-guided brachytherapy (3D-IGBT) allows adequately optimizing the dose distribution to bring a target therapeutic dose to clinical target volume (CTV), thereby minimizing an impact on critical organs, while ensuring a decrease in the incidence and severity of radiation-caused complications. Use of 3D-IGBT also allows improving the quality of life in patients with cervical cancer.

Objective – To conduct a preliminary analysis of the incidence of early and late radiation responses in 3D-IGBT of locally advanced cervical cancer (LACC).

Materials and Methods – The objects of our study were female patients with stages IIB and IIIB of cervical squamous cell carcinoma, without confirmed metastases, preceding chemotherapy (CHT) and/or radiation therapy (RT), and surgical interventions in this localization, who underwent combined chemoradiotherapy during the study.

Results – Statistically significant results were obtained when analyzing the incidence of late radiation responses. It is important to point out that when assessing early toxicity in the main group with 3D-IGBT, grade 3 responses were not diagnosed, while in the control group, they were observed in 4 (9.1%) women. For instance, the manifestation of grade 3 delayed radiation injuries in the rectum was diagnosed in 3 (6.8%) women in the control group, while in the main group, they were not detected. Grade 2 cystitis was observed in a smaller number of women in the group with 3D-IGBT, compared with the control group (9.1% vs. 13.6%, p<0.05). Grade 3 delayed radiation responses in the bladder were diagnosed in 4 (9.1%) women in the control group, whereas among the patients of the main group with 3D-IGBT, they were not recorded at all (p <0.05). Grade II reactions in the vaginal mucosa and cervix were diagnosed more often in the control group (16.7% vs. 13.6%, p<0.05).

Conclusion – Hence, the method we have used to optimize the treatment of LACC by means of 3D planning in accordance with toxicity criteria exhibited a definite advantage, compared with RT with 2D planning. Based on the results of our research, we concluded that optimization of RT for LACC using 3D-IGBT created clinically favorable conditions for effective therapy: it reduced the risk of displacement of the applicators and decreased an impact on the patient via reducing the total radiation doses and incidence of severe early and late toxic effects, providing good outcomes of local control regardless of tumor size and clinical stage.

Keywords: cervical cancer, radiation therapy, brachytherapy, 3D image-guided brachytherapy.

Introduction

Cervical cancer (CC) in the female population continues to occupy one of top places, and radiation therapy (RT) remains the main method in the arsenal of specialized CC treatment [1]. Consequently, further improvement in the results of therapy depends largely on the development and mastering of new RT techniques, since the possibilities for effective RT for CC have not yet been exhausted [2]. Fundamentally new equipment for external beam radiation therapy (EBRT) and contact radiotherapy is being developed and put into practice. A whole range of devices for high-precision imaging of tissues and organs emerges, computer technologies are developed for processing and visualizing data. All of these provide the technical possibility of accomplishing a stable therapy for patients with locally advanced forms of cervical cancer (LACC) [3, 4].

Recent studies demonstrated that RT in combination with chemotherapy (CHT) has a large survival advantage, compared with RT alone [5]. Increasing the dose in combination with the insufficient use of contemporary technologies of combined RT and an inadequate approach to the choice of radiation technique enlarges the likelihood of irreversible damage to normal tissues of the bladder and rectum that are inevitably affected by combined radiation therapy. However, combined RT remains the gold standard in the treatment of patients with LACC, while the effectiveness of RT is increasing due to the brachytherapy (BT) stage, which allows delivering high doses of ionizing radiation directly to the tumor with minimal impact on surrounding healthy organs and tissues. In this regard, dose fractionation regimen and an appointment of total doses are decisive factors for reducing an incidence of complications during RT without worsening the treatment results [6, 7].

Despite the fact that a large number of different BT regimens are currently known and used in practice, the choice of the optimal regimen is still a matter of debate. When developing methods of combined RT for CC, aimed primarily at improving the results of treatment, the issue of achieving an antitumor effect with a simultaneous decline in the likelihood of radiation complications remains relevant [8, 9]. Novel dose planning technologies would allow optimizing radiation programs, taking into account the following factors: individual parameters of the tumor process, spatial relationships of the tumor and organs at risk, and constitutional features of the patient. Such technologies could also ensure that adequate levels of absorbed radiation doses are achieved to accomplish an antitumor effect while reducing the level of radiation exposure ton the part of surrounding tissues [10, 11, 12].

Previously, 2D planning was used during BT. However, this approach does not allow choosing the exact beam width in the tumor section and empirically takes its cylindrical geometry as a basis; it does not take into account individual peculiarities of the tumor location in each patient, thereby causing a risk of excessive radiation to adjacent organs. 3D planning takes into account the individual features of the tumor in each section, which makes it possible to model an optimal irradiated tumor volume and to include three-dimensional dose distribution calculations based on tomography data [13, 14]. Radiation complications of moderate and severe degree, manifested by ulcerative changes in risk organs, the formation of rectal and vaginal fistulas, along with intrapelvic fibrosis, significantly impair the quality of life in patients, and could lead to disability and even death [15]. In this regard, the fractionation regimen and the choice of total doses are decisive factors in reducing the incidence of complications in RT while not worsening the outcomes of treatment [16, 17]. The use of 3D image-guided brachytherapy (3D-IGBT) allows adequately optimizing the dose distribution to deliver a specified therapeutic dose to clinical target volume (CTV), thereby minimizing an impact on critical organs, while ensuring a decrease in the incidence and severity of radiation-caused complications and improving the quality of life in patients with CC [18, 19].

BT is an important part of RT of CC when there is an extensive tumor process in the pelvic cavity: combined chemoradiotherapy is the main choice in therapy. Accordingly, it requires ongoing improvement. All directions of BT development are due to dissatisfaction with its long-term results; the currently available arsenal of means and options for RT methods does not guarantee women from the development of relapses and metastases of this disease. In this regard, the search and implementation of a unified approach to RT requires continual search with simultaneous implementation in practice [20].

Increasing the effectiveness of RT in patients with CC and reducing the frequency of radiation complications is largely associated with the modernization of technical means for intracavitary gamma therapy via widely used radioactive sources (cobalt, cesium, iridium) [21]. An integral part of the patient's preparation for intracavitary irradiation is dosimetric planning based on information about the dosimetric characteristics of selected radiation sources and patient's topometric data. Three-dimensional planning of intracavitary irradiation makes it possible to obtain a more accurate distribution of a specified dose over the target volume, depending on the geometry of the applicator location, which is very important for large volumes of the tumor process [22].

The objective of our study was to analyze an incidence of early and late radiation responses during 3D-IGBT of LACC.

Material and Methods

The study was conducted at the Center for Nuclear Medicine and Oncology in Semey, Republic of Kazakhstan. The study objects were female patients with stages IIB and IIIB of squamous cell carcinoma of the cervix without confirmed metastases, preceding CHT, RT, or surgical interventions for this localization, who underwent complex chemoradiation therapy in the period from 2018 to 2020 as part of the study.

Table 1. Characteristics of the study groups according to main treatment criteria

Indicator (according to the treatment regimen)	Study groups	
	Main, n=22, 3D-IGBT	Control, n=44, 2D RT
TFD, EBRT, Gy	50	50
TFD, brachytherapy, Gy	24-28	30-35
Brachytherapy sessions, number	4	5
TFD of combined RT, Gy	74-78	80-85
Number of bed-days	50±3	57±3

3D-IGBT, 3D-image-guided brachytherapy; 2D RT, conventional (2D) radiation therapy; TFD, total focal dose; EBRT, external beam radiation therapy; RT, radiation therapy.
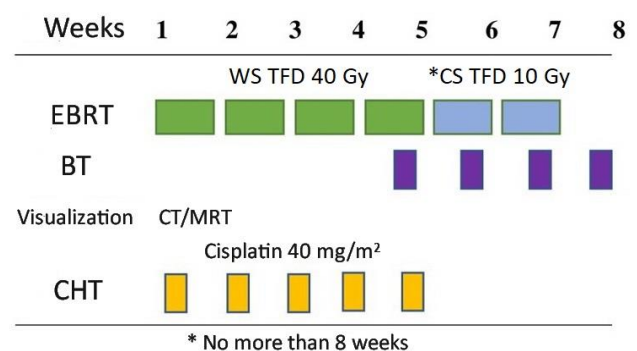

Figure 1. Chemoradiotherapy with 3D-IGBT.

EBRT, external beam radiation therapy; TFD, total focal dose; CS, central shielding; BT, brachytherapy; CT, computed tomography; MRT, magnetic resonance tomography; CHT, chemotherapy; WS, whole pelvis.

Table 2. Socio-demographic and clinical patient data

Parameter		Study groups		Statistical test	
		Main, n=22, 3D-IGBT	Control, n=44, 2D RT	χ²	p-value
Mean age, years		55.4±13.2	56.0±12.8		
Stage sensu TNM (FIGO)	Stage IIB	10 (45.5%)	17 (38.6%)	0.282	0.595
	Stage IIIB	12 (54.5%)	27 (61.4%)		
Tumor size, cm:	< 5	9 (40.9%)	19 (43.2%)	0.031	0.860
	≥ 5	13 (59.1%)	25 (56.8%)		
The nature of tumor growth	Exophytic	12 (54.5%)	25 (56.8%)	0.169	0.919
	Endophytic	7 (31.8%)	12 (27.3%)		
	Mixed	3 (13.6%)	7 (15.9%)		
Degree of differentiation	Low	6 (27.3%)	14 (31.8%)	0.176	0.916
	Moderate	13 (59.1%)	25 (56.8%)		
	High	3 (13.6%)	5 (11.4%)		
Histological type of tumor	Nonspecific	7 (31.8%)	12 (27.3%)	0.315	0.854
	Keratinizing	8 (36.4%)	15 (34.1%)		
	Non-keratinizing	7 (31.8%)	17 (38.6%)		

TNM (tumor, nodus, metastasis), International Classification of Malignant Tumors; FIGO, International Federation of Gynecology and Obstetrics; 3D-IGBT, 3D-image-guided brachytherapy; 2D RT, conventional (2D) radiation therapy.

Table 3. Criteria for evaluating a 3D dosimetry plan

Indicator	Volume	Dose
CTV (clinical target volume)	85-90%	≥ 90% (of prescribed dose)
Bladder	2%	4-5 Gy
Rectum	2%	4-5 Gy
Sigmoid colon	2%	5 Gy

Inclusion criteria:

1. Squamous cell carcinoma of the cervix;

2. Stages IIB (4 cm in diameter) and IIIB, sensu 2008 classification by the International Federation of Gynecology and Obstetrics (FIGO);

3. Age range: 20 to 70 years old;

4. The general condition of the patient as expressed via performance status (PS) sensu Karnofsky Performance Status and WHO/ECOG Performance Status Scale: 0-2;

5. No previous CHT, RT, or surgical interventions for this localization;

6. Life expectancy of over 6 months;

7. Normal functioning of the bone marrow, liver and kidneys (laboratory parameter values: leukocytes ≥3.0×10⁹/L, hemoglobin ≥100 g/L, platelets ≥100×10⁹/L, total bilirubin ≤ 25.65 µmol/L), the level of AST/ALT ≤80 units/L, serum creatinine ≤ 132.6 µmol/L);

8. Written informed consent;

9. Diagnostic imaging prior to the onset of RT: computed tomography (CT) of the abdominal cavity organs, magnetic resonance imaging (MRI) of the pelvic cavity;

10. No metastases in the para-aortic lymph nodes (PALN) (over 1 cm in minimum diameter, as shown by CT).

Exclusion criteria:

1. Concomitant somatic diseases in severe form;

2. History of other malignant neoplasms in the past 5 years, with the exception of basal cell carcinoma or squamous cell carcinoma of the skin;

3. Tumor with infiltration of the lower one-third of the vagina;

4. Pregnancy or lactation.

Study groups

According to the above criteria, the present study included 66 patients who formed the following groups (*Table* 1):

(1) The *main group* included 22 patients who underwent RT within the framework of this study using 3D-IGBT. BT planning was carried out in the 3D volumetric mode (required dose distribution over CTV with a maximum in the tumor zone and minimum impact in the area of adjacent healthy tissues. The number of BT sessions was 4 with a single dose of 6.0-7.0 Gy. Total focal dose (TFD) during BT was 24-28 Gy. TFD for EBRT was 50 Gy. TFD for combined RT was 74-78 Gy. The dose of the CHT preparation Cisplatin was 40 mg/m²;

(2) The *control group* (retrospective group) included 44 patients. They were subjected to LT in the mode of two-dimensional planning (2D) of BT sessions with the distribution of doses over single-plane sections of the body in the middle of the target. The number of BT sessions was 5 with a single dose of 6.0-7.0 Gy. The TFD during BT was 30-35 Gy. TFD for EBRT was 50 Gy. TFD for combined RT was 80-85 Gy. The dose of the CHT preparation Cisplatin was 40 mg/m².

The socio-demographic and clinical data of patients included in the study are presented in *Table* 2.

The distribution of patients by CC stages sensu FIGO looked as follows: the proportion of women with stage IIB of CC was 10 (45.5%) patients in the main group and 17 (38.6%) in the control group. The number of cases of stage IIIB cervical cancer was 12 (54.5%) in the main group and 27 (61.4%) in the control group. The tumor size according to MRI in 9 (40.9%) women of the main group and in 19 (43.2%) women of the control group was less than 5 cm, whereas in 13 (59.1%) study group women and in 25 (56.8%) control group women was greater than 5 cm. According to the degree of differentiation, the patients of both groups were distributed as follows: the number of cases with a low degree was 6 (27.3%) in the main group and 14 (31.8%) in the group control. A moderate degree was diagnosed in 13 (59.1%) women of the main group and 25 (56.8%) females of the control group. Cases of a high degree of differentiation were detected in 3 (13.6%) patients in the 3D group and in 5 (11.4%) women in the 2D group. According to the nature of tumor growth, the patients included in the study were distributed as follows: formations with exophytic growth were registered in 12 (54.5%) women of the main group and in 25

(56.8%) females of the control group. Endophytic growth in the main group was represented in 7 (31.8%) cases in the main group and 12 (27.3%) cases in the control group. Patients with mixed growth of CC were registered in 3 (13.6%) cases in the group with 3D planning, and in 7 (15.9%) cases in the group with 2D planning.

Study subject

Study subjects included early and late radiation responses in the course of using the technique of 3D-IGBT in the program of RT for CC.

External beam radiation therapy with 3D planning

EBRT with a fractionation regimen of 2.0 Gy, 5 fractions per week, the total focal radiation dose (TFD) for the pelvic cavity was 50 Gy (*Figure* 1. Chemoradiotherapy with 3D-IGBT).

From the first day of EBRT, both groups of patients underwent competitive CHT using intravenous infusions of Cisplatin. The dose calculation was carried out individually for each patient: 40 mg/m^2; weekly administration before intracavitary RT session, at least 5 injections.

Starting from week 5, when the radiation dose delivered via EBRT was at least 40 Gy, 3D-IGBT sessions were commenced with a single radiation dose of 6.0-7.0 Gy per week (while maintaining the limitation of the dose impact on risk organs), while TFD was 28 Gy.

When choosing the volume and distribution of radiation doses, the recommendations of the International Commission on Radiation Units and Measurement (ICRU) were applied to determine the gradations of volumes.

The 3D planning process was started by generating a 3D model of each patient using a series of parallel CT scans. Anatomical structures and planned target volume were determined on each of the scans using an automatic procedure based on the knowledge of the range of Hounsfield units for each of the critical organs and other anatomical structures. The construction of contours corresponding to the volume of the tumor, along with the clinical and planned volume of the target, was performed taking into account not only CT data, but also all clinical data about the patient.

To assess the quality of the treatment plan, Dose Volume Histogram (DVH) monitoring was performed. DVH is a plot of dose distribution in the irradiated volume. To achieve the most effective distribution of the dose in relation to the planned volume of the target, the dose-volume histogram had the shape of a rectangle. Using histograms, the following characteristics of dose distributions could be determined: standard deviations of the dose, minimum and maximum doses, mean doses, and median doses for critical organs (*Figure* 2. Scheme of 3D planning with a dose-volume histogram).

A medical physicist calculated several treatment plans for each case, and plotted dose-volume histograms for each plan: planned target volume (PTV) and each critical organ. Based on the DVH analysis, an optimal plan was chosen, for which the dose for the tumor was maximum (at least 95% of the dose should fall on PTV), whereas it was minimal for critical organs (*Table* 3).
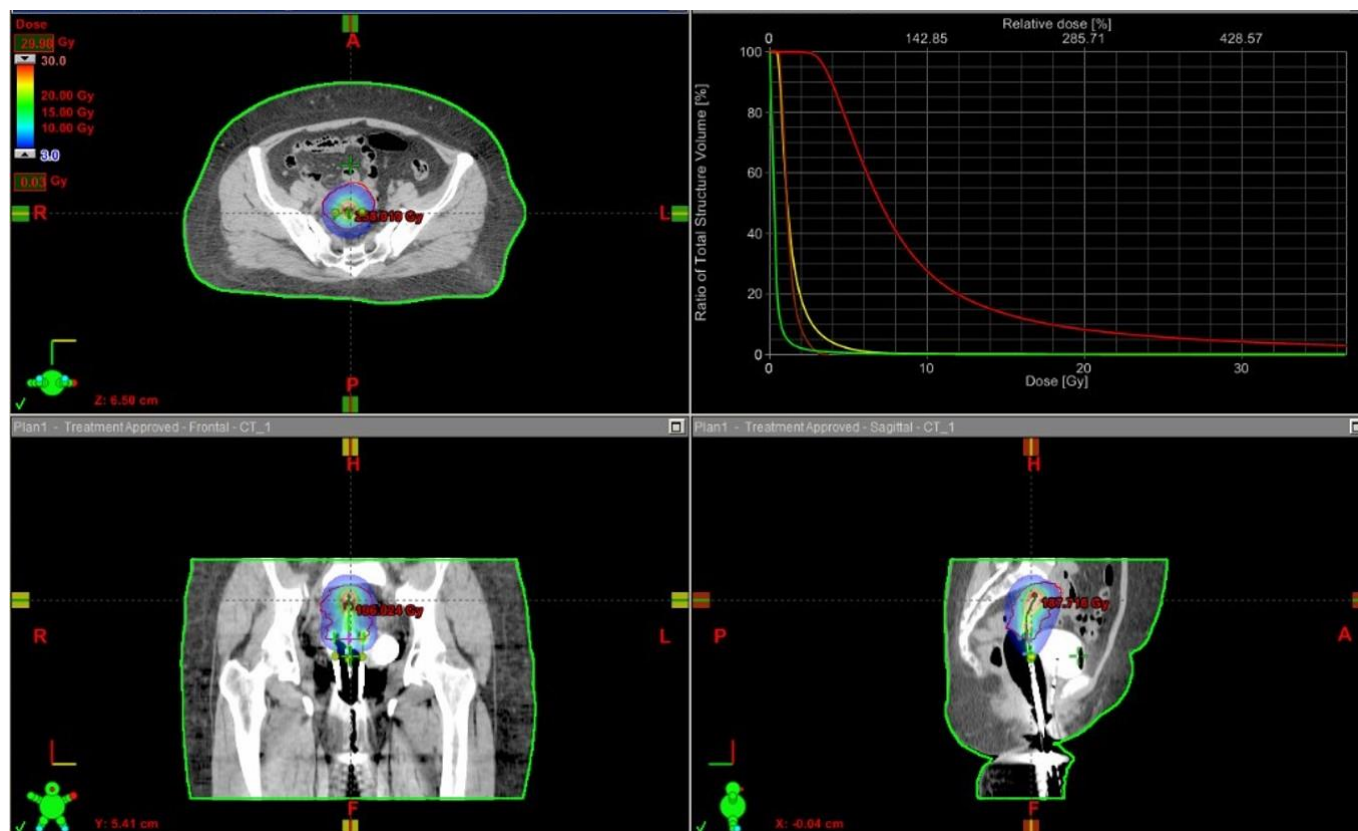

Figure 2. Scheme of 3D planning with a dose-volume histogram.

Table 4. Determination of acute treatment toxicity sensu NCI/CTCAE/RTOG

Radiation response	Grades of acute toxicity				
Organ/tissue	0	1	2	3	4
Intestine	No changes	Increased stool frequency not requiring medical correction, discomfort in the pelvic area	Diarrhea requiring medical correction, small amount of mucous discharge, pain in the pelvic area	Diarrhea requiring parenteral hydration, profuse mucus or bleeding, abdominal distension	Acute or subacute obstruction, perforation, bleeding requiring transfusion
Bladder	No changes	Increased diuresis or nocturia, twice as often as before treatment, dysuria not requiring medical correction	Frequency of diuresis or nocturia no more than every hour, dysuria requiring medical correction	Frequency of diuresis or nocturia once an hour or more, dysuria, pain, spasms requiring narcotic pain medications, massive hematuria	Hematuria requiring transfusion, ulceration, necrosis, acute bladder obstruction
Vaginal mucosa/cervix	No changes	Erythema and/or mild pain not requiring analgesics	Signs of insular epitheliitis, as well as the presence of moderate pain requiring the prescription of adequate pain relief	Membranous epitheliitis, severe pain requiring the appointment of a stronger painkiller	Ulceration, hemorrhage and/or necrosis of the irradiated area (cervix)

NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group.

Table 5. Determination of delayed treatment toxicity sensu RTOG/EORTC

Radiation response	Delayed toxicity grades				
Organ/tissue	0	1	2	3	4
Intestine	No changes	Mild diarrhea Mild spasms Stool up to 5 times a day Discharge or bleeding in a small amount	Moderate diarrhea or colic Stool more than 5 times a day Severe mucus discharge or bleeding	Obstruction or bleeding requiring surgical intervention	Necrosis, perforation Fistula
Bladder	No changes	Mild atrophy of the epithelium Mild telangiectasia Microhematuria	Increased diuresis of moderate degree Generalized essential telangiectasia Intermittent gross hematuria	Severe dysuria Severe generalized essential telangiectasia Frequent gross hematuria Bladder volume reduction (<150 cm^3)	Necrosis Shriveled bladder (<100 cm^3) Severe hemorrhagic cystitis
Vaginal mucosa/cervix	No changes	Moderate atrophy Telangiectasia Reduced mucus	Atrophy with complete dryness	Severe induration and telangiectasias	The development of persistent non-healing ulceration, difficult to correct and treat

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer.

Table 6. Incidence of hematological toxicity in study groups

Group	Parameter				Statistical test	
	n	%	n	%	χ^2	p-value
	anemia		normal hemoglobin			
3D-IGBT	8	36.36	14	63.64	0.032	0.857
2D RT	17	38.64	27	61.36		
	leukopenia		normal leukocytes			
3D-IGBT	9	40.91	13	59.09	0.031	0.860
2D RT	19	43.18	25	56.82		
	thrombocytopenia		normal platelets			
3D-IGBT	6	27.27	16	72.72	0.039	0.842
2D RT	11	25.00	33	75.00		

3D-IGBT, 3D-image-guided brachytherapy; 2D RT, conventional (2D) radiation therapy.

* differences tested via Mann-Whitney U test.

There were four 3D-IGBT sessions; the TFD of combined RT was 74.0-78.0 Gy. Doses were normalized according to the Manchester method. BT was performed using the tandem-ovoid applicator.

Methodology for assessing early and late toxicity of radiation therapy

Within the framework of this study, indicators of early toxicity were prospectively determined in patients receiving RT with 3D planning (main group) and with 2D planning (control group), including laboratory parameters (complete blood count, complete urinalysis, biochemical blood test, physical examination), during treatment and after discharge, within 90 days of the onset of therapy. Hematological and non-hematological toxicity indicators were evaluated on the international scale, NCI/CTCAE (National Cancer Institute's Common Terminology Criteria for Adverse Events), according to which early and delayed radiation injuries were identified. The former included radiation damage developing during RT or in the next three months after its completion. The latter included radiation damage developing after three months.

Staging of early and late radiation responses of all CC patients included in the study was carried out in accordance with the international scale, RTOG/EORTC (Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer) (*Tables* 4 and 5) [23, 24].

Statistical data processing

To describe and search for differences in the groups, we applied the methods of descriptive statistics. The database was generated in Excel and transferred to SPSS 20 for further procedures. Categorical variables are expressed as absolute numbers and their percentages, while quantitative variables are expressed as mean values and their standard deviations. To search for differences in categorical variables between groups, the chi-squared test (χ^2) was employed, whereas for quantitative variables, the Mann-Whitney test was used, taking into account the asymmetry of the distribution. Differences were considered statistically significant at p<0.05.

Results

The average follow-up period ranged 6-28 months. To determine the effectiveness of the developed and implemented RT method, two groups were identified, as indicated in the Materials and Methods section.

When assessing hematological toxicity, the content of hemoglobin, leukocytes and platelets in the blood prior to the treatment, as well as the lowest levels during the treatment period, were examined. *Table* 6 presents data on the incidence of anemia, leukopenia and thrombopenia (sensu Common Terminology Criteria of Radiation Therapy Oncology Group, CTC/RTOG) depending on the RT method of treatment.

For instance, the development of correctable anemia, leukopenia and thrombocytopenia was observed in 8 (36.4%), 9 (40.9%) and 6 (27.3%) women of the main group, respectively, during weeks 4-5 of EBRT treatment. In the control group, these were diagnosed in 17 (38.6%), 19 (43.2%) and 11 (25.0%) cases, correspondingly, during weeks 5-7, both at the stage of EBRT and during BT sessions.

Among non-hematological complications, dyspeptic disorders were noted, in the form of decreased appetite, nausea and vomiting of grade 0-I, as an expected response to weekly CHT sessions, were equally common in the study groups. Other early non-hematological complications were radiation responses from organs at risk, which demonstrated that the 3D-IGBT method had an advantage over the standard 2D planning scheme (*Table* 7).

E.g., the development of grade 1 proctitis occurred in 59.1% of cases in the main group, while in the control group, in 65.9% and 61.4% of cases. Grade II proctitis and grade II cystitis were diagnosed in 5 (22.7%) and 6 (27.3%) cases in the main group, respectively, while in the control group, they were recorded more frequently: in 13 (29.6%) and 14 (31.8%) cases, respectively.

Grade 3 complications were not registered in the main group due to the optimization of the RT regimen. There were no cases of grade 4 proctitis development in both main and control groups.

Grade 1 radiation responses of the vaginal mucosa and cervix developed in 12 (54.6%) women of the main group, and in 25 (56.8%) women of the control group. Grade 2 radiation responses were recorded in 6 (27.3%) women of the main group vs. 14 (31.8%) cases in control group. It is important to point out that in the main group with 3D imaging, grade 3 responses were not diagnosed, while in the control group with 2D planning, grade 3 responses were noted in 4 (9.1%) women.

After 90 days from the onset of treatment, delayed toxicity of the large intestine, bladder, vaginal mucosa and cervix was identified in 22 women of the main group and 44 women of the control group (*Table* 8).

In the main group, grade 1 radiation responses of the intestine were diagnosed in 15 (68.2%) cases, and only in 32 (72.7%) women in the control group. Grade 2 responses of the large intestine in the group with 3D planning were diagnosed in 2 (9.1%) women, while in the group with 2D planning, they were detected in 7 (15.9%) cases. It is important to note that the manifestation of grade 3 late radiation injuries of the rectum was diagnosed in 3 (6.8%) women in the control group, while they were not registered at all in the main group.

Grade 2 responses were detected in 13 (59.1%) women of the main group, while in the control group, they were registered in 33 (75.0%) cases. Grade 2 cystitis was reported in fewer women in the 3D

planning group vs. the 2D imaging group (9.1% vs. 13.6%, p<0.05). Grade 3 radiation responses of the bladder in the late period were diagnosed in 4 (9.1%) women in the control group versus none among the patients of the main group subjected to 3D planning (p<0.05).

Grade 1 radiation responses of the vaginal mucosa and cervix among women of the main group were noted in 13 (59.1%) cases, while in the control group, grade 1 radiation responses of the irradiated volume were observed in 33 (75.0%) patients. Grade 2 responses of the mucous membrane of the vagina and cervix were diagnosed more often in the control group (16.7% vs. 13.6%, p<0.05). Grade 3 responses of the vaginal mucosa and cervix were detected in 4 (9.1%) women in the control group, while a combined problem in the late period occurred in 2 (4.5%) women. Overall, grade 3 radiation injuries in the control group amounted to 9 (25.0%) cases, while in the main group, in the case of the implemented 3D technology, no grade 3 responses were registered (p<0.05).

Discussion

In their study, Sadiq S. et al. noted that despite the frequent use of CT and MRI technologies, there was a lack of data regarding treatment outcomes, and particularly acute non-hematological toxicity, in 3D BT of CC based on CT. Previous studies reported solely chronic side effects [26].

Table 7. Incidence of delayed radiation responses sensu NCI/CTCAE/RTOG

Organ/tissue	Radiation exposure grades, absolute number (n)/%										Statistical test	
	0		1		2		3		4		χ^2	p-value
Intestine	n	%	n	%	n	%	n	%	n	%	5.212	0.157
3D-IGBT, n=22	4	18.2	13	59.1	5	22.7	0	0	0	0		
2D RT, n=44	0	0	29	65.9	13	29.6	2	4.6	0	0		
Bladder	0		I		II		III		IV		3.331	0.343
	n	%	n	%	n	%	n	%	n	%		
3D-IGBT, n=22	3	13.6	13	59.1	6	27.3	0	0	0	0		
2D RT, n=44	0	0	27	61.4	14	31.8	3	6.8	0	0		
Vaginal mucosa/cervix	0		1		2		3		4		3.557	0.313
	n	%	n	%	n	%	n	%	n	%		
3D-IGBT, n=22	3	13.6	13	59.1	6	27.3	0	0	0	0		
2D RT, n=44	1	2.3	25	56.8	14	31.8	4	9.1	0	0		

NCI, National Cancer Institute; CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; 3D-IGBT, 3D image-guided brachytherapy; 2D RT, conventional (2D) radiation therapy.

Table 8. Incidence of delayed radiation injuries vs. treatment method sensu RTOG/EORTC

Organ/tissue	Radiation exposure grades, absolute number (n)/%										Statistical test	
	0		1		2		3		4		χ^2	p-value
Intestine	n	%	n	%	n	%	n	%	n	%	5.134	0.162
3D-IGBT, n=22	5	22.7	15	68.2	2	9.1	0	0	0	0		
2D RT, n=44	2	4.5	32	72.7	7	15.9	3	6.8	0	0		
Bladder	0		I		II		III		IV		11.548	0.009*
	n	%	n	%	n	%	n	%	n	%		
3D-IGBT, n=22	7	31.8	13	59.1	2	9.1	0	0	0	0		
2D RT, n=44	1	2.3	33	75.0	6	13.6	4	9.1	0	0		
Vaginal mucosa/cervix	0		I		II		III		IV		9.409	0.024*
	n	%	n	%	n	%	n	%	n	%		
3D-IGBT, n=22	6	27.3	13	59.1	3	16.7	0	0	0	0		
2D RT, n=44	1	2.3	33	75.0	6	13.6	4	9.1	0	0		

RTOG, Radiation Therapy Oncology Group; EORTC, European Organization for Research and Treatment of Cancer; 3D-IGBT, 3D image-guided brachytherapy; 2D RT, conventional (2D) radiation therapy.

Our study assessed early and late hematological and non-hematological toxicity in both groups. When measuring early hematological toxicity, the development of correctable anemia, leukopenia and thrombocytopenia, was observed in 8 (36.4%), 9 (40.9%) and 6 (27.3%) women of the main group, respectively, at weeks 4-5 of EBRT treatment; while in the control group, these were diagnosed in 17 (38.6%), 19 (43.2%) and 11 (25.0%) cases, correspondingly, both at the stage of EBRT and during BT sessions.

Among the early non-hematological complications, dyspeptic disorders were noted in 5 (22.7%) cases in the 3D-IGBT group, and 10 (22.7%) women in the control group. Other early non-hematological complications were radiation responses of risk organs: grade 3 complications were registered in 5 (11.4%) patients in the control group, while in the main group they were not detected at all due to optimization of the RT regimen. Early radiation responses of grade 3 of the vaginal mucosa and cervix were not diagnosed in the main group with 3D visualization, while in the control group with 2D planning, grade 3 responses were noted in 4 (9.1%) women in the form of membranous epitheliitis, severe pain, requiring an appointment of a stronger anesthesia

The assessment of late toxicity was carried out after 90 days from the onset of treatment. In their study, Dang Y. et al presented late toxicity data using CT for BT: 37% of patients had grade 2 radiation responses of the rectum, whereas 7% had grade 3 radiation responses [26]. When conducting this study, the evaluation of late toxicity disclosed that the manifestation of late grade 3 radiation damage of the rectum was diagnosed in 3 (6.8%) women in the control group, while such damage was not detected in the main group. Grade 2 cystitis was reported in fewer women in the 3D planning group than in the 2D imaging group (9.1% vs. 13.6%, p<0.05). Grade 3 radiation responses of the bladder in the late period were diagnosed in 4 (9.1%) women in the control group, while among the patients of the main group with 3D planning, those were not observed (p<0.05). Grade 2 responses of the vaginal mucosa and cervix were diagnosed more habitually in the control group (16.7% vs. 13.6%, p<0.05).

Kusada T. et al. indicated in their study that the rate of severe late complications (grade≥3) during two years was 3% for the bladder and rectum and 0% for the sigmoid colon and small intestine [27]. When conducting this study, we revealed that in the main group, in the case of using the introduced 3D technology, grade 3 responses were not observed (p<0.05). At the same time, grade 3 responses of the vaginal mucosa and cervix were registered in 4 (9.1%) women in the control group, while a combined problem occurred in the late period in 2 (4.5%) women. Overall, grade 3 radiation injuries in the control group amounted to 9 (25.0%) cases.

Study advantages and limitations

It should be noted that the region in which the study was conducted is one of the territorial units adjacent to the Semipalatinsk nuclear test site. Most of the population are descendants of individuals affected by the effects of the tests. A number of epidemiological studies on the health of the population and the risks of developing various neoplasms have been carried out in the region [28, 29]. Data on contamination of the territory with trace elements also create prerequisites for aggravating the negative impact on the health of residents living in the region [30]. Hence, our study possesses an important practical scope, which has a scientific basis and provides prerequisites for further research.

The advantages of this study encompass the establishment of a cause-effect relationship, and the evaluation of the applied treatment method effectiveness through the analysis of toxicity indicators.

The limitations of our study include the presence and/or absence of required equipment and the high cost of the method. The disadvantages of this study comprise limited applicability of proposed treatment for patients requiring emergency care, along with a large number of factors influencing the outcome of the therapy.

Conclusion

Hence, the method we used to optimize the treatment of LACC via 3D planning, based on toxicity criteria, exhibited a definite advantage in comparison with RT employing 2D planning. The patients in the main group had a lower percentage of early hematological responses to irradiation, while there were no grade III responses of risk organs in the early and late periods. The percentage of overall survival in the main group was higher than in the control group, which confirmed the clinical effectiveness of proposed method for optimal choice of therapy for patients with LACC.

Based on the results of our study, we conclude that optimization of RT for LACC via 3D-IGBT creates clinically beneficial conditions for effective therapy: it reduces the risk of applicator displacement and diminishes an impact on the patient via reducing total radiation doses, the frequency of severe early and late toxic effects, thereby providing adequate local control, regardless of tumor size and its clinical stage.

The study demonstrated that the choice of rational fractionation schemes and the methodology for taking into account the dose impact allowed optimizing radiation programs considering individual parameters of the tumor process, spatial relationship of the tumor and organs at risk, as well as the constitutional characteristics of the patient. Such choice also ensured a higher level of quality of life via reducing both early and late radiation responses and complications. We established that the introduction of 3D-IGBT in clinical practice for the treatment of CC, compared with traditional methods, provided higher social and economic efficacies, both by reducing the number of RT courses and by reducing the degree and risk of early and late post-radiation responses.

Ethical approval

All procedures performed in studies involving humans were in accordance with the ethical standards of the institutional and/or national

research committee, as well as 1964 Declaration of Helsinki and its later amendments, or comparable ethical standards. Ethical issues related to this study were observed in accordance with the Order of the Ministry of Healthcare of the Republic of Kazakhstan No. 142 of April 2, 2018, *"On Approval of the Rules for Conducting Biomedical Experiments, Preclinical (Nonclinical) and Clinical Studies, as well as Requirements for Preclinical and Clinical Bases."* The Local Ethics Committee at non-public joint-stock company, Semey Medical University, issued a positive opinion on ethical issues related to the study (Protocol No. 9, September 13, 2017).

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