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Research Article

Clinical Results of Chemoradiation Therapy and Adjuvant Chemotherapy of Locally Advanced Cervix Cancer

Kravets OA*

Doctor of Medical Sciences, Brachytherapy Department, Institute of Nuclear Medicine, JSC "Medicine" (Clinic of Academician Roitberg), Moscow, Khimki, Department of Therapy, General Medical Practice and Nuclear Medicine, N.I. Pirogov, Russian National Research Medical University, Russia

***Corresponding Author:** Kravets OA, Doctor of Medical Sciences, Brachytherapy Department, Institute of Nuclear Medicine, JSC "Medicine" (Clinic of Academician Roitberg), Moscow, Khimki, Department of Therapy, General Medical Practice and Nuclear Medicine, N.I. Pirogov, Russian National Research Medical University, Russia.

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Abstract

Purpose: This study reported clinical results of patients with locally advanced cervical cancer who treated with radiotherapy and image-guided adapted brachytherapy and combinations of cytotoxic drugs.

Material and Methods: This study included 190 patients with cervical cancer IIb, IIIb, IVb (metastases in para-aortic lymph nodes) during 2011-2015 treated with external-beam radiotherapy or chemoradiotherapy, total dose for D95 50Gy for 25 fractions following Image-guided brachytherapy HDR with prescribing dose for CTV-HR D90 7.5 Gy weekly 4 fractions. Total dose CTV-HR D90 40 Gy (EQD2). Total dose for HR-CTV D90 was 95.0 ± 0.67 Gy (EQD2). Presented group A (n = 72) - radiation therapy, B (n = 40) - chemoradiation therapy with cisplatin C (n = 39) - chemoradiation therapy with a combination of irinotecan + cisplatin, 2 courses of adjuvant chemotherapy D (n = 39) - chemoradiation therapy with a combination of paclitaxel + cisplatin, 2 courses of adjuvant chemotherapy. Clinical outcomes including local control (LC), cancer-specific survival (CSS), overall survival (OS), and toxicity were analyzed.

Results: Three-year OS and CSS in groups A were: 88.4% ± 4.5% and 64.4% ± 7.3%; B - 77.7% ± 7.6% and 77.5% ± 7.1%; C - 69.8% ± 9.6% and 66.3% ± 8.9%; D - 81.3% ± 6.4% and 62.1% ± 8.0%, respectively (p> 0.05). The use of chemoradiotherapy in the groups did not increase the 3-year OS in cervical cancer stage IIIb: in group A - 84.0% ± 7.5%, B - 76.2% ± 9.4; C - 77.2% ± 9.1% and D - 84.9% ± 7.0% (p> 0.05). But CSS was higher on the 1st year of observation in group C - 96.3% ± 3.6% compared with group A - 74.2% ± 7.5% (p = 0.049). With a 3-year observation - 75.7% ± 9.6% and 59.0% ± 11.4%, respectively (p = 0.31). Combined chemoradiation therapy in patients with cervical cancer increases the time to progression: from 9.5 months (in groups A and B) up to 19.4 months and 16.4 months (in groups C and D), respectively (p = 0.05). A decrease in the number of local relapses during 3 years was obtained in groups B and D compared with group A (100% versus 90.3%, p = 0.05). Local control within 3 years among 190 patients was 94.7% ± 1.6%. Gastrointestinal early toxicity was noted higher in group C compared to A, B, D (rectites G2-3 - 25.7% versus 5.6%, 5.0% and 2.6%, respectively, p = 0.05). Late cystitis G2-3 is higher in groups B, C, D compared with group A (15.4% versus 4.2%, p = 0.07).

Conclusion: The study showed high efficiency of treatment of patients with cervical cancer due to the introduction of modern technologies in radiotherapy, as well as chemoradiotherapy programs with acceptable toxicity.

Keywords: Cervical Cancer; Radiation Therapy; Chemoradiotherapy; Image-Guided Brachytherapy; Adjuvant Chemotherapy

Introduction

The statistic of 2020 for Russian Federation shows high incidence rates of gynecological malignant tumors, an increase in revealing of prevalent forms of cancer in young women and an increase of aggressive forms of cancer. Generally malignant neoplasms of the organs of the reproductive system have the largest share in the structure of oncological morbidity in women (39.9%), while tumors of the genital organs account for 18.2% of all malignant neoplasms in women. Cervical cancer is 5.2% in the structure of the total incidence of the female population in Russia in 2020 [1]. A complex of modern methodological approach of conformal radiotherapy combined with image-guided brachytherapy (IGBT) are used for the cervical cancer treatment. Moreover, brachytherapy is essential for the treatment of patients during combined radiation therapy programs and are the main prognostic factor for the local tumor control.

The literature data shows that the use of high-technology radiotherapy techniques increases the treatment efficacy of this category of patients [2-6].

Nowadays external-beam radiation therapy (EBRT) with following intracavitary CT or MRI-guided brachytherapy are priority for the treatment of cervical cancer patients. Regardless of chemoradiotherapy considered to be the method of choice for the treatment of locally advanced cervical cancer (concurrent cisplatin-based chemoradiation), new cytotoxic drugs regiments and different types of administration during radiotherapy are developing to improve clinical outcomes. There are some interesting studies where cytostatic were used in the form of dubplates: irinotecan and cisplatin, paclitaxel and cisplatin during external-beam radiotherapy, and adjuvant therapy after chemoradiotherapy of cervical cancer patients. The aim of the treatment is a decrease of tumor activity and a destruction of micro metastases for prolonging survival [7-10].

It is known that during the M-phase (mitotic phase) cells are the most radiosensitive and during S-phase (synthetic phase) - least sensitive. Cisplatin doesn't have phase specificity and acts in G0-phase of the cell cycle. Irinotecan acting mostly in S-phase of the cell cycle additionally affects tumor cells. Paclitaxel is a phase-specific drug, which acts in interphase and mitotic phase (G2 and M) and helps to achieve full exposure on a tumor. Available word literature data confirms such theoretical approaches and reports a significant increase in progression-free survival, overall survival of patients with locally advanced cervical cancer compared to mono-radiotherapy with cisplatin [7-9].

Unfortunately, conformal radiotherapy and IGBT are in developmental stages in Russia and clinical results of Russian studies are not reported. Today the further search of the optimal total dose of radiotherapy, combinations of drugs, and routes of their administration continues based on available world studies to achieve the most effective chemotherapy of cervical cancer with acceptable treatment-related toxicity.

Thus, the development of new radiation therapy and chemoradiotherapy approaches in the context of an increase of cervical cancer incidence rate in Russia seems relevant and well-timed.

The aim of the study is to improve the survival rate of the locally advanced cervical cancer patients under the age of 50-55 with modern radiation therapy techniques and combinations of cytotoxic drugs.

The analyses of overall and progression-free survival rates, time to progression, recurrence rate, as well as frequency and degree of radiation damages and complications were performed in the study groups of cervical cancer patients.

Material and Methods

This clinical study contains a retrospective and prospective clinical data for the period of 2011-2015. 190 patients with locally advanced cervical cancer, who underwent radiation therapy or chemoradiotherapy, were included in the study. The patients are divided into four groups:

- Group A (control group, retrospective): External-beam radiation therapy (EBRT) and IGBT (72 patients)
- Group B (retrospective): Chemoradiotherapy with cisplatin and IGBT (40 patients)
- Group C (prospective): Chemoradiotherapy with irinotecan + cisplatin and IGBT (39 patients)
- Group D (prospective): Chemoradiotherapy with paclitaxel + cisplatin and IGBT (39 patients).

All patients received the same course of EBRT 3D CRT, IMRT or RapidArc (VMAT) to the pelvis 50 Gy (25 x 2 Gy) with the following intracavitary IGBT HDR (^{192}Ir as a radiation source), prescribed single dose was 7.5 Gy for 4 fractions per week. Total dose per volume of D90 - 40 Gy (a dose is equivalent to that used for the "classic" irradiation in dose regimen on 2 Gy - EQD2).

The average radiotherapy course duration was 60.3 days.

The average total dose (TD) D90 (cervix) over the radiation regimen was 95.0 ± 0.67 Gy (EQD2). Group A - 92.8 Gy, B - 97.1 Gy, C - 93.8 Gy, D - 96.5 Gy (EQD2). Doses for the organs at risk (OAR) - the bladder and the rectum from the EBRT + IGBT were: group A - 78.7 Gy and 66.1 Gy; group B - 75.9 Gy and 69.8 Gy; group C - 74.6 Gy and 71.0 Gy; group D - 80.1 and 70.9 Gy, (EQD2).

The planned radiation therapy was performed for 100% of patients without any interruptions.

Group B underwent standard chemoradiotherapy with 40 mg/m^2 cisplatin was performed. 6 administrations are planned.

Group C received chemoradiotherapy with 20 mg/m^2 irinotekan and 20 mg/m^2 cisplatin while undergoing external-beam radiotherapy, 6 administrations are planned, 2 courses of adjuvant therapy according to the schedule of 65 mg/m^2 irinotekan on day 1 and day 8 + 40 mg/m^2 cisplatin on day 1 and day 8 every 21-st day 2 weeks after finishing brachytherapy.

Group D received 174 mg/m^2 paclitaxel and 20 mg/m^2 cisplatin, while receiving external-beam radiotherapy, 6 administrations were planned, 2 courses of adjuvant therapy according to the schedule of 175 mg/m^2 paclitaxel on day 1 + 75 mg/m^2 cisplatin on day 1 every 21-st day 2 weeks after finishing brachytherapy.

Table 1 shows groups' allocation and statistically significant differences p ≤ 0,05.

	% (n) of the total number of patients			
	Group A n = 72	**Group B n = 40**	**Group C n = 39**	**Group D n = 39**
Absolute number of patients	72	40	39	39
Mean age	54,7	40,7	38,7	39,6
TNM stage IIb IIIb IVb* * ** p = 0,05 , *v p = 0,05	 33,3 (24) * 58,4 (42) 8,3 (6)	 17,5 (7) 62,5 (25) 20,0 (8)	 15,4 (6) ** 71,8 (28) 12,8 (5)	 10,3 (4)v 69,2 (27) 20,5 (8)
Tumor histology Squamous cell carcinoma Adenocarcinoma	 100 (72) 0	 100 (40) 0	 100 (39) 0	 89,7 (35) 10,3 (4)
The degree of the tumor differentiation Poorly differentiated Moderately differentiated Well differentiated No data * ** p = 0.05	 22,2 (16)* 22,2 (16)* 1,4 (1) 54,2 (19)	 37,5 (15) 25,0 (10) 0 37,5 (15)	 35,9 (14) 41,0 (16)** 7,7 (3) 15,4 (6)	 51,3 (20)** 25,6 (10) 15,4 (6) 7,7 (3)
Lymph node involvement Negative Iliac Para-aortic * ** p = 0.042, * v p = 0.05, * w p = 0,05 * ** p = 0.041, * v p = 0.05	 61,1 (44)* 30,6 (22)* 8,3 (6)	 27,5 (11)** 52,5 (21)** 20 (8)	 35,9 (14)v 51,3 (20) v 12,8 (5)	 33,3 (13)w 46,2 (18) 20,5 (8)

Tumor expansion: Parametric Vaginal-parametric Utero-parametric Utero-vaginal-parametric Vaginal * ** p = 0.05, * v p = 0.05 * ** p = 0.05, * v p = 0.05	26,4 (19) 55,5 (40)* 2,8 (2) 12,5 (9)* 2,8 (2)	30 (12) 32,5 (13)** 15 (6) 22,5 (9)** 0	38,5 (15) 46,1 (18)v 5,1 (3,5) 10,3 (4) 0	46,2 (18) 33,3 (13) 12,8 (5) 5,1 (2)v 2,6 (1)

Table 1: Cervical cancer patients' profiles in the study.

Note: * - metastases in Para-aortic lymph nodes.

The analysis showed that Group A, which received combined radiotherapy, was the most favorable from a prognostic point of view: 33.3% of IIb stage cervical cancer patients and 58.4% - IIIb. Regional lymph node involvement was not found in 61% of patients.

The groups, which underwent chemoradiotherapy, had the poorest prognosis: Group B included 62.5% of cervical cancer patients with IIIb stage, Group C - 71.8% and Group D - 69.2%; the lymph nodes involvement was 52.5%, 51.3%, and 46.2%, respectively. The mean age of the women was below 41. The analysis of the histological structure showed that squamous cell carcinoma was prevalent in all groups, however, there were 10.3% of cases with adenocarcinoma in the Group D. It appeared to be 41% of moderately defined and 35.9% of poorly defined tumors among all cases of squamous cell carcinomas in Group C. Group B contained mostly cases of poorly defined squamous cell carcinoma (51,3%, p = 0,05).

Thus, evaluating the presented clinical material, according to the TNM stage, groups of patients with advanced cervical cancer included in the study are homogenous and comparable to perform the outcome analysis. Nevertheless, three groups, which underwent chemoradiotherapy, appeared to have the most unfavorable prognosis according to clinical signs (such as iliac lymph node involvement and the degree of the squamous cell carcinoma differentiation).

Statistical data processing methods

Statistical data processing based on the created database was performed with Excel, SPSS Statistics v. 10.0. The choice of main characteristics was done after studying of the tumor expansion. Descriptive characteristics were used for the analysis of signs severity and incidence. Assessment of differences between distribution and the Laplace—Gauss distribution was performed with Kolmogorov—Smirnov test.

Paired-comparison method with Student t-test was used to test the hypothesis that there are statistically significant differences between groups. The exact p-value was calculated (the differences were considered significant when $p \leq 0,05$). The average value and its' 95% confidence interval, error of mean, media, and the limits of value fluctuation, absolute and relative frequencies were also calculated. Assessment of frequency differences was performed with distribution-free test ci-2, for small samples - Fisher's exact test.

Cox proportional hazards regression model was applied for assessment of predictive measures taking into account a risk of failure of loco-regional tumor control, tumor-specific and overall survival. Hazard ratio and 95-% confidence interval (95% CI) were presented together.

Kaplan—Meier method was used to analyse dose-survival curves, and log-rank test - for assessment of significance of survival differences.

Results

The clinical results of 190 cervical cancer patients were analyzed considering frequency and time of recurrences and distant metastases, and survival rates.

The median of observation for Group A was 39.7 months, Group B - 41.4, Group C - 35.7, and Group D - 31.

The results of tumor progression study don't demonstrate the decrease in number of distant metastases in groups with combined chemotherapy (irinotecan/paclitaxel + cisplatin). There were 19.4% of cases in Group A, 20% - Group B, 20.5% - Group C, and 30.8% - Group D, $p > 0,05$ (Picture 1). Most frequently metastases appeared to be in the para-aortic lymph nodes, lungs, liver (Table 2).

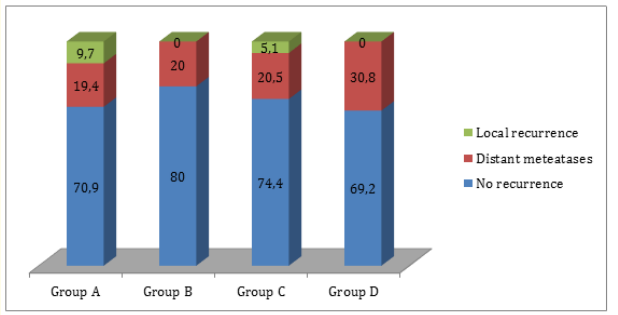
Metastases	Group A n = 72	Group B n = 40	Group C n = 39	Group D n = 39
Lungs	1 (1,4%)	3 (7,5%)	3 (7,7%)	5 (12,8%)
Liver	4 (5,5%)	0	1 (2,55%)	0
Para-aortic lymph nodes	3 (4,1%)	2 (5%)	3 (7,7%)	1 (2,6%)
Supraclavicular lymph nodes	0	0	1 (2,55%)	0
Peritoneum	1 (1,4%)	0	0	1 (2,6%)
Bones	1 (1,4%)	0	0	
Iliac lymph nodes	2 (2,8%)	1 (2,5%)	0	1 (2,6%)
Mediastinal lymph nodes	0	0	0	2 (5,1%)
Combined metastases	2 (2,8%)	2 (5%)	0	2 (5,1%)
Overall	14 (19,4%)	8 (20%)	8 (20,5%)	12 (30,8%)

Table 2: Localisation of metastases.

Three-year local control among all 190 patients was 94.7% ± 1.6%; for groups A, B, C and D - 90.3 ± 3. 6%, 100%, 94.9 ± 3.5% and 100%, respectively. The decrease of the local recurrences number was noted in groups B and D for 9.7% compared to Group A: for each of group's B and D - 100% compared with Group A - 90.3% (p = 0,05). For remained groups the difference was not observed (p > 0,05).

Cancer recurrence was revealed in 9 (4.7%) patients. The main number of metastases was observed in Group A - 7 (9.7%) patients (6 patients developed pelvis recurrences, 1 - in the posterior vaginal wall area). There were 2 (5.1%) patients in Group C who developed recurrence in the pelvis and parametrial tissue. Groups B and D showed no recurrences (Picture 1).

It is noted, that radiotherapy with combined chemotherapy, which was added with adjuvant courses, allows to increase the time to progression nearly twice in the most prognostically unfavourable groups: for Group C - up to 19.4 months and for Group D - up to 16.4



Picture 1: Recurrence rate (%) of the cervical cancer in patients.

months compared with Groups A and B, where time to progression was 9.5 months for both groups (p = 0,05).

Survival analysis in 190 patients with cervical cancer regardless of the stage didn't reveal statistically significant differences in 3-year overall survival (OS) and progression-free survival (PFS) in groups (Table 3). OS in Group A was 88.4% ± 4.5%, in Group B - 77.7% ± 7.6%, in Group C - 69.8% ± 9.6%, in Group D - 81.3% ± 6.4% (p = 0,45). The same tendency is observed in PFS: Group A - 64.4% ± 7.3%, Group B - 77.5% ± 7.1%, Group C - 66.3% ± 8.9%, Group D - 62.1% ± 8.0% (p > 0,05).

	OS, %	Significance	PFS, %	Significance
Group A (n = 72)	88,4 ± 4,5		64,4 ± 7,3	
Group B (n = 40)	77,7 ± 7,6	Vs Group A: p = 0,23	77,5 ± 7,1	Vs Group A: p = 0,34
Group C (n = 39)	69,8 ± 9,6	Vs Group A: p = 0,11	66,3 ± 8,9	Vs Group A: p = 0,87
Group D (n = 39)	81,3 ± 6,4	Vs Group A: p = 0,43	62,1 ± 8,0	Vs Group A: p = 0,69

Table 3: 3-year overall survival and relapse-free survival rates in the groups of cervical cancer patients.

Comparative analysis of survival rates in patients with IIb and IVb stages cervical cancer was not performed for small subgroups. Thus, analysis of survival rate was done only for subgroup of patients with IIIb stage cervical cancer, for this subgroup was the largest in the study.

Analysis of OS in patients with IIIb stage cervical cancer didn't reveal statistically significant increase depending on a treatment

regimen. 3-year OS in Group A was 84.0% ± 7.5%, B - 76.2% ± 9.4%, C - 77.2% ± 9.1%, D - 84.9% ± 7.0% (Table 4).

Groups	Overall survival (OS, %), Stage IIIb			
	1 year	2 year	3 year	Significance
Group A (n = 42)	97,2 ± 2,7	88,9 ± 6,1	84,0 ± 7,5	
Group B (n = 25)	91,7 ± 5,6	76,2 ± 9,4	76,2 ± 9,4	Vs Group A: p = 0,28
Group C (n = 28)	92,3 ± 5,2	82,3 ± 8,1	77,2 ± 9,1	Vs Group A: p = 0,54
Group D (n = 27)	92,6 ± 5,0	84,9 ± 7,0	84,9 ± 7,0	Vs Group A: p = 0,9

Table 4: Overall survival in patients with stage IIIb cervical cancer in groups.

In groups B and D PFS rates in patients with stage IIIb cervical cancer during 1st year of observation were 79.2% ± 8.3% и - 88.9% ± 6.0%, respectively, and did not statistically significantly differ from Group A - 74.2% ± 7.5% (p = 0.65 и p = 0.17, respectively). However, PFS in Group C during the 1st year of observation appeared to be higher compared to Group A and amounted to 96.3% ± 3.6% versus 74.2% ± 7.5% (p = 0,049). Statistically significant difference in the results was not revealed over next 2 years of observation (75.7% ± 9.6% и 59.0% ± 11.4%, respectively, p = 0,31). Statistically significant differences was not observed when comparing 3-year PFS in groups B (73.9% ± 9.3%) and D (69.3% ± 9.0%) compared to Group A (59.0% ± 11.4%), p = 0.49 и p = 0.69, respectively (Table 5).

Thus, It was noted that chemoradiotherapy regimen combined with irinotecan + cisplatin followed by two adjuvant courses allow to increase time to progression for patients with stage IIIb cervical cancer. Analysis of survival rates depending on the degree of the squamous cell carcinoma differentiation was performed. Small groups of patients were excluded from the study.

Groups	PFS, stage IIIb, %			P-value
	1 year	2 years	3 years	
Group A (n = 42)	74,2 ± 7,5	67,5 ± 9,4	59,0 ± 11,4	
Group B (n = 25)	79,2 ± 8,3	73,9 ± 9,3	73,9 ± 9,3	Vs Group A 1 year: p = 0,73 2 years: p = 0,89 3 years: p = 0,49
Group C (n = 28)	96,3 ± 3,6	75,7 ± 9,6	75,7 ± 9,6	Vs Group A 1 year: p = 0,049 2 years: p = 0,62 3 years: p = 0,31
Group D (n = 27)	88,9 ± 6,0	77,4 ± 8,1	69,3 ± 9,0	Vs Group A 1 year: p = 0,64 2 years: p = 0,81 3 years: p = 0,69

Table 5: Progression-free survival of patients with stage IIIb cervical cancer depending on the type of treatment.

Three-year PFS rates in patients with moderately differentiated squamous cell carcinomas were 88.9% ± 10.5% in Group B and appeared to be higher than in Group A - 34,3% ± 14,5%, p = 0,031. There were no other statistically significant differences in the groups. PFS rates in groups C and D were 57.5±13.5% и 55.6±16.6%, respectively (Table 6).

Groups	Progression-free survival, %			
	1 year	2 year	3 year	P-value
A (n = 16)	70,7 ± 12,4	55,0 ± 13,7	34,4 ± 14,5	
B (n = 10)	88,9 ± 10,5	88,9 ± 10,5	88,9 ± 10,5	Vs Group A: p = 0,031
C (n = 16)	81,3 ± 9,8	57,5 ± 13,5	57,5 ± 13,5	Vs Group A: p = 0,35
D (n = 10)	77,8 ± 13,9	55,6 ± 16,6	55,6 ± 16,6	Vs Group A: p = 0,57

Table 6: Progression-free survival of patients with moderately differentiated squamous cell carcinomas of the cervix.

Median PFS in Group A was 24.4 months, and was not achieved in groups B, C, and D.

A statistically significant improvement in 3-year PFS rates in subgroups, which contained patients with poorly differentiated

squamous cell carcinoma of the cervix, was found after analysis in Group C (80.8% ± 12.3%) compared to Group B (42.1% ± 11.3%), p = 0,036. Statistically significant advantages in PFS rates were not obtained for groups A and D (Table 7).

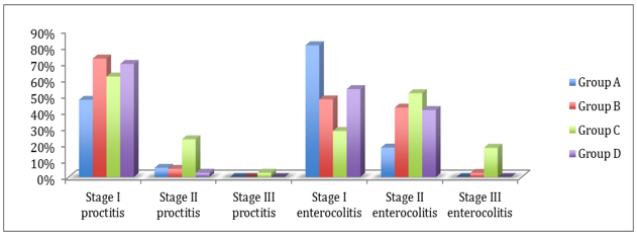
Groups	Progression-free survival			P-value
	1 year	2 years	3 years	
Group A (control) (n = 16)	73,9 ± 11,3	73,9 ± 11,3	73,9 ± 11,3	
Group B (n = 15)	63,2 ± 13,2	42,1 ± 15,0	42,1 ± 11,3	vs Group A: p = 0,3
Group C (n = 14)	100	80,8 ± 12,3	80,8 ± 12,3	vs Group A: p = 0,37 vs Group B: p = 0,036
Group D (n = 20)	79,2 ± 9,3	68,6 ± 10,6	62,4 ± 11,35	vs Group A: p = 0,83

Table 7: Progression-free survival of patients with poorly differentiated squamous cell carcinomas of the cervix.

Toxicity

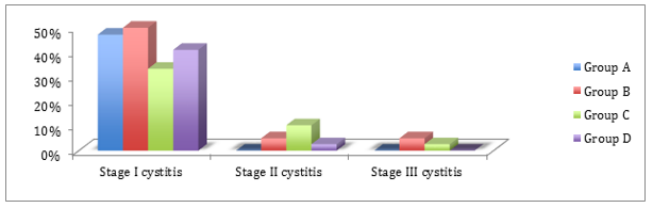
When performing comparative analysis of early damages in groups, statistically significant increase of frequency and degree of gastrointestinal toxicity was found in Group C G2-3 proctitis more frequently developed in Group C (25.7% ± 7.0%) then in groups A, B, and D (5.6% ± 2.7%, 5.0% ± 3.5% and 2.6% ± 3.5%, respectively, p = 0,05) (Picture 2).

An increase enterocolitis incidence G2 was noted in Group C compared to Group A (51.3% ± 8.0%) and 18.1% ± 4.5%, respectively, p = 0,04. Enterocolitis G3 was registered only in Group C (17.9% of patients). Thus, an increase in the incidence of gastrointestinal toxicity may occur due to toxic effects of irinotecan on the intestinal mucosa (Picture 2).



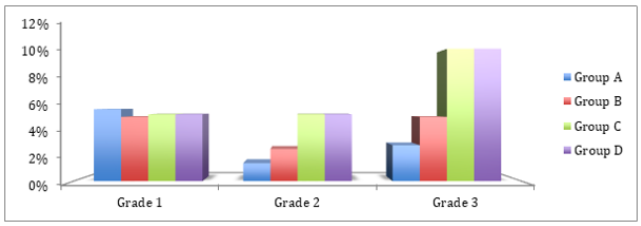
Picture 2: Gastrointestinal toxicity in groups of cervical cancer patients.

Cystitis G1was revealed in the majority of patients (Picture 3). Cystitis G2 was registered in 5% of patients in Group B, 10% - Group C, 2.6% - Group D, and was not revealed in Group A. Cystitis G3 was observed in Group B - 5%, Group C - 2.6%, and was not registered in groups A and D.



Picture 3: Early urinary tract toxicity in cervical cancer patients.

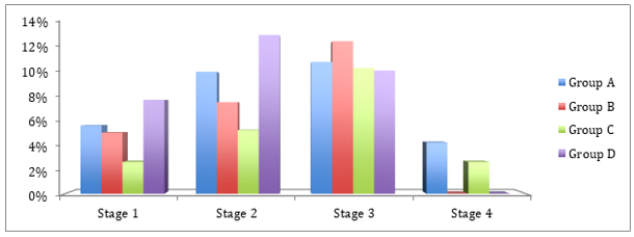
The frequency of G1 late bladder toxicity was from 5.0% to 5.6% in all groups (Picture 4). However, groups C and D shows a tendency to an increase in the frequency of G1 and G3 toxicity compared to the Group A (15.4% ± 5.8% of patients identical in groups C and D vs 4.2% ± 2.4% - in Group A, p = 0.07). This is probably due to the manifestation of cisplatin nephrotoxicity as well as potentiating action of the two drugs on the bladder mucosa.



Picture 4: Late bladder toxicity in patients with cervical cancer.

There were no statistically significant differences in the stage and frequency of late proctitis. Nevertheless, attention is drawn to the frequency of hemorrhagic proctitis detection in all the study

groups: 11.1% of patients in Group A; Group B - 12.5%; Group C - 10.3%; Group D - 10.1%, p > 0,05 (Picture 5). Four cases of rectovaginal fistulas were detected: 3 (4.2%) patients in Group A and 1 (2.6%) in Group C.



Picture 5: Late radiation proctitis in groups of cervical cancer patients.

Thus, it can be noted that the use of chemotherapy with a combination of irinotecan + cisplatin increases early gastrointestinal radiation toxicity (p = 0.05). Chemoradiotherapy in combine with irinotecan/paclitaxel + cisplatin has a tendency to increase in the frequency and grade of bladder toxicity (p = 0.07).

Discussion and Conclusion

According to the literature, there is a significant improvement in the treatment outcomes of the cervical cancer patients from the moment of development of conformal radiotherapy and IGBT brachytherapy. American brachytherapy task report performed the review of literature data covering the period of 2000-2015 years with an emphasis on modern approaches including concurrent chemotherapy, radiation, and high dose-rate (HDR) brachytherapy in the treatment of IB1 - IVA cervical cancer.

The review paper included: 16 prospective and 51 retrospective clinical studies of survival rates, and also 13 retrospective studies, which showed early and late radiation complications taking into account the type of applicator used for brachytherapy. There were 57 studies, where calculations were carried out for A point, 33 of which were with chemotherapy, 10 - with 3D brachytherapy, and 8 - with chemotherapy. The results of the prospective studies with follow up > 24 months showed that local control after radiotherapy (RT) was 73% versus 82% after chemoradiotherapy (CRT); progression-free survival (RT) 55% vs 65% (CRT); overall survival (RT) 66% vs 70% (CRT). Retrospective studies showed 57% local control after RT vs 80% after CRT; progression-free survival rates - 55% and 63%, respectively. The local control and progression-free survival rates were higher when CRT with 3D brachytherapy were used compared to 2D brachytherapy (p < 0,01). Grade 3 gastrointestinal complications amounted to 4-11% for RT, and 1-11% for CRT. Late grade 1-2 genitourinary complications were noted in one of 16 studies: 17% - for RT, 9% - for CRT. Thus, the improvement of the treatment outcomes for patients with cervical cancer is demonstrated in the world literature after introduction chemoradiotherapy and IGBT brachytherapy with acceptable toxicity into clinical practice. The increased use of IGBT HDR brachytherapy in clinical practice allows to improve the local control of the tumor process [11].

Even though concurrent cisplatin-based chemoradiation is the standard treatment cervical cancer, the search continues for new schemes of cytotoxic drugs and different modes of administration in the background of radiation therapy to improve clinical results. Interesting and promising studies on the issue of adjuvant chemotherapy in patients for locally advanced cervical cancer. The purpose of this type of cytostatic regimens is to suppress the activity and destruction of micro metastases to increase the survival of patients. There are not many such data in the literature, there are separate works to which we paid attention.

Tanqiitqamol S., *et al*. compared chemoradiotherapy with cisplatin and a combination of cisplatin + gemcitabine followed by 2 adjuvant courses. The study involved 978 women with IIb-IVa stages of cervical cancer. The authors proved a significant improvement in progression-free survival, overall survival in the group with adjuvant chemotherapy compared with the chemoradiotherapy group: 3-year progression-free survival was 74.4% versus 65% in the control group (p = 0.027), 3-year overall survival was 80% vs. 69% (p = 0.022) [10].

Later Tanqiitqamol S., *et al*. demonstrated a randomized controlled trial which compared the outcomes achieved with standard concomitant chemoradiation versus those achieved with addition of 3 cycles of paclitaxel and carboplatin to concomitant chemoradiation, in patients 18-70 aged with stages IIB to IVA cervical cancer. Notable features of the study population include exclusion of patients with paraaortic lymph nodes, approximately three-fourths of patients having squamous cell carcinoma, more than 95% patients having stage IIB or IIIB cancer and an

imbalance between concomitant chemoradiation arm (20.9%) and adjuvant chemotherapy arm (26.9%) with respect to radiologically detected pelvic lymph nodes. The main result of the study was lack of significant improvement in progressive-free survival and overall survival with the addition of adjuvant chemotherapy to concomitant chemoradiation, at a relatively short median follow-up of 27.4 months. However, systemic recurrences were significantly lower in arm of those who had adjuvant chemotherapy than in group of chemoradiation therapy arm: 5.4% vs. 10.1% (p = 0.029). Severe grades (3-4) of neutropenia, thrombocytopenia, and several non-hematological toxicities (gastrointestinal, genitourinary, and neurological) were numerically higher in the adjuvant chemotherapy arm [12].

Later the same author group reported the 5-year progression-free survival and 5-year overall survival of patients in both arms were not significantly different. Although systemic failure tended to be higher in chemoradiation arm than in arm of those who had adjuvant chemotherapy: 13.2% versus 6.9% (p = 0.094) [13].

Another study by Jelavic T.B., *et al*. presented the results of cisplatin and ifosfamide chemoradiotherapy followed by 4 courses of adjuvant chemotherapy. The study involved 118 patients with stages Ib2-IVa. Against the background of low dose rate, 2 courses of chemotherapy were performed, followed by 4 courses of adjuvant chemotherapy. 18 patients had relapses after the end of treatment, of which 3 had local recurrence, 15 had distant metastases, and 1 had local recurrence and distant metastasis. Overall survival at a median follow-up of 96 months was 86.4% [8].

In randomized study on 515 patients compared CCRT with cisplatin and gemcitabine followed by two cycles of adjuvant cisplatin and gemcitabine, and conventional CCRT. They showed that PFS (HR 0.68, 95% CI 0.49-0.95, p = 0.023) and OS (HR 0.68; 95% CI 0.49-0.93, p = 0.022) at 3 years were both significantly improved in the gemcitabine arm. There was an increased benefit in patients with stages III-IVA. However, here was also an increased occurrence of grade 3-4 hematologic toxicities and diarrhea (86.5% vs 45.3%, p < 0.001) [14,15].

A Cochrane review based on these 2 trials concluded that there are insufficient data and a need for further RCTs to definitively test the utility of adjuvant CT in this context [16].

Despite conflicting literature data, the addition of adjuvant chemotherapy after chemoradiotherapy can improve the survival of patients with advanced cervical cancer. Adjuvant chemotherapy is still not considered the standard of care, mainly due to statistical errors, excessive toxicity of some experimental treatments. However, further randomized trials are needed.

In our study with complex regimes of radiotherapy and chemoradiotherapy we note the acceptable clinical results. 3-year local control among all 190 patients with cervical cancer was 94.7%. The numbers of local recurrences were 9.7% lower in groups underwent chemoradiotherapy with cisplatin, and paclitaxel+cisplatin versus the group with combined radiotherapy; 100% vs 90.3%, respectively (p = 0,05).

Our clinical results were significantly improved compared to the previously presented results of O.A. Kravets dissertation (2010). Three year overall survival rates in patients with IIIb cervical cancer who underwent EBRT and brachytherapy over the period of 1982-2009 years (n = 84) were 53.8% ± 9.0%, progression-free survival - 45.2% ± 7.4% vs in period of 2011-2015 these rates were 84.0% ± 7.5% and 59.0% ± 11.4%, respectively, in the group that received chemoradiotherapy with cisplatin - 76.2% ± 9.4% and 73.9% ± 9.3%; in the group that received chemoradiotherapy with irinotecan+cisplatin - 77.2% ± 9.1% and 75.7% ± 9.6%; in the group that received chemoradiotherapy with paclitaxel+cisplatin - 84.9% ± 7.0% and 69.3% ± 9.0%, respectively [17].

An acceptable toxicity was achieved despite of the fact that early gastrointestinal toxicity was higher in the group underwent chemoradiotherapy with irinotecan+cisplatin versus groups received combined radiotherapy, chemoradiotherapy with cisplatin/paclitaxel + cisplatin (recurrence rate G2-3 was 25.7% vs 5.6%, 5.0% and 2.6%, respectively, p = 0,05). The number of late grade 2-3 cystitis was higher in groups underwent chemoradiotherapy with irinotecan/paclitaxel + cisplatin versus the group received combined radiotherapy (15.4% vs 4.2%, p = 0,07). Thus, after comparing our results, the increase of OS and PFS rates were noted for all the study groups (p = 0,05).

This improvement in treatment outcomes for patients with locally advanced cervical cancer became possible after introducing modern technologies of radiotherapy into clinical practice, and programs of chemoradiotherapy given that the Russian statistics

confirm an increase in the frequency of detection of advanced cervical cancer in young women up to 40 years of age in the structure of mortality from cervical cancer.

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