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# The addition of paclitaxel in chemoradiotherapy of anal squamous cell carcinoma: a prospective randomized phase 3 trial

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**ABSTRACT** *AIM: to compare late outcomes and safety of the addition of paclitaxel to chemoradiotherapy for squamous cell anal carcinoma.*
*PATIENTS AND METHODS: a prospective phase 3 randomized trial included patients with histologically verified non-metastatic anal squamous cell carcinoma. Patients received radiotherapy 52–54 Gy (for T1-T2 tumors) and 56–58 Gy (for T3-T4 tumors) in 2 Gy daily fractions during chemotherapy with mitomycin C (10 mg/m² i.v.day 1), capecitabine (625 mg/m² 2 times a day orally on days of radiation therapy), paclitaxel (45 mg/m²i.v.on days 3, 10, 17, 24, 31) during 2013-2019. In the control group patients received a similar course of RT and chemotherapy with mitomycin C (12 mg/m²i.v.day 1), capecitabine (825 mg/m² 2 times a day orally on radiotherapy days).The primary endpoint was 3-year disease-free survival (DFS). Secondary endpoints included complication rate (NCI-CTCAE 4.0), complete clinical response rate at 12 weeks and 26 weeks after completion of CRT, and 3-year overall survival (OS).*
*RESULTS: the study and control groups included 72 patients each. The median follow-up was 39.5 months. A complete clinical response at the 26-week follow-up was recorded in 64 (88.9%) patients in the study group and in 54 (75.0%) patients in the control group ($p = 0.049$). There were no differences in the incidence of complications of grades 3–4 in the two groups (41/72 [56.9%] in the study group versus 19/72 [26.4%] in the control group ($p < 0.0001$)). Three-year progression-free survival in the study group was 87.1%, in the control group — 64.4% ($p = 0.001$). Three-year overall survival in the study group was 95.5%, in the control group — 80.0% ($p < 0.001$).*
*CONCLUSION: CRT with paclitaxel for squamous cell anal carcinoma has acceptable toxicity and may improve late treatment outcomes.*

**KEYWORDS:** *squamous cell carcinoma, anal cancer, CRT, Nigro, paclitaxel, complete clinical response*

**CONFLICT OF INTEREST:** *The authors declare no conflict of interest*

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## INTRODUCTION

In non-metastatic squamous cell carcinoma of the anal canal, the main treatment method is chemoradiotherapy with mitomycin C and fluoropyrimidines [1].

To date, only one alternative regimen of chemoradiotherapy (CRT) with the use of 5-fluorouracil and cisplatin has been studied, which is somewhat inferior to standard treatment (5-year disease-free survival of 67.8% vs. 57.8%; $p = 0.006$; 5-year overall survival of 78.3% vs. 70.7%; $p = 0.026$) [3]. It is known that paclitaxel is successfully used in CRT schemes in the treatment of squamous cell carcinoma of other sites — head and neck [4–7], esophagus [8, 9], cervix [10], while its use in CRT of

squamous cell carcinoma of the anal canal has not been studied to date.

The CRT regimen using fluoropyrimidines and mitomycin C is associated with a high risk of severe side effects of treatment: the rate of hematological complications of the 3–4 grade reaches 26%-61%, non–hematological — 62%-74% [2, 3]. For a long time, this did not allow considering the possibility of adding new components to the scheme with initially low tolerance. The development of radiation therapy technologies, in particular, the widespread introduction of intensity-modulated radiation therapy (IMRT), has reduced the incidence of complications. So, according to Chuong M. et al. [11], the use of IMRT reduced the incidence of non-hematological complications of the 3–4 grade from 59.5% to 21.2% ($p < 0.0001$). The rate of hematological complications can be reduced by the refusal of the second administration of mitomycin, without affecting the overall effectiveness of the treatment, which was shown in 2 phase — 2 studies [12, 13].

The study was based on the hypothesis that the reduction in toxicity achieved with the help of IMRT technology and the rejection of the second administration of mitomycin will allow us, by adding a new drug to standard treatment, to improve the effectiveness of CRT.

The safety of this approach was previously demonstrated by us in the framework of a pilot study, which served as the basis for initiating a phase 3 study [14].

## AIM

Comparison of late treatment results and safety profile with the addition of paclitaxel to chemoradiotherapy of squamous cell carcinoma of the anal canal.

## PATIENTS AND METHODS

This study is a prospective randomized phase-3 trial. In the study group, a course of CRT was performed using capecitabine (625 mg/m$^2$ twice a day *per os* on the days of radiation), mitomycin C (10 mg/m$^2$*i.v.* bolus on day 1), paclitaxel (45 mg/m$^2$ intravenous weekly). The doses of capecitabine and mitomycin were reduced taking into account the expected increase in the toxicity of the treatment regimen. In the control group, patients received CRT against the background of the use of capecitabine (825 mg/m$^2$twice a day *per os*) and mitomycin C (12 mg/m$^2$*i.v.* bolus on day 1). As part of the phase-3 study, it was planned to include 157 patients in each group to demonstrate an increase in 3-year DFS from 70% to 85% with a confidence of 0.05 and a power of 80%. It was registered in 2015 (NCT02526953); recruitment was started in 2016. However, the study was terminated prematurely in 2019 due to the fact that the drug mitomycin C was not re-registered in Russia and is no longer available in the clinic. We present the preliminary results of the study taking into account the accumulated data. During randomization, stratification was used according to the criteria T (T1-T2 or T3-T4) and N (N0 or N+).

The inclusion criteria were: histologically verified squamous cell carcinoma of the anal canal, absence of distant metastases, Karnovsky's index > 70%, age from 18 to 75 years, absence of synchronous or metachronous malignant tumors, Hb > 90 g/l, leukocytes > 3.5 × 10*9 Units/l, platelets > 120 × 10*9 Units/l, creatinine < 150 mmol/l, bilirubin < 30 mmol/l.

The exclusion criteria were: tumors of the perianal skin and anal margin, metachronous and synchronous tumors, pregnancy, breast-feeding, severe concomitant diseases that exclude chemotherapy and radiation therapy, previous chemotherapy or radiation therapy, patients with contraindications to magnetic resonance imaging (MRI) of the pelvis, patients with HIV-positive status.

The radiation therapy was performed using IMRT technology in consecutive daily fractions of 1.8–2.2 Gy.

The planned dose for the primary tumor was 52–58 Gy (52–54 Gy for T1 — 2 tumors and 56–58 Gy for T3 — 4 tumors), for affected lymph nodes ⩽ 3 cm in size — 50–52 Gy, > 3 cm in size — 54 Gy.

Staging was carried out in accordance with the TNM system (UICC, 2010, the 7th edition) based on pelvic MRI data. The examination also included: disease history and clinical examination, general and biochemical blood analysis, coagulogram,

**Table 1.** *Patient characteristics*

| Characteristics | Study group | | Control group | | *P*-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Number of patients | 72 | 100 | 72 | 100 | – |
| Male | 8 | 11.1 | 11 | 15.3 | 0.46 |
| Female | 64 | 88.9 | 61 | 84.7 | |
| Median age, years | 55 (29–68) | | 58 (33–81) | | 0.18 |
| Median tumor size, cm | 4.3 (1–11) | | 4.25 (1–12) | | 0.946 |
| T1-T2 | 35 | 48.6 | 35 | 48.6 | 1 |
| T3-T4 | 37 | 51.4 | 37 | 51.4 | |
| N0 | 20 | 27.8 | 20 | 27.8 | 1 |
| N1-N3 | 52 | 72.2 | 52 | 72.2 | |
| Stage I | 7 | 9.7 | 3 | 4.2 | 0.217 |
| Stage II | 8 | 11.1 | 13 | 18 | |
| Stage IIIA | 25 | 34.7 | 18 | 25 | |
| Stage IIIB | 32 | 44.4 | 38 | 52.8 | |
| Low differentiated | 19 | 26.4 | 16 | 22.2 | 0.449 |
| Moderately differentiated | 49 | 68 | 48 | 66.7 | |
| High differentiated | 4 | 5.6 | 8 | 11.1 | |

digital rectal examination, anoscopy, computed tomography (CT) of the abdominal cavity and thoracic organs with intravenous contrast.

The toxicity of the treatment was assessed according to the criteria of adverse events (NCI-CTCAE v.4.0), with the exception of cutaneous and genitourinary toxicity, which were assessed according to the criteria of RTOG.

Treatment was partially or completely suspended with the development of grade 3–4 toxicity, which did not stop against the background of adequate accompanying therapy (as well as with grade 2 thrombocytopenia) until the toxicity was reduced to grade 2 or lower (with thrombocytopenia, the treatment was resumed with a decrease in toxicity to grade 1).

Forced changes to the treatment plan were divided into significant and insignificant. Insignificant changes were understood as a break in radiation and/or chemotherapy lasting less than 7 days. Significant ones were understood to mean similar breaks lasting 7 days or more. A single omission of paclitaxel administration in the study group was considered insignificant; omissions of paclitaxel administration more than 1 time were considered a significant change in the treatment plan.

All the patients included in the study were dynamically monitored every 3 months for the first 2 years and every 6 months for the next 3 years.

The examination included: digital rectal examination, anoscopy, pelvic MRI, CT of the thoracic and abdominal cavity with intravenous contrast.

The assessment of the response to CRT was carried out in 12 weeks after the end of the treatment, and the decision on the implementation of surgical treatment was made no earlier than 26 weeks after CRT.

The complete clinical response was defined as the complete absence of palpable formation during physical examination and the absence of a tumor according to pelvic MRI data. Anything less than a complete response was defined as a partial response.

Progression was defined as an increase in the tumor by more than 25% or the appearance of new foci.

The main parameter to be evaluated was: 3-year DFS, additional — 3-year OS (overall survival), which were evaluated using Kaplan-Mayer's log-rank test and were defined as the time between enrollment in the study and the progression of the disease or death.

Also, additional parameters evaluated were: the rate of a complete clinical response, the rate of progression, the morbidity rate of the 3–4 grade, the incidence of significant changes in the treatment plan in each of the groups, survival without stoma (including stomas before the treatment).

**Table 2.** *Treatment toxicity*

| Toxicity | Study group N (%) | | | | | Control group N (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 grade | 1 grade | 2 grade | 3 grade | 4 grade | 0 grade | 1 grade | 2 grade | 3 grade | 4 grade |
| Non-hematological toxicity | | | | | | | | | | |
| Skin reactions | 11 (15.3) | 21 (29.2) | 33 (45.8) | 7 (9.7) | 0 | 4 (5.6) | 28 (38.9) | 33 (45.8) | 7 (9.7) | 0 |
| Allergy | 71 (98.6) | 1 (1.4) | 0 | 0 | 0 | 72 (100) | 0 | 0 | 0 | 0 |
| Diarrhea | 31 (43) | 9 (12.5) | 22 (30.6) | 10 (13.9) | 0 | 34 (47.2) | 18 (25) | 15 (20.8) | 5 (6.9) | 0 |
| Nausea | 57 (79.1) | 11 (15.3) | 4 (5.6) | 0 | 0 | 66 (91.7) | 5 (6.9) | 1 (1.4) | 0 | 0 |
| Vomiting | 48 (66.7) | 13 (18) | 8 (11.1) | 3 (4.2) | 0 | 60 (83.3) | 10 (13.9) | 2 (2.8) | 0 | 0 |
| Proctitis | 8 (11.1) | 22 (30.6) | 33 (45.8) | 8 (11.1) | 1 (1.4) | 15 (20.8) | 25 (34.7) | 28 (38.9) | 4 (5.6) | 0 |
| Cystitis | 46 (63.9) | 16 (22.2) | 9 (12.5) | 1 (1.4) | 0 | 49 (68) | 14 (19.4) | 8 (11.1) | 1 (1.4) | 0 |
| Vaginitis | 72 (100) | 0 | 0 | 0 | 0 | 70 (97.2) | 0 | 2 (2.8) | 0 | 0 |
| Palmar-plantar syndrome | 71 (98.6) | 0 | 0 | 1 (1.4) | 0 | 72 (100) | 0 | 0 | 0 | 0 |
| ART increase | 67 (93) | 2 (2.8) | 2 (2.8) | 1 (1.4) | 0 | 69 (95.8) | 3 (4.2) | 0 | 0 | 0 |
| Increased bilirubin levels | 70 (97.2) | 2 (2.8) | 0 | 0 | 0 | 72 (100) | 0 | 0 | 0 | 0 |
| Hyperthermia | 63 (87.5) | 6 (8.3) | 3 (4.2) | 0 | 0 | 68 (94.4) | 4 (5.6) | 0 | 0 | 0 |
| Hematological toxicity | | | | | | | | | | |
| Leukocytopenia | 15 (20.8) | 11 (15.3) | 26 (36.1) | 19 (26.4) | 1 (1.4) | 21 (29.2) | 28 (38.9) | 15 (20.8) | 8 (11.1) | 0 |
| Neutropenia | 20 (27.8) | 15 (20.8) | 25 (34.7) | 11 (15.3) | 1 (1.4) | 33 (45.8) | 22 (30.6) | 10 (13.9) | 7 (9.7) | 0 |
| Thrombocytopenia | 50 (69.4) | 17 (23.6) | 4 (5.6) | 1 (1.4) | 0 | 39 (54.2) | 27 (37.5) | 5 (6.9) | 1 (1.4) | 0 |
| Anemia | 71 (98.6) | 0 | 0 | 1 (1.4) | 0 | 69 (95.8) | 0 | 2 (2.8) | 1 (1.4) | 0 |

The data were analyzed using IBM SPSS Statistics 22 software. To compare qualitative variables, the $\chi^2$-test, its bilateral asymptomatic significance was used. Quantitative variables were compared using Mann-Whitney's U-test.

## RESULTS

### *Characteristics of Patients*

In the period from 2014 to 2020, 72 patients were recruited into each of the both groups. The characteristics of the patients are presented in Table 1.

The majority of the patients at the time of inclusion in the study had stage III disease: 57 (79.2%) patients in the study group and 56 (77.8%) patients in the control group.

### *Toxicity*

The rate of complications of treatment is presented in Table 2.

The overall complication rate is relatively high. Complications of the 3–4 grade were found in 41 (56.9%) patients in the study group and in 19 (26.4%) patients in the control group ($p < 0.0001$). No deaths during the treatment were recorded in any of the groups.

The developed complications caused significant changes in the treatment plan in 7 (9.7%) patients in the study group and in 9 (12.5%) patients in the control group ($p = 0.176$).

***Effectiveness***

All patients underwent a follow-up examination in 12 and 26 weeks and were evaluated for a complete clinical response to CRT.

At the 12-week control check-up, a complete clinical response was noted in 54 (75.0%) patients from the study group and in 44 (61.1%) patients from the control group ($p = 0.107$).

At the 26-week control check-up, a complete clinical response was noted in 64 (88.9%) patients from the study group and in 54 (75%) patients from the control group ($p = 0.049$).

The progression rate in the study group: 10 (13.9%) patients, of whom with local recurrence — 6 (8.3%) patients, with distant metastases — 7 (9.7%) patients.

The progression rate in the control group: 15 (20.8%) patients, of whom with local recurrence — 10 (13.9%), with distant metastases — 9 (12.5%).

There were no significant differences in the progression rate ($p = 0.38$), recurrences ($p = 0.427$) and metastases ($p = 0.792$).

The median follow-up was 39.5 months (minimum follow-up time was 6.77 months, maximum 94.42 months).

Three-year DFS in the study group was 87.1%, in the control group — 64.4% ($p = 0.001$). The chart of disease-free survival is shown in Figure 1.

The three-year overall survival in the study group was 95.5%, in the control group — 80.0% ($p < 0.001$). The chart of overall survival is shown in Figure 2.

An additional parameter evaluated was the 3-year survival rate without stoma, which was 83.2% in the study group versus 67.5% in the control group ($p = 0.029$). The chart of survival without a stoma is shown in Figure 3.

## DISCUSSION

This study demonstrates a significant increase in the effectiveness of the treatment of the anal squamous cell carcinoma (ASCC) with the addition of paclitaxel to the standard CRT regimen.

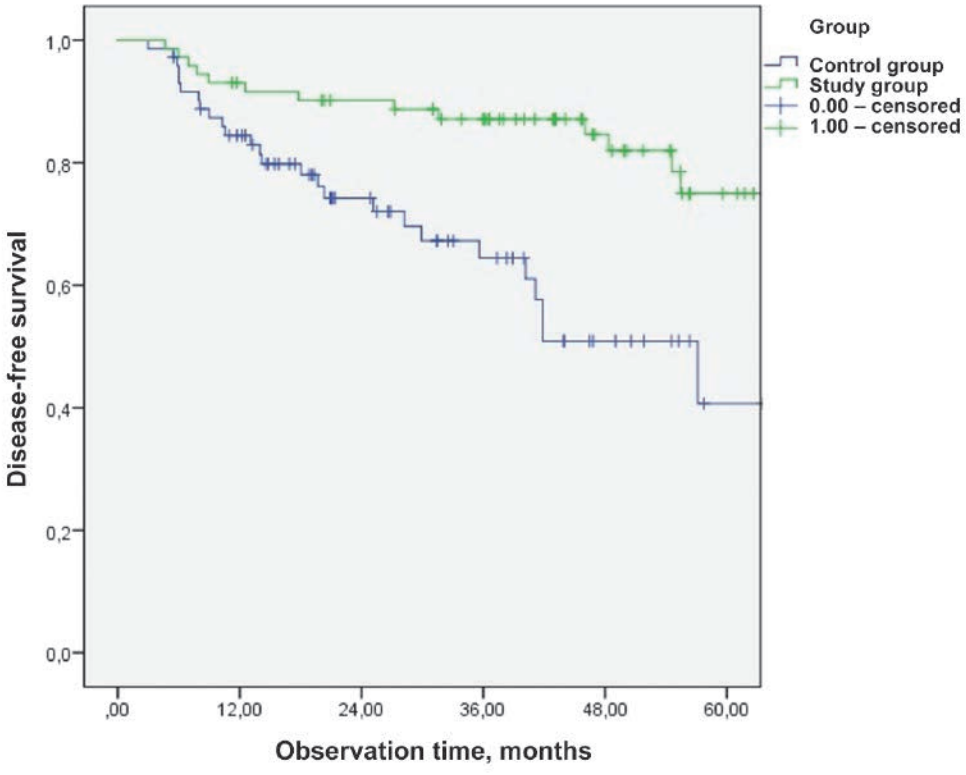


**Figure 1.** *Disease-free survival chart*

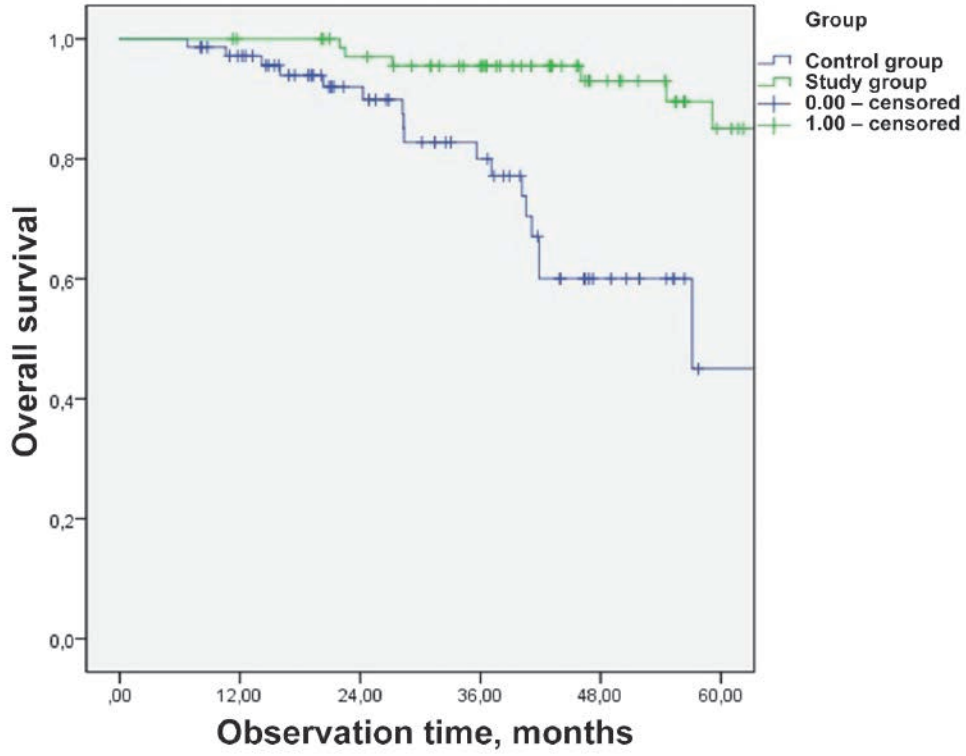


**Figure 2.** *Overall survival chart*

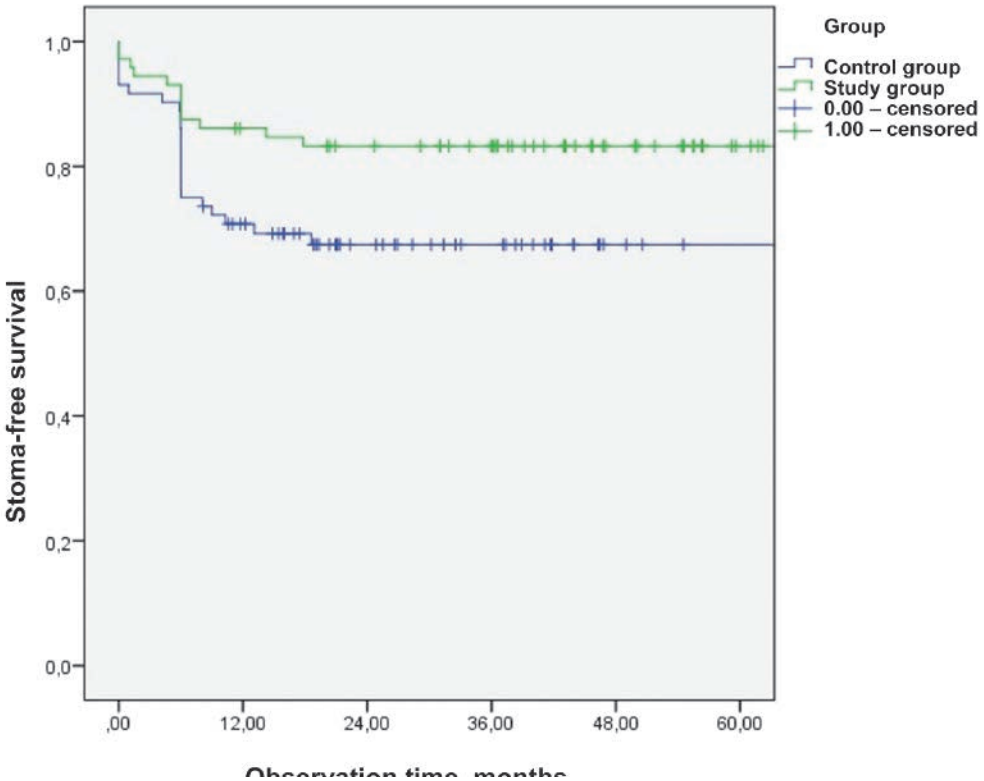


**Figure 3.** *Colostomy-free survival chart*

CRT using fluorouracil and mitomycin has been the standard of treatment for most patients with ASCC for several decades. However, the incidence of disease progression or the formation of a permanent stoma still reaches 30% or higher [15]. We planned to strengthen the standard CRT, despite the likelihood of increased toxicity due to the addition of a third agent.

In order to reduce the toxicity of the treatment, IMRT technology was used with a proven safety advantage [16] over other types of RT.

In this study, the incidence of grade 3–4 toxicity was significantly higher in the study group, but comparable with the data from other studies (56.9% vs. 26.4%, $p < 0.0001$). In the study of RTOG 98–11 [3], the rate of only hematological toxicity of the 3–4 grade was 61.8% when using the CRT scheme with fluorouracil and mitomycin C. In the ACT II study [2], the proportion of patients with grade 3–4 adverse events in the mitomycin and fluorouracil group was 71%.

Probably, the higher toxicity rates in this study are associated with the use of a radiation therapy protocol involving two-phase radiation using conformal and nonconformal radiation therapy.

Existing scientific data [17, 18] demonstrate a significant decrease in locoregional control in patients with a longer break in radiation therapy. Therefore, in our practice, we sought to reduce the duration of the break in treatment due to accompanying therapy. Our results show that, despite the toxicity, about 90% of patients in both groups were able to complete the CRT protocol without significant interruptions in treatment.

In the ACT II study [2], 3-year DFS in the mitomycin and fluorouracil group was 74%. In our study, this indicator was lower in the same group (control group) (64.4%). Perhaps this result is due to the fact that in our study, initially 78% of patients had a locally advanced process, while in the ACT II study only 32% of patients had N + (for patients with regional lymph node lesions in ACT II, 3-year DFS was 68%). The more significant the indicator of the three-year DFS looks for the group with the addition of paclitaxel (87.1%).

In ACT II the 3-year survival rate without a stoma (72%) was assessed, which differs slightly from our indicator in the control group (67.5%). On the chart of colostomy-free survival, the curve diverges sharply at the point of 6 months of follow-up, which is justified, given the different levels of the frequency of complete response in the groups.

Our study has several drawbacks. First of all, the study did not reach the originally planned capacity due to the disappearance of one of the key drugs. Also, our study lacks detailed data on late complications of CRT.

## CONCLUSION

In conclusion, CRT with the addition of paclitaxel in ASCC has an acceptable toxicity profile and can lead to improved treatment results.

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**AUTHORS CONTRIBUTION**

Concept and design of the study: *Sergey S. Gordeyev, Marina V. Chernykh*

Collection and processing of the material: *Sergey S. Gordeyev, Aleksandra A. Naguslaeva, Marina V. Chernykh, Valeriy A. Ivanov*

Statistical processing: *Sergey S. Gordeyev, Aleksandra A. Naguslaeva, Valeriy A. Ivanov*

Writing of the text: *Aleksandra A. Naguslaeva, Albina A. Zagidullina, Alen Seydinovich*

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