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*ORIGINAL ARTICLE*

# Cisplatin monotherapy with concurrent radiotherapy versus combination of cisplatin and 5-fluorouracil chemotherapy with concurrent radiotherapy in patients with locoregionally advanced cervical carcinoma

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## Summary

***Purpose:*** *To compare the efficacy, toxicity and survival of cisplatin monotherapy with concurrent radiotherapy versus combination of cisplatin and 5-fluorouracil (5-FU) with concurrent external beam radiotherapy (EBRT) in patients with locoregionally advanced cervical carcinoma FIGO stages IIB-IV.*

***Methods:*** *134 patients with locoregionally advanced, histologically confirmed carcinoma of the uterine cervix were analysed. The first group of patients (n=70; 52.24%) started concomitant chemotherapy on the second day of radiotherapy with single-agent cisplatin 40 mg/m$^2$ given 2 h before radiotherapy, once a week for 6 courses. The second group of patients (n=64; 47.76%) started concomitant chemotherapy on the second day of radiotherapy with cisplatin 75 mg/m$^2$. Treatment was continued with 96-h infusion of 5-FU 4 g/m$^2$ (1 g/m$^2$ per day for 5 consecutive days). The patients were irradiated by EBRT followed by intracavitary brachytherapy (ICB).*

***Results:*** *24- and 42-month survival in the first group were 71.9 and 57.81% and 52.5 and 35.4% in the second group, respectively (p=0.012). Mean time to progression in the first group was 24 months and in second group it was 15.9 months (p=0.012). After 2 years progression was noted in 38.3% of the first and in 62.9% of second group patients (p=0.003). After 40 months 60 patients were without relapse, 35 (57.81%) patients in the first group and 25 (37.14%) patients in the second group (p=0.018).*

***Conclusion:*** *Treatment with combined cisplatin and 5-FU with concurrent EBRT was more efficient in comparison to cisplatin monotherapy with concurrent radiotherapy in patients with locoregionally advanced cervical carcinoma, in terms of 12- and 24-month overall survival and disease relapse after 2 years.*

**Key words:** advanced cervical carcinoma, chemoradiotherapy, cisplatin based chemotherapy, 5-fluorouracil, radiotherapy, survival

## Introduction

Carcinoma of the uterine cervix is the second most common cancer in females worldwide and is the cause of death for 275,000 women every year. In Serbia 1,380 women are diagnosed with this type of cancer and 720 die of it every year [1]. In countries with the organized screening for early detection of cervical cancer it is a generally curable disease. Locoregional failure, however, still occurs frequently and represents a therapeutic problem. Therapy of relapsing and metastatic disease includes palliative chemotherapy and radiotherapy. A previous Gynecologic Oncology Group's (GOG) prospective randomized phase III study [2] demonstrated improvement in outcome concerning the treatment of locoregionally advanced disease after concurrent cisplatin-based chemoradiotherapy, while other chemotherapeutic single agents which were added to the radiotherapy yielded poorer results. The role of additional concurrent chemotherapy was to potentiate the effects of

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radiotherapy. However, the objective response of concurrent administration of single-agent cisplatin with radiotherapy barely reaches 20-30%, with an average response duration of 4-6 months. Many studies also point to a better effect of giving 3-weekly cisplatin in combination with radiotherapy, with a somewhat poorer quality of life (QoL) due to the increased toxicity which depends on the agents added to cisplatin [3-10]. The results of the most recent prospective phase III studies point to a similar disease control through the addition of another chemotherapeutic agent. In patients with locally advanced, metastatic or recurrent cervical carcinoma attention should be paid to increased toxicity, both acute and late [11-13]. The RTOG-90-01 study [14] comprehensively analysed pre-treatment factors which influenced the selection of patients who would have had most benefit from the combined chemotherapeutic regimen. 5-FU was added to cisplatin with objective response similar to other combined regimens and with acceptable toxicity. The combination of cisplatin and 5-FU with concurrent radiotherapy has already been validated through various studies and with various tumor sites with squamous cell carcinomas. The obtained results in the RTOG 90-01 study demonstrated that there was a substantial benefit for patients treated with radiotherapy in combination with cisplatin and 5-FU, resulting in 51% reduction of relapse risk and 52% reduction of death risk. The stratification of subgroups of patients who would have achieved better disease control with the combined chemotherapy regimen could be predicted through analysis of predictive and prognostic factors. Also, adequate QoL for these patients should be preserved because chronic and acute complications may occur [5].

## Methods

In this study we analysed adult female patients with locoregionally advanced cervical carcinoma classified as FIGO stage IIB to IVA, and having histologically confirmed squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma. Patients were treated at our institution from 2006 to 2008. Patients underwent standard preparation for tumor board meeting. The study included women with tumors larger than 4 cm in their maximal diameter verified by clinical examination and confirmed by CT examination. All patients signed informed consent, and were stratified into groups by the order of appearance before the tumor board.

*Inclusion/exclusion criteria*

Included were all patients with locoregionally advanced cervical carcinoma, in good general condition with ECOG PS 0-2.

Excluded from study were all patients whose biochemical and hematological values did not meet the ESMO guidelines for chemotherapy administration [15]. Other exclusion criteria were serious comorbidities (e.g. heart failure, carcinoma of other localization, bilateral hydronephrosis and/or unilateral hydronephrosis requiring percutaneous nephrostomy).

*Treatment*

Chemotherapy started on the 2nd day of EBRT with one group of patients receiving cisplatin 75 mg/m$^2$ with antiemetics and adequate hydration; treatment continued with 96-h infusion of 5-FU 4 g/m$^2$(1 g/m$^2$ over 24 h); radiotherapy was not interrupted during the days of chemotherapy administration. Chemotherapy was repeated on the 21st and 42nd day of radiotherapy for a total of 3 courses.

The second group of patients also started chemotherapy on the 2nd day of EBRT, but this time with single-agent cisplatin 40 mg/m$^2$ given for 2 h before radiotherapy, once a week for 6 courses.

The patients were irradiated by EBRT 5 days a week, followed by ICB, and the period between EBRT and ICB did not exceed 2 weeks. EBRT tumor dose (TD) was 50.4-54 Gy with standard fractionation (1.8-2 Gy daily fractions). The dose was delivered by the isocentric technique to 45 Gy with two opposite fields (anteroposterior - AP and posteroanterior - PA), with continuation to the full planned dose through lateral fields. EBRT of the pelvic fields was performed by photons from linear accelerator with 10 MV energy for AP/PA fields and 18 MV for lateral fields. In case of positive paraaortic nodes, photons with 6 MV energy were used, where the upper limit of the field was the upper edge of L1; in case of negative paraaortic lymph nodes the upper edge of the field was the lower limit of the junction L4-L5.

ICB was performed using the "remote afterloading" technique with using Ir-192 with activity from 0.5-1 Gy with high-dose-rate (HDR) irradiation regimen. The Manchester system was applied for the calculation of the dose. ICB TD at the point A ranged from 30-34 Gy in 5 fractions, with the addition of 5.4-9 Gy, depending on the level of parametrium or rectum/urinary bladder infiltration [16].

Laboratory analyses were carried out at the beginning of treatment and every week during treatment, while toxicities were graded according to CTCAE criteria (Common Terminology Criteria for Adverse Events, version 3.0) [17]. Gastrointestinal side effects included nausea, vomiting and diarrhea. Biochemical parameters were monitored - bilirubin, ALT-AST, serum urea and creatinine. The levels of hemoglobin (Hb) were monitored both before the start of treatment and during treatment and blood transfusions were carried out in patients with Hb<10 g/l. Total leukocyte and neutrophil counts were also monitored, along with thrombocyte counts.

Toxicities observed within 30 days from the end of treatment were treated as acute and the ones which occurred later as chronic (vesicovaginal fistulas, fibrosis of the urinary bladder, fibrosis of the ureter, vaginal stenosis). Patients with grade 4 neutropenia were administered granulocyte colony stimulating factor and with grade 4 thrombocytopenia they were transfused with concentrated thrombocytes; lower grades resulted in treatment postponement.

Response to therapy was defined by RECIST 1.0 criteria (Response Evaluation Criteria in Solid Tumors), based on the comparison of CT findings before and 30 days after the end of therapy [18]. Follow-up was performed every 2 months during the first year from treatment termination, then every 3 months during the second year, and every 6-8 months thereafter.

*Statistical analysis*

Overall survival was the primary end-point for comparison of the efficacy of these two treatments and was calculated from the day of the initiation of the study until the day of death or the day of the last visit. Death caused by other diseases resulted in exclusion from the

statistical analysis. Time to progression was registered from the end of treatment until the occurrence of the first signs of disease progression (diagnosed by CT and clinical examination). Depending on their nature for the description of relevant parameters, descriptive statistics were used: frequencies, percents, mean values, median values, standard deviation (SD) and ranges. Depending on their nature, testing of the differences between parameters was performed using asymptotic Wilcoxon's rank sum test, Pearson's $x^2$ test and Fisher's exact test. Kaplan-Meier product-limit method was used for constructing curves of overall survival, time to disease progression, probability of locoregional and probability of distant metastasis, and for their description we used medians of survival analysis and corresponding 95% confidence intervals (95% CI). Log-rank test was used for testing differences in overall survival, time to disease progression, probability of occurrence of locoregional recurrence and probability of development of distant metastasis in relation to relevant parameters [2].

## Results

The study included 134 patients treated at our institution between 2006 and 2008. Seventy of them were treated with weekly single-agent cisplatin along with radiation treatment, and the remaining 64 patients received the combination 3-weekly chemotherapy with radiotherapy. The mean patient age in the single-agent cisplatin group was 54 years (range 31-75) and in the combined chemotherapy group it was 51 years (range 29-65). Of the 70 patients from the single-agent cisplatin group 50 (71.43%) received 6 courses, 15 (21.43%) 5 courses and 5 (7.14%) 4 courses. In the combined chemotherapy plus radiotherapy group 57 patients (89.06%) received 3 courses and only 7 patients (10.94%) received 2 courses of chemotherapy. Both groups completed their treatments within 55-65 days and all of the patients received the planned dose of EBRT and ICB. Table 1 shows the characteristics of the two patient groups. Their age, ECOG PS and the spread to the paraaortic nodes did not differ between groups. Prognostic factors assessed before starting treatment were suboptimal in the combined chemotherapy group (tumor size p=0.06, clinical stage p=0.01, histological type p=0.04). With the exception of thrombocytopenia in the combined chemotherapy group (p<0.01), no significant differences in acute hematological toxicities were noticed between the two groups (Table 2). Late complications (occurring 30 days after the end of treatment), included vesicovaginal fistulas in 8 patients in the first group and in 10 patients in the second group; rectovaginal fistulas in 5 patients in the first group and 6 patients in the second group. In one patient in the first group fibrosis of urinary bladder was registered and in another patient from the same group fibrosis of the ureter was noted. Vaginal stenosis was recorded in 15 patients from the first group and 18 patients from the second group (Table 3).

**Table 1.** Patient characteristics. Group I: patients with single-agent cisplatin; group II: patients with combination chemotherapy

| *Characteristics* | *Group I N (%)* | *Group II N (%)* | *p-value* |
|---|---|---|---|
| Age, years | | | 0. 239 |
| Median | 54 | 51 | |
| Range | 31-75 | 29-65 | |
| ECOG PS | | | 0. 458 |
| 0 | 41 (58.57) | 38 (59.38) | |
| 1 | 25 (35.71) | 19 (29.78) | |
| 2 | 4 (5.7) | 7 (10.94) | |
| FIGO stage | | | 0. 019 |
| IIB | 45 (64.29) | 32 (50) | |
| IIIA | 11 (15.71) | 9 (14.06) | |
| IIIB | 14 (20) | 16 (25) | |
| IVA | 0 | 7 (10.94) | |
| Tumor size (cm) | | | 0. 273 |
| >5 | 54 (77.14) | 40 (62.5) | |
| <5 | 16 (22.86) | 24 (37.5) | |
| Histological type | | | 0. 049 |
| Squamous cell | 70 (52.24) | 60 (44.78) | |
| Adenocarcinoma | 0 | 4 (2.98) | |
| Paraaortic lymph nodes | | | 0. 018 |
| Positive | 13 (18.58) | 19 (29.69) | |
| Negative | 57 (81.42) | 44 (68.75) | |

**Table 2.** Acute hematological, gastrointestinal and urinary tract toxicities graded by CTCAE. Group I: patients with single-agent cisplatin; group II: patients with combination chemotherapy

| *Toxicity grades* | *Group I N* | *Group II N* | *p-value* |
|---|---|---|---|
| Hemoglobin | | | NS |
| 1 | 0 | 0 | |
| 2 | 10 | 14 | |
| Leukopenia | | | NS |
| 1 | 10 | 6 | |
| 2 | 6 | 10 | |
| 3 | 1 | 5 | |
| 4 | 2 | 1 | |
| Thrombocytopenia | | | < 0.001 |
| 1 | 0 | | |
| 2 | 0 | | |
| 3 | 0 | | |
| 4 | 0 | 1 | |
| Nausea | | | 0.02 |
| 1 | 1 | 1 | |
| 2 | 11 | 2 | |
| Diarrhea | | | NS |
| 1 | 5 | 4 | |
| 2 | 11 | 9 | |
| 3 | 2 | 6 | |
| Cystitis | | | NS |
| 1 | 0 | 3 | |

NS: non significant

**Table 3.** Late complications in both therapeutic groups. Group I: patients with single-agent cisplatin; group II: patients with combination chemotherapy

| *Complications* | *Group I N (%)* | *Group II N (%)* |
|---|---|---|
| Without late complications | 55 (78) | 48 (75) |
| With late complications | 15 (22) | 16 (25) |
| Vesicovaginal fistulas | 8 | 10 |
| Rectovaginal fistulas | 5 | 6 |
| Fibrosis of urinary bladder | 1 | 0 |
| Fibrosis of the ureter | 1 | 0 |

No statistically significant difference in the occurrence of late complications between the therapeutic groups was observed ($x^2$, p=0.624)

*Treatment outcome*

Two-year overall survival for the single-agent cisplatin group was 52.5% and for the combined chemotherapy group it was 71.9% (p=0.012). After 3.5 years the overall survival was 35.4% (33 patients) in the single-agent cisplatin group and 57.81% (45 patients) in the combined chemotherapy group (p=0.004; Figure 1). The mean time to progression in the single-agent cisplatin group was 15.9 months and in the combined chemotherapy group it was 24 months (p=0.018). After 2 years progression was noted in 62.9% of patients in the single-agent cisplatin group and in 38.3% in the combined chemotherapy group (p=0.003). After 40 months, 25 patients (37.14%) in the single-agent cisplatin group and 35 patients (57.81%) in the combined chemotherapy group were without relapse with better disease control in the combination group (p=0.008). The difference in the local disease control between the two groups was maintained after 3.5 years. Thirty-five patients (26.11%) developed metastases to the paraaortic lymph nodes after 3 years of follow-up in both patient groups. Locoregional recurrence occurred in 28 (43.75%) patients in the single-agent cisplatin group, with metastasis to the paraaortic lymph nodes in 23 patients and distant metastasis in 3 patients (2 lung, 1 liver). In the combined chemotherapy group locoregional recurrence occurred in 12 (71.4%) patients with metastases to the paraaortic lymph nodes, while 5 patients developed distant metastasis (3 liver, 2 lung; p=0.019), favoring the combination chemotherapy group) (Figure 2), while no difference in the development of distant metastasis was confirmed (p=0.121).

## Discussion

Till the last decade of the last century radiotherapy was the only therapeutic option for patients with locally advanced cervical cancer [19]. Because relapse occurs in 20-50% of patients with stage IIB and 50-75% with stage III, there are several options in choosing additional treatments [18]. Some of them include the introduction of radioprotectors (nitroimidazole), cytoprotectors (amifostine), and hyperbaric oxygenation [20-23]. A great number of clinical trials incorporated certain chemotherapeutic drugs to radiotherapy with the aim of enhancing its effects. Cisplatin-based chemotherapy with concurrent pelvic radiation therapy took central place in the therapy of locoregionally advanced uterine carcinoma [24]. The synergistic effect and absence of cross-resistance of 5-FU and cisplatin have been investigated for a long time [3-8]. In the study of Gynecologic Oncology Group, Rose et al. compared patients who underwent radiotherapy with the addition of cisplatin (group 1) with those receiving cisplatin, 5-

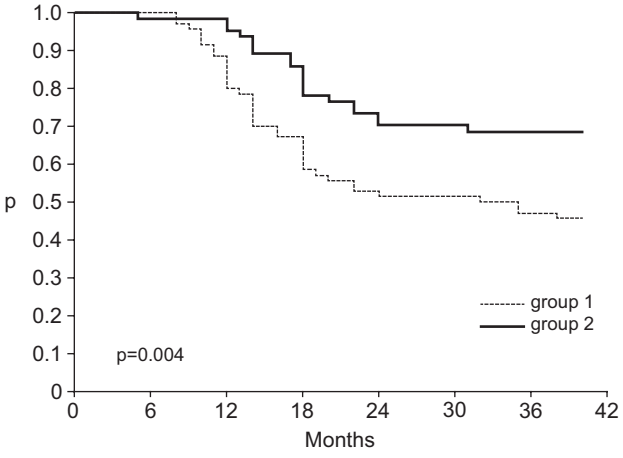


**Figure 1.** Kaplan-Meier estimates of overall survival at 3.5 years.

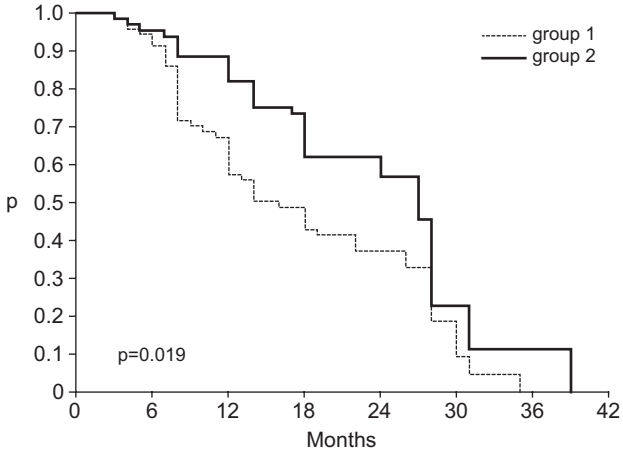


**Figure 2.** Kaplan-Meier estimates of progression free survival after 3.5 years.

FU and hydroxyurea (group 2), while group 3 patients were administered hydroxyurea only. The study included 526 patients with stage IIB-IVA cervical carcinoma. In both groups with cisplatin there was a higher rate of 5-year survival (60 and 58% respectively), in contrast to only 34% in the group with hydroxyurea. The difference in survival was maintained after 10 years (53, 53 and 34%, respectively; $p<0.001$). Similar results were obtained for the group of patients with stage IIB and III ($p<0.025$ [4]. The RTOG 9001 study, where EFRT (extended-field irradiation) was given with concomitant cisplatin 75 mg/m$^2$ on the 2nd day of radiotherapy with treatment continued with 96-h continuous infusion of 5-FU 4 g/m$^2$ (1 g/m$^2$ over 24h), administered in the same manner as in our study, indicated that the subgroups of patients with FIGO III and IVA stages had a better disease control and a trend for better overall survival after 6.6 years of follow-up [5]. In our study, a group of patients with highly unfavorable pretreatment prognostic factors was closely monitored, especially the group of patients with the 3-weekly regimen. The survival rate in 3.5 years was comparable to the results of the studies mentioned above.

The randomized phase III RTOG 0116 study has shown that combination of cisplatin chemotherapy with extended field and intracavitary irradiation for paraaortic or high common iliac nodal metastasis from cervical cancer is associated with significant acute and late toxicity [25]. In our study the number of grade 3 and 4 acute complications was lower, which could be attributed to the psychosocial status and family support during treatment, as suggested by Mylin et al. [26]. The rate of high-grade complications (21 patients; 15.67%) observed in our study may be a result of the outdated irradiation techniques. EBRT was planned on a simulator instead of CT planning which is almost universally used today. In recently published articles intensity-modulated radiotherapy (IMRT) significantly reduced the number and severity of complications of the bladder and rectum [27]. Also, an important factor may be the ICB technique, since the technique used in our study delivered high doses to the bladder and rectum. Modern ICB techniques with MRI planning can reduce the total dose given to the surrounding organs during the ICB [28]. In their study Monk et al. compared 4 groups of patients with recurrent and metastatic cervical carcinoma where cisplatin was administered in combination with either gemcitabine or paclitaxel, vinorelbine and topotecan. The authors were not able to see significant differences in overall survival and time to progression [2]. The large number of metastases to the paraaortic lymph nodes after 3 years of follow-up in both patient groups of our study (n=35; 26.11%) points to the possibility of understaging at the beginning of the study, since the assessment of parametrial invasion and the invasion of paraaortic lymph nodes was performed only by CT which has lower specificity and sensitivity than MRI and PET-CT. So the assessment of the invasion of paraaortic lymph nodes in the future should be assessed by MRI [29]. There is an option of using prophylactic EFRT to the paraaortic lymph nodes for all stages higher than IIB [14]. The latest results of a large phase III randomized study of cisplatin with gemcitabine showed that combined cisplatin/gemcitabine chemotherapy followed by brachytherapy improved survival outcomes in locally advanced cervical carcinoma when compared with single-agent cisplatin chemoradiotherapy [30].

Based on the presented results, we conclude that there is a need for individualization in the selection of patients with locally advanced carcinoma of the uterine cervix for either radiotherapy with combination of cisplatin with other chemotherapeutic agents, or with cisplatin alone. Patients without comorbidities and in good general condition, with squamous cell histology can tolerate combined chemotherapeutic regimens with radiotherapy. Cisplatin plus 5-FU represent a good combination for the group of patients having poor pretreatment prognostic factors (larger tumor diameter, higher disease stage, higher tumor grade) with tolerable acute and late complications and better time to disease progression and overall survival.

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