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The Result of Cisplatin-Based Neoadjuvant Chemotherapy in Patients Diagnosed With Non-squamous Cell Carcinoma of the Cervix in Stage IB2 to IIB: A Retrospective Cohort Study

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Abstract

Objectives: Neoadjuvant chemotherapy is one of the most important and prevalent therapeutic strategies to reduce complications and mortality in patients with cervical carcinoma. Due to the higher pathologic prevalence of squamous cell carcinoma (SCC) than non-SCC of the cervix, effective therapeutic strategies have been mostly proposed in relation to the pathology of cervical SCC and, therefore, there is insufficient evidence suggesting treatment recommendations on the pathology of non-SCC of the cervix. Thus, this study aimed to investigate the outcome of cisplatin-based neoadjuvant chemotherapy with Taxol in patients diagnosed with non-SCC of the cervix in stage IB2-IIB.

Materials and Methods: This study was a retrospective cohort study conducted on patients with non-SCC of the cervix. Patients treated with cisplatin-based neoadjuvant chemotherapy + paclitaxel were evaluated for the results and outcomes of neoadjuvant chemotherapy based on the inclusion criteria. Data were statistically analyzed using SPSS software as well as performing Kaplan-Meier procedure and the log-rank test.

Results: The mean age of the studied cases was 44.9. Tumor size after neoadjuvant chemotherapy was less than 4 cm in six cases. Tumor spread to the inner and outer half of the stroma was observed in most cases. Tumor spread to the lymph node section was observed in seven cases. Three cases showed parametric involvement, and eight cases showed pelvic lymph node involvement. Complete response to treatment was recorded in two cases (16.7%), partial response was found in six cases (50%), and stable disease was seen in one case (21.7%). The average time of disease-free survival and progression-free survival in patients was 77 months, which demonstrated no significant difference ($P=0.30$).

Conclusions: Neoadjuvant chemotherapy in cases of non-SCC of the cervix as well as SCC of the cervix produced a strong anti-tumor and inhibitory effect in our study.

Keywords: Chemotherapy, Neoadjuvant, Cisplatin, Taxol, Cervical carcinoma, IB2-IIB

Introduction

Carcinoma of the cervix is one of the most prevalent cancers in females and a major cause of mortality worldwide (1-3). This disease is the most widespread malignancy among the Iranian female reproductive system (4). From among all malignant tumors, cervical cancer is one of the cases that could be effectively controlled by screening (5). According to the International Federation of Obstetrics and Gynecology (FIGO), more than 38% of tumors are diagnosed in stage IB2-IIB (6).

The disease is mostly treated by radiotherapy, radium, and external X-rays in most treatment centers. A combination of drug therapy, which is based on Platinum, is the first therapy phase in progressive carcinoma of the cervix (4,7). The molecular pathogenesis of non-squamous cell carcinoma of the cervix (non-SCC) is different from SCC. As a result, the treatment of non-SCC requires developing a distinct treatment approach (8).

There are three methods of treatment for IB2 and IIA2 cervical cancer, namely concurrent chemotherapy, neoadjuvant chemotherapy before radical hysterectomy and lymphadenectomy with or without radiotherapy after surgery, and radical and lymphatic hysterectomy with radiation therapy or chemotherapy (6). Neoadjuvant chemotherapy in cases of cervical tumors have been found to reduce the need for vascular lymphatic invasion, deep stromal invasion, lymph node metastasis, and adjuvant radiotherapy (9). The most common treatment in early and advanced stages of cervical cancer is surgery and removal of tumor tissue (10). Although adoption of the therapeutic approach for dealing with phase IB2-IIB – phase IIB, in particular – is arguable, the chemotherapy combined with cisplatin and external pelvic radiation and brachytherapy after that is one of the common strategies

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Key Messages

- Neoadjuvant drugs had good anti-tumor effects
- After surgery, neoadjuvant treatment could have anti-tumor properties.
- After surgery, neoadjuvant treatment could improve surgical and therapeutic efficiency.

to deal with it (11). Although most patients respond to this treatment initially, the disease recurs in 22% to 41% of cases (12). Neoadjuvant chemotherapy followed by radical operation is the most widely studied therapeutic method, and has received the most attention due to its remarkable ability to improve the disease and decrease the toxicity (13).

Due to the high prevalence of squamous cell cancer compared to non-squamous cell cancer of the cervix as well as the lack of conclusive evidence suggesting therapeutic recommendations on pathological cases of non-SCC of the cervix, the present study aimed to examine the positive effects of the new cisplatin-based chemotherapy with Taxol on cases with non-squamous cervical cancer in stage IB2 to IIB.

Materials and Methods

In this retrospective cohort study, the patients with non-squamous cell cancer of the cervix in stages IB2 to IIB were included based on the inclusion criteria. These patients had referred to Imam Khomeini Medical Center in Tehran from April 2011 to April 2020 and undergone cisplatin-based neoadjuvant chemotherapy + paclitaxel.

Inclusion and Exclusion Criteria

Inclusion criteria: histologically confirmed non-SCC of the cervix, progressed local disease, stage IB2-IIB, 20 to 74 years of age, no previous treatment, existence of a large assessable mass according to the cervix in magnetic resonance imaging (MRI).

Exclusion criteria: (serious) complication, heart disease, uncontrolled diabetes mellitus, uncontrolled hypertension, several active tumors, interstitial pneumonia or pulmonary fibrosis, pulmonary effusion, history of unstable angina or Myocardial infarction within the last six months, or concomitant severe cardiac arrhythmia needing treatment, contraindications for treatment with cisplatin and Taxol, intestinal or ileal paralysis, pregnancy, lactation or subsequent pregnancy, history of severe drug allergies.

Hematological Analysis

Regarding hematological and biochemical parameters, WBC census ≥4000/mm^3, neutrophil census ≥2000/mm^3, platelet census ≥100 000/mm3, hemoglobin ≥10.0 g/dL, AST and ALT levels less than or equal to twice above the standard range of references, total serum bilirubin level less than 1.5 mg/dL, serum creatinine less than 1.5 mg/dL, and creatinine clearance 60 mL/min were evaluated.

Method Description

In Imam Khomeini Hospital, the patients diagnosed with cervical cancer with bulk mass (larger and equal to 4 cm), in stage IB2 to IIB according to the treatment protocol, were routinely treated with cisplatin-based neoadjuvant chemotherapy with a dosage of 60 mg/m^2 and paclitaxel with a dosage of 80 mg/m^2, every ten days in three courses of treatment; then all patients underwent surgery and radical hysterectomy (unless the disease was progressive according to clinical examination, in which case they underwent concomitant chemoradiotherapy), followed by radiotherapy sessions alone or combined with chemotherapy and chemoradiation if necessary (lymphadenopathy, incursion of the cardinal ligament or overt vascular incursion were performed based on the margin of positive surgery in the vagina). Granulocyte colony stimulating factor (G-CSF) was prepared and injected into patients with grade four neutropenia within the first NAC period. G-CSF prophylaxis was allowed in these patients, in the midst of the second and consequent NAC sessions. Antiemetics were used to prevent the symptoms of nausea. Hematology and urine tests were usually performed before each chemotherapy session.

Data Analysis

Frequency, percentage, and mean were used for the description of the data. The simultaneous effect of variables was investigated through logistic regression. All analyzes were performed by SPSS software version 22, and the statistical analysis was completed utilizing the Kaplan-Meier procedure and the log-rank test. The significant level was set at 0.5.

Results

A total of 12 patients with an average age of 44.9 years were investigated. The average weight was 83 ± 12 kg. Out of 12 patients, two cases were in phase IIA, six cases were in phase IIB, and four cases were IB2. Undifferentiated adenocarcinoma was the most common cancer cell line (Table 1).

The treatments are listed in Table 2. In 11 cases of patients, 3 neo-adjuvant courses were used and in 1 case, 4 neo-adjuvant courses were used . As for the surgery, three cases failed to have surgery due to the progression of the disease in clinical staging, eight cases had complete surgery, and one case had incomplete surgery. Most of the treatments were administered by chemoradiotherapy.

Examining the pathological results of the postoperative tumor showed that the tumor size in six patients was less than 4 cm. Tumor spread to the inner and outer half of the stroma was seen in most cases. Tumor spread to the lymph node section was observed in seven cases. Findings on tumor spread are shown in Table 3.

As for the treatment, no surgery was recorded for three

Table 1. Frequency Distribution of Demographic Characteristics and Clinical Stage of the Tumor

Characteristics	
Age, Mean ± SD	44.9±22
Weight (g), Mean ± SD	83 ± 12
Glucose (mg/dL), Mean ± SD	98 ± 27
AST (IU/L), Mean ± SD	22.9±4.83
ALT (IU/L), Mean ± SD	14.53±5.07
Stage of the disease, No. (%)	
IIB	6 (50.0)
IB2	4 (33.3)
IIA	2 (16.7)
Cell line, No. (%)	
Poorly diff adenocarcinoma	5 (41.7)
Adenocarcinoma	4 (33.3)
Clear cell carcinoma	1 (8.3)
Adenosquamous carcinoma	1 (8.3)
Undifferentiated adenocarcinoma	1 (8.3)
Total, No. (%)	12 (100.0)

Table 2. Results Related to the Administered Treatments

Treatments	Frequency	Percent
Number of neo-adjuvants		
3	11	91.7%
4	1	8.3%
Surgery		
Yes	9	75.0%
No	3	25%
Complementary treatment		
Radiotherapy	1	8.3%
Chemotherapy	2	16.7%
Chemoradiotherapy	8	66.7%
Unknown	1	8.3%

cases (25.0%), complete response was observed in two cases (16.7%), partial response was found in six cases (50.0%), and stable disease was seen in one case (21.7%) (Table 4).

The frequency of metastasis after neoadjuvant chemotherapy in stage IB2 to IIB suggested that three cases had parametric involvement and seven cases had pelvic lymph node involvement; no pelvic wall involvement and metastasis were observed (Table 5).

The Kaplan-Meier curves were presented based on survival probability scores (Figure 1). Analyzing the survival data showed that the median DFS (disease-free survival) and PFS (progression-free survival) were the same. The median DFS and PFS in non-operated patients were 58 months, whereas those in operated patients were 82 months. The total mean of operated and non-operated DFS and PFS was 77 months, which demonstrated no significant difference ($P=0.30$).

Table 3. Findings on the Status and Spread of the Tumor

Tumor Status	Frequency	Percent
Tumor size		
No residual	2	22.2
<4 cm	6	66.7
>4 cm	1	11.1
Tumor spread to the stroma		
No surgery	3	25.0
Negative	2	16.7
Inner half	4	33.3
Outer half	3	25.0
Tumor spread to the lymph node		
Negative	2	22.2
Positive	7	77.8
No surgery	3	25.0
Tumor spread to the uterus		
No	5	41.7
Yes	4	33.3
Tumor spread to the ovary		
No Surgery	3	25.0
Not involves	9	75.0
Tumor spread to the vaginal area		
No surgery	3	25.0
Not involves	9	75.0
Tumor spread to the Pelvic lymph nodes		
No surgery	3	25.0
Not Involves	9	75.0
Tumor spread to the paraaortic lymph nodes		
Negative	8	66.7
Single metastasis	1	8.3
No surgery	3	25.0

Discussion

The pathology of SCC is more prevalent than non-SCC, which has led to an accelerated development of effective treatment strategies in relation to cervical SCC pathology. Due to the lack of conclusive evidence concerning non-SCC pathology cases, it is important to discover reliable evidence on non-SCC cases. In the current study, the postoperative tumor diameter was found to be less than 4 cm in six patients. The overall survival of patients after neoadjuvant chemotherapy was 49 months. Examination of the data from the Kaplan-Meier chart showed that the total of DFS and PFS means were equal. The median DFS and PFS in non-operated patients were 58 months, but those in operated patients were 82 months. The total mean of operated and non-operated DFS and PFS was 77 months, which demonstrated no statistically significant difference between the operated and non-operated groups. In a similar study in 2013, Shoji et al evaluated neoadjuvant drug therapy using platinum-based and taxane-based diets for dealing with phase IB2 to IIB of cervical non-squamous cell cancer. According

Table 4. Percentage and Frequency of Treatment Responses

Parameter	Frequency	Percent
Response rate to the treatment		
No surgery	3	25.0
Complete response	2	16.7
Partial response	6	50.0
Stable disease	1	8.3

Table 5. Frequency of Metastasis After Neoadjuvant Chemotherapy

N=12		Frequency	Percent
Parametric involvement	Negative	9	75.0
	Positive	3	25.0
Lymph node involvement	Negative	5	41.7
	Positive	7	58.3
Location of lymph node involvement	None	4	33.3
	Pelvic	8	66.7
	Paraaortic	0	0.0
Pelvic wall involvement	Negative	12	100.0
	Positive	0	0.0
Metastasis	Negative	12	100.0
	Positive	0	0.0

to their findings, the overall survivance of patients was 35 months, and neoadjuvant chemotherapy in cases of non-squamous cervical cancer was detected to have anti-tumor effects and controllable side effects (14). According to the results from another similar study, the average rates of survivance in two years were 81.8 percent for phase IB2, 85.7% for phase IIA2, and 96.1% for phase IIB. The highest rates of grade three and four hematotoxicity were found for neutropenia, with 43 patients diagnosed with grade four, and with 11 patients diagnosed with grade three. Non-hematic toxicities were mainly graded one or two in terms of severity (15). Another relevant study investigating the cases with adenocarcinoma IB, II, or III showed that chemotherapy-related histological changes in cases with adenocarcinoma IB, II, or III only provided mild efficacies. In the 24 courses of treatment performed, no grade three or four toxicity was seen and no treatment-related mortality was observed. The mean follow-up period was 30 months. The average survival time was 34.7 months, and the rate of 5-year survival was 21.2% (16).

Numerous studies conducted in different parts of the world have reported positive results about the platinum and Taxol based treatments in cervical cancers (17-19). In a study in 2019, however, contradictory results were observed. In this study, a women using taxane/platinum chemotherapy was compared with another women using other diets, and it was found that using taxane/platinum diets did not significantly contribute to survival (20).

In our study, tumor spread to the inner and outer half of the stroma was observed in most cases. Tumor spread to the lymph node section was seen in seven cases. Three cases showed parametric involvement and eight cases showed pelvic lymph node involvement. In addition, complete response to the treatment was observed in two cases (16.7%), limited respond was detected in six cases (50.0%), and resistant disease was seen in one case (21.7%). According to similar studies, objective response to the treatment was observed in 26 patients (87%). Two cases showed complete response, four patients had stable disease, and the rest showed partial response. The overall survivance rate for cases with IB2 to IIB cervical carcinoma in five years was 83.1, and tumor size and lymph node metastasis were associated with survival (21). In other studies, neoadjuvant chemotherapy was determined to have a strong therapeutic effect on the cervical cancer treatment (22-24).

Our findings suggest that neoadjuvant drug therapy with Taxol and carboplatin followed by radical hysterectomy might be a useful approach for treating the cases with non-squamous cell cancer of the cervix (14). Studies with larger sample sizes in different geographical areas could be useful in approving this therapeutic approach. In addition, the findings have shown that the pathology and molecular biology of the cancer are very important determiners of the treatment response rate, which should be considered when dealing with cancer. Unintelligible points such as the origin of the fallopian tube have been observed in a vast majority of ectopic tumors, which causes confusion

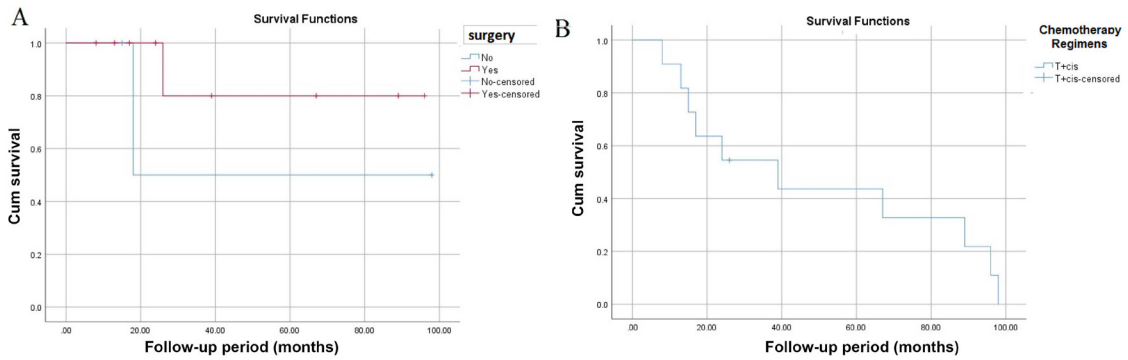

Figure 1. Kaplan-Meier Survival Chart for Cases With Non-squamous Cell Cervical Cancer. (A) Mean DFS and PFS in operated and non-operated patients; (B) General mean of DFS and PFS in patients.

in identifying the original location of the tumor and differences in tumor classification (25-27).

Several studies have explored the neoadjuvant treatment methods in Iran but more research is still required (28). Further studies in this field may increase the effectiveness of the applied knowledge of the treatment strategies and help reduce the complications and side effects in cervical carcinoma patients. A review article showed that no studies had examined the effectiveness and safety of the approaches adopted to decrease vaginal hemorrhage in female patients with progressed cervical carcinoma, which was also found important to consider (29).

Due to the higher pathologic prevalence of SCC than non-SCC of the cervix, effective therapeutic strategies have been mostly proposed to deal with the pathology of cervical SCC. The number of the cases with non-SCC cervical cancers is relatively low due to its lower prevalence in previous studies as well as in our study. Therefore, there is definitive evidence suggesting treatment recommendations for pathologic cases of non-SCC of the cervix.

This study faced some limitations. First, some medical staff refused to cooperate with our research team, which was removed after explaining the importance and different aspects of the study. Moreover, some files were incomplete in terms of some variables, which were completed after collecting the necessary information through telephone calls.

Conclusions

In sum, the patients showed positive responses to the treatment, and neoadjuvant drugs had strong anti-tumor effects. It was found crucial to provide neoadjuvant treatment after the surgery because it exhibited anti-tumor properties and improved surgical and therapeutic efficiency. It was recommended that longitudinal clinical studies should be carried out to examine the effect of treatment with various neoadjuvant medications. It was also suggested that the type of used drugs should be evaluated in terms of efficacy, and a larger population should be employed for future studies.

Authors' Contribution

Azamosadat Mousavi and Malihe Azadehrah conducted the conceptualization, data validation and methodology. Mitra Modarres-Gilani did the formal analysis and data curation. Azamosadat Mousavi, Setareh Akhavan and Shahrzad Sheikh-Hasani provided the original draft and, Malihe Azadehrah and Mahboobeh Azadehrah reviewed and edited the manuscript and carried out the supervision.

Conflict of Interests

Authors declare that they have no conflict of interests.

Ethical Issues

The study protocol has been approved by the Ethics Committee of the Tehran University of Medical Sciences, Tehran, Iran (Code: IR.TUMS.IKHC.REC.1398.298).

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References

1. Canfell K, Kim JJ, Brisson M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. Lancet. 2020;395(10224):591-603. doi:10.1016/s0140-6736(20)30157-4
2. Fitzmaurice C, Dicker D, Pain A, et al. The global burden of cancer 2013. JAMA Oncol. 2015;1(4):505-527. doi:10.1001/jamaoncol.2015.0735
3. Yousefnezhad A, Yousefi Sharami SR. Cervical carcinoma metastasizing to the orbit: a case report. International Journal of Psychosocial Rehabilitation. 2020;24:7933-7935. doi:10.37200/ijpr/v24i5/pr2020794
4. Frumovitz M, Sun CC, Schover LR, et al. Quality of life and sexual functioning in cervical cancer survivors. J Clin Oncol. 2005;23(30):7428-7436. doi:10.1200/jco.2004.00.3996
5. Papillomaviruses H. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Lyon, France: IARC; 2011.
6. Quinn MA, Benedet JL, Odicino F, et al. Carcinoma of the cervix uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95 Suppl 1:S43-103. doi:10.1016/s0020-7292(06)60030-1
7. Wood DE. National Comprehensive Cancer Network (NCCN) clinical practice guidelines for lung cancer screening. Thorac Surg Clin. 2015;25(2):185-197. doi:10.1016/j.thorsurg.2014.12.003
8. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. Lancet. 1997;350(9077):535-540. doi:10.1016/s0140-6736(97)02250-2
9. Chai Y, Wang T, Wang J, et al. Radical hysterectomy with adjuvant radiotherapy versus radical radiotherapy for FIGO stage IIB cervical cancer. BMC Cancer. 2014;14:63. doi:10.1186/1471-2407-14-63
10. Kim HS, Sardi JE, Katsumata N, et al. Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: an international collaborative meta-analysis. Eur J Surg Oncol. 2013;39(2):115-124. doi:10.1016/j.ejso.2012.09.003
11. Drokow EK, Zi L, Qian H, et al. Tolerability, efficacy and feasibility of concurrent gemcitabine and cisplatin (CGP) combined with intensity modulated radiotherapy for loco-regionally advanced carcinoma of the cervix. J Cancer. 2020;11(9):2632-2638. doi:10.7150/jca.40276
12. Yang S, Gao Y, Sun J, et al. Neoadjuvant chemotherapy followed by radical surgery as an alternative treatment to concurrent chemoradiotherapy for young premenopausal patients with FIGO stage IIB squamous cervical carcinoma. Tumour Biol. 2015;36(6):4349-4356. doi:10.1007/s13277-015-3074-2
13. Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant chemotherapy followed by radical surgery versus concomitant chemotherapy and radiotherapy in patients with stage IB2, IIA, or IIB squamous cervical cancer: a randomized controlled trial. J Clin Oncol. 2018;36(16):1548-1555. doi:10.1200/jco.2017.75.9985
14. Shoji T, Takatori E, Saito T, et al. Neoadjuvant chemotherapy using platinum- and taxane-based regimens for bulky stage Ib2 to IIb non-squamous cell carcinoma of the uterine cervix. Cancer Chemother Pharmacol. 2013;71(3):657-662. doi:10.1007/s00280-012-2052-2
15. Shimada M, Nagao S, Fujiwara K, et al. Neoadjuvant chemotherapy with docetaxel and carboplatin followed by radical hysterectomy for stage IB2, IIA2, and IIB patients with non-squamous cell carcinoma of the uterine cervix. Int J Clin Oncol. 2016;21(6):1128-1135. doi:10.1007/s10147-016-1010-0
16. Aoki Y, Sato T, Watanabe M, Sasaki M, Tsuneki I, Tanaka K. Neoadjuvant chemotherapy using low-dose consecutive intraarterial infusions of cisplatin combined with 5-fluorouracil for locally advanced cervical adenocarcinoma. Gynecol Oncol. 2001;81(3):496-499. doi:10.1006/gyno.2001.6195
17. Pignata S, Scambia G, Katsaros D, et al. Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label,

phase 3 trial. Lancet Oncol. 2014;15(4):396-405. doi:10.1016/s1470-2045(14)70049-x
18. van der Burg ME, Onstenk W, Boere IA, et al. Long-term results of a randomised phase III trial of weekly versus three-weekly paclitaxel/platinum induction therapy followed by standard or extended three-weekly paclitaxel/platinum in European patients with advanced epithelial ovarian cancer. Eur J Cancer. 2014;50(15):2592-2601. doi:10.1016/j.ejca.2014.07.015
19. Vergote I, Debruyne P, Kridelka F, et al. Phase II study of weekly paclitaxel/carboplatin in combination with prophylactic G-CSF in the treatment of gynecologic cancers: a study in 108 patients by the Belgian Gynaecological Oncology Group. Gynecol Oncol. 2015;138(2):278-284. doi:10.1016/j.ygyno.2015.05.042
20. Matsuo K, Shimada M, Yamaguchi S, et al. Neoadjuvant chemotherapy with taxane and platinum followed by radical hysterectomy for stage IB2-IIB cervical cancer: impact of histology type on survival. J Clin Med. 2019;8(2):156. doi:10.3390/jcm8020156
21. Mori T, Hosokawa K, Sawada M, et al. Neoadjuvant weekly carboplatin and paclitaxel followed by radical hysterectomy for locally advanced cervical cancer: long-term results. Int J Gynecol Cancer. 2010;20(4):611-616. doi:10.1111/IGC.0b013e3181d80aa9
22. Yang L, Guo J, Shen Y, et al. Clinical efficacy and safety of paclitaxel plus carboplatin as neoadjuvant chemotherapy prior to radical hysterectomy and pelvic lymphadenectomy for Stage IB2-IIB cervical cancer. Int J Clin Exp Med. 2015;8(8):13690-13698.
23. Dueñas-Gonzalez A, López-Graniel C, González-Enciso A, et al. A phase II study of multimodality treatment for locally advanced cervical cancer: neoadjuvant carboplatin and paclitaxel followed by radical hysterectomy and adjuvant cisplatin chemoradiation. Ann Oncol. 2003;14(8):1278-1284. doi:10.1093/annonc/mdg333
24. Angioli R, Plotti F, Luvero D, et al. Feasibility and safety of carboplatin plus paclitaxel as neoadjuvant chemotherapy for locally advanced cervical cancer: a pilot study. Tumour Biol. 2014;35(3):2741-2746. doi:10.1007/s13277-013-1361-3
25. Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease†. Ann Oncol. 2019;30(5):672-705. doi:10.1093/annonc/mdz062
26. Singh N, Gilks CB, Wilkinson N, McCluggage WG. The secondary Müllerian system, field effect, BRCA, and tubal fimbria: our evolving understanding of the origin of tubo-ovarian high-grade serous carcinoma and why assignment of primary site matters. Pathology. 2015;47(5):423-431. doi:10.1097/pat.0000000000000291
27. Singh N, McCluggage WG, Gilks CB. High-grade serous carcinoma of tubo-ovarian origin: recent developments. Histopathology. 2017;71(3):339-356. doi:10.1111/his.13248
28. Gadducci A, Barsotti C, Laliscia C, et al. Dose-dense paclitaxel- and carboplatin-based neoadjuvant chemotherapy followed by surgery or concurrent chemo-radiotherapy in cervical cancer: a preliminary analysis. Anticancer Res. 2017;37(3):1249-1255. doi:10.21873/anticanres.11441
29. Eleje GU, Eke AC, Igberase GO, Igwegbe AO, Eleje LI. Palliative interventions for controlling vaginal bleeding in advanced cervical cancer. Cochrane Database Syst Rev. 2019;3(3):CD011000. doi:10.1002/14651858.CD011000.pub3