

The Role of Neoadjuvant Chemotherapy in Non-SCC of the Cervix: A Systematic Review

Mahboobeh Azadehrah¹, Fahimeh Nokhostin², Malihe Azadehrah^{3*}

¹*Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran.*

²*Department of Obstetrics and Gynecology, Faculty of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran.*

^{3*}*Cancer Research Center, Golestan University of Medical Sciences, Gorgan, Iran.*

^{3*}*m.azadehrah@gmail.com*

Abstract: *Cervical cancer is the third most common cancer in women and the most significant cause of CC is HPV infection. One of the treatment methods for cervical cancer is pre-surgery neoadjuvant chemotherapy (NACT), which is performed to reduce the size of the tumor, facilitate the surgical process, and improve the survival of patients with this cancer. The present study is a systematic review conducted by searching the databases of Elsevier, PubMed Springer, and Wiley, and with the keywords of Cervix cancer, Adenocarcinoma, Adenosquamous carcinoma, and Neoadjuvant chemotherapy; studies conducted between 1998-2020 were reviewed. Out of a total of 1018 articles, 15 articles were selected for further review, considering the inclusion/exclusion criteria. The results showed that the use of NACT improved the patient's physical condition, reduced tumor size, reduced metastasis, facilitated surgery, and improved survival; also, it was associated with successful delivery without side effects in infants. However, further studies are needed to further understand the effect of this treatment in non-scc cancers.*

Keywords: *Neoadjuvant Chemotherapy (NACT), Cervix Cancer, World Health Organization (WHO).*

1. INTRODUCTION

Cervical cancer (CC) is one of the major health problems in the world, with 500,000 new cases being reported each year, resulting in 250,000 deaths. This complication is one of the major causes of premature death in women of childbearing age [1]. This type of cancer is the third most usual cancer in women after breast and colorectal cancer. The highest rates of cervical cancer mortality are in East Africa and South Asia. There is a wide variety of cases and deaths from cervical cancer in different parts of the world, with 86% of all cases and 88% of all deaths occurring in developing countries [2]. The most significant cause of CC is HPV infection, which has been diagnosed in 99% of cervical tumors, especially its carcinogenic subtypes such as HPV16 and HPV18. For many years, Pap smears have been the standard method for screening of CC, which reduced the occurrence of cancer by 60-90% and the mortality rate by 90%, but this test is associated with limitations such as its sensitivity (50%) and insufficient number of samples. Recently, the HPV test has been presented as a method of screening for the DNA of HPV, which could be found in nearly all cervical cancers and has been shown in several studies to be more susceptible to intraepithelial cervical neoplasia. According to the World Health Organization (WHO), there are three categories of cervical epithelial tumors: squamous, adenocarcinoma, and other epithelial tumors, such as adenosquamous carcinoma, neuroendocrine, and differentiated carcinoma. 70-80 percent of patients with this disease are diagnosed with squamous cell carcinoma (SCC) and 20% -25%

have adenocarcinoma [3]. These cancers can be treated in the early and advanced stages with radical surgery, chemotherapy, or both, but patients with metastatic cancer and cases with chronic or recurrent cancer after platinum-based chemotherapy have finite treatment options [4]. Neoadjuvant chemotherapy (NACT) plus by radical surgery (hysterectomy with pelvic lymph node dissection) (NACT + S) is the most common therapy for bulky tumors, whereas it improves the management of the disease and reduces toxicity. NACT was first presented by Feri in 1982, which caused disease-free survival (DFS) before surgery or radiation therapy in cases with head and neck cancer. After the 1990s, the use of NACT was gradually expanded to improve advanced local cervical cancer [5]. Many studies have shown that NACT + S combination therapy can reduce tumor size, reduce the risk of intraoperative spread and postoperative complications; it can also ameliorate survival rates in comparison with surgery alone or radiation therapy [6-11]. The aim of this study was to provide a systematic review of published research evidence regarding the role of neoadjuvant chemotherapy in non-SCC of the cervix.

2. MATERIALS AND METHODS

The present study is a systematic review performed by searching the databases of Elsevier, PubMed Springer, and Wiley, and with the keywords of Cervix cancer, Adenocarcinoma, Adenosquamous carcinoma, and Neoadjuvant chemotherapy. These words were often used separately and in some cases as a combination of two words.

Inclusion criteria were full-text articles in the field of the role of NACT in the treatment of cervical cancer, which were published after 1998 and written in English, and exclusion criteria were articles without full text, articles published before 1998, and review articles. In the analysis phase, the information collected from the studies included the author (s), year, purpose, method of work, and research results. No interpretation was used during the data collection and the main phrases of the articles, which were used by the author (s), were included.

3. RESULTS

In the first stage, 1018 titles were selected. At this stage, the title and, if necessary, abstract of the articles were reviewed, and finally, 128 articles were selected. In the second stage, the full text of the articles was studied and 65 articles were removed due to duplication. Out of the remaining 63 articles, 48 articles were excluded from the study based on the inclusion/exclusion criteria, and finally, full texts of 15 articles published in English on the role of neoadjuvant chemotherapy in the treatment of cervical cancer were reviewed. Reviewed studies were conducted between 1998 and 2020.

The objectives and findings of these 15 articles are listed in Table 1. The results of these studies indicate a positive association between the use of NACT, before or during surgery as well as before or after radiation therapy, and reducing tumor size and improving and increasing disease-free survival (DFS) and overall survival (OS) in patients. A total of 1309 patients with non-scc cervical cancers in different stages (age range of 13-63 years) were examined in these 15 studies; in all cases (100%) the use of NACT was associated with improvement of the patient's physical condition, reduction of tumor size, reduction of metastasis, facilitation of surgery, improvement of survival, and successful delivery without side effects.

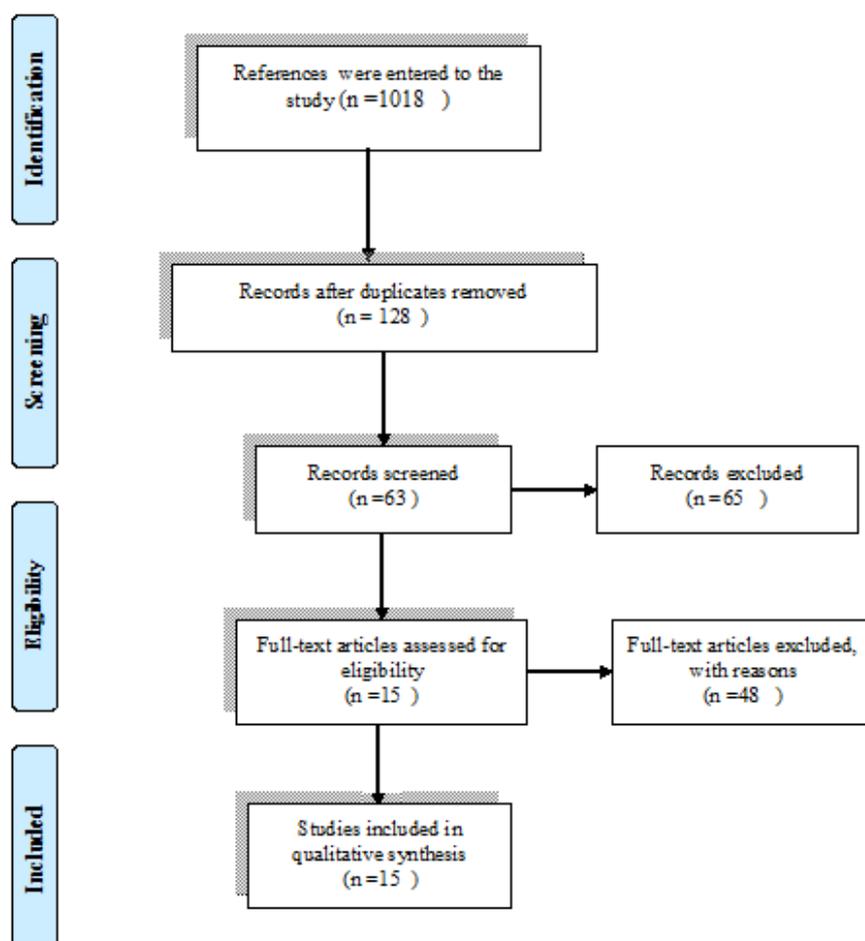


Figure 1 Diagram of the selection of articles; 15 articles were finally selected

The neoadjuvant drugs used in these 15 studies are: doxorubicin (80 mg / m²), paclitaxel (80 and 135-175 mg / m²), cisplatin (10, 15, 20, 50, 70, and 75 mg / m² doses), ifosfamide and mesna (5 mg / m²), carboplatin (5-6 mg / ml / min), mitomycin C (10 mg / m²), etoposide mitomycin C (70-100 mg / m²), epirubicin and epidoxorubicin (80 mg / m²), docetaxel (60-70 mg / m²), nedaplatin (75-80 mg / m²), FU-5 (250 mg / day), S -1 (80-120 mg / body / day), and oxaliplatin (20 mg / m²). The follow-up period in these patients was between 1-208 months. Side effects of this treatment method include hematological and non-hematological toxicities, although most of these side effects are controllable.

Table 1: Results related to the role of neoadjuvant chemotherapy in the treatment of cervical cancer

Author	Title	Objective / Number of samples and method	Neoadjuvant chemotherapy drugs / Dosage	Results
Iwasaka et al. (1998) [12]	Neoadjuvant chemotherapy with mitomycin C, etoposide, and cisplatin for adenocarcinoma of the cervix	Objective: Evaluating the efficacy of NACT in cases with cervical adenocarcinoma or Adenosquamous carcinoma. Sample number and method: 16 women with cervical adenocarcinoma or Adenosquamous carcinoma, of which 2 were in stage IB1, 5 in stage IB2, 1 in stage IIA,	These patients underwent NACT for an average of 3 periods (2-5 periods) using the MEP regimen including 50 mg / m ² cisplatin in the first 24 hours, 10 mg / m ² mitomycin C in the first 24 hours, and 100 mg / m ² etoposide on the first, third and fifth days.	The response rate of patients to the treatment method was 50%. From 16 patients, complete response could be seen in 3 cases and partial respond could be seen in 5 cases. After this therapy, radical hysterectomy was used 12 women with carcinoma (in stage I or stage II). 3 cases

		5 in stage IIB, 2 in stage IIIB, and 1 in stage IVB.		underwent adjuvant radiotherapy due to positive pelvic nodules. Standard radiation therapy was used in 1 patient in stage IIB, one in stage IIIB, and one in stage IVB, and chemotherapy with other regimen was used in one patient in stage IIIB since MEP treatment had no effect on them. Histopathological examination showed that the changes caused by chemotherapy were associated with clinical responses. The average survival period was 47.5 months for NACT respondents and 28.3 months for unresponsive patients. The complications of chemotherapy with MEP could be tolerated by cases. As a result, this methods of chemotherapy were efficient for people with cervical adenocarcinoma.
Aoki et al. (2001) [13]	Neoadjuvant chemotherapy using low-dose consecutive intraarterial infusions of cisplatin combined with 5-fluorouracil for locally advanced cervical adenocarcinoma	Objective: evaluating the response, toxicity, and survival in cases with advanced local cervical adenocarcinoma treated with NACT using 5-fluorouracil (FU -5) and cisplatin. Sample number and method: 11 cases with cervical adenocarcinoma (stage IB, II, or III) underwent preoperative NACT. The average time of follow-up was 30 months (1-65 months).	In these cases, every 3 weeks and for 2 or 3 courses, neoadjuvant chemotherapy using cisplatin injection at a dose of 10 mg/day for 30 minutes followed by 24-hour injection of FU-5 at a dosage of 250 mg/day for 10 days was used. All cases with progressive disease underwent radical hysterectomy after NACT, except one of them, and 6 patients underwent postoperative radiotherapy.	Out of 11 eligible patients, 7 (64%) responded partially to this treatment. On the other hand, in 3 cases (27%) stable disease status was observed and in 1 patient (9%) progressive disease was observed. Histopathological changes were associated with chemotherapy and showed only tolerable complications. In the 24 courses of treatment used, no grade 3 or 4 toxicity was seen and no deaths due to this treatment were reported. The average survival period was 34.7 months and the rate of 5-year survival was 21.2%. Therefore, NACT effectively reduces tumor size in cases with progressive local adenocarcinoma of the cervix, but its effect on

<p>Tabata et al. (2004) [14]</p>	<p>A pilot study of neoadjuvant chemotherapy with mitomycin C, etoposide, cisplatin, and epirubicin for adenocarcinoma of the cervix</p>	<p>Objective: Evaluating the effect and toxicity of NACT using cisplatin, mitomycin C, etoposide, and epirubicin in cases with cervical adenocarcinoma. Sample Number and Method: 14 women with adenocarcinoma of the cervix underwent MEPA followed by radical hysterectomy. 2 people were in stage IB1, 5 people were in stage IB2 and 7 people were in stage IIB. 6 patients underwent radiotherapy after surgery.</p>	<p>These patients underwent NACT every 4 weeks and for 3 courses, using MEPA regimen including 15 mg / m² cisplatin on the first to fifth days, mitomycin C at a dosage of 15 mg/m² on the first day, 70 mg/m² etoposide on the first to third days, and epirubicin at a dosage of 30 mg/m² on the first day.</p>	<p>survival is unknown. Among the 14 cases studied, 7 had complete recovery (CR) and 6 had partial recovery, and 1 demonstrated no improvement. Postoperative studies showed no disease residues in 6 cases and no microscopic disease residues (less than 5 mm) in 2 cases. These 8 patients showed significantly longer survival compared to patients with microscopic disease residues. Side effects included bone marrow inhibition. During 33 treatment cycles, grade ≥3 leukopenia was reported in 70%, and grade ≥3 thrombocytopenia was seen in 79%. No deaths were reported from this treatment. Thus, despite bone marrow suppression, there was an acceptable response rate to MEPA treatment, which resulted in an acceptable CR rate in these patients.</p>
<p>Nagai et al. (2005) [15]</p>	<p>Villoglandular papillary adenocarcinoma of the uterine cervix responding to neoadjuvant chemotherapy with docetaxel and cisplatin: a case report</p>	<p>Objective: Evaluating the effect of NACT using cisplatin and docetaxel in a patient with cervical villoglandular papillary adenocarcinoma (VGPA). Number of samples and method: 1 patient with VGPA (stage IIA)</p>	<p>The patient underwent NACT treatment for 1 period using an intra-arterial injection of 70 mg/m² cisplatin and intravenous injection of 60 mg / m² docetaxel.</p>	<p>21 days after finishing one period of this treatment, the tumor dimensions decreased from 5.3×4.4 centimeters to 2×2 centimeters (81.1% decrease). This patient then underwent a radical hysterectomy and no signs of recurrence were observed. Therefore, NACT treatment, using docetaxel and cisplatin, is recommended as an effective method in the treatment of cervical adenocarcinoma.</p>
<p>Manco et al. (2008) [16]</p>	<p>Neoadjuvant chemotherapy and conservative surgery for stage IB1 cervical cancer</p>	<p>Aim: Assessing the efficacy of combination chemotherapy-surgical therapy on cervical tumors (stage IB1) in women who want to maintain fertility. Sample number and method: 51 patients with</p>	<p>These patients were treated with cisplatin at a dosage of 70 mg/m², paclitaxel at a dosage of 175 mg/m², and ifosfamide at a dosage of 25 mg / m² for 3 periods. In cases with adenocarcinoma of the</p>	<p>30 cases (59%) did not receive this treatment method. In the remaining 21 cases, the mean age was 30 years and the mean diameter of tumor was 15 mm (10-30 mm). Adenocarcinoma was</p>

		no experience of delivery (primiparous) with a ≤ 3 cm tumor and without neoplastic involvement of uterus and lymph nodes were examined.	cervix, epirubicin was used at a dosage of 80 mg / m ² instead of ifosfamide.	observed in twelve patients (57%) and undifferentiated neoplasia in ten cases (48%). After treating these cases with NACT, it was found that five patients were complete respondents, in 12 cases micro-invasive remnants, and in 4 patients, stromal invasion greater than or equal to 3 mm was reported. No recurrence was reported after follow-up (mean 69 months). Also, 9 cases tried to get pregnant that resulted in 10 pregnancies occurring in six patients, during which 9 live infants were born and one of the cases experienced an abortion in the first trimester. These results confirm the effectiveness of the above treatment method.
Marnitz et al. (2009) [17]	The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum	Aim: Evaluating the toxicity and kinetics of drugs during chemotherapy in a woman with carcinoma of the cervix. Sample Number and Methods: A 35-year-old patient in the fourteenth week of twin pregnancy with cervical adenocarcinoma (stage IB1).	The patient received 20 mg/m ² of cisplatin for three consecutive days (days 21-23). Supportive care included oral 4 mg of dexamethasone (three times daily), ondansetron at a dosage of 8 mg, and hydration with 1 liter of saline. In addition, mannitol injection was given prior to using cisplatin.	Pelvic lymphadenectomy was used at 15 weeks of gestation. Three courses of NACT were performed using cisplatin in the second and third trimesters and were tolerable by the patient. Mild nausea and fatigue were reported for 5 days after each chemotherapy cycle. No grade 3 or 4 hematological or non-hematological toxicity was seen. Amniocentesis was performed during the second cisplatin cycle. At 8 months of gestation, a cesarean section was performed followed by a radical hysterectomy. The twins grew normally and showed no chemotherapy-related side effects. The titration of cisplatin in the umbilical cord at the time of cesarean operation was three

				times higher than in the amniotic fluid. These results confirm the effectiveness of the above treatment method during pregnancy.
Singh et al. (2011) [18]	Neoadjuvant chemotherapy followed by radical vaginal trachelectomy and adjuvant chemotherapy for clear cell cancer of the cervix: a feasible approach and review	Aim: Evaluating the effect of NACT using CP (carboplatin and paclitaxel) in a patient with CCAC (clear cell cervical adenocarcinoma). Samples and Methods: A 13-year-old girl with CCAC (stage IB1) who underwent NACT treatment using carboplatin and paclitaxel and after that using pelvic lymphadenectomy, VRT (vaginal radical trachelectomy), and adjuvant chemotherapy.	The patient underwent NACT for three periods using CP (carboplatin and paclitaxel).	These results showed that in this patient NACT was well tolerated using non-toxic CP and reduced tumor size and facilitated VRT. If there are risk factors, adjuvant therapy is recommended. The successful outcome of this treatment led to its application in similar cases.
Tang et al. (2012) [19]	Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma	Objective: To compare CCRT treatment with cisplatin-based adjuvant chemotherapy (NACT) with CCRT treatment alone in cases with progressive cervical adenocarcinoma. Number of samples and procedure: 880 cases with adenocarcinoma of the cervix in stages IIB-IVA. The average follow-up period was 5 years.	In these patients, CCRT with a neoadjuvant chemotherapy cycle using paclitaxel with a dosage of 135 mg/m ² + cisplatin with a dosage of 275 mg / m ² before radiation therapy and 2 courses of combined chemotherapy with the same medications and after radiation therapy with 3 weeks of interval were performed. Tumor control and rate of survival were assessed by the Kaplan-Meier estimator.	The therapy program was used in all 880 patients and recurrence was observed in 340 patients. DFS, cumulative survival, and long-term localized tumor control were significantly higher and longer in women treated with NACT+CCRT. Patients that were treated with CCRT had significantly more distant metastasis and pelvic insufficiency compared to cases treated with CCRT with NACT. Therefore, NACT with paclitaxel and cisplatin in combination with CCRT is an effective, safe, and useful combination therapy for advanced adenocarcinoma of the cervix.
Shoji et al. (2013) [20]	Neoadjuvant chemotherapy using platinum- and taxane-based regimens for bulky stage Ib2 to IIb non-squamous cell carcinoma of the uterine cervix	Objective: Evaluating the effect and safety of paclitaxel/carboplatin (TC) and docetaxel /carboplatin (DC) in women with non-scc of the cervix. Number of samples and method: 23 women with an average age of 50 years (32-63 years); 17	In 19 patients on DC diet and in 4 patients on TC diet, every 3 weeks for a maximum of three courses, neoadjuvant chemotherapy on the first day using 175 mg/m ² paclitaxel or 70 mg/m ² docetaxel and 6 mg/ml/min carboplatin was performed.	The response rate was 78.3%. 5 patients were complete respondents, partial respond was observed in 13 women (56.5%) and stable disease status was observed in 5 cases (21.7%). The surgery rate was 78.3%. Leukopenia or

		<p>patients (73.9%) in stage IIb and 6 patients (26.1%) in stage Ib2. Antitumor effects and side effects were evaluated in these patients.</p>		<p>neutropenia grade ≤ 3 was observed in 12 cases (52.2%) and 21 patients (91.3%), respectively, and grade 3 neutropenia with fever was seen in 2 patients (8.7%) without anemia or thrombocytopenia grade ≤ 3. The mean PFS was 26 months (13.5 - 35.5 months) and the mean OS was 35 months (20.9-49.1). Therefore, NACT showed strong antitumor effects and controllable side effects in the treatment of non-scc of the Cervix.</p>
<p>Takatori et al. (2014) [21]</p>	<p>A pilot study of oxaliplatin with oral S-1 as second-line chemotherapy for patients with recurrent adenocarcinoma of the uterine cervix</p>	<p>Objective: Effectiveness and safety of S-1 / oxaliplatin (SOX) treatment in cases with recurrent cervical adenocarcinoma. Sample number and method: 7 patients with recurrent cervical adenocarcinoma, with an average age of 49 years. Antitumor effects, side effects, PFS, and OS were assessed in these cases.</p>	<p>For these patients, S-1 was administered orally for 14 days at a dosage of 80-120 mg/body/day and oxaliplatin was injected at a dosage of 20 mg / m² on the first day. Treatment courses were 21 days and cases received a maximum of 6 cycles.</p>	<p>The tumor-inhibiting efficacy was observed as complete respond in 2 cases, partial respond in 2 cases, and stable disease in 3 patients. The rate of OS was 57.1% and the rate of disease control was 100%. Due to the hematological toxicity of grad 3 \leq tumor, the percentages of leukopenia, neutropenia, and thrombocytopenia were in 42.91%, 28.62%, and 14.31% of patients, respectively. Also, non-hematological toxicity such as grade 3 rectovaginal fistula and grade 2 fatigue occurred in 14.3% of patients. The mean of PFS and overall survival were 5 and 7 months, respectively. These results indicate that chemotherapy using SOX is useful in treating recurrent adenocarcinoma of the cervix and effective due to its promising antitumor efficacy and minimal side effects.</p>
<p>Lorusso et al. (2014) [22]</p>	<p>Phase II trial on cisplatin-adriamycin-paclitaxel combination as neoadjuvant chemotherapy for locally advanced</p>	<p>Objective: Evaluating the toxicity and efficacy of NACT using cisplatin-adriamycin-paclitaxel (TAP) in cases with local progressive cervical adenocarcinoma (LACA) in stage IB2-IIIB.</p>	<p>These 30 patients underwent NACT treatment using TAP for 3 periods.</p>	<p>Of the 30 patients studied, in fourteen cases complete respond was seen, in 10 women partial respond, and in 6 women stable disease was seen. Regarding the response to this</p>

	cervical adenocarcinoma	Number of samples and method: 30 patients. These patients underwent radical surgery after the last NACT period. Patients in terms of pathological response were classified into 3 groups including the patients with no tumor residue (pCR), disease residue with stromal invasion less than 3 mm (pR1), or disease residue with stromal invasion <3 mm (pR2).		treatment: three patients showed pCR response, 6 patients showed pR1 response and 21 patients showed pR2 response. The mean follow-up period was 45 months, during which PFS and OS were 37 and 48 months, respectively. Hematological toxicity was the most important complication of this treatment. Therefore, NACT seems to be effective and efficient for the treatment of LACA using TAP with tolerable toxicity and good response rate.
Shimada et al. (2016) [23]	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	Objective: Evaluating the effect of NACT with docetaxel and carboplatin followed by radical hysterectomy for cases with cervical non-scc. Methods: 61 patients with cervical non-scc in stage IB2, IIA2, or IIB; The average follow-up period was 1913 days (145 - 2632 days).	In these patients, neoadjuvant chemotherapy was performed every 3 weeks for 1 to 3 courses using docetaxel with a dosage of 60 mg / m ² and carboplatin with a dose of 6 mg/ml/min. 52 cases were eligible for evaluation of the effectiveness of NACT followed by radical hysterectomy. Unfavorable complications and side effects were observed in 59 patients.	The response rate of patients to this treatment was 69%. 5 cases were complete respondents, 31 cases were partial respondents, stable disease status in 15 cases, and advanced disease was observed in 1 case. among the 52 women studied, radical hysterectomy after NACT was used in 50 of them. The rate of overall 2-year survival was 81.7% in stage IB2, 85.8% in stage IIA2, and 92.7% in stage IIB. The most common hematologic toxicities were grade 3 and 4 neutropenia (43 cases with grade 4, and 11 cases with grade 3). Non-hematologic toxicities were grade 1 or 2. Therefore, this method may be a beneficial for the treatment of cases with cervical non-SCC.
Rittiluechai (2018) [24]	Survival Outcomes in Thai Patients with Stage IVB, Persistent or Recurrent Adenocarcinoma of the Uterine Cervix Treated with Platinum-Based Combination	Aim: To evaluate the OS in women with recurrent cervical adenocarcinoma in stage IVB undergoing chemotherapy. Number of samples and procedure: 40 women with an average age of 51.4 years. PFS, the overall response rate (ORR), and prognostic factors were	The chemotherapy regimens used for these patients include Cisplatin plus ifosfamide (15 patients), cisplatin plus irinotecan (13 patients), platinum-based chemotherapy plus paclitaxel (5 patients), cisplatin and cyclophosphamide (3	The respond rate was 33% in the first group, 46% in the second group, 40% in the third group, and 28.6% in the groups receiving other treatment regimens. The mean OS of these 40 women was 7.8 months. Average OS the groups receiving cisplatin / ifosfamide, cisplatin /

	Chemotherapy	assessed in cases with recurrent adenocarcinoma of the cervix.	cases), cisplatin and topotecan (2 cases), and other regimens (2 cases). The average number of treatment courses was 4 courses (2-9 courses).	irinotecan, platinum / paclitaxel was 11.2, 5.5 and 9.3 months, respectively. The most frequent complication was hematological intoxication and most of the complications were controllable. Among the various prognostic factors can be over 60 years of age, hemoglobin level less than 12 g / dl, and recurrence time of 6 months. These results indicate the effect of this therapy in cases with recurrent adenocarcinoma.
Gadducci et al. (2018) [25]	Neoadjuvant Platinum-based Chemotherapy Followed by Radical Hysterectomy for Stage Ib2-IIb Adenocarcinoma of the Uterine Cervix - An Italian Multicenter Retrospective Study	Objective: To evaluate the results of treatment with platinum-based NACT followed by radical hysterectomy in women with cervical adenocarcinoma. Samples and Method: 82 cases with adenocarcinoma of the cervix (stage Ib2-IIb) who underwent chemotherapy-surgery combination therapy. The average follow-up time for survivors was 89 months (5-208 months).	In 53 cases (64.6%) every 3 weeks for three courses, 80 mg / m ² epidoxorubicin on the first day, 175 mg / m ² paclitaxel on the first day, and 75 mg / m ² cisplatin on the second day were prescribed; in 9 patients (11%) every 3 weeks for three courses, 5 g / m ² of ifosfamide + 5 g/m ² of mesna continuously for 24 hours on the first day, paclitaxel (at a dosage of 170 mg/m ² on the second day), and cisplatin (at a dosage of 75 mg / m ² on the second day) were prescribed; in 6 patients (7.3%) every 3 weeks for three courses, 175 mg / m ² paclitaxel and 75 mg / m ² cisplatin were prescribed; in 6 patients (7.3%) weekly for 6 courses, 80 mg / m ² paclitaxel plus carboplatin were prescribed; in 3 patients (3.7%) every 3 weeks for 3 courses, 80 mg / m ² epidoxorubicin and 75 mg / m ² cisplatin were prescribed; and in 5 patients (6.1%) other platinum-based chemotherapy drugs were prescribed.	Complete pathological response, optimal (optimal) respond and below-optimal respond were seen in five (6%), 10 (12%) and 36 (44%) patients, respectively. Nineteen cases (23%) had a recurrence after an average of 12 months. In 12 patients (63%) the recurrence of the disease in the pelvis, in 5 patients (26%) outside the pelvis, and in two cases (10%) recurrence is both in the pelvic area and outside the pelvis was observed. Considering the pathological respond, tumor recurrence occurred in 10% of optimal respondents, 14% of sub-optimal respondents with residuals in the cervix, and 36% of sub-optimal respondents with residuals outside the cervix or patients with no response to the treatment. Five-year survival without recurrence and OS were 77% and 84%, respectively. In optimal or sub-optimal respondents with the intra-cervical residual disease compared with sub-optimal or unresponsive

				respondents with out-of-cervical residual disease, 5-year survival without recurrence (87% vs. 64%) and total survival (92 % Vs. 74%) were better. As a result, NACT, followed by radical hysterectomy, might be a good treatment for women with cervical adenocarcinoma in stage Ib2-IIb.
Ouyang et al. (2020) [26]	Comparison of survival outcomes of neoadjuvant therapy and direct surgery in IB2/IIA2 cervical adenocarcinoma: a retrospective study	Aim: Evaluating the effect and survival of cases with adenocarcinoma of the cervix (stage IB2 / IIA2), who underwent NACT + RS, neoadjuvant chemoradiotherapy before radical surgery (NACRT + RS), or initial radical surgery (RS). Sample number and method: 91 cases with adenocarcinoma of the cervix in stage IB2 / IIA2, of which 29 patients underwent RS treatment, 24 patients underwent NACT + RS, and 38 patients underwent NACRT + RS. The average follow-up time was 6 years.	These 24 patients underwent TP chemotherapy regimens every three weeks including 135-175 mg/m ² paclitaxel on the first day and 50 mg / m ² cisplatin on the second day, TC regimen including 135-175 mg/m ² paclitaxel on the first day and carboplatin at a dosage of 5 mg/ml/min on the second day and TN diet including 135-175 mg / m ² paclitaxel on the first day and 75-80 mg / m ² nedaplatin on the second day. treatment with three to four courses of brachytherapy followed by a platinum-based NACT course was used in 38 cases.	Patients' characteristics were balanced between the three groups; The 5-year DFS rate was 75.7% and the 5-year OS rate was 85.5%. Effect of neoadjuvant therapy, tumor size, lymph node metastases, and depth of stroma attacks are predictors of recurrence and mortality. The findings of this research also demonstrated that the rate of DFS and OS in the patients treated with RS was better than the NACRT + RS group, while there were no significant differences between the RS treatment results and the NACT + RS treatment in terms of survival.

Treatment and Follow-up

One of the treatments for carcinoma of the cervix is concomitant chemoradiotherapy (CCRT) with cisplatin singly or in combination with other medications, which is presently the standard therapy for cases with advanced local cervical cancer (stage IIB-IVA). Approximately 30% -40% of cases do not respond completely to this treatment and therefore alternative therapies are required to ameliorate the condition of these patients. Treatment with bevacizumab or Avastin in combination with chemotherapy improves survival in women with recurrent or metastatic cervical cancer. The use of paclitaxel and carboplatin weekly for 4-6 weeks as chemotherapy drugs before CCRT in stage III cervical cancer is being studied. The effect of adjuvant chemotherapy after CCRT in cases with positive lymph nodes and larger tumor size, as well as in patients in stage III-IVA of this cancer, needs further study. Also, new factors that target molecular pathways are currently under study [27]. High-dose NACT and RS have led to a high clinical response in women with cervical carcinoma and appear to be effective in managing the stage IB of this carcinoma. Neoadjuvant chemotherapy decreases the size of tumors and lymph nodes and thus reduces the need for radiotherapy and chemoradiotherapy after surgery. Reducing tumor and nodule volumes results in fewer radical surgeries (including as a modified radical hysterectomy or a nerve-sparing radical

hysterectomy). Neoadjuvant chemotherapy followed by surgery is a valid alternative to primary chemotherapy in young and sexually active patients [28].

Some of the general features of a good strategy for follow-up and monitoring after initial treatment in women with carcinoma of the cervix are: 1- Regular follow-ups with a complete physical assessment, including pelvic-rectal examination and review of the patient's history; 2- There are limited studies that demonstrate vaginal cytology has significantly improved the diagnosis of early relapse; 3- Regular usage of other radiological or biological research in asymptomatic cases is not recommended since the role of these studies has not yet been definitively assessed; 4- A sensible program for follow-ups includes visits every 3-4 months in the initial 24 months and every 6-12 months in 3-5 years. Women must undergo annual population-based general physical and pelvic assessments after 5 years of non-recurrent follow-up [29].

Chemotherapy and Neoadjuvant Drugs in the Treatment of Cervical Cancer

The major chemotherapy and neoadjuvant drugs used for treating patients with carcinoma of the cervix, which have been mentioned in various articles, are listed in Tables 2 and 3 [30].

Table 2: Single cytotoxic drugs (agents) used in the treatment of cervical cancer

cyclophosphamide	Ifosfamide	Carboplatin	Cisplatin	Doxorubicin	5-Fluorouracil	Methotrexate	Vincristine	Vinorelbine	Irinotecan	Topotecan	Paclitaxel	Docetaxel
------------------	------------	-------------	-----------	-------------	----------------	--------------	-------------	-------------	------------	-----------	------------	-----------

Table 3: Neoadjuvant Chemotherapy (NACT) regimens used for the treatment of cervical cancer

TP	MtxCVP	PVB	PF	BIP	EpP	BOP	PBI
----	--------	-----	----	-----	-----	-----	-----

Mtx: Methotrexate, P: Cisplatin, B: Bleomycin, O: Vincristine, I: Ifosfamide, Ep: Epirubicin, V: Vincristine, F: 5-fluorouracil, and T Paclitaxel.

Resistance in Cervical Cancer

Studies show that due to some mutations in the genome of cancer cells, these cells become resistant to the treatment, and as a result, grow and survive during chemotherapy. Cancer cells of the cervix may trigger the antioxidant defense system. The level of Nrf2 protein (the most important drug treatment target for diseases such as cancer) is significantly elevated in cancer cells. This protein activates cell defense pathways against oxidative damage, inflammation, and apoptosis by inducing the transcription of a great quantity of genes that are involved in phase II detoxification enzymes and antioxidant stress enzymes. The close association of the Nrf2-mediated immune system with disease progression suggests that elevated nuclear Nrf2 concentrations may lead to an inaccurate prognosis of this cancer. The use of RNA interference (RNAi) to suppress Nrf2 and its downstream genes inhibits the development of tumors and increases the efficacy of cytotoxic medications, therefore suppressing the expression of this protein during chemotherapy is a favorable method for treating women with carcinoma of the cervix [31].

4. DISCUSSION

The objective of this research was to systematically evaluate the effect of neoadjuvant chemotherapy (NACT) in non-scc of the cervix. From a total of 1018 studies with topics similar to the above topic, 15 articles were finally selected for further review. By studying these articles, it was found that in cases with non-scc of the cervix, the use of NACT before or during surgery or before and after radiation therapy is associated with reducing tumor size,

reducing metastasis, facilitating surgery, improving and increasing DFS and OS, and successful delivery. The positive effects of NACT followed by surgery in treating cervical cancers have been reported in other studies [32-36].

Timely detection of precancerous lesions by Pap smear is the main mechanism of prevention of this cancer. Once cervical cancer is diagnosed, several therapeutic methods could be used, such as surgical treatment, radiation therapy, chemotherapy, or combination therapy; the selection of method depends on the stage of the disease, lymph node involvement, multiple diseases (presence of other diseases), and risk factors of disease recurrence [37]. Despite extensive screening programs, carcinoma of the cervix is still the third most usual cancer in developing countries, but by the implementation of cervical screening programs, adopting improved and modern methods, and being aware of the important role of human papillomavirus (HPV), the occurrence of this carcinoma has reduced in developed countries [38]. One of the treatments for cervical cancer is NACT followed by surgery (NCS), which was not fully assessed in previous studies. Presently, the major NACT regimen utilized in NCS includes cisplatin. The tumor growth inhibition efficacy of NAC reduces lymph node metastasis and tumor size in women before surgical procedures, which can decrease the quantity of high-risk cases that need radiation therapy after the operation. Many randomized controlled trials (RCTs) have assessed the long-term prognosis of NCS in comparison with initial surgery, but the use of NCS is still unclear [39].

5. CONCLUSION

In this systematic review, it was shown that in women with non-scc of the cervix, the use of NACT before or during surgery or before and after radiation therapy is associated with reducing tumor size, reducing metastasis, facilitating surgery, improving and increasing disease-free survival and overall survival, and successful delivery, however, due to the fact that the number of studies performed on non-scc cancers is very limited compared to scc, conduction of further studies in this field is necessary, to better understand the role of this treatment method in cervical cancers.

6. REFERENCES

- [1] Al-Darwish AA, Al-Naim AF, Al-Mulhim KS, Al-Otaibi NK, Morsi MS, Aleem AM. Knowledge about cervical cancer early warning signs and symptoms, risk factors and vaccination among students at a medical school in Al-Ahsa, Kingdom of Saudi Arabia. *Asian Pac J Cancer Prev.* 2014; 15(6): 2529-2532. doi:10.7314/apjcp.2014.15.6.2529.
- [2] Mansori K, Khazaei S, Shadmani FK, Hanis SM, Jenabi E, Soheylizad M, Sani M, Ayubi E. Global Inequalities in Cervical Cancer Incidence and Mortality. *Middle East Journal of Cancer.* 2018; 9(3).
- [3] Marth C, Landoni F, Mahner S, McCormack M, Gonzalez-Martin A, Colombo N. Cervical cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2017; 28(suppl_4): iv72-iv83. doi:10.1093/annonc/mdx220
- [4] Tsuda N, Watari H, Ushijima K. Chemotherapy and molecular targeting therapy for recurrent cervical cancer. *Chin J Cancer Res.* 2016; 28(2): 241-253. doi:10.21147/j.issn.1000-9604.2016.02.14
- [5] Zou W, Han Y, Zhang Y, Hu C, Feng Y, Zhang H, Wang J. Neoadjuvant chemotherapy plus surgery versus concurrent chemoradiotherapy in stage IB2-IIB cervical cancer: A systematic review and meta-analysis. *PLoS One.* 2019; 14(11): e0225264. doi:10.1371/journal.pone.0225264

- [6] Robova H, Rob L, Halaska MJ, Pluta M, Skapa P. Review of neoadjuvant chemotherapy and trachelectomy: which cervical cancer patients would be suitable for neoadjuvant chemotherapy followed by fertility-sparing surgery? *Curr Oncol Rep*. 2015; 17(5): 446. doi:10.1007/s11912-015-0446-0
- [7] Peng YH, Wang XX, Zhu JS, Gao L. Neo-adjuvant chemotherapy plus surgery versus surgery alone for cervical cancer: Meta-analysis of randomized controlled trials. *J Obstet Gynaecol Res*. 2016; 42(2): 128-135. doi:10.1111/jog.12896
- [8] Kim HS, Sardi JE, Katsumata N, Ryu HS, Nam JH, Chung HH, Park NH, Song YS, Behtash N, Kamura T, 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
- [9] Behnamfar F, Azadehrah M. Factors associated with delayed diagnosis of cervical cancer in iran-a survey in isfahan city. *Asian Pacific Journal of Cancer Prevention*. 2015; 16(2): 635-639
- [10] Naghshineh E, Azadehrah M, Rouholamin S. Portal vein and superior mesenteric vein thrombosis after cesarean hysterectomy. *J Res Med Sci*. 2014;19:197
- [11] Azadehrah M, Azadehrah M, Nokhostin F. *Evaluation of Clinical Symptoms and Treatment Results of Patients with Gestational Trophoblastic Tumors Referred to the Clinic of Imam Khomeini Hospital*.
- [12] Iwasaka T, Fukuda K, Hara K, Yokoyama M, Nakao Y, Uchiyama M, Sugimori H. Neoadjuvant chemotherapy with mitomycin C, etoposide, and cisplatin for adenocarcinoma of the cervix. *Gynecol Oncol*. 1998; 70(2): 236-240. doi:10.1006/gyno.1998.5079
- [13] 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
- [14] Tabata T, Nishiura K, Yanoh K, Okugawa T, Obata H, Tanaka K, Toyoda N. A pilot study of neoadjuvant chemotherapy with mitomycin C, etoposide, cisplatin, and epirubicin for adenocarcinoma of the cervix. *Int J Clin Oncol*. 2004; 9(1): 59-63. doi:10.1007/s10147-003-0363-3
- [15] Nagai N, Hirata E, Kusuda T, Mukai K, Arihiro K, Ohama K. Villoglandular papillary adenocarcinoma of the uterine cervix responding to neoadjuvant chemotherapy with docetaxel and cisplatin: a case report. *Int J Gynecol Cancer*. 2005; 15(6): 1187-1190. doi:10.1111/j.1525-1438.2005.00186.x
- [16] Maneo A, Chiari S, Bonazzi C, Mangioni C. Neoadjuvant chemotherapy and conservative surgery for stage IB1 cervical cancer. *Gynecol Oncol*. 2008; 111(3): 438-443. doi:10.1016/j.ygyno.2008.08.023
- [17] Marnitz S, Schmittel A, Bolbrinker J, Schmidt FP, Fons G, Kalache K, Schneider A, Köhler C. The therapeutic management of a twin pregnancy complicated by the presence of cervical cancer, following laparoscopic staging and chemotherapy, with an emphasis on cisplatin concentrations in the fetomaternal compartments amnion fluid, umbilical cord, and maternal serum. *Fertil Steril*. 2009; 92(5): 1748. e1741-1744. doi:10.1016/j.fertnstert.2009.07.1000
- [18] Singh P, Nicklin J, Hassall T. Neoadjuvant chemotherapy followed by radical vaginal trachelectomy and adjuvant chemotherapy for clear cell cancer of the cervix: a feasible approach and review. *Int J Gynecol Cancer*. 2011; 21(1): 137-140. doi:10.1097/IGC.0b013e3182011236

- [19] Tang J, Tang Y, Yang J, Huang S. Chemoradiation and adjuvant chemotherapy in advanced cervical adenocarcinoma. *Gynecol Oncol.* 2012; 125 (2): 297-302. doi: 10.1016/j.ygyno.2012.01.033
- [20] Shoji T, Takatori E, Saito T, Omi H, Kagabu M, Miura F, Takeuchi S, Sugiyama T. 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
- [21] Takatori E, Shoji T, Suga Y, Niinuma H, Miura Y, Kaido Y, Takada A, Kagabu M, Takeuchi S, Sugiyama T. A pilot study of oxaliplatin with oral S-1 as second-line chemotherapy for patients with recurrent adenocarcinoma of the uterine cervix. *Int J Clin Oncol.* 2014; 19(2): 336-340. doi:10.1007/s10147-013-0539-4
- [22] Lorusso D, Ramondino S, Mancini M, Zanaboni F, Ditto A, Raspagliesi F. Phase II trial on cisplatin-adriamycin-paclitaxel combination as neoadjuvant chemotherapy for locally advanced cervical adenocarcinoma. *Int J Gynecol Cancer.* 2014; 24(4): 729-734. doi:10.1097/igc.000000000000115
- [23] Shimada M, Nagao S, Fujiwara K, Takeshima N, Takizawa K, Shoji T, Sugiyama T, Yamaguchi S, Nishimura R, Kigawa J. 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
- [24] Rittiluechai K. (2018). <http://www.remedypublications.com/clinics-in-oncology-abstract.php?aid=1691>
- [25] Gadducci A, Landoni F, Cosio S, Zizioli V, Zola P, Ferrero AM, Lapresa MT, Maggino T, Sartori E. Neoadjuvant Platinum-based Chemotherapy Followed by Radical Hysterectomy for Stage Ib2-IIb Adenocarcinoma of the Uterine Cervix - An Italian Multicenter Retrospective Study. *Anticancer Res.* 2018; 38(6): 3627-3634. doi:10.21873/anticancer.12637
- [26] Ouyang P, Cai J, Gui L, Liu S, Wu NY, Wang J. Comparison of survival outcomes of neoadjuvant therapy and direct surgery in IB2/IIA2 cervical adenocarcinoma: a retrospective study. *Arch Gynecol Obstet.* 2020; 301(5): 1247-1255. doi:10.1007/s00404-020-05505-6
- [27] Kumar L, Harish P, Malik PS, Khurana S. Chemotherapy and targeted therapy in the management of cervical cancer. *Curr Probl Cancer.* 2018; 42(2): 120-128. doi:10.1016/j.currprobcancer.2018.01.016
- [28] Robova H, Halaska M, Pluta M, Skapa P, Strnad P, Lisy J, Rob L. The role of neoadjuvant chemotherapy and surgery in cervical cancer. *Int J Gynecol Cancer.* 2010; 20(11 Suppl 2): S42-46. doi:10.1111/igc.0b013e3181f60d73
- [29] Elit L, Fyles AW, Oliver TK, Devries-Aboud MC, Fung-Kee-Fung M. Follow-up for women after treatment for cervical cancer. *Curr Oncol.* 2010; 17(3): 65-69. doi:10.3747/co.v17i3.514
- [30] Green JA, Lainakis G. Cytotoxic chemotherapy for advanced or recurrent cervical cancer. *Ann Oncol.* 2006; 17 Suppl 10: x230-232. doi:10.1093/annonc/mdl265
- [31] Ma X, Zhang J, Liu S, Huang Y, Chen B, Wang D. Nrf2 knockdown by shRNA inhibits tumor growth and increases efficacy of chemotherapy in cervical cancer. *Cancer Chemother Pharmacol.* 2012; 69(2): 485-494. doi:10.1007/s00280-011-1722-9
- [32] Mori T, Hosokawa K, Sawada M, Kuroboshi H, Tatsumi H, Koshiba H, Okubo T, Kitawaki J. 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

- [33] Benedetti Panici P, Palaia I, Marchetti C, Ruscito I, Fischetti M, Musella A, Di Donato V, Perniola G, Vertechy L, Muzii L. Dose-Dense Neoadjuvant Chemotherapy plus Radical Surgery in Locally Advanced Cervical Cancer: A Phase II Study. *Oncology*. 2015; 89(2): 103-110. doi:10.1159/000381461
- [34] Tanioka M, Yamaguchi S, Shimada M, Nagao S, Takehara K, Nishimura M, Morita S, Negoro S, Fujiwara K, Kigawa J. Cisplatin with dose-dense paclitaxel before and after radical hysterectomy for locally advanced cervical cancer: a prospective multicenter phase II trial with a dose-finding study. *Med Oncol*. 2017; 34(8): 134. doi:10.1007/s12032-017-0992-4
- [35] Gadducci A, Barsotti C, Laliccia C, Cosio S, Fanucchi A, Tana R, Fabrini MG. 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/anticancer.11441
- [36] Salihi R, Leunen K, Moerman P, Amant F, Neven P, Vergote I. Neoadjuvant Weekly Paclitaxel-Carboplatin Is Effective in Stage I-II Cervical Cancer. *Int J Gynecol Cancer*. 2017; 27(6): 1256-1260. doi:10.1097/igc.0000000000001021
- [37] Wipperfurth J, Neil T, Williams T. Cervical Cancer: Evaluation and Management. *Am Fam Physician*. 2018; 97(7): 449-454
- [38] Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, Bothou A, Galazios G. Cervical cancer: screening, diagnosis and staging. *J buon*. 2016; 21(2): 320-325
- [39] Iwata T, Miyauchi A, Suga Y, Nishio H, Nakamura M, Ohno A, Hirao N, Morisada T, Tanaka K, Ueyama H, et al. Neoadjuvant chemotherapy for locally advanced cervical cancer. *Chin J Cancer Res*. 2016; 28(2): 235-240. doi:10.21147/j.issn.1000-9604.2016.02.13