



# Neoadjuvant Chemotherapy in Cervical Cancer: A Review Article

## ARTICLE INFO

### Article Type

Systematic Review

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### How to cite this article

Elham Shirali, Fariba Yarandi, Nadereh Behtash, Omid Hemmatian. Neoadjuvant Chemotherapy in Cervical Cancer: A Review Article. Journal of Obstetrics, Gynecology and Cancer Research. 2018;3(2):87-91.

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### Article History

Received: May 14, 2017  
Accepted: May 30, 2017  
ePublished: June 21, 2018

## ABSTRACT

**Aims** Cervical cancer is one of the most common cancer in the female since 1990. Neoadjuvant chemotherapy (NACT) uses before surgery, especially in countries with limited radiotherapy facilities. The aim of the present review was to study the effect of NACT before radical surgery in comparison with other treatments and various clinical outcomes.

**Information and Methods** This study is a systematic review and includes previous publishes about cervical cancer and effect of NACT before radical surgery. Over 40 previous studies were reviewed, none of them was case report, at least 5 studies were randomized clinical trials and 6 of them were meta-analysis or systematic review.

**Findings** NACT before surgery demonstrates advantages to reduce the rate of lymph node metastasis and parametrial infiltration, so improves progression-free survival in patients with pelvic lymph node invasion (Approximately 35% of stage IB2–IIB bulky). NACT also decreases tumor volume and minimizes the need for adjuvant radiotherapy, thus NACT under consideration of quality of life and cost-effectiveness should be recommended. NACT is really effective in decreasing incidence of pathological risk factors.

**Conclusion** NACT response associated with the stage of diagnosis, tumor size and pathology of the specimen (Squamous tumor has a better response than a non-squamous tumor). NACT seems to be feasible in the management of stage IB bulky cervical cancer, NACT followed by surgery represent an alternative to primary chemoradiotherapy in young and sexually active patients.

**Keywords** Adjuvant Chemotherapy; Cervical Cancer; Chemoradiotherapy; Neoplasm Metastasis; Adenocarcinoma

## CITATION LINKS

[1] Global cancer ... [2] Global Burden of ... [3] The global burden of disease ... [4] Efficacy of neoadjuvant chemotherapy in patients with FIGO ... [5] Carcinoma of the cervix uteri. FIGO 26th annual report on the ... [6] Randomized comparison of fluorouracil plus cisplatin ... [7] Pelvic radiation with ... [8] Concurrent cisplatin-based radiotherapy and ... [9] Cisplatin, radiation, and adjuvant ... [10] Concurrent chemotherapy and pelvic radiation therapy compared ... [11] Improved treatment for cervical ... [12] Survival and recurrence after concomitant chemotherapy ... [13] Concomitant and neoadjuvant chemotherapy ... [14] Hysterectomy with radiotherapy or chemotherapy ... [15] Cost-effectiveness of radical hysterectomy ... [16] Young cervical cancer patients may be more responsive than older ... [17] Phase III randomized controlled trial of neoadjuvant ... [18] Neo-adjuvant chemotherapy ... [19] Prognostic value of responsiveness of neoadjuvant chemotherapy before ... [20] Clinical efficacy of modified preoperative neoadjuvant ... [21] Treatment patterns of FIGO Stage IB2 cervical cancer ... [22] Neoadjuvant chemotherapy for locally advanced ... [23] A review of topotecan in combination chemotherapy ... [24] Clinical efficacy and safety of paclitaxel plus carboplatin ... [25] Major clinical research advances in gynecologic ... [26] Neoadjuvant chemotherapy for locally ... [27] When does neoadjuvant chemotherapy ... [28] Radiation-sparing managements for ... [29] Evaluation of mediastinal lymph nodes ... [30] New response evaluation criteria in ... [31] Comparative study of neoadjuvant ... [32] Is there a role for postoperative ... [33] Optimal pathological response indicated ... [34] Concurrent chemoradiation versus ... [35] Improved survival with bevacizumab ... [36] Randomized trial of cisplatin and ... [37] Prognostic value of responsiveness ... [38] Cervical ... [39] Adjuvant chemotherapy ... [40] Practice patterns of adjuvant therapy for intermediate/high ... [41] Outcome of neoadjuvant intra-arterial chemotherapy and radical ... [42] What is the value of hemoglobin as a prognostic ... [43] Efficacy of neoadjuvant cisplatin ... [44] Cervical cancer in pregnant ...

## Introduction

Cervical cancer is one of the most common cancer in females that may lead to death. Incidence and mortality of cervical cancer have declined from the number one killer of woman to twelfth ranked in the United States since 1950 due to cervical cytologic screening and intervention at the in-situ stage <sup>[1]</sup>, however, 85% of its mortality is in developing country maybe because of socioeconomic factors <sup>[2, 3]</sup>. Treatment is clean cut in early and advanced stages of cervical cancer, however, the controversy of studies is in early-stage bulky (IB1 to IIA2) especially in countries with inappropriate sources of radiotherapy <sup>[4]</sup>. The International Federation of Gynecology and Obstetrics (FIGO) recommend 3 approaches for the treatment of stage IB2 and IIA2 cervical cancer: Concurrent chemoradiation, Neoadjuvant chemotherapy (NACT) before radical hysterectomy and lymphadenectomy with or without post-surgery radiotherapy and radical hysterectomy and lymphadenectomy with radiation or chemoradiation <sup>[5]</sup>.

Since 1990, NACT is one of the approaches before surgery. National Cancer Institute recommended chemoradiation (CT/RT) as a standard approach in locally advanced cervical cancer (LACC) by foreseeing 5 randomized clinical trials research with 30-50% decrease in death <sup>[6-11]</sup>.

Comparing smaller tumors at the same stage showed early stage bulky (IB2/IIA2) of cervical cancer was high-risk early-stage cervical cancer due to higher recurrence and poor prognosis <sup>[12, 13]</sup>. NACT before surgery administered in Europe, Asia, and Africa because of radiotherapy facilities limitation, no any research showed this modality is more effective than primary chemoradiation <sup>[14]</sup>.

Just 10% of patients in stage IB2 treated with radical surgery compared with 40% in neoadjuvant chemotherapy, about 50% of the patients need adjuvant pelvic radiotherapy.

Lower limb lymphedema (LLL) and decreasing quality of life (QOL) were two most complications in radical hysterectomy with radiotherapy <sup>[15]</sup>.

NACT before radical surgery decreases tumor volume, lymph node metastasis in responders, and deep cervical stromal invasion <sup>[16]</sup>; however, NACT did not affect on survival compared with only radical surgery <sup>[17]</sup>. NACT increases radiotherapy sensitivity and decreases hypoxic cell fraction; NACT also treats micrometastatic tumor so as to prevent the significant proportion of relapses <sup>[18]</sup>.

NACT decreases lymphovascular invasion (0 vs. 4.7%), deep stromal invasion (19.8 vs. 53.5%), lymph node metastasis (8.1 vs. 25.6%), and need of adjuvant radiotherapy (5.5 vs. 30.2%) compared with non-responders and primary surgery <sup>[19]</sup>. In the NACT group, pelvic metastasis and parametrial infiltration rates were significantly lower in compared with primary surgery group <sup>[20]</sup>.

The aim of the present review was to study the effect of NACT before radical surgery in comparison with other treatments and various clinical outcomes.

## Information and Methods

This study is a systematic review.

**Search Strategy:** In this study PubMed, Nature, Elsevier, Medicine Journal, Scopus, and Gynecologic Oncology-online were searched. Common keywords that used were: Cervical Cancer, Adenocarcinoma of Cervix, Neoadjuvant Chemotherapy, also references and similar articles for access more publication were used.

**Selection Criteria:** This study includes previous publishes about cervical cancer and effect of NACT before radical surgery in compared of other treatments and various clinical outcomes difference in approaching of cervical cancer, all publish were in English language and all full text of them were studied.

**Selection Identified:** Over 40 gross previous studies were used, none of them was case report, at least five studies were randomized clinical trials and six studies were meta-analysis or systematic review.

## Findings

NACT is the most studied as an alternative treatment modality for FIGO stage IB2.

The 5-year survival in stage IB2–IIA patients with tumors bigger than 4cm was 30-60% with surgical intervention, although lymph node involvement was 35%-80% so resulting in a 5-year survival rate was 30-40% <sup>[21]</sup>.

Some few studies used NACT (Especially chemotherapy with Platinum) and reported a response rate between 66.6% and 94% in cervical cancer <sup>[22, 23]</sup>, and some studies showed tumor shrinkage without severe chemotherapeutic toxicity but actually, there were some patients were non-responders that had lower overall survival and lower progression-free survival rates <sup>[24]</sup>.

A meta-analysis study includes 6 randomized clinical trial and study of Gynecologic Oncologic Group (GOG) showed NACT did not support its overall survival benefit, however, NACT before surgery demonstrated advantages of reducing the rate of lymph node metastasis and parametrial infiltration so improving progression-free survival <sup>[17, 25-27]</sup>.

Pelvic lymph node invasion was one of a strongest negative prognostic factor in patients with stage IB2–IIB bulky, most of these patients were recurrent in the first year after NACT, no any adjuvant therapy indicated for end-stage patients yet <sup>[28]</sup>.

Lymph nodes greater than 1cm in MRI or CT scan and increasing uptake value in PET–CT scan was helpful for diagnosis of metastatic disease <sup>[29]</sup>.

In patients with pelvic lymph node invasion (Approximately 35% of stage IB2–IIB bulky), NACT

under consideration of quality of life and cost-effectiveness should be recommended [27].

After NACT, response was evaluated based on Response Evaluation Criteria in Solid Tumors (RECIST) criteria: Clinical examination and imaging (MRI, CT scan, or PET-CT scan) [30], patients that respond to NACT treated with surgery, if no any response found chemotherapy continued. The result showed that chemoradiotherapy recommended in NACT non-responders group for survival, however decreasing quality of life should be considered [31]. This approach couldn't generally recommend for every patient with Locally Advanced Cervical Cancer (LACC), patients should have some criteria such as stage IB to IIA cervical cancer with greater tumor size, deep stromal invasion of the outer third of the cervix, lymphovascular invasion, and adenocarcinoma or adenosquamous carcinoma in pathology [32].

Results showed NACT is really effective in decreasing incidence of pathological risk factors and the frequency of adjuvant treatment after radical surgery, most studies found that pathology report of surgical specimen was a predictive factor for the clinical outcome in patients undertreated with NACT and radical surgery [32]. Patients with an optimal pathological response should receive two additional cycles of chemotherapy after surgery with the same NACT regimen [33], patients with positive nodes, parametrial invasion, cut-through or suboptimal response were candidates for External Beam Radiation Therapy (EBRT) or Concurrent Chemoradiation (CCRT) [34].

In poor response to NACT benefit from both additional cycles of the same induction or CCRT or EBRT were limited because of chemo-resistant tumors were often radio-resistant too [32]. GOG (Gynecologic Oncology Group) published that addition of bevacizumab to chemotherapy is associated with increasing 3.7-month overall survival in compared to chemotherapy alone in patients with recurrent cervical cancer [35]. Bevacizumab plus chemotherapy should be tested in suboptimal responder to NACT with residual tumor [32].

## Discussion

The aim of the present review was to study the effect of NACT before radical surgery in comparison with other treatments and various clinical outcomes. As limited access to radiotherapy centers in the poorly radiotherapy facilities area especially in developing country, NACT is an alternative treatment for patients with locally advanced lesions [36].

Chemotherapy had side effects, especially during preoperative intravenous chemotherapy maybe granulocytopenia, gastrointestinal toxicity, alopecia, numbness, palpitation, and electrolyte imbalance

occur, however, signs of these toxicities could resolve or disappear during a time without any significant permanent complication. Surgery had complications as involve urinary system, lymphatic cyst, delayed healing, ileus, hydronephrosis, and venous thrombosis. Rates of complication were similar in both groups; 9.7% in the NACT group and 15.3% in the primary surgery group [37].

Primary Radical Surgery had some benefits such as preserving fertility (Ovaries), the absence of radiation complications and keep the potential use of radiotherapy for recurrence in patients with stage IB-IIB cervical cancer [38], so result of GOG publish showed NACT before radical surgery in patients with stage IB2 cervical cancer had no any significant difference in comparison of radical hysterectomy alone [17]. However, NACT improves resectability and survival in the patients with stage IB2, another GOG study published CCRT with weekly cisplatin in stage IB2 increase both progression-free survival and overall survival significantly in compared with Radiation alone [39]. GOG also recommended another Cervical Cancer Detection Program should use CCRT in stage IB2 patients [34].

Most Japanese gynecologist oncologists prefer radical hysterectomy rather than CCRT in patients with stage IB-IIB cervical cancer [40]. The use of NACT before radical hysterectomy is a controversy for patients in stage IB2-IIB bulky cervical cancer [41].

For NACT approach, first should choose a right patient, patients with big size tumor (5cm or more) and patients with pretreatment hemoglobin level less than 12g/dl have lower overall survival [42]. In a greater tumor, advanced stages and patients with anemia prognosis of NACT before radical surgery is really bad [17]. NACT response associated with the stage of diagnosis, tumor size and pathology of the specimen (Squamous tumor have a better response than a non-squamous tumor) [43].

In our center, we classify the patients over 70 years old as ineligible for radical hysterectomy and we highly recommend NACT followed by radical hysterectomy in stage IB2-IIB cervical cancer patients with a bulky tumor less than diameter 4cm. Parametrial invasion is one of a prognostic factor in cervical cancer. This factor decreased significantly in the NACT approach. NACT before radical surgery and radiotherapy after surgery is really useful in a patient with stage IIB bulky and only pelvic lymphadenopathy [44].

## Conclusion

Neoadjuvant chemotherapy before surgery demonstrates advantages to reduce the rate of lymph node metastasis and parametrial infiltration, so improves progression-free survival in patients with pelvic lymph node invasion (Approximately 35% of stage IB2-IIB bulky). NACT also decreases

tumor volume and minimizes the need for adjuvant radiotherapy, thus NACT under consideration of quality of life and cost-effectiveness should be recommended. NACT is really effective in decreasing incidence of pathological risk factors. NACT response associated with the stage of diagnosis, tumor size and pathology of the specimen (Squamous tumor has a better response than a non-squamous tumor). NACT seems to be feasible in the management of stage IB bulky cervical cancer, NACT followed by surgery represent an alternative to primary chemoradiotherapy in young and sexually active patients.

**Acknowledgments:** The case was not found by the authors

**Ethical permissions:** The case was not found by the authors

**Conflicts of interests:** The case was not found by the authors

**Authors' Contribution:** Shirali E. (First author), Methodologist/ Original researcher/ Discussion author (25%); Yarandi F. (Second author), Methodologist/ Original researcher/ Discussion author (25%); Behtash N. (Third author), Introduction author/ Methodologist/ Original researcher (25%); Hemmatian O. (Fourth author), Introduction author/ Methodologist/ Original researcher (25%)

**Funding/Support:** The authors have not declared a specific grant for this research from any funding agency in the public or commercial.

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