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Comparison of Neoadjuvant Chemotherapy Followed by Radical Surgery with Chemoradiation in Stage IB2 to IIB of Cervical Cancer

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Abstract

Background: The management of locally advanced cervical cancer (stages IB2 to IIB) remains controversial, particularly in regions with limited radiotherapy (RT) resources. While chemoradiation therapy (CRT) is the standard treatment in many Western countries, neoadjuvant chemotherapy followed by radical surgery (NACT-RS) has emerged as an alternative approach.

Objectives: The comparative effectiveness and safety of NACT-RS versus CRT in terms of side effects and recurrence rates remain unclear, necessitating further investigation.

Methods: A cohort study was conducted from 2020 to 2023, involving 68 patients with cervical carcinoma (stages IB2 to IIB). The patients were stratified into two treatment groups: Neoadjuvant chemotherapy followed by radical surgery (N = 17) and CRT (N = 51). The study compared pathology reports, short-term treatment complications, and one-year recurrence rates between the two groups.

Results: Minor complications occurred in 41.2% of the NACT-RS group and 39.2% of the CRT group (P = 0.886), while major complications were observed in 23.5% and 25.5% of the groups, respectively (P = 0.872). All NACT-RS patients responded to chemotherapy with significant tumor size reduction (47.7 ± 8.0 vs. 11.2 ± 8.6, P < 0.001) and resolution of vaginal involvement. During the one-year follow-up, no recurrences were observed in the NACT-RS group, compared to eight out of 51 (16.7%) in the CRT group (P = 0.186).

Conclusions: The similar short-term complication rates and potentially lower one-year recurrence rate in the NACT-RS group suggest that this approach may be a viable alternative to CRT, particularly for young patients with bulky tumors and in areas with limited RT facilities.

Keywords: Cervical Cancer, Treatment Modalities, Chemoradiotherapy, Neoadjuvant Chemotherapy Followed by Radical Surgery

1. Background

Cervical cancer is the leading cause of cancer-related death among gynecological cancers in countries with a low and middle Human Development Index (1). It also has the highest incidence among young women (2). The incidence and mortality of cervical cancer have decreased in many parts of the world due to cervical cytology screening and interventions at the pre-invasive and in situ stages (3). However, the age-standardized death rate from cervical cancer is significantly higher in developing countries due to social and economic factors

(4). In Iran, according to a national study based on cancer registry data from 2008 to 2014 following 2,423 cervical cancer cases, the mean age at diagnosis was 52 years, with the highest proportion of disease in the 50 - 54 age group. The 5-year and 10-year survival rates were 58% and 50%, respectively, and the 5-year survival rate ranged from 34% to 70% among different geographic regions (5).

Cervical cancer treatment encompasses surgical interventions, chemotherapy, and radiation therapy, each associated with distinct side effects. Early-stage cervical cancer is typically treated with surgery, while advanced stages require chemoradiation. However, controversy exists regarding the management of bulky early-stage tumors, particularly in countries with limited radiotherapy (RT) resources. In these settings, neoadjuvant chemotherapy followed by radical surgery (NACT-RS) may be considered an alternative approach (6). The 2018 FIGO staging system has not established specific treatment guidelines for cervical cancer stages IB3 to IIB. While concurrent chemoradiation therapy (CCRT) remains the standard treatment option in most Western countries, NACT-RS has gained widespread adoption in certain regions. This approach involves administering chemotherapy before performing radical surgery, offering a potential alternative to traditional treatment methods (7, 8). Since the 1980s, NACT-RS has been introduced as a therapeutic strategy for locally advanced cervical cancer (9-12). This strategy offers potential benefits, such as tumor shrinkage, reducing surgical complications, and addressing radiotherapy-related risk factors, which may lead to improvements in quality of life and other outcomes (13). However, studies have shown conflicting findings regarding the outcomes of NACT-RS. Limited studies have shown that NACT-RS does not improve overall survival (OS) and may result in an unfavorable prognosis despite reducing pathological risk factors and the extent of adjuvant RT (14). The response rate to NACT in cervical cancer has been reported to range from 66.6% to 94%. Neoadjuvant chemotherapy followed by radical surgery has gained popularity in Asia and Africa due to limited RT facilities (15). Neoadjuvant chemotherapy followed by radical surgery leads to a reduction in tumor volume, metastatic lymph node involvement in responders, and a decrease in deep stromal invasion of the cervix, reducing the need for adjuvant therapy for pathological risk factors (16). Some studies have reported that NACT-RS does not significantly impact OS compared to radical surgery alone, but in some studies, it has been shown to potentially increase disease-free survival (DFS) (17). Studies have shown that NACT targets micrometastatic tumors, thereby significantly reducing the risk of recurrence (18).

The current therapeutic approaches for cervical cancer are burdened by significant side effects and the emergence of tumor drug resistance (19). Understanding the effectiveness of different treatment approaches is crucial for optimizing patient outcomes. Despite being practiced in various regions globally; the current level of evidence is insufficient to confidently recommend this approach.

2. Objectives

Therefore, this study aimed to compare the effectiveness and safety of NACT-RS with chemoradiation therapy (CRT) in patients with stages IB2 to IIB cervical cancer, focusing on short-term complications and recurrence rates.

3. Methods

In this cohort study, conducted from 2020 to 2023, a total of 68 patients diagnosed with cervical cancer at Imam Hussein Hospital, affiliated with Shahid Beheshti University of Medical Sciences, were enrolled and stratified into two treatment groups: Neoadjuvant chemotherapy followed by radical surgery and CRT.

The inclusion criteria encompassed patients with histologically confirmed cervical cancer (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma), FIGO stages IB2 to IIB, and tumor sizes of 4 cm or greater. Patients were required to have less than half of the parametrial involvement on MRI, no clinical evidence of parametrial involvement, and negative or reactive pelvic lymph nodes on MRI. The exclusion criteria included neuroendocrine pathology and those deemed medically unfit for surgery. Clinical examinations and MRI assessments were performed to evaluate tumor characteristics and staging.

Eligible patients in the NACT-RS group received three cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel every 21 days, followed by MRI re-evaluation to assess treatment response. A total of 17 patients were included in the NACT group, which was notably low due to a shortage of cervical cancer cases requiring radical surgery. If the tumor size reduced to less than 4 cm and any parametrial or vaginal involvement was resolved, patients proceeded to radical hysterectomy and lymphadenectomy. Those who did not respond adequately to chemotherapy were referred for CRT. The CRT group consisted of 51 patients who received CRT, serving as the comparison group. Data collected included pathology reports, short-term

treatment complications (during treatment and two months after treatment in terms of minor and major complications), and recurrence rates within one year, with follow-up planned for long-term outcomes.

A comprehensive checklist was employed to systematically collect data for both study groups. For the NACT-RS group, this checklist documented pathological findings including tumor size, presence of lymphovascular space invasion, depth of cervical stromal invasion, parametrial involvement, vaginal margin status, and lymph node involvement. Additionally, intraoperative data such as blood loss and the need for blood transfusion were recorded. For both the NACT-RS and CRT groups, the checklist captured all treatment-related and post-treatment complications occurring within the first two months. The study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences under the code IR.SBMU.RETECH.REC.1400.206.

Quantitative variables between the two groups were compared using the Student's *t*-test. The chi-square test was used to compare complications between the study groups. Data were analyzed using Stata software, version 17. A P-value of less than 0.05 was considered statistically significant.

4. Results

During the investigation period, a total of 68 patients diagnosed with cervical carcinoma were stratified into two treatment groups: Group 1, subjected to NACT-RS (N = 17), and group 2, subjected to CRT (N = 51). There was no significant difference between the two groups at the beginning of the study in terms of patient age, tumor size, histology, and FIGO stage (Table 1).

The incidence of minor and major complications during and shortly after treatment (within two months) was comparable between the two groups. In the NACT-RS group, seven (41.2%) patients experienced minor complications, while 20 (39.2%) patients in the CRT group experienced the same (P = 0.886). Major complications occurred in four (23.5%) patients in the NACT-RS group and 13 (25.5%) patients in the CRT group (P = 0.872). These results are summarized in Table 2.

All 17 patients in the NACT-RS group responded to chemotherapy, and the tumor size was significantly reduced (47.7 ± 8.0 vs. 11.2 ± 8.6, P < 0.001), with vaginal involvement disappearing. There was no parametrial involvement from the beginning.

After surgery, six out of the 17 (35.3%) cases required RT. The main reasons for administering RT were deep invasion of the cervical stroma in five out of the six cases, lymphovascular space invasion in three out of the six cases, and lymph node or parametrial involvement in one out of the six cases. In the NACT-RS group, no recurrences were observed during the one-year follow-up period. In contrast, the CRT group experienced eight (16.7%) recurrences out of 51 cases within the first year of follow-up (P = 0.186).

5. Discussion

The results of the present study revealed similar short-term complications in both groups. However, long-term complications of RT may become more apparent in the CRT group during follow-up. One common problem in patients with gynecological cancer who have undergone pelvic radiation is the higher prevalence of urinary and gastrointestinal symptoms, lymphedema, sexual dysfunction, and pelvic pain compared to those who have not received pelvic radiation (20). In one study, the long-term quality of life after five years in young women who received pelvic radiation was found to be worse. Therefore, the trade-off between the reduction in quality of life and the improvement in survival, particularly for young women, should be considered (21). Delayed toxicities observed two years after treatment completion were more severe in the CRT group compared to those who underwent NACT-RS. These complications affected the rectum, bladder, and vagina. In a cohort study by Lind et al., it was found that long-term gynecological cancer survivors who had undergone radiation therapy experienced higher rates of urinary, gastrointestinal tract, lymphedema, sexual dysfunction, and pelvic pain symptoms compared to the control group. Therefore, these specific symptoms should be actively investigated to ensure better diagnostic investigations and management (20). Similarly, a study by Yang et al. found that younger patients with early-stage cervical squamous cell cancer who received adjuvant RT had lower scores on function scales and a worse long-term quality of life compared to those who did not receive RT. These findings emphasize the importance of comprehensive counseling for young patients considering adjuvant RT, taking into account the potential impact on their quality of life (21).

Documented decreases in quality of life with pelvic RT compared to surgery, especially in young women, highlight the importance of considering differences in survival between the two treatment modalities. In the present study, chemotherapy followed by surgery resulted in no recurrences within one year, while the chemoradiotherapy group had eight recurrences. A Japanese study by Kondo et al. in 2022 compared

Table 1. Key Characteristics of Neoadjuvant Chemotherapy Followed by Radical Surgery and Chemoradiation Therapy Groups [a]

Characteristic	NACT-RS (N = 17)	CRT (N = 51)	P-Value
Age (y)	48.7 ± 11.1	52.3 ± 11.6	0.265
Tumor size (mm)	47.7 ± 8.0	50.9 ± 11.1	0.274
FIGO stage			0.397
IB2	5 (29.4)	10 (19.6)	
IIA	6 (35.3)	15 (29.4)	
IIB	6 (35.3)	26 (51.0)	
Histology			0.704
Squamous cell carcinoma	14 (82.4)	44 (86.3)	
Adenocarcinoma	3 (17.6)	7 (13.7)	

Abbreviations: CRT, chemoradiation therapy; NACT-RS, neoadjuvant chemotherapy followed by radical surgery.

[a] Values are expressed as mean ± SD or No. (%).

Table 2. Comparison of Early Treatment Complications in Neoadjuvant Chemotherapy Followed by Radical Surgery and Chemoradiation Therapy Groups [a]

Complication	NACT-RS	CRT
Intraoperative/During CRT Complications		
Minor complication		
Injury to the bladder	1 (5.9)	-
Gastro-intestinal complication (nausea and vomiting)	-	12 (23.5)
Blood transfusion	5 (29.4)	-
Major complication		
Intestinal obstruction	-	2 (3.9)
Early Postoperative/After CRT Complications (Within Two Months)		
Minor complication		
UTI	1 (5.9)	-
Vulvar ulcer	-	8 (15.7)
Major complication		
Intestinal obstruction	-	6 (11.8)
Wound infection	3 (17.6)	-
Urinary fistula	1 (5.9)	5 (9.8)

Abbreviations: CRT, chemoradiation therapy; NACT-RS, neoadjuvant chemotherapy followed by radical surgery.

[a] Values are expressed as No. (%).

surgical and RT outcomes for stage IB2-IIb cervical adenocarcinoma. Surgery had higher five-year survival rates for stage IB2 (82.1% vs. 79.7%), stage IIa (76.6% vs. 66.7%), and stage IIb (71.1% vs. 58.9%). The study suggested that surgery is a better option for patients under 65 with stage IIb adenocarcinoma, as it minimizes RT side effects (22). Wu et al. compared survival outcomes between radical hysterectomy and definitive chemoradiation in stage IB1-IIA1 cervical cancer from 1990 to 2010, finding no clear preferred treatment between the two modalities for this stage (23). In a 2019 study by Shanmugam et al., comparing neoadjuvant chemotherapy followed by radical hysterectomy with CCRT for locally advanced cervical carcinoma, out of 100 patients with a median follow-up of 28 months, those treated with radical hysterectomy had a similar treatment response, lower toxicity, and improved quality of life compared to patients receiving standard CCRT (24). A study by Gupta et al. on 633 patients (316 in the neoadjuvant chemotherapy plus surgery group and 317 in the concomitant chemoradiation group) found the five-year DFS rate to be 69.3% in the neoadjuvant chemotherapy plus surgery group compared to 76.7% in the concomitant chemoradiation group. The 5-year OS rates were 75.4% and 74.7%, respectively. Delayed toxicities observed at 24 months or later included rectal (2.2%), bladder (1.6%), and vaginal (12.0%) complications in the neoadjuvant chemotherapy plus surgery group,

compared to rectal (3.5%), bladder (3.5%), and vaginal (25.6%) complications in the concomitant chemoradiation group (25). In a study by Benedetti-Panici et al. in 2002, 441 patients with locally advanced squamous cell cervical cancer were divided into two groups: Neoadjuvant chemotherapy followed by radical surgery or external beam RT followed by brachytherapy (BRT). After five years, the NACT-RS group had higher survival and progression-free survival rates (58.9% and 55.4%) compared to the BRT group (44.5% and 41.3%). The NACT-RS group showed better survival outcomes for stage IB2 to IIB patients, but not for stage III. This study suggests that NACT-RS may provide significant survival benefits, particularly for early-stage patients (26). Sala et al. compared NACT-RS to CCRT for treating locally advanced cervical cancer. They evaluated 106 women with cervical cancer (stages IB2 - IVA) between November 2006 and January 2018. The study found that patients in the NACT-RS group had higher five-year DFS (77.4% vs. 33.4%) and five-year OS (93.8% vs. 56.5%) compared to the CCRT group. The analysis indicated that the choice of treatment was the only independent predictor for disease-free and OS. These findings support using NACT before RS as an effective alternative to standard CCRT treatment (27). In a study by Ye et al., the efficacy and safety of NACT-RS were compared to RT or CCRT for treating patients with cervical cancer in stages IB2, IIA, or IIB. The study included three randomized controlled trials and two case-control studies involving 1,275 patients. The pooled results did not show a significant difference in OS and DFS between NACT-RS and RT or CCRT. However, subgroup analysis revealed that NACT-RS had better OS and DFS in patients with long-term follow-up (over 60 months). These findings suggest that the short-term therapeutic effects of both treatments may be similar, but NACT-RS offers better long-term improvement in OS and DFS compared to RT or CCRT for stage IB2 to IIB cervical cancer patients (28). In a retrospective cohort study, Caruso et al. investigated dose-dense neoadjuvant chemotherapy before radical surgery in cervical cancer. The study included patients with stage IB1-IIA2 cervical cancer who underwent this treatment at the European Institute of Oncology in Milan, Italy, from July 2014 to December 2022. The study included 63 patients with stage IB1-IIA2 cervical cancer. The radiological response showed an 81% objective response rate, and the operability rate was 92.1%. The five-year progression-free survival and OS rates were 79% and 92%, respectively (29). Dose-dense NACT-RS may be a viable option for stage IB1-IIA2 cervical cancer, particularly for young patients who prioritize maintaining quality of life and wish to avoid RT. However, further prospective research is needed to establish strong and reliable evidence.

On the other hand, half of the African countries do not have access to RT (30). In these cases, NACT-RS is more accessible for locally advanced cancer. In many low-resource countries, there are restrictions on RT, especially BRT; in these cases, performing chemoradiation followed by radical surgery without BRT has been shown to have the same therapeutic effect as chemoradiation (24). Even in cases of limited access to RT, if there is a large number of patients and a long appointment interval between pelvic radiation and BRT, the effect of the treatment decreases. The entire course of treatment, including external RT and the second stage of BRT, must be completed within 8 weeks. Lengthening the course of treatment to more than eight weeks will reduce tumor control. Radiotherapy has higher costs for patients and healthcare systems; if it is possible to seek similar treatments with lower costs, it is more cost-effective. However, some patients prefer surgery to RT. One of the principles of treatment is consultation and attention to the patient's preferences, provided that both treatments are effective, especially in the case of replacing RT with surgery in younger patients to avoid the side effects of RT.

The primary limitations of our study are the small sample size, particularly in the NACT-RS group (N = 17), and the short follow-up period of one year. These factors significantly restrict our ability to draw definitive conclusions about long-term treatment efficacy, OS, and DFS. We plan to include new cases and continue following up with patients to enhance our data. This will allow us to report on long-term DFS and OS rates in both groups in our upcoming reports.

5.1. Conclusions

Similar short-term complications in both groups and the lower first-year recurrence rate in the surgery group from the present study strongly suggest considering NACT-RS, especially in young patients with bulky tumors, to eliminate the side effects of RT and improve quality of life without compromising survival. On the other hand, in areas with limited or no RT facilities, NACT-RS might serve as a favorable and viable option.

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Footnotes

Authors' Contribution: Study concept and design: M. A., F. H., and M. R.; analysis and interpretation of data: M. A. and F. H.; drafting of the manuscript: F. H.; critical revision of the manuscript for important intellectual content: All authors.; Gathering the data: All authors.

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