ORIGINAL ARTICLE

Neoadjuvant Chemotherapy Prior to Radical Hysterectomy versus Radical Surgery Alone for Stage IB2–IIA2 Bulky Cervical Cancer

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Abstract:

Background: The optimal management of bulky early-stage cervical cancer (tumor >4 cm) remains controversial. Neoadjuvant chemotherapy (NAC) before radical hysterectomy has been proposed to reduce tumor burden, improve operability, and potentially decrease postoperative morbidity; however, its comparative effectiveness versus primary surgery is uncertain. This study compared clinical characteristics, tumor response, surgical outcomes, and pathological findings between patients receiving NAC followed by radical hysterectomy and those undergoing primary radical surgery (PS) alone in stage IB2–IIA2 bulky cervical cancer. Methods: We retrospectively reviewed patients with stage IB2 or IIA2 cervical cancer with tumor size >4 cm on magnetic resonance imaging treated between November 2016 and September 2018. Patients receiving paclitaxel plus platinum-based NAC followed by radical hysterectomy were compared with those undergoing PS during the same period. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Surgical parameters and pathological outcomes were analyzed. Results: A total of 97 patients were included (NAC: n=50; PS: n=47). Baseline age and weight were comparable. Tumor size distribution differed significantly (p<0.001), with larger tumors (5–6 cm) more common in the NAC group. NAC was associated with shorter operative time (157±29 vs 204±24 minutes; p<0.001) and lower estimated blood loss (472±139 vs 870±183 mL; p<0.001). Resectability rates were higher with NAC (92% vs 80.9%; p=0.189). Parametrial and paravaginal involvement differed significantly between groups (p<0.001), whereas lymphovascular space invasion did not (p=0.651). Within the NAC group, Grade 2 tumors showed higher response rates (p=0.001), and responders were older than non-responders (p=0.012). Conclusion: NAC prior to radical hysterectomy may enhance surgical feasibility in bulky cervical cancer without compromising pathological outcomes. Further prospective studies are needed to determine long-term oncologic benefits.

Key words: Neoadjuvant Chemotherapy, Radical Hysterectomy, FIGO stage IB2–IIA2, Radical Surgery, Bulky Cervical Cancer.

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Introduction:

Cervical cancer remains a major public health problem worldwide and continues to be one of the leading causes of cancer-related mortality among women, particularly in low- and middle-income countries where screening and early detection programs are less widely implemented.[1] Although

early-stage cervical cancer can be effectively treated with radical surgery, patients presenting with bulky tumors greater than 4 cm represent a distinct clinical subgroup characterized by increased risk of adverse pathological features, including lymph node metastasis, deep stromal invasion, and parametrial involvement.[2]

Radical hysterectomy with pelvic lymphadenectomy has traditionally been considered the standard treatment for early-stage disease.[3] However, in bulky tumors, surgery alone frequently necessitates postoperative radiotherapy or concurrent chemoradiation due to unfavorable pathological risk factors.2 The combination of radical surgery and adjuvant radiation therapy may increase treatment-related morbidity, including urinary, gastrointestinal, and sexual dysfunction, thereby adversely affecting long-term quality of life.[4]

Neoadjuvant chemotherapy (NAC) has emerged as a potential strategy to address these challenges. The theoretical advantages of NAC include reduction in tumor size, elimination of micrometastatic disease, and improvement in surgical operability.[5] Tumor shrinkage may allow more complete resection and reduce the likelihood of positive surgical margins or extensive parametrial involvement. Additionally, improvement in pathological prognostic factors following NAC may allow some patients to avoid postoperative radiotherapy.[6]

Despite these potential benefits, the role of NAC remains controversial. Several studies have demonstrated improved pathological outcomes and reduced need for adjuvant therapy following NAC7, whereas others have failed to demonstrate clear survival benefits.[5] Differences in chemotherapy regimens, patient selection criteria, and treatment protocols have contributed to inconsistent findings across studies.

Given the ongoing uncertainty regarding the optimal management of bulky early-stage cervical cancer, comparative evaluation of NAC followed by radical hysterectomy versus primary radical surgery remains clinically important. The present study aimed to compare baseline characteristics, tumor response, surgical outcomes, and pathological findings between these two treatment approaches in patients with stage IB2–IIA2 bulky cervical cancer.

Materials and method:

This retrospective comparative study included all patients diagnosed with stage IB2 or IIA2 cervical cancer with tumor size greater than 4 cm as measured by magnetic resonance imaging (MRI), treated between November 1, 2016 and September 30, 2018. All patients had primary, previously untreated, histologically confirmed cervical cancer at the time of diagnosis. Patients who received NAC consisting of paclitaxel plus platinum-based regimens prior to surgery were included in the NAC group. Patients treated with other chemotherapy regimens were excluded. Patients with para-aortic lymph node metastasis or those diagnosed with simultaneous other malignancies after primary surgery were also excluded from the study. During the same study period, patients with tumor size greater than 4 cm who underwent radical surgery alone without prior chemotherapy were included as the control group and defined as the primary surgery (PS) group.

Clinical Evaluation and Staging: All patients underwent comprehensive clinical staging procedures at diagnosis. These included pelvic examination, chest radiography, cystoscopy, rectosigmoidoscopy, and intravenous pyelogram to evaluate local and distant disease extent. MRI was performed at the time of initial diagnosis to determine tumor size and local tumor characteristics. In patients receiving NAC, MRI was repeated prior to surgery following completion of chemotherapy cycles to assess treatment response.

Neoadjuvant Chemotherapy Protocol: NAC consisted of two cycles of intravenous paclitaxel at a dose of 135 mg/m² combined with cisplatin at 75 mg/m² or carboplatin at an area under the curve (AUC) of 5. Chemotherapy cycles were

administered at three-week intervals. Radical surgery was scheduled within three weeks after completion of the second chemotherapy cycle.[8]

Surgical Procedure: All patients underwent type III radical hysterectomy with systematic pelvic lymphadenectomy.[9] Para-aortic lymphadenectomy was performed when clinically indicated based on intraoperative findings or preoperative evaluation. Surgical procedures were conducted according to standard oncologic principles.[10]

Postoperative Adjuvant Therapy: Postoperative concurrent chemoradiation or radiotherapy alone was administered to patients classified as high risk. High-risk criteria included the presence of at least one major risk factor—positive lymph nodes, parametrial involvement, or positive surgical margin—or two or more minor risk factors including tumor size, depth of stromal invasion, and lymphovascular space invasion (LVSI).[10]

Tumor Response Assessment

Tumor response in the NAC group was evaluated based on MRI measurements obtained before initiation of chemotherapy and immediately prior to surgery. Response assessment was performed according to the Response Evaluation Criteria in Solid Tumors (RECIST).[11]

Statistical Analysis: Continuous variables were expressed as mean ± standard deviation or median with interquartile range (IQR), depending on distribution. Comparisons between groups were performed using Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact tests for categorical variables. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 26.0.

Results:

Patient Characteristics

The patients' age and weight were comparable between groups. The mean age was 43.8 ± 6.9 years in the NAC group and 45.6 ± 9.0 years in the PS group (p = 0.281). Similarly, mean body weight did not differ significantly between groups (54.7 ± 7.6 kg vs 54.2 ± 6.3 kg; p = 0.679).

Table 1 shows tumor grade distribution differed significantly between groups (p = 0.015), with Grade 1 tumors more common in the NAC group (28.0% vs 8.5%) and Grade 2 tumors predominating in the PS group (76.6% vs 50.0%). FIGO stage distribution was comparable between groups (p = 0.339). Tumor size differed significantly (p < 0.001), with larger tumors (5–6 cm) more frequent in the NAC group, whereas smaller tumors (3–3.5 cm) were predominantly observed in the primary surgery group.

Table 1: Tumour characteristics of patients

Variables	Neoadjuvant chemotherapy (N=50)	Primary surgery (N=47)	P-value
Grade (%)			
Grade 1	14 (28.0)	4 (8.5)	0.015
Grade 2	25 (50.0)	36 (76.6)	
Grade 3	11 (22.0)	7 (14.9)	
FIGO stage (%)			
Stage IB2	44 (88.0)	37 (78.7)	0.339
Stage IIA2	6 (12.0)	10 (21.3)	

Variables	Neoadjuvant chemotherapy (N=50)	Primary surgery (N=47)	P-value
Tumor size (cm) (%)			
3	0 (0.0)	2 (4.3)	<0.001
3.5	0 (0.0)	30 (63.8)	
4	17 (34.0)	11 (23.4)	
5	17 (34.0)	4 (8.5)	
6	16 (32.0)	0 (0.0)	

Tumor Response to Neoadjuvant Chemotherapy

As shown in Table 2, within the NAC group, responders were significantly older than non-responders (44.6 ± 6.3 vs 36.6 ± 9.1 years; p = 0.012). Tumor grade was significantly associated with response (p = 0.001), with all Grade 2 and Grade 3 tumors observed among responders, while non-responders were limited to Grade 1 tumors. FIGO stage, initial tumor size, and mean operating time did not differ significantly between responders and non-responders (p > 0.05).

Table 2: Tumor response relative to pretreatment variables in the NAC group

Variables	Responder	Non-responder	P-value
Age (mean ± SD)	44.6 ± 6.3	36.6 ± 9.1	0.012
Grade (%)			
Grade 1	9 (20.0)	5 (100.0)	0.001
Grade 2	25 (55.6)	0 (0.0)	
Grade 3	11 (24.4)	0 (0.0)	
FIGO stage (%)			
Stage IB2	40 (88.9)	4 (80.0)	1.000
Stage IIA2	5 (11.1)	1 (20.0)	
Initial tumor size (%)			
<5	17 (37.8)	0 (0.0)	0.232
>=5	28 (62.2)	5 (100.0)	
Operating time (min) (mean ± SD)	159.3 ± 28.5	138.0 ± 26.8	0.117

Surgical and Pathological Outcomes

Table 3 shows that resection rates were higher in the NAC group compared with PS (92.0% vs 80.9%), although the difference was not statistically significant (p = 0.189). Parametrial and paravaginal tissue involvement differed significantly between groups (both p < 0.001), with higher involvement observed in the NAC group. LVSI did not differ significantly (p = 0.651). Operative time and estimated blood loss were significantly lower in the NAC group compared with primary surgery (157.2 ± 28.8 vs 203.6 ± 24.2 minutes; 472.0 ± 138.6 vs 870.2 ± 182.9 mL; both p < 0.001).

Table 2: Comparison of surgical and pathological outcomes between treatment groups

Variables	Neoadjuvant chemo-therapy (N=50)	Primary surgery (N=47)	P-value
Rates of Resection (%)			
Resectable	46 (92.0)	38 (80.9)	0.189
Unresectable	4 (8.0)	9 (19.1)	
Parametrium (%)			
Free	14 (28.0)	39 (83.0)	<0.001
Involved	36 (72.0)	8 (17.0)	
Paravaginal Tissue (%)			
Free	13 (26.0)	41 (87.2)	<0.001
Involved	37 (74.0)	6 (12.8)	
LVSI (%)			
Free	32 (64.0)	27 (57.4)	0.651
Present	18 (36.0)	20 (42.6)	
Operating time (min) (mean ± SD)	157.2 ± 28.8	203.6 ± 24.2	<0.001
Estimated blood loss (ml) (mean ± SD)	472.0 ± 138.6	870.2 ± 182.9	<0.001

Discussion:

In this comparative study of stage IB2–IIA2 bulky cervical cancer, neoadjuvant chemotherapy (NAC) prior to radical hysterectomy was associated with improved intraoperative parameters, including significantly shorter operative time and reduced blood loss, compared with primary surgery alone. These findings suggest that cytoreduction following chemotherapy may enhance surgical feasibility in bulky disease.

Improved operability after NAC has been attributed to tumor shrinkage, restoration of pelvic anatomy, and facilitation of dissection planes.[8,12-15] Our data are consistent with this mechanism, demonstrating meaningful reductions in operative complexity without significant differences in LVSI. However, although surgical conditions improved, pathological high-risk features were not uniformly reduced. This observation aligns with prior evidence indicating that NAC may decrease macroscopic tumor burden without necessarily modifying tumor biology or metastatic potential.[14,16-18] The survival benefit of NAC in locally advanced cervical cancer remains controversial.[6] The Neoadjuvant Chemotherapy for Locally Advanced Cervical Cancer Meta-analysis Collaboration reported modest survival advantages with cisplatin-based NAC followed by surgery under specific dosing schedules.[19,20] However, subsequent trials, including the GOG phase III study, did not confirm a consistent survival advantage over primary surgery.[21]

Variability in regimens, patient selection, and treatment intervals may partly explain these discrepancies. More recent systematic reviews suggest equivalence in long-term oncologic outcomes, despite improvements in pathological parameters in some cohorts.[6]

Our findings contribute to this body of literature

by demonstrating improved surgical feasibility without clear evidence of pathological superiority. These data support a selective rather than universal role for NAC, particularly in patients with substantial tumor bulk where surgical morbidity may otherwise be increased or where avoidance of adjuvant radiotherapy is desirable.[22,23]

The association between tumor grade and chemotherapy response observed in our study further underscores the importance of tumor biology in determining treatment effect. Identification of predictive biomarkers remains an important research priority to refine patient selection and optimize therapeutic sequencing.[24,25]

This study has limitations. Its retrospective design introduces potential selection bias, particularly as patients with larger tumors were more frequently allocated to NAC. Differences in baseline tumor characteristics and limited follow-up restrict conclusions regarding long-term oncologic outcomes. Prospective randomized studies with survival endpoints are required to clarify the definitive role of NAC in this setting.

Conclusion:

NAC followed by radical hysterectomy in patients with stage IB2–IIA2 bulky cervical cancer was associated with improved intraoperative outcomes, including shorter operating time and reduced blood loss, without significant differences in LVSI compared with primary radical surgery. NAC may serve as a useful strategy to improve surgical feasibility in selected patients; however, prospective randomized studies are required to establish its definitive role in treatment algorithms.

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