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Case Series

Insights into neoadjuvant chemotherapy efficacy for stage 1B3 locally advanced cervical cancer: case series

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ABSTRACT

Cervical cancer remains a leading cause of mortality among women worldwide, particularly in developing nations. While radical surgery is the established standard of care for early-stage disease, pelvic relapse post-surgery remains a concern. Neoadjuvant chemotherapy (NACT) preceding radical surgery has emerged as a promising approach, aiming to reduce tumor burden and improve surgical outcomes. We present three cases of stage 1B3 cervical cancer treated with three cycles of NACT repeated three weekly followed by radical hysterectomy. Post-operatively two patients received radiotherapy (External beam radiotherapy and brachytherapy) and one patient got lost to follow-up for 6 months and did not receive post-operative radiotherapy now under observation and regular follow-up. All the patients exhibited significant tumor reduction following chemotherapy, enabling successful surgical intervention. All patients remained in remission post-treatment. NACT showed effectiveness in reducing tumor size and facilitating successful radical surgery in patients with stage 1B3 cervical cancer. Our case series highlights the potential of NACT followed by radical surgery as a promising therapeutic strategy for stage 1B3 cervical cancer. NACT facilitated successful surgical intervention with favourable outcomes. Further research is warranted to elucidate the optimal patient selection criteria and the long-term benefits of this approach in improving survival rates and quality of life for cervical cancer patients.

Keywords: Cervical cancer, NACT, Response, Surgery

INTRODUCTION

Cervical cancer stands as a significant cause of mortality among women, particularly in developing nations. For patients diagnosed with international federation of gynecology and obstetrics (FIGO) stages Ia-Ib1, radical surgery remains the established standard of care, boasting 5-year survival rates reaching 80% to 90%. However, pelvic relapse post-surgery remains a matter of concern.[1] In cases of FIGO stage Ib2 and beyond, radiation therapy supersedes surgery due to associated risks such as parametrial involvement and lymph node metastases. Nonetheless, radiation therapy carries its own drawbacks, potentially compromising ovarian function and sexual well-being, thus impacting patients' quality of life. To enhance treatment efficacy, recent trials have explored neoadjuvant therapy in conjunction with surgery. NACT preceding radical surgery has emerged as a promising approach. NACT aims to reduce tumor burden before surgical intervention or radiotherapy. For locally advanced cervical cancer, integrating two to three cycles of NACT has shown potential in optimizing surgical outcomes.[2]

By combining NACT with radical surgery, clinicians strive to improve both survival rates and patients' overall quality of life. This approach represents a progressive step in the management of cervical cancer, offering hope for

enhanced therapeutic outcomes and better patient experiences.

Previous trials have demonstrated the potential of NACT to eliminate tumor micro-metastases, reduce tumor size, enhance resection rates, and facilitate surgical down-staging in patients. A meta-analysis corroborated these findings, showing that NACT followed by radical surgery led to increased survival rates and decreased rates of local and distant recurrence in patients with stage Ib2–IIb cervical cancer.[3]

However, conflicting results exist, with some studies failing to demonstrate the benefits of NACT and even indicating adverse effects on efficacy.[4] As of now, consensus remains elusive regarding the significant improvement of prognosis in cervical cancer patients with the use of NACT.

CASE SERIES

Case 1

A 45-year-old, para 4, postmenopausal woman presented with a one-month history of postmenopausal bleeding. Examination revealed a cervical mass measuring 4×3 cm with contact bleeding. Biopsy confirmed moderately differentiated squamous cell carcinoma. Magnetic resonance imaging demonstrated a localized tumor confined to the cervix without evidence of local or distant metastasis. The patient was staged as carcinoma cervix stage 1B3. She then underwent NACT comprising carboplatin (AUC 5) and paclitaxel (175 mg/m^2) administered at three-week intervals for three cycles. Following the completion of chemotherapy, there was a significant reduction in tumor size without observable growth over cervix, and repeat MRI revealed localised cervical mass of 1×1 cm without any local or distant spread.

Subsequently, the patient underwent type C radical hysterectomy with bilateral pelvic lymphadenectomy. Final histopathology indicated moderately differentiated squamous cell carcinoma associated with HPV, with the presence of lympho-vascular space invasion (LVSI) and deep stromal invasion, but no parametrial involvement or pelvic lymph node metastasis. Postoperative radiotherapy was planned, and the patient has remained in remission for 2 years.

Case 2

A 35-year-old woman, para 2, presented with a six-month history of persistent vaginal discharge and post-coital bleeding. Examination revealed a cervical mass measuring 4×3.5 cm with contact bleeding, confirmed by biopsy to be a moderately differentiated adenocarcinoma of the cervix. Magnetic resonance imaging demonstrated the tumor confined to the cervix without local or distant metastasis. The patient was diagnosed with stage 1B3 cervical cancer and subsequently received NACT, which consisted of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) administered at three-week intervals for three cycles. Following completion of chemotherapy, the assessment showed a reduction in tumor size with residual growth measuring 1.5×1.5 cm over the cervix, and no evidence of local or distant spread was observed on repeat MRI, which indicated a 2×1 cm residual growth over the cervix.

Subsequently, the patient underwent a type C radical hysterectomy with bilateral pelvic lymphadenectomy. The final histopathology report revealed adenocarcinoma of the cervix, HPV-associated, with the absence of lymphovascular space invasion (LVSI) and deep stromal invasion, and no involvement of parametrium or pelvic lymph nodes. Postoperative radiotherapy was planned, and the patient has remained in remission for one and a half years.

Case 3

A 42-year-old woman, para 5, presented with complaints of persistent vaginal discharge and post-coital bleeding persisting for eight months. Upon assessment, a cervical mass measuring 4×5 cm with contact bleeding was identified, and subsequent biopsy confirmed moderately differentiated adenocarcinoma of the cervix. Magnetic resonance imaging indicated that the tumor was confined to the cervix without any evidence of local or distant metastasis. The patient was diagnosed with stage 1B3 cervical cancer and subsequently received NACT, which consisted of carboplatin (AUC 5) and paclitaxel (175 mg/m^2) administered at three-week intervals for three cycles. Following completion of the chemotherapy regimen, the assessment revealed a reduction in tumor size, with residual growth measuring 2×2 cm over the cervix. Repeat MRI demonstrated a 1×1.5 cm residual growth over the cervix, with no indication of local or distant metastasis.

Subsequently, the patient underwent a type C radical hysterectomy with bilateral pelvic lymphadenectomy. Histopathological examination of the excised tissue revealed adenocarcinoma of the cervix, HPV-associated, with a tumor size of 1×1 cm, absence of lymphovascular space invasion, and superficial stromal invasion, without the involvement of the parametrium or pelvic lymph nodes.

Despite the planned postoperative radiotherapy, the patient was lost to follow-up for six months and did not receive the scheduled treatment. However, she has since been under observation with regular follow-up and has remained in remission for one year.

Table 1: Summary of cases treated by NACT followed by surgery and adjuvant treatment.

S. No.	Age (in years)	Complaints	Stage	Biopsy histopathology	Neoadjuvant chemotherapy	Surgery and operative findings	Postop period	Follow-up
1.	45	Post-menopausal bleeding	Ca cervix stage IB3	Squamous cell carcinoma, HPV associated	Received 3 cycles of paclitaxel and carboplatin	Type C radical hysterectomy with bilateral pelvic lymphadenectomy, 1×1 cm mass over cervix, rest other findings were normal	Received concurrent chemoradiation	Patient in remission for 2 year and regular 3 monthly follow up
2.	35	Post coital bleeding and vaginal discharge	Ca cervix stage IB3	Adenocarcinoma cervix, HPV associated	Received 3 cycles of paclitaxel and carboplatin	Type C radical hysterectomy with bilateral pelvic lymphadenectomy, 2×1 cm mass over cervix, rest other findings were normal	Received concurrent chemoradiation	Patient in remission for one and half year and regular 3 monthly follow up
3.	42	Post coital bleeding and vaginal discharge	Ca cervix stage IB3	Adenocarcinoma cervix, HPV associated	Received 3 cycles of paclitaxel and carboplatin	Type C radical hysterectomy with bilateral pelvic lymphadenectomy, 1×1.5 cm mass over cervix, rest other findings were normal	Lost to follow up, didn't received Concurrent chemoradiation	Patient in remission for 1 year, under observation and regular 3 monthly follow up

DISCUSSION

The standard treatment for patients with stage IB3 disease is definitive concurrent chemoradiotherapy but in situations like long waiting periods for radiation therapy especially during COVID times, the role of neoadjuvant chemotherapy followed by surgery has emerged. NACT before radical surgery offers a valuable alternative in regions with scarce radiotherapy facilities, especially in developing countries. It proves effective for patients with locally advanced lesions.

NACT downstages the disease and makes the patient operable. Previous literature primarily concentrated on evaluating the impact of NACT on stage IB2 or locally advanced cervical cancer (FIGO 2009). Several studies have indicated that surgical intervention following NACT may significantly enhance patient prognosis, particularly among those responsive to NACT.[5] Sardi et al demonstrated improved survival and disease-free survival (DFS) rates in patients with stage IB cervical squamous cell carcinoma (lesion diameter >4 cm) who underwent NACT compared to those undergoing direct surgery or postoperative radiotherapy, aligning with the current study's conclusions.[6] Cai et al and Chen et al observed favourable outcomes in patients with stage IB cervical carcinoma (lesion diameter >4 cm) and stage IB2-IIB cervical cancer, respectively, following NACT.[7,8] Moreover, Gadducci et al underscored the efficacy of NACT followed by surgery in managing stage IB2-IIB cervical cancer, with the pathological response to NACT emerging as a pivotal determinant of prognosis.[9] The present study also shows a good response to NACT.

Surgery offers advantages over radiotherapy for stage IB3 cervical cancer, preserving ovarian function and causing less damage to sexual function and vaginal shortening, particularly in young women. The therapeutic effect of NACT followed by surgery versus radical hysterectomy alone (ARH) for stage IB3 cervical cancer has not been extensively studied. Chemotherapy, particularly preoperative intravenous administration, may result in side effects such as granulocytopenia, gastrointestinal toxicity, alopecia, numbness, palpitations, and electrolyte imbalances. Nevertheless, these toxicities typically resolve over time without significant permanent complications. Surgical interventions carry their own set of complications, including chances of bladder dysfunction, lymphatic cysts, delayed healing, ileus, hydronephrosis, and venous thrombosis. Notably, complication rates were comparable between the NACT followed by surgery and primary surgery groups, with rates of 9.7% and 15.3%, respectively.[10]

In the selection of patients for NACT, identifying the most suitable candidates is paramount. Notably, individuals with larger tumor sizes (5 cm or more) and pre-treatment haemoglobin levels below 12 g/dl exhibit lower overall survival rates. Moreover, patients with greater tumor size, advanced stages, and anaemia tend to have poorer prognoses when NACT precedes radical surgery. The response to NACT is closely associated with the stage at

diagnosis, tumor size, and histopathology of the specimen, with squamous tumors demonstrating a more favourable response compared to non-squamous tumors. In our case series, all patients had stage 1B3 disease. One patient had squamous cell carcinoma, and the other two had adenocarcinoma histology, all responding well to NACT. A limitation of the case series is the smaller number of patients who were HPV-positive, making it challenging to extrapolate these results to HPV-negative cases. The study by Li et al showed NACT followed by surgery may present a more favourable treatment option for stage IB3 cervical cancer.[5] In our case series as well, NACT followed by surgery yielded a favourable outcome.

CONCLUSION

In conclusion, neoadjuvant chemotherapy followed by radical surgery shows promise in treating stage 1B3 cervical cancer, offering significant tumour reduction and facilitating successful surgical intervention with favourable outcomes. Further research is warranted to elucidate the optimal patient selection criteria and the long-term benefits of this approach in improving survival rates and quality of life for cervical cancer patients.

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