

CASE REPORT

Integrating chemoradiotherapy and nivolumab in advanced cervical cancer: two case reports

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Abstract

Background: Cervical cancer is the fourth most common cancer among women globally, with high recurrence rates in locally advanced cases despite standard treatment with chemoradiotherapy and brachytherapy. Immune checkpoint inhibitors (ICIs), such as nivolumab, have shown promise in enhancing anti-tumor immunity, particularly when combined with conventional therapy. Emerging data suggest that integrating ICIs into treatment regimens for high-risk cervical cancer may improve survival and disease control. **Cases:** We present two cases highlighting this approach. A 77-year-old woman with clinical stage IIA cervical squamous cell carcinoma underwent radical hysterectomy with pT2a1N1M0 staging, followed by chemoradiotherapy and brachytherapy in 2021. One year later, recurrence in the para-aortic and iliac lymph nodes was detected and successfully treated with salvage radiation and concurrent chemo-immunotherapy using nivolumab. She achieved complete remission and remains disease-free at the latest follow-up. The second case involves a 39-year-old woman diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1 cervical squamous cell carcinoma with human papillomavirus (HPV)-16 positivity. She received chemoradiotherapy, brachytherapy, and immunotherapy with nivolumab, achieving complete remission and HPV clearance. In December 2021, recurrence in the para-aortic lymph nodes was treated with additional radiation, chemotherapy, and ongoing nivolumab maintenance. A hysterectomy in 2023 for abnormal bleeding revealed no residual disease, and the patient continues to be disease-free. **Conclusions:** These cases illustrate the potential benefit of combining chemoradiotherapy with maintenance immunotherapy using ICIs. This strategy may enhance progression-free survival and achieve durable disease control in advanced or recurrent cervical cancer. However, challenges such as treatment-related toxicity and resistance must be addressed. Continued research is vital to refine therapeutic protocols, identify predictive biomarkers, and optimize patient selection to maximize the benefits of this evolving treatment paradigm.

Keywords

Cervical cancer; Nivolumab; Immunotherapy; Recurrent disease; Concurrent chemoradiotherapy and immune checkpoint inhibitors

1. Introduction

Cervical cancer continues to be a major global public health challenge, ranking as the fourth most prevalent cancer among women according to epidemiological data, with an incidence of 7.6 per 100,000 women per year [1]. Cervical cancer risk is highest for women under 50 (0.3%) and decreases significantly with age. Lifetime risk is 0.7%, ranking lower than cancers like breast and lung [2]. Human papillomavirus (HPV) is identified in nearly 90% of cervical carcinomas and is the primary cause of these tumors. The E6 and E7 oncoproteins of HPV drive the disruption, proliferation and transformation of epithelial cells, leading to cancer development [3, 4]. World Health

organization's 90-70-90 target for cervical cancer elimination includes 90% HPV vaccination by age 15, 70% screening by ages 35 and 45 and 90% treatment for those diagnosed. Taiwan meets the vaccination and treatment targets but lags in screening at 43%. Improving screening rates to 70% could achieve elimination by 2038 [5]. Early-stage cervical carcinomas that are non-metastatic (measuring less than 4 cm and without detectable nodal invasion) are typically treated with surgery. On the other hand, locally advanced cervical cancer (LACC) is commonly addressed using a combination of chemoradiotherapy followed by brachytherapy [6]. Despite treatment, LACC carries a 40% risk of disease recurrence [7]. As a result, the 5-year overall survival rate for IIIC1 tumors (with pelvic lymph

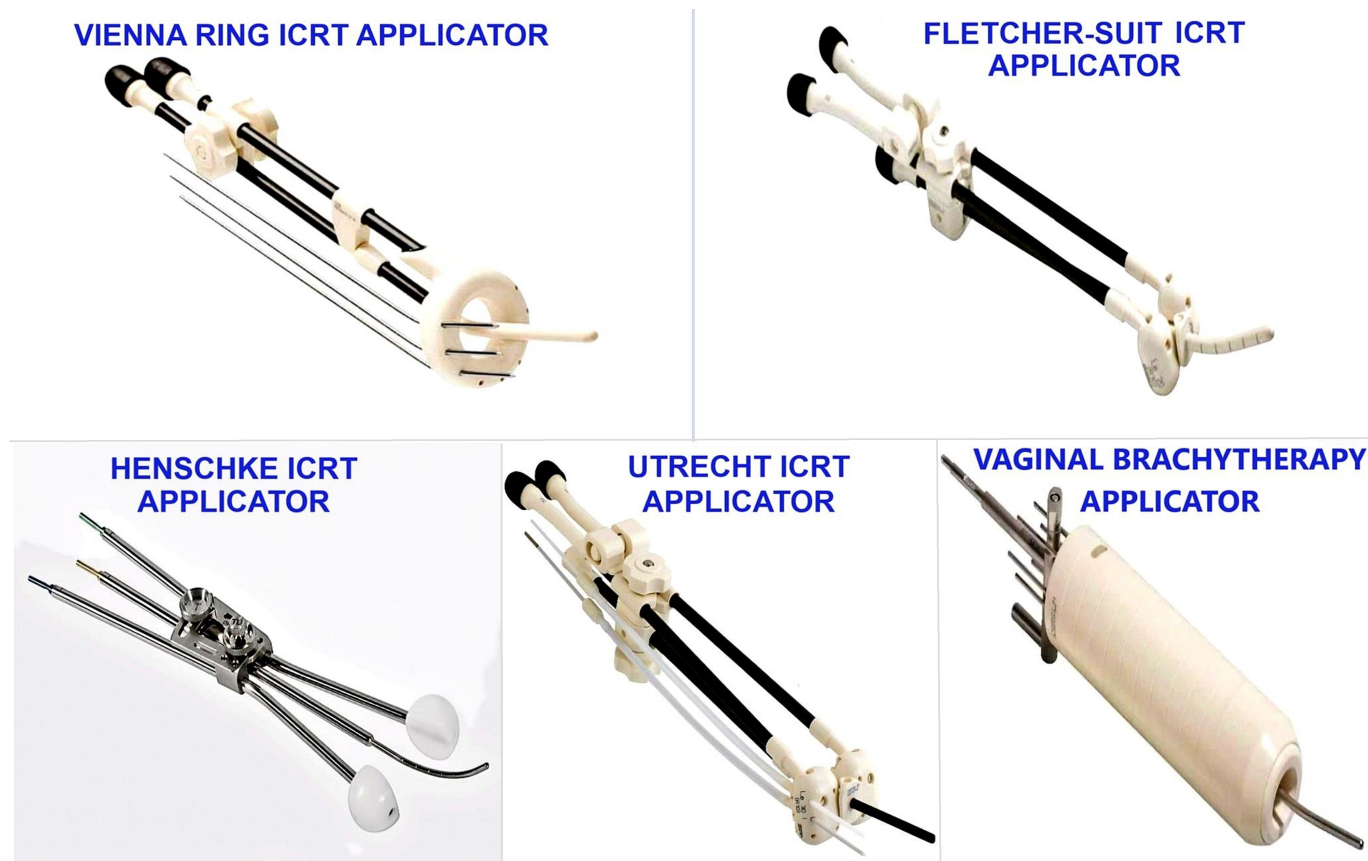


FIGURE 1. Brachytherapy instruments used in carcinoma cervix. Abbreviations: ICRT: Intracavitary radiation therapy.

node metastasis) was 76.3%, significantly higher than the 55.4% survival rate for IIIC2 tumors (with para-aortic lymph node metastasis) [8]. The primary treatments for patients with recurrent or metastatic cervical cancer include surgery, radiotherapy and chemotherapy. However, the 5-year survival rate for women with this condition is only 17%. The outlook for patients with recurrent disease remains very bleak, with an estimated overall survival of around 13 to 17 months [9]. Optimal image-guided brachytherapy significantly reduces the risk of recurrence and metastasis in locally advanced cervical cancer by precisely targeting cancerous tissues, leading to improved patient outcomes and a lower likelihood of the disease returning or spreading. The importance of these image-guided techniques is highlighted by the RetroEMBRACE study, enhancing the success of brachytherapy for cervical cancer [10] (Fig. 1). The development of T cell-targeted immunotherapies that block immune checkpoints, such as Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), Programmed Cell Death-1 (PD-1) and Programmed Death-Ligand-1 (PD-L1), has revolutionized the treatment of several solid tumors by leveraging the body's own immune system to fight cancer [11] (Fig. 2). Cervical cancer, in particular, is well-suited for this approach. The chronic infection with HPV often leads to the expression of immune-reactive viral neo-antigens and PD-L1 on cervical carcinoma cells, making the cancer more responsive to immune checkpoint inhibitors (ICI), as demonstrated in pre-clinical studies using murine models [12–14].

Nivolumab, an anti-PD-1 inhibitor, has shown promise in

this context, offering a targeted way to enhance the immune response against cervical cancer [15]. The KEYNOTE-826 phase III trial highlighted the potential of another anti-PD-1 inhibitor, pembrolizumab, when added to first-line chemotherapy. This combination significantly improved patient outcomes, increasing median progression-free survival (PFS) from 8.2 to 10.4 months and boosting 2-year overall survival (OS) from 40.4% to 50.4%. These results led to Food and Drug Administration (FDA) approval of the combination therapy, underscoring the potential of ICIs like Nivolumab in the ongoing fight against cervical cancer [16] (Table 1, Ref. [17–34]). Two cases of cervical cancer, both diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1 squamous cell carcinoma, involved a 77-year-old and a 39-year-old woman. Both patients underwent radical surgeries followed by chemoradiotherapy with cisplatin and Nivolumab. After para-aortic lymph node recurrences, additional treatments with Nivolumab were administered. Subsequent scans showed no evidence of disease, and both patients are currently alive and disease-free.

1.1 Case 1

A 77-year-old female, gravida 3 para 3 abortus 0 (G3P3A0), with a significant medical history of multiple comorbidities, including hypertension and diabetes mellitus, was diagnosed with cervical cancer following an irregular result on a routine Pap smear screening. In response to this abnormal finding, further diagnostic workup was conducted, including a Magnetic resonance imaging (MRI) of the pelvis performed

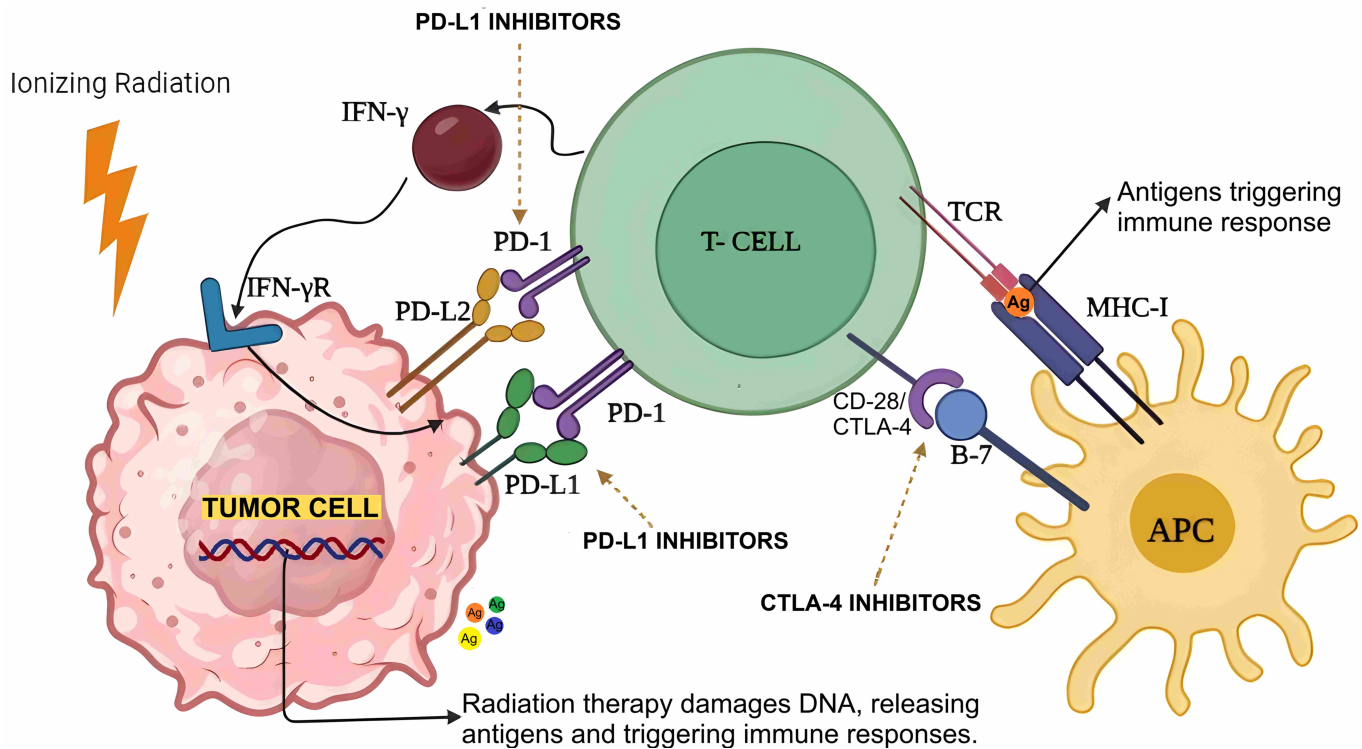


FIGURE 2. The image illustrates how immune checkpoint inhibitors (e.g., PD-1, PD-L1 and CTLA-4 inhibitors) enhance T-cell activity by blocking inhibitory signals from tumor cells, while radiotherapy promotes antigen release by damaging tumor DNA, thereby stimulating an immune response. Abbreviations: PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death-Ligand 1; PD-L2: Programmed Death-Ligand 2; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; IFN-γ: Interferon-gamma; TCR: T cell receptor; MHC-I: Major Histocompatibility Complex Class I; APC: Antigen Presenting Cells.

on 13 March 2021. The MRI revealed a uterine cervical malignancy measuring approximately $1.9 \times 1.4 \times 2.0$ cm, with involvement of the anterior fornix. Notably, there was no evidence of parametrial invasion or lymphadenopathy at the time of the scan. A biopsy of the lesion confirmed the diagnosis of squamous cell carcinoma (SCC) of the cervix.

In March 2021, the patient underwent a laparoscopic nerve-sparing radical hysterectomy, along with bilateral pelvic lymph node dissection. The histopathological report revealed squamous cell carcinoma of the cervix with a classification of pT2a1N1M0, corresponding to FIGO stage IIIC1. Given these findings, the patient was planned for adjuvant treatment with radiation therapy to the whole pelvis in combination with concurrent chemotherapy. She received a total radiation dose of 50.4 Gy to the pelvic region, delivered in 28 fractions, along with weekly cisplatin (40 mg/m^2), starting on 18 May and concluding on 30 June 2021. Following this, a parametrium boost was administered, raising the total dose to 54 Gy, delivered over 30 fractions (Fig. 3).

Further intensification of her treatment involved intracavitary brachytherapy, with two sessions of 5 Gy each, performed on 19 July and 26 July 2021. After completing the initial treatment, the patient was placed on regular follow-up. However, during her routine surveillance, a recurrence of the disease was detected in April 2022. A Positron Emission Tomography-Computed Tomography (PET-CT) scan conducted on 01 April 2022, revealed fluorodeoxyglucose (FDG)-avid nodules in the

abdominal para-aortic and paracaval regions, as well as in the bilateral common iliac lymph nodes. These findings were highly suggestive of tumor metastases outside the previous radiation treatment field. In response to this recurrence, the patient was initiated on salvage radiation therapy targeted to the para-aortic region. A total radiation dose of 45 Gy was delivered over 25 fractions, followed by a cone-down boost of an additional 18 Gy over 10 fractions (Fig. 4). This radiation treatment spanned from 27 April to 15 June 2022.

In conjunction with the salvage radiation, she was treated with concurrent chemotherapy and immunotherapy, including the immune checkpoint inhibitor nivolumab. After completing her salvage radiation and chemotherapy regimen, the patient continued on maintenance therapy with monthly infusions of nivolumab, which she received until August 2022. Throughout this period, she tolerated the treatment well, with no significant toxicity or adverse side effects reported.

A follow-up PET-CT scan, conducted after the completion of her treatment, showed no evidence of disease or metastasis, indicating a positive response to the therapy. As of the latest follow-up, the patient remains alive and disease-free.

1.2 Case 2

A 39-year-old married woman, gravida 0, para 0 (G0P0), was initially diagnosed with Cervical Intraepithelial Neoplasia grade 3 (CIN3) following a routine Pap smear screening. She subsequently underwent a conization procedure at an outside

TABLE 1. This table summarizes the use of immune checkpoint inhibitors in various gynecological cancers, along with their observed response rates (ORR), progression-free survival (PFS), and overall survival (OS) where applicable.

Cancer type	Study	Therapeutic agent	Outcome
Advanced cervical cancer	Callahan <i>et al.</i> [17], Phase I	Durvalumab + Tremelimumab	46.2% stable disease >24 wk, no partial response
Advanced cervical cancer, PD-L1+	Frenel <i>et al.</i> [18], Phase Ib	Pembrolizumab	ORR: 17%
Persistent/recurrent cervical cancer	Santin <i>et al.</i> [19], Phase I/II	Nivolumab	ORR: 4%, OS at 6 mon: 78.4%
Recurrent cervical cancer	Hollebecque <i>et al.</i> [20], Phase I/II	Nivolumab	ORR: 5%
Advanced cervical cancer, PD-L1+	Chung <i>et al.</i> [21], Phase II	Pembrolizumab	ORR: 14.3%
Advanced cervical cancer	Friedman <i>et al.</i> [22], Phase II	Atezolizumab + Bevacizumab	ORR: 0%
Metastatic/recurrent cervical cancer	Lheureux <i>et al.</i> [23], Phase II	Ipilimumab	PFS: 2.5 mon, OS: 8.5 mon, ORR: 3%
Cervical cancer with positive Lymph node	Tewari <i>et al.</i> [24], Phase III	Cemiplimab	ORR 16.4%, OS at 8.5 mon
EM with d-MMR/MSI-H	KEYNOTE 016, 158, 028 [25]	Pembrolizumab	ORR: 39.6%
EM (POLE, MSI-H)	Santin <i>et al.</i> [26]	Nivolumab	Prolonged response (>7 mon) in 2 pts
Advanced/metastatic PD-L1+ EM,	Ott <i>et al.</i> [27], Multicohort Phase 1b	Pembrolizumab	ORR: 13%
Endometrial cancer (EM) with MMR-d	Le <i>et al.</i> [28], Phase II	Pembrolizumab	ORR: 40%
Metastatic EM	Hasegawa <i>et al.</i> [29], Phase II	Nivolumab	ORR: 23%, PFS: 3.6 mon
Metastatic EM	Fleming <i>et al.</i> [30], Phase II	Atezolizumab	ORR: 13%, PFS: 1.7 mon
Recurrent EM	NCT03526432 [31], Phase III	Atezolizumab + Bevacizumab	Ongoing
Recurrent EM	Lheureux <i>et al.</i> [32], Phase II	Nivolumab + Cabozantinib	ORR + SD higher than monotherapy
Advanced/recurrent EM with MSI-H	GARNET Trial, Phase II [33]	TSR-042	ORR: 52%
Metastatic EM	KEYNOTE 775 Makkar <i>et al.</i> [34], Phase III	Pembrolizumab + Lenvatinib	ORR: 48%, DCR: 96%

Abbreviations: PD-L1: Programmed Death-Ligand 1; d-MMR: Deficient mismatch repair; MSI-H: Microsatellite instability-high; POLE: DNA polymerase epsilon.

medical center in May 2019. Further diagnostic evaluations confirmed the presence of Human Papillomavirus (HPV) type 16. Her serum squamous cell carcinoma antigen (SCC) levels were measured at 2.80 ng/mL initially, rising to 3.9 ng/mL in June 2019. Magnetic Resonance Imaging (MRI) of the pelvis revealed a 3.1 cm cervical tumor with involvement of the right iliac lymph node. A cervical biopsy confirmed the presence of squamous cell carcinoma. In December 2020, the patient underwent a laparoscopic lymph node dissection, which staged her disease as pT1N1M0, corresponding to FIGO stage IIIC1.

Given the staging of her disease, the treatment plan consisted of radiation therapy to the entire pelvic region combined with concurrent chemotherapy. The patient received pelvic radiation therapy at a dose of 50.4 Gy over 28 fractions from 29 December 2020, to 05 February 2021. Additionally, a

parametrial boost was administered, increasing the dose to 54 Gy over 30 fractions (Fig. 5). Concurrently, she was treated with cisplatin chemotherapy, delivered weekly (40 mg/m²), along with immunotherapy using nivolumab from January to March 2021. Further, the patient underwent brachytherapy with intracavitary radiation therapy (ICRT), receiving 5 Gy per fraction across five sessions on 31 March, 08 April, 15 April, 22 April and 29 April of 2021.

Upon completion of this multimodal treatment, the patient achieved complete resolution of her cervical cancer, and follow-up testing confirmed that she was HPV-negative. She was placed on a regular follow-up schedule, which included receiving Virus-like particle (VLP) vaccinations and undergoing periodic PET/CT scans. Monitoring of her SCC tumor marker levels showed an initial reduction

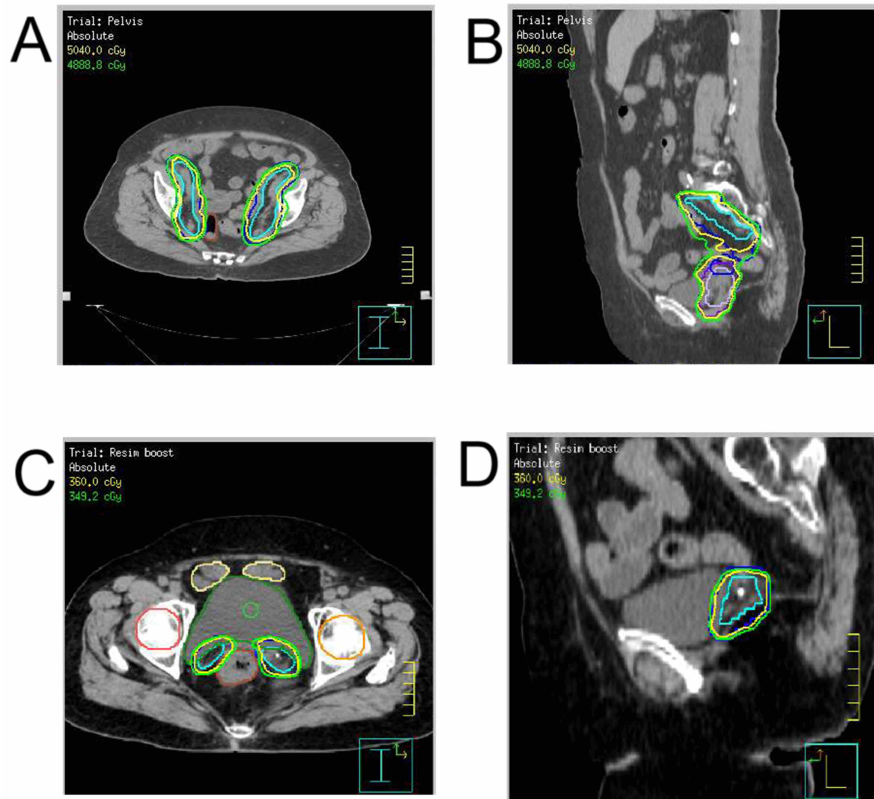


FIGURE 3. The dose distributions for Volumetric Modulated Arc Therapy (VMAT) to the pelvis are presented in axial (A) and sagittal (B) views. The isodose lines for the primary dose of 50.4 Gy (yellow) and 48.8 Gy (green) are highlighted. Additionally, the isodose lines for the boost dose of 3.6 Gy (yellow) to the parametrium are shown in axial (C) and sagittal (D) views. Isodose lines near the target shows organs at risk-left femoral head (orange), right femoral head (red) and rectum (red).

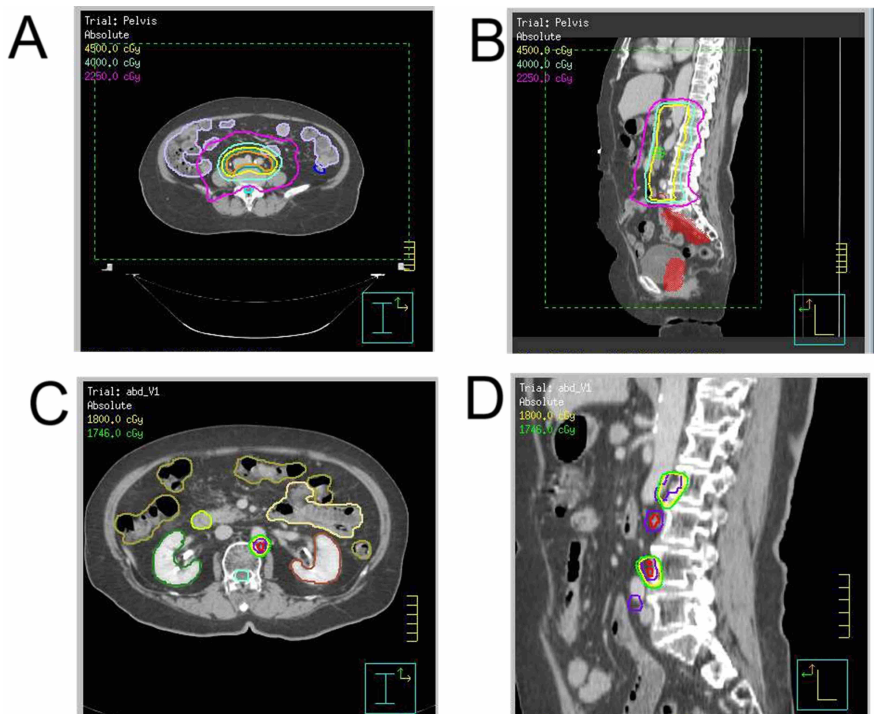


FIGURE 4. Dose distributions of Volumetric Modulated Arc Therapy (VMAT) for radiotherapy targeting para-aortic lymph nodes are shown in axial (A) and sagittal (B) views. The isodose lines for 45 Gy (yellow), 40 Gy (green) and 22.5 Gy (purple) are highlighted. The red coloured area in image B shows previously irradiated pelvic disease. Additionally, the isodose lines for the boost dose of 18 Gy (yellow) are displayed in axial (C) and sagittal (D) views. Isodose lines near the target shows organs at risk-bowel (yellow), left kidney (red) and right kidney (green).

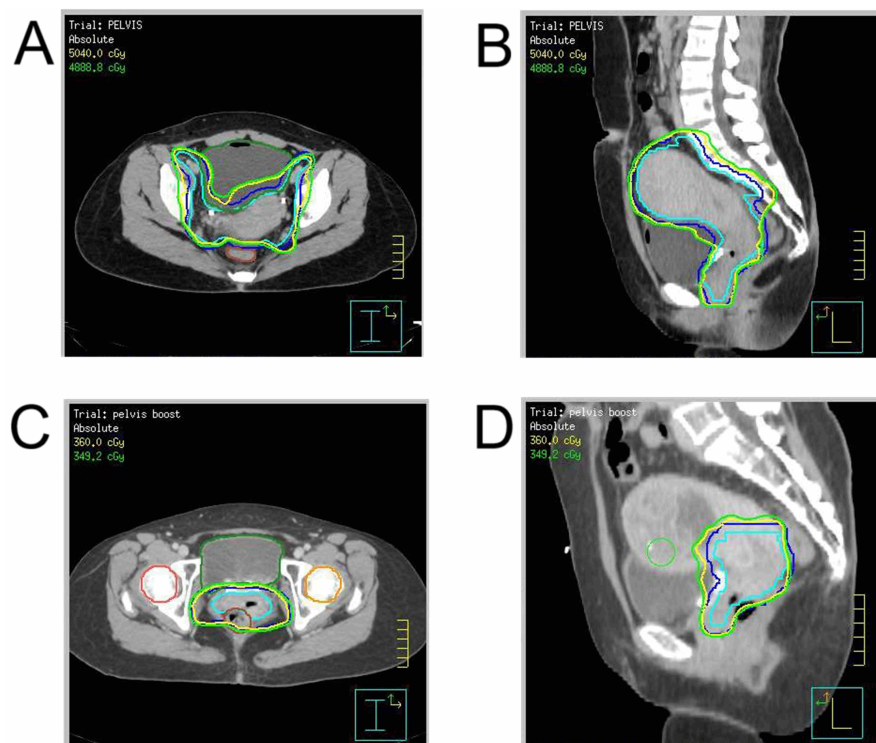


FIGURE 5. Dose distributions of Volumetric Modulated Arc Therapy (VMAT) for pelvic radiotherapy are illustrated in the axial (A) and sagittal (B) views. The isodose lines for 50.4 Gy (yellow) and 48.8 Gy (green) are highlighted. Additionally, the isodose lines for the boost dose of 3.6 Gy (yellow) to the parametrium are shown in the axial (C) and sagittal (D) views. Isodose lines near the target shows organs at risk- left femoral head (orange), right femoral head (red) and rectum (red).

post-treatment, with stability between 0.4 and 1.1 ng/mL thereafter. Her Cancer antigen-125 (CA-125) levels remained within normal limits, fluctuating between 7 and 7.1 U/mL.

However, in December 2021, a PET/CT scan revealed disease progression, with recurrence identified in the para-aortic lymph nodes (PALN). Consequently, the patient was subjected to abdominal radiation therapy, receiving a total dose of 50 Gy over 25 fractions beginning on 13 January 2022. Follow-up imaging in February 2022 indicated a partial response (PR) to this treatment. As a result, a cone-down radiation boost of 10 Gy over 5 fractions was administered from 01 March to 07 March 2022 (Fig. 6). During this period, she also continued with weekly cisplatin chemotherapy and monthly nivolumab infusions. Maintenance therapy with Nivolumab was sustained until 12 December 2022.

Throughout her treatment course, the patient tolerated the therapies well, with no significant adverse effects reported. However, a PET/CT scan conducted on 01 March 2023, demonstrated increased FDG uptake in the left uterus and cervix, suggestive of a recurrence. The right para-aortic lymph node showed regression, and a calcified uterine mass was considered likely benign. Mild FDG uptake in the hilar regions and L5 vertebra was attributed to inflammatory changes.

In response to these findings and due to abnormal vaginal bleeding, the patient underwent a laparoscopic-assisted vaginal hysterectomy in February 2023. Intraoperative findings included the presence of a myoma, but no residual carcinoma was identified. Subsequent MRI imaging in December 2023 demonstrated complete resolution of the disease. The pa-

tient has remained disease-free since and continues on regular follow-up without any signs of recurrence. She is alive and in good health at the present time.

2. Discussion

Approximately 70% of cervical cancers worldwide are attributed to persistent infections with human papillomavirus (HPV) types 16 and 18. Unlike many other gynecological cancers, the cause of cervical cancer is relatively well understood. The development of the HPV vaccine aims specifically to prevent cervical cancer by targeting these high-risk virus strains [35]. For patients with stage IB3 and stage IIA2 cervical cancer, the standard of care is pelvic external beam radiotherapy (EBRT) combined with concurrent platinum-based chemotherapy and brachytherapy. An alternative approach, considered a category 2B recommendation, is primary surgery involving radical hysterectomy with pelvic lymphadenectomy, with or without para-aortic lymphadenectomy [5]. Locally advanced cervical cancer (LACC), encompassing FIGO 2018 stages IB3 and IIA2-IVA, represents around 50% of newly diagnosed cervical cancer cases. The standard treatment for LACC, unchanged for the past two decades, involves weekly cisplatin administered concurrently with external beam radiotherapy (typically 45 Gy) followed by brachytherapy [36, 37]. Following the completion of concurrent chemoradiotherapy (CCRT), the 5-year overall survival rate is around 70% [38]. Outcomes are particularly poor for high-risk groups, specifically those with stage III and IVA disease, according to the 2018 FIGO staging system. Patients with pelvic lymph

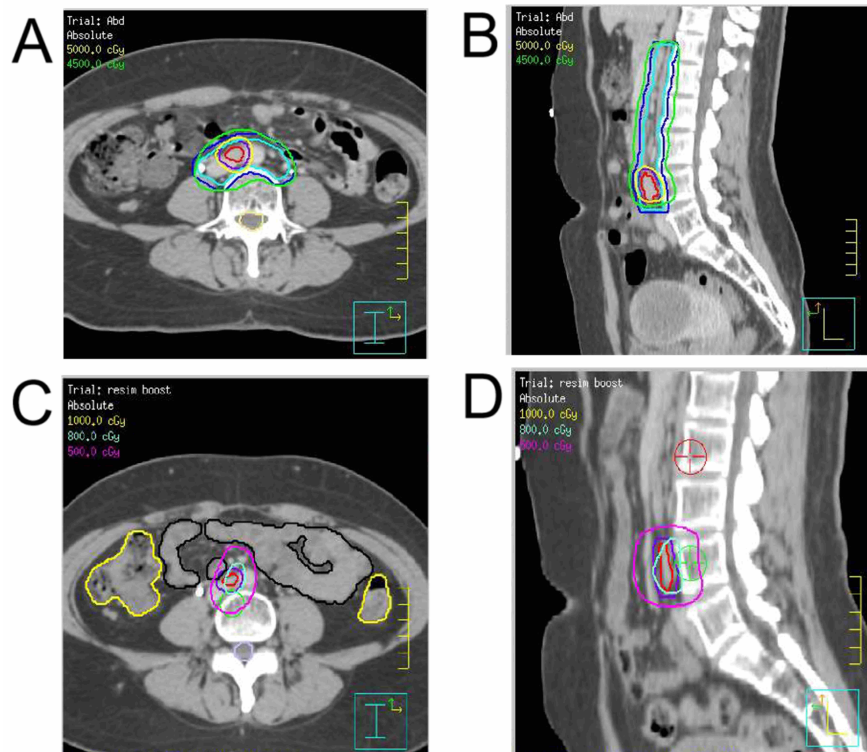


FIGURE 6. Illustrations of dose distributions for Volumetric Modulated Arc Therapy (VMAT) targeting the para-aortic lymph nodes are presented in axial (A) and sagittal (B) views. The 50 Gy (yellow) and 45 Gy (green) isodose lines are highlighted. Additionally, the isodose lines for the boost dose of 10 Gy (yellow) are shown in axial (C) and sagittal (D) views. Isodose lines near the target shows organs at risk—here only bowel (yellow) is seen.

node involvement have a 5-year overall survival (OS) rate of 34%, while those with para-aortic nodal involvement face a significantly lower 5-year OS rate of just 12% [39–43].

The combination of radiotherapy and chemotherapy became standard for treating locally advanced cervical cancer (LACC), offering improved survival rates. Technological advancements have significantly enhanced treatment precision and outcomes, transitioning from 2D techniques to modern approaches like intensity-modulated radiotherapy (IMRT) and image-guided brachytherapy. These advancements have reduced treatment toxicity and increased the efficacy of cancer management [44].

A study done to explore the effects of radiation therapy (RT) on metastatic cervical cancer in a cohort of 58 patients. Findings indicated that the RT group experienced a notably higher progression-free survival (PFS) rate compared to the non-RT (NRT) group (66.7% vs. 40.0%, $p = 0.039$), while overall survival (OS) rates remained comparable between the two groups. Interestingly, RT showed particular efficacy in specific patient subgroups, such as those over 45 years of age and those with squamous cell carcinoma. Importantly, no significant increase in treatment-related toxicity was observed in the RT group. The study also highlighted that RT, along with immunotherapy and limited metastasis, were linked to improved PFS, although this did not extend to OS [45]. Immune checkpoint inhibitors (ICIs) are a promising therapy for cervical cancer, especially in advanced stages where traditional treatments like chemotherapy and radiotherapy offer limited survival benefits. ICIs target specific immune checkpoint molecules such as PD-1/PD-L1 and CTLA-4, which tumor

cells use to evade immune detection. By blocking these molecules, ICIs enhance the body's immune response against cancer cells. Recent clinical studies have shown improved survival rates in patients treated with ICIs, making them an important advancement in the treatment of recurrent and metastatic cervical cancer [46, 47].

Numerous studies have examined the effects of ICI treatment on cervical cancer (Table 1). The phase Ib KEYNOTE-028 trial, which assessed pembrolizumab in PD-L1-positive advanced cervical cancer, reported an overall response rate (ORR) of 17% (4 out of 24 patients). While 75% of patients experienced immune-related side effects, no Grade 4 side effects or treatment-related deaths occurred [18]. The phase 2 KEYNOTE-158 study evaluated the antitumor activity of pembrolizumab in patients with advanced cervical cancer. The study demonstrated an overall response rate (ORR) of 14.3%, with 2.6% of patients achieving a complete response (CR) and 11.7% showing a partial response (PR). Notably, among patients with PD-L1-positive tumors, the ORR was higher, at 16.0%. These results highlight the potential of pembrolizumab as a targeted therapy for PD-L1-positive cervical cancer, offering hope for more effective treatments in advanced cases. The findings further support pembrolizumab's role in immunotherapy for improving outcomes in this challenging patient population [21]. These studies confirmed the therapeutic efficacy of pembrolizumab in patients with PD-L1-positive cervical cancer, leading to its FDA approval for treating progressive or recurrent PD-L1-positive cervical cancer. In a phase III trial with cemiplimab, another PD-1

inhibitor, the overall survival (OS) was significantly improved in the cemiplimab group, with a median OS of 12 months compared to 8.5 months in the chemotherapy group (hazard ratio (HR) 0.69, $p < 0.001$). Although PD-L1 testing was not conducted across all cemiplimab-treated groups, the data revealed an OS of 13.9 months for PD-L1-positive patients and 7.7 months for PD-L1-negative patients, suggesting greater antitumor activity in PD-L1-positive individuals [24].

The KEYNOTE-A18 and chemoradiotherapy for locally advanced cervical cancer (CALLA) trials both investigated the role of immune checkpoint inhibitors combined with chemoradiotherapy (CRT) in locally advanced cervical cancer, but their outcomes differed significantly due to patient characteristics and the antibodies used. KEYNOTE-A18 enrolled a high-risk population, primarily with FIGO 2014 stage III–IVA disease, with many patients having node-positive cancers, contributing to their high risk of recurrence. Pembrolizumab, a PD-1 inhibitor, was used in conjunction with CRT, and it significantly improved progression-free survival (PFS) and overall survival (OS). The success of pembrolizumab in KEYNOTE-A18 was attributed to its ability to block PD-1 on T-cells, effectively reinvigorating the immune response against tumors. Over 90% of patients in this trial completed the planned radiation doses, further enhancing treatment efficacy. Additionally, the high proportion of PD-L1-positive patients (94–95%) likely contributed to the favorable outcomes with pembrolizumab. In contrast, the CALLA trial evaluated durvalumab, a PD-L1 inhibitor, with CRT in patients who had stages IB2 to IVA cervical cancer. The trial did not show significant improvement in PFS, potentially due to a lower PD-L1 expression rate (29–33%). Unlike pembrolizumab, which targets the PD-1 receptor on T-cells, durvalumab targets PD-L1 on tumor cells. The differences in PD-L1 expression between the trials and the distinct mechanisms of action of these antibodies might have influenced their efficacy. Furthermore, a higher percentage of patients in CALLA experienced treatment-related deaths (1.2% with durvalumab vs. 0.3% with pembrolizumab), which may have affected the outcomes. Ultimately, KEYNOTE-A18's results led to pembrolizumab being approved for high-risk locally advanced cervical cancer, underscoring the importance of patient selection and biomarker expression in immunotherapy trials [48, 49].

A meta-analysis including seven studies with a total of 727 patients was done, among these, there was one phase III randomized controlled trial (RCT), four phase II RCTs, one phase I RCT and one observational study. All studies were published in the past five years (2017–2021), highlighting recent advancements in immune checkpoint inhibitors for cervical cancer treatment. Six studies utilized pembrolizumab as monotherapy, while one used a combination therapy. Of the 727 patients treated with pembrolizumab, 604 (83.08%) had squamous cell carcinoma, 93 (12.79%) had adenocarcinoma, 21 (2.89%) had adenosquamous carcinoma and 9 (1.24%) had other types. Squamous cell carcinoma was the most common, representing over 70% of cases. Treatment outcomes included a complete response rate of 2.7%, partial response rate of 10.4%, stable disease rate of 19% and disease progression rate of 54.1%. The objective response rate was 15.5% and the disease control rate was 33.1%. Median overall survival

was about 10.23 months, median progression-free survival was 4.27 months and best response time was 2.1 months. The one-year mortality rate was 38.8%. Major adverse events were manageable and included hepatic dysfunction, hypothyroidism, neutropenia, decreased appetite and fatigue, with grade 3 or higher adverse events occurring in 21.2% of patients [50]. The National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group, and Gynecologic Oncology Group (NRG) GY017 trial investigated the combination of chemoradiotherapy and atezolizumab in cervical cancer. T-cell clonal expansion was observed, mainly due to radiation rather than the immune checkpoint inhibitor. Clonal expansion occurred in both tumors and peripheral blood, with 72% disease-free survival at 12 months. No significant differences were found between treatment arms in T-cell responses. The sequencing of CRT and immune checkpoint blockade requires further exploration [51]. The Nivolumab plus chemoradiotherapy in locally-advanced cervical cancer (NICOL) study assessed overall response rate (ORR), progression-free survival (PFS), and treatment tolerance in 16 patients with locally advanced cervical cancer treated with concurrent chemoradiotherapy and nivolumab. Median age was 46 years. Tumors were predominantly HPV-positive squamous cell carcinomas. Three patients had dose-limiting toxicities including hypotension and acute kidney injury, and one developed a grade 3 immune-related adverse event after nivolumab maintenance. Two months post-brachytherapy, ORR was 93.8%. With a median follow-up of 16.6 months, 1-year PFS was 81.2%. Nivolumab with CRT shows promise for LACC, but further studies are needed [52]. This lymphopenia might indicate a higher risk of immune-related adverse events and a shorter time to progression during immune checkpoint inhibitor treatment, underscoring the need for frequent lab tests [53]. In 2021, data on the efficacy and safety of balstilimab, a monoclonal antibody targeting PD-1, were published. The phase II trial C-700-01 included 140 patients with previously treated recurrent or metastatic cervical cancer (62.7% with squamous cell carcinoma, 32.3% with adenocarcinoma and 4.3% with adenosquamous carcinoma). These patients received balstilimab at a dose of 3 mg/kg intravenously every two weeks for up to 24 months. In terms of PD-L1 status, 61.5% of patients had a combined positive score (CPS) ≥ 1 , 26.7% had a CPS < 1 and 11.8% were not evaluable. The overall response rate (ORR) was 15%, with a median duration of response (DOR) of 15.4 months in the entire population. Among patients with PD-L1-positive tumors, the ORR was 20.0% (95% Confidence interval (CI), 12.9–29.7), while it was 7.9% in PD-L1-negative patients. Responses were observed across all histologic subtypes. In terms of safety, the most common treatment-related adverse events (AEs) were asthenia, diarrhea and pruritus, with immune-mediated enterocolitis (3.1%) being the most frequent grade 3 treatment-related AE. Following these promising results, the Balstilimab Versus Investigator Choice Chemotherapy in Patients with Recurrent Cervical Cancer (BRAVA) trial (NCT04943627), a phase III randomized study, was initiated to compare balstilimab with the investigator's choice of chemotherapy in patients with recurrent, persistent or metastatic cervical cancer who had progressed after platinum-based chemotherapy. However, the

BRAVA trial was discontinued following the FDA approval of pembrolizumab as a single agent for this patient population [54].

The CheckMate 358 trial assessed nivolumab and its combination with ipilimumab for recurrent or metastatic cervical cancer. Patients received either nivolumab 240 mg every 2 weeks, nivolumab 3 mg/kg plus ipilimumab 1 mg/kg every 6 weeks, or nivolumab 1 mg/kg plus ipilimumab 3 mg/kg for four cycles followed by nivolumab. Of 193 patients, 176 were treated with various regimens. Objective response rates were 26% with nivolumab alone, 31% with nivolumab plus ipilimumab (NIVO3 plus IPI1) and 38% with the NIVO1 plus IPI3 regimen. The combination therapies showed better responses but higher rates of serious adverse events [55]. Although the small sample size limited the detection of significant transcriptomic differences, some genetic markers were identified. In patients with progression-free (PF) tumors, gene sets related to immune response, such as Interferon (IFN)-related pathways, were more prevalent [56]. In cervical cancer, immune checkpoint inhibitors and genes such as Vascular endothelial growth factor (VEGF) and Kirsten rat sarcoma virus oncogene (KRAS) play crucial roles. ICIs enhance immune response against cancer cells, but some patients develop resistance, underscoring the need for predictive biomarkers. VEGF contributes to immune evasion by promoting angiogenesis and recruiting suppressive immune cells. KRAS mutations often drive tumor progression and can influence response to ICIs. Gene expression signatures related to immune activation and inflammation, such as those involving IFN- γ and T-cell markers, are generally predictive of ICI response, while signatures related to oncogene signaling or stroma often correlate with resistance [57, 58]. In contrast, patients with progressive disease (PD) showed enrichment in gene sets linked to ICI resistance, including epithelial-mesenchymal transition (EMT), angiogenesis-related and KRAS gene sets [59]. The study also highlighted recurrent genetic alterations in cervical cancer, such as FAT atypical cadherin 1 (FAT1), serine/threonine kinase 11 (STK11), caspase 8 (CASP8), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) and yes-associated protein 1 (YAP1), which are associated with cell proliferation, metastasis inhibition and therapy resistance. However, no direct correlation between these genetic alterations and objective response rates (ORR) was found due to the small sample size [60]. With the FDA's approval of pembrolizumab combined with CRT for FIGO 2014 stage III to IVA cervical cancer, immunotherapy now offers a survival benefit for high-risk patients. The study on prolgolimab, a triplet regimen combining prolgolimab (an anti-PD-1 antibody) with chemotherapy and bevacizumab, was conducted under (NCT04058389). It demonstrated promising efficacy and safety for advanced cervical cancer. Key results include an overall response rate of 45% and a median progression-free survival of 8.6 months. The combination was well-tolerated, with manageable adverse effects. These findings suggest that the prolgolimab triplet regimen could be a potent new option for treating advanced cervical cancer [61, 62]. Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of solid tumors by targeting proteins such as CTLA-4, PD-1 and PD-L1 that suppress immune responses, thus

enabling the immune system to attack cancer cells. These drugs have shown significant success, particularly in cancers like melanoma and non-small cell lung cancer (NSCLC). Newer targets like Lymphocyte activation gene 3 (LAG-3) are also emerging, expanding the therapeutic scope. However, ICIs face challenges such as variability in treatment response, immune-related adverse events and drug resistance, which complicate their broader application. Overcoming these issues is a focus of ongoing research, with efforts aimed at optimizing biomarkers, combination therapies, and advanced technologies like oncolytic virus gene editing and mRNA vaccines [63]. The meta-analysis, published in *Medicine* (Baltimore), evaluates the efficacy of immune checkpoint inhibitors (ICIs) as maintenance therapy for patients with advanced or metastatic cancers. The analysis included five randomized controlled trials (RCTs) with 2828 participants, exploring the outcomes of progression-free survival (PFS), overall survival (OS) and objective response rate (ORR). Key findings suggest that ICI maintenance therapy significantly improves OS (HR = 0.82) and ORR (odds ratio (OR) = 2.24) compared to traditional treatments like placebo or observation. Subgroup analyses revealed that anti-PD-L1 antibodies notably increased OS, while anti-PD-1 and anti-PD-1 plus CTLA-4 antibodies significantly enhanced PFS. However, ICI maintenance therapy did not show a significant improvement in overall PFS (HR = 0.88). Additionally, patients with PD-L1-positive tumors benefited more from ICI maintenance therapy than those with PD-L1-negative tumors. In result, ICI maintenance therapy shows promise for extending OS and improving ORR in advanced or metastatic cancer patients, but its impact on PFS remains less clear. The study highlights the potential clinical value of ICIs, particularly in patients with PD-L1-positive tumors [64]. Nivolumab and pembrolizumab are key immune checkpoint inhibitors used for advanced cervical cancer, with dosing regimens of 240 mg every 2 weeks or 480 mg every 4 weeks for nivolumab, and 200 mg every 3 weeks for pembrolizumab. Both drugs demonstrate significant clinical benefits, though their cost-effectiveness may vary. Nivolumab's less frequent dosing could potentially reduce overall costs compared to pembrolizumab's every-3-week schedule. While studies reveal both drugs improve overall survival and progression-free survival, the choice may hinge on patient-specific factors and cost considerations. Nivolumab, in particular, has shown durable responses in some patients, indicating its potential for long-term benefit. Patients who could not afford standard nivolumab treatment received low-dose nivolumab (20 or 100 mg fixed dose every 3 weeks). Others received standard dose of 3 mg/kg every 2 weeks. Ultimately, selecting between these treatments involves balancing efficacy, safety profiles and economic factors, underscoring the need for further research to optimize cost-effectiveness while ensuring clinical benefits [65].

A retrospective study evaluated the use of low-dose nivolumab in patients with recurrent/metastatic cervical cancer (R/M CC) who could not afford standard dosing. The study included 20 patients treated between March 2020 and June 2023, with a median age of 54.3 years. Most patients had prior surgery (85%) and radiotherapy (85%), and 55% received nivolumab alongside platinum-based chemotherapy.

Patients received an average of 4.75 doses at a mean dose of 0.84 mg/kg. Response rates were promising, with a 50% overall response rate: 25% achieved complete response, while another 25% had stable disease. The median progression-free survival was 7.97 months. Treatment-related adverse events occurred in 40% of patients, mainly mild to moderate, with only 15% experiencing grade 3 toxicity. No severe grade 4 or 5 toxicities were reported. The study concludes that low-dose nivolumab is an effective and well-tolerated option, potentially increasing accessibility in low- and middle-income countries, where cervical cancer prevalence and financial constraints limit treatment options [66].

The COLIBRI trial (GINECO-CE108b) is a multicenter, window study designed to assess the immune impact and safety of combining nivolumab (anti-PD-1) with ipilimumab (anti-CTLA-4) before starting standard radio-chemotherapy (RTC) for patients with locally advanced cervical cancer (stage IIB to IVA). Cervical cancer, which has a high recurrence risk in advanced stages, is traditionally treated with RTC, but immune checkpoint inhibitors like nivolumab and ipilimumab have shown potential in recurrent or metastatic cases. The trial includes 40 patients who receive a pre-treatment dose of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg), followed by maintenance nivolumab every 2 weeks post-RTC for up to 6 months. Researchers aim to examine immune response and tumor environment changes through paired biopsies taken before and after the immune therapy. This phase 2 trial evaluated neoadjuvant nivolumab and ipilimumab followed by chemoradiation in cervical squamous cell carcinoma, focusing on immune modulation and outcomes. Among 40 patients (50% advanced stage), the treatment was well-tolerated, with significant increases in Cluster of differentiation 8 positive (CD8+) T cells, CD8+/Forkhead box P3 positive (FOXP3+) ratios and immune activation markers. An 82.5% complete response rate at six months post-treatment highlights its efficacy, suggesting this approach is safe, enhances immune responses and shows promising clinical results [67].

Nivolumab, a PD-1 inhibitor, played a key role in managing recurrent cervical cancer in both cases by restoring T-cell-mediated antitumor immunity. In clinical cases discussed above, *i.e.*, Case 1, it was combined with salvage radiation and chemotherapy, leading to complete disease resolution without significant toxicity. In Case 2, it was used with chemoradiation and brachytherapy, followed by salvage therapy for recurrence, achieving sustained disease control. Its low toxicity, affordability, and efficacy make nivolumab a cost-effective and tolerable option, particularly suitable for advanced cervical cancer in resource-limited settings.

Concurrent use of immune checkpoint inhibitors with radiation therapy is safe, improving outcomes in node-positive, locally advanced disease. High-quality external beam radiation and image-guided brachytherapy are recommended to reduce toxicities.

3. Conclusion and future prospective

The evolution of modern medical technology has markedly improved survival outcomes in gynecological cancers such as cervical cancer. Yet, treatment options for advanced stages remain

constrained, despite the application of surgery, chemotherapy and radiation. The ICIs have emerged as a revolutionary approach in treating advanced gynecological malignancies, including cervical cancer, by reactivating the immune system suppressed by tumors. Numerous studies have explored the efficacy of ICIs, both as monotherapy and in combination with other treatments, with ongoing research striving to unlock their full therapeutic potential. PD-1 and PD-L1 inhibitors have shown particular promise, especially in patients with favorable molecular profiles, such as MSI-H or d-MMR in endometrial cancer. Understanding the intricacies of anti-PD-1, anti-PD-L1 and anti-CTLA-4 agents, along with managing the immune-related adverse effects, is key to maximizing their clinical benefit. The cost-effectiveness comparison between nivolumab and pembrolizumab shows that the choice of treatment may vary depending on patient-specific factors, particularly weight. Nivolumab, especially when weight-based dosing is considered, tends to offer better cost-effectiveness in certain cases. Fixed-dose nivolumab may also provide cost savings compared to pembrolizumab in specific scenarios. Decision-making should therefore take into account both cost thresholds and individual patient characteristics to optimize outcomes.

Recent ongoing clinical trials underscore the promising role of integrating ICIs with concurrent chemoradiotherapy in advanced cervical cancer. The upcoming study (NCT05588219) will evaluate the efficacy and safety of combining Tislelizumab with concurrent chemoradiotherapy for treating locally advanced cervical cancer. Targeting patients with cervical masses larger than 4 cm, regional lymph node metastasis and stages IIIA, IIIB or IVA, this prospective, single-arm, phase II trial involves 30 participants, with treatments including external irradiation, brachytherapy, chemotherapy with Cisplatin (DDP), and Tislelizumab to develop a more individualized and effective treatment strategy. Another study (NCT06455072) will explore the combination of Nituzumab and Serplulimab with stereotactic body radiotherapy (SBRT) in patients with recurrent advanced cervical cancer resistant to platinum-based chemotherapy. This phase II trial focuses on the role of immune checkpoint inhibitors and the potential of SBRT to enhance immunotherapy efficacy. A clinical trial (NCT05824468) is currently evaluating the combination of zimberelimab and lenvatinib in patients with advanced cervical cancer who have experienced relapse following prior ICI therapy. The study aims to determine the potential benefits of retreatment with ICIs in this patient population. A phase II trial (NCT05824494) will evaluate cadonilimab, a bispecific anti-PD-1/CTLA-4 antibody, in combination with nab-paclitaxel for patients with recurrent or metastatic cervical cancer, assessing objective response rate (ORR), progression-free survival (PFS), overall survival (OS), and potential biomarkers for predicting treatment efficacy.

The combination of ICIs with radiotherapy presents a promising strategy to amplify anti-tumor responses, particularly in advanced or recurrent cases. This approach holds the potential to not only extend progression-free survival but also provide durable responses in metastatic disease. However, challenges such as managing treatment-

related toxicities and overcoming resistance persist. This study is limited by its case report design, which lacks generalizability and does not establish causality. The small sample size and absence of a control group make it difficult to draw definitive conclusions about treatment efficacy. Larger prospective studies are needed to validate these findings and assess long-term outcomes of integrating immunotherapy with chemoradiotherapy in cervical cancer. Future research must focus on refining therapeutic protocols, identifying predictive biomarkers, and optimizing patient selection to achieve the best outcomes. As our understanding of the intricate interplay between tumor and immune system deepens, combining ICIs with chemoradiotherapy could herald a new era in the treatment of advanced cervical cancer, offering renewed hope for prolonged survival and enhanced quality of life.

AVAILABILITY OF DATA AND MATERIALS

All data supporting the findings of this study are included within the article.

AUTHOR CONTRIBUTIONS:

JTQ—designed the research. GT—wrote the manuscript. DWQ, GT—performed the research. KCW, JTQ—analyzed the research. HLL, TW—analyzed radiation therapy part of the research. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The patient provided informed consent for the publication of this case report.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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