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A REVIEW ARTICLE ON TREATMENT STRATEGIES AND RESPONSE RATE OF ADVANCED/ RECURRENT CERVICAL CANCER

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ABSTRACT

Cervical cancer is one of the major causes of death globally. Recurrent cervical cancer must be treated aggressively in order to maintain the survival rate. Despite the fact that advanced cervical cancer cannot be cured, certain treatments can control it and improve the quality of life (QOL). A doctor will administer treatment for a patient's ailment and observe as the patient's health improves as a result. The therapy options and treatment response rates for patients with advanced or recurrent cervical cancer have been covered in this review.

Keywords: Cervical cancer, Treatment strategies, Cisplatin

INTRODUCTION:

Cervical cancer is the third most common cancer in women worldwide, affecting 530,000 people per year; 250,000 deaths are expected from this largely preventable illness **[1]**. The squamous epithelia of the vaginal tract, anal and perianal regions as well as the mucosal epithelium of the larynx are all infected by HPVs, which are tiny double stranded circular DNA viruses **[2]**. Because of screening and human papilloma

virus (HPV) vaccine, cervical cancer is regarded as a condition that is preventable **[3]**. Treatment options for cervical cancer that is in its early stages or that has spread locally include radical surgery, chemotherapy, or a combination of the two. There are few treatment options available for patients who have platinum-based chemoradiotherapy for metastatic tumors but still experience persistent or recurrent disease. Cervical cancer in advanced or recurrent stages has a poor prognosis, with a 10- to 15% one-year survival rate. Rose *et al*. used multivariable analysis to determine the predictive markers, which included histology, race/ethnicity, performance status, tumor size, International Federation of Gynecology and Obstetrics stage, tumor grade, pelvic node status, and concurrent cisplatin-based chemotherapy treatment.[1] The treatment plans for advanced/recurrent cervical cancer are outlined in this review, and the analysis of the response rate is recommended **[1]**.

RT, which is recommended for FIGO stages IIA through IVA, is primarily used to treat bulky (stage IB2) or locally advanced cervical cancer. Cisplatin reduces local/pelvic failure by about 50%, along with distant metastases and the relative risk of dying from cervical cancer. Future directions, clinical trials, and quality of life prior to, during, and following therapy are all taken into account, along with current clinical research. Staging describes the level or severity of a person's cancer based on the size of the primary (original) tumour and/or the extent to which it has spread throughout the body. Staging is important for four reasons: first, it aids clinicians in planning a patient's course of care; second, it is used to estimate a patient's prognosis; third, it facilitates the exchange of patient information between researchers and healthcare professionals; and, fourth, it provides a common language for evaluating clinical trial outcomes and comparing the results of different studies. When it comes to detecting metastases from solid tumours, functional imaging techniques, like PET, that employ radioactive tracers that accumulate in abnormal tissue, appear to be more sensitive than imaging approaches that just detect morphological aberrations. FDG-PET has the potential to improve the accuracy of cancer diagnosis, staging, and therapy choices **[4]**.

TREATMENT OPTIONS OF RECURRENT CERVICAL CANCER:

The tumor immune checkpoint is also known as programmed cell death protein 1 (PD-1) and programmed cell death ligand 1 (PD-L-1), is a key role in the pathways that control the human immune system. They are seem on tumor cells in patients with cervical

cancer, demonstrating that PD-1. PD-1 inhibitors might be useful for treating cervical cancer **[5]**. Chemotherapy is the conventional treatment for cervical cancer patients with stage IVB, persistent, or recurrent disease; however, it is neither curative nor related to long-term disease control. The historical standard of treatment for recurrent cervical cancer was the administration of the chemotherapy drug cisplatin every 21 days. The trials were evaluated and showed the effectiveness of other drugs like paclitaxel, gemcitabine, topotecan, and vinorelbine, among others. Patients with recurrent cervical cancer are now suggested to have treatment with cisplatin plus paclitaxel or paclitaxel and carboplatin. In Gynecologic Oncology Group (GOG) and Japan Clinical Oncology Group conducted numerous trials in those combinations (JCOG). Patients with treatment resistance have very bad prognoses. New therapy approaches were urgently needed at the time. For these patients, molecular targeted therapy will be beneficial. From the findings of GOG240, the overall survival (OS) can be improved by using bevacizumab and topotecan together. In general, recurrent cervical cancer is incurable, and patients who have a number of unfavourable prognostic markers should have a better OS with the current chemotherapeutic medicines. It is critical to take into consideration not only the survival benefit but also minimising the treatment toxicity as well as the enhancement of quality of life (QOL) **[1]**. Within two years of a diagnosis, the majority of recurrences can happen, and the majority of individuals die with uncontrolled disease. In those circumstances, radiation therapy and chemotherapy followed by radical surgery can be used. **Table 1** showed the recommendations for local recurrence of cervical cancer following surgery and their level of evidence. Numerous symptoms, such as discomfort, anorexia, vaginal bleeding, cachexia, and physiological issues, can be experienced by patients with recurrent or metastatic cervical cancer. Managing these symptoms is the doctor's primary goal while treating patients with recurrent cervical cancer.

Studies have shown that the combination of cisplatin and methotrexate considerably improved survival compared to hydroxyurea, a single inactive medication. The recommendations for systemic chemotherapy in metastatic cervical cancer were shown in **Table 2** together with supportive evidence.

Table 1: (Guidelines for local recurrence of cervical cancer after surgery) [6]

Guidelines for local recurrence of cervical cancer after surgery	Level of evidence
Radiation therapy is included in patients with locally recurrent cervical cancer following radical surgery	III
Concurrent chemotherapy with either fluorouracil and/ or cisplatin with radiation should be considered and may improve outcome	III
Pelvic exenteration may be alternative to radical radiotherapy and concurrent chemotherapy in selected patients without pelvic side wall involvement	III

Table 2: (Guidelines for systemic chemotherapy in metastatic cervical cancer) [6]

Guideline- systemic chemotherapy in metastatic cervical cancer	Level of evidence
The most effective treatment for cervical cancer is cisplatin.	II
Although the response rate with 100 mg/m2 of cisplatin (31%) is larger than that with 50 mg/m2 (21%), it is not related to a better progression-free or overall survival.	II
Although there is no difference in overall survival, cisplatin-based combination therapy is linked to a higher response rate and longer progression-free survival than single agent cisplatin therapy.	II
Patients with extrapelvic illness and strong performance status consistently have greater response rates to chemotherapy, while previously irradiated regions have lower response rates.	III
Chemotherapy may have a negative or positive effect on survival and palliation.	III

One of the main objectives of radiation therapy for metastatic cervical cancer is the alleviation of pain from bone metastases and symptoms connected to cerebral metastases. If the patients have a shortened life expectancy due to metastatic cervical cancer, palliative radiotherapy should be provided using higher fractions over shorter times than standard radical regimens of treatment **[4]**.

Early stage illness may be cured by surgery plus chemotherapy and radiotherapy. Unfortunately, patients with metastatic recurrent cancer have few treatment alternatives **[7]**. As previously mentioned, paclitaxel is administered as a 24 hour infusion in order to lessen its neurologic toxicity when coupled with cisplatin. Paclitaxel can, however, be used in combination to carboplatin to given as a 1 hour infusion **[8]**.

TREATMENT OPTIONS FOR ADVANCED CERVICAL CANCER:

The three main problems in LACC are locoregional control, treatment-related negative effects, and systemic disease spread. Utilizing comprehensive therapy methods that incorporate several disciplines is the key to improving the outcomes **[6]**. Concurrent

platinum-based chemoradiation is currently the standard method of therapy for patients with FIGO Stage IB2 - IVA cervical cancer. Numerous randomised controlled trials (RCTs) and meta-analyses have shown that concurrent CTRT significantly increases progression-free survival (PFS) and overall survival (OS) **[6]**. With equal 5-year disease-free survival (DFS) and overall survival (OS) rates (74 and 83%, respectively, for the surgical and radiation groups), adjuvant radiotherapy is given to roughly 84% of patients with stage IB2-IIA **[6]**. One treatment option for advanced cervical cancer is cisplatin, which decreases local/pelvic failure and distant metastases and, as a result, reduces the relative risk of mortality from cervical carcinoma by around 50%. Intravenous cisplatin at a dose of 40 mg/m^2 for six weeks in conjunction with radiation therapy (RT) has become the new standard for the treatment of locally advanced cervical cancer **[4]**.

The combination of radical hysterectomy and neo-adjuvant chemotherapy (NACT) has been found to reduce the requirement for postoperative radiation therapy and improve outcomes. In the high-risk category, CTRT might increase survival and lower the frequency of distant metastases. Similarly, based on a few retrospective studies and a Cochrane review, it has been suggested that CTRT may be more beneficial than room temperature alone as an adjuvant therapy in the intermediate-risk group. Regardless of the histology type, concurrent chemoradiation is the usual treatment for FIGO Stage IIB - IVA. The haematological and gastrointestinal acute toxicities as well as the overall treatment complexity have significantly increased with the addition of chemotherapy to radiation **[9]**.

Poor outcomes, especially in LMIC, are caused by more advanced stages of poor nutritional status, anaemia, a higher frequency of acute toxicities, an increase in the requirement for supportive care, and decreased adherence to therapy. For the treatment of cervical cancer, more recent radiation methods have been used, such as integrated imaging and delivery using intensity-modulated radiation therapy (IMRT)/volumetric arc therapy. To assure well-tolerated dose application in the tumor-related targets, to account for motion uncertainties, to reduce margins, and to achieve reduced doses on organs at risk, image-guided radiation (IGRT) is suggested for IMRT. In a phase-II randomised trial, IMRT for cervical malignancies showed a reduction in acute gastrointestinal toxicity. To support the use of IMRT in cervical cancer, there aren't any reliable data or significant RCT findings, yet **[9]**.

The effective use of image-guided adaptive brachytherapy (IGABT) in the treatment of cervical cancer. The target concept (GTV, high-risk clinical target volume (HR-CTV), and intermediate risk clinical target volume (IR-CTV) during brachytherapy), advanced treatment planning, prescription, and reporting of combined EBRT and brachytherapy dose volume parameters in the form of GYN GEC-ESTRO I - IV recommendations, have all been widely accepted for cervical cancer brachytherapy **[9]**.

Despite improvements in primary and secondary cervical cancer prevention, a sizable proportion of women still present with metastatic illness. Although approximately 5% of newly diagnosed cases of cervical cancer of stage IV disease, metastatic disease develops in 15-61% of cases typically within the first two years of finishing primary treatment in women **[10]**.

With response rates of 40-50%, the combination of taxins and platinum known to be effective in treating in advanced and recurrent cervical cancer.[11] The platinum analogue carboplatin has a milder nephrotoxicity than cisplatin. Ovarian cancer has been reported to respond well to carboplatin.[12] The chemotherapeutic treatment was stopped, if patients had either tumor remission or tumor growth or developed unacceptable toxicity **[13]**.

Patients in current study who had silent disease responded considerably better than those who had symptomatic disease, demonstrating the value of diagnosing asymptomatic disease. The onset of symptoms are described as an Positron emission tomography/ computed tomography (FDG PET/ CT). It is an accurate method for determining asymptomatic recurrence of uterine cervical carcinoma **[14]**.

CONCLUSION:

Recurrent or relapsing cervical cancer is the term used to describe cervical cancer that has been detected following surgery, radiation therapy, or chemotherapy. The type of treatment used for recurrent cervical cancer depends on the patient's prior medical history and the location of the recurrence. Many different elements eventually affect a patient's decision to receive cancer therapy. Receiving therapy for cancer may be done to lengthen a patient's time on life support, increase their chance of recovery, or minimise symptoms by managing the condition. The potential benefits and drawbacks of receiving cancer treatment must be carefully weighed against one another. Cisplatin is the first-line treatment for cervical cancer, however there is a potential that it could lead to nephrotoxicity

in patients with advanced cervical cancer. Numerous studies have shown that the combination of paclitaxel and carboplatin is a promising therapeutic option for individuals with advanced and recurrent cervical cancer. Paclitaxel and carboplatin together carry a lower risk than cisplatin alone. The GOG240 results revealed the value of molecular target drugs in cancer chemotherapy, despite the fact that people with recurrent cervical cancer still had a poor prognosis. Particularly for patients with many poor prognostic signs, current chemotherapy regimens only slightly enhance overall survival (OS) and recurrent cervical cancer is often thought to be incurable. As a result, it is crucial to examine not only the advantage of extended survival but also the decrease in treatment toxicity and enhancement of quality of life.

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