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Neoadjuvant chemotherapy in Management of cervical cancer

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Abstract: It is now recognized that cervical cancer is a rare long-term outcome of persistent infection of the lower genital tract by one of about 15 high-risk HPV types. HPV 16 and HPV 18 account for about 71% of cases; while HPV types 31, 33, 45, 52, and 58 account for another 19% of cervical cancer cases. Treatment of cervical cancer is based on stage of the disease, age, and fertility status, menopausal status of the patient and associated comorbid conditions and histopathological type. Treatment requires multidisciplinary approach involving a gynecologic oncologist, radiation oncologist and medical oncologist. Management of cervical cancer is primarily by surgery or radiation therapy, with chemotherapy a valuable adjunct. The combination of EBRT and ICRT maximizes the likelihood of locoregional control while minimizing the risk of treatment complications. The primary goal of EBRT is to sterilize local disease and to shrink the tumor to facilitate subsequent ICRT. Standard EBRT should deliver a dose of 45–50 Gy to the whole pelvis encompassing uterus, cervix, adnexal structures, parametria, and pelvic lymph nodes. Although EBRT is commonly delivered by a Cobalt-60 teletherapy machine in several low-resource countries, linear accelerators are preferred nowadays as they provide higher energy beams resulting in more homogeneous dose delivery to deep tissues with relative sparing of superficial tissues. Recently, conformal radiotherapy techniques like 3D-CRT and IMRT are increasingly being used with encouraging results in terms of reduced toxicity owing to relative sparing of normal tissues.

Keywords: *Neoadjuvant chemotherapy, cervical cancer*

Introduction.

It is now recognized that cervical cancer is a rare long-term outcome of persistent infection of the lower genital tract by one of about 15 high-risk HPV types. HPV 16 and HPV 18 account for about 71% of cases; while HPV types 31, 33, 45, 52, and 58 account for another 19% of cervical cancer cases [1].

It is well documented that nearly 90% of incident HPV infections are not detectable within a period of 2 years from the acquisition of infection and persist only in a small proportion. It is debatable whether the virus is completely cleared or whether it remains latent in basal cells with the potential for reactivation in some cases [2].
Persistent HPV infection denotes the presence of the same type-specific HPV DNA on repeated sampling after 6–12 months. Only one-tenth of all infections become persistent, and these women could develop cervical precancerous lesions [3].

This knowledge has resulted in the development of new initiatives for prevention and early detection. The two major approaches for control of cervical cancer involve:
(1) Prevention of invasive cancer by HPV vaccination.
(2) Screening for precancerous lesions.

Prevention and elimination are potential possibilities but the tragedy is that it is not yet prevented on a large scale in many LMICs due to lack of efficient and effective intervention programs [3].

Primary prevention of cervical cancer with HPV vaccination
Age-specific cross-sectional HPV prevalence peaks at 25% in women aged less than 25 years, which suggests that the infection is predominantly transmitted through the sexual route following sexual debut. Thus, prophylactic HPV vaccination as a preventive strategy should target women before initiation of sexual activity, focusing on girls aged 10–14 years [4].

Three prophylactic HPV vaccines are currently available in many countries for use in females and males from the age of 9 years for the prevention of premalignant lesions and cancers affecting the cervix, vulva, vagina, and anus caused by high-risk HPV types: a bivalent vaccine targeting HPV16 and HPV18; a quadrivalent vaccine targeting HPV6 and HPV11 in addition to HPV16 and HPV18; and a nonvalent vaccine targeting HPV types 31, 33, 45, 52, and 58 in addition to HPV 6, 11, 16, and 18. The last two vaccines target anogenital warts caused by HPV 6 and 11 in addition to the above-mentioned malignant and premalignant lesions [5].

All the vaccines are recombinant vaccines composed of virus-like particles (VLPs) and are not infectious since they do not contain viral DNA. For girls and boys aged 9–14 years, a two-dose schedule (0.5 mL at 0 and 5–13 months) is recommended. If the second vaccine dose is administered earlier than 5 months after the first dose, a third dose is recommended. For those aged 15 years and above, and for immunocompromised patients irrespective of age, the recommendation is for three doses (0.5 mL at 0, 1, 6 months). There is evidence for the effectiveness of vaccination at the population level in terms of reduced prevalence of high-risk HPV types, and reduction in anogenital warts and high-grade cervical abnormalities caused by the vaccine types among young women; there is some evidence of cross-protection from non-vaccine types also [6].

Secondary prevention of cervical cancer by early detection and treatment of precancerous lesions.

Even with the advent of effective vaccines, screening will remain a priority for cervical cancer prevention for several decades. Cervical cancer screening has been successful in preventing cancer by detection and treatment of precursor lesions, namely, high-grade cervical intraepithelial neoplasia (CIN 2 and 3) and adenocarcinoma in-situ (AIS) [7].
Several cervical screening strategies have been found to be effective in varied settings. The tests used widely include conventional cytology (Pap smear), in recent years liquid-based cytology and HPV testing, and, in LMICs, visual inspection with acetic acid (VIA). While the Pap smear is still the major workhorse of screening and is associated with substantial declines in cervical cancer risk in high-income countries, it is a challenging

and resource intensive technology that is not feasible in low-resource settings where poor organization, coverage, and lack of quality assurance result in suboptimal outcomes [8].
In the context of declining HPV infections after the introduction of HPV vaccines a decade ago, many healthcare systems are considering switching to primary HPV screening, which has higher sensitivity and negative predictive value, and allows extended screening intervals or even a single lifetime screening in low-resource settings [9].
VIA involves detection of acetowhite lesions on the cervix 1 minute after application of 3%–5% freshly prepared acetic acid. In view of its feasibility, VIA screening has been widely implemented in opportunistic settings in many low-income countries. A single-visit approach (SVA) for screening with rapid diagnosis and treatment improves coverage, eliminates follow-up visits, and makes screening more time and cost-efficient in low-resource settings [10].
VIA screening is particularly suitable for SVA and WHO has issued guidelines for implementing SVA in public health settings. A single screening modality will never be universally applicable, but it is possible to adapt cost-effective means of cervical cancer screening to each country. The screening strategy chosen must be feasible, simple, safe, accurate, acceptable, and easily accessible to highest-risk women. A judicious combination of HPV vaccination and screening has enormous potential to eliminate cervical cancer in the foreseeable future [11].

Cervical cancer screening methods in low- and middle-income countries (LMICs):

Every year 445000 women in LMICs develop cervical cancer compared to 83,000 women in high income countries (HICs). This disparity is largely attributed to the absence of organized screening programs in LMICs. Although HPV vaccination programs are being scaled up globally, implementation has been slow in LMICs. The vaccine is targeted at adolescents before sexual debut and will not help women already infected with HPV. Therefore screening programs will continue to be necessary for cervical cancer prevention [12].

However, cytology based screening programs (i.e., Pap smears) have been successful in reducing incidence of cervical cancer in high income countries (HICs), evidence suggests that it may not be the most effective screening method in LMICs due to complex infrastructure requirements and quality assurance issues [13].

Instead, the WHO recommends either human papillomavirus (HPV) testing or visual inspection with acetic acid (VIA) for screening programs [14].

A systematic review evaluated the efficacy and the cost benefit of screening tests for cervical cancer and the results indicate that cytology is the least efficient screening method to implement in developing countries.
The sensitivity of cytology was estimated to be 58.4%. This is substantially lower than the established sensitivity of HPV testing [15].

The requirement of three visits to complete a full course of cytology screening leads to greater loss to follow-up compared to VIA and HPV testing, which can be conducted in one or two visits. In LMICs, the requirement of three visits to receive a full course of screening appears to represent a significant barrier to care [16].

Comparing HPV testing and VIA, it demonstrates that HPV testing was generally more effective, yet also more costly than VIA. This is likely explained by the higher direct cost of HPV testing, as well as its greater sensitivity to detect precancerous conditions. It was concluded that HPV testing and VIA are more cost-effective screening methods than cytology in LMICs [17].

Management of cervical cancer
Treatment of invasive cervical caner

Treatment of cervical cancer is based on stage of the disease, age, and fertility status, menopausal status of the patient and associated comorbid conditions and histopathological type. Treatment requires multidisciplinary approach involving a gynecologic oncologist, radiation oncologist and medical oncologist [18].

Management of cervical cancer is primarily by surgery or radiation therapy, with chemotherapy a valuable adjunct [3].

After careful clinical evaluation and staging, the primary treatment of early stage cervical cancer is either surgery or radiotherapy. The treatment approach is determined by the FIGO stage 2018 and whether fertility preservation is desired [19].

Nodal metastasis is 1% with stromal invasion <1 mm while stromal invasion 1-3 mm has 1.5% risks in stage IA1 cervical cancer. In Stage IA1 with LVSI, lymph node metastasis & cancer recurrence rate is 5%. Lymph node metastasis is 7% and risk of disease recurrence is 4% in Stage 1A2 cancer [20].

For the Stage 1A1: the treatment is completed with cervical conization unless there is lympho-vascular space invasion (LVSI) or tumor cells are present at the surgical margin. In women who have completed childbearing or elderly women, total extrafascial hysterectomy may also be recommended [21].
Any route can be chosen, i.e. abdominal, vaginal, or laparoscopic. When LVSI is evident, pelvic lymphadenectomy should be considered, along with modified radical hysterectomy. If fertility is desired, cervical conization with close follow-up will be adequate [22].

Regarding Stage 1A2, there is a small risk of lymph node metastases in these cases; pelvic lymphadenectomy is performed in addition to type B radical hysterectomy or more radical surgery. In low risk cases, simple hysterectomy or trachelectomy, with either pelvic lymphadenectomy or sentinel lymph node assessment, may be adequate surgical treatment. When the patient desires fertility, she may be offered a choice of the following:
• Cervical conization with laparoscopic (or extraperitoneal) pelvic lymphadenectomy.
• Radical abdominal, vaginal, or laparoscopic trachelectomy with pelvic lymphadenectomy [23].

Follow-up with 3-monthly Pap smears for 2 years, and then 6-monthly for the next 3 years is recommended after treatment of micro invasive carcinoma. With normal follow-up at 5 years, the patient can return to the routine screening schedule according to the national guidelines [21].

Surgical treatment is the preferred modality for the treatment of Stage IB1, IB2, and IIA1 lesions. It would usually consist of type C radical hysterectomy with pelvic lymphadenectomy. The routes of surgery may be open or minimally invasive, i.e. laparoscopic or robotic [24].

FIGO Stage IB1 is considered as low risk as the largest tumor diameter less than 2 cm, cervical stromal invasion less than 50%, and no suspicious lymph nodes on imaging. So, the standard management is a type C radical hysterectomy, also modified radical hysterectomy may be considered in these cases. Pelvic lymphadenectomy should always be included on account of the high frequency of lymph node involvement [25].
In young women desiring fertility sparing, a radical trachelectomy may be performed, indicated for Stage IA2–IB1 tumors measuring less than or equal to 2 cm in largest diameter. The cervix along with the parametrium is removed followed by anastomosis of the uterus with the vaginal end. Trachelectomy can be done by open abdominal, vaginal, or by minimally invasive routes. When a vaginal approach is planned, the pelvic nodes are first removed laparoscopically and sent for frozen section to confirm node negativity and then proceed with

the radical trachelectomy vaginally. Alternatively, the nodes may be first be assessed by conventional pathologic methods and the radical trachelectomy done as a second surgery after 1 week [22].

In FIGO Stage IB2 and IIA1 cervical cancer, surgery or radiotherapy can be chosen as the primary treatment depending on other patient factors and local resources, as both have similar outcomes. The advantages of surgical treatment are:

- That it is feasible to determine the postoperative stage precisely on the basis of histopathologic findings, thereby enabling individualization of postoperative treatment for each patient.
- That it is possible to treat cancers that are likely to be resistant to radiotherapy.
- That it is possible to conserve ovarian function [3].

In Stage IB3 and IIA2, the tumors are larger and the likelihood of high risk factors such as positive lymph nodes, positive parametria, or positive surgical margins that increase the risk of recurrence and require adjuvant radiation after surgery are high. Other risk factors that increase the risk of pelvic recurrence even when nodes are not involved include: largest tumor diameter greater than 4 cm, LVSI, and invasion of outer one-third of the cervical stroma. In such cases, adjuvant whole pelvic irradiation reduces the local failure rate and improves progression-free survival compared with patients treated with surgery alone [26].

However, the dual modality treatment increases the risk of major morbidity to the patient. The treatment modality must, therefore, be determined based on the availability of resources and tumor-and patient-related factors [3].

Concurrent platinum-based chemoradiation (CCRT) is the preferred treatment option for Stage IB3 to IIA2 lesions. It has been demonstrated that the prognosis is more favorable with CCRT, rather than radiotherapy alone, as postoperative adjuvant therapy as well in terms of overall survival, progression-free survival, and local and distant recurrences [27].

In areas where radiotherapy facilities are scarce, neoadjuvant chemotherapy (NACT) has been used with the goal of:

- Down-staging of the tumor to improve the radical curability and safety of surgery.
- Inhibition of micrometastasis and distant metastasis.

There is no unanimity of view as to whether it improves prognosis compared with the standard treatment [28].

The extent of surgery after NACT remains the same, i.e. radical hysterectomy and pelvic lymphadenectomy. The greater difficulty is in determining the indications for adjuvant therapy which are often kept the same as those after primary surgery [27].

However, it must be remembered that NACT may give a false sense of security by masking the pathologic findings and thus affecting evaluation of indications for adjuvant radiotherapy/CCRT. NACT surgery is best reserved for research settings or those areas where radiotherapy is unavailable. This is especially true in patients with very large tumors or adenocarcinomas, which have lower response rates [29].

Rarely, patients with Stage IVA disease may have only central disease without involvement to the pelvic sidewall or distant spread. Such cases, or in case of such a recurrence, pelvic exenteration can be considered but usually has a poor prognosis [30].

Nerve sparing in radical hysterectomy

A pelvic nerve-sparing surgical procedure is recommended in patients undergoing radical hysterectomy, in so far as radical curability is maintained, as intrapelvic injuries to the autonomic nerves (i.e. hypogastric nerve, splanchnic nerve, and pelvic plexus) often lead to impairment of urination, defecation, and sexual function, and consequent deterioration of the postoperative quality of life [24].

The results of both surgery and radiotherapy are comparable for the treatment of the early stages of cervical cancer, but surgical treatment is the favored modality, especially in young women. Neoadjuvant and adjuvant chemotherapy are used in individual cases based on the stage of cervical cancer. High curability rates in women in the early stages of this disease (88–97%), which are based on individualized therapy, currently emphasize the increase in the quality of life of treated women. Morbidity related to the treatment of cervical cancer is specifically linked to the radical nature of the surgery [31].

Bladder dysfunction is one of the most common long-term complications after radical abdominal hysterectomy (RAH) and has an incidence of 8–85% [32].

The most common disorders of RAH include loss of sensation, hypertonic urinary bladder, hypo-/acontractile bladder, urgency and stress urinary incontinence [33].

Voiding disorders have been related to damage of the hypogastric nerves and of the inferior hypogastric plexus due to radical resection of the parametrial tissue [34].

The autonomic fibers innervating the bladder can be disrupted at several stages during RAH, e.g., during dissection of the presacral or superior gluteal nodes, during vaginal dissection and mobilization of the bladder, and during resection of the cardinal ligaments [32].

After radical hysterectomy, changes usually occur in two phases. The initial phase is hypertonic and is characterized by a small, usually transient, spastic bladder. During the early postoperative stage, both surgical trauma and selective denervation result in the dominance of the parasympathetic nervous system, which leads to hyperexcitability of the smooth muscle [35].

The nature of the surgical damage seems to be decentralization of nerve stimuli rather than complete denervation. The second phase is hypotonic, which is characterized by an over distended bladder. Nerve-sparing radical hysterectomy (NSRH) has emerged for reducing surgery-related dysfunctions without compromising oncological outcomes [36].

The nerve-sparing technique includes four main steps:

• The preservation of the superior hypogastric plexus at the level of the presacral area during presacral lymphadenectomy.

• The preservation of the hypogastric nerve dorsal to the ureter and lateral to the utero-sacral ligament during resection of the utero-sacral ligaments;

• The preservation of the inferior hypogastric plexus during resection of the cardinal ligament, as the plexus lies dorsal to the parametrial vessels at the level of the deep uterine vein; a

• The preservation of the bladder branch during resection of the deep layer of the cervico-vesical ligament [34].

Comparative studies of RAH and NSRH support the current opinion that the nerve-sparing technique is associated with faster postoperative restitution of lower urinary tract function. Similarly, laparoscopic NSRH should be related to shorter catheterization time and a lower rate of voiding dysfunctions compared with laparoscopic radical hysterectomy [36].

Sentinel lymph node (SLN) concept in cervical cancer

Sentinel lymph node (SLN) biopsy, instead of systematic pelvic lymph node dissection (PLND), is increasingly being used in the standard management of early-stage cervical cancer. The benefit for the patient is obvious. Less-radical lymph node (LN) dissection diminishes the risk of lower-leg lymphoedema, which is a severe morbidity that persists for life. New ESGO/ESTRO/ESP (European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology) guidelines recommend performing SLN biopsy as the first step of the primary surgical management in all early stages of

cervical cancer (except T1a1) and submitting the SLNs for intraoperative assessment to triage patients towards radical surgery or definitive chemoradiotherapy [37].

These guidelines even accept SLN biopsy without additional PLND as a preferred method of LN staging in stage T1a cervical cancer. The National Comprehensive Cancer Network (NCCN) guidelines also recommended performing SLN biopsy in addition to PLND as an alternative option for LN staging in the early stages of cervical cancer [38].

SLN biopsy is considered to be more accurate in the assessment of pelvic LN involvement than a complete PLND. Higher accuracy, manifested as more frequent detection of positive LNs, is a result of an intensive pathological assessment of a small number of SLNs. This pathological ultrastaging increases the probability of finding smaller metastases. For the pathologist (and pathology department), this is a demanding and time-consuming technique, which cannot be applied to all pelvic LNs in systematic PLNDs [39].

Dual labeling using blue dye and radiocolloid increases the accuracy of sentinel lymph nodes can be performed with. Indocyanine green dye with near infrared technique has been used in robotic surgery and laparoscopy. Pelvic lymphadenectomy needs to be considered if LVSI is present [40].

Clinical practice has been shifting towards the acceptance of the replacement of full PLND by SLN biopsy in the management of cervical cancer patients. Besides decreasing morbidity due to the abandonment of PLND, SLN biopsy offers other benefits. It enables intraoperative assessment of key pelvic LNs and tailoring of patient management in one step. It also improves LN staging by detecting up to 15% of additional patients with LN involvement secondary to intensive pathological utrastaging [41].

Non-surgical management of cervical cancer

In LMICs, the majority of patients present with locally advanced disease, where surgery plays a limited role, and radiotherapy has an important role. Over the last two decades, development of sophisticated planning and delivery techniques, and introduction of computer technology and imaging have galvanized the practice of radiotherapy, resulting in improved clinical outcome and reduced toxicity [42].

Although surgery is preferred for early stage disease, in cases with contraindications for surgery or anesthesia, radiotherapy provides equally good results in terms of local control and survival. Patients with microinvasive disease have been treated by intracavitary radiation therapy (ICRT) alone with good results if surgery is contraindicated owing to medical problems. Selected patients with very small Stage IB1 disease (less than 1 cm) may also be treated with ICRT alone, particularly if there are relative contraindications to external beam radiation therapy (EBRT). A dose of 60–65 Gy equivalents is usually prescribed to Point A. Combination of EBRT and ICRT is also an option for such patients [43].

Following radical hysterectomy, postoperative radiotherapy with or without chemotherapy is indicated for patients with adverse pathologic factors such as positive pelvic nodes, parametrial infiltration, positive margins, deep stromal invasion, etc. According to various prognostic factors, patients may be categorized into high-risk, intermediate-risk, or low-risk disease [43].
High-risk disease includes patients with either positive surgical margins or lymph node metastases or parametrial spread, and such patients should be offered PORT with chemotherapy. Intermediate-risk patients with any two of three factors (tumor size more than 4 cm, lymphovascular invasion, deep stromal invasion) require PORT and no chemotherapy should be offered to these patients. All other patients following radical hysterectomy are termed as low-risk disease patients and do not need any adjuvant therapy [44].

PORT consists of whole pelvic EBRT to cover the tumor bed and draining lymph node areas. A dose of 45–50 Gy is usually prescribed. Intensity modulated radiation therapy (IMRT); an advanced and refined technique of irradiation has been explored in the postoperative setting to reduce the toxicity [45].

Although feasible, surgery as initial treatment is not encouraged for patients with Stage IB3 and IIA2 disease since 80% of them require PORT or CCRT. It is well known that the addition of adjuvant radiotherapy to surgery increases morbidity and thus compromises the quality of life. Additionally, combined modality treatment will unnecessarily overburden the surgical and radiation facilities, which are already inadequate in low-resource countries. Therefore, CCRT is the standard of care for Stage IB3 and IIA2 disease. CCRT includes external radiation and intracavitary brachytherapy [46].

Concurrent chemoradiation is considered the standard treatment for patients with locally advanced cervical cancer (LACC). The chemotherapy regimen is intravenous administration of weekly cisplatin during the course of EBRT [47].
A once-weekly infusion of Cisplatin (40 mg/m2 weekly with appropriate hydration) for 5–6 cycles during external beam therapy is a commonly used concurrent chemotherapy regimen. For patients who are unable to receive platinum chemotherapy, 5–fluorouracil-based regimens are an acceptable alternative. Data on the toxicity associated with concurrent chemotherapy and extended field irradiation are limited [48].

The combination of EBRT and ICRT maximizes the likelihood of locoregional control while minimizing the risk of treatment complications. The primary goal of EBRT is to sterilize local disease and to shrink the tumor to facilitate subsequent ICRT. Standard EBRT should deliver a dose of 45–50 Gy to the whole pelvis encompassing uterus, cervix, adnexal structures, parametria, and pelvic lymph nodes. Although EBRT is commonly delivered by a Cobalt-60 teletherapy machine in several low-resource countries, linear accelerators are preferred nowadays as they provide higher energy beams resulting in more homogeneous dose delivery to deep tissues with relative sparing of superficial tissues. Recently, conformal radiotherapy techniques like 3D-CRT and IMRT are increasingly being used with encouraging results in terms of reduced toxicity owing to relative sparing of normal tissues [3].
Complications of Therapy
• Radiation-related complications
During the acute phase of pelvic radiation therapy, the surrounding normal tissues (eg, intestines, bladder, and perineal skin) often are affected. Acute adverse gastrointestinal (GI) effects include diarrhea, abdominal cramping, rectal discomfort, and bleeding. Cystourethritis also can occur, leading to dysuria, frequency, and nocturia. Late sequelae of radiation therapy usually appear 1-4 years after treatment. The major sequelae include rectal or vaginal stenosis, small bowel obstruction, malabsorption, radiation enteritis, and chronic cystitis [49].
• Surgical complications
The most frequent complication of radical hysterectomy is urinary dysfunction resulting from partial denervation of the detrusor muscle. Other complications include shortened vagina, ureterovaginal fistula, hemorrhage, infection, bowel obstruction, stricture and fibrosis of the intestine or rectosigmoid colon, and bladder and rectovaginal fistulas. Invasive procedures (eg, nephrostomy or diverting colostomy) sometimes are performed in this group of patients to improve their quality of life. [50]
Treating cervical cancer with radical surgery alone usually leads to high recurrence rate and greatly affects the patient quality of life [51].
In Stage IB3 and IIA2, the tumors are larger and the likelihood of high risk factors such as positive lymph nodes, positive parametria, or positive surgical margins that increase the risk of recurrence and require adjuvant radiation after surgery are high. Other risk factors that increase the risk of pelvic recurrence even when nodes

are not involved include: largest tumor diameter greater than 4 cm, LVSI, and invasion of outer one-third of the cervical stroma. In such cases, adjuvant whole pelvic irradiation reduces the local failure rate and improves progression-free survival compared with patients treated with surgery alone [26].
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In areas where radiotherapy facilities are scarce, neoadjuvant chemotherapy (NACT) has been used with the goal of:
• Down-staging of the tumor to improve the radical curability and safety of surgery.
• Inhibition of micrometastasis and distant metastasis.
The mechanism of chemotherapy is to prevent the proliferation infiltration and metastasis of cancer cells. Clinically, postoperative chemotherapy is often adopted to eliminate microscopic cancer lesions remaining after surgery and improve the efficacy of surgery [52].
Mahmoud et al. demonstrated in their study that neoadjuvant chemotherapy can improve the quality of life of patients with cervical cancer [53].
Whether preoperative neoadjuvant chemotherapy combined with radical surgery can significantly improve the efficacy of traditional radical treatment and the survival of patients is very worthy of exploration [54].
Cisplatin, one of the most widely used chemo¬therapeutic agents in oncology, which is com¬monly used in the treatment of reproductive sys¬tem tumors, is one of the most typical drugs in combination chemotherapy. Cisplatin mainly achieves its anti-tumor effect by inhibiting DNA replication. Its inhibition on the human hemat¬opoietic system usually occurs after around 3 weeks of chemotherapy. Scandurra et al found that the combination of paclitaxel-ifosfamide-cisplatin (TIP chemotherapy), was highly efficient in treating advanced or recurrent cervical cancer with low tox¬icity [55].
Paclitaxel is a taxane with anticancer activity, which has good effica¬cy in ovarian cancer when combined with cisplatin. Therefore, paclitaxel and cisplatin were selected as drugs of the preoperative neoadjuvant chemo-therapy in this study [56].

Patients received neoadjuvant chemotherapy before surgery: liposomal Paclitaxel for in¬jection was intravenously injected at a dose of 135 mg/m2, Cis¬platin injection was intravenously injected at a dose of 100 mg/m2. The second chemotherapy cycle followed after three weeks of the first chemotherapy. After 2 to 3 cycles of chemo¬therapy, patients who met the surgical conditions were radically operated for cervical cancer [54].
On the one hand, the application of preoperative neoadjuvant chemotherapy in pa¬tients with cervical cancer can significantly im¬prove the treatment efficacy and reduce metastasis to the lymph nodes; while on the other hand, it can increase the incidence of adverse reactions, impact the patient quality of life and create worries about complications [54].

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