

# Management of Cervical Precancerous Lesions in Pandemic COVID-19 Era

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**Abstract:** *Cervical cancer in Indonesia is still a major problem for women because it is the third most common type of cancer found and also the second leading cause of cancer death. Screening at the beginning of the disease prevents cancer by detecting precancerous lesions (CIN), and early management of precancerous lesions can prevent progression to cancer. There is currently the coronavirus disease 2019 (COVID-19) pandemic throughout the world, including in Indonesia, how is a cervical cancer treatment in the COVID-19 pandemic era.*

**Keywords:** cervical cancer, management, COVID-19

## 1. Introduction

Cervical cancer is the third most common cancer in women worldwide and an estimated 529,000 new cases each year and 275,000 deaths per year in 2008. Worldwide mortality ratio with cervical cancer incidence is 52%. In Indonesia, cervical cancer is the most gynecological cancer in women, in Dr. Cipto Mangunkusumo, cervical cancer constituted 58.41% of 820 gynecological cancers in 2013.<sup>1</sup>

According to GLOBOCAN 2012, cervical cancer ranks 7<sup>th</sup> globally in terms of the number of cases (6<sup>th</sup> in the underdeveloped countries) and 8<sup>th</sup> as a leading cause of death (contributing 3.2% mortality, equal to leukemia mortality rate). Based on GLOBOCAN 2018, there was a significant increase in cervical cancer rank as the 4<sup>th</sup> with a mortality number was 7.5%. Cervical cancer ranked in 1<sup>st</sup> as a leading cause of death in developing countries, ranked in 10<sup>th</sup> in developed countries, and ranked in 5<sup>th</sup> globally. In Indonesia, cervical cancer was the second of the 10<sup>th</sup> most common cancer based on the data from Pathology Anatomy in 2010 with an incidence rate was 12.7%. According to the Indonesian Ministry of Health estimates, the number of cervical cancer new cases in women ranges from 90-100 cases per 100,000 population, and approximately 40 thousand cervical cancer new cases were found every year.<sup>2</sup>

Cervical cancer is developed through precancerous stages, termed cervical intraepithelial neoplasia/CIN, and caused by infection with Human Papilloma Virus (HPV) especially subtypes 16 and 18. Cervical cancer risk factors included early sexual intercourse and having multiple sexual partners, smoking, multigravida, low socioeconomic, using birth control pills, sexually transmitted diseases and impaired immunity.<sup>2</sup> Early signs of cervical cancer are nonspecific such as the presence of vaginal secretions which are rather numerous and somewhat smelly, sometimes with bleeding spots.<sup>1</sup> Screening with the use of the Papanicolaou (PAP) test prevents cancer by detecting precancerous lesions (CIN), and early treatment of precancerous lesions can prevent progression to cancer. Conventional cytology allows the detection of abnormal findings leading to colposcopy with biopsy for a definitive diagnosis if there is the persistence of atypical squamous cells with undetermined

significance or low-grade or high-grade squamous intraepithelial lesion (LSIL, HSIL).<sup>3</sup>

Management options for LSIL (CIN1 grade) on histology vary, ranging from simple observation to excisional therapies. Patients with persistent LSIL should be treated chiefly with the use of office-based ablative therapies. Management guidelines for HSIL (CIN2/3 grade) are well established and recommend a colposcopy-directed biopsy. Cold-knife conization or electroconization should be performed in all patients with biopsy-confirmed HSIL to exclude invasive disease.<sup>3</sup> The success rate of treatment is very good at an early stage and is almost untreated if cancer has spread to the pelvic wall or surrounding organs such as the rectum and bladder.<sup>1</sup>

## 2. Management of Cervical Precancerous Lesions

In 2013, the ASCCP published 2012 consensus results about CINs based on the histological diagnosis following the consensus regarding the management of cervical cytological abnormalities. The recommendation for CIN 1 is follow-up without treatment. However, treatment is also an acceptable option. In the follow-up without treatment, in addition to HPV DNA testing, one of the options, which are cytology and colposcopy, can be used. The related flow-chart is presented in. For the treatment, ablative therapies or excisional procedures (LEEP or cold conization) can be selected. Excisional procedures are necessary for recurrent CIN 1, and it is preferred for the diagnosis of co-existing high-grade lesions, as it provides a histological diagnosis. If colposcopy is unsatisfactory, a diagnostic excisional biopsy is necessary. However, for pregnant women, adolescents, and patients taking immunosuppressive agents, with unsatisfactory colposcopy, follow-up without treatment is recommended. The treatment schema for CIN 2 and 3 confirmed by biopsy. Although ablative therapy is an acceptable option in this group of patients with adequate colposcopy, excisional therapies should be preferred for recurrent cases. As excisional procedures may cause complications, such as excessive bleeding and risk for preterm delivery in pregnant women with CIN 2 and 3, it should be performed only in patients with suspicion of invasive cancer. Twice-a-week 5-fluorouracil (5-FU) cream

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is reported to be the most effective treatment in HIV (+) patients using immunosuppressive agents. Follow-up is

more recommended for adolescents with CIN 2, as it is in CIN 1.<sup>4</sup>

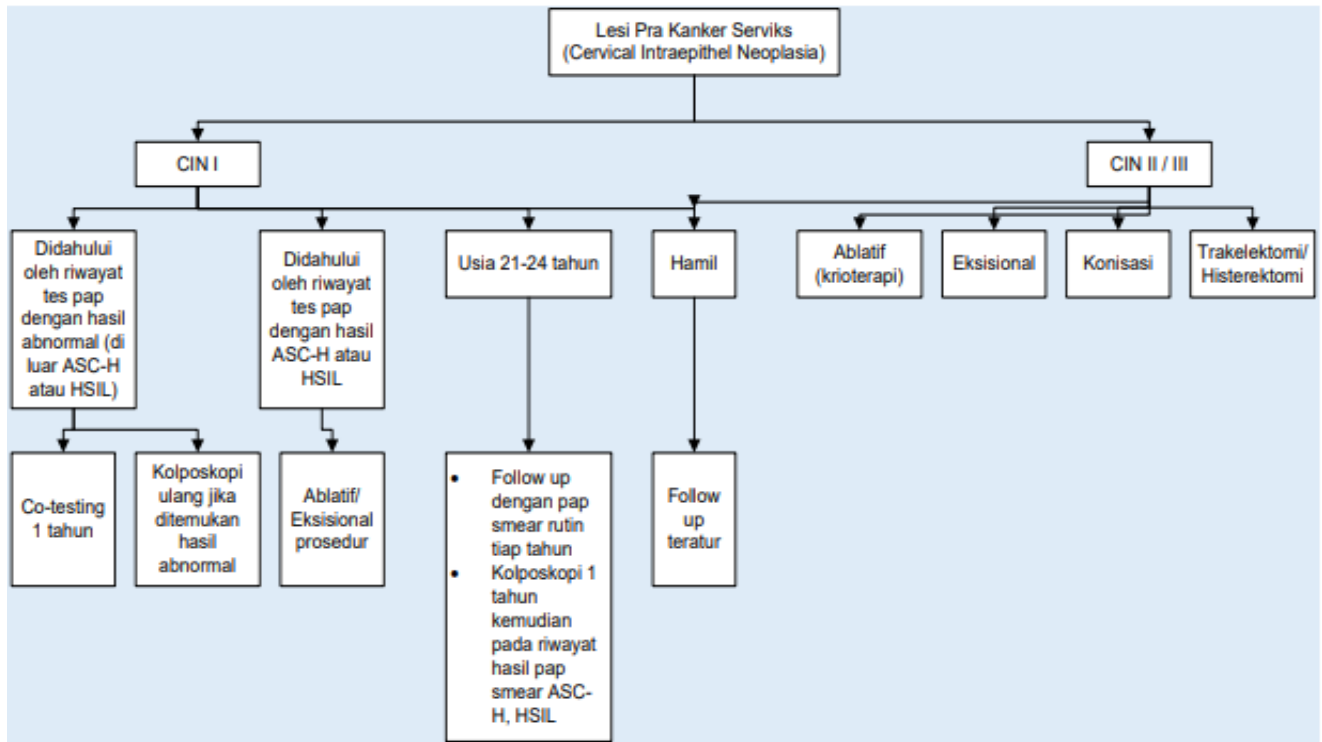


Figure 1: Guidelines for the management of cervical precancerous lesions<sup>4</sup>

Locally advanced cervical cancer is often treated with primary chemoradiation. Currently, treatment is based on combination therapy with platinum-based regimens. Radiation involves external beam and high-dose intracavity brachytherapy. Post treatment hysterectomy is not associated with increased survival rates and therefore is generally not recommended. However, hysterectomy may be performed in patients who have large, bulky tumors or high post treatment tumor volumes.<sup>5</sup>

Treatment of recurrent disease includes medical or surgical options. For women with local recurrence, surgical resection with hysterectomy or pelvic exenteration is an option. Exenteration is an ultraradical surgical procedure that involves en bloc removal of female reproductive organs, the lower urinary tract, and a portion of the rectosigmoid. Exenteration is generally used for women who have had previous unsuccessful radiation treatment, with or without hysterectomy, and it has a 50% cure rate. However, the procedure has a 3% to 5% mortality rate, 50% of patients have major complications, and there are no controlled trials to evaluate its effectiveness. Women with advanced metastatic disease are treated with chemotherapy (and radiation if not previously offered). Bevacizumab (Avastin) is an antivascular endothelial growth factor monoclonal antibody that inhibits tumor angiogenesis.<sup>5</sup>

### 3. Type of Cancer Management

#### 1) Cryotherapy

The cryotherapy method is a relatively easy procedure done for precancerous lesions, by damaging uterine cervical precancer cells using carbon dioxide (CO<sub>2</sub>) or nitric oxide

(N<sub>2</sub>O) gas. The basic method of cryotherapy is that cancer cells will damage and die at temperatures below -20°C. Using CO<sub>2</sub> or N<sub>2</sub>O gas for 5 minutes can reduce the temperature of the cervix to -60°C to -80°C. Indications Cryotherapy is used to damage tissue of cervical precancerous lesions, at lesion size <75% of the cervix, or not exceeding 2mm from the diameter of the cryotherapy probe. The effectiveness of cryotherapy is higher in CIN1 / 2 but less effective in CIN 3. The effectiveness of cryotherapy according to WHO CIN 1 (86-96%), CIN 2-3 (<80%), according to ACCP CIN 1 (86%), CIN 2- 3 (77%), and according to India (CIN 1 96.4%), CIN 2-3 (82.1%).<sup>1,6</sup>

#### 2) Large loop excision of the transformation zone (LEEP/LLETZ)

Electrocautery is a method to destroy tissue by touching hot metal produced by direct electrical current through high impedance conductor. Electrocautery consists of two techniques, namely the Loop Electrosurgical Excision Procedure (LEEP) and the Large Loop Excision of the Transformation Zone (LLETZ), an excision method, using a thin electric wire to remove a part of the entire transformation zone and therefore removes the affected tissue which can be examined further. Loop excision is indicated as for biopsy to determine the degree of NIS, abnormal pap test findings, abnormal colposcopy findings It has advantages such as 90% effective in treating women for precancerous lesions the first time used, minimal side effects, and good healing. The effectiveness of LEEP / LLETZ is 93% - 98% in CIN 3 and 95.4% in CIN 2.<sup>1,6</sup>

#### 3) Cold knife conization (CKC)

Cervical conization is the surgical removal of a cone-shaped portion of the cervix using a scalpel, this technique is

considered a traditional therapy for CIN patients. However, conization with the scalpel can better reach the extent of the lesion and reach the cone tissue for histopathological examination. It is indicated to HSIL (CIN II / CIN III), Microinvasion (Cervical Cancer Stage IA1), Desiring fertility, Negative LVSI (Lymphovascular space invasion), Close follow up after treatment, Extent exceeds the capability of LEEP (1.5 cm). The role of conization as CIN therapy is closely related to the accuracy of histopathological assessment, especially in determining the boundaries of lesion-free incisions or not. The incision-free incision line is expected to show good prognosis, although there are several reports of recurrences. The results of conization therapy are considered satisfactory when a lesion-free incision is reached, although further observation must be monitored closely and sometimes problems can occur including uterine ostium stricture.<sup>1,6</sup>

#### 4) See and treat programs

The see and treat program is an excellent screening and therapy method for cervical cancer in countries with limited resources. The team consisting of doctors, public health experts, nurses, or midwives work together to find early cervical precancerous lesions. During a visit to a certain area, public health experts provide counseling to increase public knowledge about cervical cancer and other matters regarding reproductive health such as safe sex, family planning, and sexually transmitted diseases. After being recorded/registered, women are screened with an IVA test or a Pap test by a doctor. If any abnormalities are found, the patient is immediately treated with cryotherapy right away.<sup>1</sup>

In October 2004 the Female Cancer Program (FCP) started a see and treat program in Indonesia in 3 locations namely in Jakarta, Tasikmalaya (Bandung), and Bali. In this program, a screening effort was made for women to look for cervical cancer and cervical precancerous lesions with IVA test and a Pap test and a cryotherapy procedure at that time if precancerous lesion abnormalities are found, whereas if invasive cancer is found, refer to the tertiary service center for re-evaluation and action if proven. The program shows that cytology and IVA examinations are very useful and are relatively inexpensive techniques for screening programs in areas with limited resources.<sup>1</sup>

#### 4. Management in Pandemic COVID-19 Era

In February 2020, COVID-19, caused by the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), was declared as a public health emergency of international concern by the World Health Organization [1]. Since its inception in December 2019, the number of cases is rising exponentially worldwide. Since this is a novel virus, the human population does not have any prior immunity to fight against the disease nor there is any vaccine or therapy available.<sup>8</sup> The latest data from WHO on July 20<sup>th</sup>, 2020, reports that 14,348,858 confirmed COVID-19 cases worldwide with a mortality rate of 603,691 people.<sup>9</sup> In Indonesia on July 20<sup>th</sup>, 2020, the government reported 88,214 confirmed positive cases of COVID-19 and 4,239 deaths related to COVID-19.<sup>10</sup>

Considering the unprecedented dynamic situation and uncertain epidemiological trends, new policies and recommendations continue to evolve daily. Currently, routine surgical procedures are almost at a halt worldwide, but whether cancer procedures can be delayed remains an ethical issue. Most of the advisories do not recommend a stoppage of care for cancer patients for low COVID census areas. However, the current unprecedented lockdown enforced to reduce community transmission poses an ethical challenge to gynecologic oncologists as there is insufficient evidence to determine the impact of this novel infection on cancer care and therefore no clarity on how women with gynecological cancers should be managed in this critical time.<sup>8</sup>

The potential threat of COVID-19 to women with gynecological cancers is substantial. In the current scenario, there will be delays in diagnosis, seeking treatment, and actual treatment administration. Treatment delay is known to be an independent risk factor for increased mortality due to cancer.<sup>8</sup>

The following practical points may be considered while considering the reinstallation of cancer care services if the COVID crisis continues in India:<sup>8</sup>

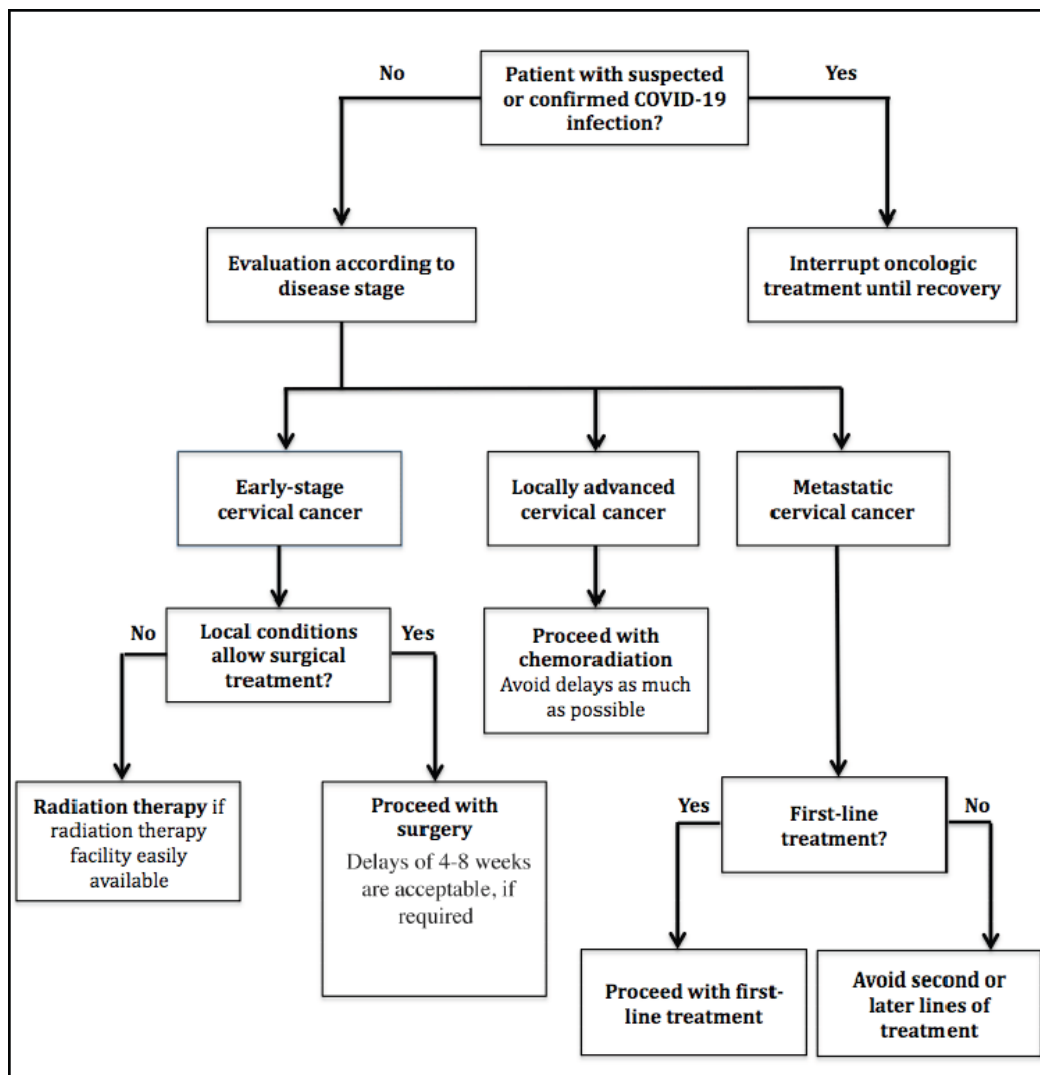
- 1) Since it is preferred that women with suspected cervical cancer should ideally receive a diagnostic evaluation within 4 weeks from the initial presentation, such cases may be scheduled for diagnostic conization/LEEP (loop electrosurgical excision) after careful counseling and evaluation. Those with high-grade lesions on cytology screening may wait up to 3 months and those with low-grade lesions may be counseled for following up after the crisis is resolved (6–12 months).
- 2) Women with early cervical cancer who have been waiting for the last 6–8 weeks should be re-evaluated for operability and COVID census and resources. Definitive surgery is preferred if resources permit; otherwise, NACT may be considered in situations with ongoing crises beyond 8 weeks.

For patients with early-stage cervical cancer, both surgery and radiation therapy are acceptable treatment strategies. To decide between the two treatment options during the COVID-19 pandemic, local conditions of the health systems should be considered. Although surgery has the disadvantage of requiring patient hospitalization, it allows the conclusion of treatment in a single moment. If required by local conditions, a surgical procedure delay of 4–8 weeks would be acceptable in this situation.<sup>11</sup>

For locally advanced cervical cancer, the standard treatment is definitive chemoradiation. Once again, since this treatment is potentially curative, it should remain a priority. Previous studies have shown that delays to initiate chemoradiation after diagnosis of locally advanced cervical cancer and duration greater than 8 weeks to conclude the therapy are both associated with poorer overall survival. Thus, an early chemoradiation therapy, ideally without interruptions, should continue to be pursued. To decrease the number of visits to the health care facility, hypofractionated radiation therapy could be discussed in selected cases.<sup>11</sup>

For patients with metastatic cervical cancer, first-line chemotherapy (with or without bevacizumab, according to availability) should also be considered as a priority

treatment. This therapy is associated with a clear survival benefit, justifying its continuation as long as local conditions allow it.<sup>11</sup>



**Figure 2:** Flowchart of recommendations for the management of cervical cancer patients in active treatment during COVID-19 pandemic<sup>11</sup>

## 5. Conclusion

Cervical intraepithelial neoplasia (CIN) is a premalignant lesion that may exist at any one of three stages: CIN1, CIN2, or CIN3. If left untreated, CIN2 or CIN3 (collectively referred to as CIN2+) can progress to cervical cancer. Instead of screening and diagnosis by the standard sequence of cytology, colposcopy, biopsy, and histological confirmation of CIN, an alternative method is to use a 'screen-and-treat' approach in which the treatment decision is based on a screening test and treatment is provided soon or, ideally, immediately after a positive screening test. Available treatments include cryotherapy, large loop excision of the transformation zone (LEEP/LLETZ), and cold knife conization (CKC). To decide treatment options during the COVID-19 pandemic, those with high-grade lesions on cytology screening may wait up to 3 months and those with low-grade lesions may be counseled for following up after the crisis is resolved (6–12 months).

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