NATIONAL GUIDELINES FOR THE MANAGEMENT OF CERVICAL CANCER IN SRI LANKA

National Cancer Control Programme
Ministry of Health
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Message from the Director General of Health Services

Cervical cancer is the commonest gynecological cancer in Sri Lanka. It is the fourth commonest cancer among the females since 2015 in the country. The incidence of Breast cancer increases yearly, making it a public health burden. Early detection and effective treatment is important in cervical cancer, as it is a preventable and a curable cancer. Therefore, it is important to initiate the national strategies in early detection of cervical cancer and to establish proper and effective treatment pathways for the diagnosed cervical cancer patients.

The National Cancer Control Programme, as the focal point of the national response to prevention and control of cancer activities in Sri Lanka, has initiated and developed the "National Guidelines for the Management of Cervical Cancer in Sri Lanka". This guideline would provide evidence based recommendations in treatment and would improve the quality of care received by the cervical cancer patients. The enhancement of early detection and diagnosis of cervical cancer by the Ministry of Health, through the establishment of cancer early detection centers in all provinces of the country would be further boosted by this guideline, improving the survival and the cure rate of the cervical cancer patients.

It is my utmost pleasure to wish the National Cancer Control Programme for initiating the development and publishing this worthy guideline. I would like to acknowledge the Sri Lanka College of Oncologists and the international reviewers for their technical contribution, the World Health Organization for their partnership and all other stakeholders who contributed to the successful completion of this worthy publication.

Dr. Asela Gunawardena
Director General of Health Services
Ministry of Health

Message from the Deputy Director General-Non-Communicable Diseases

The goal of the National Strategic Plan (2020-2024) of the National Cancer Control Programme (NCCP) is to reduce the incidence of preventable cancers, to detect early detectable cancers at an early stage and to provide a continuum of cancer care to all cancer patients in the country in an equitable manner. The diagnosis and treatment of cancer is considered as one of the key components in the said strategic plan.

Cervical cancer is the commonest gynecological cancer in Sri Lanka. According to the estimates, 7% of all newly diagnosed cancers among women, are cervical cancers. According to the WHO, interim targets to eliminate cervical cancer by 2030, 90% of women identified with cervical disease should receive treatment. Adding to that cervical cancer is one of the cancers that can be prevented and cured with early detection and effective treatment. Sri Lanka to achieve above targets "National Guidelines for the Management of Cervical Cancer in Sri Lanka" will be a great boost. This would improve the quality of care and the survival of the cervical cancer patients as well.

I would like to thank the Diagnosis and Treatment Unit of the National Cancer Control Programme, Sri Lanka College of Oncologists, international reviewers, the World Health Organization and all other stakeholders for their contribution in developing this important guideline.

Dr. Champika Wickramasinghe
Deputy Director General-Non-Communicable Diseases
Non-Communicable Disease Bureau
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Message from the Director, National Cancer Control Programme

The National Strategic plan on prevention and control of cancer in Sri Lanka (2020-2024) has identified the development of management guidelines for common cancers as one of the strategic priorities. Cervical cancer is the most common gynecological malignancy and the fourth most common cancer among females in Sri Lanka. It is a preventable cancer and is curable when detected early and treated effectively.

The World Health Organization has declared a global strategy to accelerate the elimination of cervical cancer by achieving interim targets by 2030. Achieve 90% coverage of vaccination of HPV vaccine of girls before the age of 15 years, coverage of 70% of females at the age of 35 and 45 year using a quality assured cervical cancer screening test and 90% comprehensive treatment coverage of females with cervical cancer or pre- cancer are the interim targets to be achieved by 2030. The whole world is aligned to this elimination of cervical cancer as the first cancer to be eliminated in the world history. Sri Lanka being the partner of this global strategy has committed to reach this goal by achieving the interim targets by 2030.

In the process of achieving the interim targets providing equitable and quality care for patients diagnosed with cervical cancer is a must. To fulfil this task, National Cancer Control Programme presents the "National Guidelines for the Management of Cervical Cancer in Sri Lanka". This guideline would refine the process of decision making on diagnosis, management and treatment of cervical cancer to achieve maximum clinical effectiveness, cost-effectiveness and to maintain the quality of care in an equitable manner.

Multi-disciplinary technical expert committee has contributed to developing this guideline with aim of providing best possible options for Sri Lankan patients, to improve their survival and quality of life. The National Cancer Control Programme appreciate the experts of the guideline development committee including the international reviewer, Prof. Peter Hoskin, Consultant in Clinical Oncology, Mount Vernon Cancer Centre, Northwood & Christie NHS Foundation Trust Manchester for their continuous support to make this guideline a reality. The National Cancer Control Programme sincerely thank the Sri Lanka College of Oncologists and the College of Pathologists for their technical contribution. I would like to convey my gratitude for the World Health Organization for their partnership in developing this important guideline.

Further I would like to thank the Diagnosis and Treatment Unit of the National Cancer Control Programme for coordinating this activity.

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National Guidelines for the

Management of Cervical Cancer in Sri Lanka

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INTRODUCTION

1.0. Introduction

Cervical cancer is the fourth most common cancer among women globally. An estimated 604,127 women diagnosed with cervical cancer (6.5%) and around 341,831 women died due to cervical cancer (3.3%) globally in 2020 [1]. Cancer of uterine cervix is the commonest after carcinoma breast in women in Asia. In Sri Lanka cervical cancer is the commonest gynaecological malignancy among women. There were 1114 new cases reported in 2019 [2]. According to World Health Organization (WHO) statistics for 2012, 690 women in Sri Lanka die due to cervical cancer per year [1].

However, majority of these patients, about 70% are diagnosed at an advanced stage of the disease [2].

With early detection and treatment in early stages, about 93% of patients survive at least 5 years. However, in advanced stages this survival drops to about 50-60% [3].

Cervical cancer incidence increases with the age and it commonly occurs between the ages of 50 to 75-year-old women in Sri Lanka [2].

This guideline aims to ensure that equitable standards of care are available to all women who develop cervical cancer in Sri Lanka.

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2

PREVENTION OF CERVIX CANCER

2. Prevention of Cervix Cancer

2.1. Primary prevention:

The prophylactic vaccination against the major cause of cervical cancer, the carcinogenic human papillomavirus types 16 and 18, is now available and offers additional protection from cervical cancer.

Three vaccines are available to date: the bivalent HPV virus-like particle vaccine (2vHPV), the quadrivalent HPV virus-like particle vaccine (4vHPV) and nine-valent HPV virus-like particle vaccine (9vHPV). All 3 vaccines provide protection against HPV 16 and 18. 4vHPV also includes HPV 6 and 11 which cause 90% of genital warts. The 9vHPV covers 5 more oncogenic HPV viruses (HPV 31, 33, 45, 52 and 58) in addition to the types already included in 4vHPV [1,2].

WHO recommends, girls aged 9 to 13 years should be vaccinated against HPV [3].

Quadrivalent human Papillomavirus (HPV) vaccine is introduced into the National Immunization Programme from July 2017 in Sri Lanka.

The vaccine scheduled at completion of 10 years to girls in Grade 6 through the school immunization programme and 2-doses schedule with a minimum interval of 6 months between doses [4].

2.2. Secondary Prevention

Secondary prevention aims at detection and treatment of precursor lesions and prevents these lesions transformed into cancerous lesions.

2.2.1. Screening for premalignant lesions

Early detection of cervical cancer can cure the disease with an excellent prognosis. Unlike in ovarian cancer, cervical cancer has a clearly identifiable pre-cancerous stage in the spectrum of cancer progression.

According to WHO countries with resource constraints should not screen women prior to 30 years of age, since cervical cancer is very rare before this age and screening women at a younger age detects many low-grade lesions that are self-limiting and will never progress into cancer [3].

The screening interval should not be less than five years in countries with limited resources and many competing health priorities. The screening frequency can be increased to 10 years if a highly sensitive test such as detection of HPV DNA is used [5].

Pap smear cytology has been used successfully in many resource-rich countries. However, cytology has certain drawbacks that limit its usefulness especially in resource limited settings [6].

Different screening methods are being used in cervical cancer screening. Conventional Pap Smear is the screening method practiced in Sri Lanka [7].

Screening test	Sensitivity to detect CIN2+	Specificity to detect CIN2+	Test provider	Personnel for processing and interpretation	Major limitations
Conventional cytology	53%	96.3%	Doctor / nurse/ midwife/ reproductive health care provider	Cytotechnician/ cytopathologist	Result not immediately available Laboratory necessary Highly trained personnel required Low to moderate sensitivity
Liquid-based cytology	79%	78.8%	Doctor / nurse/ midwife/ reproductive health care provider	Cytotechnician/ cytopathologist	Same as conventional cytology Expensive
HPV DNA	96%	90.7%	Doctor / nurse/ midwife/ reproductive health care provider	Laboratory technician	Result not immediately available Laboratory necessary Expensive
VIA	80%	92%	Doctor / nurse/ midwife/ reproductive health care provider	Not necessary	Sensitivity moderate High false-positives Subjective. performance variable and depends on training of providers.

Source: World Health Organization. Regional Office for South-East Asia[3].

HPV DNA carries a higher sensitivity in detecting premalignant lesions compared to other screening tests [5]. Although it is currently not included in to the national cervical cancer screening programme in Sri Lanka. However, it was successfully completed as a pilot project in one district and ongoing testing is carrying out in few districts.

Visual inspection using acetic acid (VIA) or Lugol's iodine (VILI) has been done in some centers in Sri Lanka, but not widely available.

Cervical smear results could be benign, premalignant or malignant. The updated terminology has some changes and groups the risk mainly as low or high risk.

Once an abnormal smear is reported, a colposcopy may be recommended depending on the abnormality.

Colposcopy is indicated when the cervical smear reports a high grade squamous intraepithelial lesion of the cervix. It is also indicated in the presence of persistent low grade abnormality. Colposcopy is considered adequate when the entire transformation zone is visible during the procedure [8, 9].

Both 5% acetic acid and Lugol's iodine are used in colposcopy, help in demarcating the abnormal area thus helping to target the biopsy/ excision procedure.

Natural history of Cervical Intraepithelial Neoplasia (CIN)

Persistent infection of the cervical epithelium with the HPV is a pre-requisite to the development of carcinoma of the uterine cervix. It is well known that majority of CIN lesions would regress back to normal. However, about 30% to 50% of CIN2 and CIN3 lesions, together referred to as high-grade squamous intraepithelial lesions (HSIL), will progress to invasive cancer if they remain undetected and untreated [3].

2.2.2. Management of Cervical lesions based on Cytological and Histological Classifications:

Category	**Recommendation for follow up and referral**
1. Negative for intraepithelial lesion and malignancy (NILM)	Routine re-screening in 5 years
2. Low grade squamous intraepithelial lesion (LGSIL)	Follow up by Medical officer of Health (MOH) Two repeat smears 6 months apart - IF negative, routine re-screening in 5 years - IF Positive, refer to a Gynecologist
3. High grade squamous intraepithelial lesion (HGSIL)	Refer to a Gynecologist for colposcopy and biopsy
4. Atypical squamous cells of undetermined significance (ASCUS) – Low grade	Follow up by Medical Officer of Health (MOH) Repeat smear in 6 month
5. Atypical squamous cells of undetermined significance (ASCUS) – High grade	Refer to a Gynecologist for colposcopy and biopsy
6. Glandular cell atypia	Refer to a Gynecologist
7. Benign endometrial cells in a woman >40 years	Refer to a Gynecologist to investigate based on clinical details
8. Squamous or glandular malignancy	Urgent Gynecological referral for appropriate management

2.3. Treatment of Cervical Intraepithelial Neoplasia (CIN)

Treatment involves completely removing the abnormal epithelium either by an excisional technique or by destruction. Excisional techniques include Large Loop Excision of Transformation Zone (LLETZ) or Loop electrosurgical excision procedure (LEEP). Cone biopsy is carried out as an excisional procedure mostly in menopausal women where the TZ is not fully visible on colposcopy [8].

Ablative techniques such as cold coagulation heats the abnormal epithelium to approximately 100°C which destroys it. Another method is cryotherapy which involves freezing the abnormal epithelium. Both these methods are not available in Sri Lanka.

2.3.1. Repeat Excision

a. High grade CIN extending to margins

High grade CIN extending to the deep lateral or endocervical margins of excision (or uncertain margin status) results in a higher incidence of recurrence but does not justify routine repeat excision if:

- there is no evidence of glandular abnormality
- there is no evidence of invasive disease
- the individual is under 50 years of age

b. Individuals over the age of 50

All individuals over the age of 50 years who have CIN3 at the deep lateral or endocervical margins and in whom satisfactory screening samples and colposcopy cannot be guaranteed must have a repeat excision performed to try to obtain clear margins.

2.3.2. Immunocompromised patient with abnormal cervical smear

Women living with HIV have a significantly increased risk of cervical cancer as HIV enhances human papillomavirus (HPV)-induced carcinogenesis [10].

All individuals newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing the HIV infection. Annual screening should be performed with an initial colposcopy if resources permit. Subsequent colposcopy for any screening abnormality should follow national guidelines.

Despite the higher cervical treatment failure rate, high grade CIN should be managed according to national guidelines. Lesions less severe than CIN2 should generally not be treated as these are likely to represent persistent HPV infection of the cervix which responds poorly to treatment and may clear spontaneously. Regular cytological surveillance will detect progression.

Cervical cancer screening in women who are infected with HIV should continue throughout a woman's lifetime without stopping at age 65 years [11].

Hysterectomy should not be practiced for the treatment of CIN lesions. All invasive cancer cases should be referred to appropriate facilities for further management based on FIGO clinical staging.

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3

DIAGNOSTIC WORK-UP AND STAGING

3.Diagnostic work-up and staging

Multidisciplinary team working should ensure a consistent and equitable approach to diagnosing, planning, and managing care.

3.1. Investigations

a. Examination under anaesthesia (EUA) and Biopsy

- EUA may be required to gain tissue for diagnosis and to adequately assess for vaginal/parametrial extension. Proper documentation of the tumour extension with the relevant diagram is important.
- Cystoscopy and Sigmoidoscopy for locally advanced disease or patients with relevant symptoms

b. Radiological assessment

- **MRI pelvis**
- CT Chest/Abdomen/Pelvisor whole body PET/CT
    - ⋆ The choice of imaging for staging should be modified based on the availability of the technology and expertise.
    - ⋆ **MRI is preferred over CT for measuring primary tumour size as it best defines the geometry of tumour growth in the central pelvis. Also, MRI best delineates tumour spread into the uterine corpus, pelvic sidewalls, and adjacent viscera such as bladder and bowel. [1].**
    - ⋆ The status of the pelvic and para-aortic lymph nodes (stage IIIC) can be determined with imaging or pathological assessment [2].
    - ⋆ PET/CT is the most sensitive imaging examination for detection of lymphadenopathy [3].
    - ⋆ If PET/CT is not available, then CT or MRI is a second-line alternative with both modalities showing similar diagnostic performance [4].

c. Fitness assessment aiming optimization

- Basic Investigations: FBC, RFT, LFT
- Cardiac assessment

3.2 Histopathological diagnosis

A diagnosis of cervical cancer is made by the histopathological examination of cervical biopsies.

Squamous cell carcinomas account for 70%–80% of cervical cancers and adenocarcinomas for 20%–25% [3,5].

A. Histopathology of cervical biopsy

- Histological type
    - Squamous lesions
        CIN – Mild, moderate, severe

Squamous cell carcinoma
- Glandular lesions
  Adenocarcinoma in situ
  Adenocarcinoma
- Other epithelial tumours
- Neuroendocrine tumours
- Mesenchymal tumours
- Mixed epithelial & mesenchymal tumours
- Miscellaneous tumours

- Tumour grade –
  G1 - Well differentiated
  G2 - Moderately differentiated
  G3 - Poorly differentiated
  G4 - Undifferentiated
- Tumour site – Right superior quadrant (12 to 3 o'clock)
  Right inferior quadrant (3 to 6 o'clock)
  Left superior quadrant (9 to 12 o'clock)
  Left superior quadrant (6 to 9o'clock)

- Tumour size – all dimensions are important
- Stromal invasion - Depth of invasion& horizontal extension or extent of spread cannot be assessed
- Lymph vascular invasion
- Associated pathology – Koilocytes, inflammation, etc.
- Margins – Adequacy of local excision should be assessed Comment on end cervical & ectocervicalmargins and deep margin
  – margin(s) cannot be assessed
    or
  – involved / uninvolved by intraepithelial neoplasia / invasive carcinoma
  – focal / diffuse
  – specify location if possible

Immunohistochemistry;

Immunohistochemical studies may be considered if necessary.

B. Post- operative histopathology

Pathology reports following definitive surgery of cervical tumours should include the following histological features [6,7,8,9,10].

- Specimen type & dimensions
- Histological type of tumour
- Histological grade
- Tumour size – Maximum horizontal dimension (mm)
  Maximum depth (mm)
- Tumour site
- Extent of local spread
- Cervical wall thickness (include paracervical tissue thickness) ……mm
- Distance to closest radial resection margin (include paracervical tissue

thickness ……..mm)

- Vaginal involvement: Yes / No
  Distance from distal vaginal margin:…..….mm
- Paracervical involvement: Yes / No
- Parametrial involvement: Yes / No
- Lymphovascular invasion: Yes / No
- CIN: Yes / no Grade 1/2/3
- CGIN: Yes / no Grade: low / high
- Pelvic nodes:(pelvic group includes obturator, internal, external and common iliac nodes)
  Total number-
  Number involved-
  Extra nodal spread: Yes / No
- Para-aortic nodes: Positive / negative
- Extra nodal spread: Yes / No
- Other tissues and organs
  Endometrium
  Myometrium
  Right adnexum
  Left adnexum

Provisional pathological FIGO stage

3.3. Staging of Cervical Cancer

The tumour should be staged according to the Revised 2018 FIGO staging, which allows incorporation of imaging and/or pathological findings, and clinical assessment of tumour size and disease extent[2].

FIGO staging of carcinoma of the cervix uteri (2018)

Stage I:

The carcinoma is strictly confined to the cervix uteri (extension to the corpus should be disregarded)

- **IA** Invasive carcinoma that can be diagnosed only by microscopy, with maximum depth of invasion <5mm[a].
  - **o IA1** Measured stromal invasion <3 mm in depth
  - **o IA2** Measured stromal invasion ≥3mm and <5 mm in depth
- **IB** Invasive carcinoma with measured deepest invasion ≥5 mm in depth (greater than stage 1[A]), lesion limited to the cervix uteri[b].
  - **o IB1** Invasive carcinoma ≥5 mm depth of stromal invasion and >2cm in greatest dimension
  - **o IB2** Invasive carcinoma ≥2 cm and <4 cm in greatest dimension
  - **o IB3** Invasive carcinoma ≥4 cm in greatest dimension

Stage II:

The carcinoma invades beyond the uterus, but has not extended onto the lower third of the vagina or to the pelvic wall

- **IIA** Involvement limited to the upper two-thirds of the vagina without parametrial involvement
    - **o IIA1** Invasive carcinoma <4 cm in greatest dimension
    - **o IIA2** Invasive carcinoma ≥4 cm in greatest dimension
- **IIB** Withparametrial involvement but not up to the pelvic wall

Stage III

The carcinoma involves the lower third of the vagina and or extends to the pelvic wall and/or causes hydronephrosis or non-functioning kidney and/or involves pelvis and/or paraaortic lymph nodes

- **IIIA** Carcinoma involves the lower third of the vagina, with no extension to the pelvic wall
- **IIIB** Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney (unless known to be due to another cause)
- **IIIC** Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent (with r and p notations)[c].
    - **o IIIC1** Pelvic lymph node metastasis only
    - **o IIIC2** Paraaortic lymph node metastasis

Stage IV:

The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such m does not permit a case to be allotted into stage IV

- **IVA** Spread of the growth to adjacent organs
- **IVB** Spread to distant organs

a Imaging and pathology can be used, when available, to supplement clinical findings with respect to tumor size and extent, in all stages

b The involvement of vascular or lymphatic spaces does not change the staging. The lateral extent of the lesions is no longer considered.

c Adding notation of r (imaging) and p (pathology) to indicate the findings that are used to allocate the case to stage IIIC. For example, if imaging indicates pelvic lymph node metastasis, the stage allocation would be stage IIIC1r and, if confirmed by pathological findings, with would be stage IIIC1p. The type of imaging modality or pathology technique should always be documented. When in doubt, the lower staging should be assigned.

Source: Bhatla et al [2].

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4

MANAGEMENT OF EARLY STAGE CERVICAL CANCER

4. Management of Early Stage Cervical Cancer

Surgical management of early invasive Cervical Cancer

Surgical management of early invasive cervical cancer ranges from less invasive conization to radical hysterectomy. Surgery is possible with curative intent up to stage II-A where the parametrium is not involved by the tumor [1,2]. Fertility wishes and disease stage are key factors that determine the extent of the surgery [1,2].

Stage IA1 - Cervical conization or simple hysterectomy is an option in stage IA1. However, if the family is completed, a simple hysterectomy is preferred [1]. If there is positive LVSI, modified radical hysterectomy with pelvic lymphadenectomy is preferred [1]. If the patient has fertility wishes,it can be treated with conization alone and follow up [1,3] .

Stage IA2 - Modified radical hysterectomy with pelvic lymphadenectomy is the option in stage IA2 disease. However, in cases where the fertility wishes are present, cervical conization or radical trachelectomy with pelvic lymphadenectomy is an option [1,3].

Stage IA1 - The standard surgical management is a type C radical hysterectomy, but modified radical hysterectomy maybe considered when tumor is less than 2 cm, stromal involvement is less than 50% and no nodal involvement in imaging. Nerve-sparing procedures should be done in order to prevent postoperative complications. Due to the higher chance of lymph node involvement, pelvic lymphadenectomy should be performed with the radical hysterectomy [1,2,4].

In young patients with fertility wishes, a radical trachelectomyis an option by the laparoscopic, open, or vaginal route. Lymphadenectomy also should be considered in fertility sparing treatment [3,6,7,8].

Criteria for considering radical trachelectomy;

- Stage between Ia1 with lymph vascular space involvement (LVSI) and IB1 (tumor size <2 cm)
- Cervical tumour at least 1 cm away from internal cervical os on MRI.
- No evidence of pelvic lymph node metastases
- Squamous cell carcinoma or adenocarcinoma histology with deep stromal invasion and positive LVSI
- No clear cell, serous carcinoma or neuroendocrine carcinomahistlogy

Stage IB2 - Type C radical hysterectomy with pelvic lymphadenectomy is the option in stage IB2 disease. However, fertility-sparing treatment not possible in this stage and in more advanced stages of the disease [1,6,7].

Stage IB3 - Surgical management is not recommended [1,2,4,5,8]

Stage IIA1 - Radical hysterectomy with pelvic lymphadenectomy can be performed in this stage [1,2,5,8]

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5

MANAGEMENT OF LOCALLY ADVANCED STAGE CERVICAL CANCER

5. Management of locally advanced stage Cervical Cancer

Primary treatment for Stage IB2, Stage IB3, Stage IIA2,Stage IIB, III, IVA Cervical Cancer

It is important to select and decide carefully in the initial management of stage IB2 and IIA either primary surgery or primary radiotherapy as each treatment alone gives equivalent local control and survival benefit. But combined modality of treatment can cause more morbidity.[1]

Primary chemo-irradiation is the treatment of choice for stage IB2, stage IB3,stage IIA2 and advanced cervical cancer.

It is essential to optimize the patient with correction of anaemia, renal functions and infections before offering the specific treatment. Patient's haemoglobin level should be monitered and corrected if it falls below 12g/dL.

For primary radical radiotherapy;

External baem radiotherapy (EBRT) with concurrent chemotherapy followed by intra-cavitary brachytherapy boost (BT) is recommended [1,2,3].

5.1. Outline of Treatment Modality

5.1.1. Pelvic Radiotherapy:

For tumour with lymph node negative or involved nodes confined to the obturator, internal or external iliac and pre-sacral nodes [4].

Planning Technique

With standard field borders, geographical miss is a possibility. Therefore, cross Sectional imaging is very useful to decide the volumes [4].

CT simulation

- Position: Supine with knee/ankle supports and arms on the chest
- Skin tattoos: Midline and laterally over a bony point
- Bladder/ bowel protocol: Comfortably filled bladder with empty rectum
- CT simulation (3mm slices) from L3 to 5cm below the ischial tuberosities.
- IV contrast – preferable to identify the nodes

Target delineation:

A. Conventional planning:

Field borders:

Antero-posterior projection:

- Superior margin – L4/L5 or L5/S1
- Inferior margin – 3cm below the inferior aspect of vaginal disease or lower border of Obturator foramen
- Lateral margin – 2cm lateral to the deepest curvature of pelvic brim

Lateral projection:

- Superior & inferior: Same as above
- Anterior margin – 1cm anterior to the anterior symphysis pubis.
- Posterior volume boarder – S2/S3 junction or include the entire sacrum (In stage III disease)

B. 3-Dimentional CT based planning

Target volumes:

GTV -primary - The gross disease according to the EUA findings and imaging (CT/MRI)

GTV nodes - Involved nodes on diagnostic imaging

CTV_primary

- GTVp + 5-10 mm margin
- Cervix and include whole uterus.
- Parametria.
- If minimal or no extension, include upper half of vagina.
- If upper vaginal involvement, include upper 2/3rd vagina.
- If extensive vaginal involvement, include entire vagina.
- If stage III and IV disease, include uterosacral ligaments.
- Ovaries

CTV nodes

• GTV nodes + 7 mm margin

Include:

o obturator nodes

o external iliac lymph nodes

o internal iliac lymph nodes

o pre-sacral nodes.

o common iliac nodes.

o a small pelvic field not including the common iliac nodes may be considered in low- and intermediate-risk T1b1 patients with negative LNs on imaging and no LVI.

o a 7mm margin around vessels extending to the pelvic sidewall and any visible node are recommended for the pelvic nodal regions

- If common iliac nodes involved, include para-aortic nodes or **at least** 2 cm above highest involved node [4].
- If para-aortic nodes involved, include **at least** 2 cm above highest involved node [4].

PTV_primary– CTVp +5-10mm margin

PTV_nodes– CTVn + 5mm margin

Technique:

4-field box technique (fields are shaped to the 3D volume) Beam energy: 6 -15 MV

Plan evaluation

- PTV to be covered by 95% - 107% of the prescribed dose
- Minimize hot and cold spots
- Check for dose homogeneity

C. Intensity Modulated Radiotherapy (IMRT)

There are potential benefits of IMRT in the radical treatment of cervical cancer patients, both in terms of dose escalation and decrease of toxicity.

IMRT is preferred for patients receiving extended field radiotherapy and when OAR dose constraints cannot be met [5].

Organ and target motion is constant and unpredictable at the pelvis, thus posing a challenge to the safe execution of IMRT. Therefore, an internal target volume (ITV) is defined in IMRT. ITV is taken with a margin to CTV that includes the variation for organs and target movements.

To add the ITV, patient should be simulated in empty and full bladder.

Target volumes:

Same as 3-D CT based planning except for ITV & PTV margins

ITV: CTVp + margin to include movement of target with bladder filling

PTV p : ITV + 7 -10 mm

PTVn:CTVn + 7-10mm

OAR s and dose constraints[5,6]

Organ	Dose constraints
Small bowel	• ALARA. • V45 Gy<195 cc. • V40 Gy<30%. • If extended field treatment used: o V40 Gy<300 cm o V30 Gy<650 cm.
Rectum	• V40 Gy<60%
Bladder	• V45 Gy<35%.
Femoral heads	• V45 Gy<50%. • V50 Gy<10%.
Kidneys (for EFRT)	o mean dose <15 Gy o V12 Gy<55% o V20 Gy<32% o V23 Gy<30% o V28 Gy<20%.
Spinal cord (for EFRT)	Dmax<45Gy

- Generally, target coverage takes priority over non-critical organs at risk.
- Suggested contouring atlas: https://www.nrgoncology.org/About-Us/Center-for-Innovation-in-Radiation-Oncology/Female-RTOG-Normal-Pelvis
- The dose to the rectum, bladder and sigmoid colon should be recorded for use in assessing cumulative dose with brachytherapy treatment.

Technique:

IMRT

Plan evaluation

- D98 to be covered at least by 95% of the prescribed dose
- D2 to be less than 107% of the prescribed dose
- Minimize hot and cold spots

Target verification:

- Electronic Portal Imaging device (EPID) or cone-beam CT (CBCT) scans daily and compared to the reference images. (the set up error should be <3-5mm)[5]

Dose Prescription:

External Beam Radiotherapy (2D / 3D / IMRT) ;

45 Gy -50.4 Gy, 1.8 -2Gy per fraction (25 - 28 fractions) over 5 to 6 weeks.

- **Timing:** Ideally the chemo-irradiation and brachytherapy is completed in 56 days to optimize local control [7,8,9].
- **If this timing is not met in resource limited setting, compensation could be made by adding 0.6Gy for every delayed day** [7,8].
- NB: When intracavitary treatment is not possible, a second phase of EBRT should be delivered with a small CT planned volume. PTV for this - GTV+ 10mm margin

Dose Fractionation: 16 – 20Gy in eight fractions prescribed to the isocenter or median PTV dose

5.1.2. Concurrent Chemo Radiotherapy

Any patient with cervical cancer and adequate renal function suitable for definitive radiotherapy should have concurrent chemotherapy with a platinum based agent

Recommended regimen- weekly cisplatin 40 mg/m2 (maximum 70mg)

5.1.3. Extended field radiotherapy (EFRT)

For patients with involved common iliac or para-aortic lymph nodes.

The superior border should be extended to accommodate the next echelon of uninvolved nodal region or least 2cm beyond the highest involved nodal level.

5.1.4. Postoperative adjuvant chemoradiotherapy/radiotherapy

Absolute Indications for adjuvant radiotherapy

i. Presence of tumour at the resection margin

ii. More than one node with metastatic infiltration or extracapsular nodal spread

iii. Inadequate surgery such as an incidental finding at simple hysterectomy

a. Post-Surgery - Positive lymph nodes

Patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemo radiotherapy using platinum based chemotherapy [10].

b. Post Surgery – Negative Lymph nodes

- **At least two of the following risk factors [4]**

  I. Lympho-vascular invasion

  II. Deep stromal invasion

  III. Poorly differentiated tumour

  IV. Tumour diameter of >4 cm

  V. Invasive tumour less than 5mm from the resection margin

Consideration should be given to the relative risks and benefits of treatment for each individual patient. Concurrent chemo radiation should be considered in preference to radiation alone.

Target Volume & Definition

Target Volume:

- upper 3 to 4 cm of the vaginal cuff (vaginal vault)
- paravaginal tissue
- the parametria
- immediately adjacent nodal basins (such as the external , obturator and internal iliac nodes)

- For documented nodal metastasis, the common iliac nodes are included and the superior border of the radiation field should be appropriately increased

Radiotherapy Dose

- A dose of 45-50.4Gy in 1.8 Gy/fraction in 25-28 fractions, delivered over 5 weeks.
- Grossly involved unresected nodes may be evaluated for boosting with an additional 10 to 20 Gy of highly conformal (and reduced-volume) EBRT.
- Weekly cisplatin 40mg/m2 (maximum 70mg) for 5 weeks is administered concurrently [1,2,3].

5.1.5. Definitive Brachytherapy boost for Cervical Cancer

Purpose: Curative intent boost radiotherapy to the residual tumour following chemo-irradiation to the whole pelvis or extended field radiotherapy. [7,8,9].

Timing: Ideally the chemo-irradiation and brachytherapy is completed with 56 days to optimize local control.

Dose: 80 -90Gy -EQD2 (α/β= 10, EBRT plus brachytherapy) [11,12]

Needs to be calculated based on the whole pelvis dose
Some recommended dose regimes to offer the minimum dose to point A.
Link ABS calculator

EBRT prescribed dose	EBRT (EQD2)	Brachytherapy dose	Total Point A prescription dose (EQD2)
45Gy/25#	44.3Gy	24Gy/3#	79.6Gy
46Gy/23#	46Gy	24Gy/3#	81.2Gy
50.4Gy/28#	49.6Gy	22Gy/3#	80.5Gy
50Gy/25#	50Gy	22Gy/3#	80.9Gy

A. Conventional Brachytherapy

Dose Prescription:

- To Point A

- A minimum dose of 80Gy EQD2 (α/β = 10, EBRT plus brachytherapy) to be delivered to point A.

- **Organs at risk (Figure 01)**

- Bladder point – to be documented

- Rectal point – to be documented

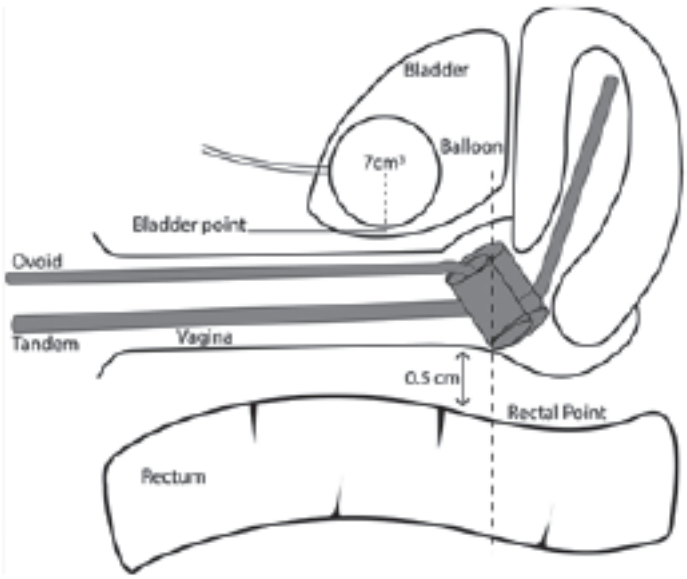

Figure 1

- **Applicators:**

  Tandem: Length to be determined by the uterine sound during the procedure

  Ovoids: Size to be determined during the procedure (Small, medium, large)

  Vaginal cylinder: To be used for patients with vaginal extension where ovoids can not cover the entire length of disease.

- **Procedure:**

  - Procedure under anaesthesia is recommended

  - Patient in lithotomy position

  - Do a vaginal examination to assess residual disease and the size of the vagina.

  - Bowel preparation:

  - Laxatives to be started 2 days prior to the intervention
  - Antispasmodics IV/IM before procedure to reduce bowl movement

  - Bladder preparation:

  - Insert an indwelling catheter into the bladder and instil, 7ml of diluted gadolinium into the balloon and pull the catheter down to bring the balloon against the urethra.
  - Empty the bladder and then instil 50 ml of N/saline prior to MRI scanning
  - The urinary catheter is then left open throughout the entire treatment planning procedure and the 50 ml saline solution is then again instilled prior to the BT delivery process

- Vaginal preparation:

- o 30–50 cc of the gel injected with a sterile syringe into the vagina until reflux is obtained
- Dilate the cervix
- Measure the length of the uterine cavity with uterine sound and select the appropriate tandem. Use ultrasound guidance to prevent perforation if available.
- Select the most appropriate sizes of ovoids (Small, Medium or Large)
- Insert the tandem into the uterine cavity and place the ovoids in the vaginal fornix and fix the applicators.
- Pack vagina with gauze soaked in radio-opaque gel
- Use rectal spatula to push the rectum away from the vagina
- Take antero-posterior and lateral radiographs and make sure the applicators are in the

Ideal positioning of applicators:

- Tandem bisecting the midpoint of the pelvis in both anterior and lateral projections [11]
- Get the most appropriate library plan
- Deliver treatment
- Discharge the patient home

- **Documentation**

1. Document dose at point A
2. Bladder reference point: Draw an antero-posterior line on the lateral radiograph, from the centre of the catheter balloon to the posterior surface of the bladder wall. Document the dose at this point [13,14].
3. Rectal points: On the lateral radiograph, draw a line from the lower end of the intra-uterine source or the mid source of the ovoid. The rectal point is located 5mm behind the posterior vaginal wall. Document dose at this point.[13,14].

B. Three dimensional (3D) conformal brachytherapy (GEC-ESTRO recommendation)

- **Dose Prescription**

o Total dose of 80-90Gy (ideally >85Gy) EQD2 (α/β = 10, EBRT plus brachytherapy) to HR-CTVbrachy [15].

o Total dose of 60Gy EQD2 (α/β = 10, EBRT plus brachytherapy) to IR-CTVbrachy.

- **Target volumes [15,16] (Figure 2)**

GTV brachy:

Macroscopic tumour extension at the time of brachytherapy as detected by clinical examination and MRI imaging

High risk CTV brachy:

GTVbrachy+ whole cervix and presumed extra-cervical extension at the time of brachytherapy as detected by clinical examination and MRI imaging

Intermediate risk CTV brachy:

HR CTVbrachy + safety margin of 5 -15mm

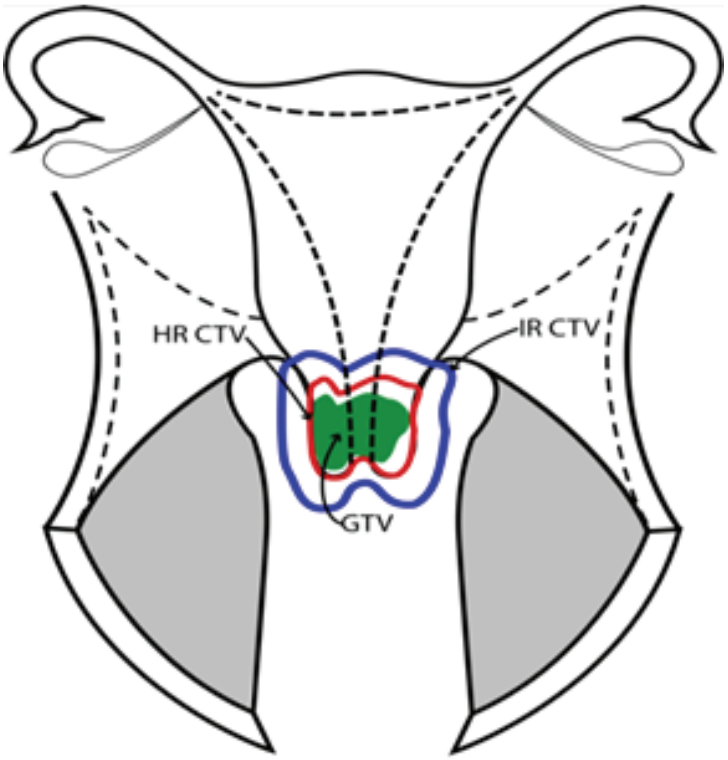

Figure 2

- **Organs at risk**

OAR	Dose constraints
Bladder	Maximum: D2cc < 90Gy EQD23 Planning aim: D2cc < 80Gy EQD23
Rectum	Maximum: D2cc < 75Gy EQD23 Planning aim: D2cc < 65Gy EQD23
Sigmoid	Maximum D2cc < 75Gy EQD23
Adjacent bowel	Maximum D2cc < 75Gy EQD23 Planning aim: D2cc< 70Gy EQD23

• **Applicators:**

Applicators should be MRI compatible

• **Procedure:**

- As above
- The applicators should be further stabilized with sutures as the patient needs to be wheeled to the MRI scanner

• **Documentation:**

- Doses to High risk CTVbrachy, Intermediate risk CTVbrachyand the OAR maximum D2cc to be documented

C. CT based 3D conformal brachytherapy

- As MRI is not freely available for brachytherapy planning in Sri Lanka, CT based conformal brachytherapy is preferable to 2D planning to improve outcomes.
- Simulation: After the insertion and stabilization of the applicators, a CT scan of the pelvis, 3mm slices should be done

• **Dose prescription:**

As per GEC-ESTRO recommendation [15]

• **Target volume**

As the tumour and extension into uterus and adjacent structures cannot be assessed clearly on the CT scan, the target can be defined using clinical information and CT findings as follows;

Target: Entire cervix and the uterus excluding a rind of fundus [16,17,18]

OR

GTV: Delineate macroscopic tumour as appropriate as possible [19,20,21]

CTV: Add a safety margin of 10mm to GTV [20]

OR

Follow the IBS-GEC-ESTRO-ABS guidelines [22]

OAR: Same as for GEC-ESTRO recommendations as above [15,16]

D. Trans abdominal ultrasound scan (TAUS) based brachytherapy

Target: Entire cervix and the uterus excluding a rind of fundus [18]

E. Post-operative brachytherapy

Indication:

- There is a lack of robust data regarding the advantages of brachytherapy in the adjuvant radiation setting [23, 24]
- Brachytherapy may be considered in the postoperative setting in the presence of a positive or close vaginal mucosal margin.

Technique:

- Using vaginal ovoids or vaginal cylinder to deliver dose to the vault and the proximal 3-4 cm of the vagina

Prescription:

- To the surface of the applicator

Dose:

- Aim to deliver **54-60Gy EQD2 ($\alpha/\beta = 10$)**
- Brachytherapy dose needs to be calculated based on the whole pelvis dose
- Some recommended dose regimes to offer approximately 60Gy to the vagina.

EBRT prescribed dose	EBRT (EQD2)	Brachytherapy dose	Total Point A prescription dose (EQD2)
45Gy/25#	44.3Gy	12Gy/2#	60.3Gy
46Gy/23#	46Gy	11Gy/2#	60.2 Gy
50.4Gy/28#	49.6Gy	9Gy/2#	60.5Gy
50Gy/25#	50Gy	8.4Gy/2#	60.0Gy

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6

MANAGEMENT OF RECURRENT DISEASE, METASTATIC DISEASE, COMPLICATION OF CERVICAL CANCER AND FOLLOW UP

6. Management of recurrent disease, metastatic disease, complication of cervical cancer and follow up

6.1. Curative Intent Treatment of recurrent Cervical Cancer

- Multidisciplinary approach is important
- Diagnostic workup to exclude distant metastases and loco regional tumour extension beyond curative treatment
- The recurrence should be confirmed by histological examination
- Patient should be carefully counselled regarding the treatment options and the involved risks and consequence.

a. Local recurrence of cervical cancer (central recurrence) following primary surgery

- Patients with central recurrences have better prognoses than those with pelvic sidewall recurrence [1].
- Definitive chemo radiotherapy or radiotherapy combined with image guided adaptive brachytherapy is the treatment of choice (see Chapter 5 for radiotherapy) [1,2].
- The use of boost by external beam techniques to replace brachytherapy is not recommended [2].
- Pelvic exenteration is an alternative option if radiotherapy cannot be considered [1].

b. Pelvic sidewall recurrence after primary surgery

- Definitive chemo radiotherapy is the preferred option [2]
- Extended pelvic surgery may be considered in highly selected patients

c. Central pelvic or pelvic sidewall recurrence after radiotherapy or Chemo radiotherapy

- Pelvic exenteration is recommended for central pelvic recurrence where there is no involvement of the pelvic sidewall and extra pelvic nodes [2]
- Laterally extended pelvic resection may be considered for a recurrence that extends close to or involves the pelvic sidewall [2]

D. Nodal and Oligo metastatic recurrences

- Localized para-aortic, mediastinal, and/or periclavicular recurrences above previously irradiated fields may be treated by radical external beam radiotherapy (EBRT) if possible in combination with concomitant chemotherapy [2].
- It is recommended to electively irradiate the immediate regional nodal stations below and upstream.
- The management of isolated organ metastases (lung, liver, etc) should be discussed in a multidisciplinary team.

6.2. Palliative Intent Treatment of recurrent or metastatic Cervical Cancer

Recommended for patients with extensive recurrence or metastatic disease.

For these patients, total palliation including physical, functional, psychological, social and spiritual symptom management should be offered with the multi-disciplinary team approach.

6.2.1. Palliative Chemotherapy

- Palliative chemotherapy with the aim of relieving symptoms and improving quality of life is indicated if the patient has a PS < 2 and no formal contraindications.
- Cisplatin-based doublets with topotecan or paclitaxel have demonstrated superiority to cisplatin monotherapy in terms of response rate and PFS [3,4].
- Paclitaxel and cisplatin combined chemotherapy with/ without bevacizumab is the preferred option based on the balance between efficacy and toxicity profile [5].
- Best supportive care addressing physical, psychological, social and spiritual suffering of the patient and the family.

6.2.2. Palliative Radiotherapy

- Palliative radiotherapy: Suggested fractionation- 14Gy/4#, 8Gy/1#, 20Gy/5#
- The treatment volume should be kept as small as possible to reduce toxicity [6].

Whole pelvis

- 30 Gy in 10 fractions to mid-plane dose over 2 weeks.
- 20 Gy in 5 fractions to mid-plane dose over 1 week.
- 14Gy in 4#bd at 4 weeks interval x 3

CT planned volume

- 27–30 Gy in 6 fractions prescribed to the isocentre treating twice weekly over 3 weeks.

In Advanced disease – to control bleeding or pain - to a small volume

- 15–21 Gy in 3 fractions treating on alternate days.
- 10 Gy single fraction.

6.3. Management of complications of Cervical Cancer

- Palliative radiotherapy (single fraction/short course) to control bleeding, discharge, and pain due to pelvic disease or bone metastases should be considered.
- For spinal cord compression due to bone metastases, neurosurgical intervention or short-course fractionated radiotherapy schedule should be considered [7,8,9].
- Surgical interventions including diversion stoma and/or stenting should be considered, in case of obstructive symptomatic disease [7,8.9].
- Management of fistulas must be tailored to the individual patient.
- A prolonged use of a bladder drainage catheter may trigger the spontaneous closure of vesico-vaginal fistulae.

Patients who are suitable for surgical intervention should be refereed to Gynae-Onco Surgeons for surgical repair or urinary diversion and the patients who are unfit for surgical interventions should be evaluated by the palliative care team for optimization of symptom control. Palliaitve care team will help to assess the patient's as well as her family's physical, psycological, social and spiritual sufferings and will facilitate the holistic palliaitve care.

6.4. Follow up

The recommended surveillance is based on the patient's risk for recurrence.

1. Clinical history & examination in 3 months interval for 2 years. Then, 4 -6 months interval for 3-5 years followed by annual follow up.

   As the detection rate of recurrent cervical cancer is low using cervical and vaginal cytology alone, a good clinical evaluation is mandatory [10].

2. For patients who have had fertility-sparing surgery, annual cervical or vaginal cytology tests can be considered as indicated for detection of lower genital tract dysplasia.
3. MRI pelvis 3 months after completing definitive treatment (only if available)
4. Investigate with biopsy and imaging if patient becomes symptomatic
5. Hormone Replacement Therapy (HRT) is recommended with risk assessment for women who have lost ovarian function as a result of either surgery and /or radiotherapy for cervical cancer [11]

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7

MANAGEMENT OF CERVICAL CANCER IN PREGNANCY

7. Management of Cervical Cancer in Pregnancy

Cancer of the cervix is the most common gynaecological malignancy diagnosed during pregnancy with an incidence rate of 0.1 to 12per10,000 pregnancies [1]. Almost 2/3 of cervical cancer cases in pregnancy are diagnosed in the first and second trimester [2].

Presenting symptoms do not differ between pregnancy and non-pregnancy state and may easily confused with pregnancy related symptoms [3].

All patients presenting with suspected cervical abnormality in pregnancy require an accurate pelvic examination including colposcopy assessment regardless of gestational age [4]. This will help to exclude invasion and to defer treatment until after delivery for pre invasive lesions. If suspicion of invasion at colposcopy, need to have a biopsy adequate for diagnosis [5].

For staging MRI scan is the ideal imaging during pregnancy. But with limited resources, ultrasound scan may be considered.

Treatment options

1. Cervical intra epithelial lesions in pregnancy

a. Patient with LSIL -Review after 6weeks of post-partum by the gynecologist

b. Patient with HSIL- Review every 12weeks during pregnancy by the gynecologist

2. Invasive cervical cancers

a. Stage 1A1- conization – can arrange during 2nd trimester should not be too deep as can lead to early abortion and bleeding

b. Stage 1A2-1B1 - before 22-25 weeks of gestation- simple cervical resection can be done. If tumour is progressing, to control the tumour until maturity of fetus neoadjuvant chemotherapy (NACT) can be given after 22weeks.

c. Stage 1B2 and higher stages - NACT with Carboplatin is recommended until planned early delivery. Single agent carboplatin has similar efficacy but less nephrotoxicity and ototoxicity compared to cisplatin.

NACT is not recommended before 20 week of gestation to avoid spontaneous abortion, fetal malformation and death. And after 33 weeks to avoid premature delivery and haematological complications at delivery.

Choice of delivery mode;

Delivery should be considered as early as possible when it is safe for mother and baby.

Caesarian section is the preferred mode as vaginal delivery can lead to massive bleeding and risk of vaginal ulceration and metastasis at episiotomy scar.[7]

Placenta should be sent to pathological examination to exclude metastasis.

Definitive management of cervical cancer according to the stage either surgical or with concurrent chemo radiotherapy like for standard treatment can be arranged after 6 weeks of post-partum care.

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