

Original article

Cancer of the Cervix: The Uganda Guidelines.

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Introduction

Cancer of the cervix (Ca Cx) is the commonest gynecological malignancy among women in Uganda contributing about 80% of all female malignancies. The incidence rate is 40:100 000. It is the leading cause of cancer related deaths in females in Uganda. Unfortunately 80% of the patients present late and this makes treatment outcomes unsatisfactory. Most patients can only be treated palliatively. It is therefore important that the disease be detected in early stages so as to improve outcome.

Objectives of the guidelines

Main Objective: To improve the quality of care and prognosis of cancer of the cervix in Uganda.

Specific objectives: Enable early detection, harmonize treatment, improve referral of patients and to create a referral document for health workers dealing with cancer of the cervix.

Risk Factors

Several risk factors have been implicated. These include early sexual intercourse, early pregnancy (below 18 years), multiple sexual partners and high parity. The risk is also higher in women whose husbands have multiple sexual partners. It has been suggested that male circumcision plays a protective role but this has not been fully proven.

There is a strong association with Human Papilloma Virus (HPV) infection - Types 16 and 18 which are sexually transmitted diseases. Herpes Simplex Virus (type II) infection has also been implicated. There is emerging evidence that suppression of the immune system

promotes the development of the cancer, as is the case with HIV/AIDS and organ transplant patients.

Ca Cx is commoner in women of low socio-economic class but the low socio-economic class is not an independent risk factor. A diet low in vitamins A, C, Beta carotene and Folic acid has also been implicated. Tobacco use has been identified as an independent risk factor. However the role of alcohol consumption has not been confirmed.

Prevention

Prevention is interactive with that of sexually transmitted infections (STI) and is aimed at delayed sexual intercourse and use of condoms. A vaccine against HPV is being developed.

Screening

Currently, there is no infrastructure for a nationwide screening programme in Uganda. However, the following are the established procedures, which should be routinely carried out.

- Unaided visual inspection of the cervix
- Visual inspection aided by acetic acid and Lugol's iodine (may be done in Health center IV)
- Colposcopy, Pap smear (Papanicolaou smear)

Clinical Presentation

Early Clinical Features

Most of the patients present in the 4th and 5th decades. The early symptoms of cervical cancer

include postcoital or contact bleeding, offensive vaginal discharge and inter-menstrual vaginal bleeding. The early signs are difficult to demonstrate. In the early stages one may see nothing suspicious on a speculum examination; this does not exclude presence of disease! However, a hyperemic cervix or even an ulcer on the cervix may be noted.

Late Symptoms and Signs.

These include abnormal vaginal bleeding such as contact, spontaneous intermenstrual and postmenopausal bleeding. This is usually associated with an offensive vaginal discharge, lower abdominal pain, deep dyspareunia and backache. Other features may arise as a result of complications and or metastases from the disease process such as those due to ureteric involvement /obstruction and uremia, anemia, swelling of the lower limbs, fistulae formation such as vesico-vaginal fistula (VVF) and recto-vaginal fistulae (RVF), haematuria and urethral obstruction.

With the development of metastases, other features such as cough, ascites and bone pains may be observed depending on the site of the secondaries, however these are rare as patients usually succumb to complications due to local invasion.

Diagnosis

A vaginal speculum examination is essential. This is followed by an examination under anaesthesia (EUA), biopsy and staging of the disease.

Diagnostic Investigations

A Pap smear/Cytology

It is useful especially in the diagnosis of the cervical intraepithelial neoplasia. This involves scraping cells from the cervix, fixing and staining them on a glass slide and having them evaluated. All reproductive health clinics in the country should do a Pap smear and transport the slide to a referral center for the pathologist to report on. The following are included in a cytological report:

- Degree of dysplasia

- Nuclear atypia (ratio of nucleus / cytoplasm)
- Number of cells that are normal and abnormal.
- Inclusion bodies
- Abnormal division leading to microinvasion.
- Quality of the smear specimen.

Colposcopy

When acetic acid is applied on the cervix, abnormal areas appear greyish white (aceto-white). Areas that are aceto-white are biopsied.

Staging Investigations

1. **EUA**-Examination under anaesthesia.
2. **Radiological**

i). Abdominal And Pelvic Ultrasound.

The following are checked for:

- Cervical mass.
- Parametrial infiltration.
- Local and para-aortic lymph nodes (LN).
- Bladder infiltration (mucosa and wall).
- Rectal invasion.
- Ascites.
- Kidneys for Hydronephrosis
- Abdominal metastases –Liver and spleen.
- Pleural effusion

ii). **CXR:** For secondaries or other disease complications

iii) **Intravenous Urography (IVU)** gives additional information regarding renal function and level of ureteric obstruction.

iv.) **CT Scan.** (Where available) to check for:

- Lymph nodes (Para-aortic and regional)
- Size and site of tumor mass.
- Parametrial involvement.
- Secondaries in the liver and spleen.

V). **Other Plain Radiographs:** as indicated.

3. Laboratory

The most common complications of cervical cancer are anemia, renal failure and hypercalcaemia. Laboratory abnormalities include: anemia, electrolyte imbalances, elevated blood urea and serum creatinine levels. Hypercalcaemia may occur in advanced disease with bone involvement.

4. **Cystoscopy:** for bladder mucosal invasion.

5. **Proctoscopy:** for rectal mucosal involvement.

Other investigations are indicated by the patient's condition and presentation. For example

sentinel node biopsy, **bone scan** and **tumor markers** like carcino-embryonic antigen (CEA) which is used to monitor response to therapy and follow up. Squamous carcinoma antigen (SCA) can also be used to monitor the response.

Figo Staging

Stage I. Strictly confined to cervix

1A. Preclinical carcinoma of cervix diagnosed only by microscopy.

Invasion is limited to measured stromal invasion with maximum depth of 5.0mm and no wider than 7.0mm.

1A1. Stromal invasion no greater than 3.0mm and no wider than 7.0mm.

1A2. Maximum depth of invasion of stroma greater than 3mm but less than 5mm (taken from the base of epithelium-either squamous surface or glandular- from which it originates). The horizontal invasion should not be more than 7mm.

1B. Clinical lesions confined to the cervix or preclinical lesions greater than stage 1A2.

1B1. Clinical lesions less than 4.0cm in size

1B2. Clinical lesions greater than 4.0cm in size

Stage II. Extension beyond cervix but not to pelvic wall or lower third of the vagina.

IIA. Without parametrial invasion

IIB. With parametrial invasion

Stage III Extension to pelvic wall, involves lower third of vagina, or causes hydronephrosis or non-functioning kidney.

IIIA. Involves lower third of vagina, no extension to pelvic wall

IIIB. Extension to pelvic wall or causes hydronephrosis or non-functioning kidney.

Stage IV

IVA. Extension beyond true pelvis or involvement of bladder or rectal mucosa. (Bullous edema does not permit a case to be assigned to stage IV)

IVB. Distant metastasis

Referral System.

Midwives are trained to recognize the clinical features and then refer the patient to Health center IV, where a pap smear / Biopsy can be done. Staging and treatment are done at Regional referral hospitals.

Treatment of Cervical Cancer

Surgery or radiotherapy when used alone or in combination are curative in early cervical cancer.

Factors, which influence the choice of treatment, include the age and general condition of the patient, the stage of the tumor and the patient's own preference.

1. SURGERY

Early Disease: Stage 1-11a

Surgery plays an important role in the management of early disease.

Cervical Intra-epithelial Neoplasia (CIN)

- CO₂ Laser.
- Cryosurgery.
- Cone Biopsy

Stage IA1. Simple hysterectomy is treatment of choice. A cone biopsy is done with strict life long follow up in selected patients who have not completed their families.

Stage IA2. A modified radical hysterectomy ±pelvic Lymphadenectomy is the recommended treatment (where the medial parametrium and the vaginal cuff are excised.) Doing a lymph node dissection on frozen section first is recommended.

- If negative, a simple hysterectomy is done
- If positive, then a Wertheim's hysterectomy is done.

Stage IB1 – IIA Surgery:

For Wertheim's Hysterectomy

Treatment of Late Disease: Stage Iib And Beyond

The main treatment is radiotherapy. Surgery has only a limited role in late disease. Palliative Hysterectomy is not recommended.

2. RADIOTHERAPY

Radiation therapy has a very important and effective role in the management of cancer of the cervix. In specifying the total dose to the pelvic wall the contribution from the intracavitary treatment will depend on the exact geometry of the sources and the size of the pelvis. In designing these regimens an approximation is made that the pelvic side wall receives 20% of the point a dose when a uterine tube and vaginal ovoids are used and almost nothing when ovoids alone are used. The philosophy behind the regimens is that the dose to a point A, 2 cm lateral to the central uterine canal and 2cm superior to the external source should be equivalent to the conventional intracavitary dose of 75-80 grays (Gy). Low dose rate and high dose rate brachytherapy may be used.

Postoperatively the tolerance of the pelvis (after a Wertheim's hysterectomy) is reduced to about 45 Gy. If there is residual disease in the nodes or excision margins then an attempt to deliver a total of 60 Gy should be made by either additional external beam radiotherapy (EBRT) or intracavitary treatment (ICT).

Early Disease

Stage IA.

If surgery can't be done, radiotherapy can be curative.

If a patient is unsuitable for surgery, intracavitary therapy (ICT) alone is sufficient. 68-70 Gy is delivered in 2 insertions with a gap of 10 days.

Stage IB / IIA.

In young women with bulky tumor and positive lymph nodes, the treatment is external beam therapy (EBRT) of 50 Gy in 25 fractions over 5 weeks. This is followed by ICT of 20-30 Gy, single fraction to point A. For patients who are older or have positive lymph nodes demonstrated at CT, or are not fit for or refuse surgery, EBT and ICT are given as above.

Late Disease (Stage IIB and Beyond)

Stage IIB – IIIB

Radical radiotherapy is the treatment of choice. This requires both EBT of 50Gy in 25 fractions, 2Gy daily over 5 weeks, and ICT of 22-30Gy to point A.

Stage IVA

These patients receive EBT of either 30Gy in 10 fractions over 2 weeks or 50Gy in 25 fractions in 5 weeks depending on the patient's clinical condition. ICT may be given in selected patients.

Stage IVB

Treatment of metastases should be individualised depending on the site. The pelvis should be treated as above depending on the patients' condition. A single pelvic EBRT of 8-10 Gy can be given if the patient's condition is poor.

Special Cases

Obese Patients

These are patients with an A-P separation of more than 21 cm. In these patients a dose of 50.4 Gy in 28 fractions over 5.5 weeks is given (i.e. 1.8 Gy per fraction daily). This is followed by ICT according to the stage of the disease.

Cervical Cancer in Pregnancy

The management depends on the extent of the disease at the time of diagnosis, stage of pregnancy and wishes of the patient.

In the first trimester of pregnancy, stage I disease is treated by Wertheim's hysterectomy.

If the disease is of more advanced stage, radical radiotherapy is given.

In the second trimester, for stage I disease, the pregnancy is terminated by hysterotomy followed by a Wertheim's hysterectomy at the same sitting. For stage II or more advanced

disease, radical radiotherapy (EBRT & ICT) are given as above.

In the third trimester with a viable fetus, a caesarian section is carried out at 34-36 weeks for stage I disease followed by Wertheim's hysterectomy at the same sitting. For stage II or more advanced disease, radical radiotherapy is given following a caesarian section.

Recurrent Disease.

If the disease recurs locally after primary surgery, radical radiotherapy is advised with EBT of 50.4Gy in 28 fractions over 5.5 weeks followed by a single ICT insertion of 20-30Gy. The patient may experience a greater than usual toxicity because of the previous operation. If the disease recurs after primary radiotherapy, it is often too advanced for salvage surgery.

Radical hysterectomy for recurrent or persistent cervical cancer following radiotherapy can offer an alternative procedure to exenteration in highly selected patients (with FIGO Stage IB-IIA, no clinical parametrial involvement and with a tumor less than 4cm in diameter at the time of the recurrence.)

Positive Pelvic Lymph Nodes (after imaging or surgery)

A dose of 50.4gy in 28 fractions over 5-6 weeks is given to the whole pelvis. This is followed by ICT according to stage.

Positive Para-Aortic Lymph Nodes (On Imaging)

Radiotherapy is the treatment of choice. An extended spade shaped parallel opposed pair to cover extended pelvis and L1-L4 inclusive is given aiming at 45 Gy in 25 fractions over 5 weeks, followed by an extra 5Gy in 3 fractions to the extended pelvis.

Cancer of the Cervical Stump

In the rare cases of cancer of the cervical stump, this is treated according to stage as above.

3. CHEMOTHERAPY

The tumor is quite chemoresistant.

Chemoradiation: This is where chemotherapy is given during radiotherapy as it has a radiosensitiser effect. There is now increasing evidence of chemo-sensitivity of cervical

tumours to Platinum based chemotherapy regimens when given as concurrent chemoradiation. Chemoradiation is now the treatment of choice for those patients who are fit enough for Platinum based treatment, and when they have sufficient resources.

Chemotherapy is rarely used in the palliative setting, as the most active drug (Cisplatin) has significant toxicity, and the aim of symptom control without causing side effects is difficult to achieve. The dose given is 40 mg per m² weekly during EBRT.

Patient Follow-Up

The follow-up policy is 1month after treatment and 2-monthly for the first year, 3-monthly in the second year then 6monthly from years 3 to 5. Thereafter yearly follow up. This is because most recurrences occur in the first 2 years after treatment. The likelihood of relapse after 5 years is small. A pap smear six monthly for two years is recommended

4. Palliative Care

A multidisciplinary team approach is very important in the care of these patients and should be patient and family centered.

Managing Physical Signs and Symptoms:

Pain

Pain is managed according to the WHO 3-step analgesic ladder.

Somatic Pain. Non-steroidal anti-inflammatory drugs (NSAIDS), may be needed for bone pain, which is very common in carcinoma of the cervix. The NSAIDS may have to be combined with opioids, as this is usually severe pain.

Neuropathic Pain. Cervical cancer may invade nerve tissues manifesting with Neuropathic pain. Amitriptyline, anticonvulsant such as phenytoin, or both may be beneficial in treating this complication.

Vaginal Discharge

It could be composed of blood, pus, tissue, urine, stool or a combination of the above. Clean strips of cloth or sanitary pads or bundles of cotton could be utilized and changed regularly to ensure that the patient is dry and comfortable.

To prevent skin excoriation, zinc paste or Vaseline may be applied to the surrounding areas.

There is need to decrease on the amount of bacterial growth by gently packing the vagina with clean cloths soaked with water mixed with bicarbonate soda powder (about one teaspoon in 500ml of warm water) or metronidazole I.V. solution. A metronidazole solution can also be made by dissolving 5-10 crushed 200mg- tablets [non coated] in 500ml of water. The vaginal pack is left in situ for a couple of hours per day for about 5 days. Tablets of metronidazole can as well be inserted vaginally and serve the same purpose. A patient can easily apply this than the vaginal packing. Vaginal douching can be used, once or twice a day.

Vesico-Vaginal Fistula And/Or Recto-Vaginal Fistula

Plastic panties with cotton cloth or cotton wool pads are used and can be comforting to the patient as she will remain dry. Covering the bed with a plastic sheet can help to protect the linens or bed cloths.

Vaginal Bleeding

Simple bed rest may help. Vaginal packs can effectively control bleeding. Radiotherapy may also help in controlling the bleeding.

Leg Swelling (Lymphoedema)

Raising the leg or bandaging it or support stockings are used.

Skin care: avoiding any skin injuries e.g. extra care should be taken when cutting the nails. Lymph is a very good culture medium for bacteria and so the patient is susceptible to serious infection. If lymphangitis sets in, broad spectrum antibiotics e.g. Erythromycin or Septrin are administered.

Massage to the limb may help in stimulation of lymphatic flow and may reduce on the swelling.

Social, Emotional And Spiritual Issues

Family stress Sexuality problems. It is important to support and discuss salient issues with the patient, husband, children and close family friends.

Sexual problems. Discussing with the couple may make them understand what is happening and helps them decide what is better for them. Avail opportunities for open and honest discussions for the patient and partner including alternatives to sexual intercourse.

Spiritual issues. Spiritual beliefs can be comforting when death is approaching. Patients have questions about what is to happen. She may need to make peace with God so that her soul is safe after death. A spiritual advisor will play a role but it is important to respect people's spiritual beliefs. Patients may need someone to talk to or pray with like religious leaders or someone else they respect.

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