Cervical Cancer

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Cervical cancer is the second leading malignancy affecting women world wide [1]. It constitutes about 10% of all cancers in women [2]. It is the leading cause of cancer death among women in the developing world. The incidence and mortality from cervical cancer show a wide geographic variation between developed and developing countries. Developed countries have been able to reduce the incidence and mortality from cervical cancer through the introduction of screening and adequate treatment of cervical premalignant lesions [3]. It was among the leading malignancies affecting women in the USA but over the last 40 years the overall incidence has declined steadily with only about 10,370 new cases and 3710 deaths in 2005.[4]

Annually over 294,000 new cases are diagnosed globally with about 273,000 deaths. Over 80% of the new cases and 85% of the deaths occur in the developing countries [5]. It generally affects multiparous women in the early post menopausal years with enormous social impact. It is thus an important public health problem in the developing countries.
The incidence is high in sub-Saharan Africa with an estimated 57,000 cases in 2000, comprising 22% of all cancers in women, equivalent to an age-standardized incidence of 31 per 10,000.

In Nigeria there is no accurate figure for the incidence and death from cervical cancer as there is no population-based cancer registry.

The age-specific incidence in Nigeria has been quoted to range from 18.8 per 100,000 in the age group 20-24 years to a high 373.75 per 100,000 in the age group 60-64 years [6, 7, 8]. These figures are mainly hospital-based and are mostly underreported, because majority of the patients do not come to the hospitals. Also, over 98% of individuals presenting in the hospitals are seen in the advanced stages III and lV.

Survival too is also low for developing countries mainly because of late presentations, and poorly developed facilities for management of cancer cases and that a significant proportion of patients do not receive or complete their prescribed treatment [9].

RISK FACTORS

A sexually transmitted aetiology for cervical cancer has long been suggested based on the observations that nuns do not develop cervical cancer and those prostitutes had an increased risk for the development of cervical cancer. Later epidemiological studies (mainly case-control studies) showed a consistent association between risk and early age at initiation of sexual activity, increasing number of sexual partners of females or of their sexual partners.

Over time, the suspected linkage between sexual behaviour and the development of cervical cancer was confirmed to transmission of the human papillomavirus (HPV) during sexual intercourse. Nuclei of HPV are found in almost all preinvasive lesions of the cervix as well as in invasive lesions. More than 100 serotypes of the HPV have been identified and based on their association with cervical cancer have been divided in high-risk, intermediate-risk. and low-risk. One of the main differences between the high risk and low-risk is the possibility of viral integration into the host genome.
Examples of the high risk HPV are serotypes 16, 18, 31,33,39,45,51,52,54.

The most common serotypes are 16 and 18. These two serotypes are responsible for an estimated 70% of cervical, anal, and genital cancers. Examples of the low risk types are 6 and 11 and are responsible for an estimated 90% of cases of genital warts. HPV-16 is by far the most common serotype detected in cervical pre cancer and cancerous lesions. It accounts for more than 50% of all cervical cancer cases, ranging from 45% in Asia to 62.6% in North America and Australia [10].

The risk of cervical cancer among HPV positive women has been reported to range from 16-fold to 122-fold [11,12].

Since approximately 1% of the-risk HPV types and only 0.1% of the low-risk HPV types will lead to the development of cervical cancer, this suggests that HPV is a necessary link and not a sufficient cause for cervical neoplasia and that other factors may be involved.

Parity: High parity or number of live births has been associated with cervical pre-malignant conditions and

cervical cancer [13, 14]. At the Ife hospital unit (a unit of Obafemi Awolowo University Teaching Hospital Complex) the average parity was 7 [15]. Although there is no clear mechanism to support the association between cervical cancer and high parity, repeated trauma during child birth could lead to breaches in cervical epithelium thereby facilitating the establishment and persistence of HPV infection. Hormonal, immunologic and nutritional factors have been also been suggested.

Oral Contraceptive: Results from studies evaluating the effects of combined oral contraceptives in cervical carcinogenesis have been conflicting [16,17]. This is because the interpretation of these studies is limited by the strong correlation among OC use, sexual behaviour (and thus HPV), and patterns of Pap smear screening; by the selection of adequate comparison groups and by the lack of control for HPV status [18]. What has consistently shown, however, is increased use of OC (more than 5 years) and cervical cancer. The strongest association is with Adenocarcinoma in situ and invasive adenocarcinoma. The effects of OC may be due to hormonal influences that maintain the transformation zone n the ectocervix, facilitating exposure to HPV and other co-factors.

Smoking: Most studies have shown that smokers have at least two-fold increased risk of cervical cancer than non-smokers. The risk of high grade squamous intraepithelial lesions and cervical cancer among HPV- positive women who were smokers ranged from 2 and 5, and the risk increased with amount and duration of smoking [19,20].

Immunosuppression: In 1992, the American Centres for Disease Control (CDC) included invasive cervical cancer in the definition of AIDS-related conditions.
Immunosuppression is a known risk factor for the development of invasive lesion of the cervix and HIV+ women have been shown in studies done in the western world to have a higher incidence of cervical smear abnormality, larger lesions and higher grades of lesions [21,22 23].
The biologic mechanism for HIV infection as a co-factor for HPV related carcinogenesis is not completely understood. Increasing HIV-associated immunosuppression (levels below 500/mm^3) is hypothesized to decrease HPV-specific immunity and progression to preinvasive and invasive cervical cancer.

Pathology: The different histological types of cervical cancer are

i) Squamous cell carcinoma: It comprises the majority of cervical malignancies.

ii) Adenocarcinoma. It comprises a small proportion of cervical carcinoma but the incidence appears to be rising. It has been said to have a poorer 5-year survival compared to squamous cell carcinoma.

iii) Adenosquamous carcinoma. This is a mixture of malignant squamous and glandular elements and it is distinct from endometrioid adenocarcinoma with squamous differentiation. It has a worse prognosis than either squamous carcinoma or adenocarcinoma especially on advanced staged disease.

iv) Other rare histological types are Glassy cell carcinoma, Adenoid cystic carcinoma, Adenoid basal carcinoma and neuroendocrine carcinoma, Leiomysarcoma, Adenosarcoma, malignant Mixed Mullerian tumour, malignant melanoma, and lymphoma.

Clinical Presentations: Cervical cancer is a disease of post- and premenopausal women. Most patients present with abnormal vaginal bleeding which may be post menopausal, Intermenstrual and post coital bleeding. The second most symptom is abnormal vaginal discharge.
At the OAUTHC (IHU) 38.4% of the patients presented with post menopausal bleeding[15]. Late presentation is common in this environment. In a review done in OAUTHC over 98% of the patients presented more than one month after the appearance of the first symptoms and 94.4% of our patients in this hospital presents at late stages of the disease [15]. Symptoms of late presentation include anaemia from chronic blood loss, uraemia from obstructive uropathy, bone pains from metastases to the bone and genital fistula.

MANAGEMENT OF CERVICAL CANCER

Management of cervical cancer is very expensive and not very effective.
1 Complete physical and Gynaecological examination
2 Complete blood count and urine analysis and chest x-ray.
3 Ultrasonography or CT scan
After these initial investigations, the disease is staged clinically, this involves Examination under Anaesthesia, clinical staging and cervical biopsy.
Cervical cancer is staged clinically. The clinical staging as recommended by the International Federation of Obstetricians and Gynaecologists in 1994 is as follows:

Stage 0 Carcinoma in situ, cervical intraepithelial Neoplasia
Stage 1 Carcinoma strictly confined to the cervix (extension to the corpus is disregarded)
$1a_1$ Invasive cancer that can be diagnosed only be microscopy, no greater than 3mm depth and no wider than 7mm.

$1a_2$ Tumour is less than 5mm below the basement membrane (BM) and less than 7mm in transverse diametre.

1B Tumour is more than 5mm below BM and more than 7mm wide but limited to the cervix.

$1B_1$ Tumour is less than 4cm in size
$1B_2$ Tumour is more than 4cm in size.

Stage11 Tumour has spread beyond the uterus but not to the lower 1/3 of the vagina or the pelvic side wall.
11A without parametrial invasion
11B with parametrial invasion

Stage 111 Tumour extending up to the pelvic side wall, lower 1/3 of the vagina, hydronephrosis or non- functioning kidney.
111A No extension to the pelvic sidewall but involved the lower 1/3 of the vagina.
111B Extension to the pelvic sidewall, hydronephrosis or Non functioning kidney.

Stage 1VA Invasion of bladder and/ or rectum
Stage 1VB Disease outside the pelvis. Para-aortic nodes are regarded as metastasis.

TREATMENT OPTIONS

Extent of the disease is the most important factor in the treatment decision.
The other factors that also influence the treatment decision include the age of the patient, fertility preservation and other medical conditions.

Generally radiation therapy can be used for all the stages but for premenopausal women, surgery is preferred for early invasive disease (stages 1 to 11A) because radiotherapy would lead to premature cessation of ovarian function.
Studies have shown that surgery and radiotherapy have equal efficacy for early invasive disease.

In February 1999, based on the results from five randomized clinical controlled trials, the National Cancer Institute issued an alert that strong consideration should be given to incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer.

Concurrent chemoradiation with cisplatin improve the rates of survival and progression-free survival among women with stages 1B to 1VB cervical cancer as well as high risk patients after hysterectomy.

Stage 0 Carcinoma in situ

For ectocervical lesions the treatment options are:

- Loop Electrosurgical Excision Procedure(LEEP)
- Laser therapy
- Conization
- Cryotherapy

For Endocervical canal involvement the available treatment options are:

- Laser Conization may be used for selected patients to preserve the uterus and avoid radiation therapy and/or more extensive surgery
- Total abdominal or vaginal hysterectomy is an accepted therapy for the postmenopausal women and is especially indicated when the lesion extends to the inner cone margin that is positive margin.
- For medically inoperable patients, a single intracavitary insertion to a dose of 8000cGy vaginal surface dose may be used.

STAGE IA_1

Conization may be used provided that there are no vascular or lymphatic channels involvement and provided that the margins of the cone are negative. This is particularly indicated in patients who wish to preserve their fertility

Total abdominal or vaginal hysterectomy may be used provided that there are no lymphovascular channels are involved.

Intracavitary radiation only. This is indicated for patients that are not fit for surgery. The dose of radiation of about 10,000-12500cGy is considered adequate.

STAGE IA_2

Radical hysterectomy (TypeII). This is the recommended treatment because the incidence of lymph node involvement may be up to 10%, but a study has suggested that the incidence of lymph node involvement may be lower.
However if fertility is desired, the available options are:

(i) Large cone biopsy plus extra peritoneal or laparoscopic pelvic lymphadenectomy.
(ii) Radical trachelectomy and extra peritoneal or

laparoscopic pelvic lymphadenectomy

Radiation Therapy: Radical intracavitary radiotherapy or intracavitary plus external pelvic irradiation may be considered in women who are not fit for surgery.

STAGES IB and IIA
Similar cure rates are obtained with radical hysterectomy with pelvic lymphadenectomy and radiation treatment. The factors determining which treatment options to choose are the age of the patients, desire to preserve ovarian function co-morbid conditions, associated gynaecological conditions, the expertise and facilities available.

Radical hysterectomy. This involves the removal of the uterus and upper vagina, bilateral parametrial, uterosacral and bilateral pelvic lymph node dissection. Bilateral salpingo oophorectomy is discretional

After radical surgery patients are classified into three risk groups based on requirement for adjuvant therapy.
I **High risk**: These are patients with one of the followings of the histopathological examination of the malignancy.
a) Lymph node metastases, Positive surgical margins and parametrial extension of the tumour.
Adjuvant chemoradiation with external pelvic radiation with weekly concurrent cisplatin is recommended.

II **Intermediate risks**: Patients with two or more of the followings are classified as intermediate risk. Deep cervical stroma invasion, lymphovascular space invasion, and tumour size of more than 4cm.
Radiation therapy is recommended as adjuvant treatment for this group.

III **Low risks:** All other patients with none of the above risk factors are classified as low risk for recurrence of disease and thus require no adjuvant treatment.

RADICAL RADIATION THERAPY
A combination of external-beam pelvic irradiation covering the uterus, parametrial and pelvic lymph nodes and intracavitary radiation is used.

STAGES IIB AND IIIB
Radical radiation therapy remains the only means of achieving cure in these patients. Surgery cannot be curative in this group of patients.

STAGE 1V
Patients in this stage are given individualized treatment based on the degree of organ involvement.
Treatment options are:
Pelvic exenteration
Palliative radiotherapy.

RECURRENT CERVICAL CANCER.

Management of patients with recurrent cervical cancer depends of the initial therapy the patient has had, extent of the recurrent disease, performance status of the patients and the facilities available.
Post surgical recurrence. Patients with predominantly central recurrence, with no spread to the pelvic side wall and no extra pelvic disease and with good performance status, may be offered pelvic exenteration.

Post radical radiation therapy with only central recurrence may be offered extrafascial hysterectomy or pelvic exenteration.

Patients that have had prior surgery and chemoradiation may be offered palliative chemotherapy.

CONCLUSION

In conclusion cervical cancer is a highly preventive cancer; ideally all sexually active women in any given community should be screened for cancer of the cervix. However, in a low resource country like Nigeria such mass screening would be difficult and too expensive to execute; and it may never be completed. Screening should therefore be done on the basis of age groups and the targeted age group should be between 30 and 60 years, which is the most vulnerable group for cervical cancer in Nigeria. Carcinoma in Situ peaks at about 30 years. The majority of women below the age of 30 years usually have varying degrees of Cervical Intraepithelial Lesions, most of which regress. Cervical cancer usually develops after age 30 years and it is most frequent in women in their fifties and sixties.

From the limited studies done in Nigeria, the average age of presentation of cervical cancer is 55 years. The age group between 30 and 60 years constitute the group that is most at risk of developing cervical cancer.
Of equal importantce is the fact that many resource poor countries like Nigeria cannot adopt the Pap smear technique that has been successfully adopted in the developed countries because of lack of trained manpower, infrastructure, logistics and cost.

One of the alternatives that has been evaluated and that may be easier to implement in developing countries like Nigeria is the Visual Inspection technique. This method has been found to be cheap, easy to use and the results are obtained immediately making it possible to apply

treatment at the same clinic visit thus reducing the loss to follow-up rate which is a big problem in the management of patients with malignancies in Nigeria.

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