

Original Article

Analysis of 100 consecutively visiting uterine cervical cancer patients in cancer hospital.

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Abstract

Background: Cervical cancer is the most common cancers in female population of Nepal. Though considered a slow growing cancer, majority of patients still present very late.

Methodology: One hundred patients of cancer cervix were retrospectively analysed to see their spectrum of clinical presentation and care pathway from January 2012 to April 2012.

Results: The clinical spectrum showed they presented to clinic after average of 9 months of symptoms. Squamous cell cancers were the main histology. Majority of cases were in FIGO stage of II and IIIB. Radiation therapy with tele-therapy and brachytherapy was the main modality of treatment (94%) of cases.

Conclusion: Late stage of presentation is a very common phenomenon in the patients with cancer of cervix. Need screening programs in systematic manner to detect early stage diseases and for better care.

Key words: Cervical Cancer, Treatment, Radiotherapy, Surgery

Introduction:

Cervical cancer is a malignant neoplastic disease that tends to begin slowly when there is a disruption of the cervical epithelium, near the squamo-columnar junction of the uterine cervix. Initially, this pre-invasive process is limited to the cervical epithelium and is known variably as cervical intraepithelial neoplasia (CIN), according to the classification scheme mostly used in histopathology, or as squamous intraepithelial lesion (SIL), as per the classification system favored for cytopathological diagnosis Low-grade SIL (LSIL) (equivalent to CIN 1) and high grade SIL (HSIL, equivalent to CIN 2 and 3) are invariably asymptomatic and can be detected through cytological examination using the Papanicolaou technique (the Pap test). Their presence is confirmed by magnification during colposcopic examination and by biopsy.¹ If left untreated, LSIL may become HSIL, and the latter may eventually extend to the full thickness of the

cervical epithelium, a condition that is recognized as cervical carcinoma in situ (CIS). Subsequently, the disease may become invasive. This process may take a decade or longer. There are two main histological types of invasive cancer: squamous cell carcinomas and adenocarcinomas. The invasive lesion may metastasize to nearby pelvic and distant lymph nodes and other body sites. The symptoms and signs in most women with invasive cervical cancer include post-coital bleeding, recurrent bladder infections and ulcers on the cervix. Pressure against nerve trunks and the sacral plexus produces persistent pain. As soon as lymph node metastasis occurs the disease worsens considerably.²

Cancer of uterine cervix is commonest malignancy among females in Nepal. Globocan 2020 suggests it to be first common cancer in females of Nepal followed by breast, lungs, gall bladder and ovary. Though the incidence of cancer of cervix has

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come under control in western world and even in neighboring China, it remains same in Nepal.³ Lack of awareness among population, no systematic screening programs are contributing to this. The screening remains opportunistic and HPV testing still remains a test of Luxury in Nepali context.

In this article, we tried to make an analysis of a typical walk in 100 patients to see their distribution and care pathway in B. P. koirala memorial cancer hospital.

Methodology:

We retrospectively analyzed case notes of 100 consecutively coming patients diagnosed with cancer of uterine cervix from January 2012 to April 2012. Case notes were retrieved from Medical record section of the hospital and plotted in excel file for subsequent evaluation in SPSS ver 25.

Results:

Total of 100 case notes were analyzed. The average age of patients was 54 years, range 34- 85 years old. They were coming from 44 out of 77 districts of Nepal. The majority of symptoms were per vaginal bleeding and discomfort in 92.5% of patients. As majority of patients were post menopausal, re-bleeding after stopping of menstruation was also a significant symptom. Majority of patients had growth in cervix 81.1%, Endocervical type in 6.6% and ulcerative type in 5.7% of cases. 13% had extensions towards fornices and into the vagina. Average time from symptoms to hospital visit was 9 months.

Patients were evaluated with ultra sonogram in majority of cases. Tomography with CT and MRI were also performed in about 30% of cases.

Among those patients, FIGO stage II B and IIIB disease were the predominant disease consisting of 82% of the patients.(Table 1) In pathological type, the squamous cell cancers were 93%, Aden-squamous in 6% and adenocarcinoma in 1%. (Table 2) Therapeutic radiation therapy in the form of tele therapy and brachytherapy was delivered in 94% patients. Radical hysterectomy and Pelvic lymph node dissection were performed in 6% cases, 2 of them further required adjuvant RT for positive lymph nodes.

Majority of patients (94%) received radiation therapy in the form of Tele-therapy combined with brachytherapy. Most patients (88%) received 23 fractions 200 centi-grey of tele therapy in 3 field

conformal manner totaling 46 grey, other 10% received 25 fraction totaling 50 grey. Both types of tele therapy were added with 3 sessions of 8 grey of Brachytherapy using iridium source reaching total dose of 24 grey. Eleven percent of patients did not receive total of 3 sessions of brachytherapy after tele-therapy. There were delays in tele therapy to brachytherapy times due to logistics issues in some of the cases (Iridium source not reaching in time etc). Chemotherapy were used in concurrent with RT in 30 % of cases and the drug used in paclitaxel and cisplatin. (Table 3)

The mode of surgery was radical hysterectomy with standard pelvic lymph node dissection under general anaesthesia. Specimen was sent for analysis in pathology department and analyzed for size of tumor, depth of invasion, marginal status, lymph node status. Vaginal and para-metrial margins were negative in all cases. Lymph-node yield was 15.2 in average number (range 10-30). Immediate surgical complications of clavier-dindo 1-2 were seen in 2 patients.

Follow up of 9 patients were noted alive at the time of writing of this article.

Table 1 : FIGO staging of the patients

FIGO Stage	Number of patients	Percentage
IA1	0	0
IA2	0	0
IB1	5	5
IB2	3	3
IIA	3	3
IIB	48	48
IIIA	3	3
IIIB	34	34
IVA	3	3
IVB	1	1

Table 2: Pathological type of the disease

Particulars	Number of patients	Percentage %
SCC	93	93
Adenocarcinoma	1	1
Adenosquamous	6	6

Table 3: Care pathways

Treatment Options	Number of patients	%
Surgery (RH+PLND)	6	6
Radiotherapy (Teletherapy + Brachy therapy)	94	94
Chemotherapy (as a sensitizer Chemo)	34	34

Discussion

The Global Burden of Cervical Cancer Cervical cancer is one of the most common malignant diseases of women. An estimated 471,000 new cases of invasive cervical carcinoma are diagnosed annually worldwide, with a disproportionately heavy burden of the disease (380,000 new cases) occurring in developing countries. In 2000 there were an estimated 233,000 deaths from cervical cancer worldwide.³ Its worldwide incidence represents nearly 10% of all female cancers, and it is the third most common anatomic location among women, after breast and colorectal cancer.³ The highest risk areas are in South Asia, Central and South America, southern and eastern Africa, and the Caribbean, where average incidence rates exceed 40 per 100,000 women per year.³ Cervical cancer is the most common female neoplasm in regions such as eastern Africa and the Caribbean, accounting for 20% to 30% of all malignancies.³ The risk in western Europe and North America is considered relatively low, at fewer than 10 new cases annually per 100,000 women, whereas in high-incidence countries the rates are 10 times greater than this and the cumulative lifetime risk can approach 10%.

Risk Factors

1. The Role of HPV

HPVs are small, double-stranded DNA viruses. As infectious agents, they are highly specific to their respective hosts. More than 120 different HPV types, derived from DNA sequence homology, have been catalogued so far.⁴ Clinical, sub-clinical and latent HPV infections are the most common sexually transmitted viral diseases today,⁵ with a peak in prevalence among young women soon after the onset of sexual activity.^{6,7} Latent genital HPV infection can be detected in 5% to 40% of sexually active women of reproductive age.⁸ In

most cases, genital HPV infection is transient or intermittent.⁹ In epidemiologic studies conducted during the past 10 years, the relative risks (RRs) for the association between HPV infection (detected by viral DNA testing) and risk of cervical cancer are high – in some studies greater than 100.¹⁰ No other risk factor for cervical neoplasia is of comparable magnitude. In fact, few associations in cancer research are as strong as that between HPV and cervical neoplasia, notable exceptions being the link between heavy smoking and lung cancer, and chronic hepatitis B infection and liver carcinoma.¹¹

Today, it is well established that infection with the HPV types associated with high oncogenic risk (types 16,18,31,33,35,39,45,51,52,56,58,59 and 68) is the central causal factor in cervical cancer.¹² It may even be a necessary cause of this disease and its precursors. HPV infection should be considered as a risk exposure, however, since most women who engage in sexual activity will probably acquire HPV infection over a lifetime. The vast majority of these infections will be transient, only a small proportion becoming persistent. A substantial increase in the risk of CIN exists for women who develop persistent, long-term infections with oncogenic HPV types as defined above.¹³

2. Behavioural and Lifestyle Characteristics

2.1 Sexual Behaviour

See "The Role of HPV." Other prominent risk factors are the role of two measures of sexual activity, namely, number of sexual partners and age at first intercourse, and the sexual behaviour of the woman's male partner(s).¹³

2.2 Smoking

Tobacco smoking has consistently emerged as a risk factor for cervical cancer.¹⁴ A direct carcinogenic action on the cervix is conceivable, since nicotine metabolites can be found in the cervical mucus of smokers. Another plausible mechanism is suppression of the local immune response to HPV infection.¹⁵ However, a clear assessment of the association is confounded by other variables. Since smoking is associated with sexual behaviour it cannot be easily determined whether its association with cervical neoplasia is genuine or spurious. Studies that have controlled for the effects of age at first intercourse and

number of sexual partners have generally found an independent role for tobacco smoking in cervical neoplasia, reporting RRs among current versus never smokers in the range of 1.5–4.5, and evidence of a trend with number of cigarettes smoked and duration of smoking.¹⁶ On the other hand, a few studies have failed to find an association with cigarette smoking.^{17,18}

2.3 Parity

The number of live births per woman is a consistent risk factor for cervical cancer. There is a linear trend in the parity- risk association, as seen in large studies in North America and in Latin America.¹⁹ It is possible that multiple pregnancies have a cumulative traumatic or immunosuppressive effect on the cervix, thereby facilitating the acquisition of HPV infection.²⁰ Another non-mutually exclusive mechanism is the pregnancy-induced hormonal effect on the cervix, which could affect HPV genome elements that are responsive to progesterone.²¹

2.4 Oral Contraceptive Use

An increased risk of cervical cancer among oral contraceptive (OC) users is found mainly among long-term users. The plausibility of the association rests on the potential for hormonal effects on HPV-containing cervical cells, as it has been shown that steroid stimulation may trigger viral oncogene-related events that could culminate in integration of the virus into the host's genome.²² Confounding factors are that women who use con-traception tend to be more sexually active than those who do not, and women using OC are less likely to use barrier methods of contraception, which have been shown in some studies to exert a protective effect against CIN and cervical cancer.²² It is also possible that some associations may be due to detection bias, since OC users undergo more frequent gynecological examinations than non-users, thereby enhancing detection of early disease.²³

2.5 Dietary Factors

High intake of foods (fruits and vegetables) containing carotenoids and vitamin C and, to a lesser extent, intake of vitamins A and E seem to reduce the cervical cancer risk.²⁴ The results of dietary surveys have been corroborated by assays of plasma micronutrient levels. There is biological plausibility for a protective effect of diet in cervical

neoplasia. Carotenoids, tocopherols and ascorbic acid are potent antioxidants that can quench intracellular reactive radicals, thus potentially preventing DNA damage. Beta-carotene, in particular, serves as a metabolic precursor to retinoic acid, which acts by modulating epithelial cell growth and differentiation. Dietary factors may also have a role in cervical immunity.²⁵ Randomized controlled trials of dietary supplementation to prevent CIN have been conducted or initiated in different populations.

3 Human Immunodeficiency Virus Infection

Patients infected with HIV are prone to develop a variety of infections attributed to their debilitated immune system. HIV infection impairs cell-mediated immunity, thus increasing the risk of HPV-associated diseases, such as genital warts and malignancies. Latent HPV infection and SIL are much more common among HIV-infected women than HIV-negative women from the same populations.^{26,27} HPV and HIV infection seem to interact synergistically to increase the risk of CIN, with some further mediation by the degree of immunosuppression.²⁸ With the successful adoption of antiretroviral therapy in the last few years women are surviving longer with their HIV disease. Little is known, however, about the potential impact of HIV therapy on the natural history of cervical neoplasia among HIV-infected women.

4 Primary Prevention

4.1 Behaviour Modification

Primary prevention of cervical cancer can be achieved through prevention and control of genital HPV infection. Health promotion strategies geared to a change in sexual behaviour and targeting all sexually transmitted infections of public health significance can be effective in preventing HPV infection.^{29,30} Although there is consensus that symptomatic HPV infection (genital warts) should be managed by treatment, counselling, and partner notification, active case-finding of asymptomatic HPV infection is currently not recommended as a control measure.

4.2 Immunization Against HPV

Two main types of HPV vaccine are currently being used: prophylactic vaccines to prevent HPV infection and associated diseases, and therapeutic

vaccines to induce regression of precancerous lesions or remission of advanced cervical cancer. Such vaccines are already under evaluation in phase I and II trials in different populations.³¹ Immunization against HPV may have greatest value in developing countries, where 80% of the global burden of cervical cancer occurs each year and where Pap screening programs are less likely to be effective. At present, it is difficult to speculate about the direction of research in this area. Although the preliminary results from phase II trials of prophylactic vaccines have been successful, it will take many years before vaccines can be assessed as a cervical cancer prevention strategy.³²

5 Secondary Prevention

Cervical cancer screening is currently one of the most active areas of research in cancer prevention (see "Other Cytology Methods" below). Several new technologies are under evaluation, and professional and government groups are considering their contribution in a reassessment of practice guidelines currently being undertaken.

5.1 Pap Cytology Screening

Efficacy of Pap Cytology Screening: There have been no controlled trials of Pap screening efficacy, either randomized or not. The evidence for the efficacy of Pap smear screening in cervical cancer comes mainly from three sources: (i) epidemiologic studies reporting a risk of invasive cervical cancer 2–10 times greater among women who have not been screened and an increased risk with time since last normal smear or with lower frequency of screening; (ii) cervical cancer incidence and mortality rates, which decreased sharply following the introduction of cytology screening in Scandinavian countries, Canada and the United States, and did so in proportion to the intensity of the screening efforts; and (iii) multiple national and international consensus panels worldwide.³³

In spite of its success, cytology has important limitations, false negative results being the most significant. One recent meta-analysis indicated that the average sensitivity of a single Pap test to detect HSIL or cervical cancer was 51%, whereas its specificity was 98%.³⁴ The solution to minimizing false-negative errors in cytology is to improve the quality of smear taking, slide processing

and overall diagnostic performance of cervical cytology. False-negative diagnoses have important medical, financial and legal implications.

5.2 Other Cytology Methods

There are several automated systems being tested and marketed. In one of these, liquid-based cytology, the sample recovered from the cervix is suspended in a cell-preserving solution rather than placed on a glass slide. Excess blood and inflammatory cells are lysed, and approximately 50,000 diagnostic cells are randomly transferred by the equipment as a thin layer onto a glass slide by a robotic cell processor. The slides are stained and then read by cytotechnologists. Results from clinical studies have shown that automated thin-layer slides can improve detection of atypical cells, precursor lesions and cancer by producing uniformly cleaner slides free of blood, debris and cell clumps that interfere with microscopic reading.³⁵ A recent meta-analysis concluded that liquid based cytology had superior sensitivity and equivalent specificity to conventional cytology, and economic models have indicated that it could lead to lower cost per life-years saved in the United States.³⁶ Computer-assisted scanners map the smear in order to detect abnormal cells, thereby separating any slides that contain suspect images for subsequent reading by a cytotechnologist. A key advantage is the potential to alleviate the shortage of qualified workers in cytopathology. Comparative trials, mostly funded by the private sector, are taking place in many laboratories in North America and Europe to answer questions related to screening efficacy and the cost-effectiveness of automated devices. Screening by HPV Testing Since the mid-1990s there has been substantial interest in the use of standardized HPV DNA testing as a cervical cancer screening tool under the premise that it will provide acceptable diagnostic performance while being more reproducible and more easily adapted for clinical practice than conventional Pap cytology. Several studies have assessed the test's diagnostic performance (for high-risk types) in a variety of populations, using cross-sectional or short-term follow-up rather than more extended review of incidence or mortality rates.³⁷ Lesion definition varied across studies and included either CIN of all grades or CIN 2 or 3 or worse lesions. HPV DNA

testing has been shown to have, on average, a 25% greater sensitivity than Pap cytology but somewhat lower specificity (on average, 10% lower) for detecting CIN 2/3 or cancer. Screening of women aged 30 or older tended to improve the specificity considerably, because viral infections in this age group are less likely to be of a transient nature than those in younger women. An important finding of most studies was that the combination of cytology and HPV testing attained very high negative predictive values (approaching 100%), which, at least in theory, could safely permit longer screening intervals, thus lowering costs. Definitive evidence of efficacy is still needed from long-term follow-up studies with invasive cancer as an outcome and from randomized controlled trials. One other screening application of HPV testing is in the secondary triage of equivocal Pap smears. Results from two large-scale studies have indicated that HPV testing has greater sensitivity than a repeat Pap test for detecting hidden HSIL or cancer among women referred because of an equivocal Pap smear. At the same time it results in reduced costs in terms of colposcopy referrals.³⁸

Conclusion

In the current case series, the majority of cases were in FIGO stage of II or above and were treated with radiation therapy as a predominant method of treatment. So the intervention in terms of prevention by anti-HPV vaccination and screening by systematic manner for early detection are mandatory for the detection of precancerous lesions and to find early disease.

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