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REVIEW ARTICLE

Managing cervical cancer in Nepal: Need of consensual guideline.

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Abstract

The purpose of this review is to bridge the pattern of intervention in optimal and sub-optimal facility level. Several guidelines for the screening and treatment of cervical cancer are reviewed. Routine screening is found grossly lacking and non existent outside major health institution. Only nominal data and intervention efforts found published. There are three prongs of intervention level namely prevention/screening, treatment and palliation together. Pap smear test is the standard screening tool wherever the cyto-diagnostic facility exists. Visual Inspection with Acetic acid and Lugol's Iodine will be the feasible alternative at low resource setting. Primary surgical treatment for early cervical cancer is the best option. Likewise chemo-radiation with or without surgery will be the alternative option. Need of at least an operational guideline in each institution is realized at this moment as a recommendation.

Key words: Cervical intraepithelial neoplasia (CIN); colposcopy; Pap smear (Papanicolou stain); radical hysterectomy; visual inspection with acetic acid (VIA).

Introduction

Despite having several service providing institutions in Nepal, there is hardly any inter-communication on managing cervical cancer. That's why uniformity is out of question. Published data on cervical cancer are hard to get at present.[1,2,3] Regular screening service is available in major hospitals only. Adequate primary treatment facility after screening is also lacking in general. One or two published data on radical treatment are also lacking survival status because of an initial experience with it.[4] Multimodality treatment facility is grossly lacking except an exception.[3,4] Post treatment pattern is also not uniform. Review of adequacy of treatment is virtually absent. Thus, at least an operational guideline has to be prepared for minimal intervention for cervical screening and treatment. Definite national guideline is yet to be prepared.

Level of intervention

There are three phases of cervical cancer intervention from implementation point of view.

1. Phase of precancerous stage: - Primary prevention by health education, behavioral changes and vaccination as well as screening for early detection.
2. Phase of early cancer stage:- Treatment to prolong survival.
3. Phase of advanced cancer stage:- Palliative treatment and care. Cervical cancer prevention is not about doing the best test but about doing the best test we can do even at low resource setting because testing itself has no intrinsic preventive value unless linked to pre-cancer treatment. So screening and its primary treatment should be operational at the same time. Preventive, curative and palliative care[5,6] should go together for optimum management of cervical cancer.

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Magnitude of problem

Carcinoma of uterine cervix is considered one of the preventable cancers of female populations. It is the third most common cancer in women worldwide with highest incidence rates in Central and South America, eastern Africa, South and South-East Asia, and Melanesia.[7] According to WHO estimation in 2005, out of half a million of new cases of cervical cancer, over 90% were in developing countries. Amongst a quarter of million dying from the disease, nearly 95% were also in developing countries, making cervical cancer one of the gravest threats to women's lives, most of whom have not been diagnosed, or have no access to treatment that could cure them or prolong their life.[7] Common mortality factors[8] like malnutrition, communicable diseases, diarrheal diseases and respiratory problems are distracters to focus on cancer at present. Lack of cancer health awareness and health protection scheme are other obstacles. The main reasons for the higher incidence and mortality in developing countries are:[7] lack of awareness of cervical cancer among the population, health care providers and policy-makers; absence or poor quality of screening programs for precursor lesions and early-stage cancer. In women who have never been screened, cancer tends to be diagnosed in its later stages, when it is less easily treatable; limited access to health care services and; lack of functional referral systems. There is strong association of early age of sexuality, smoking and poor socioeconomic status with the occurrence of cervical cancer. But the causal association has been established with HPV (human papilloma virus) to justify vaccination against HPV to prevent cervical cancer.[9,10] The difference between developed and developing countries reflects apparent inequalities in health status, and represents a challenge for health services. But we are still unaware of its gravity in the underdeveloped world as because no tests have been done and no specific reporting system has been developed. So we have to work on projected data there.

Health education

Key cervical cancer messages set by WHO[7].

1. Cervical cancer is the leading cause of cancer deaths in women in their 40s, 50s and 60s in developing countries.
2. Cervical cancer occurs after many years of sexually transmitted infection with human papillomavirus; condom use offers partial protection from HPV; most HPV infections do not persist and do not cause cancer.
3. Women need to seek medical care promptly if they have abnormal discharge, vaginal bleeding, bleeding after sexual intercourse or any bleeding after menopause; these may be signs of cervical cancer.
4. Screening is relatively simple, quick and painless; can detect pre-cancer; and highly recommended for women.
5. Precancerous lesions can be treated simply, and a hospital stay is not usually required; if cancer is found and treated early, it can be cured.

Screening

Cervical screening guidelines within US and other part of the world also vary from one authority to another, so National Comprehensive Cancer Network (NCCN) guideline has come to bridge the discrepancy.[11,12,13,14,15,16] According to NCCN guideline[11] cervical cancer screening should begin approximately 3 years after the sexual intercourse and not later than 21 years of age. Women at 70 years and above, with an intact cervix, who have had three or more documented, consecutive, technically satisfactory negative cervical cytology test, within the 10 years period prior to 70 years of age may elect to cease cervical screening. After initiation of screening, cervical cancer screening should be performed annually with conventional cytology smear test or every 2 years using liquid based cytology test; at 30 years or above, woman who have had 3 consecutive, technically satisfactory negative cytology report may be screened every 2-3 years; or every 3 years if HPV DNA testing is done together with Pap smear.

According to WHO we should start screening women aged 30 years or more, and include younger women only when the highest-risk group has been covered but not less than 25 years of age. If a woman can be screened only once in her lifetime, the best age is between 35 and 45 years. For women over 50 years, a five-year screening interval is appropriate. In the age group 25-49 years, a three-year interval can be considered if resources are available. Screening is not necessary for women over 65 years, provided the last two previous smears were negative.[7]

Cervical cancer is rare in women under 30 years of age and most common in women over 40 years, with the greatest number of deaths usually occurring in women in their 50s and 60s.[7] Most pregnant women are younger than the target age group of WHO recommendation for cervical cancer screening in developing country like in Nepal. So fertility sparing intervention may be on least priority. In order not to miss a cancer it is better to make cervical cytology examination as an opportunist screening as well as a routine procedure of gynecology/obstetrics examination if resource permits. Even for the patients with past hysterectomy, but not fully assured of benign condition by past

document or by the present examination should undergo screening.

On analyzing 2288 Pap tests done in a hospital of Nepal had found precancerous and malignant lesion in 65 cases. These cases were analyzed by their age groups which revealed similar proportion of abnormalities in between 26-35 years and 36-45 years of age group.[2] Cervical Pap smear is the frequently done test by many gynecologists at present but at the cytodiagnostic facility level only and the impact studies as well as the data organization are lacking. But the peripheral hospitals and practitioners are scarcely involved. There is a need of cancer health messages as well as the introduction of simple and cost effective tests like VIA, VILI and cervical Pap smear cytology.[17]

Screening tools

1. Cytological:- VIA, VILI, Pap smear, colposcopy, HPV DNA testing/typing,
2. Histological:- Cervical biopsy, endocervical curettage (ECC), cone biopsy, LEEP

Aforementioned one or more cytological tools can be used whenever indicated and where-ever available.[18-21] If entire squamocollumnar junction (SCJ) is visible colposcopic guided biopsy with 3-5% acetic acid application will be sufficient. If not then either we have to do cervical biopsy plus ECC or cone biopsy or LEEP (Loop Electrocautery Excision Procedure) or large loop excision of transformation zone (LLETZ). Abnormalities are identified by inspection of the cervix without magnification, after application of dilute acetic acid (vinegar) (in VIA) or Lugol's iodine (in VILI).[18,22] When vinegar is applied to abnormal cervical tissue, it temporarily turns white (acetowhite) allowing the provider to make an immediate assessment of a positive (abnormal) or negative VIA and VILI (normal) result. If iodine is applied to the cervix, precancerous and cancerous lesions appear well-defined, thick, and mustard or saffron-yellow in color, while squamous epithelium stains brown or black, and columnar epithelium retains its normal pink color.

VIA has been shown to have an average sensitivity for detection of precancer and cancer of almost 77%, and a range of 56% to 94%.The specificity ranges from 74% to 94% with an average of 86%. One study has shown that VILI can detect 92% of women with precancer or cancer, a sensitivity considerably higher than that of either VIA or cytology. Its ability to identify women without disease is similar to that of VIA (85%), and lower than that of Pap smears.[7]

A controlled study from India reveals that out of 31343 cases screened by VIA 10% were positive who underwent colposcopy. Biopsy was performed in 82% and CIN and cancer was detected in 6.2% i.e. 5% of positive report on VIA had disease.[23]One hospital based study carried out in a hospital in Nepal revealed 4.8% of abnormal cytology with 0.25% of invasive cancer out of 800 total patients screened with Pap smear.[1] Both studies had a similar rate of detecting cancer. In a study single visit VIA screening and treatment at age 35 years has shown 26% reduction in cervical cancer incidence with cost saving verses 32% from HPV testing without cost saving, yielding cost effective method.[24]A Phillippino study[25] with 13105 women between 25-65 years of age screened with VIA and Pap smear and confirmed by colposcopy was concluded with recommendation based on their sensitivity and specificity as the acetic acid aided visual method be used as the initial screen for cervical epithelial abnormalities at health centers where Pap smear is not available, all women showing abnormalities be referred for colposcopy, and biopsy, if necessary.

In screening for cervical cancer, VIA offers the following advantages over alternatives:[26] simple, easy-to-learn approach, low startup and ongoing costs, less reliance on infrastructure or medical specialists to perform procedure, no need of cyto-technician or pathologist to report the test, immediacy of results, potential for integration into primary health care services. These need to be weighed against the disadvantages: moderate specificity (resulting in higher referral and potential over-treatment), dependence on the person doing the evaluation (need for standard training methods and quality assurance), lower accuracy in postmenopausal women. Thus VIA seems to be a feasible alternative approach to cytology screening in low facility and low income level like countryside in Nepal.[6,22]

Any one of the conventional Pap smear or liquid based cytology can be used as a laboratory cytology method. Latter one would be the better due to its less false negative report and can be done less frequently like every two years verses each year. Cervical smear can be done even less frequently if we have HPV DNA testing facility though it can not substitute the cervical cytology test.

Indications of colposcopy are summarized.[27] Suspicious-looking cervix; Acetopositivity on visual inspection with acetic acid (VIA); Acetopositivity on visual inspection with acetic acid using magnification (VIAM); Positive on visual inspection with Lugol's iodine (VILI); CIN 1,CIN 2 or CIN 3 on cytology; persistent low grade cytology; Persistently unsatisfactory quality on cytology; Invasive carcinoma on cytology; Infection with oncogenic human papillomaviruses (HPV).

Cytology interpretation and Reporting

Reporting and management criteria should be standardized in order to compare outcome and improving modality of treatment. So Bethesda system[28] is the one which physicians and pathologists can follow and become conversant with the terminology (Table 1).[7] Cytological report is expected to produce as below:

1. Negative for intraepithelial lesion or malignancy.
2. Squamous cell abnormality: - ASC (ASCUS, ASC-H), LSIL, HSIL, Carcinoma.
3. Glandular cell abnormality: - AGC (AGC-NOS, AGC-favor neoplasia, AIS), Adenocarcinoma.

Table 1. Different terminologies used for cervical cytological and histological reporting[7]

Cytological classification (used for screening)		Histological classification (used for diagnosis)	
Pap	*Bethesda system*	*CIN*	*WHO descriptive classifications*
Class I	Normal	Normal	Normal
Class II	ASC-US, ASC-H	Atypia	Atypia
	LSIL	CIN 1 (+ flat Condyloma)	Koilocytosis
		CIN 2	Moderate dysplasia
Class III	HSIL	CIN 3	Severe dysplasia
Class VI	HSIL	CIN 3	Carcinoma in situ
ClassV	Invasive carcinoma	Invasive carcinomaa	Invasive carcinoma

NB. CIN cervical intraepithelial neoplasia; LSIL: low-grade squamous intraepithelial lesion; HSIL: high-grade squamous intraepithelial lesion; ASC-US: atypical squamous cells of undetermined significance; ASC-H:atypical squamous cells, cannot exclude a high-grade squamous epithelial lesion. AGC: atypical glandular cells; NOS: not otherwise specified; AIS: adenocarcinoma in situ.

Follow up protocol for abnormal screening report [29]

1. Counseling on value of follow up, further management procedure and availability of test and treatment options.
2. It is better to follow with colposcopy for all abnormal cytology except ASCUS in which we can decide after repeat cytology in 6 months.
3. If no colposcopy or unsatisfactory colposcopy visualization, proceed for cervical biopsy plus ECC for LSIL and LEEP for HSIL.
4. If colposcopy reveals negative or CIN I repeat cytology.
5. For CIN II, CIN III and even for CIN I in HSIL go for LEEP, ablation or hysterectomy as appropriate. Then do cytology after 6 months and decide.
6. For positive margin re-excision can be considered.
7. For AGC directly go for cervical biopsy, ECC and endometrial biopsy (preferably D&C).
8. Only CIN cervical histology and AGC-NOS with negative histology can go for repeat cytology.
9. Rests of the AGC are the candidate of LEEP (preferably CKC in order to minimize incidence of positive margin) or hysterectomy if appropriate especially for AIS.
10. Endometrial pathology if detected needs respective treatment.

Any abnormal cytology during pregnancy can be evaluated with caution and invasive tools should be exercised in postpartum unless invasion suspected.

Pre-treatment evaluation

Once screening tests reveal cervical cancer then we run certain defined tests to evaluate extent and operability of tumor. Evaluation procedure based on FIGO staging[30] does not include high tech imaging tools because it is only for comparison purpose. That's why colposcopy, biopsy and cone excision of cervix are enough tools for up to stage IB1. Cystoscopy and proctosigmoidoscopy will be enough for tumor IB2 and larger to see bladder and bowel involvement if any.

There are other usually available but less sensitive tools to utilize like USG (to see lymph nodes and viscera), CXR (to see lung metastasis if any), IVP (to see renal anatomy and function), barium enema (to see colorectal invasion).

More sensitive tests if available are the best for therapeutic value like CT, MRI and PET or PET-CT. Sensitivity in detecting pelvic nodal metastasis in

patient with untreated cervical cancer is 80% for 18-Fluorodeoxyglucose-PET, 70% for MRI and 48% for CT. PET is superior in detecting lymph node metastasis, unknown primary cancer and viable tumor tissue. Obviously clinical history and physical examination, CBC and platelets, LFT, RFT are the mandatory tests prior to surgical intervention.[7,29,31,32] Lymph node involvement is less than 1% in stage IA1, 3-6% in IA2, 16% in IB (6% in IB <2cm tumor size and 36% in IB2).[31]

Urodynamic study prior to surgery and at 3 months or 9 months after surgery will be needed to see its effectiveness if pelvic nerve sparing (hypogastric nerve $T_{11,12}$ $L_{1,2}$-sympathetic, pelvic splanchnic nerve $S_{2,3,4}$-parasympathetic, inferior hypogastric plexus and its bladder branches) radical hysterectomy is planned.[33] It takes longer time to regain near normal bladder function, even if achieved, if nerve sparing radical surgery is not performed. But therapeutic purpose of cancer surgery is the radicality in terms of survival status.[32]

Treatment

There are certain principles for the treatment of cervical cancer to follow. [5,7]

1. Precancer should be treated on an outpatient basis whenever possible. Both cryotherapy and the loop electrosurgical excision procedure (LEEP) may be suitable for this purpose, depending on eligibility criteria and available resources.
2. Histological confirmation of cervical cancer and staging must be completed before embarking on further investigations and treatment.
3. Surgery and radiotherapy are the only recommended primary treatment modalities for cervical cancer. Concurrent chemo-radiation (CCRT) has shown the better prognosis.
4. Brachytherapy is a mandatory component of curative radiotherapy of cervical cancer. [34,35]
5. Surgery for treatment of cervical cancer should be performed only by surgeons with focused training in gynecological cancer surgery.

Based on the NCCN guidelines [29,36] primary surgical treatment (Table-2)[29], primary non-surgical treatment (Table-3) [29] and adjuvant treatment (Table-4) [29] are summarized below.

Scottish Intercollegiate Guidelines Network (SIGN) guideline recommends simple hysterectomy for stage IA1(no PLND unless LVSI) and IA2(with or without PLND), radical hysterectomy for stage IB and IIA for tumor size 4 cm or less with PLND/PALND and no

Table 2. Primary surgical treatment[27]

Stage	Hysterectomy	PLND	PALND	M-biopsy
IA1	+	±	-	-
IA2	+ (MRH)	+	±	-
IB1/IIA≤4cm	+ (RH)	+	+	-
IB2/IIA>4cm	+ (RH)	+	+	±
IIB/III/IV	-	+	+	+

NB:RH=Radical hysterectomy, MRH=Modified Radical hysterectomy, PLND=Pelvic lymph node dissection, PALND=Para-aortic lymph node dissection, M-biopsy=Metastatic focus biopsy; '+' indicates respective condition applied; '-' indicates respective condition not applied

Table 3. Primary non-surgical treatment [27,33]

Stage	Pelvic RT	Brachytherapy	Cisplatin based chemo~	PALN RT	Systemic
IA1	-	-	-	-	-
IA2	+	+	-	-	-
IB1/IIA≤4cm	+	+	±	-	-
IB2/IIA>4cm	+	+	+	±	-
IIB/III/IVA	+	+	+	+	±
IVB					+

'+' indicates respective condition applied; '-' indicates respective condition not applied

Table 4. Adjuvant treatment by post surgery status [27]

Post surgery status				→	Adjuvant Therapy				
Surgical margin	PLN	PALN	M-biopsy		Pelvic RT	Cisplatin based chemo~	Brachy-therapy	PALN RT	Systemic therapy
-	-	-	-	→	-	-	-	-	-
+	+	-	-	→	+	+	±	-	-
+	+			→	+	+	±	+	-
+	+	+		→	-				+

'+' indicates respective condition applied; '-' indicates respective condition not applied

surgery for tumor more than 4cm.Type II and type III radical hysterectomy both are equally effective for surgical treatment of IB/IIA cervical cancer.[31]

WHO also recommends a similar guideline like SIGN guideline: IA1-simple hysterectomy, IA2-simple hysterectomy with lymph node dissection (preferably modified radical hysterectomy like in NCCN guideline), IB/IIA with tumor size ≤4cm -radical hysterectomy and higher stages-radiotherapy / chemotherapy.[7,37]

Frozen section biopsy is helpful for primary therapeutic as well as staging surgery. In absence of it either we should do diagnostic as well as cyto-reductive surgery based on clinical judgment or take a tumor impression as a viable alternative to minimize over surgical treatment.

Radiotherapy is applicable to almost all stages of cancer. Surgery for stage I and IIA is reserved for young patients in whom ovarian function is desired and vaginal preservation is expected. Availability of adjuvant therapy like chemotherapy, radiotherapy or concurrent chemo-radiation in the vicinity or within the center is the key service for the completeness of cancer management. CCRT like cisplatin[37,38] alone or with paclitaxol [39,40,41] or topotecan[39,42,43] along with radiotherapy has been considered the effective mode of adjuvant treatment.[32] Chemo-radiotherapy is the standard of care for locally advanced and early stage cancers with poor prognostic factors[44] and for less recurrence rate.[45] Cisplatin based chemo-radiation seems cost effective and optimum.[46,47,48,49] Contraindication to radiotherapy includes pregnancy, pelvic inflammatory disease, inflammatory bowel disease and previous irradiation.

At times cervical cancer is diagnosed in retrospect while hysterectomy is performed for non cancer indication or if hysterectomy was performed without adequate evaluation especially in resource constraint set up. Obviously it will be a simple hysterectomy. Then we have to perform all baseline tests and evaluate the parameters like LVSI, surgical margin, nodal status on imaging and type of cancer for further mode of treatment. We can observe for stage IA1 without LVSI. In case of higher stage cancer chemo radiation is the choice if surgical margin is positive for cancer with or without positive report on imaging. If surgical margin and imaging both are negative then either complete the surgery and follow or go for pelvic RT and Brachytherapy (with or without cisplatin).[50] For aggressive cancer like neuroendocrine type there is no optimal treatment modality established yet, so plan for aggressive non-surgical therapy.[51,52]

Follow up after treatment of cancer is 4x1st year, 3x2nd year, 2x3rd year then annually.[29] Five years survival rate with optimum treatment of cervical cancer decreases as the stage of cancer increases at the time of diagnosis and intervention: IA1-98%;IA2-95%;IB1-85%;IB2/IIA-75%; IIB-65%;III-30%;IVA-10%;IVB-5%.[7]

Conclusion

At least an operational guideline has to be prepared for screening and treatment of cervical cancer in Nepal. Whatever level of service is being provided in different institution within the country has to be recorded and reported in scientific way. An organized work and data only validate our future principle of service delivery pattern. Pap smear test is the standard screening tool wherever the cyto-diagnostic facility exists. VIA/VILI will be the cost effective and good alternative at low resource setting. Primary surgical treatment for early cervical cancer is the best option. Likewise chemo-radiation with or without surgery will be the alternative option. It will be the best way to follow at least NCCN, SIGN or WHO guideline wherever feasible. Post treatment review, detail follow up record and survival status has to be maintained. It is mandatory to run preventive, curative and palliative care together. Referral

system for further treatment should be functional for complete care. These all efforts will make us capable of making our own national guideline of cancer care in the future.

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