

Management of Pre-invasive Cervical Cancer in Low-Resource Setting

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Cervical cancer is one of the health burdens in many developing countries. The advanced knowledge in the past decade reassured the important role of human papillomavirus as the necessary cause of cervical cancer and makes a clear understanding of its natural history.

Cervical cancer has a long period of pre-invasive stage, and only a small proportion of cervical intraepithelial neoplasia (CIN) that can progress to be an invasive lesion. Appropriate management of CIN can prevent invasive cervical cancer. The contemporary treatment of CIN is more conservative and requires effective follow-up process. However inappropriate management of CIN is still be found at the international and national survey of less developed countries.

Although no apparent superior surgical technique for treating CIN, loop electrosurgical excision procedure (LEEP) and cryotherapy are fascinated for the low-resource setting. Other alternative approach, which eliminates cytology and colposcopy may be considered in the ultrashort- resource setting with a high prevalence of cervical cancer.

In this article, the contemporary knowledge about the natural history of cervical cancer, especially the implication of human papillomavirus (HPV) for pre-invasive cervical cancer, is summarized. The current approaches for treatment of CIN are reviewed from the perspective of low-resource settings. The various strategies for management approaches are demonstrated, and the cost-effectiveness is discussed. The pattern of pre-invasive cervical cancer management in developing countries, including in the south of Thailand is exhibited, and the single-visit service for cervical cancer prevention in the northeast is challenged.

Keywords: Cervical, Pre-invasive, Low-resource setting

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Introduction

Cervical cancer is still a disease burden on women in developing countries. In Thailand, the data from the cancer registries estimates 6 268 new cases in a year, with the age-standardized incidence rate 19.5 per 100 000⁽¹⁾. The stage at diagnosis is advanced, compared with developed countries. It can be concluded that, cervical cancer is the disease of the poor societies, in which widespread screening program is not available.

Cervical cancer is the disease that qualified the criteria for deciding to screen. Its natural history is clearly understood, especially the role of HPV as the causal cause, and a long pre-cancerous stage. There are many modalities of treatment for CIN, and

the consensus on whom to treat is well established. However the lack of effective screening programs to detect the pre-invasive stage and treating them efficiently are the main reasons for the high incidence of invasive cervical cancer in developing countries. Based on the natural history of this cancer that pre-invasive stage is 2-5 times more than invasive stage, thus, as many as 7,000,000 women worldwide harbor high-grade dysplasia that need treatment⁽²⁾. Certainly, most of them are in the developing countries.

The Evolution of Cervical Intraepithelial Neoplasia

The concept of pre-cancerous lesion of the cervix emerged in the late nineteenth century, when area of noninvasive lesion, which was recognized later as carcinoma in situ (CIS), was found adjacent to invasive lesion. The term carcinoma in situ represents

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the lesions with cancer-like cells involved the whole thickness of the epithelium with intact basement membrane. Reagan⁽³⁾ was the first one who introduced the term “dysplasia” as the intermediate lesion between normal epithelium and CIS. The severity of the dysplasia depends on the extents of atypical cells involvement of the epithelial thickness. Based on the observational studies of the dysplastic and CIS lesions that led to the conclusion of the continuum process of pre-cancerous lesions and invasive cervical cancer. In 1968, the term cervical intraepithelial neoplasia was introduced by Richart⁽⁴⁾. It ranged from CIN I to CIN III, in which the latter included both severe dysplasia and CIS. It should be emphasized that the natural history of CIN in this phase came from the knowledge at the histological level.

The evolution of HPV infection and cervical cancer has been started in 1930 in which the cotton-tail rabbit papillomavirus was identified as the first tumor-inducing virus. The intensive studies in 20 years later gave the important principles about the roles of serological and cellular mediated immunity in immunoprophylaxis and immunotherapy of viral disease. The cytomorphological characteristics of koilocytes were described by Ayre in 1950⁽⁵⁾ and was linked to HPV infection by Meisels and Fortins⁽⁶⁾ later. The koilocytotic atypia also related to unusual pattern of squamous epithelium of the cervix. The first study of HPV DNA was started in 1965 and the advance development of molecular biology made the resurgence of HPV studies again. In 1977 zur Hausen⁽⁷⁾ suggested that HPV might be the sexually transmitted etiological agent in cervical neoplasia. HPV 16, 18 were first cloned during 1980s. In this period, there was more understanding about the regulation of viral gene expression provided biological plausibility for a casual link between HPV infection and cervical carcinogenesis. This molecular biological based knowledge led to revise the histopathological terminology to be low-grade and high grade CIN. The former was the koilocytotic atypia and CIN I. The latter that composes of CIN II and III were true precursors of invasive cervical cancer⁽⁸⁾.

Implications of Human Papillomavirus for Pre-invasive Cervical Cancer

The HPV is a small, non-enveloped, double-stranded virus. It is an epitheliotropic intranuclear virus and is transmitted via sexual contact. The common sites of infection are uterine cervix and anal canal at both squamous and glandular epithelium of these sites.

Molecular epidemiologic evidence clearly indicates that certain types of HPV are the principal cause of invasive cervical cancer⁽⁹⁻¹¹⁾. More than 80 HPV types were identified and about 40 types cause genital tract infection⁽¹²⁾. The high-risk types are 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82⁽¹³⁾. The HPV types 26, 53, and 66 are probably carcinogenic⁽¹³⁾.

Most of the women with HPV infection have a transient infection. CIN lesion is presented in approximately 20% of these women. The development of cytotoxic T-cell response against the high-risk HPV types is essential to clear the virus and then CIN lesion. If the HPV infection is still persist, the changes in the cellular genome occur. The viral oncogene proteins E6 and E7 bind the gene products of the human tumor suppressor genes P53 and Rb. This interaction in proliferating cells leads to irregularity in cell cycle control and shortcomings in DNA repair, resulting in instability and an increased risk of obtaining changes and mutation. Besides of the activation of oncogenes and loss of tumor suppressor genes, there are other possibilities of how HPV causes dysplasia. Those are individual's chromosome alterations, which making them more susceptible to dysplasia, increased telomerase activity, insulin-like growth factor, and sequence variations within particular strains of the HPV genome.

HPV is the most common sexually transmitted disease. Fortunately, most of those infected finally clear the infection. The time of clearance is between 8-24 months. Early age at first intercourse with multiple sexual partners is the important risk factors for HPV infection in young women. Others risk factors are smoking, oral contraceptive pill, multi-parity, immunocompromised status, sexually transmitted diseases, poverty, poor nutrition, alcoholism, and risked male partner. The highest peak of infection occurs at 25 years of age, and then decreases sharply after that. The risk remains low until menopause, although a small peak is observed after 50 years of age.

The effect of HPV infection towards cervical cells has a varying degree of severity. In the early phase, HPV invades the basal epithelial cells without evident of disease. The size and shape of infected cells appear to have minimal changes. When having persistent infection, the cells lose both their structure and arrangement in rows or columns on the cervical surface. This is CIN. If the abnormal cells, which are called dysplastic cells, replace almost of the normal cells on the surface of the cervix, the lesion is classified as CIN III. Untreated CIN III may progress to be

invasive carcinoma, in which dysplastic cells break the basement membrane, and then, grow deeply into the underlying tissue. The amount of HPV DNA can predict cancer risk at the stage when current screening methods are negative. It can distinguish between infections those have a high- or low- risk of cervical cancer⁽¹⁴⁾.

Natural History of Cervical Intraepithelial Neoplasia

The risk factors of CIN and HPV infection are quite similar, because HPV is the initiation of the CIN process. The jeopardized sexual pattern is the important risk factor. Suppression of the immune system due to HIV infection is another significant risk factor, because it makes the lining cells of the lower genital tract more easily infected by the oncogenic types of HPV⁽¹⁵⁾.

Other less common immunosuppressive conditions, such as chronic corticosteroid usage is also the risk factor of CIN. Poor behaviors known to suppress the immune system; such as using the recreational drugs, alcoholic drinking, and cigarettes smoking can increase the risk of CIN.

Concerning about smoking, nicotine and its byproducts concentrates in the cervical mucus, and decreases the immune capability of Langerhan's cells to protect cervical tissue from invading oncogenic factors, such as HPV infection⁽¹⁶⁾. There is a strong epidemiological evidence for a genetic link to the development of cervical cancer and its precursor. Magnusson and colleagues⁽¹⁷⁾ compared the incidence of dysplasia and CIS in relatives of women with disease and in age matched controls. For biological mothers, the relative risk was 1.8 compared to control cases. For adoptive mothers the relative risk was not significantly different from controls. The more significant risk was also found in biological full sisters.

CIN is a premalignant lesion of cervical squamous cell carcinoma. It may regress, persist, or progress. HPV infection is a significant determinant of CIN, and rates of progression correlate directly with CIN grade. A strong relationship exists between persistent HPV 16 and 18 infections and squamous intraepithelial lesion incidence⁽¹⁸⁾. Survey of HPV infection and CIN in Thai women confirms the association between high-risk HPV types and CIN development⁽¹⁹⁾. The data from met-analysis study⁽²⁰⁾ shows that approximately one-half of low-grade squamous intraepithelial lesion (LSIL), and one-third of high-grade squamous intraepithelial lesion (HSIL) will resolve spontaneously. Of those lesions that regress,

most will do so in 6 months. From the long-term cohort study during the time that CIN were managed conservatively yielded the data that can estimate the rates and relative risks of progression/regression of mild and moderate dysplasia⁽²¹⁾. The risk of progression from mild to severe dysplasia or worse is only 1% per year, but the risk of progression from moderate dysplasia was 16% within 2 years and 25% within 5 years. Most of the excess risk of cervical cancer for severe and moderate dysplasia occurred within 2 years since the initial dysplastic smears. After 2 years, the relative risks for progression from severe or moderate dysplasia to carcinoma in situ or worse was 4.2 and 2.5 respectively, in comparison to mild dysplasia. There is a low risk of progression to invasive cancer during a brief period of observation for most cervical dysplasia.

Many attributes are explored to identify determinants of CIN I, and CIN II/III, as well as predictors of CIN I progression. It is concluded that CIN I is a sexually transmitted, productive HPV infection, whereas CIN II/III is a dysplastic lesion resulting from repeated exposure to a HPV infection and possibly an additional agent. High-risk HPV DNA detection and persistence are predictive of CIN I progressing to CIN II/III. Other possibilities are persistence of a high-risk HPV variant, altered cell immunity, and cigarette and oral contraceptive use. Possible biomarkers include aneuploidy, aneusomy of chromosomes 1 and 3, Ras and bcl-2 oncogene over expression, and cytokeratin 13 protein underexpression.

Treatment of Pre-invasive Cervical Cancer

Generally, the management of CIN will be established after the histopathological diagnosis is confirmed. Colposcopy is the necessary procedure for obtaining the tissue for that purpose, and diagnostic conization is occasionally required for particular lesion. Factors that determine the treatment modalities include age and fertility desire, the characteristic and severity of CIN lesion, associated gynecological disease, patient's compliance, physician's expertise, and feasibility of the equipment. More than that, the woman herself should involve in the decision-making process.

Before the colposcopy era, electrodiathermy, cold knife conization or even hysterectomy is the treatment of choice for pre-invasive lesion. After the introduction of colposcopy, clear understanding of the natural history of CIN, and effective out-patient treatment technologies, the management strategy of

CIN in developed countries is observation the low-grade lesion and eradicate only high-grade pre-cancerous lesions. The method of treatment can be categorized into 2 groups, conservative and radical treatment. Most of the CIN lesions are suitable for less invasive approaches. Hysterectomy, which is considered as radical treatment is preserved for specific condition, such as adenocarcinoma in situ of the cervix or high grade CIN associated with benign gynecological disease.

The conservative treatment can be classified as local ablative therapy and excision methods. The common ablative therapy included cryosurgery and laser vaporization. The excision methods are LEEP, and conization. Both traditional cold knife conization (CKC) and laser conization can be used, depend mainly on the physician's expertise, and feasibility of the equipment. Certainly, in developing countries, laser procedure is not appropriate due to high cost, sophisticated technique, and require more expertise. Ablative therapy should provide to patient with satisfied colposcopic examination, no suspicion of neither invasion nor glandular lesion, and no discordance between cytology and histology. In case that invasion or glandular lesion is suspicious and colposcopy is unsatisfy, excision method is preferred. It yields the certain nature and denotes the completeness of lesion removal. Cryotherapy is practical for low-resource setting, because of its simplicity and low cost. It is a painless procedure. Theirs common side effects, which include malodorous discharge and vasomotor symptoms, are not serious. Bleeding is extremely rare and cervical stenosis is less than 1%. Cryotherapy has no adverse effect on fertility and pregnancy. However, this procedure may increase HIV transmission due to HIV shedding in the vaginal discharge⁽²²⁾, thus condom usage should be emphasized for at least 4-6 weeks after treatment⁽²³⁾. To prevent the post-operative infection, which is quite common in developing countries, presumptive treatment with doxycycline and metronidazole should be considered for 7 days⁽²³⁾. The inferiority of cryotherapy is that, it appears to be an effective treatment of low-grade diseases but not of high-grade disease⁽²⁴⁾. The effectiveness of this procedure is about 80-90%. Besides the strict criteria for ablative treatment, there are more eligibility criteria to be concerned before performing cryotherapy. The CIN lesion should be entirely located in the ectocervix, and its size should be less than 2.5 cm in diameter. To ensure higher success rate, cryotherapy should only used with a double freeze technique.

LEEP is a common out-patient excision

method. This procedure reduces the chance of missed invasive cancer, require less training compared to laser surgery, and effective for high-grade lesion. Its effectiveness is 90-95%⁽²⁵⁾. The important eligibility criteria before performing LEEP is the boundary of the lesion in the endocervical canal should be seen. Although the basic equipment is not sophisticated, its cost is relatively high compared to cryotherapy. Moreover it requires electricity, which may be unavailable in ultra-short resource setting. The potential side effects of LEEP is bleeding and infection. The bleeding can occur during or post operation, which is usually controllable. The infection can be prevented by the same regimen of antibiotic using in cryotherapy. The increase possibility of HIV transmission is also similar to cryotherapy.

Other long-term sequelae is the displacement of squamocolumnar junction in the endocervical canal. It is detected in approximately 2%⁽²³⁾. Cervical stenosis is rarely found. Conization is recognized as both diagnostic and therapeutic method. Knife, laser, or loop excision can perform it. For the diagnostic purpose, conization is preferred in cases with HSIL and unsatisfied colposcopy, positive dysplastic cells in endocervical curettage, suspected of invasive lesion by colposcopy but not confirmed by histopathological diagnosis, major discordance between cytology and histopathological report, cytological diagnosis of adenocarcinoma in situ, and microinvasive carcinoma. Almost all of these situations, LEEP performed by a skilled physician can be replaced. Cold knife conization is usually mandatory for adenocarcinoma in situ and microinvasive carcinoma. The reason is that the margin and specimen interpretability in these circumstances is very important to determine the following management. For the therapeutic purpose, conization is suitable for high-grade lesion. In developing countries, conization is considered as a minor operation, but may cause a major complication, such as hemorrhage, and infection. Routine Sturmdorf sutures usually are performed in traditional cold knife conization for the hemostatic purpose. However, its advantages are not consensus⁽²⁴⁾ in both prevention of primary and secondary hemorrhage. More than that it may has an effect on adequate colposcopy follow-up rate and dysmenorrhea.

Compared to loop excision, the data from the systematic review⁽²⁴⁾ did not showed any difference primary hemorrhage and cervical stenosis outcomes between either methods. Although loop excision might have a higher residual rate, it significantly had better

adequate colposcopy rates at follow-up.

The clinical management of CIN I include immediate treatment or follow up by cytology or colposcopy for 18-24 months. The treatment by cryotherapy or LEEP is initiated, if the lesion is persistent or progressive. Follow-up visit at 9-12 months after treatment is appropriate before returning to routine screening. If the lesion is still found during follow-up period, reevaluation and repeat treatment with the previous method should be performed depending on the severity of the lesion. Due to the low patient's compliance in developing countries, immediate treatment with cryotherapy in CIN I may be appropriate.

The management of CIN II, and CIN III require immediate treatment. Although the evidence from many randomized control trials suggests that there is no overwhelming superior surgical technique for eradicating CIN, LEEP or CKC is preferred more than cryotherapy in high grade-lesion. Adequate excision and certainty of negative of disease in endocervical canal are the keys of successive treatment. CKC should be considered in cases of large severe lesion and undesired fertility. Every woman with high-grade lesion has to receive closed follow-up at least 12 months.

The interval of the follow-up period is tailored to each individual. In non-complicated cases, cytology with or without colposcopy should be done at 6 and 12 months before discharging them to a routine screening program, if available. In a case with a possibility of an inadequate excision involving ectocervical or endocervical margins, there are three options to be considered.

For low compliance women, re-treatment with LEEP as a LEEP cone or even CKC should be done. Hysterectomy may have a role in these women with previous conization and undesired fertility. For more compliance women, intensive follow-up, every 4 months for 2 years, with cytology and colposcopy should be strictly performed. If persistent disease is detected, the patient should be retreated appropriately. If everything is fine during the follow-up period, she may be discharged to a routine screening program. The women with a history of high-grade CIN should have a long-life screening. In a place with out on-going screening program, these women should receive follow-up with reliable cytology once in three or 5 years⁽²³⁾.

Adenocarcinoma in situ is a strong precursor of adenocarcinoma. Due to difficulty in endocervical assessment, CKC is the procedure of choice for definite diagnosis. Hysterectomy should be done in

case with negative margin of cone and fertility is not desired, otherwise repeat cone should be undergone, and treatment is done accordingly.

In pregnant women with high-grade CIN, follow up with cytology and colposcopy should be regular scheduled to ascertain the stable of the disease. Biopsy is usually avoided except there is a slight doubt about the invasive disease. The definite treatment will be done at two to three months postpartum, and is similar to nonpregnant women.

Cost Consideration for CIN Treatment

The World Bank has identified cervical cancer as a very cost-effective intervention compared with other cancer control effort, but moderately cost-effective intervention compared with other health intervention. The Bank estimated that screening women at five-year intervals would cost about US\$ 100 per disability-adjusted life year (DALY) gained, while cervical cancer treatment/palliative care would cost about US\$ 2600 per DALY^(26,27).

According to the Program of the Appropriate Technology (PATH), CIN treatment cost vary according to the cost and accuracy of the selected method, the service delivery strategy, the type of provider, the severity of the treated CIN, and the rate of side effects and complications. It is rather difficult to directly compare the cost for varying treatment modalities, and is very difficult to compare the treatment modalities in different context. Cryotherapy is more privileged than other modalities when cost is concerned. Its initial cost is not high, and recurrent cost is low. The salary costs can be reduced if non-physician can provide the method. The overhead is reduced because electricity is not required. In contrast to LEEP, both initial cost and recurrent cost is higher. CKC and hysterectomy are in-patient procedure and certainly are very costly. In assumption, the total cryotherapy and LEEP costs per CIN case treated is \$33 and \$47 respectively⁽²⁾.

More recent data about the cost-effectiveness of cervical cancer strategies in the low-resource settings were addressed in many studies. The study of Mandelblatt et al.⁽²⁸⁾ used a population-based simulation model to evaluate the incremental societal costs and benefits in Thailand of many screening strategies. It was concluded that all strategies saved life with a varying cost, but visual inspection with acetic acid (VIA) performed at 5 years intervals in women 35-55 years old with immediate treatment if abnormalities are found was the least expensive option. Its cost was

\$517 per year of life saved (LYS). The study of Sellors⁽²⁹⁾ also supported the cost-effectiveness of single life time test and immediate cryotherapy where indicated. Colposcopy and LEEP service should be available on a referral basis. Goldies et al.⁽³⁰⁾ used a mathematical model and a hypothetical cohort of previous unscreened 30-year-old black South African women to evaluate the clinical benefit and cost-effectiveness of screening strategies. It was found that HPV testing followed by treatment of screen-positive women at a second visit, which cost \$39/LYS, was the most effective. The study suggested that incorporate DVI or HPV DNA testing and eradicate colposcopy may be the alternative approach to conventional screening.

The Pattern of Pre-invasive Cervical Cancer Management in Developing Countries

A survey of current CIN treatment practices and preferences in developing countries was conducted by PATH 1995⁽³¹⁾. A majority of responses came from Africa and Asia. Although most of the information regarding CIN treatment was collected in centralized facilities, it seemed to be that; CIN treatment services were available at urban centers. Survey data strongly suggested that conization and hysterectomy was a main treatment of CIN. Cryotherapy and LEEP were the next common methods. Surprisingly, about seven percent of survey respondents, predominantly from Asian countries, were currently using laser therapy to treat CIN. Several respondents rely on cryotherapy, electrocoagulation diathermy, or cauterization to treat CIN I and II, and on LEEP, hysterectomy, or conization to treat CIN III. This reflected the perception of more effectiveness of LEEP in treating severe CIN compared to cryotherapy.

The main barriers to treatment were lack of a comprehensive screening program, cost of equipment, inability to follow-up women, lack of trained personnel, inability to identify women with early treatable disease, and women's resistance to treatment. Concerning about availability of basic supplies and equipment, 62% of respondents indicated that they were equipped with a colposcope, with 38% indicating that they only sometimes or never equipped with one. With regard to supplies specifically for cryotherapy, carbondioxide was the most commonly used as refrigerants, followed by liquid nitrogen, and nitrous oxide in developing countries regions. Of those respondents who perform cryotherapy, over one-third experienced delays in re-supply of refrigerants or

other necessary supplies for cryotherapy.

Regarding to the personnel, it appeared that CIN treatment was permitted only doctor, especially gynecologist to perform, only a few countries that allowed nurses-midwives to do so. Most developing countries did not include CIN treatment as part of public health services, thus, made a significant barrier for asymptomatic women.

Many countries had a limited and less organized screening program, and continue to treat all low-grade dysplasia. The latter raised the cost of care. More than that, the predominant use of conization and hysterectomy had serious effect for financial cost to the system and to women as well. It resulted in unnecessary invasive procedure in many cases.

Multiple steps for management of women suspected of CIN were major obstacle to reach the effective cervical cancer control. Usually there were at least 3 steps for the phase of management, cytology screening, tissue biopsy, and treatment. The repeated periodic follow-up visits were scheduled at least 2 times to ensure cure. The dropout rate was high at each stage for a variety reasons. The multi-step approach was not suitable in resource-limited setting and rarely to yield the cost-effectiveness.

Treatment Strategies for CIN⁽²⁸⁾

The advanced knowledge about the role of HPV towards a natural history of CIN leads to the more conservative method for CIN treatment. The standard treatment strategy in adequate resource settings is focusing to women with high-grade lesions (CIN II/III). Although it requires a great ability to monitor women with low-grade lesions, this approach can reduce cost and decrease the burden of health care system.

The first alternative treatment approaches rely on resource adequacy. In regions with very scarce resources, treatment is preferred only in women with severe lesions (CIN III). It bases on the evidence that CIN II can regress, although at a lower rate than CIN I. It also requires an effective monitoring process, and has to take risk of lesions progress. The anxiety of the women who have to harbor the pre-invasive lesion is the important thing to be concerned.

The second alternative approaches confides to the high incidence rate of cervical cancer and inability to monitor the women with low-grade CIN. Treatment all grade of CIN as out-patient with a simple, low cost, low complication equipment may be justified. LEEP should be the method of choice. However,

this approaches is still cause a major burden on the health care system, and the risks of over treatment is unavioded.

The modification of the See and Treat technique is another approach for low-resource setting. The aim of the original technique is to reduce the clinic visits for screening and treatment. This technique is also decreasing patient anxiety, reducing service delivery cost, and reducing the lost of follow-up rate. It has been shown to be very cost-effective as well as clinically effective⁽³²⁾.

The prerequisite for using this approach is accurate colposcopic finding of unequivocal invasive cancer, and histological sample for further evaluation. LEEP is usually the treatment of choice for the See and Treat method.

The aim of modified the See and Treat technique is that only one visit is required. The acetic-acid soaked cervix is examined with naked eye or magnification device to find the abnormal area. If indicated, it is treated immediately with a simple method, such as cryotherapy. This modified technique is certainly less accurate than the original one. It takes risk for being treated unnecessarily, and takes serious risk in ablating CIN without biopsy specimen. The modified See and Treat technique may be suitable in high prevalence areas where screening and treatment are not available at all.

The last strategy is prophylactic ablation of the transformation zone (TZ). All of the previous mentioned strategies have a rationale of "presumed innocent" on the abnormalities lesions of the cervix, but the last strategy has a rationale of "presumed guilty" on all cervix of the high-risk women. Ablating of the TZ can be done safely and provides long-term protection against development of cervical neoplasia. This approach might be appropriate in a high prevalence of CIN where screening is never available nor become available soon. Beside the major risk of unnecessary treatment, serious ethical questions should be considered when this strategy is implemented.

The Situation Analysis of the Management of abnormal Pap smears in the Lower Southern Thailand⁽³³⁾

The study of the resources for management of the abnormal Pap smears has been carried out in the lower southern Thailand under the support of PATH during the year 2002-2003. The project is the first main step for establishing the effective referral system in women with abnormal smears. It was found

that the cervical screening is opportunistic. The coverage rate is about 15%.

The quality of cytological service is still obscure and the process of patient notification for the result of the smears is not convincing. There is a limitation of the pathological laboratory service.

The incidence of abnormal smears, defined as atypical squamous cells of undetermined significance (ASCUS) or above, and high-grade squamous intraepithelial lesions (HSIL) are 1.24% and 0.36% respectively. Ten out of eleven hospitals have colposcopy services, but only one hospital can provide standard service. In the view of health providers, patient's unawareness is the most important obstacles in providing an effective management of the abnormal smears.

Observation is the treatment of choice of mild dysplasia. Due to the limited of colposcopy service, conization is the common tool to obtain pathological diagnosis for HSIL smears. In cases with conization specimen reveals pre-invasive lesions equal to or less than CIN II, most of the hospital agree that it is an adequate treatment. However, a few hospitals suggest hysterectomy in moderate dysplasia. In cases with CIN III, a hysterectomy is a common suggestion.

A Demonstration Project of a Single-visit Approach to Cervical Cancer Prevention in Rural Thailand⁽³⁴⁾

The modified the See and Treat technique was used to increase screening and treatment coverage. A single-visit approach combining visual inspection of the cervix with acetic acid (VIA) and cryotherapy were assessed. The services were provided by the well trained nursed in mobile and hospital-based teams. If the VIA test is positive, cryotherapy was offered after counselling both risks and benefits. Specific indicators represented safety, acceptability, feasibility, and programme effort themes were measured. The VIA test-positive rate was 13.3% and a very high percentage of those eligible accepted cryotherapy. No major complications were developed. The VIA test-negative rate was 94.3% at 1-year follow up. It was concluded that a single-visit approach with VIA and cryotherapy seems to be safe, acceptable, and feasible in rural Thailand, and is a potentially efficient method of cervical cancer prevention in such settings.

Conclusion

The appropriate management of pre-invasive lesions of the cervix is one of the key factors in cervical cancer control program. More understanding about

the important role of HPV and the natural history of CIN make the treatment of this disease is more conservative in developed countries. Observation for minor lesion and eradicate high-grade lesion are suitable in the context of qualified colposcopy services, effective follow-up system, and high patient's compliance. The different situation in developing countries has an effect toward the treatment methods, which tends to be more aggressive. The unnecessary radical treatment of CIN creates a financial burden to the health system, as well as the patient's risk. Although no obviously superior surgical technique for treating CIN, cryotherapy and LEEP seem to be more fascinated for the low-resource setting. Other alternative approach, which eliminates cytology and colposcopy may be considered in the ultrashort- resource setting with a high prevalence of cervical cancer.

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