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Treatment technologies for precancerous cervical lesions in low-resource settings: review and evaluation

Introduction

Cancer of the cervix is preventable but continues to cause the deaths of an estimated 275,000 women worldwide each year, more than 88 percent of them in developing countries. Vaccination against human papillomavirus, a means of primary prevention, has been shown to be over 90 percent effective in protecting against the lesions that lead to the majority of cervical cancer cases, but only if administered before viral infection, which occurs soon after initiation of sexual activity.[1,2] Secondary prevention is accomplished with cervical screening followed by treatment of precancerous lesions and is essential for protecting women who have been sexually active.

Screening, with treatment when necessary, has been the key to the 70 percent or more reduction in cervical cancer cases in industrialized countries, and it is critical to reducing the huge burden of cervical cancer in low-resource countries. Screening technologies appropriate for low-resource settings have advanced considerably in the past decade, but treatment technologies have lagged behind. Treatment methods for developing countries must be low-cost, effective, and adaptable for areas with limited resources in terms of infrastructure and health care providers.

The purpose of this study was to review technologies for treatment of precancerous cervical lesions and to evaluate how each option meets a core set of technical and programmatic specifications for low-resource settings. The review was used to provide information for a matrix of technologies scored for their usefulness in low-resource countries. The matrix can inform decisions about pursuing the use or refinement of potentially appropriate treatments in these settings.

Methods

In order to define the features important in low-resource settings, a cervical cancer team at PATH identified attributes to consider and presented these to a gathering of cervical cancer experts at a WHO meeting in April 2012, along with a draft list of surgical treatment methods; i.e., excisional and ablative methods. Experts were asked to consider the following questions in regard to the lists generated by PATH:

- How would you rank each feature in terms of importance for increased treatment effectiveness and availability in the field? Is the feature “more important” or “less important” for attaining that goal?
- Are other important features or specifications missing from this assessment?
- Are there any other promising treatments to add to the list?

After the features were reviewed by experts, the PATH team conducted a literature search of treatment technologies to determine how each met the requirements considered important by the expert reviewers. With this information, an evaluation matrix was created, where each technology was scored as strong, moderate, or weak in terms of the specifications necessary in low-resource settings.

The literature review of surgical treatment technologies was a systematic PubMed search of English-language literature for original papers and reviews on treatments for cervical intraepithelial neoplasia, with no restriction on publication dates or on whether studies were performed in high-or low-resource areas. The search included combinations of the following terms: cervical intraepithelial neoplasia, precancerous cervical lesion, treatment, ablation, excision, coagulation, LEEP/LLETZ, cryotherapy, laser, electrocautery, conization, diathermy, fulguration, and randomized trial. We also searched the Cochrane Library and Google (including Google Scholar), reviewed articles cited in the papers found in the initial searches, and asked colleagues in the field for references. Articles with a major focus on screening methods or treatment of cervical cancer were excluded.

Because of interest in non-surgical methods for treating precancerous cervical lesions, we also conducted a literature review for these methods. The volume of literature was small compared with that for surgical methods. Two recent reviews[3,4] were a major source of information and other articles were found as for surgical methods, by searching PubMed, the Cochrane Library, Google, and the bibliographies of references found in these papers. Online searches included combinations of the terms cervical intraepithelial neoplasia, precancerous cervical lesion, treatment, pharmaceutical, medical, chemoprevention, and various treatment terms found in the initial searches (e.g., retinoids, hexylaminolevulinate).

Results

Surgical treatments

Surgical treatments for precancerous cervical lesions, also known as cervical intraepithelial neoplasia (CIN), include both ablation and excision (Table 1). Ablative modalities are solely for treatment, while excisional methods provide a tissue specimen for histological assessment to define the severity of disease and the margins of abnormal tissue, for ensuring completeness of treatment. With ablative methods, biopsy specimens must be taken before treatment, if they are desired.

Table 1 Surgical treatments for precancerous cervical lesions[5,6]

Excision	**Ablation**
LEEP/LLETZ[Ψ]	Laser vaporization (CO_2)
Electrosurgical needle conization[α]	Cryotherapy
Laser conization (CO_2)	CryoPen
Cold-knife conization	Cold coagulation
Hysterectomy[β]	Electrocoagulation[§]
	Electrocautery

[Ψ] Loop electrical excision procedure/large loop excision of the transformation zone

[α] Similar to LEEP except that a straight needle rather than a loop is used. (Not included in the scoring matrix.)

[β] Hysterectomy is no longer considered appropriate for management of CIN2,3 unless there are other considerations.

[§] Electrocoagulation (also known as fulguration) produces coagulation of tissue by passage of high-frequency current, whereas electrocautery burns tissue with a red-hot needle.

Scoring matrix for surgical treatment technologies for precancerous cervical lesions

Taking into account the features considered important by expert reviewers and the information from our literature search, we created the scoring matrix in Table 2. We included some older technologies that have fallen out of favor in high-income areas with the advent of effective but expensive newer treatments, in order to ascertain whether they might still be appropriate for low-resource areas, with or without modifications. Technologies are scored as strong, moderate, or weak in meeting requirements for low-resource settings and are color-coded for easier comprehension. The scoring was based on accumulated evidence from discussions with experts and literature review; references used for the matrix are listed in the Bibliography at the end of the document.

Table 2 Surgical treatment technologies for precancerous cervical lesions Features scored for potential use in low-resource settings[ω]									
Features	**Treatment technology**								
	Excision			**Ablation**					
	LEEP/LLETZ	**LASER CONIZATION**	**COLD KNIFE CONIZATION**	**LASER ABLATION**	**CRYOTHERAPY**	**CRYOPEN[α]**	**COLD COAGULATION**	**ELECTRO-COAGULATION[§]**	**ELECTRO-CAUTERY**
Technical features									
Consumable material									
Electricity (power grid) (Y/N)[β]	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Battery: (Y/N)	Yes	No	No need	No	No need	Possible (several car batteries)	Uncertain	Uncertain	Uncertain
Compressed gas tank required (Y/N) Note the type/weight of gas container used. Specify adaptor required	No	No (Sealed tube of gas)	No	No (Sealed tube of gas)	CO_2 or N_2O	No	No	No	No
Consumable parts (Y/N) Specify parts required; e.g., single-use tips, guards, filter for smoke extractor.	Wire loops	No	Scalpel blades	No	No	No	No	Occasional replacement of needles	Occasional replacement of needles
Potential use case scenario **Strong**: Remote campaign locations **Moderate:** Any health facility **Weak:** Tertiary health center	Moderate	Weak	Weak	Moderate	Yes	Yes	Yes	Yes	Yes

Table 2 Surgical treatment technologies for precancerous cervical lesions Features scored for potential use in low-resource settings[ψ]									
Features	**Treatment technology**								
	Excision			**Ablation**					
	LEEP/LLETZ	**LASER CONIZATION**	**COLD KNIFE CONIZATION**	**LASER ABLATION**	**CRYOTHERAPY**	**CRYOPEN[α]**	**COLD COAGULATION**	**ELECTRO-COAGULATION[§]**	**ELECTRO-CAUTERY**
Portability (Y/N) Safely transported by truck/SUV on rough road? Note weight and fragility. Possible two-component answers: cryo units easy to transport but gas tank are not.	Yes	Laser equipment is fragile, must be carefully packed.	Yes	Laser equipment is fragile, must be carefully packed.	Yes/No Cryo units easy/ Gas tanks heavy and dangerous	Yes	Yes	Yes	Yes
Ease of repair **Strong**: provider/local technicians **Moderate:** trained professionals in country **Weak:** must be performed by manufacturer	Moderate	Moderate	Strong	Moderate	Strong/Moderate	Strong/Moderate	Moderate	Strong/moderate	Strong/moderate
Ease of cleaning **Strong:** 10 to 20 min disinfecting procedure **Moderate:** > 20 min disinfecting procedure **Weak:** autoclave only	Strong	Strong	Strong	Strong	Strong	Strong	Strong	Strong	Strong

Table 2 Surgical treatment technologies for precancerous cervical lesions
Features scored for potential use in low-resource settings[ψ]

Features	Treatment technology								
	Excision			Ablation					
	LEEP/LLETZ	LASER CONIZATION	COLD KNIFE CONIZATION	LASER ABLATION	CRYOTHERAPY	CRYOPEN[α]	COLD COAGULATION	ELECTRO-COAGULATION[§]	ELECTRO-CAUTERY
Clinical/programmatic features									
Appropriate for non-physician provider (Y/N)	No	No	No	Probably	Yes	Yes	Yes	Yes	Yes
Training requirements for provider **Strong:** ~3 days **Moderate:** ~one week **Weak:** > one week Depends on inherent difficulty of technique and inherent safety risks.	Strong (physician only)	Strong/moderate (physician only)	Strong/moderate (physician only)	Strong	Strong	Strong	Strong	Strong	Strong
Efficacy for treating high grade lesions **Strong:** > 80% **Moderate:** 60% to 80% **Weak:** < 60%	Strong	Strong	Strong	Strong	Strong (for lesions covering 25% to 75% of cervix)	Uncertain: no data	Strong (for lesions covering 25% to 75% of cervix)	Strong/moderate	Strong/moderate
Treatment capability for sizes or types of lesions **Strong:** lesions covering > 75% of cervix/into endocervix **Moderate:** lesions covering 25% to 75% of cervix **Weak:** lesions covering < 25% of cervix	Strong	Strong	Strong	Strong	Moderate	Moderate	Moderate	Strong/moderate	Strong/moderate

Table 2 Surgical treatment technologies for precancerous cervical lesions
Features scored for potential use in low-resource settings[ψ]

Features	Treatment technology								
	Excision			Ablation					
	LEEP/LLETZ	LASER CONIZATION	COLD KNIFE CONIZATION	LASER ABLATION	CRYOTHERAPY	CRYOPEN[α]	COLD COAGULATION	ELECTRO-COAGULATION[§]	ELECTRO-CAUTERY
Safety									
Rate of severe complications Specify nature and whether for women or for pregnancy outcomes **Strong:** < 1% **Moderate:** 1 to 3% **Weak:** > 3%	Moderate/weak	Weak	Weak	Strong	Strong	Strong (probable)	Strong	Strong	Strong
Ease of managing most likely complications **Strong:** field health station **Moderate:** urban clinic **Weak:** hospital	Weak	Weak	Weak	Strong	Strong	Strong	Strong	Moderate	Moderate
Need for anesthesia **Strong**: no anesthesia **Moderate:** local **Weak**: regional block/general	Moderate	Moderate	Weak	Moderate	Strong	Strong	Strong/moderate	Moderate	Moderate
Provider time required for procedure **Strong**: < 10 minutes **Moderate:** 10 to 20 minutes **Weak:** > 20 minutes	Strong	Strong/moderate	Weak (time required for regional anesthesia)	Strong	Strong	Strong	Strong	Strong	Strong

Table 2 Surgical treatment technologies for precancerous cervical lesions Features scored for potential use in low-resource settings[ψ]									
Features	**Treatment technology**								
	Excision			**Ablation**					
	LEEP/LLETZ	**LASER CONIZATION**	**COLD KNIFE CONIZATION**	**LASER ABLATION**	**CRYOTHERAPY**	**CRYOPEN[α]**	**COLD COAGULATION**	**ELECTRO-COAGULATION[§]**	**ELECTRO-CAUTERY**
Patient recovery time **Strong:** ambulatory (observation ~30 min) **Moderate**: observation 1-3 hours **Weak**: > 3 hours	Moderate	Moderate	Moderate/weak	Strong	Strong	Strong	Strong	Strong	Strong
Patient acceptability features									
Ease of management after procedure									
Ease of pain management **Strong:** patient decision (may or may not need) **Moderate**: non-steroidal anti-inflammatory drugs (e.g., aspirin, ibuprofen) **Weak**: narcotics or IV pain medication	Moderate	Moderate	Moderate	Strong	Strong	Strong	Strong	Strong	Strong
Ease of post-treatment recommendations **Strong:** none **Moderate**: no intercourse/douching ≤ 3 weeks **Weak**: return visits to clinic are essential part of treatment	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

Table 2 Surgical treatment technologies for precancerous cervical lesions
Features scored for potential use in low-resource settings[ψ]

Features	Treatment technology								
	Excision			Ablation					
	LEEP/LLETZ	LASER CONIZATION	COLD KNIFE CONIZATION	LASER ABLATION	CRYOTHERAPY	CRYOPEN[α]	COLD COAGULATION	ELECTRO-COAGULATION[§]	ELECTRO-CAUTERY
Market/commercial features									
Low estimated cost per procedure (Y/N) Includes consumable supplies (gas, water) & parts (tips, guards); electricity. Difficult to estimate these. Does not include amortized cost of equipment.	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Initial equipment cost **Strong:**< US$1,000 **Moderate:** US$1,000 to $5,000 **Weak:** >US$5,000	Weak (Moderate if use standard electrocautery power source)	Weak	Moderate	Weak	Moderate	Moderate	Moderate	Moderate	Moderate

[ψ] Color coding: green: strong; yellow: moderate; red: weak; grey: uncertain

[α] The CryoPen recently gained FDA approval for treating precancerous cervical lesions.

[β] Because of the increase in availability of electricity in many low-resource settings, technologies that require electricity are not rated as weak.

[§] Electrocoagulation heats tissue by passing electric current, as does electrocautery, but uses a different type of unit to generate the current, and apparently at lower temperatures, with less chance of severely burning the tissue and causing side effects such as stenosis of the cervical os.[13]

Nonsurgical treatments

Precancerous cervical lesions have also been treated with nonsurgical methods, which may be grouped broadly as pharmaceutical and micronutrient agents. The volume of literature available for these treatments was much less than for surgical methods, and none appear to be approved or studied as rigorously as the former. Total numbers of women treated with these methods is much smaller than the number treated with surgical technologies. Treatments that have been published are listed in Tables 3 and 4, but no attempt was made to score them, as was done for the surgical treatments.

Table 3 was generated from the reviews[3,4] mentioned in the Methods section. According to the reviews, all had histologically confirmed CIN of the grades reported. Because no treatments had efficacy > 55%, many of the details, such as total number enrolled, dose, and timing of treatments have not been included. Table 4 summarizes additional papers found in searches described in Methods, and citations are included for these.

Table 3 Nonsurgical treatments for precancerous cervical lesions: studies reported in reviews[3,4]

Treatment	N	Route	Response
COX-2 inhibitors (2 trials) (NB: all trials with COX-2 inhibitors were stopped because of CV toxicity)	25	Oral	Complete response (CR): Tx (treatment group): 33%; placebo: 15%
	16	Oral	Regression: Tx: 25%; placebo: 12% (regression not defined)
DFMO (alpha-difluoromethylornithine) (inhibitor of polyamines involved in cell proliferation)	141	Oral	No difference Tx vs. placebo
Retinoids (modulation of epithelial cell proliferation/differentiation)	301	Topical	CIN2: CR Tx: 43%; placebo: 27%; CIN3: Tx group worse than placebo
	NA	Oral	Tx group worse than placebo
	114	Oral	No difference Tx vs. placebo
Beta-carotene (two trials) (anti-oxidant)	NA	Oral	No difference Tx vs. placebo
	NA	Oral	Tx group worse than placebo
Indole-3-carbinol (I3C) (negative regulation of estrogen)	30	Oral	Tx: regression in 50% Placebo: no regression
ZYC101a (encapsulated plasma DNA)	NA	IM	Tx: regression in 43%; Placebo: regression in 27% (women >25 yrs)
MVA-E2 (therapeutic vaccine)	34	Intra-uterine injection	Tx 9 wks: regression in all; CR in 50% Tx 1 yr: no recurrent disease Placebo: 15% recurrent CIN3 after conization
Hsp E7 HPV16 (heat shock protein fused with E7 oncoprotein)	NA	IM	CR in 22% to 55% in preliminary studies

Table 4 Nonsurgical treatments for precancerous cervical lesions: individual studies

Treatment	N	Route	Response
Imiquimod[7] (used on genital warts) (Initial diagnosis: biopsy)	56	Topical	No difference in recurrence TX vs. placebo
Hexylaminolevulinate (HAL)* (photo-activated)[8] (there was a larger study in CIN1) (initial diagnosis: biopsy)	14	Topical	CIN2: Tx: CR in 5/7; no control group CIN3: Tx: CR in 5/7; no control group
Escharotic treatment[9 β] Topical: ZnCl, bloodroot, Bromelain (enzyme in pineapple), Calendula succus, Vit A; Systemic: Vit C, beta carotene, folic acid selenium; vegan diet. (initial method of diagnosis not stated)	43 7: cervical atypia; 26: CIN; 10: carcinoma *in situ*	Topical and systemic	"38 had complete regression, 3 had partial regression, 2 had persistent lesions (low-grade dysplasia)." (no information on which groups responded) No controls.
TG4001[10] (therapeutic vaccine candidate) (method of initial diagnosis not stated in abstr but post-Tx assessments were colpo, cytol, HPV DNA/RNA)	21	3 Sub-Q injections (weekly)	13 had conization at 6 mo 10 were "clinical responders" (not clear if all had conization) 12 months: 1 pt lost to f/u. remaining 7:no suspicion CIN2/3 nor HPV 16 infection No controls.
Interferon[11] (initial diagnosis: biopsy)	8	Intra-lesional injection	"5 had a good clinical response, while 3 had therapeutic failure." No controls.
Diindolylmethane (DIM) [12] (naturally occurring compound found in Brassica vegetables such as broccoli) (initial diagnosis: biopsy)	60	Oral	RCT No statistically significant difference in any outcome between the DIM and placebo group.
Cidofovir[13] (anti-viral drug used experimentally to treat RRP) (initial diagnosis: biopsy)	48	Topical	RCT Tx: no CIN in 61% Placebo: no CIN in 20%

*Photodynamic therapy (PDT) using blue light and the potent precursor for protoporphyrin IX, hexyl aminolevulinate (HAL), has been shown to induce apoptosis and necrosis in cancer cells. This method is early in testing. It requires laser activation so may not be useful in low-resource settings.

βThe original paper was Hudson TS. Escharotic treatment for cervical dysplasia and carcinoma. *Journal of Naturopathic Medicine.* 1993;4:23. The journal is no longer published and the article is not available.

Discussion

When presented with a proposed list of features important for treatment methods for precancerous cervical lesions in low-resource settings, experts agreed on the need for technical attributes such as low maintenance, ease of repair, no need for gas (e.g., CO_2), durability, and portability. A number remarked that access to electrical power was becoming more common in low-income areas, so having a technology that requires power is not the drawback it once was. Important clinical and programmatic features included high efficacy and safety, usability by low- to mid-level health care providers, low

training requirements, no need for general anesthesia, and short time required for procedure. Other important considerations are high patient acceptance and low cost—for the capital investment as well as per procedure.

While nonsurgical methods for treating cervical lesions have been reported, none appear sufficiently efficacious or clinically advanced to be approved for treatment in the near term; thus, our scoring matrix did not include any of these. Among surgical technologies, excision methods (LEEP/LLETZ, laser conization, and cold knife conization) are highly efficacious, and equipment is relatively easy to maintain and transport, but they are unsuitable for low-level providers and remote areas, come with higher risk of complications, and are quite costly.

In assessing ablative methods, laser ablation has many of the drawbacks of excision methods because of the skill level needed for performing the procedure, risk of complications, and cost. Electrocoagulation and electrocautery are older methods not now in use in developed countries, where LEEP/LLETZ are used for most procedures, and the reports on these older methods did not always include complete information on efficacy and safety. There was also uncertainty or disagreement over issues such as whether these would be appropriate for low-level providers and whether the procedures were painful for women.

Cold coagulation, an older method first reported in a 1966 paper,[14] has generated recent interest because it uses relatively low temperatures (100 to 120 degrees C), is likely to be appropriate for low- to mid-level providers, and is low cost. It is uncertain, however, if the units are still commercially available.

Cryotherapy has been the method of choice in low-income settings for many years[15-17] but is widely known to present challenges because it requires large tanks of CO_2 or N_2O and because the freezing units can malfunction.[18] The newly developed CryoPen avoids the problems of obtaining and transporting high-quality gas in developing countries and of malfunction of the freezing units. The CryoPen units are easily transported, can be run from a car battery, and are appropriate for low-level health care providers. The CryoPen has been used for treating skin lesions and was recently approved by the FDA for treating cervical lesions (http://www.cryopen.com/). Further testing will be necessary to determine its efficacy and safety for various grades of cervical lesions.

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