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SPECIAL COMMUNICATION

World Health Organization Guidelines: Use of cryotherapy for cervical intraepithelial neoplasia

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ABSTRACT

Background: In 2008, cervical cancer was responsible for 275 000 deaths, of which approximately 88% occurred in low- and middle-income countries. In 2009, the World Health Organization (WHO) committed to updating recommendations for use of cryotherapy for cervical intraepithelial neoplasia (CIN). *Methods and results:* We followed the WHO Handbook for Guidelines Development to develop present guidelines. An expert panel was established, which included clinicians, researchers, program directors, and methodologists. An independent group conducted systematic reviews and produced evidence summaries following the GRADE approach. GRADE evidence profiles were created for 16 key questions about the effects of cryotherapy in the presence of histologically confirmed CIN compared with no treatment and with loop electrosurgical excision procedure, as well as the use of different cryotherapy techniques. We identified a small number of randomized controlled trials or independently controlled observational studies. Surrogate outcomes were reported when evidence about outcomes critical to decision making were not available. The panel made 14 recommendations and documented factors that determined the strength and direction of the recommendations in decision tables. *Conclusion:* The present document summarizes new evidence-based WHO recommendations about the use of cryotherapy in women with histologically confirmed CIN for low-, middle-, and high-income countries.

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Introduction

In 2008, cervical cancer was responsible for 275 000 deaths, of which approximately 88% occurred in low- and middle-income countries (LMIC). Cervical cancer is the third most common cancer in women worldwide and the most common cancer in many LMIC [1]. Because there is a typically slow progression from atypical cells to cervical intraepithelial neoplasia (CIN) and to invasive carcinoma, precancerous lesions can be treated and invasive cervical cancer prevented. The screening methods currently available in a wide range of settings include cytologic (Pap) smears, visual inspection with acetic acid (VIA), and human papillomavirus (HPV) testing. A diagnosis of CIN can be confirmed by histologic interpretation of biopsies, either with or without colposcopy. Furthermore, a variety of treatment methods are available, including cryotherapy, loop electrosurgical excision procedure/large loop excision of the transformation zone (LEEP/LLETZ; these are the same techniques, and LEEP is used in the remainder of the document), cold knife conization, laser vaporization, cold coagulation, and hysterectomy. In 2004, the World Health Organization (WHO) and other international organizations developed and published *Comprehensive Cervical Cancer Control: a Guide to Essential Practice* [2] as a comprehensive guide to assist healthcare providers at multiple levels of the health system to prevent, detect, and treat cervical precancer and cancer.

In 2009, WHO committed to updating these guidelines following the WHO revised process for guideline development [3]. The *Guide* presently includes recommendations on major treatment procedures for precancer of the cervix: cryotherapy; LEEP; and cold knife conization. Because many countries are moving toward marked revisions in their national programs based on “single visit” or “screen and treat” approaches using cryotherapy following a positive screening test, and because of widespread use, ready availability of cryotherapy, and limited availability of confirmatory colposcopy diagnosis, the use of cryotherapy was, therefore, deemed a priority for the update of the *Guide* to support program managers and clinicians to scale-up national programs.

The present document provides recommendations for the use of cryotherapy compared with no treatment and compared with LEEP in the presence of histologic confirmation of precancerous lesions (CIN 1, 2, or 3). The document also addresses the use of different techniques of cryotherapy for CIN and provides recommendations for treatment of CIN in women who are pregnant, as well as for women who are HIV positive. In keeping with WHO guideline terminology, the recommendations are labeled as either “strong” or “conditional,” according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [4]. For strong recommendations, the words “we recommend” are used, and for conditional recommendations “we suggest.” We offer suggested interpretations of strong and conditional recommendations in Table 1. Understanding the interpretation of these 2 grades is essential for healthcare decision making.

Methods

The methods for developing the present guidelines followed the *WHO Handbook for Guideline Development* [3].

Formulating questions and determining outcomes

In March 2009, experts invited by WHO drafted a list of 45 general questions about the effects of cryotherapy among women with CIN. These experts were then asked to rank the questions by priority.

Expert guideline panel

WHO selected a multidisciplinary expert guideline panel comprising clinicians with cryotherapy experience, researchers in cervical cancer prevention and treatment, program directors, epidemiologists, public health officers, and methodologists. The methodologists (evidence review team) were based at the McMaster University WHO Collaborating Center for Evidence-informed Policy Making and had expertise in guideline development and evidence synthesis. A steering group of 7 members was then created from the expert guideline panel to guide the process.

Following a review of the suitability of the initial 45 general questions, these questions were refined to 16 questions for which an evidence review was deemed necessary. The steering group also decided to assess the evidence for the effects of cryotherapy among women with histologically confirmed CIN to provide the best estimate of the benefits and adverse effects of cryotherapy without the potential for confounding the outcomes owing to false-positive screening tests or diagnoses.

To determine the outcomes, a scoping review of cryotherapy studies was conducted by the evidence review team. The expert guideline panel was also consulted. A list of outcomes to be considered when making the recommendations was compiled. Nineteen members of the expert guideline panel independently and anonymously scored the outcomes, via electronic survey, according to importance to decision making [5]. The mean and median importance of each outcome (1 [least important] to 9 [critical]) was calculated and 16 outcomes were identified as important or critical (Box 1).

Preparation of evidence profiles and grading of evidence

The evidence review team conducted a series of systematic literature reviews following the methods of the Cochrane Collaboration and prepared GRADE evidence profiles for each question [6]. During this process, the steering group held conference calls to discuss issues about the available evidence, the presentation of the results, and their impact on making recommendations.

MEDLINE, EMBASE, LILACS, the Cochrane Library, and the WHO Clinical Trials Search Portal were searched up to July 2009 using key subject and text words for cryotherapy and cervical cancer, depending on the database (MEDLINE search strategy shown in Supplementary Material S1). The search was not limited by language or by study type. The evidence review team screened titles, abstracts, and full text of potentially relevant literature in duplicate. The first screen was for controlled trials (randomized or non-randomized) but, because only a few controlled trials were identified, observational studies without independent controls were also included as evidence. Authors in the field and the expert guideline panel were also contacted to identify missing studies, studies in progress, or studies not yet published.

Table 1
Interpretation of strong and conditional recommendations.

Implications	Strong recommendation	Conditional recommendation
For patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the intervention. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
For policy makers	The recommendation can be adopted as policy in most situations.	Policy making will require substantial debate and involvement of various stakeholders.