Effectiveness, Safety, and Acceptability of Cryotherapy: A Systematic Literature Review

Cervical Cancer Prevention Issues in Depth #1

Alliance for Cervical Cancer Prevention (ACCP)

January 2003

About this Publication

Authors: Wendy Castro, M.H.S., PATH
Julia Gage, M.P.H., PAHO
Lynne Gaffikin, Dr.P.H., JHPIEGO
Catterina Ferreccio, M.D., M.P.H., PAHO
John Sellors, M.D., PATH
Jacqueline Sherris, Ph.D., PATH
Paul Blumenthal, M.D., M.P.H., JHPIEGO

Graphic Design: Barbara Stout, PATH
Elizabeth Sanders, Elizabeth Sanders Design

For additional copies of this publication, please contact
The Alliance for Cervical Cancer Prevention c/o PATH
1455 NW Leary Way
Seattle, Washington 98107 USA
Tel: (206)285-3500
email: accp@path.org
url: www.alliance-cxca.org

Acknowledgements

Support for the development of this document was provided by the Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention (ACCP).

Many thanks to the following individuals for their thoughtful suggestions and editorial contributions: Martha Jacob, F.R.C.O.G., M.P.H., EngenderHealth; Rengaswamy Sankaranarayanan, M.D., IARC; Irene Agurto, Ph.D., PAHO; Jose Jeronimo, M.D., PAHO; Silvana Luciani, M.H.Sc., PAHO; Sylvia Robles, M.D., M.Sc., PAHO; Michele Burns, M.A., PATH

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Executive Summary

The Alliance for Cervical Cancer Prevention (ACCP) conducted a systematic review of the literature on the use of cryotherapy as an out-patient treatment option for women with cervical intraepithelial neoplasia (CIN)—the precursor to cervical cancer. The main objective of the review was to examine the available data on the effectiveness, safety, and acceptability of cryotherapy, and to communicate the evidence base to health professionals and policy makers in developing countries. Developing countries overwhelmingly carry the burden of disease of cervical cancer, where over 80 percent of incident cases occur. Yet, cervical cancer is a preventable cancer if women have access to adequate screening and treatment of precancerous lesions.

Cryotherapy offers a simple means of treating many women with precancerous cervical lesions. The evidence presented in this review has relevance not only to those program managers or health policy makers deciding upon appropriate treatment methods, but also to programs already using cryotherapy. As cervical cancer screening programs are implemented or expanded in low-resource settings, appropriate treatment for precancerous lesions must be available, and providers, program managers, and policy makers need to be informed and confident about treatment effectiveness, safety, and acceptability.

Findings

Effectiveness. In the 32 studies reviewed for effectiveness, cryotherapy produced an overall cure rate of 89.5 percent (summary statistic). The data suggest that, overall, cryotherapy is as effective as other out-patient treatment methods. Generally, cryotherapy resulted in higher cure rates for less severe lesions (CIN 1 and CIN 2). More severe lesions (CIN 3), especially larger lesions extending into the endocervical canal, have lower cure rates with cryotherapy. For the treatment of large lesions (that cover 75 percent or more of the cervix) or lesions complicated by endocervical canal involvement, a different treatment method may be more appropriate. Questions remain about whether the length of freeze or type of refrigerant used affect treatment effectiveness. Data assessing the impact of women's age and parity on cure rates also are inconclusive.

Safety. Cryotherapy offers women a safe treatment option for treating precancerous cervical lesions in an outpatient setting. In the 38 articles reviewed for safety, major complications such as severe bleeding, pelvic inflammatory disease (PID), or other problems rarely developed after cryotherapy. Providing women with effective counseling about warning signs of complications will help inform women on when to seek additional medical care if problems develop following treatment.

HIV Infection and Cryotherapy Complications. The HIV epidemic has special implications for screening and treatment of precancerous cervical lesions. In general, the research does not support an overall increased risk of complications among HIV-positive women unless she is already very ill and has a decreased CD4 cell count. Concern has been raised about whether the treatment site temporarily leaves a woman more vulnerable to acquiring HIV or whether, if HIV-infected, her risks of transmitting the virus increase after treatment; data are not currently available to adequately address these issues.

Long-Term Sequelae. Based upon the studies reviewed, cryotherapy does not appear to be a major contributing factor to the development of cervical stenosis post-treatment. Other long-term sequelae, such as a negative impact on a woman's future fertility and obstetrical outcomes, also are not supported in the literature.

Acceptability. Cryotherapy is associated with several side effects. In the 45 articles reviewed for acceptability, vaginal discharge for approximately 2 to 4 weeks after the procedure was the most frequent side effect reported. Other side effects included feeling flushed or faint during or immediately after the treatment, feeling discomfort (pain or cramping) during or immediately after the treatment, and experiencing spotting or light bleeding following the procedure. Additional research is needed on the acceptability of these side effects, as well as the acceptability of the overall procedure.

Considerations

The studies included in this review often were from studies conducted by medical specialists trained in colposcopy and cryotherapy, working in countries with highly developed health systems and appropriate resources and supplies. This literature provides a rich evidence base on the effectiveness, safety, and acceptability of cryotherapy in these countries, but the conclusions should be validated in less developed settings. Several large trials are underway in India, Kenya, Peru, South Africa, Thailand, and other developing countries that will produce additional data to inform health managers and policy makers in developing countries on how cryotherapy will perform in their settings. Effectiveness, safety, and acceptability may be affected by provider skill, familiarity, and comfort with the procedure. If providers in developing countries receive appropriate training, cryotherapy should produce cure rates comparable to the studies in this review, and women should experience few complications and have minimal difficulty with side effects.

Recommendations

- Cryotherapy is a relatively simple outpatient procedure that is easy to learn and requires no electricity to perform. This ease of use, combined with its level of effectiveness, safety, and acceptability, make cryotherapy a feasible treatment technology appropriate for use in low-resource settings.
- Health providers should give women clear messages about the relative safety of cryotherapy and information on when to return for additional medical care if symptoms such as fever or severe pain, with or without malodorous discharge, develop.
- Pretreatment counseling can help alleviate anxiety about pain and discomfort during and after the treatment and will prepare women for anticipated side effects.
- Health providers should provide counseling that addresses women's questions about long-term sequelae associated with cryotherapy and alleviates fears about impaired fertility or obstetrical problems.
- Additional research is necessary to answer questions about the effectiveness of a single freeze compared to a double freeze. Current treatment protocols use a double freeze and programs should continue to do so.
- Additional research is needed to determine the interaction between cryotherapy and HIV transmission and acquisition.
- Further research is needed to assess women's perceptions of the procedure and their experiences with side effects.

I. Overview

Cryotherapy, which uses extremely low temperatures to freeze and destroy abnormal tissue, was first reported being used for the destruction of cervical intraepithelial neoplasia (CIN) in 1967 (Crisp, 1967). Cryotherapy increased in popularity as an inexpensive and easy-to-perform treatment option in many countries throughout the 1970s and 1980s, though its use decreased somewhat with the introduction of newer technologies such as loop electrosurgical excision procedure (LEEP) and laser ablation. Cryotherapy, however, has several advantages compared to LEEP and laser therapy that make it an acceptable and appropriate treatment option, particularly in low-resource settings. Cryotherapy is a relatively simple procedure that is easy to learn, inexpensive in comparison to methods such as cone biopsy and hysterectomy, and requires no electricity—all of which can be important considerations in low-resource areas, where staffing, supplies, and infrastructure are often severely limited. In addition, studies and anecdotal evidence have pointed consistently to satisfactory effectiveness with few complications or severe side effects.

In recent years, global awareness has been raised about the impact of cervical cancer on women's health and life expectancy in developing countries; every year women in developing countries account for 80 percent of the cervical cancer cases and approximately 200,000 deaths worldwide (Ferlay et al., 2001). Prevention efforts in less developed countries are focusing on implementing screening programs to detect CIN, and programs are seeking low-cost, effective treatment methods appropriate for use in low-resource settings. Providers and program planners need accurate, evidence-based information on treatments' effectiveness, risks, and expected side effects. Adequate cure rates and minimal complications are crucial in countries where follow-up of patients can be difficult.

To address the demand for a clear, comprehensive discussion of these issues as they relate to cryotherapy, the Alliance for Cervical Cancer Prevention (ACCP) has undertaken a systematic literature review on the effectiveness (cure rates), safety (complications), and acceptability (side effects) of cryotherapy as a treatment for precancerous lesions of the cervix. The goal of the review is to provide an understandable synthesis of available data upon which policy makers, public health and medical professionals, and women's advocacy groups working in low-resource settings can base their recommendations and decisions.

II. Methodology

A. Data Sources

Studies addressing cryotherapy for treatment of human papillomavirus (HPV) or precancerous lesions of the cervix, published between 1955 and June 2001, were identified by searching the MEDLINE database of the U.S. National Library of Medicine, reviewing reference lists of retrieved articles, and contacting researchers in the field.

The OVID version 4.1.0 search and retrieval software was used to access the MEDLINE database. Initially, the search identified all studies with at least one of the following Medical Subject Heading (MeSH) subject headings (both exploded and limited to a MeSH major topic): cervix dysplasia, cervical intraepithelial neoplasia, cervix neoplasms, cervix uteri, and cervicitis.

The search was narrowed to those publications that also included the keywords "cryotherapy" and "cryosurgery" in the title, abstract, registry number word, or MeSH subject heading. The authors also searched through the reference lists of retrieved articles and contacted other researchers in the field.

B. Initial Eligibility Criteria

Figure A (page 12) illustrates the article selection process. The authors reviewed the titles, abstracts, and, when necessary, the text of the identified articles. Those that met the following three criteria were examined further:

- Articles presented data on effectiveness, safety, or acceptability.
- Articles reported on cryotherapy used to treat the cervix for CIN or HPV.
- Articles written in English or Spanish.

The authors reviewed these articles, abstracting data on the following study characteristics: study design, sample size, sample population, length of follow-up period, percent of patients lost during the follow-up period, technique used to diagnosis initial lesion, success and failure following treatment, and description of cryotherapy technique (probe tip, refrigerant, time of freeze, extension of iceball).

C. Final Selection Criteria

In the review of the effectiveness of cryotherapy, the authors included both randomized controlled trials and observational follow-up studies that used clinically acceptable methods to determine when treatment was indicated, had clinically acceptable follow-up protocols to determine cure and treatment failure, and had low rates of loss to follow-up. The authors determined that separate selection criteria were necessary for articles that evaluated treatment effectiveness, compared with articles that provided data on treatment safety and acceptability. Below is a list of selection criteria specific to articles evaluating treatment effectiveness, followed by a discussion of the criteria for articles on

treatment safety and treatment side effects. Eligible articles could meet the selection criteria and be included for discussion in more than one section.

1. Criteria for including articles on effectiveness

Articles were limited to reports on studies that provided information on treatment effectiveness and met the following criteria:

- Article clearly described the cohort of women followed and provided information on the outcome (success, failure, and loss of follow-up) of all subjects. If loss to follow-up was not explicitly mentioned, information was provided that allowed for its estimation.
- Indication for treatment was determined by either persistently abnormal cytology (two consecutive positive results), colposcopy, or histologically determined diagnosis of CIN.
- Follow-up protocol used to determine failure following treatment consisted of either persistently abnormal cytology (two consecutive abnormal results), colposcopy, or histologically determined diagnosis of CIN.
- Follow-up protocol used to determine cure following treatment consisted of at least two consecutive negative cytology results, or normal colposcopy, with or without normal histology.
- Results were clear and adequately presented—cure rates and percent of patients lost to follow-up were reported separately for each treatment therapy group.
- Article reported the length of follow-up (interval, mean, or range).
- Proportion of patients lost to follow-up was 20 percent or less.
- Article was not simply a report of failures.
- Article was published in or after 1967.

Observational follow-up studies tracking a group of women attending or referred to gynecology or colposcopy clinics for abnormal Pap smear results were more common than randomized controlled trials. Randomization into treatment groups increases the likelihood that the treatment groups are equal in terms of selection factors that could potentially affect study outcome. This report refers to evidence from randomized trials before discussing evidence from follow-up studies.

2. Criteria for including articles on safety and acceptability

Because complications appeared to be relatively rare and few articles reported complications or side effects as a primary outcome of the study, and because the authors wished to capture all relevant safety data, the selection criteria for articles on safety and acceptability were less stringent than for effectiveness. Relevant randomized controlled trials and observational follow-up studies that reported a complication or described experience with side effects were included in the review.

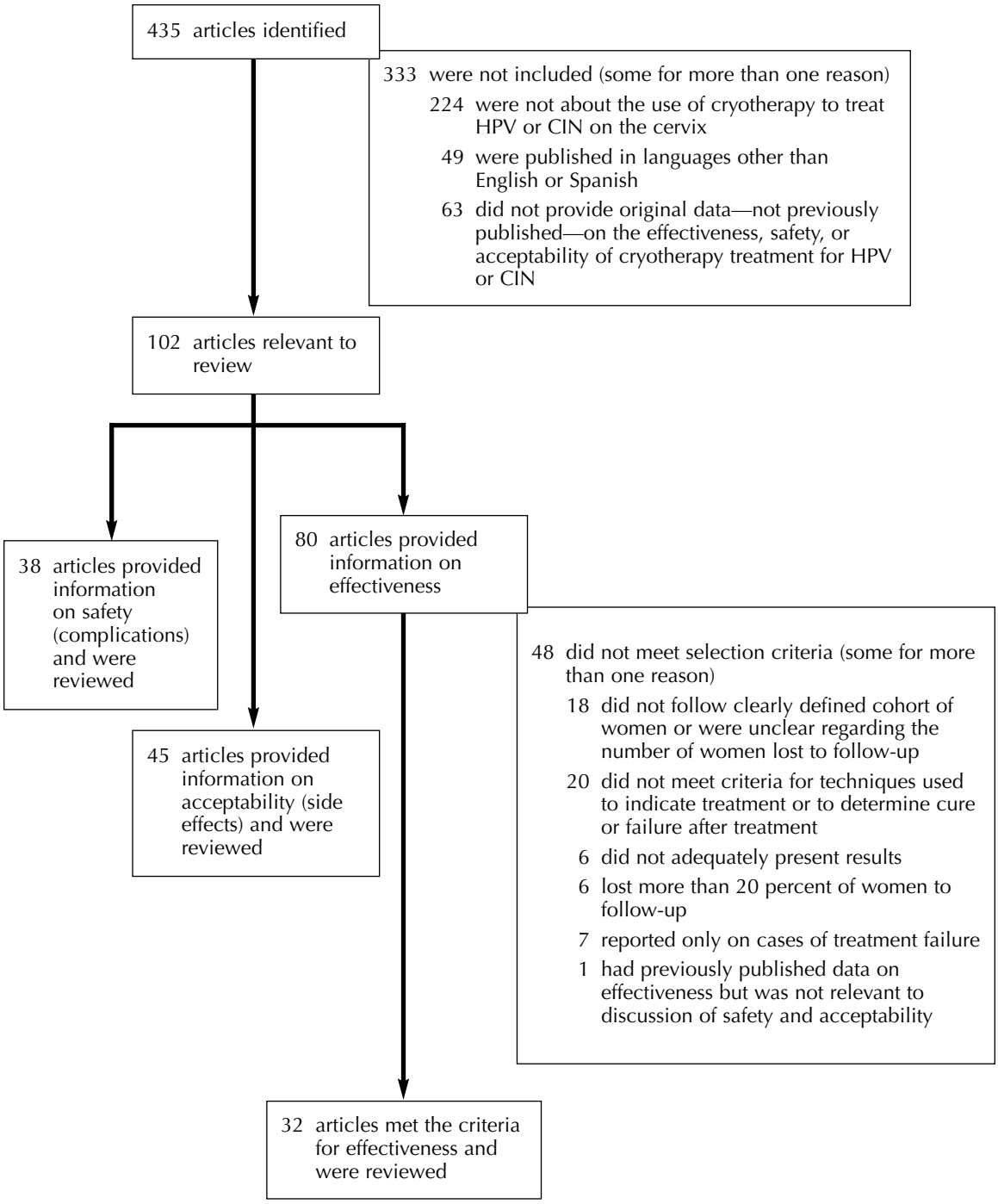
The articles on complications and side effects were stratified by whether patient follow-up was performed in an active or passive manner. For the purposes of this review, **active follow-up** was defined as an *a priori* decision to follow treated women with a predefined set of questions (which

could have been accomplished by visiting women at their home, telephone interviews, or control visits at the health unit). Complication rates for articles reporting active follow-up were calculated by using the number of women treated as the denominator and were considered to be a baseline rate for complications experienced. **Passive follow-up** consisted of collecting data as they were received, relying upon patient compliance or unanticipated return visits to the clinic or emergency room. Passive follow-up may underestimate the rates and types of complications or side effects that occurred. For this review, the authors gave priority to studies that gathered evidence using active follow-up mechanisms.

D. Selection of Articles

Figure A shows the results of the selection process. The Medline search identified 414 articles. Another 21 publications were found by searching the reference lists and through contacts with researchers in the field, bringing the total number of identified articles to 435. The search did not identify any unpublished studies. Based on the initial criteria, 102 articles relevant to the topic of the review were chosen. Of these, 32 articles on effectiveness were selected. Two additional meta-analyses and several studies conducted in less developed countries were also included for discussion. The primary reasons that articles were excluded were that articles did not clearly present loss to follow-up or that the methods used to indicate treatment and determine cure and failure were not adequately described. The authors included 38 articles that described looking for complications, only 19 of which reported an actual complication occuring. These studies are discussed in the section on safety. Forty-five articles that described side effects were selected for the discussion of acceptability. Of these, only 13 used an active follow-up method. The discussion emphasizes articles that used active methods to follow women posttreatment.

Figure A. Article Selection Process



III. Effectiveness: Cure Rates

Effectiveness Summary Points

- Cure rates after one treatment generally are between 86 percent and 95 percent.
- Cure rates typically are lower for patients with more severe lesions (CIN 3 or high-grade squamous intraepithelial lesions [HSIL]) and/or lesions that cover 75 percent or more of the cervix.
- Cryotherapy generally is less effective on lesions that extend into the endocervical canal.
- Studies show minimal difference between cure rates using single or double freezes.
- In general, cryotherapy has cure rates comparable to those of other treatments; for treating CIN 3 and/or lesions covering 75 percent or more of the cervix, however, cryotherapy generally is less effective than laser ablation.
- The majority of treatment failures are detectable at one year.

This section summarizes the results from the 32 selected studies on effectiveness, which included 7 randomized controlled trials and 25 follow-up studies. At the end of this section, the data on other important factors that may influence cure rates, such as lesion size, endocervical canal involvement, number of freeze-thaw cycles (single versus double freeze), type of refrigerant, patient age, and parity are also presented.

A. Description of Selected Studies

1. Follow-up duration and loss to follow-up

Tables 1 and 2 summarize background information for the effectiveness studies on sample size, length of follow-up, and percent of women lost to follow-up. Approximately half of the studies presented cure rates that were calculated at one or more specified endpoints (e.g., 12 months, 24 months). The remaining studies did not present cure rates at a given endpoint, but provided a mean and/or range of the number of months that patients were followed.

Eight of 13 studies that followed patients for more than 12 months found that 50 to 80 percent of failures were detected within the first year; between 75 to 95 percent of failures were detected in the first two years. We compared cure rates at 12 months of follow-up when available to maintain consistency and clarity in this review. Because the studies differed in the endpoints they selected, there is some variation in the time at which the studies calculated cure rates; cure rates recorded at shorter or longer time periods are noted in the tables and text.

Table 1. Sample Size, Length of Study, and Loss to Follow-Up: Randomized Trials Comparing Treatment Therapies

	Number of women treated		*Length of time when cure rate calculated (in months)*[1]		*Number lost to follow-up (%)*[2]	
Study	**Cryotherapy**	**Laser or other technique(s)**	**Cryotherapy**	**Laser or other technique(s)**	**Cryotherapy**	**Laser or other technique(s)**
Berget et al., 1991	101	103	Mean: 50 Range: 12–75	Mean: 50 Range: 12–80	2 (2.0)	5 (4.9)
Ferenczy, 1985	155	155	Endpoint: 12	Endpoint: 12	8 (5.2)	8 (5.2)
Guijon et al., 1993	276	160	Range: 12–48	Range: 12–48	0	0
Kwikkel et al., 1985	52	53	Endpoint: 18	Endpoint: 18	2 (3.9)	2 (3.8)
Singh et al., 1988	68	92*	Range: 3–48†	Range: 3–48†	1 (1.5)	2 (2.2)*
Townsend and Richart, 1983	100	100	Range: 12 or more	Range: 12 or more	0	0
Yliskoski et al., 1989	38	54	Mean: 14.8 SD: 5.8	Mean: 13.8 SD: 5.8	1 (2.4)	1 (1.8)

* cold coagulation
† 81% of women followed 12 or more months

Table 2. Sample Size, Length of Study, and Loss to Follow-Up: Observational Follow-Up Studies

	Number of women treated	*Length of time when cure rate calculated (in months, unless otherwise noted)*	*Number lost to follow-up (%)*
Andersen and Husth, 1992	315	Mean: 84 Range: 60 or more	54 (17.1) at 60 mo
Andersen et al., 1988	197	Endpoint: 12	0 at 12 mo
Benedet et al., 1992	962	Endpoint: 12	56 (5.8) at 12 mo
Benedet et al., 1987	1675	Endpoint: 12 and 60	81 (4.8) at 12 mo 118 (14.0) at 60 mo
Bloch and Davies, 1980	111	Range: 1.5 to 2	0 at 1.5 to 2 mo
Coney et al., 1983	251	Mean: 30 Range: 3–130	11 (4.6) at 3 mo
Creasman et al., 1973	75	Range: 1.5 to 3	0 at 1.5–3 mo
Draeby-Kristiansen et al., 1991	96	Endpoints: 1, 2, 3, 4, 7 and 10 yrs	2 (2.1) at 1 yr 3 (3.1) at 2 yrs 4 (4.2) at 4 yrs 9 (9.4) at 7 yrs 12 (12.5) at 10 yrs

	Number of women treated	*Length of time when cure rate calculated (in months, unless otherwise noted)*	*Number lost to follow-up (%)*
Einerth, 1988	117	Endpoints: 2, 4, 8 yrs	0 up to 4 yrs 1 (1.0) at 8 yrs
Fray and Sims, 1982	154	Range: 12 or more*	0
Gondos and Ostergard, 1973	16	Endpoint: 11	0
Hellberg and Nilsson, 1990	104	Mean: 124, SD 3.9 Range: 6–240	0
Hemmingsson et al., 1981	181	Not given (5+ yrs)	11 (6.1) at 60 mo
Hemmingsson and Stenson, 1983	105	Range: 3–5 yrs	0
Javaheri et al., 1981	315	Range: 12–60	43 (13.7)
Kaufman and Irwin, 1978	433	Range: 2–96†	43 (9.9)
Loizzi et al., 1992	153	Range: 12–60	22 (16.8)
Nielsen and Stakemann, 1973	11	Mean: 6.5 wks Range: 4–10 wks	0
Olatunbosun et al., 1992	73	Endpoint: 12, 24, 36	3 (4.1) at 12 mo 8 (11.0) at 24 mo 12 (16.4) at 36 mo
Rojas et al., 1993	60	Endpoint: 3	0
Schantz and Thormann, 1984	142	Mean: 27 Range: 24–42	0
Sedlis et al., 1981	221	Range: 60 or more	43 (19.5)
Tangtrakul et al., 1983	35	Range: 12–24	5 (14.3)
Tredway et al., 1972	118	Mean: 6	0
Walton et al., 1980	152	Mean: 23.5 Range: 2–110	14 (9.2)
TOTAL	6072	6.5 weeks–124 mo (6 weeks–20 yrs)	388–425 (0.0–19.5)

* 36% of women followed 12 months, 44 % followed 13–18 months, 20 % followed 19+ months
† 28% of women followed 2–6 months, 16 % followed 7–12 months , 20 % followed 13–24 months, 22 % followed 25–48 months , 14 % followed > 48 months

1 The "Length of time when cure rate calculated" column corresponds to the endpoints at which authors calculated cure rates. When a specific endpoint was not given, the mean, standard deviation, and/or range of follow-up is presented.

2 The numbers in the "Number lost to follow-up" column correspond to the point in time when cure rates were calculated; in some instances, they cover the entire study duration.

The seven randomized trials reported between 0 and 5 percent of patients lost to follow-up. The 25 follow-up studies, some of which tracked loss to follow-up over a 5- or 10-year period, tended to have higher loss to follow-up rates that ranged from 0 to 19.5 percent (Table 1).

2. Indication for treatment and follow-up protocols

Most studies in this review used the highest diagnostic standards to indicate treatment and determine cure and failure. The majority of the studies visually (using colposcopy) or histologically determined whether the lesion had endocervical canal involvement; eight studies gave no indication of whether endocervical canal involvement had been assessed, however. All but three used histology to verify a treatment failure; the three that did not specify using histology (Draeby-Kristiansen et al., 1991; Javaheri et al., 1981; Kwikkel et al., 1985) either used two consecutive abnormal cytologies or abnormal cytology coupled with colposcopy to determine a treatment failure. Patients typically were followed up with conventional cytology and/or colposcopy three months after treatment and then at three- to six-month intervals thereafter. Histology was typically used when indicated by abnormal cytology or colposcopy exam. Most studies continued to follow women through at least four to five exams after treatment. Four studies (Bloch and Davies, 1980; Creasman et al., 1973; Nielsen and Stakemann, 1973; Rojas et al., 1993) performed hysterectomy or conization within three months after treatment. A few studies routinely performed endocervical curettage on women as part of the posttreatment follow-up exam as well.

3. Type of refrigerant

Of the 28 studies that provided information on the type of refrigerant used for the cryotherapy procedure, 18 used nitrous oxide, 2 studies (Sedlis et al., 1981; Bloch and Davies, 1980) used carbon dioxide, 3 studies used either carbon dioxide or a different refrigerant such as freon, liquid nitrogen, or another refrigerant, and 5 studies used freon, liquid nitrogen, or several other refrigerants.

B. Cure Rates by Grade of CIN

Common cytology terminology used to classify precancerous cervical lesions

There are two formal classification systems used for cytological identification of precancerous cervical conditions. In the cervical intraepithelial neoplasia (CIN) system, mild cervical dysplasia is referred to as CIN 1, moderate dysplasia as CIN 2, and severe dysplasia as CIN 3. Carcinoma *in situ* (CIS) is commonly included in the CIN 3 category; early studies often categorized CIS separately. The Bethesda Classification System includes atypical squamous cells of undetermined significance (ASCUS); low-grade squamous intraepithelial lesions (LSIL), which include CIN 1; and high-grade squamous intraepithelial lesions (HSIL), which include CIN 2 and CIN 3. (Herdman and Sherris, 2000)

1. Randomized controlled trials

Table 3 presents the cure rates after one cryotherapy treatment at 12 months posttreatment or the nearest time range. To calculate a summary statistic, the number of women cured and the number of women treated were combined across all studies to determine the numerator and denominator of the overall average.[3] While the summary statistics help simplify and summarize the data, readers should be aware that the studies may be substantially heterogeneous, and therefore the range of results from the selected studies may be more informative than the summary statistics.

The results from the seven randomized controlled trials (RCTs) show that the cure rates after one treatment with cryotherapy are approximately 90 percent. The cure rates generally decrease with higher grades of CIN. The RCTs offer comparisons between cryotherapy and laser ablation. The effectiveness of cryotherapy appears comparable to treatment with laser ablation, except when treating more severe lesions.

Cryotherapy cure rates by grade of CIN appeared relatively consistent across the seven RCTs, ranging between 86.0 and 94.6 percent for all grades, 90.9 to 100.0 percent for CIN 1 lesions, 75.0 to 95.9 percent for CIN 2 lesions, and 71.0 to 91.7 percent for CIN 3 grade lesions.

For CIN 1, the summary statistic for cure rates was 87.5 ± 5.1 percent for cryotherapy and 84.7 ± 5.9 percent for laser ablation treatment. For CIN 2, the summary statistic was 87.9 ± 4.5 for cryotherapy, and 87.9 ± 4.8 for laser ablation. For CIN 3, the summary statistic was 84.1 ± 6.1 for cryotherapy, and 88.6 ± 5.6 for laser ablation. Treatment with laser ablation appears to have marginally better cure rates for severe lesions.

The exceptions to the cure rates were two articles by Singh et al. (1988) and Yliskoski et al. (1989). In Singh et al., the cure rate after cryotherapy was 79.1 percent for all lesions, 86.7 percent for CIN 1 lesions, 64.7 percent for CIN 2 lesions, and 80.0 percent for CIN 3 lesions. In Yliskoski et al., the cure rate after cryotherapy was 56.8 percent for all lesions, 53.6 percent for CIN 1, and 66.7 percent for CIN 2. The small numbers of women treated in these two trials—Yliskoski et al.'s study had a total sample size for cryotherapy treatment of 37 women—may contribute to these results. Other factors may be present, however, since several randomized trials with very small sample sizes obtained more favorable results. One such factor may be the study's use of a very strict definition of cure: any indication of HPV disease in Pap smear, colposcopy, or punch biopsy following treatment for the lesion constituted a treatment failure.

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3 The normal approximation to the binomial distribution was used to calculate the standard deviations and 95 percent confidence intervals. This assumes the data are normally distributed, which they may not be. Also, techniques used in a meta-analysis involve a statistical test for homogeneity and then weighting of data from homogeneous studies according to their variances. Since these steps were not taken, the reader should use caution in drawing conclusions based on this type of summary statistic.

Table 3. Initial Cure Rates: Randomized Trials Comparing Treatment Therapies

Study	Months follow-up when cure rate calculated	*Cure rates of cryotherapy by CIN grade (%)*				*Cure rates of other techniques by CIN grade (%)*				
		All	CIN 1	CIN 2	CIN 3	Technique	All	CIN 1	CIN 2	CIN 3
Ferenczy, 1985	12	91.2 n=147	97.0 n=67	95.9 n=49	71.0* n=31	Laser	95.9 n=147	97.0 n=67	95.9 n=49	93.6* n=31
Kwikkel et al., 1985	18	86.0 n=50	100.0 n=14	75.0 n=24	91.7 n=12	Laser	70.6 n=51	60.0 n=15	70.0 n=20	81.3 n=16
Berget et al., 1991	Mean 50 Range: 12–80	90.0 n=99	90.9 n=11	90.9 n=66	86.4 n=22	Laser	87.8 n=98	88.9 n=9	86.4 n=66	91.3 n=23
Guijon et al., 1993	12–48	94.6 n=276	Not given	Not given	Not given	Laser	91.9 n=160	Not given	Not given	Not given
Singh et al., 1988	3–48	79.1 n=67	86.7 n=30	64.7 n=17	80.0 n=20	Cold coagulation	84.4 n=90	88.4 n=43	84.2 n=19	78.6 n=28
Townsend and Richart, 1983	12+	93.0 n=100	100.0 n=10	94.6 n=37	90.6 n=53	Laser	89.0 n=100	90.0 n=10	91.9 n=37	86.8 n=53
Yliskoski et al., 1989	Mean 14–15	56.8 n=37	53.6 n=28	66.7 n=6		Laser	71.7 n=53	72.1 n=43	77.8 n=9	
Summary statistic (95% confidence interval) and total†		89.5 (87.3–91.7) n=776	87.5 (82.4–92.6) n=160	87.9 (83.4–92.4) n=199	84.1 (78.0–90.2) n=138	Laser	88.2 (85.6–90.8) n=609	84.7 (78.8–90.6) n=144	87.9 (83.1–92.7) n=181	88.6 (83.0–94.2) n=123

* CIN 3 patients responded comparatively better to laser than cryotherapy, but this observation was confounded by lesion size (15% of CIN 1–2 and 84% of CIN 3 lesions were larger than 30 mm).

† See page 17 for an explanation of how summary statistics and 95% CIs were calculated.

Table 4. Initial Cure Rates: Observational Follow-Up Studies That Calculate Cure Rate at a Specified Endpoint in Time

Study	Point in time when calculated (month)	*Cure rates by lesion grade (%)*				
		All	CIN 1	CIN 2	CIN 3	CIS
Rojas et al., 1993	3	71.7 n=60			71.7 n=60	
Gondos and Ostergard, 1973	11	93.8 n=16			88.9 n=9	100.0 n=7
Andersen et al., 1988	12	86.8 n=197		92.7 n=123	77.0 n=74	
Benedet et al., 1992	12	88.4 n=906	92.9 n=156	88.0 n=275	88.8 n=303	84.3 n=172

Study	Point in time when calculated (month)	*Cure rates by lesion grade (%)*				
		All	**CIN 1**	**CIN 2**	**CIN 3**	**CIS**
Benedet et al., 1987	12	95.2 n=1594	95.1 n=143	95.7 n=448	94.5 n=529	92.4 n=474
	60	89.4 n=725	88.2 n=51	89.8 n=177	91.0 n=211	88.1 n=286
Draeby-Kristiansen et al., 1991	12	93.6 n=94		93.6* n=94		
	24	93.6 n=93		93.6 n=93		
	36	92.4 n=92		92.4 n=92		
	48	92.2 n=90		92.2 n=90		
	84	90.8 n=87		90.8 n=87		
	120	90.5 n=84		90.5 n=84		
Einerth, 1988	12	93.2 n=117	100.0 n=38	95.0 n=20	88.1 n=59	
	24	93.2 n=117	100.0 n=38	95.0 n=20	88.1 n=59	
	48	92.2 n=116	Not given	Not given	Not given	
	96	90.1 n=101	Not given	Not given	Not given	
Javaheri et al., 1981	12	92.3 n=272†	95.9 n=73	93.3 n=149	83.8 n=37	84.6 n=13
Olatunbosun et al., 1992	12	88.6 n=70	83.3 n=12	96.9 n=32	80.8 n=26	
	24	84.6 n=65	Not given	Not given	Not given	
	36	82.0 n=61	Not given	Not given	Not given	
Summary statistic (95% confidence intervals) and total at 12 months		91.9 (91.0–92.8) n=3326	94.5 (92.3–96.7) n=422	93.0 (91.5–94.5) n=1047	89.4 (87.6–91.2) n=1050	90.2 (87.9–92.5) n=666

* Shaded areas indicate where data were not available for each column. Original authors provided data combining more than one category; shading reflects categories covered by combined data.

† Assumed that all 43 patients that were lost to follow-up were lost within 12 months.

Table 5. Initial Cure Rates: Observational Follow-up Studies That Calculate Cure Rate Over a Range of Time

Study	Mean and/or range of time when calculated	*Cure rates by lesion grade (%)* All	CIN 1	CIN 2	CIN 3	CIS
Nielsen and Stakemann, 1973	Range: 4–10 weeks	18.2 n=11				18.2 n=11
Bloch and Davies, 1980	Range: 6-8 weeks	2.7† n=111			0.0† n=42	4.4† n=69
Creasman et al., 1973	Range: 6 weeks– 3 months	74.7 n=75			74.7* n=75	
Tredway et al., 1972	Mean: 6 months	81.4 n=118	86.7 n=30	92.3 n=39	69.4* n=49	
Kaufman and Irwin, 1978	Range: 2–96 months	87.4 n=390	Not given	Not given	Not given	Not given
Fray and Sims, 1982	Range: 12+ months	78.6 n=154	87.5* n=112		54.8 n=42	
Tangtrakul et al., 1983	Range: 12–24 months	83.3 n=30	88.9 n=9	85.7 n=7	83.3 n=12	50.0 n=2
Loizzi et al., 1992	Range: 12–60 months	90.1 n=131	Not given	Not given	Not given	
Walton et al., 1980	Mean: 23.5 months Range: 2-110 months	92.0 n=138		96.8 n=62	87.8 n=76	
Schantz and Thormann, 1984	Mean: 27 Range: 24-42 months	89.4 n=142	96.6 n=58	84.5 n=84		
Coney et al., 1983	Mean: 30 Range: 3-130 months	89.2 n=240	89.2 n=240			
Hemmingsson and Stenson, 1983	Range: 36-60 months	87.6 n=105		90.7* n=43		85.5 n=62
Hemmingsson et al., 1981	Range: 60+ months	83.5 n=170		90.0* n=40		81.5 n=130
Sedlis et al., 1981	Range: 60+ months	89.9 n=178	89.9* n=178			
Andersen and Husth, 1992	Mean: 84 months Range: 60+ months	83.5 n=261	94.4 n=18	87.5 n=152	74.7‡ n=91	
Hellberg and Nilsson, 1990	Mean: 124 months Range: 6-240 months	86.5 n=104	Not given n=2	Not given n=15	Not given n=87	
Summary statistic (95 % confidence intervals) and total		82.8 (81.4–84.2) n=2690	91.4 (88.7–94.1) n=428	90.3 (87.7–92.9) n=493	67.2 (62.4–72.0) n=360	61.3 (55.7–66.9) n=287

* Shaded areas indicate where data were not available for each column. Original researchers provided data combining more than one category; shading reflects categories covered by combined data.

† This table does not include the 24% of CIN 3 patients that improved to CIN 1 and 30% of CIS patients that improved to CIN 1 or CIN 2

‡ Statistically significantly lower than CIN 1 or CIN 2.

2. Observational follow-up studies

Of the 25 follow-up studies selected for this review, 9 presented cure rates at a specific point in time (Table 4). All but two of these 9 studies presented results at 12 months of follow up.[4] Overall cure rates were reported to be between 71.7 percent and 95.2 percent. As seen with the randomized trials, the data from the follow-up studies suggest that effectiveness of cryotherapy decreases with the increase in the grade of CIN.

Sixteen of the 25 follow-up studies did not provide cure rates specifically at an endpoint, but rather reported cure rates that were calculated during a range of months of follow-up (Table 5). Twelve of the 16 studies reported following the women for a range of months that included 12 months. In these studies, the cure rates appear consistent with other studies included in this review. Three follow-up studies (Creasman et al., 1973; Bloch and Davies, 1980; Nielsen and Stakemann, 1973), followed women for three months or less and reported highly varying cure rates.

Because the studies varied in the methods used to conduct follow-up assessment, some variation in the definition of cure and failure was observed, and may account for the variation in cure rates. In, four of the follow-up studies (Nielsen and Stakemann, 1973; Bloch and Davies, 1980; Creasman et al., 1973; and Rojas et al., 1993), the cure rates were evaluated with histology of a cervical specimen obtained either through conization or hysterectomy within three months of cryotherapy treatment.

- Nielsen and Stakemann reported an overall cure rate of 18.2 percent among 11 women with CIS who were treated with cryotherapy and assessed 4 to 10 weeks later.
- In Bloch and Davies' 1980 study, 111 women, all of whom had CIN 3 or CIS, had a histologic specimen examined 6 to 8 weeks later. Improvement was noted in 29 percent, but only 2.7 percent had no residual disease.
- Creasman et al.'s study of 75 women with CIN 3/CIS reported an overall cure rate of 74.7 percent evaluated between 6 weeks and 3 months after treatment.
- Rojas et al. achieved a 71.7 percent cure rate at 3 months among 60 women treated with cryotherapy for CIN 3.

What this means in terms of these studies' validity and comparability to the studies that evaluated cure at one year is unclear as the ability to accurately assess cure may well be dependent on the physiology of the healing cervix.

C. Study Characteristics That Influence Cryotherapy Effectiveness

The literature indicates that numerous factors other than the grade of the lesion can influence the effectiveness of cryotherapy. Larger lesions and lesions that extend into the endocervical canal have been cited as more difficult to treat successfully with cryotherapy. Similarly, some studies have examined variations in treatment techniques that are thought to produce higher cure rates. Patient

4 Gondos and Ostergard (1973) reported results for 16 women at 11 months of follow-up, with an overall cure rate of 93.8 percent. This result appears comparable to studies with 12 months of follow up. Rojas et al. (1993) reported results for 60 women with CIN 3 who underwent conization three months after cryotherapy treatment. Overall cure rate was 71.7 percent.

characteristics such as age or parity may make a woman a better candidate for successful treatment with cryotherapy.

Overall, few studies included in this review set out to examine all potential influences on treatment. As a result, it is difficult to determine if characteristics of the lesion or the patient are independently associated with cure rates. The following section summarizes the information available on these variables from the pertinent studies.

1. Lesion characteristics

Lesion size

Although differences in cure rates were consistently found by lesion grade, some researchers have argued that treatment success is related more directly to lesion size than lesion grade. Three randomized trials in this review analyzed the effect of lesion size on cure rates and reported lower cure rates for larger lesions (Table 6). Trials by Townsend and Richart (1983) and Kwikkel et al. (1985) categorized lesions into three sizes: lesions that covered less than 25 percent of the surface of the ectocervix, lesions that covered 25 to 75 percent, and lesions that covered greater than 75 percent of the ectocervix. Lesion size was based on colposcopy prior to treatment (Townsend and Richart) or determined retrospectively using colpo-photographs and colpo-drawings (Kwikkel et al.). For these three categories (from smallest lesion size to largest), Townsend and Richart reported cryotherapy cure rates of 95.1 percent (41 women), 92.9 percent (42 women), and 11.8 percent (17 women). Kwikkel et al. reported cryotherapy cure rates (from smallest lesion size to largest) of 96.8 (31 women), 75 (16 women) and 33.3 percent (3 women).

The trial conducted by Ferenczy (1985) used a different classification system, stratifying patients prior to treatment randomization into a group of 121 women with small lesions (less than 30 mm) and 26 women with large lesions (greater than 30 mm). Cryotherapy results at 12 months posttreatment showed a statistically significant difference in cure rates reported by lesion size. The cure rate for the group with smaller lesions was 95 percent compared to a 61.5 percent cure rate for large lesions.

These three studies allow comparisons of the treatment effectiveness of cryotherapy versus laser ablation for large and small lesions. Ferenczy (1985) reported a cure rate after laser ablation of 92.3 percent for large lesions, compared to the 61.5 percent cure rate achieved from cryotherapy for similarly large lesions. Townsend and Richart (1983) reported a laser ablation cure rate of 78.6 percent for large lesions, compared to the 11.8 percent cure rate with cryotherapy. In contrast, Kwikkel et al. (1985) found treatment with laser ablation had poor cure rates for curing large lesions, although the authors noted that laser treatment patients also tended to have larger lesions compared to the lesion size of cryotherapy patients. In this study, the cure rate for the smallest lesion category (covering less than 25 percent of ectocervix) was 93.1 percent (n=29) for laser ablation and 96.8 percent (n=31) for cryotherapy; for the larger lesions (covering 25 to 75 percent of the ectocervix) the cure rate was 58.3 percent (n=12) for laser ablation and 75.0 percent (n=16) for cryotherapy; for lesions covering 75 percent or more of the ectocervix the cure rate was 20.0 percent (n=10) for laser ablation and 33.3 percent (n=3) for cryotherapy.

Table 6. Initial Cure Rates by Lesion Size: Randomized Trials Comparing Treatment Therapies

	Cryotherapy			*Other techniques*			
Study	**Lesion covers ≤ 25% ectocervix surface area**	**Lesion covers 25–75% ectocervix surface area**	**Lesion covers ≥ 75% ectocervix surface area**	**Technique**	**Lesion covers ≤ 25% ectocervix surface area**	**Lesion covers 25–75% ectocervix surface area**	**Lesion covers ≥ 75% ectocervix surface area**
Ferenczy, 1985	95.0* n=121	None	61.5†‡ n=26	Laser	95.9* n=121	None	92.3† n=26
Kwikkel et al., 1985	96.8§ n=31	75.0 n=16	33.3 n=3	Laser	93.1§ n=29	58.3 n=12	20.0 n=10
Townsend and Richart, 1983	95.1 n=41	92.9 n=42	11.8 n=17	Laser	91.5 n=47	89.7 n=39	78.6 n=14
Summary statistic (95% confidence interval) and total number treated	95.3 (92.3–98.3) n=193	88.0 (79.6–96.4) n=58	41.3 (27.1–55.5) n=46		94.4 (91.2–97.6) n=197	82.3 (71.8–92.8) n=51	74.0 (61.8–86.2) n=50

* Lesion is smaller than 30 mm.
† Lesion is larger than 30 mm.
‡ Statistically significant difference between cryotherapy and laser therapy cure rates for lesions larger than 30 mm.
§ Statistically significant difference between cure rates for small lesions versus other lesions ($P < 0.01$).

In summary, the data from these three studies suggest that both cryotherapy and laser ablation are less effective at curing large lesions in comparison to smaller lesions. Furthermore, for the largest lesions, the cure rates following cryotherapy are much lower than cure rates after laser ablation. None of the 25 follow-up studies included in this review reported cure rates by differing lesion size, although Benedet et al. (1992) remarked on the tendency for the success rate to decrease slightly as lesions increased in size.

Endocervical canal involvement

Clinicians have hypothesized that cryotherapy may be an inappropriate treatment option for women with lesions that extend into the endocervical canal. This review sought evidence on the relationship between endocervical canal involvement and success of cryotherapy (Tables 7 and 8). The majority of studies selected, however, excluded women who had lesions that extended into the canal (visualized colposcopically or histologically determined by endocervical curettage [ECC]). Eight studies did not provide any data on endocervical canal involvement. Two of the randomized trials (Ferenczy, 1985; Kwikkel et al., 1985) allowed women with either positive or negative endocervical canal involvement to be treated with cryotherapy. In Ferenczy's 1985 study, results showed patients who were ECC positive had a lower cure rate following cryotherapy than those who were ECC negative. In addition, ECC-positive women treated with laser ablation had higher cure rates as compared to the ECC-positive patients treated with cryotherapy. The study by Kwikkel et al. (1985) found that ECC-positive patients had higher cure rates than ECC-negative patients, but the authors suggested that positive endocervical curettage with normal colposcopy often indicated ectocervical fragments had been inadvertently taken during curettage. Two follow-up studies conducted by Andersen and Husth (1992) and Andersen et al. (1988) reported that women with CIN 2 or CIN 3 and positive ECC results had statistically significantly lower cure rates than women with negative ECC results.

In summary, the summary statistics presented in Tables 7 and 8 show that when patients are ECC negative, the cure rate is similar for cryotherapy and other techniques, but in women who are ECC positive, the cure rate is lower for cryotherapy in comparison to other techniques.

2. Cryotherapy technique

Variation in how the cryotherapy procedure was conducted also may contribute to differences in cure rates across studies. The studies included in this review did not provide enough evidence to draw valid conclusions on the effect that characteristics such as the length of freeze (single versus double freeze), type of refrigerant used, and probe type have on the treatment outcome. Nevertheless, the available information is presented below.

Single- or double-freeze technique

As presented in Table 9, the summary statistics for cure rates from single- versus double-freeze randomized trials were 91.9 ± 3.4 percent and 88.3 ± 2.7 percent. The difference in the summary statistics is not statistically significant ($p < 0.05$). In addition, the absolute difference is relatively small. The summary statistics from follow-up studies showed no statistical significance between single- and double-freeze cure rates (88.0 ± 1.2 percent versus 87.3 ± 1.5 percent) (Table 10).

Among the follow-up studies reviewed, two studies (Rojas et al., 1993; Schantz and Thormann, 1984) randomized women to receive either a single or double freeze. Both studies found the double freeze produced higher cure rates than a single freeze.

- Rojas et al. treated 26 women with CIN 3 using a three-minute single freeze, and 34 women with CIN 3 using a double freeze of three minutes each with a three-minute thaw in between. At three months posttreatment when a conization was performed on all women, the cure rate for cryotherapy from the single freeze was reported to be 61.5 percent compared to 79.4 percent cured by the double freeze.
- Schantz and Thormann used a single freeze of one to three minutes to treat 23 women with CIN 1 and 38 women with CIN 2. They used a double freeze of one to three minutes each separated by a four-minute thaw to treat 35 women with CIN 1 and 46 women with CIN 2. After an average of 27 months of follow-up, the cure rate for CIN 1 was 95.7 percent and 97.1 percent for single versus double freeze, respectively. The cure rate for CIN 2 was 76.3 percent and 91.3 percent for single versus double freeze, respectively (see Table 10).

The majority of the observational follow-up studies did not randomize women to receive either a single or double freeze. Comparing the observational follow-up studies that used a single freeze to studies that used a double freeze does not clarify, however, whether there is a significant difference (and of what magnitude) between the two approaches; it would be beneficial to pool the data and perform a meta-analysis.

Refrigerant

Few studies included in this review used a refrigerant other than nitrous oxide. Several studies used refrigerants that are not commonly being used in cryotherapy today, such as freon or liquid nitrogen. As a result, the cure rates among the small number of studies that use nitrous oxide, carbon dioxide, freon, or liquid nitrogen can not be compared.

3. Population characteristics

Certain characteristics in the patient population selected for cryotherapy also may influence the effectiveness of the treatment. As previously mentioned, there was insufficient data in the selected studies to determine whether patient attributes such as age and parity affected the treatment outcome. The limited data reviewed, however, is presented below.

Age

Four studies presented results stratified by age group. One randomized trial and two follow-up studies (Kwikkel et al., 1985; Andersen and Husth, 1992; Hemmingsson et al., 1981) compared cure rates for women divided into categories of roughly 30 years of age and younger or older than 30 years of age. The effect of age on treatment outcome is difficult to infer from these studies, however. These studies reported a trend towards slightly lower cure rates in women over 30 years old. In contrast, results from Guijon et al. (1993) suggest that older women were less likely to fail therapy, although the difference was not statistically significant. The mean age of women in Guijon et al. who failed treatment with cryotherapy or laser ablation combined was 24.1 years (17 to 33), while the mean age of the cohort successfully treated was 25.7 (14 to 55) (p=.074).

Table 7. Initial Cure Rates by Endocervical Canal Involvement: Randomized Trials Comparing Treatment Therapies

	Cryotherapy (%)		*Other techniques (%)*		
Study	**ECC negative***	**ECC positive***	**Technique**	**ECC negative***	**ECC positive***
Berget et al., 1991	89.9 n=99	None	Laser	88.7 n=97	None
Ferenczy, 1985	82.2† n=129	50.0‡ n=18	Laser	90.7 † n=129	88.9‡ n=18
Guijon et al., 1993	94.6† n=276	None	Laser	91.9 n=160	None
Kwikkel et al., 1985	83.9 n=31	89.5 n=19	Laser	70.3 n=37	71.4 n=14
Singh et al., 1988	79.1 n=67	None	Cold coagulation	84.4 n=90	None
Townsend and Richart, 1983	86.0 n=100	None	Laser	89.0 n=100	None
Yliskoski et al., 1989	56.8† n=37	None	Laser	71.7† n=53	None
Summary statistic (95% confidence intervals), and total number treated	86.9 (84.5–89.3) n=739	70.3 (55.6–85.0) n=37	Laser	87.3 (84.6–90.0) n=576	81.2 (67.7–94.7) n=32

* Based on curettage prior to treatment.
† Based on colposcopic or histological diagnosis.
‡ Based on colposcopic diagnosis < 5 mm in endocervical canal.

Table 8. Initial Cure Rates by Endocervical Canal Involvement: Observational Follow-Up Studies

	ECC negative					*ECC positive*				
Study	**Total**	**CIN 1**	**CIN 2**	**CIN 3**	**CIS**	**Total**	**CIN 1**	**CIN 2**	**CIN 3**	**How determined**
Andersen and Husth, 1992	86.3* n=197	92.9 n=14	91.0* n=111	77.8* n=72		75.0* n=64	100.0 n=4	78.0* n=41	63.2* n=19	Curettage
Andersen et al., 1988	89.6* n=135		94.9* n=78	82.5* n=57		80.7* n=62		88.9* n=45	58.8* n=17	Curettage
Benedet et al., 1987	95.2 n=1594	95.1 n=143	95.7 n=448	94.5 n=529	92.4 n=474	None				Colposcopy

	ECC negative					*ECC positive*				
Study	**Total**	**CIN 1**	**CIN 2**	**CIN 3**	**CIS**	**Total**	**CIN 1**	**CIN 2**	**CIN 3**	**How determined**
Coney et al., 1983	88.8 n=231	88.8 n=231				100.0 n=9				Colposcopy or curettage
Draeby-Kristiansen et al., 1991	93.6 n=94		93.6† n=94			None				Colposcopy & curettage
Einerth, 1988	93.2 n=117	100.0 n=38	95.0 n=20	88.1 n=59		None				Colposcopy‡
Gondos and Ostergard, 1973	93.8 n=16			88.9 n=9	100.0 n=7	None				Colposcopy & curettage
Hellberg and Nilsson, 1990	86.5 n=104	Not given n=2	Not given n=15	Not given n=87		None				Curettage
Javaheri et al., 1981	92.3 n=272	95.9 n=73	93.3 n=149	83.8 n=37	84.6 n=13	None				Curettage or colposcopy
Kaufman and Irwin, 1978	94.1 n=238					79.2 n=48				Curettage
Loizzi et al., 1992	90.1 n=131					None				Colposcopy and curettage
Olatunbosun et al., 1992	88.6 n=70	83.3 n=12	96.9 n=32	80.8 n=26		None				Curettage
Rojas et al., 1993	91.9 n=37					None				Curettage
Schantz and Thormann, 1984	89.4 n=142	96.6 n=58	84.5 n=84			None				Not given
Sedlis et al., 1981	89.9 n=178	89.9† n=178				None				Curettage
Tredway et al., 1972	81.4 n=118	86.7 n=30	92.3 n=39	69.4† n=49		None				Curettage
Walton et al., 1980	92.0 n=138		96.8 n=62	87.8 n=76		None				Colposcopy or curettage
Summary statistic (95% confidence interval) and total	92.2 (91.3–93.1) n=3812	92.5 (90.4–94.6) n=599	93.8 (92.3–95.3) n=1023	90.4 (88.4–92.4) n=865	92.3 (89.9–94.7) n=494	79.3 (73.4–85.2) n=183	100.0 n=4	83.7 (75.9–91.5) n=86	61.1 (45.2–77.0) n=36	

* Statistically significant.
† Shaded areas indicate where data were not available for each column. Original researchers provided data combining more than one category; shading refelcts categories covered by combined data.
‡ Two of the eight failures were misdiagnosed ECC positive.

Table 9. Initial Cure Rates by Single and Double Freeze: Randomized Trials Comparing Therapies

	Single Freeze				*Double Freeze*			
Study	**All**	**CIN 1**	**CIN 2**	**CIN 3**	**All**	**CIN 1**	**CIN 2**	**CIN 3**
Berget et al., 1991					90.0 n=99	90.9 n=11	90.9 n=66	86.4 n=22
Ferenczy, 1985	91.2 n=147	97.0 n=67	95.9 n=49	71.0 n=31				
Guijon et al., 1993					94.6 n=276	Not given	Not given	Not given
Kwikkel et al., 1985					86.0 n=50	100.0 n=14	75.0 n=24	91.7 n=12
Singh et al., 1988					79.1 n=67	86.7 n=30	64.7 n=17	80.0 n=20
Townsend and Richart, 1983	93.0 n=100	100.0 n=10	94.6 n=37	90.6 n=53				
Yliskoski et al., 1989					56.8 n=37	53.6 n=28	66.7 n=6	
Summary statistic (95% confidence intervals) and total	91.9 (88.5–95.3) n=247	97.4 (93.8–100) n=77	95.3 (90.8–99.8) n=86	83.4 (75.4–91.4) n=84	88.3 (85.6–91.0) n=529	78.3 (69.4–87.2) n=83	82.3 (75.3–89.3) n=113	85.2 (75.7–94.7) n=54

Table 10. Initial Cure Rates by Single and Double Freeze: Observational Follow-Up Studies*

	Single Freeze					*Double Freeze*				
Study	**All**	**CIN 1**	**CIN 2**	**CIN 3**	**CIS**	**All**	**CIN 1**	**CIN 2**	**CIN 3**	**CIS**
Andersen and Husth, 1992						83.5 n=261	94.4 n=18	87.5 n=152	74.7 n=91	
Andersen et al., 1988						86.8 n=197		92.7 n=123	77.0 n=74	
Benedet et al., 1992	88.4 n=906	92.9 n=156	88.0 n=275	88.8 n=303	84.3 n=172					
Benedet et al., 1987	95.2 n=1594	95.1 n=143	95.7 n=448	94.5 n=529	92.4 n=474					
Bloch and Davies, 1980	2.7 n=111			0.0† n=42	4.4† n=69					

* When cure rates were calculated at more than one point in time, the rate calculated closest to 12 months was used. When study used more than one refrigerant and results were for both methods combined, their results were excluded from this study.

Study	*Single Freeze* All	CIN 1	CIN 2	CIN 3	CIS	*Double Freeze* All	CIN 1	CIN 2	CIN 3	CIS
Creasman et al., 1973	51.9 n=27					81.3 n=48				
Draeby-Kristiansen et al., 1991						93.6 n=94		93.6‡ n=94		
Einerth , 1988						93.2 n=117	100.0 n=38	95.0 n=20	88.1 n=59	
Fray and Sims, 1982						78.6 n=154	87.5‡ n=112		54.8 n=42	
Hellberg and Nilsson, 1990						86.5 n=104	Not given n=2	Not given n=15	Not given n=87	
Hemmingsson et al., 1981						83.5 n=170		90.0‡ n=40		81.5 n=130
Hemmingsson and Stenson, 1983						87.6 n=105		90.7‡ n=43		85.5 n=62
Javaheri et al., 1981						92.3 n=272	95.9 n=73	93.3 n=149	83.8 n=37	84.6 n=13
Loizzi et al., 1992	90.1 n=131	Not given	Not given	Not given						
Nielsen and Stakemann, 1973	18.2 n=11				18.2 n=11					
Olatunbosun et al., 1992						88.6 n=70	83.3 n=12	96.9 n=32	80.8 n=26	
Rojas et al., 1993	61.5 n=26§			61.5 n=26§		79.4 n=34§			79.4 n=34§	
Schantz and Thormann, 1984	83.6 n=61§	95.7 n=23§	76.3 n=38§			93.8 n=81§	97.1 n=35§	91.3 n=46§		
Sedlis et al., 1981						89.9 n=178	89.9‡ n=178			
Tangtrakul et al., 1983						83.3 n=30	88.9 n=9	85.7 n=7	83.3 n=12	50.0 n=2
Summary statistic (95% confidence interval) and total	88.0 (86.8–89.2) n=2867	94.1 (91.5–96.7) n=322	92.0 (90.1–93.9) n=761	87.2 (85.0–89.4) n=900	81.0 (78.1–83.9) n=726	87.3 (85.8–88.8) n=1915	95.7 (92.8–98.6) n=185	91.5 (89.1–93.9) n=529	77.1 (72.8–81.4) n=375	82.6 (77.4–87.8) n=207

† Table does not include the 24% of CIN 3 patients that improved to CIN 1 and 30% of CIS patients that improved to CIN 1 or CIN 2.
‡ Shaded areas indicate where data were not available for each column. Original researchers provided data combining more than one category; shading reflects categories covered by combined data.
§ Patients were randomly allocated to single or double freeze.

Parity and gravidity

Very little data were available in the selected studies to help assess whether characteristics such as parity or gravidity affect the success of cryotherapy. Guijon et al. (1993) found that neither the number of pregnancies (p=0.07) nor the number of live births (p=0.49) were significantly associated with treatment failures for cryotherapy or laser ablation combined. Kwikkel et al. (1985) reported a slightly higher cure rate for 11 nulliparous women (cure rate: 91 percent) versus 39 multiparous women (cure rate: 85 percent).

D. Other Considerations

1. Cure rates after repeat treatment

Several studies presented results for women for whom the first cryotherapy treatment for CIN failed and were given a second cryotherapy treatment. The results of the 113 patients who were retreated are presented in Tables 11 and 12. Cure rates after a second treatment ranged between 41.7 percent (Hemmingsson et al., 1981) and 100 percent (Anderson and Husth, 1992; Olatunbosum et al., 1992). The lower cure rate observed by Hemmingsson et al. (1981) was possibly due to the type of women selected for treatment (all women were initially referred for persistent abnormal Pap smears or had failed other treatment methods).

2. HIV infection and treatment considerations

Women infected with HIV tend to have a higher prevalence of CIN than do HIV-negative women (Abercrombie and Korn, 1998). In addition, HIV-infected women tend to have larger lesions, more advanced dysplasia, and more vulvovaginal lesions than do HIV-negative women (Abercrombie and Korn, 1998; Tate and Anderson, 2002). Dysplasias can be persistent, progressive, recurrent, and difficult to treat in women with HIV. Because CIN appears to recur with greater frequency among HIV-positive women, cure rates may be lower at 12 months than in non-HIV infected women (Abercrombie and Korn, 1998; Tate and Anderson, 2002).

E. Meta-Analyses and Other Prominent Studies

1. Meta-analyses

Two meta-analyses (Nuovo et al., 2000; Martin-Hirsch et al., 2001) have been published on randomized trials that compare cryotherapy with other treatment therapies. The main criterion for inclusion in the meta-analyses was that the trial randomly allocated patients to treatment modality. Because this review used different selection criteria for articles assessing treatment effectiveness than the meta-analyses, there were two randomized trials (Mitchell et al., 1998; Jobson and Homesley, 1984) that were included in the Nuovo et al. and Martin-Hirsch et al. meta-analyses but were not included in this review. The conclusions from both meta-analyses, however, are consistent with the conclusions drawn here. Nuovo et al. concluded that there was no statistically significant difference in cure rates at a median of 12 months (persistence or resolution) among treatment therapies (cryotherapy, laser ablation, LEEP, cone biopsy). The Martin-Hirsch et al. meta-analysis also concluded that there was no statistically significant difference in the effectiveness of cryotherapy versus laser ablation. Martin-Hirsch et al. reported a trend towards higher cure rates for CIN 3 lesions treated with laser ablation (not a statistically significant difference).

Table 11. Cure Rates After Re-Treatment of Failures: Randomized Trials Comparing Therapies

	Cure rates of failures retreated with cryotherapy by CIN grade (%)				*Cure rates of failures retreated with laser by CIN grade (%)*				
Study	**All**	**CIN 1**	**CIN 2**	**CIN 3**	**Technique**	**All**	**CIN 1**	**CIN 2**	**CIN 3**
Berget et al., 1991	75.0 n=4	0.0 n=1	100.0 n=1	100.0 n=2	Laser	62.5 n=8	100.0 n=1	60.0 n=5	50.0 n=2
Singh et al., 1988	66.7 n=12	75.0 n=4	100.0 n=5	0.0 n=3	Cold coagulation	69.2 n=13	60.0 n=5	100.0 n=3	60.0 n=5
Summary statistic (95 % confidence interval) and total	68.8 (46.1–91.5) n=16	60.0 (17.1–100) n=5	100.0 n=6	40.0 (0.0–82.9) n=5					

Table 12. Cure Rates After Re-Treatment of Failures: Observational Follow-Up Studies

	Cure rates of failures retreated with cryotherapy by CIN grade (%)			
Study	**All**	**CIN 1**	**CIN 2**	**CIN 3**
Andersen and Husth, 1992	100.0 (n=3)	Not given	Not given	Not given
Coney et al., 1983	89.5 (n=19)	89.5 (n=19)		
Draeby-Kristiansen et al., 1991	66.7 (n=9)		66.7* (n=9)	
Fray and Sims, 1982	85.7 (n=14†)	Not given	Not given	Not given
Hemmingsson et al., 1981	41.7 (n=12)	Not given	Not given	Not given
Hemmingsson and Stenson, 1983	75.0 (n=4)	Not given	Not given	Not given
Kaufman and Irwin, 1978	72.7 (n=11)	Not given	Not given	Not given
Olatunbosun et al., 1992	100.0 (n=4)	100.0 (n=2)	100.0 (n=1)	100.0 (n=1)
Schantz and Thormann, 1984	75.0 (n=8)	Not given	Not given	Not given
Sedlis et al., 1981	76.9 (n=13‡)	Not given	Not given	Not given
Summary statistic (95% confidence interval) and total	76.3 (67.8–84.8) n=97	90.5 (78.0–100) n=21	72.8* (46.5–99.1) n=11	

* Shaded areas indicate where data were not available for each column. Original researchers provided data combining more than one category; shading reflects categories covered by combined data.
† The two patients who failed the second treatment were cured after a third treatment.
‡ One patient who failed the second treatment was cured after a third treatment.

One of the two randomized trials excluded from our overview (Mitchell et al., 1998) reported comparable cure rates between cryotherapy, laser ablation, and LEEP, but used a follow-up protocol for determining a treatment failure that did not meet the selection criteria for this review. Three hundred and ninety women with CIN were randomly assigned to be treated with cryotherapy, laser ablation, or LEEP and followed for 6 to 37 months with a 16 percent loss to follow-up. At six months after treatment, 95 percent of cryotherapy, 95 percent of laser, and 97 percent of LEEP patients were cured. After six months, cure rates fell to 81 percent, 87 percent, and 87 percent, respectively (not a statistically significant difference).

The other randomized trial (Jobson and Homesley, 1984) gave results that were comparable to cure rates reported in this review; however, the trial was excluded from our discussion on treatment effectiveness because 35 percent of their patients were lost to follow-up within the first year. Jobson and Homesley randomly assigned 125 women with CIN to laser ablation or cryotherapy. At one-year posttreatment only 64.8 percent of the women were available for follow-up evaluation. The cure rates for both techniques were comparable—89.7 percent of women receiving cryotherapy and 90.5 percent of women receiving laser ablation were cured at four months. Cure rates remained constant at one year.

2. Studies conducted in less developed countries

Few studies that were selected for this review were based in developing-country settings. Four of the eight studies conducted in developing countries, including Chile, Mexico, Nigeria, South Africa, and Thailand, met our selection criteria (Rojas et al., 1993; Olatunbosun et al., 1992; Tangtrakul et al., 1983; Bloch and Davies, 1980).[5]

For the developing-country studies not included in this reveiw, cure rates varied widely from 30 to 95 percent. The authors of some of these studies hypothesized that the low cure rates may be due to glandular involvement or lack of endocervical canal evaluation. Among the studies conducted in less developed countries, all conducted cryotherapy in a hospital, colposcopy clinic, or polyclinic, and all but one used colposcopic guidance. Because the vast majority of cervical cancer cases occur in low-resource countries where colposcopy is not always available, additional developing-country studies are needed.

F. Conclusions From the Effectiveness Data

The results from this review reinforce reports based on clinical experience that cryotherapy is an effective treatment for precancerous lesions of the cervix. Data support the assumption that practitioners should recognize the limitations of cryotherapy when treating large lesions covering 75 percent or more of the cervix or lesions with endocervical canal involvement, and may need to refer women with such lesions for a different form of treatment. Cryotherapy is often cited as less effective at curing CIN 3 lesions, but this is possibly due to the confounding factors of lesion size and ECC involvement. The literature also highlights the value of careful follow-up whenever possible, even when treating less severe lesions (CIN 1 and CIN 2) with cryotherapy; cure rates show that approximately 10 percent of women treated will present with a persistent lesion on follow-up examinations in the first year.

5 Bloch and Davies (1980) included an additional study in their article. Only data from the additional study was included in this review.

IV. SAFETY: COMPLICATIONS

Safety Summary Points

- Cryotherapy is a safe method of treatment with no significant morbidity or mortality risks.
- Severe bleeding (during and/or after cryotherapy treatment) requiring further medical attention or blood transfusion is a very rare occurrence.
- Development of pelvic inflammatory disease (PID) following cryotherapy is a rare occurrence in older women; practitioners should counsel women appropriately about warning symptoms.
- Local cervical infections related to the use of cryotherapy are not well documented in the literature, and appear to be infrequent.
- Women infrequently experience severe pain and/or cramping related to the cryotherapy treatment (within one month of treatment) that causes them to seek medical services.
- Long-term sequelae, such as stenosis and a negative impact on fertility and obstetrical outcomes, are not evident from the literature.

Cryotherapy is a relatively quick and simple outpatient procedure, and appears to result in relatively few complications. Nevertheless, in regions where transportation and distance may limit or delay a woman's access to medical care, any complications could become serious. This section reviews the available evidence on the safety of cryotherapy by focusing on studies that provide follow-up of patients after treatment. The data from such studies provide estimates of complication rates. Observational evidence from studies without active follow-up procedures also are provided for completeness, although results may be biased due to likely incomplete reporting.

This section reviews reports of the following complications:

- Severe bleeding during or after treatment requiring further treatment or transfusion.
- PID.
- Local cervical infections.
- Other complications indicated by severe pain following treatment.
- Unintended major surgery.[1]

For purposes of this review, reports of these conditions that occurred within one month of treatment were assumed to be a complication of cryotherapy. When the conditions were reported as

1 Though there were no reports of unintended major surgeries in the selected articles, one case report described a woman who suffered a cervical amputation after becoming startled and pulling away from the cryotherapy unit (Levin, 1975).

occurring more than one month after treatment, it was less likely that the effects were attributable to cryotherapy or other treatment. In this review, we have noted when the timing is ambiguous.

Of the 102 articles on cryotherapy eligible for this review, 38 articles noted whether or not complications occurred. Nineteen articles recorded complications that the providers attributed to the cryotherapy treatment (see Table 13). The remaining 19 articles reported no complications. Two of the 19 studies that reported complications used active methods of patient follow-up, and the remaining 17 studies that reported complications used passive follow-up (that is, complications were recorded only when women returned to the study facility for subsequent medical care). One of the 17 studies using passive follow-up compared an HIV-infected population to a non HIV-infected population. The results from this study are analyzed separately (see page 40 for discussion of Cuthill et al., 1995) Among the 19 studies in which there were no complications reported, comparison data were sometimes available for other treatment methods. These data add to the evidence base that supports cryotherapy as a safe treatment option for women and also are presented in Table 13.

The following sections review complications by type, emphasizing the results from the two studies with active follow-up methods. Separate sections follow that review data from one article that specifically compared the rates of complications among HIV-positive women versus HIV-negative women, data on long-term sequelae of cryotherapy, and other safety considerations.

A. Severe Bleeding Posttreatment

In low-resource settings, severe bleeding following treatment can pose a major risk to a woman's health, since she may be unable to quickly access medical care and blood transfusions may not be available. This review suggests that severe bleeding requiring medical intervention is a very unlikely event following cryotherapy and occurs less often than after laser ablation treatment or LEEP.

1. Active follow-up

Between the two articles (Berget et al., 1987; Mitchell et al., 1998) that reported active follow-up of patients to assess complications, neither reported severe bleeding needing sutures, cauterization, or blood transfusion following cryotherapy treatment for CIN. In comparison data from these studies, however, between 1 percent and 5.4 percent of women treated with laser ablation or LEEP experienced severe bleeding. In each study, one woman experienced severe bleeding during or within 24 hours of treatment. In Mitchell et al. an additional 9 women presented with severe bleeding more than 24 hours posttreatment. Ferric subsulfate solution (Mitchell et al., 1998) or sutures (Berget et al., 1987) were used to control the bleeding. These data are presented in Table 13.

2. Passive follow-up

In the 16 studies using passive follow-up, among cryotherapy patients heavy bleeding requiring management by a medical provider was noted in two studies, and moderate bleeding requiring no further management was reported in one study. In one study of 1,675 women, one woman (0.0006 percent) required treatment for severe vaginal bleeding associated with an infection six days after treatment (Benedet et al., 1987). In Lickrish and Fortier's (1977) study of 164 women treated with cryotherapy, one woman (0.6 percent) experienced heavy bleeding requiring further treatment 10 days after cryotherapy. In Hemmingsson et al.'s 1981 study, two (1.2 percent) of 170 of women

Table 13. Frequency of Complications as Reported in Studies With Active and Passive Follow-Up of Patients

Study	Number of women treated	Total no. (%) with comp.	No. (%) with severe bleeding	No. (%) with PID	No. (%) with infection	No. (%) with other comp.	Comments
Active Follow-Up							
Berget et al., 1987	Cryo (n=101) Laser (n=103)	2 (2.0) 2 (1.9)	0 1 (1)	1 (1) 1 (1)		1 (1)* 0	Complications during treatment were "registered immediately"; complications after treatment were recorded at the 3-month follow-up visits (0% loss).
Mitchell et al., 1998	Cryo (n=139) Laser (n=121) LEEP (n=130)	1 (0.7) 4 (3.3) 9 (6.9)	0 3 (2.5) 7 (5.4)†	1 (0.7) 1 (0.8) 1 (0.8)		0 0 1 (0.8)‡	Patients were asked about complications at follow-up visit.
Passive Follow-Up							
Ferenczy, 1985	Cryo (n=147) Laser (n=147)	1 (0.6) 11 (7.4)	0 8 (5.4)§	1 (0.6) 3 (2.0)			No description was given about how complications were assessed.
Singh et al., 1988	Cryo (n=65) Cold Coag. (n=89)	1 (1.5) 1 (1.1)			1 (1.5) 1 (1.1)		Patients instructed to return if fever or bleeding occurred with pelvic or abdominal pain.
Benedet et al., 1987	(n=1,675)	1 (0.0)	1 (0.0)		1 (0.0)		1 case of vaginal bleeding caused by infection.
Creasman et al., 1973	(n=75)	4 (5.3)		4 (5.3)			Lower abdominal pain w/ infection, pyometra (1); tuboovarian abscess (1).
Hemmingson et al., 1981	(n=170)	12 (7.0)	2 (1.2)	10 (5.9)			1 confirmed PID, 9 suspected PID; 2 moderate bleeding not requiring treatment.
Hemmingsson and Stenson, 1983	(n=105)	1 (1.0)		1 (1.0)			Suspected salpingitis at 3 weeks.
Hillard et al., 1991	(n=59)	7 (11.9)		6 (10.2)	1 (1.7)		Adolescent population: 1 tuboovarian abscess; 2 patients with PID also had hemotometra.
Lickrish and Fortier, 1977	(n=164)	5 (3.0)	1 (0.6)	4 (2.4)			Endometritis and parametritis (upper tract infections) within one month.

continued next page

Table 13. ***(continued)***

Passive Follow-Up ***(continued)***							
Study	***Number of women treated***	***Total no. (%) with comp.***	***No. (%) with severe bleeding***	***No. (%) with PID***	***No. (%) with infection***	***No. (%) with other comp.***	***Comments***
Monaghan et al., 1982	(n=159)	2 (1.2)			1 (0.6)	1 (0.6)	Severe urinary tract infection (1); heavy menstrual loss (1).
Olatunbosun et al., 1992	(n=70)	4 (5.7)		4 (5.7)			4 treated with antibiotics for presumed salpingitis.
Popkin et al., 1978	(n=208)	1 (0.5)		1 (0.5)			Bilateral acute salpingitis.
Schantz and Thormann, 1984	(n=142)	7 (4.9)		1 (0.7)		6 (4.2)*	6 with severe pain due to necrotic tissue obstructing cervix; 1 developed tuboovarian abscess.
Teaff et al., 1990	(n=6)	5 (83)				5 (83)	Slow vaginal healing and/or prolonged discharge in postmenopausal women.
Tronstad and Kirschner, 1980	(n=93)	1 (1.1)			1 (1.1)		Lower genital tract infection (PID ruled out by laparoscopy). Patient had clinical cervicitis at treatment.
Van Lent et al., 1983	(n=102)	4 (3.9)		1 (1.0)	3 (2.9)		4 with painful abdominal cramps treated with antibiotics (1 had fever & 1 had symptoms of PID).
Walton et al., 1980	(n=138)	2 (1.4)				2 (1.4)	Acute cervical necrosis with delayed healing (1); severe dysmenorrhea with 1st menstrual cycle (1).

Comparison data from studies that found no complications for cryotherapy patients

Study	*Number of women treated*	*Total no. (%) with comp.*	*No. (%) with severe bleeding*	*No. (%) with PID*	*No. (%) with infection*	*No. (%) with other comp.*	*Comments*
Adewole et al., 1998	Cryo (n=23) Conization (n=11)	0 5 (5.4)	0 5 (5.4)				Method of evaluation not stated; Assumed passive follow-up.
Benedet et al., 1992	Cryo (n=962) Laser (n=1811)	0 87 (4.8)	0 87 (4.8)				Method of evaluation not stated; Assumed passive follow-up.
Javaheri et al., 1981	Cryo (n=272) Conization (n=127)	0 14 (11)	0 14 (11)				Method of evaluation not stated; Assumed passive follow-up.
Jobson and Homesley, 1984	Cryo (n=39) Laser (n=42)	0 0	0 0	0 0	0 0	0 0	Randomized trial. Patient examined and questioned 7-14 days following treatment
Kirwan et al., 1985	Cryo (n=35) Laser (n=71)	0 3 (4.2)	0 3 (4.2)				Randomized trial. Method of evaluation not stated; Assumed passive follow-up.
Kwikkel et al., 1985	Cryo (n=50) Laser (n=51)	0 3 (5.9)	0 3 (5.9)				Randomized trial. Patients were given survey to fill out.
Loizzi et al., 1992	Cryo (n=131) Open Cone (n=83) Sutured Cone (n=332)	0 9 (10.8) 2 (0.6)	0 9 (10.8) 2 (0.6)				Method of evaluation not stated; Assumed passive follow-up.
Townsend and Richart, 1983	Cryo (n=100) Laser (n=100)	0 1 (1)	0 1 (1%)				Pseudo randomized. Patients were "carefully followed"; all seen at 6 wks.
Wright and Davies, 1981	Cryo (n=152) Laser (n=131)	0 3 (2.3)	0 3 (2.3)	0 0			Method of evaluation not stated; Assumed passive follow-up.

* Necrotic plug.
† 1 < 24 hrs after treatment, 6 > 24 hrs after treatment.
‡ Severe pain requiring medication.
§ 2 interoperative bleeding, 6 postoperative bleeding.

presented with moderate bleeding following cryotherapy treatment, but the authors noted that no procedure was required to control the bleeding.

B. Pelvic Inflammatory Disease

PID, if left untreated, can result in chronic pain, infertility, or even death. Concern has been raised that there is an increased risk of PID following cryotherapy, presumably developing from a cervical infection present at treatment that ascends to the upper genital tract. In areas where women may have difficulty returning for follow-up after cryotherapy treatment, resolving questions about the risk of PID is crucial. Differences in the clinical criteria used for the diagnosis of PID limit researchers' ability to draw conclusions on such risks, however. Although a definitive diagnosis of PID requires an exam with laparoscopy (Sellors et al., 1991), several studies in this review diagnosed PID either by the patients' symptoms or by indicators such as tenderness and other established criteria.

In this review, confirmed PID that developed within one month of treatment was considered to likely be a complication associated with cryotherapy. Review of the available evidence suggests PID is a relatively rare occurrence following treatment with cryotherapy, though more common than severe bleeding. Less than one percent of women develop PID related to treatment with cryotherapy (within one month of treatment).

1. Active follow-up

The two studies with active follow-up reported PID as a rare complication of cryotherapy treatment. In fact, PID was diagnosed with comparable frequency (less than or equal to one percent) in cryotherapy, laser ablation, and LEEP clients.

- In Mitchell et al. (1998), a randomized controlled trial comparing the outcomes of cryotherapy with those of CO_2 laser ablation and LEEP, 1of 139 women (0.7 percent) treated with cryotherapy developed an infection that was assumed to be PID. Similarly, 1 (0.8 percent) of 130 women in the LEEP group and 1 (0.8 percent) of 121 women in the laser treatment group also were diagnosed with PID, based on their clinical symptoms (Mitchell et al., 1998).
- Berget et al., in their 1987 randomized controlled trial comparing cryotherapy to laser ablation, reported similar results with 1 (1 percent) of 101 women treated with cryotherapy and 1 (1 percent) of 103 women treated with laser ablation developing PID. According to their methodology, however, the investigators did not identify complications until the women returned for a three-month follow-up visit, so the cases of PID may not have been outcomes of cryotherapy (Berget et al., 1987).

2. Passive follow-up

Of the 16 articles with passive follow-up, 10 studies reported cases of PID or suspected PID. It is difficult to draw conclusions from these studies given the variability in methods, and in the accuracy of the diagnosis of PID. Furthermore, only four of these ten studies (Hemmingsson and Stenson, 1983; Hillard et al., 1991; Schantz and Thormann, 1984; Lickrish and Fortier, 1977) specifically stated that they had diagnosed PID within one month of cryotherapy. Lickrish and Fortier, in their 1977 study, reported that within one month of treatment, 4 of 164 (2.4 percent)

women developed endometritis and parametritis (upper genital tract infections) associated with local infections posttreatment and were treated with antibiotics.

It is important to note that the study with the highest percentage of patients developing PID was conducted with an adolescent population (Hillard et al., 1991). Results from this study, which reported that 7 (12 percent) of 59 patients developed infections, including PID, may be difficult to generalize to an older population of women who are targeted by most cervical cancer prevention programs in developing countries. Adolescents may be more susceptible to ascending genital tract infections as a result of anatomy and sexual behavior patterns that place them at higher risk for acquisition of sexually transmitted infections that are known causes of PID. In Hillard's subsequent clinical practice, providing antibiotics posttreatment to a high-risk group of adolescents significantly reduced the incidence of confirmed PID following cryotherapy (Hillard, personal communication).

C. Cervical Infections

The frequency with which infections of the cervix associated with cryotherapy are cited in the literature is relatively low. It should be noted that it is methodologically difficult to attribute cervical infection posttreatment to cryotherapy.

1. Active follow-up

Between the two studies with active follow-up measures, none reported any cervical or vaginal infections developing within one month after cryotherapy treatment.

2. Passive follow-up

Among 6 of the 16 studies with passive follow-up that reported other infections, the percent of women developing infections was 2.9 percent or less. Tronstad and Kirschner (1980), who treated 93 women with cryotherapy, reported that only 1 (1.1 percent) developed a lower genital tract infection. PID was ruled out with laparoscopy and the patient was treated in the hospital with antibiotics. However, after reviewing the patient's records, the authors realized that the patient had presented with an infection at the time of treatment and should have been excluded from the treatment group. Singh et al. (1988), in a randomized controlled trial comparing cryotherapy to cold coagulation, describes a local cervical infection developing in 1 (1.5 percent) of the 65 cryotherapy patients and in 1 (1.1 percent) of the 89 cold-coagulation patients. Both patients responded well to an antiseptic cleaning of the cervix and self-application of triple sulfonamide vaginal cream plus oral antibiotics. Benedet et al. in their 1987 study of 1,675 women, reported that 1 woman (0.0006 percent) was hospitalized for a cervical infection that developed six days posttreatment, causing vaginal bleeding.

D. Other Complications (Often Indicated by Severe Pain Posttreatment)

Minor pain and cramping is a common side effect of cryotherapy treatment (see page 47 for a discussion of mild pain and cramping). Severe or debilitating pain and cramping, however, can indicate a more serious problem, such as an infection or PID. This section reviews studies in which women sought additional medical care for severe pain and cramping within one month following

cryotherapy. The literature suggests that severe pain and cramping is an infrequent complication following cryotherapy. The implication of this complication for clinical practice is that women experiencing severe pain and cramping for several days should return for evaluation, as these effects could be an indication of an infection or blockage of the cervix.

1. Active follow-up

In the two studies with active follow-up methods of patients, one study (Berget et al., 1987) reported one (1 percent) of 101 women experienced severe pain and cramping following cryotherapy consistent with what is described in the literature as a "necrotic plug."

2. Passive follow-up

Three of the four studies that reported other complications described instances of women seeking medical care for severe lower abdominal pain and cramping within the first days following cryotherapy. In one study (Schantz and Thormann, 1984), 6 (4.2 percent) of 142 women had the cervix obstructed by a necrotic plug. The pain and cramps subsided immediately when the necrotic tissue blocking the cervix was removed. In the other two studies (Creasman et al., 1973; Hillard et al., 1991), 3 women presented in severe pain after treatment with a blockage that coexisted with an infection and the presence of pyometra or hematometra (a buildup of pus or blood, respectively, in the uterus) was described. The women were successfully treated with antibiotics and dilation to release the fluid buildup.

E. HIV Infection and Cryotherapy Complications

Cervical cancer became an AIDS-defining illness in the 1990s (CDC, 1992). Among HIV-infected women, CIN has a greater prevalence, is more persistent, and is more likely to recur. Issues surrounding HIV transmission create unique considerations regarding the safety and effectiveness of treating CIN with cryotherapy. Among the questions that have been raised is safety of treatment for CIN in HIV-infected women, as being immuno-compromised may lead to a greater risk of complications following treatment.

One study in this review specifically addressed the issue of using cryotherapy to treat CIN in HIV-infected women. Cuthill et al., in their 1995 study, compared treatment complications among HIVnegative and HIV-infected women receiving cryotherapy, laser therapy, or cone biopsy treatment. The results showed no statistically significant differences in complication rates between the 20 HIV-positive and 44 HIV-negative women undergoing cryotherapy. Of the 20 HIV-positive women treated with cryotherapy, 1 (5 percent) experienced severe bleeding 3 days after treatment and was hospitalized and treated with cauterization for the bleeding. A second HIV-positive woman reported experiencing severe painful cramps post-cryotherapy. Among HIV-negative women, 1 (2 percent) also experienced severe cramps following treatment and 4 (9 percent) others acquired candida infection, vaginitis, or urinary tract infections. Overall, the rate of complications following cryotherapy was 10 percent for HIV-infected women and 11 percent for HIV-negative women (a non-statistically significant difference). While the overall rate of complications for HIV-negative women appears higher than reported in other studies, the authors caution that they were extremely scrupulous in calculating complication rates and included any asymptomatic cervical infections

and slight cervical bleeding that may not have been noticeable to the women themselves. While this allowed valid comparisons between the HIV-positive and HIV-negative women in the study, overall complication rates may be overestimated compared to other studies.

Of note is that 10 (67 percent) of the 15 HIV-positive women receiving laser treatment/cone biopsy experienced a complication. In the laser/cone group there was a statistically significant difference in the rates of complications for HIV-positive and HIV-negative women, with HIV-positive women experiencing higher rates of overall complications, severe bleeding, and infections. Three (20 percent) of the HIV-infected women experienced severe bleeding that caused them to return for an unscheduled clinic visit compared to 1 (2 percent) HIV-negative woman ($p < .05$). In addition, among the laser/cone group, there was a statistically significant difference in the rate of infections following treatment, with 8 (53 percent) of HIV-infected and 8 (18 percent) of HIV-negative women having an infection ($p=.02$). (Infections were based on clinicians' observations during pelvic exams and on patients' reports.)

F. Long-Term Sequelae of Cryotherapy

Potential long-term sequelae of cryotherapy are also important to consider. In low-resource areas where providers may only see women once at the time of treatment and follow-up may be difficult to achieve, it is important to ensure that the treatment is not associated with sequelae that could present years after treatment. A few articles in this review specifically addressed long-term sequelae. Concerns regarding the development of cervical stenosis (a narrowing of the cervical canal) and cryotherapy's potential impact on fertility and pregnancy outcome are discussed in this section.

1. Stenosis

Overall, the articles in this review refer infrequently to cervical stenosis, and those that do highlight the inconsistencies in defining and diagnosing a stenotic condition. Development of anatomical cervical stenosis post-cryotherapy would likely result in consistent reports of infertility, dysmenorrhea, or labor difficulties. None of these effects were commonly found in this review. In two articles (Berget et al., 1987; Mitchell et al., 1998), the authors clearly defined what they considered stenosis (which was not always consistent with a definition of anatomical stenosis, which is the physical narrowing or obstruction of the cervical canal). Mitchell et al., in their 1998 article, defined stenosis as those cases where the cervix required dilation by a medical provider, but their report does not describe why the providers felt dilation was necessary, nor the amount of dilation or effort needed to dilate. Women were evaluated at one month after treatment and at four-month intervals thereafter. Of the 139 women receiving cryotherapy, 2 (1.4 percent) met their definition of stenosis requiring dilation. One (0.8 percent) of 130 LEEP patients and one (0.8 percent) of 121 laser patients required dilation for stenosis.

Berget et al., in their 1987 study, defined stenosis as the inability to insert a cotton-tipped swab into the external opening of the cervical canal. At three months posttreatment the authors reported stenotic cases in 3 (3 percent) of 101 cryotherapy patients versus 6 (6 percent) of 103 laser patients. The authors noted that none of these patients had symptoms of stenosis, and there was no physiological evidence of stenosis. In addition, they noted that the cotton-swab method of diagnosis that they used has been challenged elsewhere in the literature.

Three additional studies (DiSaia et al., 1974; Kirwan et al., 1985; Walton et al., 1980) report finding 12 cases of stenosis among 339 women, but do not provide a description of how stenosis was determined and what qualified as cervical stenosis. DiSaia et al. (1974) noted a "relative" stenosis of the cervical canal in 6 (3.6 percent) of 166 women. The authors attributed the stenosis to the design of the probe; no further information about probe types is given, however. Kirwan et al. (1985) concluded that 2 (5.7 percent) of 35 cryotherapy patients had cervical stenosis, and Walton et al. (1980) reported 4 cases (2.8 percent) of cervical stenosis among 138 patients, but neither study provides further definition or description of the condition. An additional 13 articles in this review did not explicitly state they were evaluating stenosis but commented that they saw no evidence of stenosis in follow-up visits. Based on the available evidence, it appears that anatomical stenosis does not constitute a major long-term sequela, nor are cases of stenosis more frequent in cryotherapy patients than in patients undergoing other treatment methods for CIN.

2. Fertility and obstetrical outcomes

Very few articles assessed fertility and obstetrical outcomes as primary outcomes of the study. Overall, cryotherapy did not appear to be associated with reduced fertility or obstetrical outcomes. In fact, three articles (Laubstein and Petrie, 1974; DiSaia et al., 1974; Elmfors and Stormby, 1979) reported pregnancies occurring after cryotherapy in women who previously had primary or secondary infertility. Similarly, the data available suggest that cryotherapy has no adverse affect on pregnancy outcome among women who conceive posttreatment (Benrubi et al., 1984; Crisp, 1969; Crisp et al., 1970; Crisp, 1972; Einerth, 1978; Einerth, 1988; Elmfors and Stormby, 1979; Hemmingsson, 1982; Henriksen, 1979; Laubstein and Petrie, 1974; Lickrish and Fortier, 1977; Loizzi et al., 1992; Monaghan et al., 1982; Olatunbosun et al., 1992; Popkin et al., 1978; Tangtrakul et al., 1983; Weed et al., 1978).

In Benrubi et al.'s case-control study (1984), 53 women who had previously been treated with cryotherapy and subsequently gave birth were matched with 53 controls who gave birth and had no prior history of cryotherapy. The authors noted a trend toward more cases experiencing shorter labor than controls. Hemmingsson (1982), in a study that compared the outcomes of 115 pregnancies post-cryotherapy to the outcomes of 65 previous pregnancies in the same group of women, observed a six-fold increase in the rate of cesarean deliveries in the post-cryotherapy group. None of the cesarean deliveries, however, was a result of the cryotherapy, and the increase mirrored the overall increase in the use of cesarean deliveries in Sweden during that time period. Overall, the studies reviewed suggest that cryotherapy does not play a major role in fertility and obstetrical complications in pregnancies posttreatment.

G. Other Considerations for Safety

1. Pregnancy outcomes for women treated during pregnancy

Although cryotherapy is not generally recommended during pregnancy, there is limited information on this safety consideration from the literature on using cryotherapy for CIN. In Olatunbosun et al. (1992), one patient was treated at 12 weeks gestation and a second patient was treated at 16 weeks gestation. Their pregnancies were reported as uneventful, with no adverse affects on labor and

delivery or the fetus. Crisp et al. (1967) treated one woman at 34 weeks gestation with no disturbance to the pregnancy, membranes, or fetus.

Additional data on obstetrical outcomes for women treated during pregnancy were presented in two studies of cervical polyps and condylomata (wart-like growths associated with HPV infection). In these cases, cryotherapy was recommended for women during pregnancy in an effort to reduce the risk of the condylomata causing obstetrical complications or infection of the infant during vaginal delivery (Matanyi, 1989; Bergman et al., 1987). In neither study was cryotherapy found to have a detrimental effect on pregnancy and labor. Bergman et al. (1987) treated 28 women for cervical condylomata acuminata during their second or third trimester of pregnancy. The rate of preterm deliveries (10.7 percent) and cesarean deliveries (7.1 percent) among the women treated during pregnancy did not differ from the overall rates for the hospital, nor were any of the preterm deliveries or cesarean deliveries thought to be associated with the cryotherapy treatment. The cervix dilated properly in all patients, and there were no adverse effects observed for the fetus on any measures of fetal growth and health. In the second study (Matanyi, 1989), 44 women were treated during their pregnancies (23 in first trimester, 12 in second trimester, 9 in third trimester). Follow-up through the completion of gestation was available for only 29 (66 percent) of the 44 women. For the remaining 15 women, pregnancy outcomes could not be determined. Of the 29 women with complete follow up, 25 had full-term pregnancies, 2 had preterm deliveries at 29 and 34 weeks, 1 had a spontaneous abortion six weeks after cryotherapy (thought to be related to influenza), and 1 had an induced abortion. Neither cervical incompetence nor stenosis occurred. Labor and delivery were not shown to significantly differ from the control group in terms of the course of labor and delivery or five-minute Apgar scores for the infant (Matanyi, 1989).

2. Visibility of the transformation zone after healing

The inability to fully visualize the entire transformation zone following cryotherapy is reported in several instances in the literature. While not considered an actual complication of cryotherapy, the issue is sometimes discussed in terms of its effect on the ease of visual follow-up screening of patients. This concern is based on the necessity of inspecting the entire transformation zone for residual or new disease (Ferenczy, 1985; Wright and Davies, 1981; Stienstra et al., 1999). Colposcopy is considered inadequate unless this can be achieved. The location of the squamocolumnar junction (the upper extent of the transformation zone), however, is somewhat dependent on a woman's age and parity. In addition, the size and type of probe tip used may affect the amount of movement of the squamocolumnar junction after cryotherapy. Obtaining data on women's ages, parity, and the probe type used will be helpful to future measurements of the impact of cryotherapy on visibility of the transformation zone.

In this review, nine studies provided information on the visibility and/or location of the transformation zone after cryotherapy. Though not consistent, the results appear to show a trend towards the squamocolumnar junction moving toward or deeper into the cervical canal after cryotherapy.

Five randomized trials (Berget et al., 1987; Jobson and Homesley, 1984; Kwikkel et al., 1985; Kirwan et al., 1985; Ferenczy, 1985) that compared cryotherapy to CO_2 laser ablation reported a trend in which cryotherapy patients were more likely than laser patients to have inadequate

colposcopy exams at the three- or four-month follow-up visit due to the location of the transformation zone deep within the cervical canal. For two of the randomized trials (Berget et al., 1987; Jobson and Homesley, 1984), the difference in the visibility of the squamocolumnar junction for cryotherapy and laser ablation patients was statistically significant.

- In Berget et al.'s study, 47 (50 percent) of 94 cryotherapy patients had a fully visible squamocolumnar junction at follow-up colposcopy compared to 77 (79 percent) of 97 laser treatment patients ($p < 0.001$).
- Jobson and Homesley reported 20 (51 percent) of 39 cryotherapy patients had satisfactory colposcopy, compared to 36 (86 percent) of 42 laser patients ($p < 0.01$).
- Kirwan et al. (1985) and Kwikkel et al. (1985) reported the transformation zone was fully visible in more laser patients than cryotherapy patients, but differences were not statistically signficant.
- Comments in Ferenczy (1985) indicate that only the 18 patients whose lesions extended into the endocervical canal had the squamocolumnar junction located deep within the cervical canal at the three-month follow-up visit. The authors attribute this to the deeper freeze needed in these patients and suggest that cryotherapy may not be the optimal treatment choice when lesions extend into the endocervical canal (Ferenczy, 1985). (See page 24 for more discussion of endocervical canal involvement and treatment effectiveness.)

One study randomized women to treatment with either a flat-tip probe or a shallow conical-tip probe. The purpose of this study was to examine the relationship between the shape of the cryotherapy probe tip and the movement of the squamocolumnar junction. The study was able to follow only 84 (72 percent) of 117 women with a post-treatment colposcopy exam. In all cases, the squamocolumnar junction was completely visible at follow-up and no differences were noted between the flat and conical tips (Stienstra et al., 1999).

Three follow-up studies also discuss the visibility of the transformation zone. In Wright and Davies' study (1981), which retrospectively compared cryotherapy patients to an earlier group of patients treated with CO_2 laser in the same clinic, the results show that the transformation zone was typically located deeper in the cervical canal in women who underwent cryotherapy as compared to CO_2 laser ablation. Saidi et al. (1977) reported an average of six months follow-up for 65 of 74 patients treated with cryotherapy at their clinic. In these patients, 24 (37 percent) had inadequate colposcopy at follow-up. In comparison, percentages of unsatisfactory colposcopy in other groups in the clinic population were as follows: pregnant patients, 1.8 percent; premenopausal women, 2.8 percent; postmenopausal women, 25.2 percent; conization patients, 20.7 percent; with the entire clinic population reported as 7.2 percent (Saidi et al., 1977). In contrast, Crapanzano (1978) found that in a study of 32 patients, the squamocolumnar junction remained visible after cryotherapy "in most instances."

V. ACCEPTABILITY: SIDE EFFECTS

Acceptability Summary Points

- Limited data are available on women's experience with cryotherapy and its side effects.
- Discharge after cryotherapy can be heavy and have an unpleasant odor, causing women to feel uncomfortable; discharge can last up to four weeks.
- Discomfort during and after treatment appears to be brief and at a level generally acceptable to women.
- Though the use of lidocaine can help alleviate pain and cramping during the procedure, women experience the injection itself as painful.
- Reactions such as fainting, nausea, dizziness, or hot flushing can occur after cryotherapy and are perceived by women as unpleasant.
- Light bleeding and spotting do occasionally occur, but are mild and occur less frequently than after treatment with laser ablation.

Side effects are anticipated outcomes of a medical procedure. While side effects may vary in the level of discomfort and inconvenience experienced by the patient, they do not have a long-lasting negative impact on health and are not life threatening. Depending on the intensity of and inconvenience caused by side effects, however, they can be detrimental to a patient's perceptions of her recovery, follow-up, and continued service-seeking behaviors. Appropriate patient information and education explaining possible side effects prior to the procedure can help alleviate anxiety and give women the opportunity to make an informed choice about their treatment.

Early studies of cryotherapy often grouped side effects and complications together and offered a general observation of the effects of the treatment, such as "treatment was well tolerated." Studies have not often attempted to measure the frequency or severity of the side effects, nor have many tried to assess the acceptability of cryotherapy from a woman's perspective. This review includes 45 studies that mentioned side effects. Only 13 of these articles actively assessed the type of side effects experienced by the women receiving treatment. Of these, five (Harper et al., 2000a; Harper et al., 2000b; Harper and Cobb, 1998; Harper, 1994; and Townsend and Richart, 1983) quantified the level of discomfort perceived by the women as a measure of acceptability. While passive follow-up may underestimate the rates of side effects, active follow-up in some instances may result in an overestimate of the frequency or severity of some side effects.

It is important to note that most of the available information on women's experiences with treatment side effects has been collected in the United States and Canada. Cultural contexts are important to consider. For instance, women's perceptions of discharge may be put into perspective of the everyday conveniences and inconveniences of their lives. Heavy discharge may be perceived as

more or less acceptable depending on how much it disrupts their work, whether it's on a rural farm or in an office setting. Other factors such as the availability and use of things like sanitary supplies or pain medication can affect perceptions of acceptability.

A. Discharge

Discharge is a common side effect of cryotherapy. The literature typically describes discharge by using terms such as "watery," "mucoid," "heavy," or "profuse." In this review, 32 studies reported discharge; seven used active follow-up to obtain more detailed data on discharge. Few studies, however, have looked at whether the amount of discharge was acceptable to the women.

Overall, eight studies (four active follow-up, four passive follow-up) provided information on discharge experienced by cryotherapy patients as compared to laser ablation and conization patients. A higher percentage of women in the cryotherapy treatment groups complained of discharge than women receiving other treatments. In addition, the discharge following cryotherapy was consistently described as heavier and of longer duration than the discharge following laser ablation or conization.

Table 14. Women's Experience with Discharge as Reported in Studies with Active Follow-up

Study	Percent of women with discharge	Percent of women with malodorous discharge	Duration of heavy/severe discharge	Average total duration (days)
Berget et al., 1987	88 percent	36 percent	22 days	Total 18; moderate 18
Harper et al., 2000a	—	97.2 percent; 51.4 percent rate it "foul" to "very foul"		
Harper et al., 2000b*	—		7 days (8.9 for malodorous discharge)	Avg. 12.4
Jobson and Homesley, 1984	—	—	Heavy mucoid increased in 1st week, then decreased	—
Kwikkel et al., 1985	—	—	8 days (0–28) Percentage days heavy: 33 percent	Median: 29 days (7–59)
Nahhas et al., 1981*	—		No debride: 23.1 days severe; Debride: 15.9 days severe	No debride: 36.4 Debride: 33.1
Townsend and Ostergard, 1971	100 percent	—	—	—

* Compared cervical eschar debridement to no debridement and found no significant difference in course of healing, duration or severity of discharge.

1. Active follow-up

The data suggests that discharge is frequently heaviest during the first week after treatment and lasts, on average, two to four weeks. In Harper et al.'s 2000a study, "Healing experiences after cervical cryotherapy," women completed a detailed survey to evaluate their experience with discharge. Women whose menses were normally light more often perceived the amount of discharge to be heavy. Older women, multigravid women, and obese women in this study found the changing of pads to be more bothersome than other women did. In addition, a statistically significant larger percent of women reported that their activities were more restricted by the associated discharge than by their normal menses. Several studies also reported that women complained the discharge was malodorous, with one study finding the odor was most disagreeable to younger women aged 15 to 18 years (Harper et al., 2000a). Two studies (Harper et al., 2000b and Nahhas et al., 1981) randomized women to a process of removing the necrotic tissue several days after cryotherapy (eschar debridement) to evaluate whether this helped with the healing process. Neither study found any statistically significant difference in the amount of discharge, duration of discharge, nor strength of malodor experienced. See Table 14 for discharge results from studies with active follow-up methods.

2. Passive follow-up

Among the studies with passive follow-up, the percentage of women reporting discharge after cryotherapy ranged from 9 percent to 100 percent. The majority of these studies reported the duration of discharge as approximately two to three weeks.

B. Mild Pain and Cramping During and After Treatment

Patients' perceptions of discomfort during procedures are subjective and therefore difficult to evaluate. To date, the cryotherapy literature mostly reports providers' perceptions of a woman's pain and cramping. Few studies obtained data on pain and cramping as reported directly by the woman. Although direct reports from women may result in reporting bias against telling researchers anything negative, such reports, as well as their correlation with provider perceptions, are important to collect in order to better understand the level of discomfort associated with cryotherapy.

Table 15. Mean Pain and Cramping Scores (0–100 Visual Analog Scale [VAS])

			Pain score			*Cramping score*			*Injections*	
Study	**No. of women treated**	**No. of injections**	**1st freeze**	**2nd freeze**	**Total**	**1st freeze**	**2nd freeze**	**Total**	**Pain**	**Cramp**
Harper and Cobb, 1998	48 w/lidocaine	4	12*	12*	28*	13*	18*	21*	36	20
	39 no lidocaine	0	39	24	44	49	32	51	—	—
Harper, 1997	45 w/lidocaine	2	26	19	44	37	18	32	21	7
	40 no lidocaine	0	37	14	43	50	25	50	—	—
Sammarco et al.†, 1993	19 w/lidocaine	2			1.6					
	20 no lidocaine	0			4.27					

* Statistically significant.
† 0–10 VAS.

1. Active follow-up

In recent years, a number of studies have developed scales and other measures to assess women's (as opposed to providers') perceptions of the level of discomfort during the treatment. Ten such studies used active methods to assess the level of pain and cramping experienced by women. Three of the ten studies examined whether the use of a local anesthetic reduced the levels of pain and cramping experienced (see Table 15 and discussion of Harper, 1997; Harper and Cobb, 1998; and Sammarco et al., 1993, below).

In general, the results from the studies with active assessment seem to suggest that while women may experience pain and cramping during treatment, the level of pain appears to be less than pain experienced by women receiving treatment by laser ablation. Overall, none of the studies reported that a cryotherapy patient asked that the procedure be stopped due to discomfort from pain or cramping.

In three randomized controlled trials (Berget et al., 1987; Jobson and Homesley, 1984; Kwikkel et al., 1985), fewer women in the cryotherapy group reported experiencing pain and cramping during treatment than in the laser ablation group.

- Berget et al. reported more laser patients than cryotherapy patients experienced moderate to severe pain during treatment (18 [20 percent] of 92 laser patients versus 6 [6 percent] of 100 cryotherapy patients) (p=.05).
- Kwikkel et al. reported 7 (14 percent) of the 51 laser treatment patients experienced pain during treatment, compared to none of the 50 cryotherapy patients. Three laser patients also needed the procedure to be stopped prematurely due to pain.
- Jobson and Homesley reported occasionally needing to pause the laser treatment due to uterine cramping, but stated that both the laser ablation and cryotherapy appeared well tolerated by the women.

Most women perceived cramping associated with cryotherapy to be comparable to the intensity of normal menstrual cramps. Only five percent of women in Townsend and Richart's 1983 study perceived the cramps to be more severe than normal menses and more comparable to cramps during childbirth (Townsend and Richart, 1983). Harper (1994) developed scales to assess the intensity of pain and cramping separately and reported that more women reported experiencing pain than cramping from the cryotherapy procedure. In addition, in this study Harper compared differences in pain and cramping by freeze length. Results showed that with the five-minute double freeze more women reported pain and cramps as compared to women receiving a shorter freeze length (three-minute single freeze, three-minute double freeze, or five-minute single freeze).

The use of lidocaine blocks prior to treatment: Three studies with active assessment compared the level of cramping and/or pain experienced during treatment by women who received a lidocaine injection prior to treatment to those who did not (Sammarco et al., 1993; Harper, 1997[1];

1 Harper (1997) administered a two-quadrant "paracervical block" by injecting lidocaine at the cervical-vaginal junction in order to block the nerve.

Harper and Cobb, 1998). The results from all three studies suggest that a pretreatment injection with lidocaine may reduce the amount of pain and cramping experienced during treatment. Sammarco et al. (1993) gave women a submucosal lidocaine injection in two quadrants of the cervix, while Harper and Cobb (1998) used a submucosal lidocaine injection in four quadrants. Patients in the studies were then asked to evaluate the level of pain they felt during treatment using a visual analog scale (VAS) (0-10 scale for Sammarco et al., 1993; 0-100 scale for Harper, 1997, and for Harper and Cobb, 1998). Both Sammarco et al. and Harper and Cobb found that women who received the lidocaine injection reported statistically significant lower pain scores than their counterparts who underwent the normal course of treatment without the lidocaine. In Harper and Cobb (1998) and Harper (1997) women who received lidocaine had statistically significantly lower cramping scores on all measures (first freeze, second freeze, composite total). Results are reported in Table 15.

Pretreatment with a lidocaine injection does have some disadvantages. Harper and Cobb caution that clinicians should pay careful attention to the amount of lidocaine given to the patient and not exceed recommended dosages. Harper and Cobb also caution that women do report feeling pain from the injection itself (Harper and Cobb, 1998). In addition, in low-resource settings, the availability and additional costs of providing lidocaine may limit the feasibility of using lidocaine blocks.

2. Passive follow-up

Studies with passive follow-up report observations of women experiencing mild cramping during treatment that subsides soon after treatment. Occasional references are found of complaints about mild lower-back pain for a few days after treatment.

C. Fainting and Flushing

Vasomotor reactions to the cryotherapy procedure such as dizziness, fainting, or flushing can be unpleasant and/or embarrassing for the woman; they do not pose a severe threat to the woman's health and are typically considered an inconvenient side effect. Five articles in this review mentioned women fainting or feeling faint following treatment, and six studies reported women experiencing a flushing sensation. Limited data are available from these studies on whether these side effects make cryotherapy a less acceptable treatment choice for women, or whether the reactions such as fainting were related to the pain experienced during cryotherapy.

1. Active follow-up

The data from studies that used active follow-up are inconclusive. Jobson and Homesley (1984) report that "several" of the 39 women fainted during or immediately after cryotherapy. They reported, however, that two women who fainted said they would not undergo cryotherapy again if repeat treatment were needed, implying that the fainting experience may influence their treatment choice in the future. The 1971 study by Townsend and Ostergard reports 10 (10 percent) of 95 women receiving cryotherapy experienced a flushing sensation accompanied by a headache.

2. Passive follow-up

Data from the studies with passive follow-up provides little additional information. Articles report anywhere from 0 to 40 percent of women react to treatment with fainting, dizziness, or flushing (see Table 16). From the limited amount of data, it appears that flushing may be more common (20 to 60 percent) than fainting.

D. Mild Bleeding and Spotting

As discussed previously, severe bleeding following cryotherapy is a relatively rare occurrence (see page 34). In contrast, mild bleeding or spotting that sometimes requires protection with sanitary pads has been mentioned in the literature as a side effect. Of twelve articles that mentioned spotting as a possible side effect, three actively followed up patients to assess this side effect. Results suggest bleeding and spotting may occur several days after cryotherapy treatment, but that the spotting is not severe and occurs less frequently than in women treated with laser ablation.

Table 16. Frequency of Fainting and Flushing

Study	No. (%) of women treated with cryotherapy	No. (%) of women experiencing fainting reaction	No. (%) of women experiencing flushing
Active follow up			
Jobson and Homesley, 1984	39	"several"	—
Townsend and Ostergard, 1971	95	—	10 (10)
Passive follow up			
Benedet et al., 1987	1,675	—	"most"
Ferenczy, 1985	147	—	102 (70) "hot flashes"
Matanyi, 1992/93	1,248	—	374–499 (30–40)
Popkin et al., 1978	208	2 (1.0)	—
Schantz and Thormann, 1984	142	—	28 (20)
Townsend and Richart, 1983	100	20 (20)*	—
Tronstad and Kirschner, 1980	93	—	55 (60) during thaw
Van Lent et al., 1983	102	5 (5)	—
Walton et al., 1980	138	1 (0.7)	—

*20 percent of patients felt lightheaded or faint after treatment.

1. Active follow-up

Because so few studies with active follow-up assessed bleeding and spotting, the results do not present a clear picture of how frequently women experience light bleeding. Available data are presented in Table 17). In one study, none of 39 women in the cryotherapy treatment group reported spotting as a side effect of cryotherapy treatment (Jobson and Homesley, 1984). In another study, 22 (22 percent) of 99 women undergoing cryotherapy experienced bleeding, but this was significantly less than 49 (49 percent) of 99 women in the CO_2 laser group who experienced bleeding ($p < .001$) (Berget et al., 1987). The third study with active follow-up reported that spotting was "more common" among laser ablation patients, but reported that cryotherapy patients experienced an average of three days of spotting posttreatment compared to an average of two days for laser patients (data not presented in table) (Kwikkel et al., 1985).

2. Passive follow-up

Among the passive studies, the data are even more inconsistent, with percentages ranging from 0 to 55 percent of women experiencing spotting or bleeding.

Table 17. Frequency of Spotting or Bleeding Reported Posttreatment

Study	*No. of women treated*	*No. of women with spotting or bleeding (%)*
Active follow-up		
Berget et al., 1987	Cryo (n=99) Laser (n=99)	22 (22) 49 (49)
Jobson and Homesley, 1984	Cryo (n=39) Laser (n=42)	0 1 (2.3)
Passive follow-up		
Einerth, 1978	Cryo (n=59)	2 (3.4)
Einerth, 1988	Cryo (n=117)	3 (2.6)
Ferenczy, 1985	Cryo (n=147) Laser (n=147)	0 29 (20)
Loizzi et al., 1992	Cryo (n=131)	Small %
Olatunbosum et al., 1992	Cryo (n=70)	2 (2.8)
Townsend and Richart, 1983	Cryo (n=100) Laser (n=100)	0 31 (31)
Townsend and Ostergard, 1971	Cryo (n=95)	52 (55)
Underwood et al., 1976	Cryo (n=65)	"many"
Wright and Davies, 1981	Cryo (n=152) Laser (n=131)	0 "some"

VI. DISCUSSION

A. Effectiveness

The evidence presented in this review supports the conclusion that, when used appropriately, cryotherapy appears to work as well as other outpatient methods (such as laser ablation and LEEP) used to treat CIN. Overall cure rates from the randomized trials range from 56.8 to 94.6 percent for cryotherapy (summary statistic, 89.5 percent; 95 percent confidence interval, 87.3–91.7), and from 70.6 to 95.9 percent for laser ablation (summary statistic, 88.2 percent; 95 percent confidence interval, 85.6–90.8). Cryotherapy appears to be less effective when used on severe lesions. The summary statistic for CIN 3 lesions was 84.1 percent (95 percent confidence interval, 78.0–90.2). Further analysis suggests that lesion size rather than lesion severity is an important factor in the effectiveness of cryotherapy.

Because of substantial heterogeneity between the studies, it is difficult to determine which factors were independently associated with failures. Failure rates may have been associated with treating lesions that would have been better managed by another approach (for example, lesions covering greater than 75 percent of the cervix, or lesions with significant extension into the endocervical canal). Because CIN 3 lesions tend to be complicated by factors such as large size and endocervical canal involvement, practitioners need to take care in assessing these lesions to ensure they are suitable for cryotherapy treatment.

For cryotherapy, questions also remain relating to whether the use of a double freeze produces a better cure than the use of a single freeze. The literature reviewed suggests that the double-freeze technique may not have as much of an advantage as previously assumed, although the data are inconsistent and occasionally weak.

It is important to keep in mind that most of the data discussed in this review were gathered from studies implemented in developed countries using high-level providers performing cryotherapy procedures with colposcopic guidance. Health care providers in low-resources settings will need to consider not only treatment effectiveness and safety when making decisions about appropriate treatment interventions, but also accessibility of equipment and supplies, ease of training and necessary provider skills, and costs. In comparison to treatment methods such as laser ablation and LEEP, cryotherapy has significant advantages in these areas. Because of its relative simplicity, it is possible to train mid-level providers to perform the procedure. This, coupled with the fact that cryotherapy does not rely on electricity, means that it can be made accessible to women at the local level. One possible impediment to its use in low-resource settings is securing a reliable source of clean carbon dioxide or nitrous oxide gas canisters.

In contrast, it is more probable that laser ablation and LEEP treatments will only be provided in a central or regional hospital or clinic setting in developing countries. Both of these techniques have heavier equipment and facilities requirements, require considerably more training and skills, and are associated with higher risks of severe bleeding than cryotherapy. The equipment for laser

ablation in particular is very expensive and highly technical, making it unfeasible to purchase, maintain, repair, or replace in a low-resource setting. LEEP does have the advantage of allowing the provider to remove the entire squamocolumnar junction, which produces a specimen for histological evaluation and confirmation. Because of this, it is suitable to treat the larger lesions or those that extend into the endocervical canal. Ideally, a screening and treatment program in a low-resource setting would be able to refer women with such lesions to a central location for treatment with LEEP.

B. Safety

Cryotherapy treatment appears to be quite safe. Severe bleeding and PID, two of the most serious potential complications, are extremely rare. As part of good quality care, service providers need to provide women with clear, accurate information and education about the need to return for care if severe pain or fever, alone or in conjunction with malodorous discharge, are present, as these could be an indication of a more serious infection.

Long-term sequelae from cryotherapy treatment also appear to be uncommon. There is no evidence from this literature review that cryotherapy is linked to cervical stenosis or that cryotherapy has any long-term impact on fertility or pregnancy outcomes. Hypotheses that cryotherapy may result in cervical incompetence that could cause miscarriages or premature delivery and/or cervical stenosis that could cause infertility or labor difficulties were not supported (Montz, 1996). The data available from this review, although limited (most studies excluded pregnant women from the treatment group), also suggest that treatment during pregnancy does not have a detrimental impact on the course of the pregnancy or pregnancy outcome posttreatment.

The available data suggest that there may be some movement of the squamocolumnar junction into the cervical canal after cryotherapy. It is difficult to determine, however, whether age, parity, or the type of cryotherapy tip used during cryotherapy was independently associated with movement of the squamocolumnar junction. While movement of the squamocolumnar junction deeper into the canal makes it more difficult to visualize, there is still debate over whether this is a serious problem. Data from RTCOG/JHPIEGO's Thailand study, in which cryotherapy was used to treat women aged 35 to 45 years who had parity of one or greater, suggest that movement is minimal in this age group. Smaller and shallower cryotherapy tips have been produced in recent years, which also may reduce the amount of movement of the squamocolumnar junction. Further observation is necessary to see if these assumptions hold true.

C. Acceptability

Studies designed to address the acceptability of cryotherapy are limited. Studies of provider perceptions of women's side effects, a proxy for the acceptability of the treatment procedure, generally report that women find the treatment tolerable and associated side effects to be moderately uncomfortable and irritating. What is acceptable to a provider, however, may not be acceptable to the patient. In addition, perception of pain and acceptable levels of pain vary among people and may vary by culture. The perception of acceptability of a side effect such as profuse discharge or

cramping may be related to how disruptive the experience is to the woman's ability to carry out her roles and responsibilities at home and work.

While this review confirmed that there is some discomfort associated with cryotherapy treatment, results suggest that the discomfort experienced by women is at an acceptable level. There is a clear need, however, for information and high-quality supportive care for women undergoing this procedure, given the associated pain and the possibility of dizziness, fainting, or flushing. These physical sensations can cause fear and anxiety that could be eased through appropriate pretreatment information and support throughout the treatment and healing process.

The research on acceptability of side effects also points to a need for good information and education for women about what to expect in the posttreatment period. Women should be advised that they might experience discharge that is profuse (perhaps requiring several changes of protective pads per day), possibly malodorous, and lasting several weeks.

Additional data from developing-country settings would help provide information on women's experiences and feelings towards the cryotherapy procedure and the associated side effects. Preliminary data are available from post-cryotherapy studies in Peru, Kenya, Thailand, South Africa, and Ghana. Data from ACCP projects in Thailand and South Africa indicate satisfaction among women regarding their cryotherapy experiences. Preliminary data from Ghana indicate similar attitudes. It will be important in the coming years to ensure that women are properly informed about all possible side effects in a culturally appropriate manner.

D. HIV and Cryotherapy

When a woman presents for screening and treatment for precancerous cervical lesions, it is unlikely that she or the provider will be aware of her HIV status. Yet, HIV status could affect treatment effectiveness and complication rates. Studies have shown that across all treatment methods, CIN tends to be more prevalent, persistent, and more likely to recur in HIV-positive women. Because of this, specific counseling issues should be addressed prior to treatment. Women should be counseled that cryotherapy, as well as other outpatient treatment methods, may be less effective in treating lesions in HIV-positive women. All women, regardless of their HIV status, should be encouraged to return for regular screening.

The data from the Cuthill et al. (1995) study suggest that, compared to treating an HIV-infected woman with laser or cone biopsy, treating her with cryotherapy should not increase her risk for complications unless she is severely immuno-compromised. Providers should be aware of the range of possible adverse outcomes and counsel all women appropriately to abstain from intercourse after cryotherapy and seek medical care if needed (see box on page 55).

Researchers are beginning to explore whether the treatment of CIN in HIV-infected women increases transmission risk following treatment. There is some evidence that HIV shedding increases substantially, but temporarily, at the site of cryotherapy. This increased shedding potentially could

increase risk of transmission to an uninfected partner if instructions to abstain from sexual activity during healing are not followed (Wright et al., 2001).

There is little research on whether the cervical tissue exposed by cryotherapy increases a woman's susceptibility to HIV infection. Effective counseling on the importance of abstaining from sexual intercourse during the healing period could prove critical to reducing the risk of HIV transmission or acquisition. Issues surrounding the interaction between HIV and cryotherapy will be explored more in depth in a future paper.

A note on posttreatment recommendations of abstinence:

It is common for treatment protocols in both developed and developing countries to recommend that women abstain from sexual intercourse during the initial healing phase (one month) after cryotherapy treatment to ensure prompt healing and reduce risk of infection. None of the articles in this review have assessed the acceptability of this recommendation or compliance with the recommendation. In some cases, gender inequalities and power differences in the relationship may preclude a woman from being able to negotiate abstinence with her partner. In light of the HIV epidemic in many developing countries and the possible interaction between cryotherapy and HIV acquisition, it is vital that future research not only explore the issues surrounding women's compliance with abstinence instructions, but also investigate ways to increase involvement of and support from male partners in these issues. One ACCP project in South Africa is exploring ways of involving men in cervical cancer prevention and encouraging men to support their partners including observing the abstinence recommendation.

In developing-country settings, where health facilities are often difficult to reach, it may be advisable to schedule treatment at a time that facilitates a woman's ability to remain abstinent during the healing phase, for example, when the woman's partner is traveling away from home. Male partners should be included in the counseling discussions of abstinence when appropriate to increase their acceptance of the treatment recommendations. Finally, couples should be given condoms and encouraged to use them to protect against sexually transmitted infections if they are not able to abstain from sex during the healing phase.

This overview of the literature on cryotherapy attempted to use rigorous methodology where possible, but it is acknowledged that it may have certain limitations that could influence the validity of our conclusions. Our primary method for identifying studies was through searching the MEDLINE database and hand searching the reference lists of retrieved articles. While an attempt was made to identify unpublished studies by contacting researchers in the field, our search did not examine gray literature databases for doctoral theses or unpublished works. Therefore, as in most reviews of this type, it is possible that ours might be subject to publication bias and a possible overestimation of the treatment effect of cryotherapy. Our initial selection criteria excluded articles not written in

English or Spanish. As a result, the data from studies published in other languages are not presented here and the results of this overview could be biased depending on the quality of these studies. One reviewer assessed the retrieved studies for relevancy and two reviewers assessed studies on selection criteria. They were not blinded to each other's assessments and it is possible that the selection criteria might not have been applied equally across all studies. One reviewer extracted the data from studies judged to be relevant. Our review found much variability on certain key variables (lesion characteristics, cryotherapy technique, length of follow-up, and method of assessing disease status), but the extent of heterogeneity remains to be examined in a meta-analysis.

The results of this systematic review of the literature provide evidence that cryotherapy is an effective, safe, and acceptable procedure for the treatment of precancerous lesions. There is a clear need for continued research on the effectiveness, safety, and acceptability of cryotherapy when performed by mid-level providers in a range of settings to provide the most complete information possible to policy makers and health practitioners in low-resource settings. A supplement to this report, based on data being gathered from ACCP country studies, will be provided in 2004.

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