

# A Clinical Decision Analysis of Cryotherapy Compared with Expectant Management for Cervical Dysplasia

Robert M. Hamm, PhD; Vickie Loemker, MD; Kathryn L. Reilly, MD, MPH; Gary Johnson, MD; Peggy Dubois, MD; Kathleen Staveley-O'Carroll, MD; James Brand, MD; Tomas Owens, MD; and Kenneth Smith, MD  
Oklahoma City, Oklahoma

**BACKGROUND.** Screening for precursors of cervical cancer with colposcopic examination for women with abnormal Papanicolaou (Pap) smears identifies those with cervical dysplasia. Though the majority of mild dysplasias (CIN I) will regress, many are treated with cryotherapy.

**METHODS.** We used decision analysis to compare immediate cryotherapy with expectant management (following with another Pap smear or colposcopy, with treatment reserved for progression or a duration of 2 years). The decision tree included the possibility of more invasive surgical procedures if the cryotherapy was ineffective or if the dysplasia progressed in extent of cervical involvement or in grade. Probabilities were derived from literature review and expert judgment. The analysis considered the disutility of the follow-up examinations, cryotherapy, and the more invasive procedures, using expert assessment.

**RESULTS.** Using the baseline assumptions, expectant management led to a better outcome for most patients (57%), who recover with no procedure. However, more patients treated with expectant management required surgical procedures (loop electrosurgical excisional procedure, conization, or, rarely, hysterectomy) than did those treated with immediate cryotherapy. In the expected disutility analysis, expectant management was better than immediate cryotherapy. Sensitivity analysis showed that three factors had the potential to change the recommendation of the analysis: (1) the probability the dysplasia will regress, (2) the disutility of the process of expectant management, and (3) the disutility of invasive procedures compared with cryotherapy.

**CONCLUSIONS.** The analysis indicated that expectant management is preferable to immediate cryotherapy for women with histologically proven mild cervical dysplasia. However, this conclusion depended on assumptions about three factors for which there is insufficient evidence in the literature. More research is needed.

**KEY WORDS.** Cervical intraepithelial neoplasia; decision analysis; cryotherapy; colposcopy. (*J Fam Pract* 1998; 47:93-201)

**F**amily physicians and gynecologists who perform colposcopic examinations of the cervix to evaluate abnormal Papanicolaou (Pap) smears face competing recommendations for patients who have mild cervical dysplasia (histologically proven cervical intraepithelial neoplasia, or

CIN I): to treat immediately with cryotherapy, or to wait and see if the dysplasia will regress. We performed a structured decision analysis to clarify the issue, analogous to recent analyses of breast biopsies<sup>1</sup> and prostate cancer treatments.<sup>2</sup>

Cervical cancer was once a major cause of cancer-related deaths in the United States.<sup>3</sup> From the 1940s to the 1980s, the incidence of cervical cancer diminished dramatically, due in part to Papanicolaou screening and the early treatment of precancerous conditions.<sup>3,8</sup> Currently cervical cancer is the sixth most common cancer in the United States, diagnosed in approximately 15,000 women each year.<sup>9</sup> Cervical cancer remains the second most common cancer among women worldwide,<sup>10</sup> with 490,000 new cases annually.<sup>11</sup>

While the incidence of cervical cancer has decreased in the United States, the incidence of cervical dysplasia, a precursor lesion, has increased significantly in recent years in the United States<sup>12</sup> and worldwide.<sup>13,14</sup> This is possibly because of lifestyle changes or changes in the epidemiology of the human papillomavirus (HPV) infec-

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An earlier version of this work was presented as a poster at the Society for Medical Decision Making annual meetings, Tempe, Arizona, October, 1995. From the Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, Oklahoma City (R.M.H., V.L., K.L.R., P.D., K.S.O., J.B., K.S.); the Department of Obstetrics and Gynecology, University of Oklahoma Health Sciences Center, Oklahoma City (G.J.); and the Great Plains Family Practice Residency Program, Integris Baptist Medical Center and Deaconess Hospital, Oklahoma City (T.O.). Requests for reprints should be addressed to Robert M. Hamm, PhD, Department of Family and Preventive Medicine, University of Oklahoma Health Sciences Center, 900 NE 10th Street, Oklahoma City, OK 73104. E-mail: robert-hamm@ouhsc.edu

tion, a significant cofactor in the development of cervical dysplasia and cancer.<sup>4,11,12</sup> It may also be a result of increased discovery through screening. Our analysis addresses the treatment decision for cervical dysplasia confirmed by histologic analysis of colposcopically guided biopsies to be CIN I. Management without colposcopy is not currently recommended.<sup>15</sup>

The bulk of cervical dysplasias are mild (CIN I)<sup>16,17</sup> and many clinicians have treated mild dysplasia routinely with cryotherapy.<sup>18,19</sup> The natural history and appropriate management of mild dysplasia of the uterine cervix has been controversial for decades.<sup>4,18,20,21</sup> Many studies have concluded that treatment with cryotherapy is appropriate.<sup>4,19</sup> More recently researchers and clinicians have offered patients the expectant management option: follow up their dysplasia with no further treatment unless there is evidence of progression.<sup>12,18,22-25</sup> Ongoing trials will define the optimum treatment for patients with mild dysplasia, but those data will not be available for several years.<sup>26</sup>

Aggressive treatment to eradicate premalignant cells is obviously beneficial for those women in whom cancer would have developed.<sup>18,27,28</sup> However, it would be preferable to avoid expensive, potentially hazardous treatments in women whose abnormalities will regress without intervention.<sup>5,6,17</sup> Since it is impossible to discriminate between those who will and those who will not get cancer, an approach is needed that will prevent the cancers while doing little harm to those who would not have gotten cancer.<sup>22</sup> Therefore, the focus of our analysis is on the natural history and appropriate treatment of the earliest grade of dysplasia (CIN I).

Multiple studies have demonstrated the progressive potential of moderate and severe cervical intraepithelial neoplasia (CIN II and III). Approximately 46% of these dysplasias will persist, and about 20% will progress to invasive cervical cancer.<sup>20</sup> The fate of mild dysplasia (CIN I) is less clear-cut. Progression rates from 2% to 34% are described (best estimate, 12%).<sup>20</sup> The high regression rate and the slow pace of progression have led many clinicians to handle mild dysplasia by expectant management, using repeated Pap smears or colposcopic examinations.

Each management approach has advantages and disadvantages. Patients managed by watchful waiting may progress to higher grades of dysplasia, with the attendant risks for invasive cancer or the need for treatment with more invasive procedures.<sup>4,24</sup> It is expensive to treat every early lesion, however, and the treatments carry the risk of undesirable sequelae,<sup>29-31</sup> so it is not clear which treatment is best.<sup>4</sup> Thus, the core of our decision analysis must be the question of the most appropriate approach to the management of mild cervical dysplasia.

Patients with CIN I are usually treated by cryocauterization of the cervix to destroy the lesion.<sup>4,32</sup> It has a low complication rate, few sequelae, and a cure rate of approximately 95%.<sup>18,19,32,33</sup> The main concerns are its wide application to a relatively benign condition<sup>12,18</sup> and its ability to change the anatomy of the cervix.<sup>33,34</sup>

Cryotherapy frequently leads to endocervical relocation of the squamo-columnar junction as well as relative stenosis of the cervical os. This increases the likelihood of future false-negative Pap smears. In addition, if colposcopy is needed to evaluate future Pap smear abnormalities, it may be difficult to visualize the transformation zone, thus necessitating more invasive diagnostic procedures. The issue of alteration of cervical anatomy will become increasingly important because the rate of teenagers' Pap smear abnormalities and dysplasia is increasing. Therefore, greater numbers of younger women are being found to have CIN I.<sup>19,31,34,35</sup> If cryocautery is applied to their lesions, these young women will probably have complete remission of their lesion postcryotherapy. However, they would have a slightly increased risk of recurrence of dysplasia that may be difficult to evaluate without more invasive procedures,<sup>33</sup> or may be missed altogether because of a false-negative Pap smear.<sup>15</sup>

We have developed a decision analytic framework for choosing a treatment for mild cervical dysplasia.<sup>36,37</sup> Decision analysis<sup>38</sup> uses a decision tree to represent a decision, identifying (1) options that are available, (2) the events that might follow those options, and (3) the consequences of those events occurring. Then data are gathered from the literature and other sources to produce the most credible estimates of the probabilities of these events and the utility of the outcomes. Finally, the overall expected utility of each of the options is calculated.<sup>38,39</sup>

Our decision analysis evaluates the two treatment approaches, immediate cryotherapy and expectant management, at the point when an initial diagnosis (by colposcopy and biopsy) of mild dysplasia has been made. From this point the decision tree considers the possible events in the management strategies, consistent with achieving cure of the cervical dysplasia within 2 years. This length of time was chosen because it is a clinically realistic horizon (most cases will have resolved by that time) and this time span was most common in published studies. The decision tree included the key elements of cure rate, recurrence rate, and probabilities of complications or sequelae with each of the management plans.

## METHODS

### DECISION ANALYTIC FRAMEWORK

The DATA 3.0 program (TreeAge Software, Williamstown, Mass)<sup>40</sup> was used for the analysis (Figure 1). This analysis supports estimation of the likelihood that each type of procedure (cryotherapy, loop excision of the endocervix [LEEP], laser ablation or excision, cone excision, or hysterectomy) will be required for a patient who has been managed by expectant management or by immediate cryotherapy.<sup>36</sup> It also permits measurement of a form of expected utility of each option.

In Tree A ("Mild Dysplasia") in Figure 1, the upper option is expectant management, and the lower option is

immediate cryotherapy.\* The probability of each path from the decision at the left to a terminal branch on the right is the product of the probabilities of all the branches on the path. The consequences at each terminal node can be measured on a disutility scale. The impact of a possible outcome on the attractiveness of an option is measured by multiplying the disutility of the outcome by the probability of taking the path. The addition of all these impacts together produces an overall measure of how beneficial the option is, in this analysis an expected disutility.

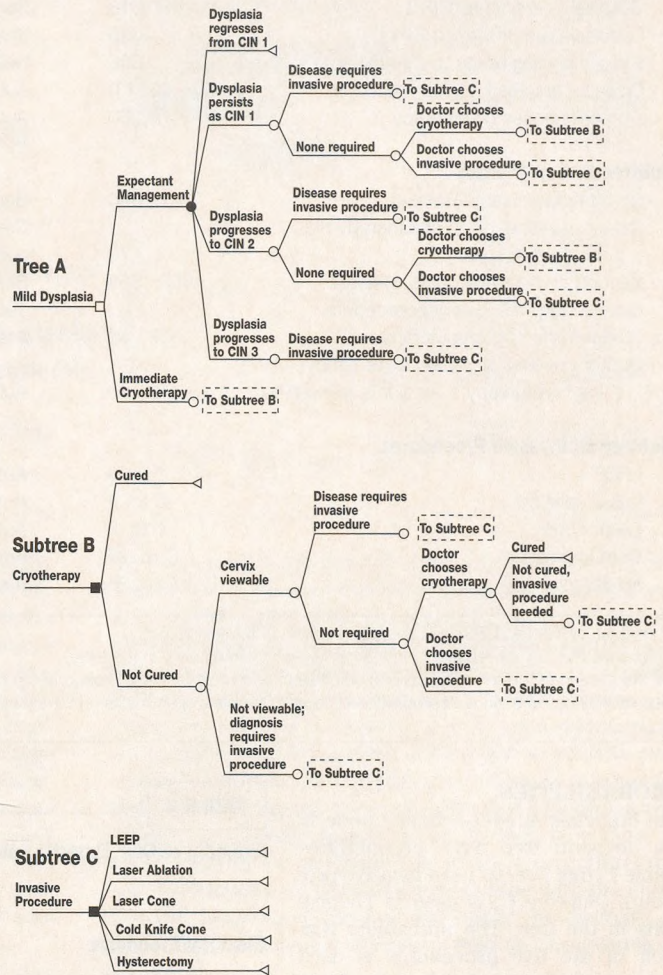
Our analysis includes as its key elements the cure rate with each of the management plans, the possibility that the expectantly followed patient's dysplasia will regress or progress, and the procedures likely to be needed in case of progression, persistence of lesion, or cryotherapy that does not cure the dysplasia. The tree structure groups cervical dysplasias that progress to cancer with the moderate or severe dysplasias that require the more invasive surgical procedures. It is assumed that no treated cervical dysplasia will become metastatic cancer. The events the analysis describes are all the procedures required to control the patient's disease and assure that cancer will not develop or, if it should develop, that it will be treated effectively. The disutilities include all aspects of the process and procedures, as evaluated on a subjective scale. We do not measure life expectancy or quality of life because we assume the patients will be cured and the treatment will not permanently affect their quality of life. There is no discounting of the disutility of procedures or costs that occur late rather than early.

The decision tree does not address the state of the dysplasia at each point. Rather it addresses the probability that each surgical procedure would be selected, whether that be for wide spread or endocervical CIN I, for CIN II, or for CIN III or carcinoma in situ.

This analysis takes the unusual tactic of treating future clinician choices as chance events, even though they technically could be considered decisions (whose options would be analyzed, and the option with the highest expected value selected).<sup>8</sup> This is done for the choices of whether to use cryotherapy or a more invasive surgical procedure when the dysplasia does not regress, and which surgical procedure to use. The later decision about what procedure to use is outside the decision maker's control or prediction. If the followed dysplasia should progress or if the initial cryotherapy should fail to cure the dysplasia,

FIGURE 1

The decision tree for management of mild cervical dysplasia. Tree A includes the decision: cryotherapy or expectant management. To construct the complete tree, Subtrees B and C are inserted multiple times, as indicated. The probabilities of the branches and the utilities of the outcomes in Subtrees B and C can be different, in different instances (see Table 1 and the *Journal's* Web site for more information).



LEEP denotes loop excision of the endocervix.

this clinician may refer to another. Those who receive such referrals find it reasonable to make statements such as, "In such a situation, I use option A approximately 40% of the time." Taking the future decision as an event external to the decision maker, whose probability can be estimated, rather than as something within the control of the decision maker, is a faithful representation of the position of many clinicians faced with the decision how to manage a patient with mild cervical dysplasia.

\* A complete presentation of the decision tree and supporting tables can be found at <http://www.jfp.denver.co.us>

**TABLE 1**

**Probabilities for Decision Tree**

Branch*	P†	Source
<b>Tree A: Initial Decision and Expectant Management Option</b>		
Dysplasia regresses from CIN I	.57	Ostor, 1993 <sup>30</sup>
Dysplasia persists as CIN I	.318	Ostor, 1993 <sup>30</sup>
Dysplasia progresses to CIN II	.056	Nasiell, 1986; <sup>42</sup> Ostor, 1993; <sup>30</sup> Authors' judgment
Dysplasia progresses to CIN II	.056	Nasiell, 1986; <sup>42</sup> Ostor, 1993; <sup>30</sup> Authors' judgment
Disease requires invasive procedure	.07; .20; 1.0	Authors' judgment
Doctor chooses cryotherapy	.75; .60	Authors' judgment
<b>Subtree B: Cryotherapy</b>		
Cryotherapy cures dysplasia	.931; .903	Benedet, 1987; <sup>32</sup> Berget, 1991; <sup>43</sup> Ostergard, 1980; <sup>44</sup> Creasman, 1981; <sup>19</sup> Authors' judgment
Cervix viewable, given cryotherapy did not cure dysplasia	.70	Jobson, 1984; <sup>34</sup> Einerth, 1988; <sup>33</sup> Ferenczy, 1985 <sup>30</sup>
Second cryotherapy cures dysplasia	.903; .808	Benedet, 1987; <sup>32</sup> Ostergard, 1980; <sup>43</sup> Creasman, 1981; <sup>19</sup> Authors' judgment
Disease requires invasive procedure, after ineffective cryotherapy	.352; .58	Authors' judgment
Doctor chooses to repeat cryotherapy if first cryotherapy does not cure dysplasia	.15; .10; .25	Authors' judgment
<b>Subtree C: Invasive Procedures</b>		
LEEP	.3 to .9	Authors' judgment
Laser ablation	0 to .4	Authors' judgment
Laser cone	0 to .2	Authors' judgment
Cold knife cone	0 to .25	Authors' judgment
Hysterectomy	0 to .25	Authors' judgment

P denotes probability; LEEP denotes loop excision of the endocervix.

\*Branches that appear repeatedly in the tree are only named once in the table.

†If branches have different probabilities on different occurrences, these probabilities are given in descending order. For Subtree C, where each branch occurs 17 times, the range of probabilities is given. Complete specification of the probabilities in the tree is available at the Web site named in the text.

**PROBABILITIES**

The branches at every chance node in the decision tree have probabilities (Table 1) that sum to 1. An invasive procedure (Subtree C) is used at 17 locations in the tree. The probability that each of the five procedures is used varies according to the situation. Four experienced colposcopists (one gynecologic oncologist and three family physicians) collaborated to produce the probability estimates.\*

**OUTCOME MEASUREMENT**

Experts' subjective judgments measured the disutility of the procedures involved in producing the outcomes. We summed ratings of the cost and severity

\* The probabilities for each situation are available on the Internet (see footnote on page 195 for address).

**TABLE 2**

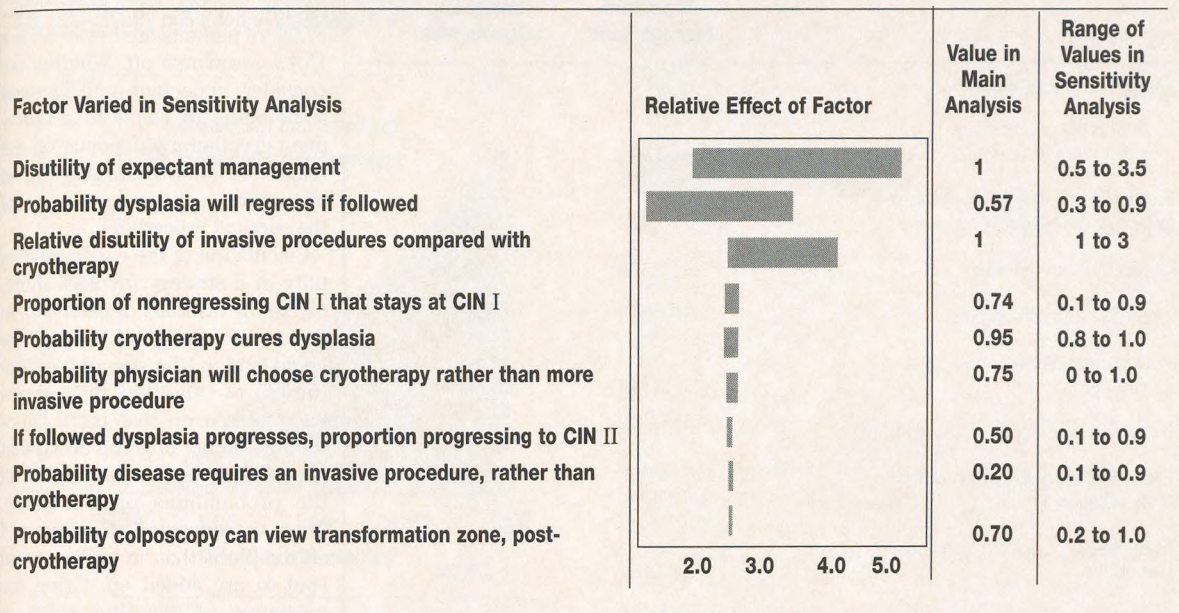
**Example of One Expert's Subjective Measure of the Disutilities of Procedures**

Strategy/Procedure	Cost/Severity of Procedure	Morbidity, Effects on Quality of Life, Possible Long-term Sequelae	Sum
Expectant management with regression	1	0	1
Cryotherapy	1.5	1.5	3
LEEP	2	1	3
Laser ablation	3	1	4
Laser cone	3	2	5
Cold knife cone	3	2	5
Hysterectomy	4	4	8

LEEP denotes loop excision of the endocervix. Scale: 0 = no disutility.

**FIGURE 2**

**Sensitivity analysis: Tornado diagram comparing the effects of changing assumptions about nine variables. Each bar indicates the range over which the expected disutility of the expectant management option would vary, as a function of varying the factor over the indicated range.**



of the procedure itself, and the procedure's morbidity, effect on quality of life, and possible long-term effects (including potential surgical diagnostic procedures for future cervical abnormalities). Raters were only instructed to use a scale where 0 would indicate no disutility, so the units are arbitrary. The values in Table 2 for all procedures included in the analysis were produced by one experienced colposcopist. A second expert's independent judgments correlated  $r = .97$  with these judgments. The disutility of expectant management (inconvenience and discomfort of repeated appointments, pelvic examinations, and ongoing uncertainty, for 2 years on the average) was applied to every patient in the expectant management branch. The disutility of every other procedure was accrued if it happened.

**SENSITIVITY ANALYSIS**

Sensitivity analysis is a method of determining whether and how the results of an analysis depend on the assumed values of its parameters. For example, if we assume there is a low probability that the dysplasia will regress, immediate cryotherapy might seem to be the better management strategy. However, if there truly is a high probability that the dysplasia will regress, then expectant management may be the better strategy. In this case, it could be said that the analysis' recommendation is sensitive to the value assumed for the probability that dysplasia will regress if followed.

We performed sensitivity analyses for the following fac-

tors: the probability that the dysplasia will regress if followed; the proportion of nonregressing dysplasia that persists as CIN I rather than progressing to CIN II or CIN III; the proportion of progressing dysplasia that progresses to CIN II rather than CIN III; the probability that cryotherapy will cure dysplasia; the probability that a colposcopic exam can adequately view the cervix, post cryotherapy; the probability that dysplasia will require an invasive procedure rather than cryotherapy, given it can be adequately seen with colposcopy; the probability that a physician will choose cryotherapy rather than an invasive procedure, in situations that do not require an invasive procedure; the relative disutility of cryotherapy compared with the more invasive surgical procedures; and finally the disutility of expectant management compared with the procedures in Subtree C.

Several of the probabilities we analyzed occur at multiple branches in the decision tree. For example, the probability that cryotherapy will cure dysplasia is a factor for the expectant management strategy, in Subtree B following the "persist as CIN I" branch and following the "progress to CIN II" branch, as well as for the immediate cryotherapy strategy. The probabilities are not identical, but related. To allow them to vary together in a sensitivity analysis, they are constructed as functions of a common variable.\* For each such family of probabilities, a sensitivity analysis

\* Details about these relations are available on the Internet (see footnote on page 195).

**TABLE 3**

**The probability that each treatment approach would resort to each invasive procedure**

	Treatment Approach	
	Expectant Management*	Immediate Cryotherapy
Cured with no procedure	.570	0
<i>Total proportion cured without any procedure</i>	.570	0
Expected number of cryotherapies (effective or ineffective)	.2499	1.061
Cured by 1 cryotherapy	0.2308	0.9500
Cured by 2 cryotherapies	0.0010	0.0055
<i>Total proportion cured with cryotherapy</i>	.2318	.9555
Expected probability of having LEEP	0.1118	0.0332
Expected probability of having laser ablation	0.0235	0.0033
Expected probability of having laser cone	0.0182	0.0024
Expected probability of having cold knife cone	0.0336	0.0043
Expected probability of having hysterectomy	0.0111	0.0013
<i>Total proportion requiring procedure more extensive than cryotherapy</i>	.1982	.0445

\*Do cryotherapy procedure only if required.  
LEEP denotes loop excision of the endocervix.

on the common variable will vary all the probabilities in the related branches, in a logically coordinated manner.

The decision tree of Figure 1 is used with the probabilities in Table 1 to calculate the probability that each procedure (cryotherapy, LEEP, laser ablation, laser cone, cold knife cone, or hysterectomy) will be used. While it is assumed that each of the more invasive procedures would cure the patient, explicit provision is made for the possibility of recurrence after cryotherapy. For example, a patient might have two ineffective cryotherapies and ultimately require a laser cone.

**RESULTS**

The probabilities with which each treatment approach would resort to each procedure are shown in Table 3. They illustrate the essential tradeoff inherent in the decision between expectant management and immediate cryotherapy.

With expectant management, most people (57%) recov-

er with no procedure, but more expectantly managed people require invasive surgical procedures than immediately treated people (19.8% vs 4.5%). Thus, 57.0% of patients are better off but 15.4% are worse off. Whether we consider expectant management to be better or worse than immediate cryotherapy depends on the relative disutilities of receiving no procedure, cryotherapy, or one of the surgical procedures.

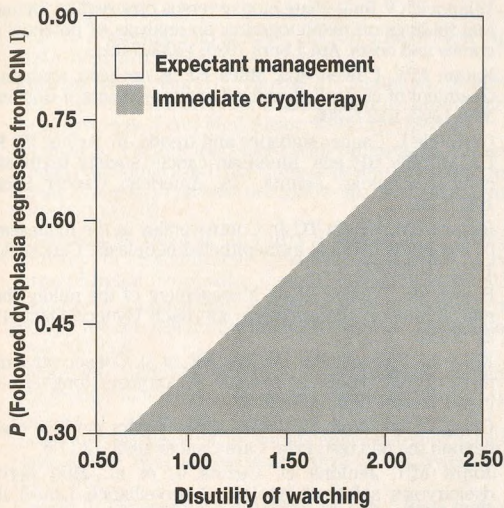
Calculation of the expected disutility of a strategy involves multiplying the disutility of each path in the decision tree that the strategy could lead to (the sum of the disutilities of all the procedures encountered on that path) times the probability of going down that path (which is the product of all the probabilities on the path). Then the expected disutilities of all the paths that an option could lead to are added up. Using the measures of disutility given in Table 2, the expected disutility of expectant management is 2.53 and the expected disutility of immediate cryotherapy is worse, at 3.18. Thus the analysis would recommend expectant management rather than immediate therapy.

**SENSITIVITY ANALYSIS RESULTS**

The conclusion that expectant management is superior to immediate cryotherapy depends on the assumptions of the analysis, including the numerical estimates of the probabilities (Table 1) and the disutilities (Table 2). To compare the possible effects of these variables, Figure 2 shows a tornado diagram for nine variables. The x-axis represents the expected disutility of the alternative that is better in the baseline analysis, expectant management. The bar graphs show how much the estimated disutility of expectant management would change, as an effect of varying each factor over a range of possible values. Consider, for example, the second factor, the probability that the dysplasia would regress. The analysis assumed this probability is .57. If the probability of regression were varied up to .9, the expected disutility of expectant management would decrease from 2.53 to 1.35. If the probability of regression were as low as .3, then the expected disutility of expectant management would increase from 2.53 to 3.40. This latter change would make expectant management worse than immediate cryotherapy, whose

FIGURE 3

Two-way sensitivity analysis: The preferred option depends on the combination of assumptions about the disutility of expectant management and the probability that expectantly managed dysplasia will regress.



expected disutility in the baseline analysis is 3.18.

When they are varied individually, three of the factors have the potential to change the recommendation: the probability the dysplasia will regress, the disutility of the process of expectant management, and the disutility of invasive procedures compared with cryotherapy. The less likely it is that the dysplasia will regress, the less attractive expectant management becomes. The more disutility is attributed to the process of expectant management (repeated visits for colposcopies or Pap smears, the uncertainty of living with a possible cancer precursor), compared with the disutilities assigned to the other procedures, the less attractive expectant management becomes. The more disutility is attributed to invasive procedures compared with cryotherapy, the less attractive expectant management becomes. None of the other variables displayed in Figure 2 could reverse the recommendation of the analysis if varied in isolation, even if varied far beyond realistic possibilities.

The impact of each of the factors that affect the recommendation depends on the value of other factors. For example, Figure 3 shows a two-way sensitivity analysis of the effects of two factors, the disutility of the process of following and the probability that the dysplasia will regress, on the overall disutility of the expectant management strategy. In the upper left triangular region, expectant management is the preferred strategy, while in the lower region immediate cryotherapy is preferred. The threshold value of each factor (the particular value where the options are equally preferred) is different for different

values of the other factor. For example, if the disutility of the expectant management process were 1 (which is one third as bad as cryotherapy), then the probability that the CIN I dysplasia would regress would have to be lower than .38 before immediate cryotherapy would be preferable to expectant management. If the disutility of expectant management were 2, however, then immediate cryotherapy would be preferable if the probability that dysplasia would regress were less than .65.

## DISCUSSION

The analysis indicates a recommendation of expectant management over immediate cryotherapy for mild cervical dysplasia. To most clinicians it may seem paradoxical that the initially less invasive approach eventually produces more invasive procedures, and counterintuitive that the recommendation is for the approach that leads to more bad outcomes. That result is, of course, a function of the assumptions of the decision analysis, including the scope of the analysis, the structure of the tree (Figure 1), and the particular probability and disutility estimates (Tables 1 and 2). The possibility that expectant management will lead to more of the invasive procedures is determined by the nature of the disease and the treatment. In contrast, the relative disutility of cryotherapy, compared with the more invasive procedures and with the supposedly benign process of repeated cervical examinations to track the dysplasia, is a matter of evaluative judgment.

Physicians uncomfortable with the recommendation might first consider that the assumptions to which the recommendation is sensitive are the probability of regression and the evaluations of waiting and of the procedures. Beyond this, they could question the simplifying assumptions of the analysis. We measured only the disutility of the procedures, rather than life expectancy adjusted for the quality of life.<sup>38</sup> We assumed that all cancers will be treated and all cancer deaths avoided (a reasonable assumption given the close monitoring and the low likelihood that this grade of dysplasia will progress to cancer). Hence the treatments themselves were the most significant consequences of the competing strategies. Costs were recognized only as an element in the subjective assessment of the procedures. The approach was essentially atemporal and subjective. All procedures were viewed as identical no matter when they occurred. Subjective estimates of the severity of the procedures were used because we lacked research data. Any of these assumptions might have skewed the analysis.

A major benefit of this analysis is the identification of the significant gaps in our knowledge base about this disease. Currently ongoing studies will further clarify issues regarding real risks and rates of progression, risk stratification, and treatment sequelae.<sup>20</sup> Some of these studies will also clarify the type of follow-up appropriate for an expectant management strategy.

The sensitivity analysis demonstrated the potential key

importance of patient-felt disutilities related to the factors of repeated visits and examinations, long-term uncertainty, and feelings about various procedures and their sequelae and side effects. None of these factors has previously been examined in a fashion useful to the clinician considering the management alternatives. The need to measure patient-felt disutilities related to the treatment options and procedures realistically was recognized by the April 1996 NIH Consensus Development Conference on Cervical Cancer,<sup>45</sup> which called for research on the quality-of-life effects of follow-up only compared with active intervention: "The impact of frequent follow-up visits and the uncertainty of receiving no treatment for a preinvasive lesion with an unknown natural history may be significant and should be studied."<sup>45</sup>

The costs associated with evaluating and treating patients with mild dysplasia are substantial. Colposcopic examination may cost \$100 to \$800, cryotherapy \$100 to \$200, LEEP \$500 to \$800, and cone biopsy \$2000 to \$3000 (including operating room costs). Costs could be incorporated in the decision tree framework with the cost-effectiveness approach.<sup>46</sup> This would require measurements of two factors about each option, not only the utility of the outcome (or some other measure of the good that is accomplished) but also the cost. Dividing the cost by the effect (the change in outcome) provides a measure of the cost per unit of the outcome that can guide the allocation of scarce resources.

The decision analysis is general, using population estimates of risks of progressing and experts' assessments of the disutilities of the procedures for the average patient. The framework developed here could be applied to an individual patient. Information about risk factors (eg, HPV typing,<sup>37</sup> nutritional or immunological factors, coexisting medical conditions, and so forth) could be used to identify patients at low or high risk for progression of dysplasia. Information about the patient's resources and responsibility could be used to identify patients who may not adhere to the recommended follow-up schedule. The patient's own evaluations of relative disutilities of the treatment procedures and outcomes could have a significant effect on the choice of treatment strategy for an individual patient.

The long-term, and perhaps most useful, outcome of the analysis may be its identification of the elements that are most crucial in the decision between the two currently accepted therapeutic approaches to mild cervical dysplasia. Identification of key elements in the decision allows the clinician and patient together to assess the real tradeoffs applicable to the patient's situation. As new data come in to fill in the gaps of our knowledge, this type of assessment, together with the patient's individual feelings about the various options and tradeoffs, could allow a much more realistic and satisfactory management plan consistent with our goal of preventing cervical cancer.

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## REFERENCES

1. Velanovich V. Immediate biopsy versus observation for abnormal findings on mammograms: an analysis of potential outcomes and costs. *Am J Surg* 1995; 170:327-32.
2. Kattan MW, Cowen ME, Miles BJ. A decision analysis for treatment of clinically localized prostate cancer. *J Gen Intern Med* 1997; 12:299-305.
3. Garfinkle L. Cancer statistics and trends. In: Arthur IH, Fink DJ, Murphy GP, eds. *American cancer society textbook of clinical oncology*. Atlanta, Ga: American Cancer Society; 1991:1-24.
4. Richart RM, Wright TC Jr. Controversies in the management of low-grade cervical intraepithelial neoplasia. *Cancer Suppl* 1993; 71:1413-21.
5. Brown MS, Phillips GL Jr. Management of the mildly abnormal pap smear: a conservative approach. *Gynecol Oncol* 1985; 22:149-53.
6. Kirby AJ, Spiegelhalter DJ, Day NE, et al. Conservative treatment of mild/moderate cervical dyskaryosis: long-term outcome. *Lancet* 1992; 339:828-31.
7. Grana G, Engstrom PF. Office screening for cervical cancer: beyond the pap test. *Prim Care Cancer* 1992; 12:11-6.
8. Jones MH, Jenkins D, Cuzick J, et al. Mild cervical dyskaryosis: safety of cytological surveillance. *Lancet* 1992; 339:1440-3.
9. American Cancer Society. *Cancer facts and figures*. American Cancer Society; 1996.
10. Petro R, zur Hausen H. *Viral etiology of cervical cancer*. New York, NY: Cold Springs Harbor Laboratory; 1986.
11. Cox JT, Lorincz AT, Schiffman MH, Sherman ME, Cullen A, Kurman RJ. Epidemiology of cervical intraepithelial neoplasia: the role of human papillomavirus. *Baillieres Clin Obstet Gynaecol* 1995; 9:1-37.
12. Larsen NS. Invasive cervical cancer rising in young white females. *J Natl Cancer Inst* 1994; 86:6-7.
13. MacCormac L, Lew W, King G, Allen PW. Gynaecological cytology screening in South Australia: a 23-year experience. *Med J Aust* 1988; 149:530-6.
14. Kainz C, Gitsch G, Heinzl H, Breitenacker G. Incidence of cervical smears indicating dysplasia among Austrian women during the 1980s. *Br J Obstet Gynaecol* 1995; 102:541-4.
15. Ferris DG, Wright TC Jr, Litaker MS, et al. Triage of women with ASCUS and LSIL on Pap smear reports: management by repeat Pap smear, HPV DNA testing, or colposcopy? *J Fam Pract* 1998; 46:125-34.
16. Luthra UK, Prabhakar AK, Seth P, et al. Natural history of precancerous and early cancerous lesions of the uterine cervix. *Acta Cytol* 1987; 31:226-34.
17. Montz FJ, Monk BJ, Fowler JM, Nguyen L. Natural history of the minimally abnormal papanicolaou smear. *Obstet Gynecol* 1992; 80:385-7.
18. Brotzman GL, Apgar BS. Cervical intraepithelial neoplasia: current management options. *J Fam Pract* 1994; 39:271-8.
19. Creasman WT, Clarke-Pearson DL, Weed JCJ. Results of outpatient therapy of cervical intraepithelial neoplasia. *Gynecol Oncol* 1981; 12:S306-16.
20. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol* 1993; 12:186-92.
21. Ho GYF, Bierman R, Beardsley L, Chang CJ, Burk RD. Natural history of cervicovaginal papillomavirus infection in young women. *New Eng J Med* 1998; 338:423-8.
22. Shafi MI, Luesley DM. Management of low grade lesions: Follow up or treat? *Baillieres Clin Obstet Gynaecol* 1995; 9:121-31.



23. Figge DC, Alvarez R, Brown DV, Fullington WR. Long-range studies of the biologic behavior of the human uterine cervix: atypical epithelial hyperplasia. *Am J Obstet Gynecol* 1962; 84:638-47.
24. Richart R, Barron B. A follow-up study of patients with cervical dysplasia. *Am J Obstet Gynecol* 1969; 105:386-93.
25. Robertson JH, Woodend BE, Crozier EH, Hutchinson J. Risk of cervical cancer associated with mild dyskaryosis. *BMJ* 1988; 297:18-21.
26. Titus K. Abnormal Pap smears, ASCUS still Ob/Gyn puzzle. *JAMA* 1996; 276:1014-5.
27. Kurman RJ, Henson DE, Herbst AL, Noller KL, Schiffman MH. Interim guidelines for management of abnormal cervical cytology. *J Am Med Assoc* 1994; 271:1866-9.
28. Syrjanen K. Factors associated with progression of cervical human papillomavirus (HPV) infections into carcinoma in situ during a long-term prospective follow-up. *Br J Obstet Gynecol* 1988; 95:1096-102.
29. Creasman W, Weed JC Jr, Curry S, Johnston W, Parker R. Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia. *Obstet Gynecol* 1973; 41:501-6.
30. Ferenczy A. Comparison of cryo- and carbon dioxide laser therapy for cervical intraepithelial neoplasia. *Obstet Gynecol* 1985; 66:793-8.
31. Hillard PA, Biro FM, Wildey L. Complications of cervical cryotherapy in adolescents. *J Reprod Med* 1991; 36:711-6.
32. Benedet JL, Miller DM, Nickerson KG, Anderson GH. The result of cryosurgical treatment of cervical intraepithelial neoplasia at one, five, and ten years. *Am J Obstet Gynecol* 1987; 157:268-73.
33. Einert Y. Cryosurgical treatment of CIN I-III: a long term study. *Acta Obstet Gynecol Scand* 1988; 67:627-30.
34. Jobson VW, Homesley HD. Comparison of cryosurgery and carbon dioxide laser ablation for treatment of cervical intraepithelial neoplasia. *Colposcopy Gynecol Laser Surg* 1984; 1:173-80.
35. Draeby-Kristiansen J, Garsaae M, Bruun M, Hansen K. Ten years after cryosurgical treatment of cervical intraepithelial neoplasia. *Am J Obstet Gynecol* 1991; 165:43-5.
36. Hamm RM, Dubois PC, Loemker V, et al. Watchful waiting versus cryotherapy for mild cervical dysplasia demonstrated by colposcopy-guided biopsy (meeting abstract). *Med Decis Making* 1995; 15:422.
37. Hamm RM, Loemker V, Johnson G, Reilly K. Role of HPV DNA testing for decision on how to manage mild cervical dysplasia. *Med Decis Making* 1997; 17:529.
38. Weinstein M, Fineberg H. *Clinical Decision Analysis*. Philadelphia: WB Saunders Company; 1980.
39. Detsky AS, Naglie G, Krahn MD, Naimark D, Redelmeier DA. Primer on medical decision analysis: Part 1-Getting started. *Med Decis Making* 1997; 17:123-5.
40. TreeAge Software, Inc. *DATA 3.0 User's Manual*. 1075 Main Street, Williamstown, MA, 01267, 800-354-1911: TreeAge Software, Inc; 1996.
41. Nasiell K, Roger V, Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1986; 67:665-9.
42. Nasiell M. Behavior of mild cervical dysplasia during long-term follow-up. *Obstet Gynecol* 1986; 67:665-9.
43. Berget A, Andreasson B, Bock JE. Laser and cryo surgery for cervical intraepithelial neoplasia: a randomized trial with longterm follow-up. *Acta Obstet Gynecol Scand* 1991; 70:231-5.
44. Ostergard D. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstet Gynecol* 1980; 56:231-3.
45. Braly PS, Lichter AS. NIH Consensus Development Conference Statement: Cervical Cancer. National Institutes of Health; 1996.
46. Kamlet MS. A framework for cost-utility analysis of government health care programs. US Department of Health and Human Services, Washington, DC; 1992.