

2001 Consensus Guidelines for the Management of Women with Cervical Intraepithelial Neoplasia

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OBJECTIVE: The study was undertaken to provide consensus guidelines for the management of women with histologically confirmed cervical intraepithelial neoplasia (CIN) that can act as a precursor to invasive cervical cancer and represents one of the most common significant gynecologic diseases of women of reproductive age.

PARTICIPANTS: An independent panel of 121 experts in various aspects of the diagnosis and management of cervical cancer precursors, including representatives from 29 participating professional organizations, federal agencies, national and international health organizations, and others were invited by the American Society for Colposcopy and Cervical Pathology (ASCCP).

CONSENSUS PROCESS: Guidelines for the management of women with CIN were developed through a multistep process. Draft management guidelines were developed by working groups who performed formal literature reviews and obtained input from the professional community at large by way of an interactive internet-based bulletin board. At the ASCCP Consensus Conference, September 6 through 8, 2001, in Bethesda, Md, all guidelines were discussed, revised, and adopted by formal vote.

CONCLUSION: Evidence-based guidelines have been developed for the management of women with biopsy-confirmed CIN. (Am J Obstet Gynecol 2003;189:295-304.)

Key words: Cervical intraepithelial neoplasia, LEEP, colposcopy

Once a leading cause of cancer death in the United States, invasive cervical cancers are now relatively uncommon. This shift is often attributed to the adoption of cytologic screening, but cervical cytology alone is insufficient to prevent cervical cancer. Prevention requires the eradication of cancer precursor lesions referred to as cervical intraepithelial neoplasia, or CIN, and these constitute one of the most commonly encountered significant health problems among women of reproductive age in the United

States. Although exact figures are not available, laboratory surveys from the College of American Pathologists (CAP) indicate that more than 1 million women each year are diagnosed with low-grade intraepithelial lesions, referred to as cervical intraepithelial neoplasia (CIN) grade 1, and 500,000 will be found to have high-grade cervical cancer precursor lesions, referred to as CIN-2 and CIN-3.¹

During the past decade, new data on the epidemiology, natural history, and treatment of CIN have become available, but efforts to integrate this information into clinical management have been limited. In September 2001, the American Society for Colposcopy and Cervical Pathology (ASCCP) held a consensus workshop to develop evidence-supported consensus-based guidelines for the management of women with cytologic abnormalities and cervical cancer precursors. This meeting had representatives from 29 participating professional organizations, federal agencies, and national and international health organizations. Input from the professional community was obtained through a novel approach that incorporated internet-based discussion groups. This report provides a summary of recommendations from that meeting with respect to managing biopsy-confirmed cervical cancer precursors. Management guidelines for cytologic abnormalities from the 2001 Consensus Conference have already been published.²

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General comments

The 2001 Consensus Conference and the process used to develop the Consensus Guidelines have previously been reported.² Each guideline is rated by using a 2-part grading system.^{3,4} The “strength of recommendation” for or against the use of a particular option is indicated by the letters A through E. It is important to recognize that several criteria that included the possibility for harm to a patient if a specific intervention did not take place, the possible complications that could be associated with a given intervention, as well as the quality of the evidence for a specific recommendation, were all taken into account when determining the “strength of recommendation.” Therefore, an exact correlation does not exist between the “quality of evidence” and the “strength of a recommendation.” “Quality of evidence” was designated by using roman numerals I through III as defined in Table I. A number of terms that are used in the guidelines were specifically defined at the beginning of the Consensus Conference, Table I. These include the terms *recommended*, *preferred*, *acceptable*, and *unacceptable*.

The 2001 Consensus Guidelines are designed to help standardize the management of women with cytologic abnormalities and cervical intraepithelial neoplasia. It is important to recognize, however, that it is impossible for guidelines to apply to all clinical situations and therefore clinical discretion is critical when developing a management plan for a specific patient. A full discussion of the limitations inherent in the use of clinical guidelines and definitions of terms used in the 2001 Consensus Guidelines have been published and are also available at www.asccp.org.²

Cervical intraepithelial neoplasia grade 1 (CIN-1)

General comments. Women with a diagnosis of CIN-1 on a colposcopically directed biopsy represent a heterogeneous group. Numerous studies have documented a high level of intraobserver and interobserver variability in the histologic diagnosis of CIN-1.⁵⁻⁷ In the National Cancer Institute’s ASCUS/LSIL Triage Study (ALTS) clinical trial, only 43% of the cervical biopsies initially diagnosed as CIN-1 were classified as CIN-1 by the expert pathology review committee, 41% were downgraded to normal, and 13% were upgraded to CIN-2 and CIN-3.⁷ In addition, a colposcopically directed biopsy represents a limited sampling of the cervix that may be influenced by a number of factors, including the skill of the colposcopist and only moderate specificity of colposcopic findings.⁷ Studies of women with CIN-1 diagnosed on a colposcopically directed biopsy, who undergo a loop electrosurgical excision procedure (LEEP), have identified CIN-2 and CIN-3 in 23% to 55% of the excised specimens.⁸

The natural history of untreated CIN-1 is characterized by high rates of spontaneous regression and low rates of progression to cancer. A comprehensive literature review

that included information on 4504 patients with CIN-1 found that spontaneous regression occurs in 57% of patients and 11% progress to CIN-2 and CIN-3 or cancer.⁹ Overall, the rate of progression to invasive cervical cancer observed in these studies was 0.3%. A recent meta-analysis of the natural history of CIN-1 arrived at similar conclusions.¹⁰ Similar rates of detection of CIN-2 and CIN-3 have been noted in the 2-year follow-up of biopsy-confirmed CIN-1 in the National Cancer Institute’s ALTS (Mark Schiffman, written communication, Sept 7, 2001). There is no definitive method to identify which CIN-1 lesions will spontaneously regress and which will persist or progress. Loss of heterozygosity at specific chromosomal loci, *FHIT* (a candidate tumor-suppressor gene) expression, telomerase activity, DNA ploidy, Ki-67 expression, human papillomavirus (HPV) type and variants, and p16 expression have been evaluated as potential biomarkers of clinical outcome.¹¹⁻¹⁶ Although the available data are promising, there is currently insufficient information to support the routine clinical use of any of these biomarkers.

The poor reproducibility of the histologic diagnosis of CIN-1, as well as the uncertain biologic potential of lesions that are classified on the basis of their histologic appearance as CIN-1, makes management of these women problematic. It is also important to note that with the use of either cytologic or histologic methods alone, it is impossible to determine whether a CIN-1 that appears to be persistent is a truly persistent lesion or represents a new lesion.

Approaches to managing women with CIN-1

Follow-up of biopsy-confirmed CIN-1. Because most cases of CIN-1 spontaneously regress without therapy, many experts advocate follow-up without treatment if the colposcopic examination is satisfactory.^{17,18} It is important to recognize, however, that although invasive cancers have been observed in most large series, these have usually occurred among women who were lost to follow-up.¹⁹⁻²¹

Follow-up protocols for women with CIN-1 vary and have not been compared in prospective trials. Some protocols use cytology alone, others a combination of cytology and periodic colposcopy. Follow-up intervals vary from 3 to 12 months, and the length of time during which women are followed with CIN-1 before treatment is recommended varies from months to years. Prospective follow-up studies indicate that the risk a woman with biopsy-confirmed CIN-1 undergoing conservative follow-up will subsequently develop, or will be subsequently found to have, biopsy-confirmed CIN-2 and CIN-3 is 9% to 16%.^{19,22} This is approximately the same risk that a woman with a cytologic result of atypical squamous cells of undetermined significance (ASC-US) has of having biopsy-confirmed CIN-2 and CIN-3.²³⁻²⁵ This suggests that women with biopsy-confirmed CIN-1 can be safely followed by using a program of repeat cervical cytology similar to that considered acceptable for women with a

Table I. Rating the recommendations*

Strength of recommendation†	
A	Good evidence for efficacy and substantial clinical benefit support recommendation for use.
B	Moderate evidence for efficacy or only limited clinical benefit supports recommendation for use.
C	Evidence for efficacy is insufficient to support a recommendation for or against use, but recommendations may be made on other grounds.
D	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
E	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use.
Quality of evidence†	
I	Evidence from at least 1 randomized, controlled trial.
II	Evidence from at least 1 clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than 1 center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.
III	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.
Terminology‡	
Recommended:	Good data to support use when only 1 option is available.
Preferred:	Option is the best (or 1 of the best) when there are multiple other options.
Acceptable:	One of multiple options when there are either data indicating that another approach is superior or when there are no data to favor any single option.
Unacceptable:	Good data against use.

*Used with permission from Wright et al.²

†Modified from Kish⁴ and Gross et al.⁹⁰

‡The assignment of these terms represents an opinion or vote by the Consensus Conference and the assignment is not directly linked to the “strength of evidence” or “quality of evidence.”

cytologic diagnosis of ASC-US.² ALTS longitudinal follow-up data confirmed that testing for HPV at 12 months is an alternative to 2 repeat cervical cytology tests in the follow-up of women with CIN-1.²⁶ HPV DNA testing detected 95% of the CIN-3 found over the 2-year follow-up, with re-referral of 55% of women. In contrast, repeat cytology at 6 and 12 months cumulatively detected 85% of the CIN-3 with re-referral of 60% of women to colposcopy and an extra office visit for all. This data, combined with evidence that only persistent HPV progresses to CIN-3, and that testing for high-risk HPV detects most CIN-3, indicates that HPV DNA testing at 12 months provides an acceptable follow-up approach for women with CIN-1.²⁷

Incorporating periodic colposcopic examinations during follow-up would help assure that CIN-2 and CIN-3 are not missed, but would be expected to increase the costs of follow-up and necessitates access to colposcopic services. However, there are no studies demonstrating the superiority of follow-up protocols incorporating colposcopy as opposed to cytology alone. Follow-up of women with CIN-1 beyond 24 months has been shown to result in both increased cumulative rates of spontaneous regression, as well as higher rates of progression to CIN-2 and CIN-3.²⁸ However, there are no data to suggest that follow-up of patients with persistent CIN-1 for more than 24 months is unsafe in compliant populations.

A conservative follow-up protocol is more controversial when patients with biopsy-confirmed CIN-1 have an unsatisfactory colposcopic examination because these patients may have occult disease of higher grade within the

endocervical canal. One series of women undergoing cone biopsies for CIN-1 reported that for those women with an unsatisfactory colposcopy, regardless of the endocervical sampling results, the rate of detection of CIN-2 and CIN-3 in the conization specimen was about 10%.²⁹ Because data are limited and the consequences of missing an occult invasive cancer are significant, a diagnostic excisional procedure is more appropriate than follow-up without treatment for women with biopsy-confirmed CIN-1 and an unsatisfactory colposcopic examination, regardless of the endocervical sampling results.

Treatment options: Both ablative modalities that destroy the effected cervical tissue in vivo and excisional modalities that remove the effected tissue and allow pathologic examination have been widely used to treat CIN-1 in women with satisfactory colposcopic examinations.^{30,31} Although several topical agents are currently being evaluated for efficacy and tolerance in the treatment of women with biopsy-confirmed CIN-1, at the current time there is insufficient published data to develop recommendations either for or against their use.

Ablative modalities include cryotherapy, electrofulguration, laser ablation, and cold coagulation. Ablative procedures have usually been recommended only for women who have a satisfactory colposcopic examination and in whom invasive cervical cancer has been ruled out through a combination of colposcopy and endocervical sampling with cytologic correlation.²⁹ This is because a number of studies have shown that pretreatment endocervical sampling can help identify women with occult invasive cervical cancer.^{32,33} In 1 study of 391 women

undergoing a diagnostic excisional conization, none of the women with a negative endocervical curettage were subsequently found to have invasive disease, whereas all the 17 with invasive disease had positive endocervical sampling.³² Studies of patients presenting with invasive cervical cancer after ablative therapy have shown that many either did not have endocervical disease excluded by endocervical sampling before treatment or underwent an ablative procedure despite a positive endocervical sampling.³⁴⁻³⁶

Excisional modalities include LEEP, laser, and cold-knife conization (ie, diagnostic excisional procedures). It is often recommended that posttreatment recurrence of CIN be treated by using excisional as opposed to ablative methods.³⁷ This is because recurrent/persistent CIN frequently occurs in the endocervical canal where it is not colposcopically detectable and therefore not suitable for ablative therapy. In addition, many women with recurrent CIN are considered unsuitable for ablative therapy either because their colposcopic findings, a suspicion of invasive disease, or because they are considered to be at high-risk for having occult invasive disease.³⁸⁻⁴¹ Hysterectomy carries a substantially greater risk of morbidity, and even mortality, when compared with excisional and ablative procedures, and this outweighs any potential benefit to its use as primary therapy for women with CIN-1.

A randomized clinical trial comparing cryotherapy, laser ablation, and LEEP as treatment for CIN of all grades reported no significant difference in complication or clearance rates associated with the different treatment modalities.⁴² Other studies comparing cryotherapy with laser vaporization have also reported similar success rates for both modalities, as have studies comparing laser vaporization with LEEP.^{43,44} A systematic review of published controlled and randomized trials reported no significant difference in outcomes with respect to recurrence of CIN between cryotherapy, laser ablation, or LEEP, in women with satisfactory colposcopic examinations.⁴⁵ Similarly, all the approaches used for diagnostic excisional procedures (ie, LEEP, laser conization, and cold-knife conization) have been shown to be effective. Although loop electrosurgical conizations have been associated with lower blood loss, better posttreatment colposcopic visualization, and shorter operative times than cold-knife conizations in some studies, pathologic margins are often more frequently involved and more difficult to interpret than with cold-knife conizations.⁴⁶⁻⁴⁸ Therefore, a decision as to which therapeutic option is best for an individual patient depends on factors such as the training and experience of the clinician, the preferences of the patient, the resources available, the expected clinical value of a given treatment modality for that patient, and whether cancer has been excluded.

Recommendations for managing women with biopsy-confirmed CIN-1

Women with satisfactory colposcopic examination. Management options for women with biopsy-confirmed CIN-1 are follow-up without treatment or treatment with the use of ablative or excisional modalities, Table II. Follow-up with a program of either repeat cervical cytology, at 6 and 12 months, or HPV DNA testing for high-risk types of HPV at 12 months, is the preferred management approach for women with biopsy-confirmed CIN-1 and a satisfactory colposcopic examination (AII). When follow-up is used, referral to colposcopy is preferred if a repeat cytology is reported as ASC or greater or the woman is high-risk HPV DNA positive at 12 months (AII). After 2 negative, consecutive cervical cytology tests or a negative DNA test for high-risk types of HPV at 12 months, it is preferred that patients return to annual cytologic screening (BII). In clinical settings where colposcopy is available, a combination of repeat cytology and colposcopic examination at 12 months is an acceptable approach to follow-up (AII). Women found to have cytologic or combined cytologic and colposcopic regression during follow-up continue to be at higher risk, and it is recommended that they have follow-up with repeat cytology at 12 months (BIII). The decision to treat persistent CIN-1 should be based on patient and provider preferences (BIII).

Provided the colposcopic examination is satisfactory and treatment is selected, the following treatment modalities for biopsy-confirmed CIN-1 are considered acceptable: cryotherapy, electrofulguration, laser ablation, cold coagulation, and LEEP (AI). If treatment is selected, the choice of treatment should be determined by the judgment of the clinician and should be guided by experience, resources, and clinical value for the specific patient (AI). It is recommended that endocervical sampling be performed before ablation of CIN-1 (AII). Excisional modalities are preferred for patients who have recurrent biopsy-confirmed CIN-1 after undergoing previous ablative therapy (BII).

Women with unsatisfactory colposcopic examination. The preferred treatment for patients with biopsy-confirmed CIN-1 and an unsatisfactory colposcopic examination is a diagnostic excisional procedure (ie, LEEP, laser conization, or cold-knife conization) (AII). Exceptions where follow-up are acceptable are pregnant and immunosuppressed women (see CIN-2 and CIN-3 special circumstances), and adolescent women in whom, based on limited experience, CIN-2 and CIN-3 are rare in the setting of biopsy-confirmed CIN-1 and an unsatisfactory colposcopy (CIII).

Unacceptable treatment approaches. Ablative procedures are unacceptable for CIN-1 in patients with an unsatisfactory colposcopic examination (EII). Podophyllin or podophyllin-related products are unacceptable for use in the vagina or on the cervix (EII). Hysterectomy as the

Table II. Synopsis of management guidelines for biopsy-confirmed CIN

	<i>Strength</i>	<i>Quality</i>	<i>Terminology</i>
Women with biopsy-confirmed CIN-1			
When colposcopy is satisfactory:			
Options are follow-up without treatment or treatment using ablative or excisional modalities.			
Follow-up without treatment			
Follow-up with repeat Pap test at 6 and 12 mo <i>or</i> HPV testing at 12 mo is preferred.	A	II	Preferred
Refer to colposcopy if repeat cytology of \geq ASC or high-risk HPV DNA positive.	A	II	Preferred
After 2 negative cytology results or a negative HPV test, return to annual screening.	B	II	Preferred
A combination of repeat cytology and colposcopy at 12 mo is also acceptable for follow-up.	A	II	Acceptable
It is recommended that women with regression during follow-up have repeat cytology at 12 mo.	B	III	Recommended
Decision to treat persistent CIN-1 should be based on patient and provider preferences.	B	III	
Treatment			
Cryotherapy, laser ablation, and LEEP are all acceptable treatment modalities.	A	I	Acceptable
Treatment modality should be determined by the judgment of the clinician.	A	I	
Endocervical sampling is recommended before ablation of CIN-1.	A	II	Recommended
Excisional modalities are preferred for recurrent CIN-1 occurring after previous ablative therapy.	B	II	Preferred
When colposcopy is unsatisfactory:			
The preferred treatment is a diagnostic excisional procedure	A	II	Preferred
Follow-up is acceptable in pregnant, immunosuppressed women, and adolescent women.	C	III	Acceptable
Women with biopsy-confirmed CIN-2,3			
Initial management			
Both excision and ablation are acceptable for women with CIN-2,3 and a satisfactory colposcopy.	A	I	Acceptable
In patients with recurrent CIN-2,3, excisional modalities are preferred.	A	II	Preferred
Diagnostic excisional procedures are recommended for CIN-2,3 and unsatisfactory colposcopy.	A	II	Recommended
Observation of CIN-2,3 with sequential cytology and colposcopy is unacceptable, except in special circumstances.	E	II	Unacceptable
Hysterectomy is unacceptable as primary therapy for CIN-2,3.	E	II	Unacceptable
Follow-up after treatment			
Follow-up using either cytology or combination of cytology and colposcopy at 4- to 6-mo intervals until at least 3 cytologic results are negative is acceptable.	A	II	Acceptable
During cytologic follow-up, the recommended threshold for referral to colposcopy is \geq ASC.	A	II	Recommended
Annual cytology follow-up is recommended after 3 negative cytologic results are obtained.	A	II	Recommended
HPV DNA testing performed at least 6 mo after treatment is acceptable for surveillance.	B	II	Acceptable
If high-risk types of HPV are identified, colposcopy is recommended.	B	III	Recommended
If HPV testing is negative, triage to annual cytology follow-up is recommended.	B	II	Recommended
Repeat conization or hysterectomy based on a single positive HPV test is unacceptable.	D	III	Unacceptable
If CIN is identified at the margins of a diagnostic excisional procedure or in a postprocedure endocervical sampling.			
A colposcopic examination and an endocervical sampling is preferred at the 4- to 6-mo follow-up.	B	II	Preferred
A repeat diagnostic excisional procedure is acceptable in this setting.	A	II	Acceptable
Hysterectomy is acceptable in this situation when a repeat diagnostic excision is not feasible.	B	II	Acceptable

primary and principal treatment for biopsy-confirmed CIN-1 is unacceptable (EII).

CIN-2 and CIN-3

General comments. The term *CIN-2,3* is used to refer to lesions previously referred to as moderate dysplasia (ie, CIN-2) and severe dysplasia/carcinoma in situ (ie, CIN-3).⁴⁹ Although natural history studies of untreated moderate dysplasia, severe dysplasia, and carcinoma in situ have reported differences in the behavior of these lesions

during long-term follow-up, the histologic diagnosis of these entities is poorly reproducible.^{5-7,45} Moreover, follow-up studies have found that despite marginal relative differences, all these lesions are more likely to persist or progress than to regress. Review of the published natural history literature indicates that 43% of untreated CIN-2 lesions will regress in the absence of treatment, whereas 35% will persist and 22% progress to carcinoma in situ or invasive cervical cancer.⁵⁰ For comparison, 32% of CIN-3 lesions spontaneously regress, 56% persist, and 14%

progress. Therefore, recommendations for the management of women with histologically confirmed CIN-2 and CIN-3 are combined in the 2001 Consensus Guidelines.^{49,51}

Treatment of women with biopsy-confirmed CIN-2,3

Satisfactory colposcopic examination. There is general agreement that either ablation or excision of CIN-2,3 reduces the incidence and mortality caused by invasive cervical cancer in women with these lesions.⁵² Multiple techniques have been used for the treatment of CIN-2,3 in women with satisfactory colposcopic examinations in whom invasion has been ruled out. These include ablative methods (eg, cryotherapy, laser vaporization, electrocautery, diathermy, and cold coagulation) as well as excisional methods (eg, LEEP, laser conization, and cold-knife conization) and hysterectomy. To be effective, it appears that treatment needs to remove the entire transformation zone, rather than selectively targeting the colposcopically identified lesion.⁵³ As discussed under the section pertaining to treatment of CIN-1, clinical trials comparing different treatment modalities have generally failed to show significant differences in outcomes among treatment modalities. However, because excisional procedures allow pathologic assessment of the excised tissue, they should reduce the risk that a microinvasive or occult invasive carcinoma is inadvertently treated as a preinvasive lesion. In 1 of the largest follow-up studies of women having undergone outpatient ablative therapy of CIN, 4 cases of microinvasive cervical cancer and 5 cases of frankly invasive cancer were subsequently diagnosed among 3783 women.⁵⁴ Because of these considerations, some authors have recommended excisional procedures be used for the management of biopsy-confirmed CIN-2,3, especially for large lesions that are at increased risk of having microinvasive or occult invasive carcinoma.⁵⁵⁻⁵⁷

Unsatisfactory colposcopic examination. Up to 7% of women with an unsatisfactory colposcopic examination and biopsy-confirmed CIN-2,3 undergoing a diagnostic excisional conization have an occult invasive cervical carcinoma.^{32,58} Therefore, diagnostic conization procedures that allow pathologic examination of tissue from the endocervical canal are usually used for women with biopsy-confirmed CIN-2,3 who have an unsatisfactory colposcopic examination. Several randomized clinical trials and clinical case series comparing the efficacy of cold-knife conization with loop electrosurgical excisional conization have found equivalent success rates and comparable rates of complications for each.^{58,59} Whether there is a significant difference between cold-knife conizations and loop electrosurgical excisional conizations with respect to pathologic margins is controversial. Some studies, but not others, have reported that pathologic margins are less frequently involved, and easier to interpret with cold-knife conizations compared with loop electrosurgical conizations.^{46-48,58}

Role of margin status in women undergoing diagnostic excisional procedures. Pathologic margin status is widely accepted as a risk factor for recurrent/persistent CIN.⁶⁰⁻⁶³ In 1 series of 381 women undergoing cold-knife conization, the rates of recurrent/persistent CIN were 16% among women with positive margins and 4% among women with negative margins.⁶³ When performed at the time of a diagnostic excisional procedure, endocervical sampling correlates with endocervical margin status, and a positive endocervical sampling is predictive of residual disease at a subsequent procedure.^{32,64}

Although a number of studies have reported that recurrent/persistent CIN occurs more often in women with involved margins, the few studies that have used multivariate analysis to adjust for contributing factors have found margin status not to be an independent predictor of residual disease.^{65,66} In addition, it is important to recognize that most women with involved margins remain disease free on follow-up. Up to 40% of women undergoing LEEP have incomplete excision of their CIN lesions on the basis of histopathologic interpretation of specimen margins.^{40,67} Therefore, most studies have recommended that women with positive margins be counseled about the relative risks of observation versus further treatment and that their management be individualized on the basis of desire for fertility, age, patient preference, and other factors. For women who elect further treatment, repeat excision offers a balance between the risk of treatment complications and the desire to eradicate potential residual CIN. Hysterectomy remains appropriate in selected instances.

Special circumstances

Pregnancy. The risk of progression of CIN-2,3 to invasive cervical cancer during pregnancy is minimal and the rate of spontaneous regression postpartum is relatively high.⁶⁸ One study of 153 pregnant women with CIN-2,3 who were followed during pregnancy reported a 69% spontaneous regression rate and identified no invasive cancers postpartum.⁶⁹ Thus, the goals of management for pregnant women with CIN-2,3 are to identify rare cases of occult invasive and invasive cancer that occur during pregnancy. Excisional procedures, including loop electrosurgical excisions and cold-knife conizations, performed during pregnancy are associated with complications that include significant bleeding and preterm births.^{70,71} They are also frequently nondiagnostic and have a high rate of recurrent/persistent disease.⁷¹ In 1 study, 47% of pregnant women undergoing loop electrosurgical excisions had residual CIN identified postpartum.⁷¹ Therefore, the use of diagnostic excisional procedures during pregnancy should be limited to women in whom invasive cancer cannot be ruled out.⁷⁰

Immunosuppressed patients. There is a high rate of recurrence/persistence of CIN-2,3 after treatment in women infected with human immunodeficiency virus-1

(HIV) and the level of risk correlates with the level of immunosuppression.⁷²⁻⁷⁵ For example, failure rates as high as 74% have been observed in certain subsets of patients after LEEP.⁷⁴ Even though the efficacy of standard therapies for biopsy-confirmed CIN-2,3 in HIV-infected women appears to be inferior to the efficacy of similar treatment in HIV-uninfected women, treatment appears to be effective in preventing the progression of CIN-2,3 to invasive cervical cancer.⁷³ The use of biweekly, topical vaginal 5-fluorouracil (5-FU) maintenance therapy has been shown in a single study to significantly reduce the rate of recurrent/persistent CIN from 47% to 28% after standard therapy of CIN-2,3.⁷⁶

Adolescent patients. Although the 2001 Consensus Guidelines combine women with CIN-2 and CIN-3 for most recommendations, the rate of spontaneous regression of CIN-2 is greater than for CIN-3.^{9,10} Because HPV-related lesions are common in younger women, and invasive cervical cancer in adolescents is virtually nonexistent, some experts at the 2001 Consensus Conference expressed the opinion that observation is appropriate for appropriately counseled adolescents with biopsy-confirmed CIN-2 considered to be reliable for follow-up.⁷⁷

Posttreatment follow-up of women with CIN-2,3

The risk of recurrent/persistent CIN-2,3 or invasive cervical cancer after treatment is relatively low, but remains higher than the background population risk for many years.^{61,78-82} A large, long-term follow-up study from the United Kingdom reported that the cumulative rate of invasive cervical cancer after 8 years of follow-up among women receiving outpatient treatment for CIN was 5.8 per 1000.⁷⁹ For comparison, the age-adjusted incidence rate of invasive cervical cancer in the United States is approximately 8 per 100,000.⁸³ Rates of recurrent/persistent CIN after treatment range from 1% to 21%.^{44,48,55,62,78,84} Lesion size appears to be an important determinant of rate of recurrence/persistence, with large lesions showing higher treatment failure rates than smaller lesions.^{42,44,80,85,86}

There are a limited number of observational trials defining the performance of various posttreatment surveillance protocols after treatment of any grade of CIN, and none compare surveillance strategies in a prospective, randomized way. Various surveillance protocols include the use of cytology alone, combinations of cytology and colposcopy, and HPV DNA testing. Typical cytology-based surveillance protocols use repeat cytology at 4 to 6 months for up to 2 years and yearly thereafter. More than 90% of recurrent/persistent CIN-2,3 lesions identified after excisional therapy are preceded by an abnormal cervical cytology.^{38,62,86} Although serial colposcopic examinations combined with cytology for the first year after treatment have been proposed, the clinical benefit of incorporating colposcopy compared with cytology alone

appears to be small.^{38,63} In 1 study of 927 women who were followed using a combination of cervical cytology and colposcopy after treatment for CIN, 27 cases of recurrent/persistent CIN were identified, all of whom, except for 1, were associated with an abnormal cervical cytology.³⁸ Recent studies have reported relatively high rates of clearance of HPV DNA from the cervix after successful treatment and suggest that HPV DNA testing may be a useful tool in posttreatment surveillance.⁸⁷ One study of 79 women who had undergone conization for CIN-2,3 found that none of the women who subsequently became HPV DNA negative had recurrent/persistent CIN develop, whereas recurrent/persistent CIN was identified in 73% of those who continued to be HPV DNA positive after treatment.⁸⁸ Similarly, another study of 58 women who had undergone conization for CIN-3 found that 80% of the women became HPV DNA negative after treatment and among women who became HPV DNA negative, no cases of recurrent/persistent CIN were identified. In contrast, 46% of the women who continued to be HPV DNA positive subsequently had a diagnosis of recurrent/persistent CIN.⁸⁹ HPV DNA testing appears to be an appropriate modality for posttreatment follow-up of women with CIN-2,3. To provide sufficient time for clearance of the HPV infection, testing should be performed at least 6 months after treatment. Unless a patient has risk factors for recurrent/persistent CIN, such as a large lesion or endocervical extension, it would seem reasonable to perform HPV DNA testing at 12 months after treatment. This is because the risk that a woman who has been treated for CIN-2,3 will subsequently be found to have recurrent/persistent CIN-2,3 is similar to the risk of identifying CIN-2,3 in a woman with biopsy-confirmed CIN-1 undergoing observation. Longitudinal studies show that recurrent CIN or invasive cervical cancer can occur many years after treatment and that it is important to continue follow-up indefinitely.^{61,82}

Recommendations for managing women with CIN-2,3

Initial management of biopsy-confirmed CIN-2,3. Management decisions in women with biopsy-confirmed CIN-2,3 are determined by whether the colposcopic examination is classified as satisfactory or unsatisfactory, Table II. Both excision and ablation of the transformation zone are acceptable for women with biopsy-confirmed CIN-2,3 and a satisfactory colposcopy (AI). However, in patients with recurrent CIN-2,3, excisional modalities are preferred (AII). A diagnostic excisional procedure is recommended for women with biopsy-confirmed CIN-2,3 and unsatisfactory colposcopy (AII). Observation of CIN-2,3 with sequential cytology and colposcopy is unacceptable except in special circumstances (see below) (EII). Hysterectomy is unacceptable as primary therapy for CIN-2,3 (EII).

Follow-up after treatment of biopsy-confirmed CIN-2,3.

After treatment of CIN-2,3, follow-up using either cervical cytology or a combination of cervical cytology and colposcopy at 4- to 6-month intervals until at least 3 cytologic results are "negative for squamous intraepithelial lesion or malignancy" is acceptable (AII). Annual cytology follow-up is recommended thereafter (AII). During cytologic follow-up, the recommended threshold for referral to colposcopy is a result of ASC or greater (AII). HPV testing performed at least 6 months after treatment is acceptable for surveillance (BII). If high-risk types of HPV are identified, colposcopy is recommended (BIII). If HPV testing is negative, triage to annual cytology follow-up is recommended (BIII). Repeat conization or hysterectomy, based on a single positive HPV test, that is not corroborated by other findings (cytology, colposcopy, histology) is unacceptable (DIII).

If CIN is identified at the margins of a diagnostic excisional procedure or in a postprocedure endocervical sampling, it is preferred that the 4- to 6-month follow-up visit include a colposcopic examination and an endocervical sampling (BII). When CIN-2,3 is identified at the endocervical margins, or in the endocervical sampling obtained after the diagnostic excisional procedure, a repeat diagnostic excisional procedure is acceptable (AII). Hysterectomy is acceptable in this situation when repeat diagnostic excision is not feasible (BII). Hysterectomy is acceptable for treatment of recurrent/persistent biopsy-confirmed CIN-2,3 (BII).

Special circumstances. Observation with colposcopy and cytology at 4- to 6-month intervals for 1 year is acceptable for adolescents with biopsy-confirmed CIN-2, provided colposcopy is satisfactory, endocervical sampling is negative, and the patient accepts the risk of occult disease (BII). Ablation or excision is required for adolescent women with CIN-3 (BIII).

We would like to thank all of the participating organizations, conference participants, and the members of the working groups. Names of the conference participants are available online at <http://www.asccp.org> and names of the participating organizations are in the Appendix.

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Appendix

Participants and participating organizations

Organizer: American Society for Colposcopy and Cervical Pathology (ASCCP)

Participating Organizations: Agency for Healthcare Research and Quality, American Academy of Family Physicians, American Cancer Society, American College Health Association, American College of Obstetricians and Gynecologists, American Medical Women's Association, American Social Health Association, American Society for Clinical Pathologists, American Society for Colposcopy and Cervical Pathology, American Society of Cytopathology, Association of Reproductive Health Professionals, Centers for Disease Control and Prevention, Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Division of Laboratory Systems, Centers for Medicaid and Medicare Services, College of American Pathologists, Eurogin, Food and Drug Administration, International Federation for Cervical Pathology and Colposcopy, International Gynecologic Cancer Society, International Society of Gynecological Pathologists, National Cancer Institute, National Association of Nurse Practitioners in Women's Health, Papanicolaou Society, Pan American Health Organization, Planned Parenthood Federation of America, Society of Canadian Colposcopists, Society of Gynecologic Oncologists, Society of Obstetricians and Gynaecologists of Canada.