Cervical intraepithelial neoplasia: Ablative therapies

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INTRODUCTION

Cervical intraepithelial neoplasia (CIN) is a premalignant cervical disease that can be treated with either excisional (ie, conization) or ablative therapy.

Ablative techniques include cryotherapy, CO_2 laser, thermal ablation (cold coagulation), and diathermy. Unlike with excision, ablation provides no pathologic specimen as the cervical tissue is destroyed. Therefore, these procedures are purely therapeutic and not of diagnostic value. They are appropriate only for select patients with previously well-characterized lesions histologically and colposcopically in whom invasive cancer has been excluded.

The ablative procedures for the treatment of CIN are reviewed here. The management of CIN, indications for ablation and excision, how to choose between the treatment options, and the procedures for excision are discussed elsewhere.

- (See "Cervical intraepithelial neoplasia: Management".)
- (See "Cervical intraepithelial neoplasia: Choosing excision versus ablation, and prognosis and follow-up after treatment".)
- (See "Cervical intraepithelial neoplasia: Diagnostic excisional procedures".)

CHOOSING AN ABLATION TECHNIQUE

In our practice, we prefer cryotherapy to laser ablation or thermal ablation. However, ablative techniques have a relatively low risk of side effects and, until there are more

informative comparative efficacy data, choice of ablative method may be dictated by other factors (eg, local resources).

For patients with CIN 1, there is some evidence that cryotherapy is more effective than laser ablation:

- In a subgroup analysis of a meta-analysis of randomized trials, patients with CIN 1 treated with laser ablation compared with cryotherapy had a higher risk of residual disease (odds ratio [OR] 3.3, 95% CI 1.1-10.1) [1]. The strength of this conclusion is attenuated by the use of an unplanned subgroup analysis and by the methodologic flaws in the included trials.

- In a randomized trial including 500 patients eligible for ablative treatment after visual inspection with acetic acid (VIA), those treated with cryotherapy or thermal ablation had similar proportions of HPV clearance six months after treatment, but the study was not powered to detect such difference [2].

- The efficacy of cryotherapy, CO_2 laser, and thermal ablation is also being evaluated in a noninferiority randomized trial including 1152 patients with CIN 2 or greater; this trial is ongoing and efficacy data have not yet been published [3].

While cryotherapy is more commonly used in the United States and more cost-effective in some settings [4], thermal ablation may have advantages in some resource-limited countries as it is available as a portable, lightweight, and battery-operated device. Both cryotherapy and thermal ablation are relatively simple, inexpensive office procedures. By contrast, laser equipment is costly, and a laser procedure may require general anesthesia in an inpatient setting [5]. A disadvantage of cryotherapy is that a malodorous vaginal discharge is a common side effect and vasomotor symptoms may occur during the procedure [1]; however, these effects are easily managed. (See 'Adverse effects' below.)

GENERAL PROCEDURAL ISSUES

Cryotherapy and thermal ablation are office procedures. Both CO_2 laser ablation and electrocoagulation diathermy may be performed in an office setting, but as they are more painful to patients, general anesthesia in an operating room may be necessary [5,6]. Routine preoperative laboratory tests, cultures, and antibiotic prophylaxis are not required.

We pretreat with an oral nonsteroidal anti-inflammatory drug (NSAID) to minimize procedure-related cramping (eg, ibuprofen 600 mg). A local anesthetic should be provided. Options include injection into the cervical stroma or as a paracervical block; we prefer a stromal block. In one decision analysis, stromal block was the most cost-effective method to avert the pain and cramping during cryosurgery (in patients who have taken an NSAID

before the procedure) [7]. (See "Pudendal and paracervical block", section on 'Gynecologic procedures'.)

For all techniques, the cervix is stained with Lugol iodine (a solution of elemental iodine and potassium iodide in water) to delineate the lesion to be ablated. If Lugol is not available, 3 to 5% acetic acid can be used.

Most patients will report minor cramping, similar to menstrual cramps, during and after the procedure. Vasomotor symptoms (eg, light-headedness) may occur, and are more common during cryotherapy than during laser ablation [8].

HEALTH CARE WORKERS AT RISK FOR OCCUPATIONAL EXPOSURE

Smoke generated from excisional and ablative procedures for CIN can expose health care workers to human papillomavirus (HPV) and increase the risk of developing HPV infection and HPV-associated oropharyngeal disease, such as papillomatosis and cancer [9]. In addition to personal protective equipment (eg, N-95 masks) and smoke evacuation systems, we agree with guidance from the American Society for Colposcopy and Cervical Pathology and others that all health care workers with this exposure (eg, physicians, nurses, operating room staff) should receive the HPV vaccine, if not already vaccinated [10].

This is discussed in more detail elsewhere. (See "Cervical intraepithelial neoplasia: Diagnostic excisional procedures", section on 'Health care workers at risk for occupational exposure' and "Human papillomavirus vaccination", section on 'Health care workers at risk for occupational exposure'.)

ABLATIVE TECHNIQUES

Cryotherapy and laser ablation are the most commonly used methods for cervical ablation. Cold coagulation and diathermy are used infrequently in the United States.

CIN can extend into glandular crypts, thus, the depth of cervical ablation should be at least 4.8 mm for all techniques. This will adequately treat greater than 99 percent of lesions [11].

Cryotherapy — Cryotherapy uses a refrigerant gas (carbon dioxide or nitrous oxide) to cool the ectocervix with a metal cryoprobe. The ectocervix must be cooled to -20°C to cause crystallization of intracellular water and destroy the lesion [12]. This can be achieved by forming an ice ball in the cervical tissue that is at least 5 mm from the tip of the probe. Cryotherapy should not be used for dysplasia that encompasses more than 75 percent of the cervix or with lesions that are larger than the selected cryoprobe [13]. (See "Cervical

intraepithelial neoplasia: Choosing excision versus ablation, and prognosis and follow-up after treatment", section on 'Factors to consider in choosing excision versus ablation'.)

Cryoprobes are either flat or cone shaped and vary in diameter (19 or 25 mm). It is not clear whether cryoprobe shape influences treatment efficacy [14,15]. Selection of the appropriate cryoprobe is controversial. In one study (n = 64), cryotherapy was performed on patients prior to hysterectomy, and postoperative histology revealed that adequate tissue destruction (in this study, defined as 4 mm depth and ≤15 mm width) was significantly more likely after use of the large cone-shaped probe (25 mm diameter) than the small flat probe (19 mm diameter; 80 versus 58 percent); results for the other probes (small cone-shaped and large flat) did not differ significantly from the others (67 and 72 percent) [14]. However, in a randomized trial (n = 117) patients with CIN were assigned to cryotherapy with either a cone-shaped or flat probe (selection of large or small probe was made according to size of cervix); rates of disease found at follow-up colposcopy were similar (77 and 76 percent) [15].

The type of refrigerant gas may also influence outcome. Tissue crystallization induced by nitrous oxide appears to penetrate deeper into the cervical stroma than CO_2 [16].

- **Technique** – Select the appropriate probe and apply a water-soluble lubricant to the probe tip to allow adequate transfer of thermal energy between the probe and the cervical tissue. A note of caution, if the cryoprobe makes contact with the speculum, vaginal tissue in contact with the speculum will also be ablated. An insulated speculum may be used, but is not required.

  Activate the cryotherapy unit and, when the optimal freezing temperature is achieved (-65 to -85°C), administer a three-minute freeze and then turn the unit off to allow the cervix to thaw for five minutes. The probe will then fall free of the cervix and a white "frost" area will be visible. Removing the probe, rather than allowing it to fall off, will cause pain and bleeding. Continue to allow the cervix to defrost and become pink.

  Perform a second freeze and again allow the cervix to defrost [17]. In a large meta-analysis of randomized trials, using two freeze/thaw cycles was more effective than one cycle (residual disease rates at 27-month follow-up were 6 versus 16 percent) [8].

CO2 laser — Laser surgery should only be performed by clinicians with specialized training. The laser is directed at the cervical lesion under colposcopic guidance. Water in the tissue absorbs the laser energy, which destroys the tissue by vaporization. To be effective, the lesion is typically ablated to a depth of 5 mm on the ectocervix and 8 to 9 mm around the endocervix.

Laser ablation of visible lesions is discussed here; a full discussion of laser conization (ie, the transformation zone is excised using a laser) and principles of laser therapy can be found

separately. (See "Basic principles of medical lasers" and "Cervical intraepithelial neoplasia: Diagnostic excisional procedures", section on 'Laser conization'.)

- **Technique** – Protective eyewear is necessary for any personnel in the procedure room. To avoid inadvertent damage to the surrounding areas from a reflected or misdirected laser beam, use a coated or brushed (ie, nonconductive) speculum and drape the patient's perineum and thighs with wet towels. Avoid paper drapes, as they are flammable.

  Visualize the cervix using a colposcope. Using a CO_2 laser with a power density of 600 to 1200 watts/cm^2 is adequate for vaporization. For example, with a spot size of 2 mm, setting the laser to 35 watts will produce a power density of 875 watts/cm^2. In general, obtaining hemostasis requires a spot size of 5 mm or greater.

Technique varies among surgeons, and there are no data comparing these methods. Some experts advocate using the laser in ultrapulse mode to decrease thermal damage to the surrounding cervical stroma. Also, some experts advise lasering the ectocervix with a defocused beam to provide a several-millimeter margin around the area previously ablated (ie, "brush" lasering).

Thermal ablation (cold coagulation) — Thermal ablation and cold coagulation are the same technique; despite the term "cold" coagulation, this method uses heat to ablate the cervical stroma. The term "cold" coagulation is used because lower temperatures are used compared with electrocoagulation diathermy ablation (see 'Diathermy' below). Similar to cryotherapy, a probe (thermosound) is used to conduct heat to the cervix. Probe temperatures vary from 50 to 120°C. Depth of penetration into the cervical stroma depends on the temperature of the probe and duration of probe application.

- **Technique** – Cold coagulation is not commonly used, and a standard technique has not been established. In the largest single-institution experience, a temperature of 100°C was applied for 20 seconds with overlapping treatment fields for a total treatment time of 40 to 100 seconds [18]. Newer thermal ablation units (eg, hand-held, rechargeable) can reach treatment temperature in six seconds; treatment time is similar at approximately 45 seconds [19].

Diathermy — The term diathermy means "electrically induced heat." This technique uses a needle that is attached to an electrosurgical generator (cautery device) to destroy cervical tissue.

Diathermy is primarily performed as an inpatient procedure requiring general anesthesia [20-22], but it can be used in the outpatient setting [6].

- **Technique –** The diathermy needle is passed into and out of the cervix multiple times to ablate the transformation zone; a spatula can be used to remove desiccated tissue. A setting of 30 to 35 watts has been described, but there does not appear to be a consensus on the optimal current [20]. The speculum should not touch the diathermy needle.

OUTCOME

Overall, all types of ablative therapy for CIN appear to be effective, with low rates of disease persistence and recurrence (generally <10 percent) at seven or more years after treatment [21,23-30].

Despite the high success rates with ablative modalities (particularly CO_2 laser and cryotherapy), CIN 2 or 3 or cancer can be missed without an excisional biopsy.

ADVERSE EFFECTS AND COMPLICATIONS

Overall, complication rates after ablative therapy are low, approximately 1 to 2 percent [30].

Adverse effects — Adverse effects are relatively uncommon and data regarding discharge, bleeding, and pain are conflicting.

- **Discharge –** In one meta-analysis, patients were less likely to experience vaginal discharge after laser ablation than cryotherapy (odds ratio [OR] 0.23, 95% CI 0.15-0.35; two trials) [8]. However, in the ongoing randomized noninferiority trial discussed above (see 'Choosing an ablation technique' above), patients treated with CO_2 laser experienced a longer duration of watery discharge [3].

  Watery vaginal discharge can continue for several weeks after treatment. When patients find the discharge bothersome, we remove the necrotic tissue from the cervix using ring forceps.

- **Bleeding –** In the above meta-analysis, patients treated with laser ablation compared with cryotherapy were more likely to experience severe bleeding (OR 7.45, 95% CI 1.68-33) [8]. By contrast, in interim data from the ongoing randomized noninferiority trial discussed above (see 'Choosing an ablation technique' above), thermal ablation was associated with more frequent bleeding (thermal ablation: 30 percent, cryotherapy: 20 percent, CO_2 laser: 19 percent) [3].

  Patients with posttreatment bleeding are evaluated with a speculum examination. Bleeding is usually minimal and will resolve with conservative measures in the office,

such as application of silver nitrate or ferric subsulfate (Monsel solution). It is rare to encounter bleeding that requires suturing or packing.

- **Infection** – Pelvic infection after ablation is infrequent but may be increased in patients with other risk factors for pelvic inflammatory disease (PID). For example, in one series of 67 adolescents treated with cryotherapy, 9 percent developed PID [31].

- **Pain** – In the above meta-analysis, laser ablation compared with cryotherapy was associated with a higher incidence of severe peri-operative severe pain (OR 2.38, 95% CI 0.9-6.28) [8]. By contrast, in a randomized trial including 500 patients eligible for ablative treatment after visual inspection with acetic acid (VIA) discussed above (see 'Choosing an ablation technique' above), those treated with thermal ablation compared with cryotherapy had similar pain scores immediately, and at two weeks, after treatment; the majority of patients rated their pain at a one to three on a nine-point scale [2].

  In interim data from the ongoing randomized noninferiority trial discussed above (see 'Choosing an ablation technique' above), thermal ablation was associated with higher pain levels during treatment (interquartile range [IQR]: 4) compared with laser (2) and cryotherapy (2) [3].

Late complications — Possible late complications are cervical stenosis or obstetric complications.

Cervical stenosis appears to be rare after cryotherapy or laser ablation; however, there are few data regarding this issue [31,32]. In the largest series of cryotherapy or laser ablation, the risk of stenosis was 1 percent or less [32,33]. Although a randomized trial found no significant difference in the incidence of cervical stenosis between the two methods, there was insufficient statistical power to detect a difference in this rare complication [8].

There is some evidence that the risk of cervical stenosis following cervical ablation is increased for patients with a history of in-utero exposure to diethylstilbestrol [34,35]. (See "Outcome and follow-up of diethylstilbestrol (DES) exposed individuals".)

The risk of obstetric complications (eg, preterm delivery) appears to be lower in patients treated with ablative rather than excisional methods. A full discussion of the association of treatment of CIN with obstetric complications can be found separately. (See "Reproductive effects of cervical excisional and ablative procedures".)

FOLLOW-UP

We see patients at 10 to 14 days after the procedure and treat any short-term complications. Appropriate follow-up after ablative treatment for CIN is especially critical, as no pathologic diagnosis is obtained at the time of treatment and some patients will go on to develop cancer [36].

After laser ablation, the squamocolumnar junction usually returns to its pretreatment location and can be visualized [8]. However, following cryotherapy, the squamocolumnar junction may recede into the cervical canal, making subsequent colposcopy difficult. Radial scar lines may also be seen with subsequent colposcopies, and are of no clinical significance.

Recommendations for follow-up after treatment for CIN are discussed in detail separately elsewhere. (See "Cervical intraepithelial neoplasia: Management".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Cervical cancer screening, prevention, and management".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Beyond the Basics topics (see "Patient education: Follow-up of low-grade abnormal Pap tests (Beyond the Basics)" and "Patient education: Follow-up of high-grade or glandular cell abnormal Pap tests (Beyond the Basics)" and "Patient education: Management of a cervical biopsy with precancerous cells (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Clinical significance**
  - While ablative therapy is an effective treatment of cervical intraepithelial neoplasia (CIN) for a select group of patients with previously well-characterized lesions histologically and colposcopically in whom invasive cancer has been excluded, most patients with CIN 2 or 3 will undergo a diagnostic excisional procedure. (See 'Introduction' above and "Cervical intraepithelial neoplasia: Choosing excision versus ablation, and prognosis and follow-up after treatment", section on 'Factors to consider in choosing excision versus ablation' and "Cervical intraepithelial neoplasia: Diagnostic excisional procedures".)
  - Ablative modalities are solely for treatment, while excisional therapy provides diagnostic information as well as therapeutic benefit. (See 'Introduction' above.)
- **Techniques –** The most commonly used techniques for cervical ablation are cryotherapy and laser ablation; thermal ablation and electrocoagulation diathermy are used infrequently in the United States. Most procedures can be performed in an office setting. (See 'Ablative techniques' above.)
- **How to choose –** For patients with CIN 1 who are candidates for ablative therapy, we suggest cryotherapy rather than laser or thermal ablation (**Grade 2C**). For patients with CIN 1, there is some evidence that cryotherapy is more effective than laser ablation. However, ablative techniques have a relatively low risk of side effects and, until there is more informative comparative efficacy data, choice of ablative method may be dictated by local resources. (See 'Choosing an ablation technique' above.)
- **Cryotherapy –** For patients undergoing cryotherapy, we recommend two freeze/thaw cycles rather than one cycle (**Grade 1A**). (See 'Cryotherapy' above.)
- **Outcome –** Overall, all types of ablative therapy for CIN appear to be effective, with low rates of disease persistence and recurrence (generally <10 percent) at seven or more years after treatment. (See 'Outcome' above.)
- **Adverse effects and complications –** Incidences of adverse effects and complications after ablative therapy are low, approximately 1 to 2 percent. (See 'Adverse effects and complications' above.)
- **Follow-up**
  - We see patients at 10 to 14 days after the procedure. Appropriate follow-up after ablative treatment for CIN is especially critical, as no pathologic diagnosis is obtained at the time of treatment and some patients will go on to develop cancer. (See 'Follow-up' above.)

- Recommendations for follow-up after treatment for CIN are discussed in detail separately elsewhere. (See "Cervical intraepithelial neoplasia: Management".)

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