Large-Loop Excision of the Transformation Zone: Effect on the Pathologic Interpretation of Resection Margins

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Objective: To determine the effect of large-loop excision of the transformation zone (LLETZ) on the ability to interpret adequately the pathologic specimen and surgical margins.

Methods: Fifty consecutive LLETZ specimens were used for repeat histopathologic assessment with emphasis on the interpretability of the surgical specimen and margin. All reevaluations were performed by a single pathologist. Complete lesion evaluability was defined as satisfactory accuracy of the histologic diagnosis and the ability to evaluate thoroughly all surgical margins. Medical records of the patients from whom the specimens were obtained were reviewed and analyzed for possible correlates to the status of specimen interpretability.

Results: Histologic accuracy was sufficient in 46 cases (92%). Extensive heat distortion precluded full assessment of the ectocervical margins in ten (20%) and the endocervical margins in 22 (44%) of the cases. There was no difference in complete lesion evaluability whether LLETZ was performed solely for treatment in cases suitable for ablative procedures or for both diagnosis and treatment in patients who traditionally would have undergone a cone biopsy. If the latter group ($N = 25$) was analyzed separately, extensive heat distortion made histopathologic diagnosis impossible in four cases (16%) and precluded full assessment of the ectocervical margin in eight (32%) and the endocervical margin in 12 (48%).

Conclusion: The high rate of surgical-margin thermal destruction, with related limitation of interpretability, may represent a serious diagnostic and therapeutic limitation of the LLETZ procedure when considered as an alternative to cold knife conization. *(Obstet Gynecol 1993;81:976–82)*

Large-loop excision of the transformation zone (LLETZ) has become a widely used diagnostic and therapeutic tool in the management of patients with abnormal Papanicolaou smears and presumed cervical dysplasia. It has been claimed that LLETZ is superior to colposcopically directed punch biopsy for histologic evaluation of cervical intraepithelial neoplasia (CIN), as LLETZ is more likely to reveal microinvasive tumor[1] and can provide the entire transformation zone for pathologic evaluation. Presumably, such a specimen would increase the grading accuracy in the diagnosis of CIN.[2,3] Similarly, LLETZ appears to offer a therapeutic advantage to local destructive techniques. When compared with carbon dioxide laser vaporization, LLETZ-treated patients had fewer side effects and the LLETZ procedure offered a cost advantage. However, the greatest advantage when compared to laser vaporization was that LLETZ provided histologic material for confirmation of the diagnosis.[4]

A cold knife cone biopsy in which there is margin involvement with dysplasia is known to be strongly predictive of disease persistence,[5,6] especially in cases of high-grade dysplasia[7] and positive endocervical margins.[8] When considering the LLETZ procedure as a diagnostic and therapeutic alternative to this standard method of conization,[9] there is concern that the LLETZ specimen margins may not be interpretable because of heat distortion. As is known from studies of CO_2 laser cervical conization, there is controversy regarding the degree and impact of thermal damage on histopathologic interpretation of the specimen. Various authors have noted that this effect can range from compromised diagnostic accuracy in more than half of the specimens,[10] to no important impact on margin adequacy in either laser or LLETZ cone specimens.[11]

We conducted this study to analyze the histopathologic evaluability of 50 LLETZ cervical cone specimens, with an emphasis on assessing thermal injury zones at the ecto- and endocervical margins, the degree of heat artifact, and the latter's impact on histopathologic accuracy and interpretation of the specimen margins.

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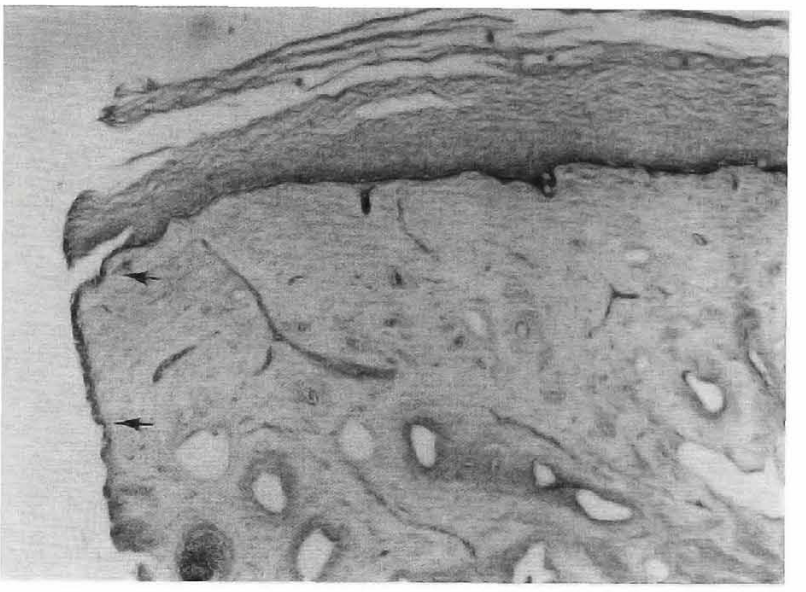


Figure 1. Mild diathermy artifact (*arrows*), minimal coagulative necrosis, and epithelial elevation (hematoxylin and eosin, × 9.5).

Materials and Methods

We retrospectively reviewed the medical records and histopathologic specimens of 50 consecutive patients who underwent loop diathermy conization of the cervix at the University of California-Los Angeles Medical Center between November 1991 and September 1992. For all LLETZ procedures, the same electrosurgical unit was used (Leep System 6000; Cooper Surgical, Shelton, CT). The unit was set to deliver 36–46 W of power for the cone-like excision of the transformation zone. If it was elected to obtain an additional apical specimen of the endocervical canal, the power was set in the range of 26–40 W. In 48 cases, the unit was set at blend (interrupted 550-KHz sinusoid waves, 80% duty cycle). In two cases the unit was set at pure cut. The loops used to perform the conization ranged from 2.0 × 0.7 cm to 2.0 × 1.0 cm for excision of the transformation zone, and from 1.0 × 1.0 cm to 2.0 × 0.7 cm for apical excision of the endocervical canal, with the diameter of the tungsten wire being 0.0001 in (2.5 μm). All specimens were fixed in 10% formalin, serially sectioned (ten to 30 sections), entirely embedded, processed with the standard overnight technique, and stained with hematoxylin and eosin. The margins of the conization specimen were marked with black ink for identification by the pathologist.

One pathologist (LDRT) evaluated in detail each slide of the 50 cases. The depth of thermal injury was measured with a micrometer at every ecto- and endocervical margin, perpendicular to the epithelial lining at the areas most severely affected. The measurements were made between the outer cauterized zone and the beginning of normal stroma or epithelium. The degree of thermal artifact was categorized into three groups (mild, moderate, or severe) according to the following: 1) the degree of detachment of the epithelium from the basement membrane or denudation and stripping of the epithelium; 2) the extent of alterations of size or shape of preexisting structures, such as glands, cells, or nuclei; and 3) the severity of coagulation necrosis with shrinkage or enlargement of cellular details (Figures 1–4).[10] Histologic accuracy was defined as sufficient when the primary and reviewing pathologist could, within one grade, agree on the pathologic diagnosis. When there was heat distortion to such an extent that consistent diagnosis was precluded, the histologic accuracy was called poor. Full evaluability of the cone specimen required sufficient histologic accuracy and completely assessable ecto- and endocervical margins. The lesion was unevaluable when heat distortion precluded either interpretation of the margins or accurate histologic diagnosis.

Statistical comparisons were done by a *t* test using a pooled variance or a paired *t* test, as appropriate.

Results

The 50 LLETZ procedures were performed by seven physicians, with a frequency of two to 20 per physician. Each of these physicians had adequate experience with the LLETZ technique before the samples for this study were obtained.

Thirty of the LLETZ specimens were submitted to pathology as a single cone specimen, which was accompanied by an additional apical endocervical specimen in 23 cases. Twenty of the LLETZ specimens were

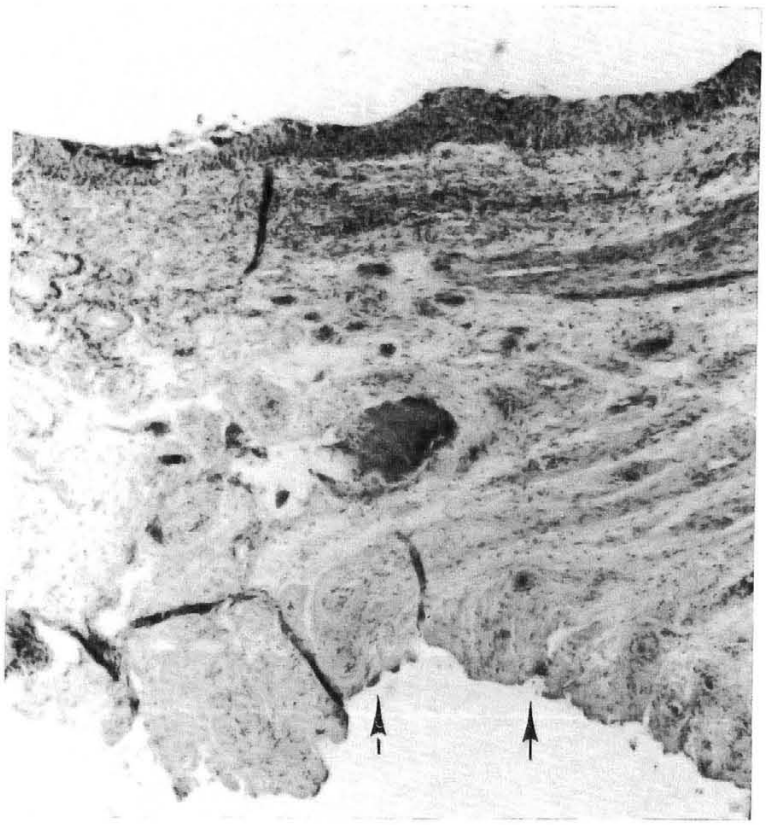


Figure 2. Squamous carcinoma in situ with mild stromal electrocautery artifact (*arrows*) (hematoxylin and eosin, × 24.5).

submitted in fragments. In six of these cases, in addition to the cone, the operating surgeon submitted separate ecto- and endocervical specimens. Table 1 details the relationship between specimen type, degree of coagulation artifact, and surgical margin status.

The patients could be divided into two groups de-

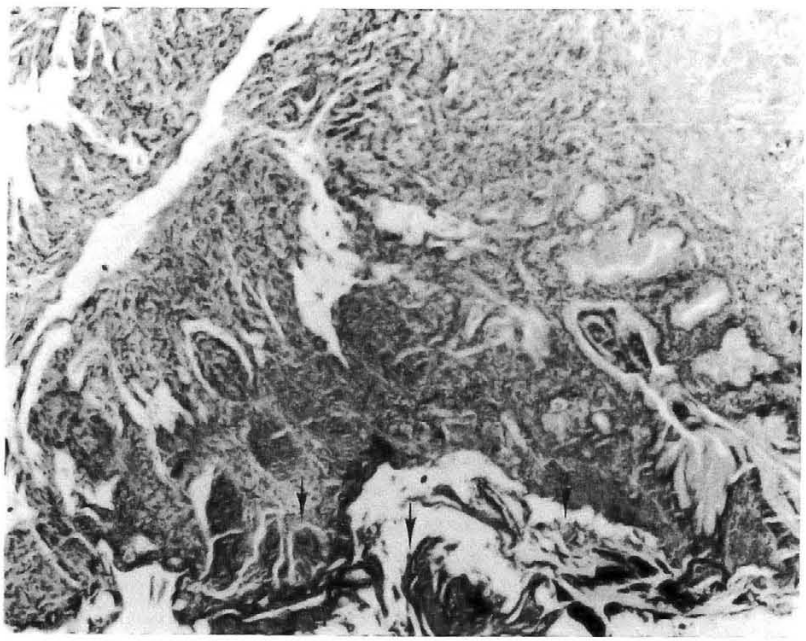
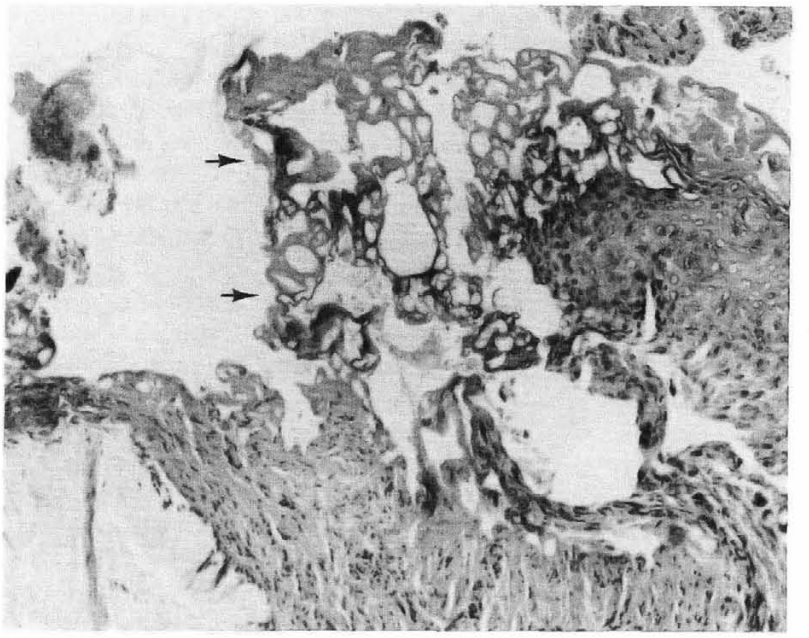


Figure 3. Squamous carcinoma in situ with severe electrocautery artifact (*arrows*). Margin is unassessable (hematoxylin and eosin, × 76).



igure 4. Severe diathermy artifact bscuring the margin (*arrows*), aking interpretation impossible ematoxylin and eosin, × 75).

ending upon the indication for the LLETZ procedure. he first group was subjects with satisfactory colposopy and abnormal Papanicolaou smear or biopsy howing CIN II–III. These patients (N = 24) were uitable for ablative treatment. Patients with unsatisactory colposcopy or positive endocervical curettage ECC) represented the second group. This cohort (N = 5) would traditionally have been treated with cold nife conization in an outpatient setting. In one case, he indication for LLETZ was unknown.

The diagnoses made by the original and the reviewng pathologist were consistent in 46 of the 50 cases 92%). Histologic accuracy was determined by the eviewing pathologist to be sufficient in all of these 46 ases and poor in the remaining four. In 32 instances (64%), the preoperative cytologic or colposcopic/histologic findings were within one grade of the LLETZ cone histology. In 12 (24%) of the cases, the diagnosis on the LLETZ specimen was clinically significantly better than the pre-treatment cytology or histology results; three of these patients had initially been evaluated by cytology only and nine patients were evaluated by colposcopically directed punch biopsies before the LLETZ procedure. In two cases, the LLETZ specimen showed a clinically significantly worse diagnosis (4%), and four cases were impossible to evaluate. It is interesting that the two cases in which the LLETZ specimen showed a worse diagnosis and the four cases that were unevaluable all underwent LLETZ after unsatisfactory colposcopy or positive ECC, settings in

Table 1. Relationship Between Specimen Type, Degree of Coagulation Artifact, and Surgical Margin Status

Type of specimen	N	Depth of coagulation artifact (mean and range)		Degree of coagulation artifact (N)			Margins (N)		
		mm	%	Mild	Moderate	Severe	Clear	Involved	Uncertain
Ectocervix									
Single	30	0.52* (0.1–2.8)	14.8 (2–93)	21	4	5	21	2	7
Fragmented	20	1.33* (0.1–4.5)	31.2 (2–93)	15	3	2	15	2	3
Endocervix									
Single	30	0.97 (0.2–5.7)	30.1 (2–100)	12	9	9	15	2	13
Fragmented	20	1.28 (0.2–6.0)	33.9 (2–100)	5	13	2	8	3	9

* $P = .01$.

Table 2. Severity of Thermal Artifact, as Assessed by Histologic Architectural, Cellular, and Cytoplasmic Criteria, and Depth of Coagulation Artifact

Degree of thermal artifact	Location	N	Depth of thermal artifact (mm)	% of specimen depth with thermal artifact	Margins evaluable	Margins not evaluable
Severe	Ectocervix	7	2.27 ± 2.06	49.0 ± 35.8	1 (14%)	6 (86%)
	Endocervix	11	2.57 ± 2.10	59.2 ± 27.5	0	11 (100%)
Moderate	Ectocervix	7	0.35 ± 0.25	15.3 ± 14.7	6 (86%)	1 (14%)
	Endocervix	22	0.81 ± 0.40	30.3 ± 18.0	12 (55%)	10 (45%)
Mild	Ectocervix	36	0.55 ± 0.47	16.7 ± 15.6	33 (92%)	3 (8%)
	Endocervix	17	0.46 ± 0.27	15.4 ± 13.5	16 (94%)	1 (6%)

which a cold knife cone would have traditionally been performed.

A comment that thermal damage compromised the histopathologic evaluation of the lesion was found in nine (18%) of the original pathology reports. Remarkably, each of the 50 case specimens reviewed showed some thermal artifact, ranging from mild changes to 100% thermally desiccated tissue (Figures 1–4). The mean depth and range of thermal injury tended to be more severe at the endocervical margin (mean 1.08 mm; range 0.2–6.0) than at the ectocervical margin (mean 0.83 mm; range 0.1–4.5). In single LLETZ specimens, the depth of coagulation artifact at the ectocervix was significantly less ($P = .01$) when compared with that in fragmented specimens. The observed difference in the depth of heat artifact in single versus fragmented LLETZ specimens at the endocervix was not significant ($P = .42$) (Table 1). The depth of thermal injury correlated with the degree of heat distortion as assessed by histopathologic criteria of architectural, cellular, and cytoplasmic changes (Table 2). Similarly, the severity of the thermal artifact correlated with the compromise of interpretation of the resection margins (Table 2). The degree of thermal injury and the assessability of the specimen's margins were not affected by the patient's age, the adequacy of pre-LLETZ colposcopy, or the severity of dysplasia in the colposcopy specimen. There was no difference in interpretability of the surgical margins whether LLETZ was performed for treatment only or for both diagnosis and treatment.

Of the 50 LLETZ-generated specimens, 26 (52%) were fully evaluable as regards histologic accuracy and assessability of both the endo- and ectocervical margins. In the remaining 24 specimens (48%), the lesion was not fully evaluable because of poor histologic accuracy (four), unevaluable ectocervical margins (ten), and/or unevaluable endocervical margins (22).

Twenty-five of the 50 LLETZ specimens were obtained from patients who previously would have been candidates for cold knife conization of the cervix. When this group was analyzed separately, it was found that in 12 specimens (48%) the lesion was not fully evaluable. This was due to poor histologic accuracy in four cases (16%), unevaluable ectocervical margins in eight (32%), and/or unevaluable endocervical margins in 12 (48%).

Discussion

Large-loop excision of the transformation zone has become a popular tool in the evaluation and treatment of patients with cytologic abnormalities noted on screening Papanicolaou smear and with presumed CIN. The procedure offers several advantages over more traditional diagnostic and therapeutic modalities. First, it removes rather than destroys the suspicious tissue, which often allows definitive histopathologic diagnosis and treatment of cervical dysplasia at the same office visit. The procedure is well tolerated by the patient with few side effects and complications.[4,12] Similarly, LLETZ can be cost-effectively performed as an office procedure with relatively inexpensive and durable equipment.

A major disadvantage of LLETZ demonstrated by our data is the high frequency of thermal tissue injury, which precluded adequate pathologic determination of the margins. In patients who undergo LLETZ as an alternative to ablative treatment, such unevaluability may be of little concern. The colposcopist should determine lesion size, and if margin involvement is noted at repeat colposcopy following LLETZ, excision or fulguration of any residual abnormal tissue can be immediately performed. In addition to the major clinical advantage of providing a specimen for definitive histopathologic diagnosis, microscopic assessment of the margins of the LLETZ specimen may be beneficial even in this patient group, as it allows reconfirmation or correction of the colposcopist's clinical impression.

However, there are more important patient care issues; our data indicate that 32% of patients being

treated with LLETZ conization had unassessable ectocervical margins and 48% had similar distortion of the endocervical margin. This finding brings into question the value of LLETZ as a substitute for the traditional "cold knife" cone.

Management is problematic for a positive surgical margin noted on a cold knife cone specimen, which occurs in approximately 25% of women undergoing a cone as treatment of high-grade dysplasia.[13–15] Even though 12–60% of patients with positive surgical margins from high-grade dysplasia on cone biopsy have residual disease noted on hysterectomy specimens,[16] the clinical impact of this phenomenon appears to be minimal. Theoretically, though these patients with positive cone margins have an increased risk of developing recurrent dysplasia or cervical cancers,[5–8] such dysplasias should be detected early by vigilant follow-up and long-term health risks eliminated by appropriate treatment.[17] In specific situations (margin positive for the highest grade of dysplasia, presumed microscopic invasive disease, deep glandular extension, poor differentiation, or high mitotic activity), a conservative follow-up regimen is probably not adequate and repeat cone or hysterectomy is preferred.[13]

The impact on patient health care due to unevaluable margins obtained at LLETZ is not yet known. One can envision that in many of these patients the dysplastic areas were completely excised, but the margin disrupted to an extent that this could not be histologically confirmed. It is also possible that in those patients in whom the lesion was not cleared, adequate thermal injury occurred on the uterine margin to destroy any residual dysplasia. Unfortunately, neither of these scenarios can be guaranteed, and the health care provider is left to assume that the lesion was not removed in toto and that viable dysplastic cells remain in situ. Extrapolating from the cold knife cone data, present standards of practice vary from either repeat cone or hysterectomy to frequent Papanicolaou smears and ECCs. This necessity of undertaking further diagnostic and therapeutic maneuvers unquestionably increases the individual patient's health care cost as well as her and her physician's level of anxiety.

It is possible that the concerns raised by an uninterpretable margin can be lessened by improvement of the LLETZ technique. One of the clinicians whose patients were included in this study attempted to deal with this issue by resecting separate ecto- and endocervical margins and sending these in addition to the main LLETZ specimen. Unfortunately, it appears that this modification of technique offers little advantage; two of seven ectocervical and five of seven endocervical margins were unevaluable and presumed positive. The size of the loop used may be important; Wright et al[12] reported that large loops (10–20 mm) appeared superior to small loops (3–7 mm) with regard to histologic accuracy and success rates. This finding may at least in part account for our observation that thermal artifact at the ectocervix was significantly less for single LLETZ cone specimens than for fragmented LLETZ specimens. Another modification in technique that may be valuable is increasing the speed of passage of the tungsten loop through the cervix. This should decrease exposure of the tissue to the electrical current and, therefore, decrease the degree of thermal injury. The use of a pure cutting current at the lowest setting that does not impede passage of the loop would have a similar effect. In our study, the time needed to pass the loop was not noted while the powers used were within the range of those recommended by the manufacturer (1.0-cm loop: 22–30 W; 1.5-cm loop: 30–36 W; 2.0-cm loop: 34–40 W) (Cooper Surgical). It may be that, regardless of any modification of technique, an unassessable margin will persist as an associated side effect in a significant percentage of patients who undergo LLETZ.

The fact that Baggish et al[11] and Wright et al[12,18] failed to note a high incidence of thermal distortion causing margin unevaluability most likely reflects the technical skills of "experts," with their results representing the efficacy[19] of LLETZ. The percentages presented in our review are probably a more accurate reflection of what occurs when LLETZ is performed by a mixed group of community physicians, more closely representing the effectiveness[19] of LLETZ. Should this prove to be the case, one must seriously reconsider the worth of this procedure, as it will have lost much of its advantage over traditional cold knife cone biopsy in patients who are not suitable for ablative treatment. Large-loop excision of the transformation zone unquestionably produces fewer clinically significant patient side effects and is considerably less expensive "up front" when compared with cold knife conization. However, it remains to be proven whether LLETZ will indeed be more cost-effective in the long run, when one includes the cost of further management of patients in whom complete removal of the dysplastic tissue cannot be documented because of thermal destruction of the resection margins.

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