

# Large loop excision of the transformation zone (LLETZ): a pathology evaluation in the Limpopo province, South Africa

Van Bogaert LJ, MD, MMed (Obstet Gynaecol), MMed (Anat Path), MPhil, DPhil, PhD

Department of Anatomical Pathology, National Health Laboratory Service and University of Limpopo, Polokwane

Correspondence to: Prof Louis-Jacques van Bogaert, e-mail: ljfvanbo@lantic.net

Keywords: cervix, high-grade intraepithelial lesion, large loop excision of the transformation zone

## Abstract

**Objective:** To evaluate the cytological and histopathological concordance in large loop excision of the transformation zone (LLETZ) specimens, and the outcomes according to the characteristics of the excision margins.

**Method:** A prospective observational study of 413 consecutive cases of LLETZ performed for cytologically diagnosed high-grade squamous intraepithelial lesion (HGSIL)/cervical intraepithelial neoplasia (CIN) 2-3 over a three-year period.

**Results:** The discordance rate between the initial cytological diagnosis and biopsy-proven HGSIL was 24.5%. The overall rate of margins believed to be clear and of severe thermal artefacts was 30.4% and 7.4% respectively. Pathology follow-up was available only in 83 (26.5%) of the 313 biopsy-confirmed HGSIL. The persistence or recurrence rate was 78.0%; 90.5% occurred among the cases where the margins were believed to be involved. In 20.5% the reported marginal status was discordant with follow-up surgical pathology.

**Conclusion:** Reporting marginal status has limited prognostic significance.

© Peer reviewed. (Submitted: 2011-05-06, Accepted: 2011-07-19) © SASGO

South Afr J Gynaecol Oncol 2011;3(2):66-69

## Introduction

Large loop excision of the transformation zone (LLETZ) is a well-established procedure in the diagnosis and treatment of squamous intraepithelial neoplasia (SIL)/cervical intraepithelial neoplasia (CIN).<sup>1</sup> However, the method carries the risk of undertreatment (i.e. incomplete excision) and overtreatment (i.e. subsequent diagnosis of not having SIL/CIN).<sup>2,3</sup>

Follow-up of women treated with LLETZ where the margins were believed to be clear has shown treatment failure rates ranging between 1.9% and 11.5%.<sup>4,5</sup> Treatment failure rates expressed as residual or recurrent disease have been reported to reach 13.2-27.5%.<sup>6,7</sup> The predictive value of margin positivity vs. margin negativity is inconclusive.<sup>8</sup> Women with incomplete excision of SIL/CIN at initial LLETZ remain at significant risk of developing further SIL/CIN; therefore, long-term colposcopic and cytological follow-up are necessary.<sup>9</sup>

This survey was undertaken to assess the concordance between the initial cytology and the surgical pathology diagnosis, as well as between the marginal status and the follow-up results. The significance of reporting the

histopathological completeness of excision, or lack thereof, is discussed.

## Method

This was a prospective observational study of 414 cases of LLETZ specimens examined at the Polokwane/Mankweng histopathology laboratory, in the Limpopo province of South Africa, from September 2007 through August 2010. The laboratory receives all the surgical specimens from the public health sector in the province. All patients underwent LLETZ as a result of unsatisfactory colposcopy following a cytological diagnosis of high-grade squamous intraepithelial lesion (HGSIL). When colposcopy was satisfactory, colposcopically directed biopsies were taken. The procedures were carried out by more than ten different clinicians, locally or externally. The decision about the diagnostic procedure was in their hands, and thus out of the pathologist's control.

The LLETZ and hysterectomy specimens were sliced at 2 mm intervals and all slices were embedded. Between September 2007 and December 2009, two pathologists, including the author, were involved in the diagnosis; later only the author.

The clinicopathological data were retrieved from the pathology request forms and the laboratory electronic database. The following information was recorded: age, human immunodeficiency virus (HIV) status (where available), histopathological diagnosis, presence of severe diathermy artefact, completeness of the excision margins, diagnosis at histopathological follow-up, and time elapsed between the initial diagnosis and hysterectomy. Figure 1 shows a flow chart of the study material.

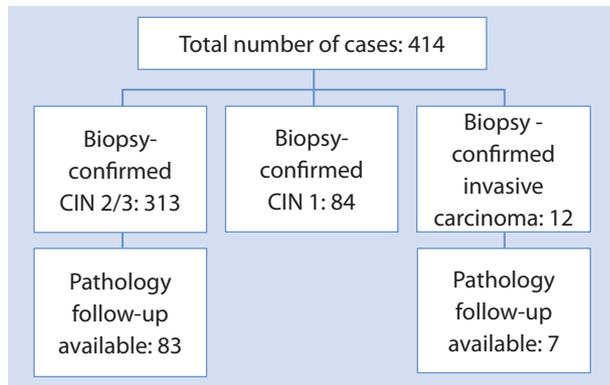


Figure 1: Flow chart of the distribution of cases

## Results

The distribution by HIV status was as follows: 248 (59.9%) were seronegative and 166 (40.1%), seropositive. The age at diagnosis was known in 244 HIV-negative and 163 HIV-positive patients. The average age (years) was  $41.6 \pm 10.6$  years (median 39.5) in the former, and  $37.2 \pm 7.6$  (median 36.0) in the latter ( $t = 4.6$ ;  $P < 0.0001$ ). The age at diagnosis of invasive carcinoma was  $44.1 \pm 10.5$  (median 40.0) in the HIV-negative, and  $37.2 \pm 7.6$  (median 36) in the HIV-positive patients ( $t = 4.6$ ;  $P < 0.0001$ ).

The initial cytological diagnosis of HGSIL was confirmed in 313 (75.6%) cases. Table I lists the 101 (24.4%) cases where there was discordance between the initial cytological and the LLETZ reports. The rate of overdiagnosis (no pathology or low-grade lesion) and underdiagnosis of HGSIL or invasive carcinoma was 9.4% and 2.9% respectively.

Table I: Cytological over- or underdiagnosis according to large loop excision histology

HIV status	Overdiagnosis		Underdiagnosis
	No lesion (%)	<sup>a</sup> LGSIL (%)	<sup>b</sup> ISCCA (%)
Positive	3 (1.2)	66 (26.7)	7 (2.8)
Negative	2 (1.2)	18 (10.8)	5 (3.0)

a = low-grade squamous intraepithelial lesion, b = invasive squamous cell carcinoma

The excision margins were reported to be clear in 95 (30.4%) out of the 313 specimens with confirmed HGSIL. Severe thermal artefacts hampering the assessment of the margins were present in 23 (7.4%). The degree of involvement at the excision margins, reported as incomplete, were as follows: crypts only 38.9%, endocervical and ectocervical margin 27.4%, endocervical margin only 18.9%, ectocervical margin only 9.5%, and all three margins involved 5.3%.

Follow-up pathology (i.e. after total hysterectomy for incomplete LLETZ) was available in only 83 (26.5%) of the 313 biopsy-confirmed HGSIL. The average length of time between the initial biopsy and the definitive surgery was comparable in the HIV-negative and HIV-positive patients:  $26.3 \pm 15.2$  (median 24.5) weeks and  $24.4 \pm 17.4$  (median 18.0) respectively. There was no significant difference in the proportion of cases with follow-up between the two groups ( $\chi^2 = 2.0$ ;  $P = 0.16$ ).

Table II shows the pathological findings according to the excision margins and the HIV status. The margins were falsely negative in three and falsely positive in 14 cases. Fifty-seven (69.5%) were true positives. Five of the invasive cancers had been diagnosed on the LLETZ specimen. The overall rate of persistent or recurrent disease was 78.0%.

Table II: Follow-up after loop excision

<sup>a</sup> LLETZ pathology report	HIV positive	HIV negative
	n = 48	n = 35
Margins clear	No lesion: 2/3	-
	<sup>b</sup> HGSIL: 1/3	2/2
Severe diathermy artefact	<sup>c</sup> LGSIL: 2/4	-
	HGSIL: 1/4	1/2
	<sup>d</sup> ISCCA: 1/4	1/2
Margins incomplete	No lesion: 2/41	3/31
	LGSIL: 5/41	4/31
	HGSIL: 31/41	21/31
	ISCCA: 3/41	4/31

a = large loop excision of the transformation zone, b = high-grade intraepithelial lesion, c = low-grade intraepithelial lesion, d = invasive squamous cell carcinoma

## Discussion

Cervical carcinoma is the most common type of cancer in black African women in sub-Saharan Africa in general, and in South Africa in particular.<sup>10</sup> The National Cervix Cancer Screening Programme was launched in 2000.<sup>11</sup> However, many factors continue to contribute to the low levels of coverage and further intervention is needed.<sup>12,13</sup>

An audit of LLETZ specimens carried out at the Chris Hani Baragwanath Hospital showed a slightly younger population (mean age 38.7 years), and a higher rate of documented HIV positivity (50.4%) than ours.<sup>14</sup> The topic of margin status was not addressed in that study. The correlation between cytology and histology was similar to our results at 71.8%. However, our rate of overtreatment on the basis of cytology was double that quoted by Adam et al (21.5% vs. 11.1%). It was of concern in their results that more than one third of patients were lost to follow-up. In our study, follow-up was only available in one quarter. This may be partly attributed to the limits imposed by relying on an electronic database, the performance of which depends on the skills of the person feeding in the data, namely the correctness of the spelling of names and file numbers. However, this is unlikely to account for the large number of patients lost to follow-up.

Recently, Kabir reported the results of 576 HIV-positive patients who underwent a LLETZ.<sup>15</sup> The mean age was similar to our HIV-positive cases. The follow-up rate was 54.9%. The rate of persistent disease was 63.9%. That study did not address the marginal status either. For many socio-economic, educational and geographical reasons, comparisons can only be made with international data on the diagnostic characteristics of the initial LLETZ. Table III illustrates the high variability of the reported data.

The highest reported rate of incomplete excision margins was 27.5%.<sup>7</sup> The high rate of incomplete excision margins in our material, at least for the cases with follow-up, is likely to be attributable to the lack of qualified and seasoned gynaecologists in the public service in the province. However, it is now widely accepted that the persistence of high-risk human papilloma virus (HRHPV), rather than the completeness of excision, determines the prognosis and evolution of HGSIL. Therefore the concept of LLETZ with therapeutic intent might be challenged. Traditionally, clinicians expect the surgical pathology report to include full information on the marginal status in order to plan the follow-up.<sup>6</sup> This concept, however, is now challenged because it lacks prognostic significance.<sup>5</sup> Studies have

shown that the most important predictor of recurrence is a positive HRHPV status at six months' follow-up.<sup>20</sup> Persistence of HRHPV is more accurate and predictive of recurrence/persistence of disease than cytology or section margin status.<sup>19</sup> The fact that, in one out of five LLETZ, the reported margin status was discordant with the surgical pathology follow-up supports the concept that margin status of LLETZ specimens lacks prognostic value.

## Declarations

The author declared no personal or financial conflict of interest in conducting this study.

The research was approved by the Polokwane/Mankweng and University of Limpopo Research and Ethics Committee.

## References

1. Lindeque BG. Management of cervical premalignant lesions. *Best Pract Res Clin Obstet Gynaecol.* 2005;19:545-561.
2. Ghaem-Maghami S, Sagi S, Majeed G, Soutter WP. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol.* 2007;8:985-993.
3. Gazvani MR. Large loop excision of the transformation zone: an outpatient procedure. *Turk J Med Sci.* 2001;31:435-438.
4. Paraskevidis E, Lolis E, Koliopoulos G, et al. Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins. *Obstet Gynecol.* 2000;95:828-831.
5. Fadare O, Cardoza-Favarato G. Significance of disease extent in high-grade cervical intraepithelial neoplasia excised with negative margins by loop electrosurgical excision procedure. *Ann Diagn Pathol.* 2008;12:17-20.
6. Livasy CA, Maygarden SJ, Rajaratnam CT, et al. Predictors of recurrent dysplasia after cervical loop electrocautery excision procedure for CIN-3: a study of margin, endocervical, and quadrant involvement. *Mod Pathol.* 1999;12:233-238.
7. Boonlikit S, Junghuttakarnsatit P, Asavapiriyanoont S. Treatment failure following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia in Rajavithi hospital. *J Med Assoc Thai.* 2008;91:31-36.
8. Robinson WR, Lund ED, Adams J. The predictive value of LEEP specimen margin status for residual/recurrent cervical intraepithelial neoplasia. *Int J Gynecol Cancer.* 1998;8:109-112.
9. Dobbs SP, Asmussen T, Nunns D, et al. Does histological

**Table III:** Comparative literature review of loop excision pathology

	Range of reported values				
<b>Overtreatment</b>	9.5- 11.1% <sup>14-16</sup>	21.5% <sup>a</sup>	33.8% <sup>17</sup>	50.0% <sup>18</sup>	
<b>Severe diathermy artefact</b>		7.4% <sup>a</sup>	26.0% <sup>13</sup>		
<b>Treatment failure with incomplete margins</b>	8.0- 10.5% <sup>19,20</sup>	12.0-12.7% <sup>9,16</sup>	23.0- 29.0% <sup>2,6,7,2</sup>	37.0- 40.0% <sup>21-24</sup>	45.0% <sup>25</sup>
<b>Treatment failure with complete margins</b>	4.9% <sup>4</sup>	11.5% <sup>5</sup>	34.0% <sup>20</sup>		

<sup>a</sup> Our data

- incomplete excision of cervical intraepithelial neoplasia following large loop excision of the transformation zone increase recurrence rates? A six year cytological follow up. *Br J Obstet Gynaecol.* 2000;107:1298-1301.
10. Nqoqi N, Kellett P, Sitas F, et al. Cancer in South Africa 1998-1999. Johannesburg: National Cancer Registry, National Health Laboratory Service; 2004. Available from: <http://www.cansa.org.za/unique/cansa/files/stats98.pdf>
  11. National guidelines for cervical screening in South Africa. National Department of Health [homepage on the Internet]. c2000. Available from: <http://www.doh.gov.za/docs/facts.html>
  12. Hoque M, Hoque E, Kader SB. Evaluation of cervical cancer screening program at a rural community of South Africa. *E Afr J Pub Health.* 2008;5:111-116.
  13. Fonn S, Bloch B, Cronje H, et al. Prevalence of pre-cancerous lesions and cervical cancer in South Africa – a multicentre study. *S Afr J Med.* 2002;92:148-156.
  14. Adam Y, van Gelderen CJ, Newell K. "Look and LLETZ" – a Chris Hani Baragwanath Hospital experience. *S Afr Med J.* 2008;98:119-122.
  15. Kabir F. Cervical intraepithelial neoplasia in HIV-positive women after excision of the transformation zone: does the grade change? *Gynaecological abstracts*, abstract no. 12. SASOG Congress; 2010.
  16. Baloglu A, Uysal D, Bezircioglu I, et al. Residual and recurrent disease rates following LEEP treatment in high-grade cervical intraepithelial lesions. *Arch Gynecol Obstet.* 2010;282:69-73.
  17. Moselhi M, Howells RE, Hauke A, et al. Follow-up after negative large loop excision of the transformation zone (LLETZ) of the cervix. *J Obstet Gynaecol.* 2002;22:193-196.
  18. Ayhan A, Boynukalin FK, Guven S, et al. Repeat LEEP conization in patients with cervical intraepithelial neoplasia grade 3 and positive ectocervical margins. *Int J Gynaecol Obstet.* 2009;105:14-17.
  19. Verguts J, Bronselaer B, Donders G, et al. Prediction of recurrence after treatment for high-grade cervical intraepithelial neoplasia: the role of human papillomavirus testing and age at conisation. *Br J Obstet Gynaecol.* 2006;113:1303-1307.
  20. Leguevaque P, Motton S, Decharme A, et al. Predictors of recurrence in high-grade cervical lesions and a plan of management. *Eur J Surg Oncol.* 2010;36:1073-1079.
  21. Chen Y, Lu H, Wan X, et al. Factors associated with positive margins in patients with cervical intraepithelial neoplasia grade 3 and postconization management. *Int J Gynaecol Obstet.* 2009;107:107-110.
  22. Messing MJ, Otken L, King LA, et al. Large loop excision of the transformation zone (LLETZ): a pathologic evaluation. *Gynecol Oncol.* 1994;52:207-211.
  23. Tyler LN, Andrews N, Parrish RS, et al. Significance of margin and extent of dysplasia in loop electrosurgery excision procedure biopsies performed for high-grade squamous intraepithelial lesion in predicting persistent disease. *Arch Pathol Lab Med.* 2007;131:622-624.
  24. Maluf PJ, Adad SJ, Murta EF. Outcome after conization for cervical intraepithelial neoplasia grade III: relation with surgical margins, extension to the crypts and mitoses. *Tumori* 2004;90:473-477.
  25. Kietpeerakool C, Srisomboon J, Suprasert P, et al. Outcomes of loop electrosurgical excision procedure for cervical neoplasia in human immunodeficiency virus-infected women. *Int J Gynecol Cancer.* 2006;16:1082-1088.