WALTER PRENDIVILLE AND MARIA JOSE DE CAMARGO

Treatment of cervical intraepithelial neoplasia

CHAPTER

12

Treatment of cervical intraepithelial neoplasia

WALTER PRENDIVILLE AND MARIA JOSE DE CAMARGO

INTRODUCTION

This chapter attempts to outline a practical approach to the treatment of women with cervical intraepithelial neoplasia (CIN). As with any intervention, the value of treatment needs to be balanced against the physical and psychological morbidity of that treatment.

The investigation and treatment of women with cervical intraepithelial neoplasia is based on the fundamental principle that treatment will prevent abnormal tissue within the transformation zone from progressing to invasive disease. The more likely it is that such abnormal tissue will progress the more powerful is the indication to treat. The less likely it is that transformation zone epithelium will progress to cancer, the less powerful is the indication to treat or even investigate. Hence the chance of a forty-five year old woman developing cancer in the presence of repeated normal cervical smears and/or a negative oncogenic HPV test is remote. On the other hand, a woman with a cervical smear suggesting the presence of high-grade intraepithelial neoplasia with or without a positive oncogenic HPV test warrants colposcopy and treatment.

In Europe, the referral of women for colposcopic examination varies through the full spectrum of intraepithelial change. For women attending gynaecologists in several European countries, colposcopic examination is considered part of routine assessment, whether or not she has a cytological abnormality. In other European countries, women will only be offered colposcopic evaluation in the presence of a cytological abnormality.

SELECTION OF PATIENTS FOR TREATMENT

There is little argument about the need to treat women with the suspicion of a high-grade lesion (HSIL, CIN 2 or 3). There is very real disagreement about whether or not to treat women with lesser degrees of abnormality *(Figure 1)*. As a means of discriminating genuine precancer lesions from innocent transitory viral infections, oncogenic HPV testing may prove to be a useful clinical tool in specific age populations.

It appears unlikely that oncogenic HPV positivity is clinically useful in very young women. However, in women over 30, HPV negativity does appear to afford genuine immunity from the covert development of cancer even in the presence of mild cytological abnormality.

Figure 1. Treatment balance with low-grade SIL

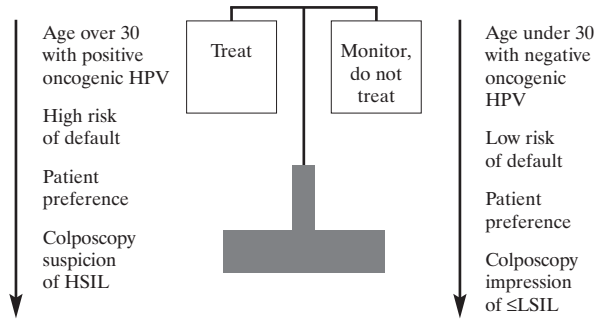

Table 1 does not represent an "absolute" list and is neither completely inclusive nor exclusive. It is useful only as a guide to practice. The clinical circumstances of the individual case and the environment in which the colposcopist is working will influence the individual decision. For example, it will not usually be appropriate to treat women with high-grade intraepithelial neoplasia during pregnancy provided that there is no suspicion of invasive disease. Likewise, it may be entirely appropriate to treat some women with low-grade abnormality if the chance of default is high or there is excessive patient anxiety.

Table 1. Common indications for treatment

1. The cytologic and/or colposcopic suspicion of a significant degree of squamous intraepithelial neoplasia (CIN 2 and 3 or high-grade SIL)
2. The suspicion of squamous microinvasive disease or adenocarcinoma in situ
3. Unsatisfactory colposcopic examination in the presence of convincing cytologic abnormality
4. Persistent CIN 1 (low-grade SIL, LSIL), or CIN 1 in which the likelihood of follow-up per attendance default is high *(Figure 1)*
5. A symptomatic cervical ectropion

TREATMENT OPTIONS

Table 2 details the currently available methods of eradicating the cervical transformation zone. Eradicating the transformation zone in women with CIN is an effective means of

Table 2. Treatment choices for cervical intraepithelial neoplasia

Excision	Destruction
Hysterectomy	Cryocautery
Cone biopsy	Cold-coagulation
LLETZ	Radical diathermy
	Laser vaporation

LLETZ large loop excision of the transformation zone

preventing the development of cancer. Logically, it follows that this be true whether the transformation zone is destroyed or excised.

ELECTROCAUTERY

In the early part of this century, electrocautery was used to treat "chronic cervicitis" or "cervical erosion", which were believed to be possible precursors of cervical cancer (1-4). A ball or spade electrode was used in these early studies. When the electric current flowed through the electrode it became "red hot" and thus destroyed the tissue. With the advent of colposcopy, the process of glandular ectopy with its subsequent metaplasia was revealed to be a normal epithelial change of the transformation zone. As a result, the routine prophylactic ablation of cervical erosions is no longer advocated. However, these studies provided the basis for the ablative treatment of CIN.

ELECTROCAUTERY SUCCESS RATES

Younge et al. (5) appear to have reported the first series of 43 women treated for CIN using electrocautery. He found that when carcinoma in situ involved only the epithelial surface the failure rate was 15%, but if gland involvement was present, the failure rate was 63%. The authors suggested that, for carcinoma in situ, electrocauterization could be offered to selected patients, who desired to maintain their reproductive function as an alternative to hysterectomy or cone biopsy. Some twenty years latter, reports of electrocautery or fulguration for CIN achieving high success rate were published. *Richart and Sciarra* (6) reported an 89% success rate in a study of 170 patients. However, 67% of these patients had CIN 1 and the number of patients with CIN 3 was very small (5 patients). Fulguration did not appear to be very effective, with a success rate of only 60%. *Deigan et al.* (7) described an initial success rate of 89-90% after three to six months of follow-up, however, long-term follow-up rates fell from 75% of the patients at one year to 46% at 5 years. *Wright, Richart and Ferenczy* (8), in a review of electrosurgery development, reported a "recessed" squamo-colunmnar junction in 70% of patients after treatment, frequent cervical stenosis in patients over 40 years, significant pain during the procedure and low effectiveness for CIN 3 as the main disadvantages of electrocautery and fulguration for CIN. Electrocautery has all but disappeared from today's range of therapy for CIN.

COLD-COAGULATION

In 1966, *Semm* presented a new apparatus for the "cold-coagulation" of benign cervical lesions. It consisted of a small electronic monitor and various exchangeable thermosounds. This technique was called "cold-coagulation" because of the recommended temperature ranged between 120 °F to 160 °F (below boiling temperature) – so it was "relatively" cold. Previously, electrocauterization had been used to burn cervical tissue and it achieved temperatures of 400 °F to 1,500 °F. Cold-coagulation was presented as painless and superior for the treatment of "chronic cervicitis". Some years later cold coagulation's potential as a treatment for CIN became a reality.

EFFECTIVENESS

Gordon and Duncan (9) showed that a single treatment was effective in restoring cervical cytology to normal in 1,518 of 1,628 women with CIN 3, which represented a 93% success rate. After 6 years of follow-up, this success rate fell to 91% (10). Using the Semm cold-coagulator, *Loobuyck and Duncan* (11) reported a "see and treat" protocol in 1,165 patients with CIN 1 and 2. After 13 years of experience, they described a primary success of 96.7%, (falling to 96.5% for CIN 1 and to 95.4% for CIN 2 after eleven years of follow-up). In Duncan's practice, the woman has a colposcopic examination, and several punch biopsies (two to four) at the first visit. If the colposcopic impression is of a lesion no worse than CIN 3 and the transformation zone is fully visible, then cold-coagulation is performed. Many other authors have reported similar results with cold-coagulation, for example *Williams et al.* (12), reported a success rate of 96.5% in 125 patients with histologically proven CIN 2 or 3 who had been followed for 18 months. In a randomized trial comparing laser with cold-coagulation for the treatment of CIN 2 and 3, *Smart et al.* (13) reported 589 patients who were followed for a minimum period of 12 months. There was no significant difference in success rates between laser (11.5%) and cold-coagulation (10%).

Gordon and Duncan (9) reported that treatment on the second occasion of 26 patients with recurrent CIN 3 resulted in 5 failures (19%), comprising one adenosquamous carcinoma, one squamous carcinoma, one CIN 3 together with adenocarcinoma in situ, one CIN 2 and one CIN 3. Due to these failures, they recommended excisional treatment where persistent or recurrent CIN 3 is suspected after primary treatment.

SELECTION CRITERIA FOR COLD-COAGULATION (10)

1. The transformation zone must be fully visible, 2. there should be no suspicion of microinvasive disease or adenocarcinoma in situ, 3. there must have been no previous treatment of the transformation zone.

COMPLICATIONS OF COLD-COAGULATION

Pain during the procedure, postoperative persistent bleeding, and vaginal discharge are the main complaints reported for cold-coagulation. *Farquharson et al.* (14) randomized 714 patients with CIN 2 or 3 to receive treatment with the Semm cold-coagulator or carbon dioxide laser and they found statistically significant differences between the two treatments with respect to pain and vaginal bleeding. In this series, 21% of patients treated with laser required local analgesia, compared with 8% of those treated by cold-coagulation. Pain after treat-

ment was relatively common in both groups. A slightly higher proportion (66.6 versus 57%, p = 0.04) of patients reported bleeding following laser treatment in this study. Postoperative vaginal discharge was not significantly different. These authors concluded that laser therapy was less acceptable to the patient in terms of pain, duration of treatment and postoperative vaginal bleeding. *Duncan* (15) reported that 1% of his patients complained about postoperative vaginal discharge, and 3.5% of persistent bleeding for 1-6 weeks after treatment. Persistent pelvic pain was reported in 1% of patients. Cervical stenosis requiring dilatation was described in up to 1% of patients.

ELECTROCOAGULATION DIATHERMY

The development of electrosurgical units, which convert standard electrical supply into high frequency alternating current, thereby generating specific wave forms, have allowed clinicians to produce different tissue effects. Since the 1970s, more sophisticated transistorised units have been available on the market for outpatient use. In 1971, *Chanen and Hollyock* (16) described the use of electrocoagulation diathermy as a specific mode of physical destruction for the treatment of preinvasive disease, initially under general anaesthesia but more recently as a local anaesthetic outpatient procedure. A speculum with a smoke extractor is necessary. The current may be applied continuously or periodically for 2-3 seconds at a time. Slower movement and direct contact onto the tissue will achieve the desired deeper coagulation. In order to destroy the deep gland crypts, a needle electrode is then inserted to a depth of at least 7 mm into the long axis of the cervix. The number of insertions is purely empirical and relates to the area and extension of the lesion. *Chanen* (17) suggests that each insertion of the needle should last for at least 2 seconds, and that the end-point of diathermy is when the area is desiccated and no further mucus exudes.

EFFECTIVENESS OF ELECTROCOAGULATION DIATHERMY

Chanen (17) has reported a success rate of 98% in 2,990 patients with first-time treatment. Almost two thirds of the patients were histologically classified as having CIN 3, and the interval between treatment and recognition of residual or recurrent disease ranged from 12 months to over 10 years. However, most of the recurrences were detected between the first and third year of follow-up.

SELECTION CRITERIA FOR ELECTROCOAGULATION DIATHERMY

1. Patients with fully visible limits of the abnormal transformation zone or when the limits can be brought into view by manipulation irrespective of the grade of CIN severity, 2. histological confirmation of CIN should be obtained before the ablation, 3. electrocoagulation diathermy is contraindicated if the abnormal transformation zone extends into the endocervical canal, if it is entirely endocervical or if there is any suspicion of microinvasion or glandular abnormality.

COMPLICATIONS

In 2,990 patients treated by electrocoagulation diathermy, *Chanen* (17) described the following complication rates: secondary haemorrhage in 1.2%, pelvic infection in 0.4%, and cervical stenosis in 0.4%.

Somewhat surprisingly long-term follow-up has not revealed adverse effects on cervical function, fertility, pregnancy or subsequent labour (18-19).

CRYOTHERAPY

The first report of cryosurgical therapy for cervical neoplasia were published in 1967 by *Crisp and colleagues* (20), followed by several others during the 1970s. In many countries, it rapidly became the most popular treatment for CIN. This technique freezes the cervical epithelium using a cryosurgical probe. The destruction of tissue is based on achieving a temperature of -20 °C with subsequent crystallisation of the intracellular water. Crystallisation in the nucleus disrupts the cell membrane, causing cell death. Many different cryosurgical probes are available, and several studies have evaluated the interaction of the cryoprobe with the cervix, the necessary freeze time in order to destroy the tissue and the effectiveness of this once popular outpatient treatment modality. The refrigerant gas which cools the probe may be carbon dioxide or nitrous oxide. Nitrous oxide has been described as the preferred gas because it has a colder freezing point (-90 °C) than carbon dioxide gas (-60 °C). The gas tank must be kept at a constant pressure (750-830 mmHg) to adequately freeze the cryoprobe. A large tank of at least 20 lb should be used, since tanks with low pressure may produce frost but do not adequately freeze the epithelium (21).

Creasman at al. (22) compared a single freeze (3 minutes at -60 °C) with a double freeze technique (3 minutes freeze, 5 minutes thaw and 3 minutes refreeze) in 75 patients with biopsy-proven severe dysplasia and carcinoma in situ. These patients then underwent either hysterectomy or conization 6 weeks to 3 months after cryotherapy. Persistent disease in the surgical specimen, was evident in 48% of patients who had a single freeze and 18% with a double freeze. Two patients had microinvasive disease revealed at conization and were thought to represent "errors" of the pre-treatment biopsies. After this report, the majority of colposcopists who still used cryotherapy advocated using the double freeze technique.

EFFECTIVENESS OF CRYOTHERAPY

The temperature, freezing time, type of probe, external os shape, size and grade of cervical lesion have each been found to be significant variables in terms of effectiveness.

Boonstra et al. (23) applied cryosurgery to the uterine cervix of 64 women the day before hysterectomy in order to evaluate the biophysical performance of cryocautery in destroying transformation zone epithelium. They measured the depth and linear extension of the cryolesions morphometrically using a computerised graphic table, and concluded that long freeze times are necessary to obtain an adequate freeze, especially in large CIN 3 lesions or with localisation of the CIN 3 at the 3 or 9 o'clock positions. The results of this study revealed that the type of probe and the anatomical clock position were two independent factors influencing the size of the cryolesion. The largest cryolesions in terms of depth and linear extension were obtained with large-cone probes. The profuse vascular supply of the cervix at the 3 and 9 o'clock positions may be the main cause of unsuccessful cryosurgery at these positions. Only when the freeze time was extended until a temperature of -20 °C was achieved, 5 mm beyond the probe edge did the adequacy of the freeze attain 100% at the 3 and 9 o'clock sites.

Hatch (21), in a comprehensive review of cryosurgery, identified several studies relating recurrence to CIN grade (24-27) with failure rates ranging from 5.6% for CIN 1 to 5.5% for CIN 2 and 10.4% for CIN 3. In 354 patients treated with cryosurgery, *Ostergard* (24) observed a failure rate of 19.6% for CIN 3 treatment. Based on his clinical experience, he considered cryotherapy to be unacceptable for the treatment of CIN 3. *Wright and Davies* (28) also found high persistent disease rates in women with CIN 3 lesions and suggested that cryotherapy should be employed with caution for this grade of disease. After eleven years of experience with cryotherapy, *Bryson et al*. (29) evaluated the treatment results of 453 patients with CIN 3 and reported a failure rate of 7.1%, concluding that cryotherapy was effective for the treatment of grade 3 cervical intraepithelial neoplasia, but a rigid protocol of patient selection and meticulous technique play a large role in achieving high therapeutic success rates. *Benedet et al.* (27) also reported excellent results with cryosurgery for all grades of CIN. After a 10-year follow-up, the authors recommended long-term continued surveillance, because of the persistent risk of recurrence.

Finally, *Hatch* (21) reviewed the use of cryotherapy for CIN in relation to the size of lesion. Reviewing three studies involving 632 patients (25, 29-30) he described failure rates ranging from 6.8% when one quadrant or 25% of the cervix was involved, to 14.1% when the lesion was greater than two quadrants (or 50%) of the cervix.

SELECTION CRITERIA FOR CRYOTHERAPY

A rigid protocol of patient selection is advised by those workers who have obtained high success rates. *Bryson et al.* (29) describe the following patient selection criteria: 1. transformation zone entirely visible on the cervix, 2. negative endocervical curettage, 3. absence of pregnancy, 4. no exposure to diethilstilbestrol, 5. no suspicion of microinvasion or invasion, and 6. patient reliability for follow-up.

Benedet and his colleagues (27) have described specific cervical and biophysical circumstances which they believe are necessary if cryotherapy is to achieve high success rates in women with CIN: 1. minimal endocervical extension of the transformation zone, 2. fully visible lesion margins, 3. excellent probe epithelium contact, 4. satisfactory iceball formation extending 3-4 mm beyond the lesion margins, and 5. adequate cryotherapy gas pressure.

COMPLICATIONS OF CRYOTHERAPY

Complications resulting from cryosurgery are rare. Post-cryotherapy infection appears to be the most common and significant complication (21). Bleeding following the procedure is extremely rare. *Benedet et al.* (27) reported one patient out of 1,675 requiring therapy for bleeding. Complete cervical stenosis resulting in haematometra and pyometra is rare, more commonly the cervix is narrowed and this may interfere with adequate cellular collection at follow-up cytology.

LASER VAPORIZATION

The term LASER is an abbreviation for "light amplification by stimulated emission of radiation". Conventional light produced by spontaneous emission travels in all directions while the main difference of laser energy is that laser produces coherent light or a parallel beam of uniform wavelengths. Therefore, the laser beam can be focused by a lens to a small area, producing a power density of very high magnitude. Radiant energy at a specific wavelength can be produced by conversion of energy such as heat, light, radiowaves or electricity by the laser. The carbon dioxide laser, most frequently used in the treatment of CIN, is produced from an electrical discharge with a wavelength of 10.6 μ in the infrared part of the spectrum. This is invisible to the naked eye. In clinical practice, a visible helium-neon laser beam is focused at the same point on the tissue surface to facilitate its use by the operator (31). The carbon dioxide laser was introduced into clinical practice in the late 1970s (32) and achieved great popularity, especially in developed countries because of its power, accuracy and, according to *Monaghan* (31), a certain twenty-first century charisma with patients, and perhaps with clinicians, too!

Laser beam energy is absorbed by materials with a high water content, for example cervical tissue. The vaporised material is a mixture of water vapour and carbon fragments, which is removed from the vagina by a speculum with a fitted smoke extractor tube. It has long been recognised that for the most effective results with any ablative techniques the whole transformation zone should be treated. Also, the knowledge of cer-

vical crypt involvement by cervical intraepithelial neoplasia is important for the effectiveness of these treatment modalities. *Anderson and Hartley* (33) studied the depth of involved and uninvolved crypts in 343 conization specimens and found 1.24 mm as the mean depth of involved crypts. For uninvolved crypts the mean depth was 3.38 mm. They concluded that a destruction of 3.80 mm would eradicate all involved crypts in 99.7% of patients (mean + 3 SD). Therefore, destruction of the entire transformation zone and the deepest crypts are necessary for successful laser ablation, as described by *Monaghan* (31). After colposcopic examination of the entire transformation zone, it is circumfirentially demarcated with laser approximately 3 mm outside the transformation zone margin. Once the outline of the transformation zone has been delineated, the area to be treated is removed down to a recommended depth of 7 or more mm.

Jordan et al. (34) reported a 90% success rate after a single laser vaporisation to a depth of 5-7 mm in 711 women. At the beginning of this study, the authors reported inadequate depth of destroyed tissue as an important cause of treatment failure, and by trial and error concluded that they should aim to achieve a 5-7 mm depth of destruction and to do so in a cylindrical fashion. These studies provided the basic rationale for subsequent laser ablation or excision of the abnormal transformation zone (33-34).

Because of the risks to the operator in material found in the plume (vaporised material), such as human papillomavirus this plume should be extracted and exhausted to the exterior with adequate filters in the extraction line (21). Finally, the procedure is usually performed under local analgesia including a vasopressor agent.

Table 3. Cryotherapy and laser case series

Reference	Cryotherapy		Laser		
	Total of patients	Treatment failure	Total of patients	Treatment failure	Follow-up (months)
Kirwan et al. (37)*	35	6%	71	8%	17-24
Kwikkel et al. (38)*	50	7%	51	15%	3-18
Berget et al. (39)*	101	9%	103	10%	3-23
Berget et al. (40)*	93	4%	94	8%	12-80
Guijon et al. (41)*	276	5.4%	160	8.1%	4-48
Mitchell et al. 1998 (42)*	139	5%	121	4%	6
Mitchell et al. (47)*	139	19%	121	13%	6-37
Wright and Davies (43)	152	22%	131	4%	12-42
Townsend and Richart (44)	100	7%	100	11%	12
Ferenczy (45)	147	13%	147	6%	12-48

* randomized

EFFECTIVENESS OF LASER ABLATION

Laser vaporisation for the treatment of CIN is acknowledged to be highly effective. *Ali and colleagues* (35) reported the results of CO_2 laser treatment in 1,234 patients with a 96.2% success rate. Their criteria of treatment success was one or more year of follow-up with negative cytology and colposcopy. *Wright and colleagues* (36) reported a 95.3% success rate in 429 cases of CIN of all degrees. Although this study included excisional laser therapy, most patients (357 cases) were treated by vaporisation. There are several reports in the literature showing similar results in terms of success with laser ablation.

SELECTION CRITERIA FOR LASER ABLATION

The selection criteria for laser ablation are very similar to those already described for the other ablative techniques (31, 34). *Monaghan* (31) suggests that 1. the patient must be examined by an experienced and skilled colposcopist, 2. the entire limits of the transformation zone must be visible, 3. there should be no suspicion of microinvasive or invasive disease, 4. there should be no suspicion of abnormal glandular epithelium.

COMPLICATIONS OF LASER ABLATION

Berget et al. (46) reported a randomized trial of 204 women treated by CO_2 laser or cryotherapy and found a small difference in complications rates. Slightly more patients experienced moderate or severe pain during laser treatment ($p = 0.05$). Postoperative vaginal discharge was more often seen after cryo-treated patients. Pelvic inflammatory disease was found in one patient in each treatment group. Postoperative spotting occurred more often in laser treated patients. At follow-up colposcopy, 3 months after treatment, the squamo-columnar junction was significantly more likely to be fully visible in laser treated patients ($p < 0.001$). *Monaghan* (31) suggests that local analgesic injection will eliminate intraoperative pain and observed that the risk of haemorrhage is higher in the presence of cervical infection and, logically, recommends its elimination before treatment.

RELATIVE EFFECTIVENESS OF LASER AND CRYOTHERAPY

Table 3 details a number of studies which compared cryotherapy and laser ablation. Most of the randomized comparative studies do not show clinically important or statistically significant differences between treatments groups. In a randomized trial comparing cryotherapy, laser vaporisation and loop excision for treatment of squamous intraepithelial lesions, *Mitchell et al.* (47) revealed a uniformly high success rate. In this study, "persistent disease" rates (up to 6 months after treatment) were higher than "recurrence rates" (more than 6 months after treatment), but the rates were similar for the three treatment modalities. The risk of persistent disease was higher among women with large lesions and the risk of

recurrence was higher among women over 30 years, with papillomavirus type 16 or 18 and for those who had prior treatment. Finally, six months is too short a period to recognize all residual disease (48-49). *Guijon et al.* (50) investigated a cohort of 436 women with CIN, randomly allocated for cryo- or laser therapy. They found that the most reliable risk factors associated with therapy failure were: 1. patient age, 2. HPV type, 3. lesion size, 4. CIN grade, and 5. parity.

LLETZ (LARGE LOOP EXCISION OF THE TRANSFORMATION ZONE)

In 1981 at the fourth World Congress of Colposcopy and Cervical Pathology, *Cartier* reported his experience using a small loop to take directed biopsies and to extirpate the transformation zone in strips. *Cartier* achieved the dual ambition of providing comprehensive tissue for histology using a technique associated with minimal morbidity. The technique known as LLETZ derived from Cartier's work and utilized larger loops in order to extirpate the entire transformation zone in one piece. LLETZ uses modern low-voltage diathermy electrosurgery units and insulated loops. Finally, the process is performed under local anaesthesia. It was introduced into clinical practice in Bristol in the early 1980s (51). It rapidly gained widespread acceptance (52). The technique is known as LLETZ but its name was changed to LEEP – on arrival in the USA.

The major advantage of LLETZ is that it achieves excision of the transformation zone using a technique that preserves histological integrity. As a result, the extripated transformation zone may be comprehensively examined, microinvasive disease ruled out, excision margins assessed and over-treatment recognized. Also the treatment is applicable to every circumstance where the transformation zone needs to be treated. Whether the transformation zone is endocervical or ectocervical, large or small, and containing squamous or glandular abnormalities, LLETZ is still applicable. Finally, the technique is office- (i.e. outpatient-) based and maintains the special advantages that the ablative methods have over the traditional cold knife cone biopsy (low morbidity and local anesthesia).

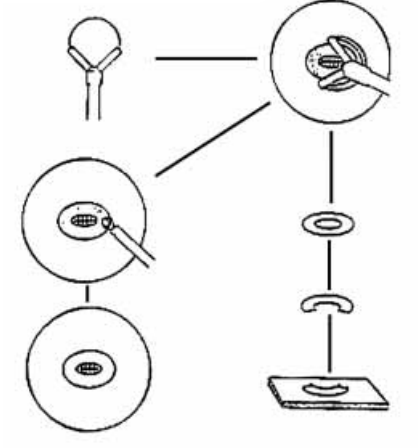

Figure 2. LLETZ excision of a small fully visible ectocervical transformation zone. A medium (white) loop is used for the procedure.

The technique has been described in detail previously (53-54). *Figure 2* illustrates the procedure in its simplest form.

LLETZ may be used for those circumstances when a local destruction is applicable (the type 1 or 2 transformation zone) but also when it would otherwise be necessary to perform a cone biopsy (type 3 transformation zone). LLETZ is associated with very low failure rates. *Table 4* details the short-term outcome reported in a series of publications during the 1990's.

Table 4. Failure rates (recurrence within one year)

Series	Abnormal cytology and/or colposcopy	Positive histology after treatment
Prendiville et al. (54)	5.6%	3.0%
Bigrigg et al. (55)	9.0%	4.9%
Luesley et al. (56)	5.6%	4.4%
Whiteley and Olah (57)	5.7%	–
Murdoch et al. (58)	6.0%	3.5%
Hallam et al. (59)	9.0%	–

In 1997, *Flannelly and colleagues* (48) reported their study of the first 1,000 women treated with LLETZ in Aberdeen. This revealed a cumulative rate of recurrence at four years of 10.1 per 100 women. Nine hundred and seventy-seven women (97.7%) were seen for follow-up at least once and 317 were followed for as long as four years. The rate of dyskaryosis in the 12 months following LLETZ was 4.4 %, which is similar to that previously reported following both LLETZ and laser ablation.

More recently, *Dobbs and colleagues* (60) reported a series of 394 women followed for up to 10 years after treatment by LLETZ during 1991-1992. The mean follow-up length was 73 months and the mean number of follow-up smears was six. They achieved complete follow-up data in 343 women (83%). Fourteen women (4%) had histological recurrence of CIN. Within this group, two women had developed invasive cancer following initial incomplete excision of CIN 3. Both were stage IA and were treated by simple hysterectomy.

THE PLACE OF ABLATIVE THERAPY IN COLPOSCOPIC PRACTICE

Destructive therapy for CIN using local analgesia in the office or outpatient setting represents a milestone in the evolution of cervical preventive health care. Coincident with the realisation that CIN is confined to the transformation zone, which is often fully visible, four safe and effective modalities of tissue destruction evolved during the 1970s. As a result, women were able to avoid the morbidity and excess of cold

knife conization or even hysterectomy. In order to minimise the risk of inadvertently treating invasive disease with destructive methods demand that certain prerequisite conditions are met.

Traditionally, the exclusion of invasive disease has been attempted by taking one or more colposcopically directed biopsies from the most apparently abnormal area within the transformation zone followed by treatment at a second visit. This approach is fundamentally flawed for three reasons: 1. colposcopists are unable to reliably recognize the worst degree of abnormality within a transformation zone, 2. colposcopically directed biopsies are an inadequate means of ruling out microinvasive disease, 3. there are not yet easily recognisable colposcopic features of adenocarcinoma in situ or lesser grades of glandular abnormalities.

The exclusion of microinvasive disease seems to be the most difficult prerequisite, whether this is because of difficulty in recognizing microinvasive disease or because of the inadequacy of colposcopically directed biopsies (54). However, it is clear from a number of publications that colposcopic examination and a colposcopically directed biopsy is an unreliable means of recognising microinvasive disease (61-64). Indeed, in a recent review by *Reis and colleagues* (65), colposcopy and colposcopically directed biopsy had a mere 50% (CI 40.1-59.04) sensitivity for recognising early invasive disease prior to conization (n = 354), hysterectomy (n = 4) or radical hysterectomy (n = 83).

This difficulty with colposcopically directed biopsies, which has been repeatedly demonstrated, may in part explain the occurrence of invasive disease following destructive ablation of the transformation zone (66-68).

WHAT IS THE BEST TREATMENT FOR CIN

There is little to choose between the different destructive methods in terms of success/failure rates. Each and all of these methods are highly effective, associated with low morbidity and in selected cases (i.e. fully visible ectocervical or type 1 transformation zones) are entirely appropriate means of managing women with CIN. Differences in success rates are not because of inherent method-related problems but are likely to be due to differences in patient selection, operator experience or the characteristics of the transformation zone.

Finally, the added value afforded by modern excisional techniques *(Table 5),* which have all the advantages of destructive methods of treatment will influence many colposcopists to choose excision over destruction for the management of women with CIN.

Table 5. Added value of local excisional techniques over destructive/ablative therapy for CIN (LLETZ, laser excision)

1.	Allows a selective "see and treat" protocol
2.	Facilitates the confident recognition of (or will rule out) microinvasive disease
3.	May recognize incomplete excision of dysplastic process
4.	May recognize (though not rule out) adjacent glandular dysplasia
5.	Facilitates quality assurance by revealing to the individual colposcopist his or her over-or under-treatment rate
6.	Allows the treatment of any type of transformation zone with any grade of CIN or GIN

THERMAL DAMAGE AND ELECTROSURGICAL EXCISION

Excision by laser or LLETZ involves artefactual damage to the wound and to the surgical specimen. This thermal artefact may sometimes destroy any incompletely removed abnormal cervical tissue, but also may compromise the assessment of the margins status. Some studies have reported extensive damage compromising the histological evaluation of the excised tissue (78, 88). But difficulty in evaluating the lesion and its margin due to the coagulation has not been reported in several series of standard LLETZ (51, 55-56, 84) and in some series of LLETZ conisation listed in *Table 3. Paraskevaides et al.* (69), in a study of 40 patients who underwent abdominal hysterectomy after cone biopsy, compared the thermal damage caused by laser versus LLETZ and concluded that for routine conisation loop diathermy caused less thermal damage.

LLETZ is associated with very low short-term and long-term morbidity rates and does not affect fertility or obstetric performance. However, most studies reporting clinical experience with LLETZ include only patients whose transformation zones are ectocervical. Because LLETZ may be modified to perform cone biopsy there is some confusion concerning nomenclature.

CONE BIOPSY IN THE MANAGEMENT OF CERVICAL INTRAEPITHELIAL DISEASE

For most patients the squamo-columnar junction is fully visible and they may be treated by a routine LLETZ procedure. Patients with significant intraepithelial abnormalities in whom, after careful colposcopic examination, the squamo-columnar junction is not visible, need to undergo a cone biopsy. Common indications for cone biopsy are listed in *Table 6.* The essential objective of cone biopsy is to excise the entire transformation zone and any abnormal glandular epithelium, so that comprehensive histological examination may be undertaken and excision margin-disease margin correlation determined. In a study of CIN lesions extending into the cervical canal beyond the limits of colposcopic vision, *Guerra and colleagues* (70) performed microcolpohysteroscopic evalua-

Table 6. Common indications for cone biopsy

1.	Suspicion of microinvasive carcinoma or occult invasive carcinoma
2.	Suspicion of glandular disease
3.	Incompletely visible transformation zone in women with high-grade SIL (CIN 2 and CIN 3)
4.	Significant disparity between cytology and colposcopy
5.	CIN in the presence of previous treatment of the transformation zone

tion of the endocervical canal prior to cone biopsy in order to establish the upper limit of the transformation zone. In 43%, (n = 174) the upper limit was visible 5 mm up the endocervical canal. In 46%, it lay between 6 and 10 mm and in 10% it extended between 10 and 20 mm up the canal. Where there is a suspicion of glandular abnormalities, conization serves to excise that portion of endocervical canal within which the glandular disease is contained. For 90% of cases of glandular intraepithelial neoplasia, this occurs in the 1.0 cm immediately adjacent to the upper limit of the transformation zone (71). These features of therapy merit careful consideration.

UNDER-TREATMENT AND OVER-TREATMENT

Over-treatment may be said to have occurred when a transformation zone has been removed (or destroyed) without need, in other words when histology reveals that there was not clinically important dysplasia present in the excised specimen. When an unselective "see and treat" policy is adopted, *Luesley et al.* (56) has shown that the resultant normal histology rate is unacceptably high. However, others (72) have shown that by adopting a selective "see and treat" policy *(Table 7)* it is possible to keep the negative histology rate below 5%. Over-treatment can be said to have occurred when an excessive amount of normal tissue adjacent to the transformation zone has been removed.

Over-treatment subjects a woman to unnecessary morbidity and anxiety. However, under-treatment is perhaps the greater sin. As one might expect, incomplete excision of the transformation zone is associated with a higher chance of there being residual disease (73-74). The fact that incomplete excision does not always (or even usually) result in residual disease is because of the combined effect of diathermy damage and the inflammatory response associated with the healing wound.

Also just as incomplete excision at histology does not equate with residual disease at cytological and colposcopic follow-up so also is it true that residual disease may occur after apparent complete excision assessed by histology (74-75). Finally, there are other important predictors of residual disease after LLETZ apart from histological incomplete excision. These include the patient's age and the severity of the disease (76). Furthermore, it should be theoretically possible to completely excise the entire transforma-

Table 7. Histology of LLETZ specimens

	1993	1994	1995	1996	1997	1998	1999
Neoplasia not confirmed	10	11	15	1,512	16	18	29
CIN 1	83	59	35	3,536	56	65	68
CIN 2	59	37	37	45	61	90	93
CIN 3	109	110	117	155	189	255	224
Glandular neoplasia only	4	2	1	3	4	1	0*
Microinvasive neoplasia	6	3	4	4	1	11	3
Invasive neoplasia	5	11	7	7	3	5	4
Total	276	243	216	262	330	445	427

* 6 women had a glandular abnormality. Each of them had an associated squamous abnormality (CIN).

(Coombe Women's Hospital Dublin Ireland Annual Clinical Report 1999)

Table 8. Incomplete excision in cone biopsy. Margins involvement (%)

Series	Margins (%) endocervical	Method	Disease	Number of patients
Cullimore et al. (71)	15.6*	Cold-knife	CIGN	51
Mathevet et al. (78)	14.0	Cold-knife	CIN, microinvasion	37
Jansen et al. (79)	22.0*	Cold-knife	CIN	316
Wolf et al. (75)	43.0*	Cold-knife	CIGN, CIN	42
Monk et al. (80)	21.0	Cold-knife	CIN, microinvasion	369
Guerra et al. (81)	5.4	Cold-knife	CIN, microinvasion	73
Gurgel et al. (82)	46.6*	Cold-knife	microinvasion	163
Partington et al. (83)	18.0*	Laser	CIN	50
Mor-Yosef et al. (84)	20.0	Laser	-	550
Lopes et al. (85)	24.0	Laser	CIN, microinvasion	313
Mathevet et al. (78)	51.0**	Laser	CIN, microinvasion	37
Andersen et al. (86)	6.6	Laser	CIN, CIGN	473
Guerra et al. (1996)	5.4	Laser	CIN, microinvasion	275
Mor-Yosef et al. (84)	10.0	Loop diathermy	CIN 3, microinvasion	50
Byrne et al. (87)	22.0	LLETZ	CIN, invasion	50
Montz et al. (88)	48.0**	LLETZ	CIN	25
Naumann et al. (93)	25.8**	LLETZ	CIN, microinvasion	120
Mathevet et al. (78)	53.0**	LEEP	CIN	36
Felix et al. (90)	28.0	LEEP	CIN, microinvasion	57
Houghton et al. (91)	42.1*	LLETZ	CIGN	19

* not defined margin ** thermal artefact

(From de Camargo et al. 1999, Diathermy cone biopsy. A randomised controlled trial of two techniques. Presented by Walter Prendiville at the Eurogin 2000 Paris April 5, 2000. Global Challenge of Cervical Cancer Prevention: Human Papillomavirus and Genital Cancers.)

tion zone by simply using bigger loops. But this would inevitably be at a cost of increased morbidity (71, 77).

Despite its obvious problems, incomplete excision is a very common entity. In a recent review by *de Camargo* of papers reporting experience with cone biopsy, incomplete excision was reported in 20% of cases, although the range was quite wide (5 to 50%), high rates were reported for all three modalities *(Table 8)*.

Why does incomplete excision occur? Is it because the excisions are too shallow for the particular transformation zone? Is it because colposcopists are incapable of reliably recognising the upper limit of the transformation zone? Is it that our pathologists are unable to recognise margin status because of artefactual damage? Or is it that we use inappropriate electrodes for different procedures?

The answer may be multifactorial. It is likely that performing excision of the transformation zone using inappropriate electrodes is at least partly to blame. The issue is further complicated by nomenclature problems in the literature. The term cone biopsy means different things in different publications. So do terms like depth of biopsy and height of specimen. Whilst some authors will use the term cone biopsy for any extirpated transformation zone, other colposcopists reserve the term cone biopsy for the circumstance where the transformation zone extends some millimeters out of view up the endocervical canal. It is in this circumstance that incomplete excision is most likely to occur.

In order that clarity prevail and that results of treatment may be properly compared between centres, a classification system should be adopted by colposcopists reporting treatment series in the literature.

This system is designed with the twin ambition of being simple and acceptable to practising colposcopists, as well as being able to accommodate every treatment circumstance that will arise in routine practice.

The system has three indices by which the transformation zone may be classified. These are: 1. the size of the ectocervical component of the transformation zone, 2. the position of the upper limit of the transformation zone, 3. the visibility of the upper limit of the transformation zone.

The three types of transformation can be characterised as being completely ectocervical, fully visible with an endocervical component, or not fully visible *(Figure 3)*.

By using these three variables it is possible to classify all transformation zones into three types. These are detailed in *Table 9*.

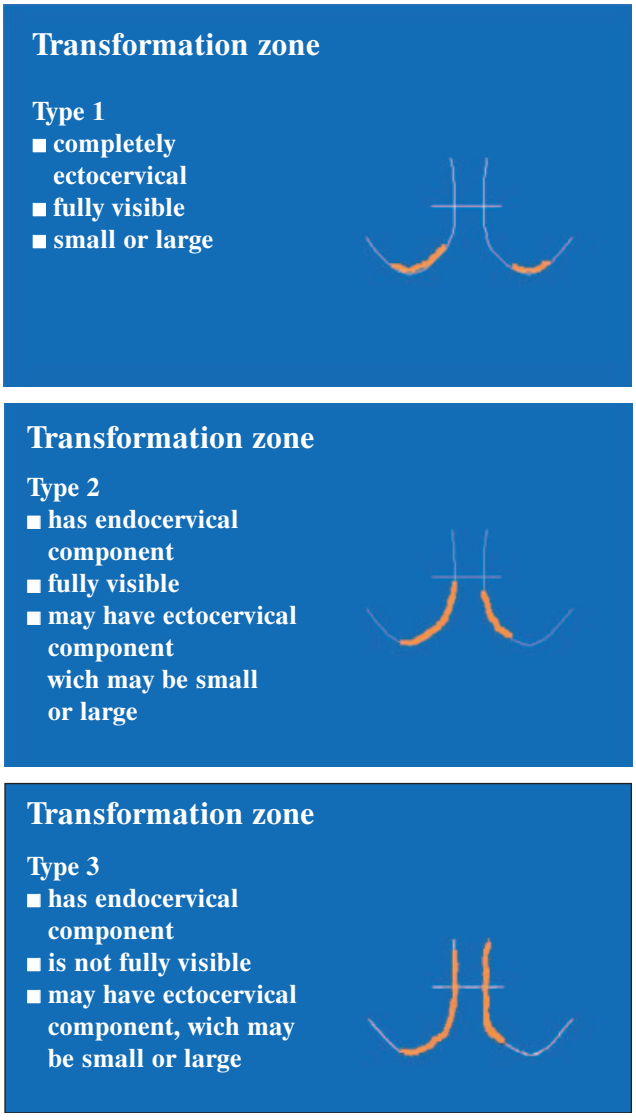

Figure 3. Classifications of transformation zone

The qualification large or small refers to the ectocervical component of the transformation zone. Large means that the transformation zone occupies more than half of the ectocervical epithelium.

Table 9. Transformation zone – geographical classification

	Size	Site	Visibility
Type 1_s	Small	Completely ectocervical	Fully visible
Type 1_l	Large	Completely ectocervical	Fully visible
Type 2_0	–	Totally endocervical	Fully visible
Type 2_s	Small	Partially endocervical	Fully visible
Type 2_l	Large	Partially endocervical	Fully visible
Type 3_0	–	Totally endocervical	Not fully visible
Type 3_s	Small	Partially endocervical	Not fully visible
Type 3_l	Large	Partially endocervical	Not fully visible

s small l large

These three different transformation zone types warrant an individualised therapeutic approach. For example it is entirely appropriate to use either an excisional or destructive methods, provided the standard criteria are met, in order to successfully treat a large or small type 1 transformation zone, whereas it is entirely inappropriate to use a destructive method of treatment for any type 3 transformation zone.

Even if one uses an excisional technique for every circumstances, it is still necessary to modify the approach according to the type of transformation zone. If one routinely uses LLETZ, the shape and size of the wire electrode needs to be modified according the transformation zone type. *Table 10* details choices which may be considered appropriate for each transformation zone type.

Table 10. Choise of wire electrods and alternative treatment according to the type of transformation zone (TZ)

TZ classification	LLETZ electrode choice	Alternative
Type 1_S	20 x 15 mm loop	Any destructive treatment
Type 1_I	Wider loop or a combination electrode treatment	Any destructive treatment
Type 2_S Type 2_I	20 x 20 mm or bigger loop or a straight wire or combination electrode treatment	Laser excision
Type 3_S Type 3_I	A longer loop or a straight wire or combination electrode treatment	Laser excision Cold-knife long cone
s small		l large

In simple terms, this means that for a type 1 transformation zone any treatment choice is likely to be successful and associated with low morbidity. For a type 2 transformation zone it may be possible to use a destructive method but an excisional one is preferable, for a type 3 transformation zone it is mandatory to use an excisional technique.

The type 3 transformation zone has a high risk of incomplete excision. It is in this circumstance that it is wise to consider alternatives to the loop. Straight wire excision is such an alternative (54) so is laser excision (84).

Determining the optimum method of performing excision of the type 3 transformation zone will be revealed by appropriately designed randomized controlled trials. If the inclusion criteria in these studies contain only type 3 transformation zones and the exclusion criteria proscribe types 1 and 2, we will be likely to discover the optimum method of management for this difficult circumstance.

REFERENCES

1. Hummer GL. The treatment of leucorrhea with actual cautery. J Am Med Assoc 1906; 46:191.

2. Huggins RR. Problems associated with the cervix. Am J Obstet Gynecol 1929; 17:589.

3. Pemberton FA, Smith GV. The early diagnosis and prevention of carcinoma of the cervix: A clinical pathologic study of borderline cases treated at the Free Hospital for Women. Am J Obstet Gynecol 1929; 17:165.

4. Payton FW, Rosen NA. Cervical cauterization and carcinoma of the cervix. Am J Obstet Gynecol 1963; 86:111.

5. Younge PA, Hertig AT, Armstrong D. A study of 135 cases of carcinoma in situ of the cervix at the Free Hospital for Women. Am J Obstet Gynecol 1949; 58:867-895.

6. Richart RM, Sciarra JJ. Treatment of cervical dysplasia by outpatient electrocauterization. Am J Obstet Gynecol 1968; 101:200-205.

7. Deigan EA, et al. Treatment of cervical intraepithelial neoplasia with electrocautery: A report of 776 cases. Am J Obstet Gynec 1986; 154:255-259.

8. Wright TC, Richart RM, Ferenczy A. Electrosurgery for HPV-related diseases of the lower genital tract. Ed Arthur Vision Inc., 1992, Text 1991 OR 1992.

9. Gordon HK, Duncan ID. Elective destruction of CIN 3 at 100 °C using Semm cold-coagulation: 14-year experience. Br J Obstet Gyn 1991; 98:14-12.

10. Duncan IA. Cold coagulation. Balliere Clin Obstet Gynaecol 1995; 9(1):145-155.

11. Loobuyck HA, Duncan IA. Destruction of CIN 1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. Br J Obstet Gynaec 1993; 100:465-468.

12. Williams OE, Bodha M, Alawattegama AB. Outocme of cold coagulation for the treatment of cervical intraepithelial neoplasia in a department of genitourinary medicine. Genitourin Med 1993; 69:63-65.

13. Smart GE, et al. Randomized trial to compare laser with cold coagulation therapy in the teatment of CIN 2 and 3. Colposcpy and Gynaecology. Laser Surg 1987; 3:48.

14. Farquharson DIM, et al. The patient acceptability of laser and cold coagulator therapy to the cervix for treatment of cervical intraepithelial neoplasia (CIN) 2-3. Colposcopy and Gynaecol. Laser Surg 1987; 3:49.

15. Duncan ID. The Semm cold coagulator in the management of cervical intraepithelial neoplasia. Clin Obstet Gynecol 1983; 26:996-1006.

16. Chanen W, Hollyock VE. Colposcopy and electrocoagulation diathermy for cervical dysplasia and carcinoma in situ. Obstet Gynecol 1971; 37:623-628.

17. Chanen W. Electrocoagulation diathermy. Balliere Clin Obstet Gynaecol 1995; 9(1):157-171.

18. Johnstone NR. Pregnancy following conservative management of dysplasia and carcinoma in situ of the uterine cervix. Aus New Zeal J Obstet Gynecol 1974; 14:9-11.

19. Hollyock VE, Chanen W, Wein R. Cervical function following treatment of intraepithelial neoplasia by electrocopagulation therapy. Obstet Gynecol 1983; 61:79-81.

20. Crisp WE, Asadourian L, Romberger W. Application of cryosurgery to gynecologic malignancy. Obstet Gynecol 1967; 30:668.

21. Hatch KD. Cryotherapy. Balliere Clin Obstet Gynaec 1995; 9:133-143.

22. Creasman WT, et al. Efficacy of cryosurgical treatment of severe cervical intraepithelial neoplasia. Obstet Gynecol 1973; 41:501-505.

23. Boonstra H, et al. Analysis of cryolesions in the uterine cervix: application techniques, extension and failures. Obstet Gynecol 1990; 75:232-239.

24. Ostergard DR. Cryosurgical treatment of cervical intraepithelial neoplasia. Obstet Gynecol 1980; 56:231-233.

25. Creasman WT, Hinshaw WM, Clarke-Pearson D. Surgery in the management of cervical intraepithelial neoplasia. Obstet Gynecol 1984; 63:145-149.

26. Andersen ES, Thorup K, Larsen G. The results of cryosurgery for cervical intraepithelial neoplasia. Gynecol Oncol 1988; 30:21-25.

27. Benedet JL, et al. The results of cryosurgical treatment of cervical intraepithelial neoplasia at one, five and ten years. Am J Obstet Gynecol 1987; 157:268-273.

28. Wright VC, Davies EM. The conservative management of cervical intraepithelial neoplasia: thew use of cryosurgery and the carbon dioxide laser. B J Obstet Gynaecol 1981; 88:663-668.

29. Bryson SCP, et al. The treatment of grade 3 cervical intraepithelial neoplasia cryotherapy: an 11-year experience. Am J Obstet Gynecol 1985; 151:210-206.

30. Townsend DE, Richart RM. Cryotherapy and carbon dioxide laser management of cervical intraepithelial neoplasia: a controlled comparison Obstet Gynecol 1983; 61:75-78.

31. Monaghan JM. Laser vaporization and excisional techniques in the treatment of cervical intraepithelial neoplasia. Balleiere Clin Obstet Gynaecol 1995; 9:173-187.

32. Stafl A, Wilkinson EJ, Mattingley RF. Laser treatment of cervical and vaginal neoplasia. Am J Obstet Gynecol 1977; 128:128-136.

33. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. Obstet Gynecol 1980; 55:546-550.

34. Jordan JA, et al. The treatment of cervical intraepithelial neoplasia by laser vaporization. Br J Obstet Gynaecol 1985; 92:394-398.

35. Ali SW, Evans AS, Monaghan JM. Results of CO_2 laser cylinder vaporization of cervical intraepithelial disease in 1234 patients. An analysis of failures. Br J Obstet Gynaecol 1986; 93:75-78.

36. Wright VC, Davies E, Riopelle MA. Laser surgery for cervical intraepithelial neoplasia. Principles and results. Am J Obstet Gynecol 1983; 145:181.

37. Kirwan PH, Smith IR, Naftalin NJA. A study of cryosurgery and the CO_2 laser in treatment of carcinoma in situ (CIN 3) of the uterine cervix. Gynecol. Oncol 1985; 22:195-200.

38. Kwikkel HJ, et al. Laser or cyrogherapy for cervical intraepithelial neoplasia: a randomized study to compare efficacy and side effects. Gynecol. Oncol 1985; 22:23-31.

39. Berget A, et al. Outpatient treatment of cervical intraepithelial neoplasia. Acta Obstet Gynecol Scand 1987; 66:531-536.

40. Berget A, Andreasson B, Bock JE. Laser and cryo surgery for cervical intraepithelial neoplasia. Acta Obstet Gynecol Scand 1991; 70:231-235.

41. Guijon F, Paraskevas M, McNicol P. Human papillomavirus infection and the size and grade of cervical intraepithelial neoplasia lesions associated with failure of therapy. Int J Gynecol Obstet 1993; 42:137-142.

42. Mitchell MF, et al. A randomized clinical trial of cyrotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. Obstet Gynecol 1998; 92(5):737-744.

43. Wright VC, Davies EM. The conservative management of cervical intraepithelial neoplasia: the use of cryosurgery and the carbon dioxide laser. Br J Obst Gynaecol 1981; 88:663-668.

44. Townsend DE, Richart RM. Cyrothewrapy and carbon dioxide laser management of cervical intraepithelial neoplasia: a controlled comparison. Obstet Gynecol 1983; 61:75-78.

45. Ferenczy A. comparision of cryo- and carbon dioxide laser therapy for cervical intraepithelial neoplasia. Obst Gynecol 1985; 66(6):793-798.

46. Berget A, et al. Outpatient treatment of cervical intraepithelial neoplasia. Acta Obstet Gynecol Scand 1987; 66:531-536.

47. Mitchell MF, et al. A randomized clinical trial of cryotherapy, laser vaporization, and loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. Obstet Gynecol 1998; 92(5):737-744.

48. Flannelly G, Langhan H, Jandial L, et al. A study of treatment failures following large loop excision of the transformation zone for the treatment of cervical intraepithelial neoplasia Br J Obstet Gynaecol 1997; 104:718-722.

49. Bigrigg A, et al. Efficacy and safety of large-loop excision of the transformation zone. Lancet 1994; 343(8888):32-34.

50. Guijon F, Paraskevas M, McNicol. P. Human papillomavirus infection and the size and grade of cervical intraepithelial neoplastic lesions associated with failure of therapy. Int J Gynecol Obstet 1993; 42:137-142.

51. Prendiville W, Cullimore J, Norman S. Large Loop Excision of the Transformation Zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1989; 96:1054-1060.

52. Kitchener HC, Cruickshank M, Farmery E. The 1993 British Society for Colposcopy and Cervical Pathology/National Co-ordinating Network United Kingdom Colposcopy Survey. Br J Obstet Gynaecol 1995; 102:549-552.

53. Prendiville W, Cullimore J, Norman S. Large loop excision of the transformation zone (LLETZ). A new method of management for women with cervical intraepithelial neoplasia. Br J Obstet Gynaecol 1989; 96(9):1054-1060.

54. Prendiville W, ed. Large Loop Excision of the Transformation Zone. A Practical Guide to LLETZ. Chapman and Hall Medical, 1993.

55. Bigrigg MA, Codling BW, Pearson P, Read MD, Swingler GR. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit. Experience of low-voltage diathermy loop in 1000 patients [see comments]. Lancet 1990; 336(8709):229-231.

56. Luesley DM, Cullimore J, Redman CWE, et al. Loop diathermy excision of the cervical transformation zone in patients with abnormal cervical smears. Br Med J 1990; 300:1690-1693.

57. Whiteley PF, Olah KS. Treatment of cervical intraepithelial neoplasia: experience with low voltage diathermy loop. J Obstet Gynecol 1990; 162:1272-1277.

58. Murdoch JB, Crimshaw RN, Monaghan JM. Loop diathermy escision of the abnormal cervical transformation zone. Gynecol Cancer 1991; 1:105-111.

59. Hallam N, Edwards A, Harper C, et al. Diathermy loop excision, a series of 1000 patients: an update. Proc Br Soc Colpos Cerv Pathol 1991.

60. Dobbs SP, Asmussen T, Nunns D, Hollingworth J, Brown LJR, Ireland D. Does histological imcomplete excision of cervical intraepithelial neoplasia following large loop excision of transformatin zone increase recurrence rates? A six year cytological follow up. B J Obstet Gynecol 2000; 107:1298-1301.

61. Benedet JL, Anderson GH, Boytes DA. Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. Obstet Gynecol 1985; 65:557-562.

62. Chappatte OA, et al. Histological differences between colposcopic directed biopsy and loop excision of the transformation zone (LETZ): a cause for concern. Gynecol Oncol 1991; 43:46-50.

63. Buxton EJ, et al. Colposcopically directed punch biopsy: a potentially misleading investigation. Br J Obstet Gynaecol 1991; 98:1273-1276.

64. Howe DJ, Vincenti AC. Is large loop excision of the transformation zone (LLETZ) more accurae than colposcopically directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? Br J Obstet Gynaecol 1991; 98:588-591.

65. Reis, et al. Validity of cytology and colposcopy-guided biopsy for the diagnosis of preclinical cervi alk carcinoma. Rev Bras Ginecol Obstet 1999; 21(4):193-200.

66. Ali SW, Evans AS, Monaghan JM. Results of CO_2 laser cylinder vaporization of cervical intraepithelial disease in 1234 patients. An analysis of failures. Br J Obstet Gynaecol 1986; 93:75-78.

67. Pearson SE, Whittaker J, Ireland D, Monaghan JM. Invasive cancer of the cervix after laser treatment. Br J Obstet Gynaecol 1989; 96:486-488.

68. Anderson M. Selection of patients for treatment – the Biritsh view. In: Prendiville W, ed. Large Loop Excision of the Transformation Zone. A Practical Guide to LLETZ. Chapman and Hall Medical, 1993: 83.

69. Paraskevaidis E, Kitchener H, Adonakis G, Parkin D, Losis D. Incomplete excision of CIN in conization: further excision or conservative management. European Journal of Obstetrics and Gynecology and Reproductive Biology 1994; 53:45-47.

70. Guerra B, Guida G, Falco P, Gabrielli S, Martinelli GN, Bovicelli L. Microcolposcopic topographic endocervical assessment before excisional treatment of cervical intraepithelial neoplasia. Obstet Gynecol 1996; 88(1):77-81.

71. Cullimore JE, Luesley DM, Rollason TP, Byrne P, Buckley CH, Anderson M, et al. A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN) – a preliminary report. Br J Obstet Gynaecol 1992; 99(4):314-318.

72. Prendiville W. Large loop excision of the transformation zone. Clin Obstet Gynecol 1995; 38(3):622-639.

73. Shafi MI, Dunn JA, Buxton EJ, Finn CB, Jordan JA, Luesley DM. Abnormal cervical cytology following large loop excision of the transformation zone: a case controlled study. Br J Obstet Gynaecol 1993; 100(2):145-148.

74. Gardeil F, Barry Walsh C, Prendiville W, Clinch J, Turner MJ. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. Obstet Gynecol 1997; 89(3):419-422.

75. Wolf JK, Levenback C, Malpica A, Morris M, Burke T, Mitchell MF. Adenocarcinoma in situ of the cervix: significance of cone biopsy margins. Obstet Gynecol 1996; 88(1):82-86.

76. Gurgel MS, Bedone AJ, Andrade LA, Panetta K. Microinvasive carcinoma of the uterine cervix: histological findings on cone specimens related to residual neoplasia on hysterectomy. Gynecol Oncol 1997; 65(3):437-440.

77. Luesley DM, McCrum A, Terry PB, et al. complications of cone biopsy related to dimensions of the cone and the influence of prior colposcopic assessment. Br J Obstet Gynaecol 1985; 92:158-164.

78. Mathevet P, Dargent D, Roy M, Beau G. A randomized prospective study comparing three techniques of conization: cold knife, laser, and LEEP. Gynecol Oncol 1994; 54(2):175-179.

79. Jansen FW, Trimbos JB, Hermans J, Fleuren GJ. Persistent cervical intraepithelial neoplasia after incomplete conization: predictive value of clinical and histological parameters. Gynecol Obstet Invest 1994; 37(4):270-274.

80. Monk A, Pushkin SF, Nelson AL, Gunning JE. Conservative management of options for patients with dysplasia involving endocervical margins of cervical cone biopsy specimens. Am J Obstet Gynecol 1996; 174(6):1695-1699.

81. Guerra B, Guida G, Falco P, Gabrielli S, Martinelli GN, Bovicelli L. Microcolposcopic topographic endocervical assessment before excisional treatment of cervical intraepithelial neoplasia. Obstet Gynecol 1996; 88(1):77-81.

82. Gurgel MS, Bedone AJ, Andrade LA, Panetta K. Microinvasive carcinoma of the uterine cervix: histological findings on cone specimens related to residual neoplasia on hysterectomy. Gynecol Oncol 1997; 65(3):437-440.

83. Partington CK, Turner MJ, Soutter WP, Griffiths M, Krausz T. Laser vaporization versus laser excision conization in the treatment of cervical intraepithelial neoplasia [see comments]. Obstet Gynecol 1989; 73(5 Pt 1):775-779.

84. Mor Yosef S, Lopes A, Pearson S, Monaghan JM. Loop diathermy cone biopsy. Obstet Gynecol 1990; 75(5):884-886.

85. Lopes A, Morgan P, Murdoch J, Piura B, Monaghan JM. The case for conservative management of "incomplete excision" of CIN after laser conization. Gynecol Oncol 1993; 49(2):247-249.

86. Andersen ES, Pedersen B, Nielsen K. Laser conization: the results of treatment of cervical intraepithelial neoplasia. Gynecol Oncol 1994; 54(2):201-204.

87. Byrne P, Ogueh O, Sant Cassia LJ. Outpatient loop diathermy conisation [letter] [see comments]. Lancet 1991; 337(8746):917-978.

88. Montz FJ, Holschneider CH, Thompson LD. Large-loop excision of the transformation zone: effect on the pathologic interpretation of resection margins. Obstet Gynecol 1993; 81(6):976-982.

89. Naumann RW, Bell MC, Alvarez RD, Edwards RP, Partridge EE, Helm CW, et al. LLETZ is an acceptable alternative to diagnostic cold-knife conization. Gynecol Oncol 1994; 55(2):224-228.

90. Felix JC, Muderspach LI, Duggan BD, Roman LD. The significance of positive margins in loop electrosurgical cone biopsies. Obstet Gynecol 1994; 84(6):996-1000.

91. Houghton SJ, Shafi MI, Rollason TP, Luesley DM. Is loop excision adequate primary management of adenocarcinoma in situ of the cervix? Br J Obstet Gynaecol 1997; 104(3):325-329.