CERVICAL INTRAEPITHELIAL NEOPLASIA (CIN): MANAGEMENT BY A GENERAL (NON-ONCOLOGICAL) GYNAECOLOGICAL UNIT

M S Goon, B L Tay

ABSTRACT

The purpose of this study is to assess how well Cervical Intraephithelial Neoplasia (CIN) was managed by a general gynaecological unit. Treatment consisted of laser ablation, conization (laser, knife, loop diathermy) and hysterectomy. Recurrence occurred in 8 (18.2%) out of 44 conizations and 2 (25.0%) out of 8 ablative procedures. While the cure rate after the first treatment was 81.1%, after subsequent treatment it became 96.2%. This study showed that it was possible for a general gynaecological unit to cure patients of their disease.

The Pap smear tests were not very accurate – the sensitivity and specificity were 75.5% and 50.0% respectively while the positive predictive value and negative predictive value were 94.9% and 14.3% respectively. Similarly, colposcopically directed punch biopsy was also found to be misleading.

Keywords: *Pap smear, punch biopsy, cone biopsy, laser ablation, recurrence.*

SINGAPORE MED J 1994; Vol 35: 587-590

INTRODUCTION

Most studies on the management of CIN have been done by Oncology units. Various methods have been used to treat the disease – conization (knife, laser, large loop excision of the transformation zone), ablative therapy (electrodiathermy, cryosurgery, laser ablation) and even hysterectomy particularly when there is another coexisting problem. Results of cure have generally been satisfactory and even up to 95% in some studies[1,2]. This study was carried out with the aim of assessing how well CIN can be managed by a general (non-oncological) unit.

PATIENTS AND METHODS

Between April 1990 and February 1992, 59 patients with suspected cervical intraepithelial neoplasia were seen in a general gynaecological unit in the Kandang Kerbau Hospital Pte Ltd in Singapore. These women were referred for abnormal Pap smears from many sources including general practitioners, government polyclinic doctors and private specialists. There was no standardisation of method of taking Pap smears and the sampling devices used were wooden spatulas, Ayre's spatula or the cytobrush. Colposcopy using 5% acetic acid solution was performed mainly by two gynaecologists with some training in colposcopy and the site of the most severe epithelial abnormalities was identified followed by a punch biopsy.

Department of Reproductive Medicine
Kandang Kerbau Hospital
1 Hampshire Road
Singapore 0821

M S Goon, MBBS, M Med (O & G), FAMS
Senior Registrar

Professional Standards and Training
Kandang Kerbau Hospital

B L Tay, MBBS, M Med (O & G), FRCOG, FAMS
Director

Correspondence to: Dr M S Goon
85 Jalan Durian
Taman Cheras
56100 Kuala Lumpur
Malaysia

Laser ablation with the carbon dioxide laser was carried out in 8 patients. Fifty patients had conization and one patient had a hysterectomy. These patients did not follow a standard protocol of treatment. Similarly, there was also no standardisation of technique of laser ablation or conization. When cervical carcinoma was diagnosed, the patient was referred to the Oncology Unit for further management.

RESULTS

The racial distribution was 54 Chinese, 2 Indians and 3 others (2 Caucasians, 1 Nepalese) in the group of 59 patients studied. The median age was 40 years with a range from 17 years to 65 years. The distribution of age groups is as shown in Fig 1. The median gravidity and parity were 4 and 3 respectively. Fourteen (66.7%) out of the 21 patients in whom the occupation was known fell into the unskilled worker group. There were 2 patients each in the skilled worker, clerical and managerial groups. One patient was a professional. Thirty-one patients were housewives. Their husband's occupation was not known. There were six others in whom the information was not available and the remaining patient was a student. The follow-up period ranged from 9 months to 3 years and the median follow-up time was one year. The time interval between Pap smear examination and colposcopy is as shown in Fig 2. The majority of patients had colposcopy done within a month of their Pap smear test. Two patients had to wait between 6 and 7 months for colposcopic examination. The time interval between colposcopic examination and cone biopsy is as shown in Fig 3. The majority (37 patients) had cone biopsies done within one month of the colposcopic examination. One had her cone biopsy delayed till 8 to 9 months after colposcopy. This was because of discrepancy between colposcopic and cytologic findings.

Only 17 out of the 59 patients (28.8%) had a previous Pap smear test. Fig 4 shows the time interval between the previous Pap smear and the present (index) Pap smear. Twelve out of the 17 patients had a previous normal Pap smear. Two patients had koilocytotic smears and one patient had a smear showing mild dyskaryosis. This last patient delayed treatment by a year during which time the lesion increased in severity. By the end of the year when a cone biopsy was done, the lesion had advanced to become microinvasive cervical cancer. The margins of the cone biopsy were inadequately resected and against medical advice,

Fig 1 – Age distribution of patients

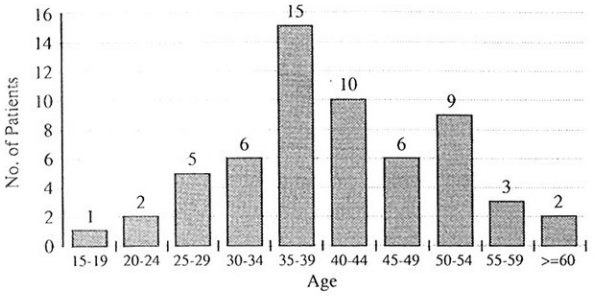


Fig 2 – Time interval between Pap smear and colposcopy

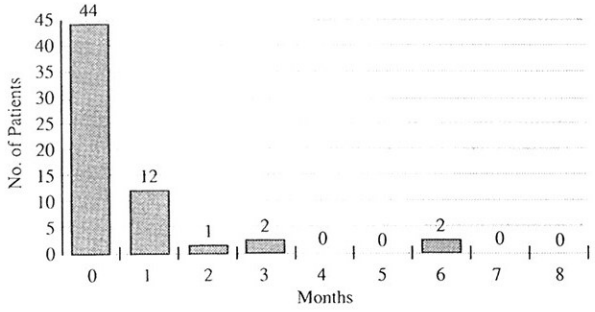


Fig 3 – Time interval between colposcopy and cone biopsy

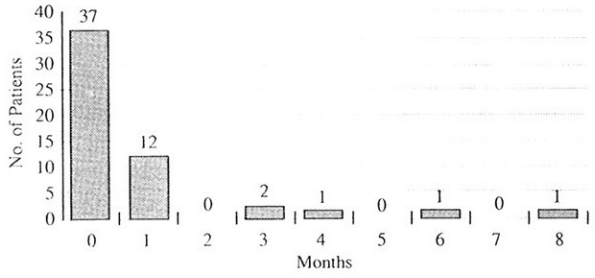
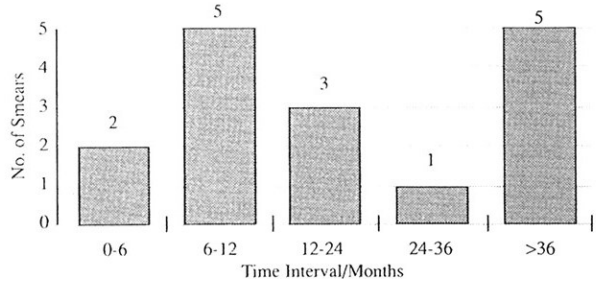


Fig 4 – Time interval between previous Pap smear & present abnormal Pap smear



NB: The result of 1 Pap smear was written on the case sheet but the date it was taken was not stated.

she defaulted further follow-up and management.

Fifty-eight conizations (including 8 repeat conizations) were carried out in 50 patients. These consisted of 50 laser cones, 6 knife cones and 2 LLETZ (large loop excision of the transformation zone). Cone biopsy was carried out for the following reasons: the squamo-columnar junction could not be seen (28 patients – 48.3%), to rule out malignancy in CIN III lesions (23 patients – 39.7%), discrepancy between Pap smear and colposcopic examination (5 patients – 8.6%) and reason unknown (2 patients – 3.4%). Following conization, no complication was noted in 51 procedures (88%), cervical stenosis occurred in 2 (3.4%), secondary haemorrhage in 3 (5.2%), secondary haemorrhage with infection in 1 (1.7%) and primary haemorrhage in 1 (1.7%). One patient with cervical stenosis was symptomatic (dysmenorrhea) and required re-dilatation of the cervical os. There was one on-going pregnancy. Adequacy of resection margins was assessed in 48 out of 59 cone specimens. Cone biopsies showing chronic cervicitis, koilocytosis or cervical carcinoma were excluded from analysis. The ectocervical and endocervical margins were adequately resected in 31 (64.6%) and 36 (75.0%) cones respectively.

There were 4 cases of microinvasive cervical carcinoma diagnosed on cone biopsy and 3 of these patients underwent hysterectomy. The fourth patient defaulted further treatment against medical advice. One case of cervical carcinoma Stage Ib (CaCxIb) was missed on colposcopy during the initial period of study but was diagnosed on cone biopsy. She underwent Wertheim's hysterectomy subsequently. Another case of CaCxIb was suspected on colposcopy but the punch biopsy revealed only CIN III. The diagnosis of cancer of the cervix was again confirmed on cone biopsy and this patient had radiotherapy.

Recurrence occurred in 10 out of the 53 patients (18.9%) with CIN – 8 out of 44 conizations and 2 out of 8 laser ablations. In the two patients with recurrence and who had undergone laser ablation, the squamocolumnar junction was seen. One patient had CIN III while the other had CIN I. In the conization group, the margins of the cone biopsy were inadequately resected in 6 patients (Table I). These patients probably had residual disease. In only 2 cone specimens were the margins adequately resected. This small number probably reflected true recurrence of the disease. Recurrence was noted between two and a half months and two years six months after the initial treatment with the majority (9 out of 10) occurring within 6 months.

Table I – Comparison of recurrence with adequacy of resected margins in patients who had conization

Recurrence Type	Resection Margins		
	Free	Involved	Indeterminate*
CIN I	2	2	2
CIN II			
CIN III		2	

*Indeterminate means denuded or burnt margins

For the treatment of the recurrences, 8 patients had conization performed. In all these cases, the surgical margins were clear of disease. Seven of the 8 patients were well on follow-up with no evidence of CIN colposcopically or cytologically. One patient had some colposcopic features of CIN. Pap smears however have been normal. One patient had a punch biopsy taken and histology revealed CIN I. No further procedure was carried out and follow-up Pap smears showed no evidence of malignancy. The punch biopsy probably removed the small amount of abnormal tissue. One patient is being planned for total abdominal hysterectomy and bilateral salpingo-oophorectomy because of denuded margins at the initial cone biopsy for CIN III and also because of discrepancy between cytology (mild dyskaryosis) and colposcopy (normal findings but the squamocolumnar junction could not be seen) on follow-up.

Histological correlation between punch biopsy and cone biopsy specimens is shown in Table II. The results of histological examination of these specimens were in agreement in only 30 out of 54 cases (55.6%). There was overdiagnosis in 12 cases (22.2%) ie the cone biopsy showed a lower grade lesion compared

with punch biopsy. Of more concern is that there was underdiagnosis in an equal number of patients (12) and there were 6 cases of cervical carcinoma that were not diagnosed by punch biopsy.

Table II – Correlation between punch biopsy and cone biopsy

Punch Biopsy	Cone Biopsy						
	Normal	Inflam-matory Atypical	Koilo-cytosis	CIN I	CIN II	CIN III	CA*
Normal							
Inflam-matory Atypical	1				1		
Koilo-cytosis							
CIN I		2	1	5	1	1	
CIN II			1		2	3	1
CIN III				4	3	23	5
CA*							

CA*: carcinoma

Correlation between cytology and histology (cone biopsy) is shown in Table IIIa. The results were in agreement in only 17 out of 53 cases. Seven out of 8 patients with koilocytotic smear actually had CIN present in the cone biopsy and of these 7, 4 had CIN III. Three out of 6 patients with mild dyskaryotic smears had CIN III present in the cone biopsy. Taking a positive Pap smear as one with presence of dyskaryotic or carcinomatous cells and a negative Pap smear as one without such features (ie normal, inflammatory, koilocytotic or atypical), the negative predictive value was only 14.3% (Table IIIb). The positive predictive value however was high – 94.9%. The sensitivity and specificity were 75.5% and 50.0% respectively while the false negative rate was 24.5%.

Table IIIa – Correlation between Pap smear and cone biopsy

Pap Smear	Cone Biopsy						
	Normal	Atypical Inflam-matory	Koilo-cytosis	CIN I	CIN II	CIN III	CA*
Normal	1			1	1		
Atypical Inflam-matory				2			
Koilo-cytosis			1	1	2	4	
Mild Dyskar-yosis	1			2		3	
Moderate Dyskar-yosis					1	7	2
Severe Dyskar-yosis	1			3	4	11	3
CA*							1

CA*: carcinoma

Table IIIb – Correlation between Pap Smear and Cone Biopsy

Pap Smear	Cone Biopsy	
	Negative	Positive
Negative	2	12
Positive	2	37

$$\text{Sensitivity} = \frac{37}{49}\left(\frac{\text{true positive}}{\text{true positive + false negative}}\right) = 75.5\%$$

$$\text{Specificity} = \frac{2}{4}\left(\frac{\text{true negative}}{\text{true negative + false positive}}\right) = 50.0\%$$

$$\text{False negative rate} = \frac{12}{49}\left(\frac{\text{false negative}}{\text{false negative + true positive}}\right) = 24.5\%$$

$$\text{Negative predictive value} = \frac{2}{14}\left(\frac{\text{true negative}}{\text{true negative + false negative}}\right) = 14.3\%$$

$$\text{Positive predictive value} = \frac{37}{39}\left(\frac{\text{true positive}}{\text{true positive + false positive}}\right) = 94.9\%$$

Following the initial treatment, only 36 out of 59 patients (61.0%) had a Pap smear test done within the first 9 months. Only 34 out of 59 patients (57.6%) had colposcopy done during the same follow-up period.

DISCUSSION

Colposcopically guided punch biopsy helps to decrease the number of cone biopsies that need to be performed in patients with CIN. This technique has certainly aided many young patients of child-bearing age-group[3]. However, it can be a potentially misleading investigation. The correlation between punch biopsy and the subsequent cone biopsy is not always accurate. This is a finding which has been shown by Buxton et al 1991[4] who found that in only 46% of patients he studied did results of punch biopsy agree with those of cone biopsy. This study showed that the biopsies tallied in only 55.6%. Overdiagnosis could be attributed to complete removal of the lesion by direct biopsy, stripping of the friable epithelium which remained or tissue destruction due to local inflammatory response after biopsy. This occurred in 22.2% of cases. Of more concern is underdiagnosis of the lesion which occurred in an equal number of patients. Six cervical carcinomas (4 microinvasive, 2 invasive) were missed by punch biopsy. This is not unusual for microinvasive carcinoma particularly as it can be difficult to differentiate it from severe CIN colposcopically[5]. Skehan et al 1990[6] noted a similar finding and concluded that excisional methods of treatment were more likely to reveal early invasion. Liu et al 1990[7] recommended diagnosing microinvasion by careful colposcopically directed cone biopsy and proper examination of the conization specimen. Five of the 6 patients with cervical carcinoma had CIN III on punch biopsy in this study. If an ablative procedure had been carried out, the correct diagnosis would have been missed with its attendant risks. Invasive disease has been reported to occur following local destructive treatment [8]. It would therefore seem prudent to perform a cone biopsy for patients with severe grade CIN in order to avoid such mistakes in management.

In the conization group, recurrence of CIN occurred in 8 out of 44 patients. Seventy-five percent of these recurrences occurred in patients with inadequately resected margins. This finding is in agreement with the findings of Demopoulos et al 1991[9], that a parameter that could predict residual disease was positive margins in the cone. However Murdoch et al 1992[2] found that incomplete excision does not equate with residual disease. Although adequacy of resection was only 56%, the success rate was 95% after the first treatment in the group of women he studied

who were undergoing LLETZ for CIN. Andersen et al[10] who treated his patients with laser conizations had similar findings. In this study, although the margins appeared to be adequately resected in a greater proportion of cases (adequacy of ectocervical and endocervical margins in 64.6% and 75.0% respectively) the cure rate was only 81.1%. This could be attributed to incomplete ablation of the cone crater after the biopsy had been taken. Undertreatment of this nature is further highlighted by the fact that patients undergoing ablative therapy had an even higher recurrence rate (25.0%) compared to those undergoing conization (18.2%). Reid et al 1984[11] found that surgeons who routinely treated the epithelium of the lower centimeter of the cervical canal had a 10% to 15% higher primary success rate than those who set the colposcopic new squamocolumnar junction as their upper limit of destruction. It is not surprising that the success rate was only 81.1% in this study as treatment was carried out in a non-oncological unit where the majority of operators are not colposcopically trained. To overcome this problem, new registrars in this hospital are now being rotated through various units including the oncology unit so that they can acquire the necessary skills.

Recurrence can occur when the cone margins are adequately resected. This was seen in 2 patients (25%) in this study and both recurrences occurred within 6 months. Murdoch et al[2] found that in 21% of patients in his study group, recurrent CIN occurred when the histological report had suggested complete excision. Follow-up examination with cytology and if possible with colposcopy within the first year of treatment is important to detect recurrences even though histology shows complete excision of disease. The report of the Intercollegiate Working Party on Cervical Cytology Screening 1987[12] also recommended cytology and colposcopy for the follow-up of treated patients up to and including the first anniversary of treatment. In this study, only 61.0% and 57.6% of patients had their Pap smear test and colposcopy repeated respectively within the first 9 months of follow-up. This follow-up is inadequate and a programme for educating patients regarding the importance of close and reliable follow-up after treatment is required. Indeed the need for this kind of teaching and screening programme is further emphasised by the fact that only 28.8% of patients in this series ever had a Pap smear test done before.

There is poor correlation between cytology and histology. Seven out of 8 patients with koilocytotic smears actually had CIN on cone biopsy and 4 out of 8 (50%) had CIN III. Three out of 6 patients with mild dyskaryosis had CIN III. The negative predictive value of cytology was only 14.3%. This is not surprising. Studies have shown that CIN grade II to III occurred in at least 30% of women in whom a single smear showed severe non-specific inflammatory atypia[13]. This figure increased to 70% if a repeat smear again showed atypia[14]. This could be due to sampling error as not all doctors know how to take a proper smear[15]. The false negative rate in this study was 24.5% which is slightly more than twice of that found in the Quality Assurance Program study by Joseph et al 1991[16] – 11%. It would appear from this study that colposcopy is advisable for all abnormal smears, especially those with koilocytotic changes. If adequate colposcopic services were not available, then a Pap smear should be repeated at 3 to 6 months from the initial smear and if it again showed atypia or abnormal cells, colposcopy is mandatory.

CONCLUSION

It appears that CIN can be successfully managed by a general (non-oncological) gynaecological unit even though it may take more than one treatment. The overall success rate was 96.2% (51 out of 53 patients). Colposcopy should ideally be carried out for all abnormal smears especially if the abnormality is koilocytosis. Microinvasion is difficult to diagnose colposcopically and as such it is advisable to perform cone biopsy in patients with severe grade CIN in order to avoid missing out cervical carcinoma. Ablative therapy particularly should be carried out by operators who are experienced in colposcopy. Finally this study highlights inadequate population screening and the need for patient education.

REFERENCES

1. Chanen W, Rome RM. Electrocoagulation diathermy for cervical dysplasia and carcinoma in situ: a 15-year survey. Obstet Gynecol 1983; 61:673-9.
2. Murdoch JB, Morgan PR, Lopes A, Monaghan JM. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow-up, not retreatment. Br J Obstet Gynaecol 1992; 99:990-3.
3. Seshadri L, Jairaj P, Krishnaswami H. Colposcopy in the diagnosis of cervical neoplasia. Indian J Cancer 1990; 27:180-6.
4. Buxton EJ, Luesley QM, Shafi MI, Rollason M. Colposcopically directed punch biopsy: a potentially misleading investigation. Br J Obstet Gynaecol 1991; 98:1273-6.
5. Benedet JL, Anderson GH, Boyes DA. Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. Obstet Gynecol 1985; 65:557-62.
6. Skehan M, Soutter WP, Lim K, Krausz T, Pryse-Davies J. Reliability of colposcopy and directed punch biopsy. Br J Obstet Gynaecol 1990; 97:811-6.
7. Liu WM, Chao KC, Kan YY, Yuan CC, Chen CJ, Ng HT. Clinical diagnosis in microinvasive carcinoma of the uterine cervix. Chung Hua T Hsueh Tsa Chih 1990; 46:167-71.
8. Ali SW, Evans AS, Monaghan JM. Results of CO_2 laser cylinder vaporization of cervical intraepithelial disease in 1,234 patients. An analysis of failures. Br J Obstet Gynaecol 1986; 93:75-8.
9. Demopoulos RI, Horowitz LF, Vamuakas EC. Endocervical gland involvement by cervical intraepithelial neoplasia grade III. Predictive value for residual and/or recurrent disease. Cancer 1991; 68:1932-6.
10. Anderson ES, Nielsen K, Larsen G. Laser conization: follow-up in patients with cervical intraepithelial neoplasia in the cone margin. Gynecol-Oncol 1990; 39:328-31.
11. Reid R, Atkinson K, Chanen W, et al. Symposium of cervical neoplasia. VI. Differing views. Colposcopy Gynecol Laser Surg 1984; 1:299-306.
12. Sharp F, Ducan ID, Evans DMD, Fox H, Havelock PB, McPherson A, et al. Report of the Intercollegiate Working Party on Cervical Cytology Screening. England: Progress Press Ltd, 1987: 15-6.
13. Soutter WP, Wisdom S, Broughs AK, Monaghan JM. Should patients with mild atypia in a cervical smear be referred for colposcopy? Br J Obstet Gynaecol 1986; 93:70-4.
14. McIndoe WA, Maclean MR, Jones RN, Mullins PR. The invasive potential of carcinoma-in-situ of the cervix. Obstet Gynecol 1984; 64:451-3.
15. Duguid HLD. Does mild atypia on a cervical smear warrant further investigation? Lancet 1986; ii:1225.
16. Joseph MG, Cragg F, Wright VC, Kontozoglou TE, Downing P, Marks FR. Cyto-histological correlates in a colposcopic clinic: a 1-year prospective study. Diagn Ctyopathol 1991; 7:477-81.