

Invasive Cancer after Treatment of Cervical Intraepithelial Neoplasia

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Abstract

This review discusses the risk of invasive cancer following treatment for cervical intraepithelial neoplasia (CIN). The emphasis is on methods in current use and the risks are calculated with life table methods.

Large, long-term follow up studies which use life table analysis show clearly that invasive recurrences continue to appear at a relatively steady rate for at least 8 years after treatment for CIN. The risk remains 4 to 5 times greater than in the background population throughout this period. It would seem prudent to continue to offer these women increased surveillance with annual smears during this time of increased risk.

All modern methods of outpatient treatment are highly effective in preventing invasive cancer of the cervix if they are used skilfully with an understanding of the disease being treated. The thoughtless use of beguilingly easy methods will lead only to disaster.

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Key words: *Cervix cancer, Cervical intraepithelial neoplasia, Long-term follow up, Treatment*

Introduction

The objective of a cervical screening programme is to prevent invasive cancer of the cervix by detecting and treating pre-invasive disease of the cervix. The impact of the programme depends both on the detection of women with cervical intraepithelial neoplasia (CIN) and upon their being treated effectively. While much work has been done on the ability of different treatment methods to eradicate CIN, few studies have been able to address the risk of subsequent invasive disease. Yet this remains the more important end-point.

Treatment of CIN

Over the past 30 years or so, there has been a quiet revolution in the treatment of CIN. Initially, radical hysterectomy was employed but this gave way to simple hysterectomy and knife cone biopsy in turn. Ablative techniques such as radical electrodiathermy, cryotherapy, cold coagulation and laser vaporisation all represented attempts to reduce the morbidity and to treat women without general anaesthesia. These depended heavily upon the skill of the colposcopist and the accuracy of his or her punch biopsy to exclude invasive disease. In consequence, laser excision under local anaesthesia and more recently loop diathermy excision became popular because the whole lesion could be submitted for histological examination.

With all these changes and increasing conservatism, it is important to ensure that the treatment remains as effective. Small, short-term studies of the rate of CIN following modern outpatient treatments did suggest that they were as effective as hysterectomy and knife cone biopsy,¹⁻⁸ but longer term studies with sufficient numbers of women to determine the risk of invasive disease were lacking.

Meta-analysis of Modern Outpatient Treatments

Because of the infrequency of invasive disease after treatment for CIN and its propensity to emerge years after the initial treatment, it is necessary to obtain data from a large number of women followed for several years. This was made possible by the collaboration of four British centres that were generous enough to make their data available for analysis.⁹

The data were first tested for homogeneity to ensure that the studies were sufficiently similar to allow the results to be combined together. The data were combined in two ways: by pooling data from individual women; and by pooling the rates of invasion from the different studies after weighing the results by the number of cases in the individual studies. There was little difference between the results obtained by these different methods. A rate of invasive cancer per 100 000 women was calculated for the homogeneous studies and a cu-

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mulative rate of invasion determined for the period of follow up. These rates were calculated with life table methods to account for differing lengths of follow up.

Results

Six groups of patients were studied from four centres, treated with four different modalities (Table I). In all, data from 12 430 women were analysed giving 44 699 woman years of follow up and 33 cancers of which 14 were microinvasive.

There were no significant differences in the rates of invasion between centres or between treatment methods and so it was possible to amalgamate the results. The pooled estimate of the cumulative rate of invasion in the 44 699 woman years of observation was 5.8 per 1000 women at 8 years when there were still 2116 women being followed up. The rate of invasion continued to increase year on year at a steady rate (Fig. 1). The overall rate of invasion was 85 per 100 000 woman years.

TABLE I: NUMBERS OF WOMEN FOLLOWED UP IN INDIVIDUAL STUDIES AND THE NUMBERS OF CANCERS

	No. of women	No. of woman years	No. of invasive cancers
Laser vaporisation			
Gateshead	4464	14 035	13
Aberdeen	2130	15 436	5
Sheffield	338	398	1
Cold Coagulation			
Dundee	2793	8991	6
Laser Cone			
Gateshead	313	1118	1
Loop diathermy			
Gateshead	2392	4721	7
Total	12 430	44 699	33

Discussion

These data confirmed the high degree of protection which can be provided by these methods of treatment. Only three studies of hysterectomy have used life table analysis.¹⁰⁻¹² They reported overall rates of invasive disease of 40 to 90 per 100 000 woman years. The British Columbia group also reported an overall rate of invasion after cone biopsy for CIN III of 123 per 100 000 woman years.¹⁰

One small, long-term follow up of 96 women treated with cryotherapy reported an 11.8 per 1000 cumulative rate of invasion and an overall rate of 113 per 100 000 woman years.¹³ A much larger study of cryotherapy with 843 women followed for at least 5 years reported one adenocarcinoma at 6 years suggesting a cumulative rate of invasion of approximately 1.2 per 1000 women.⁴

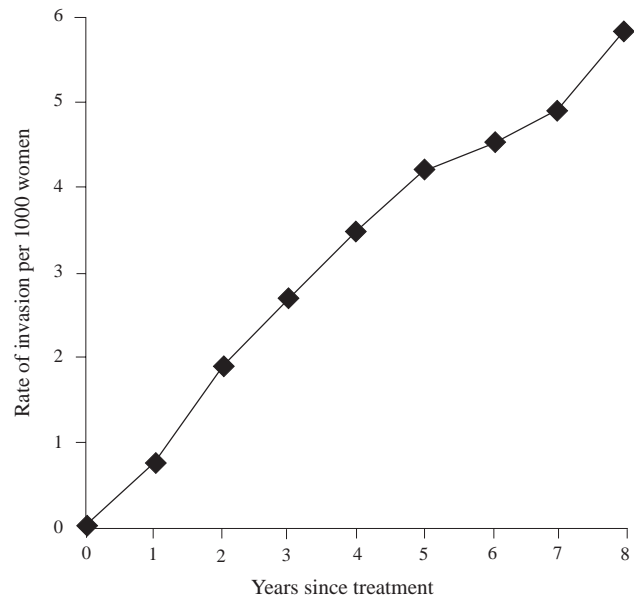


Fig. 1. The cumulative rate of invasion calculated from pooled individual patient data is shown for the first 8 years after treatment. There were 2116 women under observation in the 8th year. The cumulative rate increases steadily throughout this period without any evidence of a reduction in the risk of invasion (Reproduced with permission from *The Lancet*).

It is not possible to calculate the overall rate from the data shown.

A long-term study of laser conisation with 6540 woman years follow up of 1053 women treated mainly for CIN III showed a cumulative rate of invasive disease of 4 per 1000 women by 6 years and an overall rate of 61 per 100 000 woman years.¹⁴

There are few data with which to calculate the risk of invasive disease in women with untreated CIN but the New Zealand experience of inadequately treated CIN III would suggest a cumulative rate of around 16.3% at 9 years.¹⁵ The results of this meta-analysis suggest that these treatments reduce the rate of invasive cancer by at least 95%. However, it should be noted that these results were obtained in specialist centres. It is possible that the results obtained in less specialised units may not be as good.

Although the risk of invasion in these women is low, it is still 4 to 5 times greater than in the general population and the risk shows no sign of decreasing with time. This is consistent with older data^{10,16,17} and suggests that annual cytological follow up should be continued for at least 10 years after treatment. Because the number of women treated is small in relation to the screened population, the cost of following up these women is a very small proportion of the overall costs of the programme.

Conclusions

Large, long-term follow up studies which use life table analysis show clearly that invasive recurrences continue

to appear at a relatively steady rate for at least 8 years after treatment for CIN. The risk remains 4 to 5 times greater than in the background population throughout this period. It would seem prudent to continue to offer these women increased surveillance with annual smears during this time of increased risk.

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