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Risk of recurrence after treatment of severe intraepithelial neoplasia of the cervix. A follow-up of 896 patients

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SUMMARY

Eight hundred and ninety-six patients were followed up cytologically for up to 21 years following treatment for a CIN III lesion of the cervix. The recurrence rate (8.8%) was lower after hysterectomy than after treatment which preserved the cervix (23%). Long-term yearly follow-up is not required as all recurrences were detected by annual smears for a seven-year period after treatment in both groups. It is important to keep patients under cytological review following hysterectomy because of the appreciable recurrence rate and also evidence that intraepithelial lesions of the vaginal vault behave in an aggressive fashion.

INTRODUCTION

Following treatment of cervical intraepithelial neoplasia (CIN), periodic cervical smears are required to ensure that the lesion has been completely eradicated. Long-term follow-up has been advocated.[1, 2] In Northern Ireland, patients are not uncommonly advised to have an annual smear until the age of sixty. There would seem to be grounds for this practice. Surgical excision of the lesion is often found on histological examination to be incomplete and, even in apparently normal epithelium surrounding the lesion, there is often evidence of papillomavirus infection which is thought to be associated with the development of CIN.[3, 4] Recent suggestions that carcinoma of the cervix has become more aggressive have also served to increase caution in the management of these patients. Frequent follow-up has disadvantages for both the patient and the laboratory service. A requirement for annual smears tends to set a woman apart from her fellows, continually focuses attention on the cervix and may well engender cancer-phobia. At the laboratory, cervical smears from these patients require to be examined by senior staff and, since the Belfast City Hospital has now been engaged in community screening for 22 years, a considerable number of patients are undergoing frequent follow-up and are straining limited resources. It is therefore important to determine safe guidelines for the management of these

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patients after treatment. At the Belfast City Hospital we were able to attempt this because all patients found to have abnormal smears during our 22 years of operation have been recorded on computer together with their biopsy results and their subsequent history obtained by the follow-up programme which the laboratory has operated.

METHOD

For this study we selected from our records all those women who had had treatment for a histologically proven severe cervical intraepithelial neoplasia (CIN III lesion) between 1965 and 1983 and on whom we had follow-up cytology smears and clinical information until September 1986. Most of the patients had had annual smears following their treatment. The patients were divided into two groups: those who had had cone biopsies (even though these often resulted in apparently incomplete excisions) and those who were treated by hysterectomy. Some of the biopsy group may have had subsequent cautery to the cervix. For each of these groups we determined from our computer records the pattern of recurrence of abnormal smears over a period extending to 21 years. We also examined the biopsy reports of 100 of those patients who were treated by excisional biopsy to obtain an indication of the proportion of patients in whom it was felt that the lesion was probably not completely excised. In order to assess their risk of invasive cancer we compared a list of those eventually lost to follow-up with a register of cases of invasive cancer in Northern Ireland from 1965 to 1987 previously compiled by the laboratory.

RESULTS

There were 896 women in our records who had been kept under clinical review with cervical smears following treatment of a histologically proven CIN III lesion of the cervix. Of these, 215 had had a hysterectomy following the initial biopsy, and in 681 the lesion had been treated by excisional biopsy. The percentage of patients subsequently having normal cervical smears in these two groups is shown in life table form in the Figure, which illustrates the first 12 years of follow-up. As expected, recurrence of an abnormal smear was much less common in patients treated by hysterectomy, 19 (8.8%) of whom showed evidence of recurrence in the vaginal vault. Of those in whom the lesion had been excised, 157 (23%) had relapse in the cervix. This recurrence rate in those treated by cone excision was, however, much lower than predicted by our review of the histology, which showed that in 50% of the patients it did not appear that the whole of the lesion had been removed. A striking feature is the similarity in the time of the recurrence, whether the patient was treated by hysterectomy or excisional biopsy. Most recurrences took place during the first two years with smaller numbers relapsing until the sixth and seventh years after surgery. Thereafter we found no further relapses even on prolonged follow-up to 21 years. The life table shows the recurrence rates as determined by a further positive smear without regard to the severity of the subsequent lesion as shown by biopsy. Our records show that in all cases the recurrence was still apparently intra-epithelial when first detected. However, in 12 cases invasive cancer eventually developed. Five of these arose in the vaginal vault after hysterectomy. Three were patients in their sixth decade who had abnormal vault smears after hysterectomy,

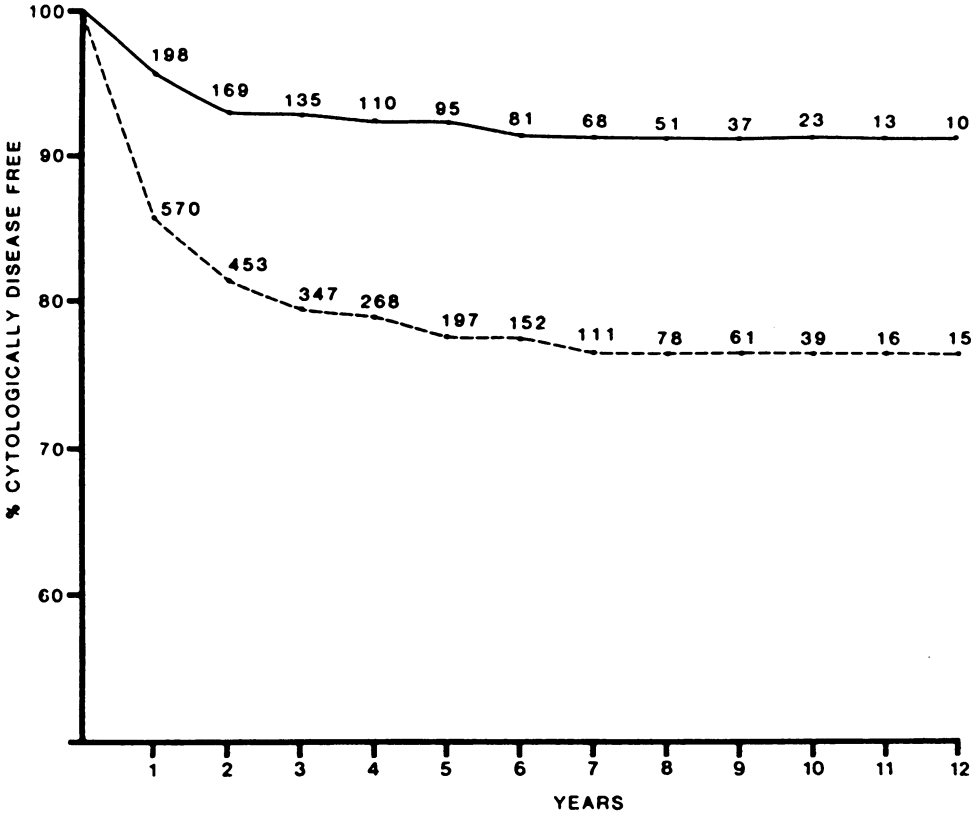

Figure. Follow-up cervical smear of patients with CIN III after hysterectomy (————, 215 patients) or local treatment to the cervix (— — — —, 681 patients). The results are given in life table form. Years 12 – 21 are not shown, there being no further relapses.

invasion occurring two years after operation. In a further two patients invasive cancer was found eight years after operation although in each case the first smear taken from the vault after hysterectomy was positive, there being no smears taken in the intervening period. Two further vaginal carcinomas arose in patients who had had their initial cervical lesion locally excised. Both had persistently positive smears after operation, the invasive lesion developing three years later in one and seven years later in the other, despite subsequent hysterectomy. There were five invasive cervical cancers, three arising within the first two years of operation. The other two developed the disease after eight and fifteen years respectively. In both it was associated with inadequate follow-up although one had a positive smear soon after cone biopsy.

DISCUSSION

Recurrence of cervical intraepithelial neoplasia (CIN) during the first two years after treatment very probably reflects incomplete excision of the lesion in the cervix or extension of the original lesion to the vaginal vault in those treated by hysterectomy. The slower relapse rate for the next five years may result from the

progressive development of epithelial changes which were only at an early stage of evolution at the time of operation, perhaps from epithelium remaining in the cervix showing no abnormality but already infected by the papillomavirus, currently thought to be closely associated with mutagenesis. Reinfection with this virus is also thought to occur frequently and could add to the relapse rate. Although in a number of patients the lesion may have been eradicated by subsequent cautery it is striking that only 23% patients relapsed. This contrasts with our biopsy review which indicated that, even on histological criteria, which probably underestimates the extent of epithelium infected by papillomavirus, about 50% of the lesions were likely to recur.

A low rate of recurrence of severe dysplasia has been noted by others.[1, 5] These surveys were, however, performed before the marked increase in prevalence of both papillomavirus infections and CIN lesions of the cervix accompanied by fears that cervical cancer was occurring in a more aggressive form. In Northern Ireland there has been a threefold increase in the prevalence of positive smears commencing in 1976 and it is reassuring that in our review, which includes patients treated between 1976 and 1983, relapse rates including mild CIN lesions remain low.

Although frequently commented upon,[6, 7] it has not been satisfactorily explained why CIN lesions may regress after partial removal. It seems possible that immunological factors are involved. There are many types of human papillomavirus some of which infect the skin producing the common wart. It has been shown that mechanical or chemical damage to the skin lesion can induce immunologic reaction with regression to the wart.[8] Conversely, in immunosuppressed patients, as following renal transplantation, both papillomavirus infection of the skin and also CIN lesions of the cervix are increased in incidence.[9] It would not be unexpected therefore if biopsy of the cervix had a similar effect in promoting immunologic resistance to the virus in the cervix.

Following excision of intraepithelial lesions of the cervix, follow-up with annual cervical smears is frequently advised for many years. Our results suggest that this is unnecessary and that after seven negative annual smears it is safe to assume that the lesion has been eradicated, further smears being taken at the normal screening interval. In contrast, after hysterectomy it is the experience of this laboratory that many clinicians are reluctant to arrange for follow-up smears in the belief that recurrence is unlikely and in the desire to spare patients the lengthy follow-up practised for women who have retained their cervix. However, an 8.8% recurrence rate is appreciable, and our results show that in this group too a seven-year follow-up should be sufficient.

A further finding of interest in this review was that of the twelve cases of invasive carcinoma known to us, seven arose in the vaginal epithelium. This suggests that intraepithelial lesions are more aggressive in this site, and indeed Koss also comments that in his experience vaginal dysplasias have a tendency to rapid progression and should not be left unattended.[10] This adds emphasis to our recommendation for review of patients treated by hysterectomy.

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