Adenocarcinoma of the Cervix

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Abstract

With the impact of screening programmes in reducing the incidence of squamous carcinoma of the cervix it is timely that attention is concentrated on glandular lesions. There is convincing evidence that adenocarcinoma of the cervix is increasing in incidence, and this may be related to either oral contraceptive use, human papillovirus infections, or both. Compared to its squamous cancer counterpart the response to therapy, particularly irradiation, is less than optimal, and it is clear that multicentre randomised trials are urgently required to delineate the optimal management of women with this disease.

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Pap Smear Screening and Adenocarcinoma of the Cervix

It is clear from studies in Canada, Scandinavia, and more recently the United Kingdom, that routine Pap smear screening has not only reduced the incidence of squamous carcinoma of the cervix but indeed in the last 10 to 15 years has halved the mortality rate from this disease.[1,2] In comparison, however, the incidence rate of adenocarcinoma has at best stabilised and at worst increased by even up to 15% in the last 10 years.[3] It certainly now seems that even well-organised screening programmes have failed to protect women from the development of adenocarcinoma of the cervix,[4] and that in time the proportion of glandular to squamous lesions is going to alter remarkably. Data from the United States have clearly shown that invasive adenocarcinoma of the cervix has been increasing in both Whites and Blacks since the mid-1920s, but that the increase is statistically significant only among Whites, reaching 4.2% per year for those born since 1935.[5]

Furthermore, reports of an increased incidence in younger women[6-8] are particularly worrying especially with the suggested link between the development of the disease and oral contraceptive use. Two major studies have examined this relationship in some detail. The first[8] reported a doubling of risk for ever users and a quadrupling of risk for those women who had more than 12 years exposure. This increased risk with duration of use has also been observed in a recent WHO collaborative study,[9] which also noted risk to be highest in recent and current users and to decline with time since cessation of use. Such trends in risk were strongest for cancers occurring in women under the age of 35, and the association with risk was somewhat stronger for high compared with low progestin potency compounds.

Molecular Biology

The presence of integrated human papillomavirus (HPV) DNA in squamous neoplasia is now well established but, in comparison, data relating to the link between HPV and glandular abnormalities are still controversial. This is true not only for invasive disease but also pre-cancerous abnormalities. For instance, one study from Michigan[10] suggested that HPV is more common in lesions with concomitant squamous abnormalities and *in situ* hybridization showed hybridization of the probe only in the nuclei of squamous epithelial cells and in no lesion did the probe localise to glandular epithelium. In comparison, other studies have shown a high incidence of HPV change in adenocarcinomas.[11-13]

Any link between HPV and the development of adenocarcinoma of the cervix may be a recent phenomenon[13]; furthermore, a consistent finding seems to show a correlation between HPV presence in glandular cancers and young age.[14,15]

A number of recent articles[14,16,17] have highlighted the inverse relationship between HPV presence and p53 over-expression. The lack of HPV and the presence of p53 over-expression may both carry a worse prognosis,[14] although this may relate to the latter being a late event in the disease process, a situation which may also exist for over-expression of c-erbB-2.[18]

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Pre-Cancerous Glandular Abnormalities

The relationship between pre-cancerous squamous change and invasive squamous lesions is now well established but the situation is far from clear in relation to the development of glandular cancers. Certainly the histological criteria used in diagnosing glandular changes which fall short of *in situ* disease have never been adequately described (terms such as glandular atypia, endocervical dysplasia and endocervical glandular dysplasia having been used) and less than 100 cases have been reported in the literature.[19] Even more controversial is the relationship between adenocarcinoma *in situ* of the cervix and the subsequent development of invasive malignancy, and also the optimal management, particularly of the younger woman who wishes childbearing who has glandular abnormalities on cytology or biopsy.

Loop excision of the transformation zone seems to be inferior as a method of management to cold-knife conization[20,21]; for instance, one study[20] has shown a recurrence in only one of 18 cases with negative margins on conization as opposed to four recurrences in 14 loop excision specimens also supposedly with negative margins. Our own research would support this approach and indeed would support the continued follow-up of women with negative cone margins with a histological diagnosis of adenocarcinoma *in situ*. This is in contrast to other reports[22-25] in which a surprisingly high frequency of recurrence in the presence of negative margins has been reported. This discrepancy in outcome may well reflect the processing of the conization specimen.[24] The situation is made even more complex by the recognition that endocervical curettage is not particularly useful in the follow-up of patients treated by conization or loop excision for pre-cancerous changes.[20,22,25] It is clear, however, that simple hysterectomy is the optimal management in women in whom child-bearing is not an issue.

Management of Microinvasive Disease

Although data on the optimal management of adenocarcinoma *in situ* are at best scanty, they are voluminous in comparison to that of microinvasive disease. Only 154 cases have been described in the literature.[26-29] The problem, of course, relates to histopathological description. Since there is no basement membrane to glandular epithelium then the definition of invasion becomes one of semantics. Nonetheless, it would seem that, with the information to date, invasion <3 mm can be managed on a basis similar to its squamous counterpart, whereas that between 3 and 5 mm at this time probably requires a more radical approach. The use of tumour volume measurements may clarify this situation further, although one patient with a tumour volume <500 cubic mm in whom recurrence eventuated has been described.[29]

Management of Established Invasive Disease

It now seems clear that stage for stage, adenocarcinoma carries a poorer prognosis than its squamous counterpart. For instance, in the most recent annual report of the International Federation of Gynecology and Obstetrics (FIGO) there was an over-representation of adenocarcinoma in early stage disease, yet despite this, survival rates were similar for pure adenocarcinoma compared to squamous carcinoma, whilst survival rates for adenosquamous and clear cell cancers were clearly inferior, a situation which is supported by other authors.[30-32] The M.D. Anderson group[32] has reported that women with Stage 1b adenocarcinoma of the cervix have an estimated risk of death almost twice that of patients with squamous disease, whilst a more recent French study[31] has shown an overall reduction in specific and disease-free survival in patients with adenocarcinoma of 10% and 14% respectively when compared to early stage squamous disease. In comparison, however, data from a Patient Care Evaluation Study of the American College of Surgeons involving 11 157 patients with cervical cancer, have failed to reveal any overall effect of histological characteristics with survival, although an analysis of patients with pathologic Stage 1 disease revealed that those with squamous disease had a significantly poorer survival than those with adenocarcinoma.[33]

With the increasing evidence that the presence of glandular disease is associated with a poorer outcome, then it is tempting to add extra modalities of treatment to standard care in the management of such patients. For instance, in those with Stage 1b adenocarcinoma in whom nodes are negative, the addition of adjuvant pelvic irradiation is tempting, although its efficacy is still unproven. Furthermore, the use of neoadjuvant cytotoxic therapy and/or combined radiation/cytotoxic therapy remains to be established, although such an approach seems attractive in view of the report of an increase in extra pelvic recurrences in women with glandular as opposed to squamous disease.[32]

The successful use of such neoadjuvant therapy has been reported from Italy, where patients were given platinum/cisplatinum in combination for two or three cycles, followed by a laparotomy if disease had shrunk to <4 cm in diameter and was regarded as potentially resectable, a situation which occurred in 33 out of 42 patients. Microscopic peritoneal spread was noted in four patients, leaving 29 to undergo radical surgery with a five-year survival of 88%. It would seem that any benefit was confined, however, to women with early stage disease. Certainly, other reports of neoadjuvant therapy have been disappointing.[34-36]

Given the link between the development of glandular abnormalities and the use of oral contraceptives, together with the presence of steroid receptors in over 20% of cases[37] then the use of hormonal therapy remains attractive. We have recently managed a woman with a serous papillary adenocarcinoma of the cervix metastatic to neck nodes with Tamoxifen who had a complete clinical response for 13 months and a further response, following recurrence, with medroxyprogesterone acetate.

The Future

Although the incidence of adenocarcinoma of the cervix is increasing, the absolute number of cases remains relatively small, and therefore any future studies will require a multicentre approach. Critical questions which need to be resolved include the use of multimodality therapy in early and advanced disease, the place of cytotoxic therapy for recurrent disease, and the place of hormonal therapy as adjuvant treatment or in the case of recurrence.

The link between the development of the disease and oral contraceptive use, particularly in the younger woman, needs to be further explored, as does the association between glandular abnormalities and human papillomavirus infections. Furthermore, the link between steroid hormones, papillomaviruses and oncogene expression, may be the key to understanding the aetiology of the disease and thereby ultimately its best management.

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