*Modern Radiotherapy*

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*Edited by*

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# *Preface*

This book is one of a series of volumes under the general title of *Modern Radiotherapy*. The series is designed to give the established clinician up-to-date knowledge of the advances that are being made in the specialty and to suggest possible ways in which future progress may be made. The radiotherapist, although primarily concerned with the treatment aspects of malignant diseases, must at the same time have a wide knowledge of these diseases—he is, in fact, a clinical oncologist. Medicine is progressively interdisciplinary and, with the hope of widening the radiotherapist's knowledge, contributions have been invited from workers in other specialties. It is hoped that the books will be of interest to workers in fields other than radiotherapy and that they will help to bring about a greater co-operation between all those who are concerned with the treatment of malignant disease.

This volume is devoted to malignant gynaecological diseases and includes chapters by gynaecologists, radiotherapists, physicians, pathologists, cytologists, physicists and radiobiologists. I would like to thank all these contributors for their willing help and co-operation.

I am extremely grateful to Miss J. M. Williams for the secretarial assistance that she has given in the preparation of this volume and it is a pleasure to acknowledge the considerable assistance given to me by the editorial staff of Messrs. Butterworths.

THOMAS J. DEELEY

# Contents

# 1—Radiotherapy in Gynaecological Cancer

*J. C. McClure Browne*

Although radiotherapy has a limited place in the induction of a premature menopause, undoubtedly its major role lies in the treatment of malignant disease of the female genital tract. In 1968 there were 51,529 deaths from cancer in females in England and Wales, and of these 7,927 or 15 per cent were caused by cancer originating in the genital tract. Of every 100 deaths from cancer of the genital tract the ovary was the primary site in 42, the cervix in 30, the endometrium in 20, and the vulva or vagina in 8.

## CERVICAL CANCER

Because of its greater accessibility, a cervical cancer is more readily available to early, often pre-symptomatic diagnosis; the same is true to a limited extent of endometrial cancer. Ovarian cancer, on the other hand, is all too often silent until it is far advanced. Vulvar cancer, fortunately rare, because of its very rarity often goes unrecognized until a late stage.

Until the discovery of radium, the only method of treatment of genital cancer was by surgical excision, still today in some parts of the world the only method available. The use of radiation, however, has made possible great advances in treatment, and the advent of supervoltage therapy, of hyperbaric oxygen and of chemotherapy have done much to improve results still further. Thus, in the years 1941–1945 the 5-year over-all recovery rate for cancer of the cervix was 36·9 per cent; in the years 1956–1960 it was 50·4 per cent.

Again and again it has been shown that whatever method of treatment is used, if the regional lymphatic nodes are involved good results cannot be expected. Therefore, emphasis has been placed on

earlier diagnosis. Although there is no direct evidence that pre-clinical cancer of the cervix invariably progresses to invasion, the fact that the peak of incidence of pre-invasive cancer precedes that of invasive cancer by 15 years suggests that such progression is highly probable, and the establishment of an efficient screening system with rescreening at 5-year, or better 3-year, intervals could lead to the virtual elimination of invasive cervical cancer.

The study of exfoliative cytology as a means of detecting early cancer, first mentioned by Dudgeon and Partick (1927) and described by Bamforth (1963), is popularly associated with the names of Papanicolaou and Traut, who in 1943 published a paper entitled 'Diagnosis of Uterine Cancer by the Vaginal Smear'. Since then the method has become increasingly popular, although British pathologists have been slow to recognize its value, and up until 1964 there were fewer than 10 centres in Britain in which cytology was employed on any but a token scale. In that year, however, the then Ministry of Health made it possible to establish a screening service on a national scale, and by 1968 1½ million smears were being examined annually. It is estimated that in England and Wales there are about 13 million women at risk of developing cervical cancer, and if smears are to be repeated at even 5-year intervals and the whole need met, the annual figure must be increased to 2½ million. The figures are deceptive, however, as many individual women may have a smear taken much more often because of attendance at ante-natal, family planning or gynaecological clinics where the procedure is routine, thus falsely inflating the over-all figure. In the initial stages, so as to make the best use of the limited facilities available, the screening programme was limited to women over the age of 35 years, but it is considered that the aim should be to begin screening at the age of 25 years, when the incidence of *in situ* carcinoma becomes significant.

Various high-risk groups have been defined, such as women of high parity, poor socio-economic status, sufferers from venereal disease and the population of women's prisons. Women in such groups are notoriously resistant to screening procedures. In a few centres, however, it has been possible to concentrate on such groups, with a noticeably higher resulting rate of detection. An example of such selective screening is the Aberdeen programme described by Elizabeth MacGregor (1967). She found that the observed incidence of clinical cancer of the cervix corresponded to that expected if all pre-clinical cases detected progressed to clinical cancer. In the years 1964–1966, after the screening programme had been in operation for 8 years, the number of clinical cases presenting in Aberdeen fell, and

the only patients under the age of 60 years were those who either had been already detected in the pre-clinical stage or who had for one reason or another escaped screening.

More recently, attention has been focused on the relationship of cervical cancer to vaginal infection with herpes simplex virus. Naib and colleagues (1969) showed that women with this infection, which is believed to be venereal, had a greatly increased incidence of cervical dysplasia, of *in situ* change and of frank invasion. The relative age curves of the two conditions suggest that the virus can transform normal cervical cells into anaplastic cells. Women with this infection therefore form another high-risk group.

There are doubts, however, as to the value of cytological screening. Green (1968) believes that detection of pre-clinical cancer has done nothing to reduce the incidence of invasive cancer in New Zealand, and that there is little to be said in favour of cytological screening for this purpose. It is believed by some workers (Ashley, 1966) that there are two types of cervical cancer: the explosive type which is invasive from the start and progresses rapidly, and the *in situ* variety which seldom progresses to invasion, and then only slowly. The British Columbia study (Fidler, Boyes and Worth, 1968) has gone on since 1962, and although at first sight there seemed to be a resulting fall in the incidence of invasive cancer of the cervix serious doubt has been cast by Knox (1968) on the statistical validity of the figures.

Despite the absence of absolute proof, most gynaecologists today believe that cytological screening is a worth-while procedure, and that no gynaecological examination is complete without it.

Other methods of screening for cervical cancer have not proved effective. Although colposcopy is widely used in many European countries it has not found favour in Britain, largely because of the clinical time involved, which renders it unsuitable for mass screening. Enzyme tests give a high proportion of false-negative results (Boyd and colleagues, 1957) and so far, have not proved rewarding. The only feasible method of screening for cervical cancer at present available is exfoliative cytology. Unfortunately the clinical and laboratory work involved in population screening by this method is very great and attempts to introduce automation have so far not succeeded.

Whatever method is used in screening, a positive result although suggestive is not diagnostic and the diagnosis must be made by biopsy. For this purpose most gynaecologists excise a cone, including the cervical canal and the squamo-columnar junction, a procedure very effective for diagnosis, but by no means devoid of complications

such as haemorrhage, infection and, when the uterus is conserved, there may be repeated abortions, premature labour and cervical stenosis in labour. Conization may also render subsequent irradiation difficult. For these reasons there is much to be said for punch biopsy of areas which fail to stain with iodine (Schiller's Test); in this procedure the colposcope may be useful. However, if the punch biopsy is negative and the cytological picture remains positive or even suspicious, conization is essential.

Recent work (Jones and colleagues, 1968) has suggested that by studying the chromosomes of cervical cells in early neoplastic lesions it may be possible to predict which will remain benign and which will progress to invasion and therefore must be treated. A diploid pattern indicates that progression to invasion has begun or will occur, while triploidy or tetraploidy suggests that the lesion is benign and will remain so. Davidsohn, Kovarik and Ni (1969) have shown that the iso-antigens A, B and H, which are detectable in normal tissues, are reduced in amount or absent when transformation to carcinoma occurs.

There is little doubt that the *in situ* lesion and the micro-invasive lesion are most satisfactorily treated by surgical extirpation. Stage I lesions are about equally well treated by surgery or by radiotherapy. In the *Annual Report on the Results of Treatment in Carcinoma of the Uterus and Vagina* (Annual Report, 1967) the 5-year recovery rate in institutions employing surgery in more than 75 per cent of Stage I cases was 78·9 per cent, while in those operating on less than 10 per cent of such cases the rate was 74·9 per cent. Of course individual workers have reported better results. Thus, Decker and Smith (1968) have reported a 5-year recovery rate of 88·6 per cent in Stage I cases treated surgically, excluding micro-invasive cases, and Sicher (1967) of Coventry has reported a rate of 88 per cent in cases treated by intracavitary radium alone.

It must always be remembered, however, that if there is node involvement (20 per cent in Stage I) the outlook is relatively poor. In planning treatment it is of the utmost importance to know if the nodes are involved, and there is no method short of surgical removal and histological study which will give the answer. Certainly venography and lymphography have proved disappointing.

Glucksmann has employed serial biopsy methods to assess the response to radiotherapy for many years. More recently Cox, Stanley and Harvey (1969) have shown that the probability of a satisfactory response can be predicted by the disappearance of mitoses after a test dose of 500 rads of megavoltage, following biopsy. They also found

that while triploid and tetraploid tumours tended to respond well to radiotherapy, those which were diploid responded badly. Knowledge of the chromosomal pattern of the growth may prove to be of great value in selecting the best form of treatment.

Few would dispute that in Stages II, III and IV treatment is best carried out by radiotherapy alone or in combination with surgery. There is some evidence (Pizey and Bullimore, 1968) that in Stages III and IV external irradiation combined with hyperbaric oxygen therapy gives improved results, 56 per cent 5-year survival in their series compared with 27 per cent in the Annual Report previously quoted.

In the treatment of distant metastases there is something to be said for chemotherapy, although at present its effect is somewhat unpredictable.

Both in planning the initial treatment and in follow-up after treatment it is important that the radiotherapist and the gynaecologist should work closely together, as only in this way can the individual needs of each case be best met. Where the case has been treated by radiotherapy, at the first sign of recurrence the possibility of surgery should be considered. One of the earliest signs of persistence of disease or of its recurrence is the finding of a high karyopyknotic index in the vaginal smear. This should evoke searching scrutiny including biopsy, so that further treatment, usually surgical, is given without waiting for clinically evident recurrence.

## ENDOMETRIAL CANCER

Endometrial cancer tends to be slower in spread and metastasis than cervical cancer. In about one-fifth of the cases the pelvic lymph nodes are involved. Like cervical cancer it is amenable to detection in the pre-clinical stage by cytological screening, although the percentage of cases detected in this way is not so high. Detection is best accomplished by aspiration of the fluid in the posterior fornix rather than by the more usual cervical scrape, as the aspirate contains representative cells collected from every part of the genital tract, including the endometrium. Even so, the small round endometrial cells are easily missed, and the 'pick-up' rate is only of the order of 75 per cent. Fortunately the symptoms of watery, brownish discharge or the passage of dark blood in a post-menopausal woman are sufficiently alarming for her to seek medical advice at a relatively early stage in many cases. Thus, in the Annual Report (1967) 87 per cent of cases presenting were still in Stage I, compared with only 26

per cent of cases of carcinoma of the cervix. Even allowing for the fact that endometrial cancer mostly occurs in elderly women with a consequently higher rate of intercurrent death, 63 per cent of cases are alive without evidence of disease 5 years after treatment, compared with only 50 per cent in carcinoma of the cervix.

Diagnosis is readily made by curettage, although in some cases this may reveal an associated pyometra and sometimes the thin uterine wall may be perforated accidentally. Both of these conditions modify treatment, the former causing delay until the infection is controlled, and the latter necessitating immediate hysterectomy.

Because, in perhaps 20 per cent of cases, there is involvement of the pelvic lymph nodes, it is probable that a combination of surgery and radiotherapy will give the best results. The combination is advocated as in 25 per cent of cases treated by radiotherapy, persistent growth is found if the uterus is removed 6 weeks later. Geisler and Gibbs (1968) reported a 5-year survival rate of 86 per cent in cases of Stage I and II treated by radiotherapy followed by surgery, the best figure (95 per cent) occurring in those cases in whom no residual disease was found at operation. If residual disease was present the 5-year survival rate was 77 per cent. In many cases, however, the patient is not fit for major surgery. Burr and Robertson (1968) gave both internal and external irradiation to 14 such cases with a 5-year survival rate of 77 per cent, and Delclos and colleagues (1969) found a 79 per cent 5-year survival rate in these cases.

The relative merits of radiotherapy followed by surgery and of surgery followed by radiotherapy have not as yet been properly compared. After surgery alone recurrences in the vault are well known, and for this reason some workers routinely employ vault irradiation immediately after primary surgery. The known tendency of recurrence to be situated in the region of the pelvic lymph nodes, as well as in the vault, however, suggests that irradiation whether given before or after surgery should include the whole pelvis. When there are recurrences after maximal irradiation, considerable improvement and control can be obtained by the use of progestogens (Peck and Boyes, 1969).

## CANCER OF THE OVARY

Cancer of the ovary not only accounts for the greatest number of deaths from genital cancer in women, but when diagnosed and treated it carries the lowest 5-year survival rate. In the vast majority of cases the diagnosis is not made until symptoms occur, and by this time the

disease is usually well advanced. Metastasis is to the pre-aortic lymph nodes and, as a result of erosion of the tumour surface, multiple peritoneal deposits commonly occur. Early diagnosis is by no means as simple as in cancer of the uterus, although a few cases have been described where the first indication of the disease came from cytological examination of the posterior fornix aspirate. Graham and Graham (1967) have employed aspiration of the pouch of Douglas as a means of pre-symptomatic detection. Of 24 patients in whom the presence of an ovarian tumour had not been detected and in whom malignant cells were recognized only 1 had an abnormality on physical examination and 13 had no gynaecological symptoms whatever.

It is difficult to imagine puncture of the posterior fornix as a routine screening procedure, and a large proportion of cases are inoperable when first seen; more than 50 per cent in the series described by Weingold, Sall and Stone (1967). Where surgery is possible, the treatment of choice is undoubtedly panhysterectomy followed by radiotherapy. The treatment of metastatic spread from carcinoma of the ovary has been greatly helped by supervoltage therapy, by intraperitoneal radioactive gold, and by chemotherapy. Villasanta and Bloedorn (1968) reviewing 169 such cases found that when surgery and radiotherapy were used the 5-year survival rate was 47 per cent, when surgery, radiotherapy and radioactive gold were used the figure rose to 53 per cent, while when surgery, radiotherapy and chemotherapy were used the 5-year survival rate was 61 per cent. The drugs chiefly used were Thio-Tepa instilled intraperitoneally and chlorambucil or cyclophosphamide given orally.

## VAGINAL CANCER

Cancer of the vagina is a relatively rare condition and its very rarity has made it difficult to assess the effect of treatment by different methods. Frick, Jacox and Taylor (1968) have reported on 52 cases seen during 1930–1966. They found that the prognosis was the same whether the tumour was situated in the upper, middle or lower-thirds of the vagina, but all 7 in whom the growth encircled the vagina died of cancer. When only the vaginal wall was involved 7 of 15 patients treated with radiotherapy and 4 of 5 treated surgically survived 5 years. When there was subvaginal involvement the respective survivals were 4 of 11 and 4 of 13. Lesions of the anterior and lateral vaginal walls are best treated by a combination of intra-vaginal radium and external irradiation, surgery being reserved

for small lesions of the upper vagina and for lesions of the posterior wall in the lower two-thirds.

## VULVAR CANCER

There can be little doubt that the best primary treatment of vulvar cancer is radical surgery. Radiotherapy has a very limited place, in palliative treatment of advanced cases in women too old and frail to withstand surgery. It is sad that so many cases are very advanced when first seen, partly on account of the reluctance of many old women to seek medical advice, and partly due to failure of the medical practitioner to realize that the lesion is not just a simple dermatological disorder but a malignant growth.

## CHORION EPITHELIOMA

In the treatment of chorion epithelioma chemotherapy has largely replaced both surgery and radiotherapy, although the latter may still be needed to control persistent bleeding or to treat localized distant metastases.

## CONCLUSIONS

It must be said again that in every gynaecological cancer, just as in cancer elsewhere, when the lymph nodes are involved the prognosis is bad. This applies particularly to those cases treated only by surgery, and to a lesser degree to those treated by irradiation or by a combination of surgery and radiotherapy. This emphasizes the importance of early diagnosis. To encourage women to present themselves at an early stage, an educational programme is needed, so that they realize that genital cancer, if diagnosed early enough, can be readily cured in a high proportion of cases. Women should be taught to seek medical advice without delay if there is abnormal discharge or bleeding from the genital tract. All women at risk should be screened cytologically at regular intervals, and this should be combined with clinical examination. Examination and screening should be repeated at 3-yearly intervals. Special efforts must be made to include in this programme women in the high-risk groups, who tend to escape the screening net.

The advent of chemotherapy has placed a new and relatively untried weapon in our hands, and the scope of adjuvant hyperbaric oxygen in conjunction with radiotherapy has yet to be fully explored.