

RADIATION THERAPY

in the Management of

CANCER

of the

UTERINE CERVIX

By

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FOREWORD

"Le traitement correct des cancers par les radiations, dans le cas de l'utérus comme dans les autres localisations, exige impérieusement deux compétences essentielles (sans compter les compétences accessoires): l'une en pathologie externe (dont la gynécologie n'est qu'une branche), l'autre en radiothérapie. Elles peuvent être réunies dans la même tête, mais elles peuvent parfaitement aussi rester distinctes, à la condition d'un échange incessant des clartés nécessaires entre les deux premiers rôles du traitement."

"The proper treatment of cancer by radiation, in cancer of the uterus as in other locations, requires two essential abilities (without taking into account other competencies): the one is in pathologic anatomy (of which gynecology is only a branch), the other is in radiation therapy. These may be combined in the same person, but they may also be distinct providing that an unceasing exchange of views exists between the two roles in treatment."

Claude Regaud, 1922

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INTRODUCTION

CANCER of the cervix uteri accounts for one in four malignant tumors in women. Of greater significance than its incidence is the possibility to control the disease in eight of ten women when recognized in an early stage and well directed radiation therapy is applied. More advanced cancer of the cervix with induration in one or both parametria still has a curability of one in three, which far exceeds the prognosis of operable cancer of the stomach. Therein lies the significance of a proper understanding of the disease and the possibilities and limitations of radiation therapy in its behalf.

It is the intent of this work to review the important clinical and pathological features of cancer of the cervix which bear upon its management by radium and roentgen therapy. No other form of cancer has had so intimate a relationship to the development of the entire field of radiation therapy. An understanding of its management, accomplishments and failures is in a large measure a review of the progress and limitations of radiant energy in combatting cancer. An understanding of the pathology and complications of the disease is the basis for sound irradiation. The work describes the evolution of radiation therapy in relation to cervical cancer, and the basic concepts which have evolved from the Swedish and French schools of radiotherapy. The role of

x-ray therapy and its technics of application are considered in detail. The problems of dosimetry, both radium and roentgen, are described, with an appendix on dosimetry for those wishing reference to this problem.

The work likewise carries reproductions of the League of Nations 1937 clinical staging of cervical cancer, which are helpful in clinical appraisal.

A comprehensive survey of the more important results from world-wide sources is tabulated.

It is hoped that this monograph will prove helpful to anyone who has to deal with cancer of the cervix, and particularly to the radiologist upon whose knowledge of the disease and its treatment the major responsibility still rests.

CLINICAL CONSIDERATIONS

THE PATIENT who presents herself with a cancer of the cervix can be in any decade. Although the incidence tends to rise after the thirty-fifth year, it can occur in the first and second decades as well.^{1, 118} Any large clinic dealing with cancer will have patients in the second and third decades with cancer of the cervix. The important factor to stress in relation to age is to forget age as a factor in differential diagnosis while examining the *individual patient*.

The incidence of cancer of the cervix is higher in the married than in single women, regardless of child-bearing. In a recent study by Maliphant* the probability of the development of cervical cancer varied from 1 in 21,000 for single, 1 in 6,500 in childless married women and 1 in 1,500 in parous women. In the latter group the probability increases with the number of children, indicating that the risk is double for six or more deliveries over the probability for the woman who has had one child.

The only racial consideration which is of importance is the rarity of cancer of the cervix among Jewish women.^{41, 115}

The clinical manifestations of cancer of the cervix which lead the patient to seek consultation may be extremely varied. They depend upon the anatomical and pathological relation-

* Maliphant, R. G.: The incidence of cancer of the uterine cervix. *Brit. M. J.*, pp. 978-982, June 4, 1949.

ships which have resulted from the growth of the disease either locally or beyond its site of origin.

Cancer of the cervix uteri originates from the epithelium or glands of the cervix distal to the internal os. It is not generally appreciated that a majority of cervical cancers arise from the epithelium or glands of the endocervical canal. Distal extension along the canal later makes its appearance as an ulceration at the external os; or, there may be direct peripheral invasion through the body of the cervix to appear as an outcropping on the portio-vaginalis. A growth arising in the endocervical canal may not be visible on inspection even though it is moderately advanced. Proximal extension into the endometrial cavity and uterine musculature or peripheral invasion into the parametria or the adjacent pelvic structures can develop to a considerable degree without ulceration of the cervix visible by speculum examination. It is this common endocervical origin of the disease which should warn the surgeon to perform a diagnostic curettage of the endometrial and endocervical canal before subjecting a patient to hysterectomy.

The most common sign associated with an early ulceration of the endocervical canal or portio-vaginalis is abnormal bleeding. This may be only an occasional spontaneous spotting, or associated at times with intercourse. In any event vaginal bleeding occurring irregularly in the pre-menopausal age must be taken seriously. In the menopausal and post-menopausal age it is to be viewed with equal care. Folklore, both professional and otherwise, accounts for many advanced cancers of the cervix.

Ulceration of the endocervical canal or cervix is invariably followed by some degree of infection. There follows in many instances a vaginal discharge, which becomes more profuse

and sanguine as the ulceration and disintegration of tumor advance. The character of the discharge may mask the more important sign of bleeding with the general mixture of effluents which ensues. Therefore the patient may complain only of the vaginal discharge when bleeding is minimal.

Although some degree of abnormal vaginal bleeding or discharge are the earliest signs of cancer of the cervix, they are unfortunately not the most common ones which bring the patient to the physician. Only one in ten cancers of the cervix is recognized while still limited to the cervix. More than one-half have invaded the parametria by the time the disease is diagnosed. The more common presenting complaints are related to advancing disease and associated inflammation. These are generally characterized by pain. Peripheral spread of cancer or inflammation to the parametria is usually associated with some degree of pelvic discomfort which may be only vague in character or progress to aggravating pain and tenderness. Referred pain to the lower back, or to one or both lower extremities is not uncommon, and is evidence of pelvic involvement by peripheral spread associated with some degree of inflammation. Edema of one or both lower extremities, due to pressure of advancing disease or associated phlebitis is at times a presenting or associated sign. Pain in the lumbar region, and particularly when associated with pain deep in the pelvis and groin, is characteristic of ureteral stenosis by advancing spread. Vaginal extension with ulceration and necrosis produces pain and tenderness in the vagina which will vary with the extent of involvement and the pain threshold of the patient. Pain in the bladder, frequency or frank hematuria result from anterior spread or pressure. Pain in the rectum, constipation or bulging hemorrhoids may be a sign of posterior spread to en-

croach upon the rectum. One still sees patients with recto-vaginal fistulae who seek help in this late stage. In still more advanced cases distant metastases beyond the pelvis give rise to pain. Upward spread paravertebrally gives rise to abdominal pain.

There is thus no distribution of pain which is characteristic of cancer of the cervix. The intricacies of the female pelvic organs, their supporting structures, vascular and nerve supply, form a varied path for the spread of the disease and the pain and complications which accompany it. Each of these is however related to the anatomical pathways of spread, and an understanding of them is important, not only from the standpoint of diagnosis, but more particularly as they affect the aims and limitations of radiation therapy.

THE PATHOLOGY AND SPREAD OF CANCER OF THE CERVIX

THE NORMAL histologic covering of the vaginal portion of the cervix is a squamous epithelium which changes to a single layer of prismatic cells at the orifice of the external os. The endocervical mucinous glands are composed of cells similar in type to those lining the endocervical canal. In the absence of metaplasia due to infection or trauma, there is an abrupt rather than a gradual transition between these two distinct varieties of epithelium. Where metaplasia has occurred, one may find squamous cells lining the endocervical canal and even extending into the uterine cavity.

Clinical observation supports the thesis that the great majority of cervical cancers arise in the endocervical canal. The earliest cancer of the cervix is intra-epithelial cancer of the endocervical canal, without signs of spread to the portio-vaginalis. The everted external os exposing the endocervix to view as a spongy membrane easily bleeding with minimal trauma, induces suspicion of early cancer. If the clinical observations are correct, and the origin is primarily endocervical, it is a paradox that most cervical cancer is classified as "squamous cell" in type, resembling the covering of the cervix distal to the cervical canal, whereas a minority of cervical cancer exhibits elements of epithelium characteristic of the glandular features of the endocervix. One can in-

voke the phenomenon of metaplasia to bridge the paradox, but this seems rather to beg the question. A more likely interpretation was presented in detail by Regaud and Gricouff,^{87, 88} who concluded that many cancers of the cervix having the appearance of squamous cell epitheliomas are derived from the prismatic cells lining the endocervical canal. In further development they assume the aspect of a stratified pavement epithelium without glandular formation, and closely resemble those epitheliomas derived directly from squamous epithelium of the portio-vaginalis. The great majority of cervical cancers are thus classified in the American literature as epidermoid carcinomas, and little attention is given to their actual ancestry. That the problem of classification of cervical cancer in its manifold varieties is not without its complexities can be learned from the excellent and illustrative section on "Epitheliomas of the Cervix Uteri" by H. Rubens-Duval, which forms a part of the *Atlas du Cancer*.⁹³

Apart from the larger groups of epidermoid carcinomas of varying degrees of cellular differentiation, there are two varieties of cervical cancer which merit particular mention. These are the true adenocarcinomas, and the intermediate group known as adenoacanthoma.

It is of prognostic and therapeutic importance to clearly differentiate between an adenocarcinoma arising in the endocervical canal and one which has invaded the cervix, but originated in the endometrium. Adenocarcinoma arising in the endocervix is relatively rare, forming 3 to 5 per cent of cervical cancer.⁷ Adenocarcinoma arising in the endometrium which has secondarily invaded the cervix is not a form suitable for surgical management, since it will have in most instances involved the vaginal mucosa or submucosa, and spread laterally to one or both parametria.

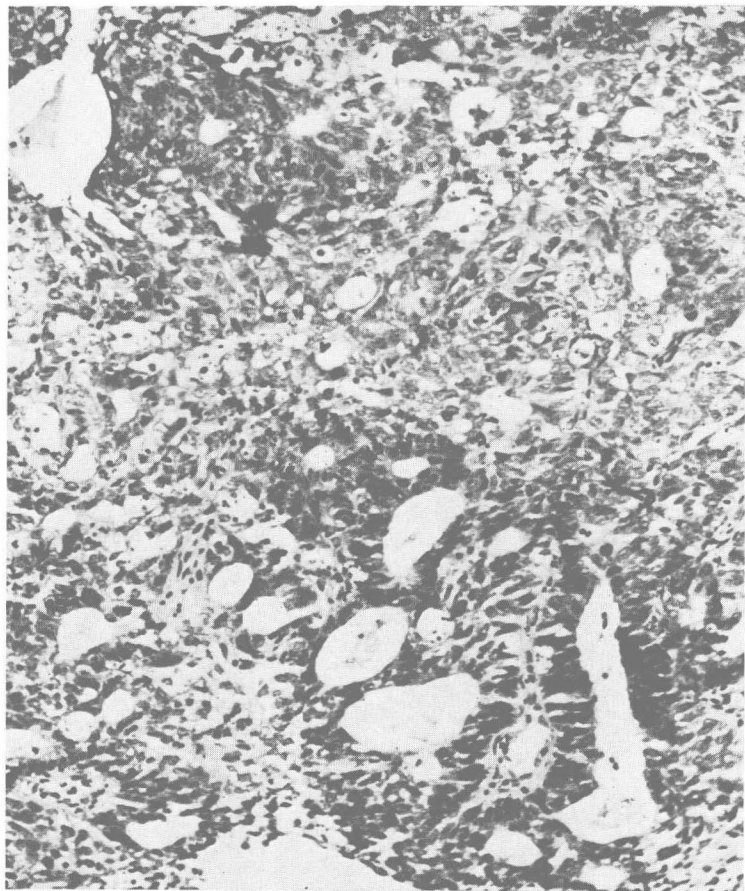


Figure 1 — Adenoacanthoma showing solid sheets of miniature epidermoid cells as well as distinct glandular structures. The blending of one cell type into another is also evident. (Courtesy Dr. Paul Lund, Pathologist, Swedish Hospital.) 160X