

Endometrial carcinoma and its treatment:

The role of
irradiation,
extent of surgery,
and approach to
chemotherapy

Edited by

Laman A. Gray, Sr., M.D.

*Clinical Professor of Obstetrics and Gynecology
University of Louisville and
University of Kentucky*

*Chairman, Professional Education Committee
American Cancer Society
Kentucky Division
Louisville, Kentucky*

Outstanding specialists in the fields of radiology, obstetrics, gynecology, pathology, and related disciplines have produced this impressive examination of the treatment of endometrial carcinoma, a disease which is rapidly replacing cancer of the cervix as the most recurring form of pelvic cancer. From well-known institutions around the world come analyses of the most progressive treatment modalities of radiotherapy, surgery, and chemotherapy. A review of this caliber is essential for physicians who are aware of the need to reevaluate the treatment of these lesions.

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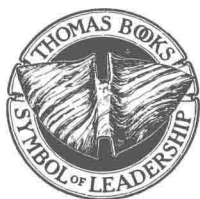
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Contributors

BORONOW, Richard C., M.D.: Professor and Acting Chairman, Department of Obstetrics and Gynecology, University of Mississippi, Jackson, Mississippi

BRADY, Luther W., Jr., M.D.: Chief of Irradiation Therapy, Hahnemann Medical College of Philadelphia, Philadelphia, Pennsylvania

BUCHLER, Dolores A., M.D.: Associate Professor, Department of Obstetrics, Gynecology, and Radiotherapy, University of Wisconsin, Madison, Wisconsin

BUTLER, Charles F., M.D.: Mayo Clinic, Rochester, Minnesota

CARR, William F., B.A.: Department of Obstetrics, Gynecology and Radiotherapy, University of Wisconsin, Madison, Wisconsin

CARTER, Stephen K., M.D.: Deputy Director, Division of Cancer Treatment, National Cancer Institute, Bethesda, Maryland

CASTANO-ALMENDRAL, A., M.D.: Department of Obstetrics and Gynecology, University of Basel, Basel, Switzerland

CHRISTOPHERSON, William M., M.D.: Professor of Pathology, University of Louisville, School of Medicine, Louisville, Kentucky

ERLICH, Clarence, M.D.: Indiana University Medical Center, Department of Obstetrics and Gynecology, Indianapolis, Indiana

GOODMAN, Robert L., M.D.: Joint Center Radiation Therapy, Harvard Medical School Boston, Massachusetts

GRAY, Laman A., Sr., M.D.: Clinical Professor, Department of Obstetrics and Gynecology, University of Louisville; Chairman, Professional Education Committee, American Cancer Society, Kentucky Division, Louisville, Kentucky

- GUSBERG, Saul B.:** Professor and Chairman, Department of Obstetrics and Gynecology, Mt. Sinai School of Medicine, New York City, New York
- HOMESLEY, Howard D., M.D.:** Assistant Professor, Department of Obstetrics and Gynecology, Bowman Gray School of Medicine, Winston-Salem, North Carolina
- KASER, Otto, M.D.:** Professor and Chairman, Department of Obstetrics and Gynecology, University of Basel, Basel, Switzerland
- KOTTMEIER, Hans-Ludwig, M.D.:** Profesor Emeritus of Gynecology, Radiumhemmet, Stockholm, Sweden
- LEWIS, John L., Jr., M.D.:** Chief, Gynecology Service, Memorial Sloan-Kettering Cancer Center, Cornell University Medical Center, New York, New York
- MARCK, Abraham, M.D.:** Joint Center Radiation Therapy, Harvard Medical School, Boston, Massachusetts
- MURTHY, Amantha, M.D.:** Joint Center Radiation Therapy, Harvard Medical School, Boston, Massachusetts
- PECKHAM, Ben M., M.D.:** Professor and Chairman, Department of Obstetrics, Gynecology, and Radiotherapy, University of Wisconsin, Madison, Wisconsin
- PIVER, M. Steven, M.D.:** Associate Chief, Department of Gynecology, Roswell Park Memorial Institute, Buffalo, New York
- PRATT, Joseph H., M.D.:** Consultant Gynecologist, Mayo Clinic, Rochester, Minnesota
- RUTLEDGE, Felix N., M.D.:** Chief of Gynecology, M.D. Anderson Hospital, Houston, Texas.
- SILVERBERG, Steven G., M.D.:** Department of Pathology, University of Colorado, Denver, Colorado
- SIMON, Norman, M.D.:** Clinical Professor, Department of Radiology, Mt. Sinai School of Medicine, New York, New York
- VALLE, Giuseppe B., M.D.:** Professor and Chairman, Department of Obstetrics and Gynecology, University of Roma, Rome, Italy
- VECCHIONE, A., M.D.:** Department of Obstetrics and Gynecology, University of Roma, Rome, Italy.
- VONGTAMA, Vitune, M.D.:** Department of Gynecology, Roswell Park Memorial Institute, Buffalo, New York

Preface

THE AMERICAN CANCER SOCIETY, Kentucky Division, Inc., sponsored a meeting in Louisville, Kentucky on November 3 and 4, 1975 relating to endometrial carcinoma and its treatment. This two-day meeting was to explore in depth the present status of the treatment of the disease, particularly in regard to the role of irradiation, the extent of surgery, and the possible new approaches with chemotherapy. Under the planning of the Professional Education Committee of the Kentucky Division, a group of outstanding specialists from well-known institutions in the world were brought together for this discussion.

The clinical data included in this book contains more detail than ever assembled in a single volume previously. The opinions expressed are as authoritative as one may obtain at this time. However, the differences of opinions expressed and their documentation are the important points in this book. The combinations of modalities of treatment and sequence have been discussed in detail.

Although a firm and unanimous conclusion as to the best treatment for all cases was not agreed upon, it is apparent that while selective cure rates are improving, there is no room for complacency. It is important that we look at the failures of cure, and that an intensive effort be made to provide better results. Perhaps somewhere in this book there may be an answer which a researcher or clinician may find as a signpost for the complete treatment.

The Committee responsible for bringing these authorities together for this meeting are, indeed, appreciative of the support and aid of the American

Cancer Society, Kentucky Division, Inc. The cooperation of Charles C. Thomas, Publisher, and particularly that of Mr. Payne E. L. Thomas, the son of the distinguished founder of that organization, are thanked warmly for their cooperation and aid in the preparation of this book.

LAMAN A. GRAY, SR., M.D.

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Endometrial carcinoma and its treatment

Introduction

Laman A. Gray, Sr., M.D.

A CHANGE FROM THE COMBINED TREATMENT of endometrial carcinoma with radium followed by hysterectomy has been appearing in various areas of the country in the past two years. In part, this was stimulated in the Kentucky area by remarks by Professor Hans Kottmeier who voiced doubt of the value of preoperative intrauterine radium preceding hysterectomy, particularly in the Stage I cases with low-grade malignancy. Previous to that time in this area, preoperative intrauterine radium has been considered the standard treatment for all patients and any deviation has been questioned. But deviation has occurred in the Louisville area, as reported later in this book, largely because of the feelings of certain general surgeons and of a few gynecologists that the final role of preoperative radium had not been satisfactorily delineated even after fifty-five years or longer.

The Louisville Radiation Center, under the direction of Doctor Ralph Scott, decided to reserve preoperative intrauterine radium for the unusual case and to apply preoperative external therapy or postoperative external therapy as a more or less routine (personal communication). This change has caused some confusion and met with resistance from those who adhered to the firmly entrenched combined methods. Similar approaches have been appearing in various areas of the country.

The incidence of endometrial carcinoma not only is increasing relative to carcinoma of the cervix (which is decreasing), but the true incidence rate of endometrial lesions appears to be increasing, the cause of which is not clear. Positive Papanicolaou (Pap) smears and the discovery of early preinvasive malignant lesions of the cervix have allowed cure of most early cervical cancers with possible prevention of lesions becoming advanced, but as yet no satisfactory method of early detection of endometrial carcinoma has appeared. This lesion is now the prime malignant problem in the pelvis, at least insofar as numbers are concerned. Christopherson, in this book, presents some im-

portant statistical epidemiological data which indicates areas for concern and research. Increasing age alone appears the greatest risk factor in the increase in this disease, which is related to the increasing longevity of women today. That estrogenic hormone therapy for the menopause may represent a factor, at least to some extent, appears likely but this appears not the only etiologic agent. It is not the purpose of this book to theorize on the causes or the early detection of endometrial cancer, but to present the best treatment methods used today.

The pathology of this disease has been documented well for a century. The term *adenoma malignum*, discarded today, indicated the low Grade I cancers of the endometrium, the most common type that has been encountered in the uterus. But certain authors have pointed out a new or overlooked form of endometrial cancer, the adenosquamous type, highly malignant with an exceedingly poor cure rate by any treatment means available. This mixed type of malignant tumor, which differs from the adenoacanthoma with its benign component of squamous metaplasia and malignant component of glandular epithelium, has been found by Reagan and associates in as many as 20 percent of cases. Strangely enough, this incidence has not been corroborated in other geographic areas and, in fact, it is rarely diagnosed by pathologists in general. Further attention by the pathologists may indicate that this is, indeed, a distinct and important form of a cancer about which little or nothing has been known in the past. The fact that endometrial carcinoma does occur in young women, especially those with polycystic ovaries or receiving contraceptive hormonal preparations, especially of the sequential type, though only sporadically, is of distinct importance in the overall review of this problem, as has been emphasized here by Silverberg.

In the general review and evaluation, Gusberg stated that advancement of knowledge of this disease has been delayed by a number of erroneous ideas. One is that cancer of the corpus is always benign or represents a low grade cancer. The second is that postmenopausal bleeding accompanying estrogens is always physiological. Thirdly, widely accepted is the concept that all corpus cancers must be treated by one modality. Fourthly, the concept that the Pap smear is satisfactory for all uterine cancer surveillance. Fifthly, he believed that the slow acceptance of adenomatous hyperplasia as a significant cancer precursor has delayed cure of premalignant disease. Finally, he stated that staging must include the virulence factor.

The historical review of the development of treatment over the past fifty-five years, the attempts to meet the various theoretic and actual problems and complications, and the variations of methods of application of irradiation and surgery bring us up to the present. Gusberg has pointed out an increasing tendency to individualization of treatment in recent years. This includes study of the virulence factors, size of the uterus, differentiation

of cervical involvement, degree of invasion of the uterus itself, and the grade of the tumor. Simple hysterectomy, combined treatment, and finally radical hysterectomy, usually with preoperative radiation, are the prominent methods of treatment today. Gusberg emphasized that if the uterus is greatly enlarged, preoperative external irradiation may be more effective than radium packing of the endometrial cavity.

Staging, pretreatment evaluation, and factors in outcome are, indeed, important considerations for each clinician involved in the treatment of this disease.

In this symposium the role of radiation therapy is advanced not only by leading radiotherapists, who present their data and opinions, but also by the exponents from leading cancer centers and universities as well. In most areas preoperative irradiation apparently continues as the standard treatment, although variations in methods are appearing in the cancer centers with large numbers of patients. Of particular interest is the method from the University of Michigan in which deep external therapy has been used unwaveringly for some forty years. The cure rate of 90 percent in Stage IA cases is most impressive.

In this country we have believed that surgery without irradiation has been used rarely for treatment of endometrial cancer, particularly because essentially all medical schools have taught this method of treatment in the past generation. But it is surprising to note the data in Table I-I from the International Federation of Gynecologists and Obstetricians (FIGO) material (kindly brought together by William M. Christopherson) which clearly shows that in the participating institutions in the FIGO annual reports, surgery alone is performed more often than the combined treatment or radiation alone. It is of real interest to learn of the unusual results of vaginal hysterectomy alone for early endometrial carcinoma by Pratt of the Mayo Clinic where some 15 percent of cases are handled in this manner. These were early lesions with low grade.

TABLE I-I
CARCINOMA OF CORPUS
Treatment Methods In Fifty-two Reporting Institutions
FIGO 1954 - 1963

	<i>TOTAL</i>
Hysterectomy	7,155
Preoperative Radiation and Hysterectomy	3,497
Radiation Alone	7,092
Other	15
TOTAL	17,759

In the report from Louisville by Gray, the statistics indicate that surgery alone is superior to the combination of preoperative intrauterine radium followed by hysterectomy some six weeks later. But a factor analysis has not been carried out, the patients have not been matched accurately, and it is quite possible that conscious or unconscious selection occurred in these patients. Possibly the case with greater extension of disease was treated with the combined method, although that does not appear true from the statistical data. This author directs attention (very importantly in his mind) that a small but definite percentage of patients do die of this disease, even those with Grade I and Stage I lesions. Though this group of fatalities may make up only 8 or 10 percent of the total patients, the remainder of fatal cases comprising those with extended tumors or higher grade lesions, yet this represents a real mortality. The apparently increasing cure rate through the past fifty years appears due largely to earlier discovery of the disease and not to superior surgery or any combination of treatments. It is also emphasized that some additional treatment, such as chemotherapy, should be administered to patients with this disease in addition to surgery.

The chemotherapeutic armamentaria for the treatment of this disease are undeveloped. Little has been reported in this phase except for the use of progestins. That this hormone may cause regression or remission of recurrent cancers in perhaps one-third of cases for varying periods of time but not for cure is, indeed, an advance. The experience in Rome is of interest but we suspect that a more dynamic and destructive agent must be used in combination with presently used treatments.

While no conclusions are reached in this book, a great deal of data is there for perusal by the serious student. Almost every approach has its adherents, so that there is something for every one. However, there remains a disquieting overtone that we must find newer approaches, almost certainly in the chemotherapeutic field.

Part I

General considerations