

Modern Concepts of Gynecologic Oncology

Edited by
John R. van Nagell, Jr.
Hugh R. K. Barber

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FOREWORD

Gynecologists have been vital to the great improvements in diagnosis and management of patients with malignant disease. They have led the way in the practical use of exfoliative cytology, advanced surgical techniques, the successful use of chemotherapy in such dread diseases as choriocarcinoma as well as the investigations into immunotherapy, while also caring for tremendous numbers of potential victims of cancer. These improvements are just beginning. Invasive cervical cancer, once such a frequent killer of women, can now be diagnosed in its earliest form of cellular aberration and obliterated by comparatively simple means. Indeed, it is entirely possible to eliminate invasive cervical cancer and to reduce significantly the incidence of other diseases, such as squamous cell cancer of the vagina and vulva, by the end of this century. That the future of gynecologic oncology is extremely promising is well recognized by physicians in training who, in ever-increasing numbers, seek fellowship leading to certification in this subspecialty. In addition, the recognition of gynecologic oncology as a subspecialty has given great impetus to interest in this area and indicated a need for a concise, authoritative, complete text on this subject.

This volume directed as it is to medical students, residents, Fellows and practicing oncologists, should play an important role in defining for them the natural history, demography, diagnosis, and management of the diverse and unique diseases of this discipline. The various chapters in this text dealing with surgical procedures, radiation therapy, nutrition, chemotherapy, and immunology extend the range of interest to include not only gynecologic oncologists but all others interested in the correct management of patients with malignant neoplastic disease. While new specialty journals have been initiated and the older established ones have devoted increased space to gynecologic oncology, there has been a definite need for an organized presentation of the large volume of important new and established information as interpreted by experienced clinicians and teachers. Such has been the accomplished endeavor of this book. Its concise format and straightforward presentation give evidence of the authors' experience and the importance of this text and its subject to womankind.

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PREFACE

Gynecologic oncology has evolved as a specialty over the past four decades. However, it was first identified as a subspecialty of obstetrics and gynecology on April 5, 1974. On that day the Division of Gynecologic Oncology of the American Board of Obstetrics and Gynecology examined candidates for special competence in gynecologic oncology. The Division of Gynecologic Oncology recognized the increasing importance of special knowledge areas, techniques, and skills within the discipline and specialty of obstetrics and gynecology.

Although the Division of Gynecologic Oncology has been firmly established as a discipline of obstetrics and gynecology, the greatest number of cases will be first seen, diagnosed, and treated by the nongynecologic oncologist. The purpose of this book is to establish guidelines to help the busy practitioner. The volume of material, the changing concepts, and the new advances in diagnosis and management make it difficult for the clinician engaged in a busy practice to keep abreast of the many changes sweeping over the specialty of oncology. The aim of this book is not originality but, rather, it is directed to bringing current concepts in gynecologic oncology together in a readable format. We have tried to make the presentation concise and practical without being superficial. The book is designed to serve both the needs of continuing education and the optimal delivery of health care.

The bibliographies have been chosen because they have historical value, represent an important point, or cover the most updated material that is available in gynecologic oncology. This provides a broad area of reference for those physicians desiring to explore a given phase of oncology in greater depth than is presented in the book.

A great number of physicians have been discouraged with the results of cancer therapy. However, significant advances have been made in the field of oncology. Among these advances have been: the wide application of the Pap smear, the conquest of gestational trophoblastic disease, the cure of eleven cancers with chemotherapy, the predictable control of eleven additional cancers and a great amount of palliation with chemotherapy, the treatment and rehabilitation of the patient with advanced gynecologic cancer, and the team approach and exciting research in the field of immune complexes and hybridomas.

Although the results, stage for stage, have improved only slightly, the overall mortality rate is decreasing because more patients are having their cancer diagnosed in an early stage of disease. This achievement is to the everlasting credit of the practicing physicians who have, by training and motivation, been successful in being able to advance both professional and public education. This is the keystone of early diagnosis and successful treatment.

The editors are grateful to their respective housestaff for the help, suggestions, and the stimulation they have provided. Colleagues have been most helpful by their interest and the advice that has been generated by our conversations with them. Each editor has some individual gratitude that must be expressed.

One editor (HRKB) wants to express his gratitude to Marcia Miller for her help and encouragement as well as her superb skill in the proofreading of this book. She has been ably helped by Ruzena Danek. Shirley Dansker and her library staff have been most helpful in supplying references, abstracts, and photocopies of important articles. My co-workers, Bridie McGuire and Ann McGuire, have lessened my burden by running my private practice office with their excellent handling of the problems that arise in any private office. To my wife, Mary Louise, I express my thanks and gratitude for her patience and help.

One editor (JRvN) would like to thank the members of the Department of Obstetrics and Gynecology, University of Kentucky Medical Center. To my wife, Betsy, I would like to express my gratitude for her help and encouragement throughout the preparation of this book.

The editors want to express their thanks to John Wright • PSG Inc for their help, support, and the opportunity to bring *Modern Concepts of Gynecologic Oncology* to our colleagues.

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increased use of Papanicolaou tests, regular checkup examinations, as well as improved amniocentesis and postpartum care. There was also a decline in stomach cancer.

However, the lung cancer rate has more than tripled from 4.0 per 100,000 in 1950 to 13.0 in 1975. The death rate increase of smokers of cigarettes over nonsmokers can be estimated by multiplying the number of cigarettes smoked per day by 0.2. Thus, 20 cigarettes smoked each day produces a twofold increase in mortality from lung cancer. This smoking history is made more important by the fact that the risk of lung cancer begins at age 25, 2.5 times the risk for nonsmokers. It should be kept in mind that this mortality excess to be

disregarding the slightly longer smoking history. It should be kept in mind that girls and young women are among the heaviest smoking segments of our population. The proportion of smokers among girls in this age group increased by 2% from 1964 to 1975, a level of 27%. The number who smoke a pack or more of cigarettes a day quadrupled.

The American Cancer Society estimates that 76,400 new genital cancers will be reported in 1981, with invasive cancer of the cervix accounting for 16,000, endometrium 32,000, ovary 18,000 and other genital sites 4400. The deaths due to genital cancer in 1981 are estimated to total 22,700, with 7300 from cervical cancer, 3100 from endometrial, 11,400 from ovarian, and 1000 from other genital sites. It is estimated there will be 45,000 in situ cervical cancers reported in 1981. In 1981 there will be 110,000 new breast cases reported, with 36,800 estimated deaths. Therefore, if the breast is considered part of the upper genital tract, there will be 126,400 new genital cancers and 59,500 deaths. Exclusive of the breast, an estimated 11,000 plus patients will die in

Gynecologic cancer is best divided into the lower and upper genital tracts. The lower genital tract includes the vulva, vagina, and cervix, while the upper genital tract includes the endometrium, tubes, and ovaries, as well as the breast.

Cancer continues to be the second overall cause of death in women in the United States, and is the primary cause in women from ages 35 to 54. The overall incidence of invasive cancer has decreased slightly in the past 25 years. The incidence decreased substantially for cancers of the stomach, uterus, rectum, and esophagus. In general, cancer between the ages of 20 and 40 is three times as common in women as men, but between the ages of 60 and 80, men account for more cancer cases. For women, a decrease in incidence has been noted for cancers of the uterus (both cervical and endometrial), bladder, and stomach. The incidence of breast and colon cancers remains unchanged, but lung cancer has steadily increased. For women, since 1950, the death rate has declined by 8% for blacks and 10% for whites. This is due mainly to a sharp reduction in deaths caused by cancer of the uterine cervix, which is attributed to in-

creased use of Papanicolaou tests, regular checkup examinations, as well as improved antepartum and postpartum care. There was also a decline in stomach cancer.

However, the lung cancer rate has more than tripled from 4.0 per 100,000 in 1950 to 13.0 in 1975. The death rate increase of smokers of cigarettes over nonsmokers can be estimated by multiplying the number of cigarettes smoked per day by 0.5. Thus, 20 cigarettes smoked each day produces a tenfold increase in mortality from lung cancer. This smoking history is made more ominous by an early age of onset of smoking. The beginning of cigarette smoking at age 15 causes this mortality excess to be 2.5 times the risk of the smoker who has begun smoking at age 25, disregarding the slightly longer smoking history. It should be kept in mind that girls and young women are now among the heaviest smoking segments of our population. The proportion of smokers among girls in this age group increased by 5% from 1964 to 1975, a level of 27%. The number who smoke a pack or more of cigarettes a day quadrupled.

The American Cancer Society estimates that 76,400 new genital cancers will be reported in 1981, with invasive cancer of the cervix accounting for 16,000, endometrium 38,000, ovary 18,000 and other genital sites 4400. The deaths due to genital cancer in 1981 are estimated to total 22,700, with 7200 from cervical cancer, 3100 from endometrial, 11,400 from ovarian, and 1000 from other genital sites. It is estimated there will be 45,000 in situ cervical cancers reported in 1981.

In 1981 there will be 110,000 new breast cases reported, with 36,800 estimated deaths. Therefore, if the breast is considered part of the upper genital tract, there will be 186,400 new genital cancers and 59,500 deaths.

Exclusive of the breast, an estimated 11,000 plus patients will die in 1981 of genital cancer, who might have been saved by available methods of early detection followed by prompt, proper treatment. Seventy-two hundred patients died from cervical cancer, even though it is theoretically a preventable disease.

The prevalence rate includes the number of in situ and invasive cancers present in a given population at any specific period of time. The incidence rate indicates the numbers of cancers that are developing at any specified period of time. After the invasive cancers are removed, it is then possible to identify the number of individuals who are developing cancer.

The term "mean" (also called average) is the value which is derived by dividing the sum of the measurements by the total number of measurements, ie, $10, 20, 50, 80, 100 = 260 \div 5 = 52$. The median is the value which lies in the middle of all values when they are placed in sequence, ie, 1, 3, 5, 8, 9, 10, 16, 30. Nine is in the middle and represents the median value. Mode is the value which occurs most frequently.

These measurements of a patient's survival include the observed survival rate, median survival time, and relative survival time. The observed

survival time is a measure of the percentage of patients alive at the end of a specified interval of observation after the date of diagnosis. The actuarial or life table method of calculation is used because it utilizes all survival information accumulated to date. For example, the data available for a report included follow-up information into 1970 or 1971. By employing the life table method, it is possible to compute ten-year survival rates for patients diagnosed in the period of 1955 to 1964, even though the patients diagnosed in 1962, 1963, and 1964 were observed for less than a full ten years.

The median survival is reviewed above. It is the midway point in the survival experiences of a defined group of patients; half have died and half are still alive. For example, for women with cancer of the breast, the median survival is six years. This means that under present conditions a woman with breast cancer has a 50:50 chance of living at least six years after diagnosis.

The relative survival rate is the ratio of the observed survival rate to the survival rate expected in persons drawn from the population at a comparable time, with the same characteristics by race, sex, and age as the patient group.

CERVIX

On the basis of the incidence rates of cancer recorded in the Third National Cancer Survey, it has been calculated that 1.6% of newborn girls, about one out of 63, will develop invasive cancer of the cervix sometime during their lives.

The number of cancer cases diagnosed for a particular site in a given age group depends on the population at risk and the probability of developing that particular cancer at that age. The probability of developing invasive cancer of the cervix uteri increases with age until the menopause, then, after a slight dip, increases slightly and then levels off in older ages. However, the incidence then remains stable for the remainder of life.

The distribution of cases by age for cervical cancer shows the greatest number of cases is found in age groups 40-44 to 45-49 years. The mean age of cases of cervical cancer is 53.8 years, while the median age is 51.5 years.

The incidence rate for all ages in the Third National Cancer Survey compared to the 1947-1948 National Survey by the National Cancer Institute, shows a decrease in cervical cancer from 42.4 per 100,000 population to 17.8 per 100,000 population. The Third National Cancer Survey rates by race also declined. For white females, the rates were down to 15.3

per 100,000 population from 38.4, and, for black females, from 74.6 to 34.2 per 100,000 population. The incidence of cervical cancer is higher in low income groups. Puerto Rican immigrant women have about four times as much cervical cancer as mainland United States women.

Population-based data from the State of Connecticut show a reversal in the frequency of invasive versus in situ carcinomas of the cervix for the time periods 1955-1959 and 1965-1969. In the early period, two thirds of the cancers were invasive, whereas in the latest period two thirds of the cancers were diagnosed while still in situ. Among cancers diagnosed in 1969 and reported by the Third National Cancer Survey, the same relationship of two in situ cancers for each invasive cancer exists. The trend has continued up to the present time.

When the age distribution for patients with cervical cancer is considered, a distinct difference is noted between in situ and invasive diagnoses. Only 9% of women with invasive cancers are under the age of 35 at diagnosis, while 53% of the in situ carcinomas occur in women under age 35.

There has been little improvement in survival since 1950-1959 for patients with invasive cancer of the cervix. About half of these cancers continue to be diagnosed as localized disease and about one-third as regional disease. For black patients diagnosed from 1955 through 1964, the proportion diagnosed in the localized stage was only 40% compared to 52% for white patients, while the proportion of black patients diagnosed with regional involvement was 45% compared to 34% for white patients.

Unfortunately, there are no studies that directly count the mortality of cervical cancer patients with and without early detection. The evidence is less direct and depends on observations of the incidence and mortality of the disease in screened and unscreened populations. For example, if invasive cancer of the cervix is preceded by carcinoma in situ, and if early detection detects and treats carcinoma in situ, the incidence rate of invasive cancer of the cervix should drop. This has been observed in several studies. MacGregor examined women in Aberdeen, Scotland and found the incidence rate of invasive cancer of the cervix among screened women over age 30 to be 55 per 100,000, as opposed to 310 per 100,000 in unscreened women. Data from British Columbia show a similar pattern, with a difference of about 5 per 100,000 to 29 per 100,000 women over age 20. Many biases such as self-selection, immigration and emigration, and misregistration of patients confuse interpretation of these data, but they are very suggestive.

The observed median survival times by age for white patients are: All ages, 6.8 years; under 35, more than 10 years; 35-44, more than 10 years; 45-54, 8.6 years; 55-64, 5.5 years; 65 and over, 2.6 years. For black patients; All ages, 3.5 years; under 35, more than 10 years; 35-44, 7.2 years; 45-54, 2.9 years; 55-64, 2.8 years; 65 and over, 1.8 years.

VAGINA

Cancer of the vagina is the rarest of female genital cancers and is also among the rarest of all female cancers. It is less common than cancer of the vulva. In the Third National Cancer Survey, cancer of the vagina accounted for 0.2% of all female cancers, or a rate of 0.6% per 100,000 females.

Vaginal cancers (see Müllerian clear cell cancer below) are found predominantly in older women. Cancer of the vagina usually occurs after 70 years of age, and well over half of the women are over age 65 at the time of diagnosis.

There are about 300 deaths from cancer of the vagina annually, a rate of 0.2 per 100,000 females or about 0.2% of all female deaths. Since 1960, almost half of the vaginal cancers were diagnosed as localized. About one third of the patients had regional disease while one-sixth were diagnosed with distant metastases. The percentage of women who have localized disease decreases steadily as age increases, from 59% for patients under 45 years of age to 39% for patients 75 years of age and older.

The genital tract is divided into the lower and upper tracts. The lower tract includes the vulva, vagina, and cervix, while the upper tract includes the endometrium, Fallopian tubes, ovary, and the breast.

The observed median survival times by age for white patients are: All ages, 2.6 years; under 45, more than 5 years; 45-54, more than 5 years; 55-64, 2.2 years; 65-74, 2.3 years; 75 and over, 1.4 years. For black patients: All ages, 1.7 years; under 45, 55-64, 65-74, and 75 and over, not available.

VULVA

Cancer of the vulva is not a common cancer. Invasive squamous cell carcinoma accounts for 90% of all malignancy of the vulva. Only 1% to 4% of all female cancers are reported as occurring in the vulva. Melanomas are not included in these statistics. In the Third National Cancer Survey, cancer of the vulva accounted for 0.7% of all female cancers at the rate of 1.8 per 100,000 females. Cancer of the vulva occurs most frequently after the age of 65 years. Over three fourths of all patients with this disease are 55 years of age or older when the disease is diagnosed. Thirty percent of these cancers occur in women 75 years of age or older.

There are about 500 deaths annually in the United States, and the death rate is about 0.3 per 100,000 females or about 0.3% of all female cancer deaths.

The proportional distribution of patients by stage of the disease is that almost two-thirds are diagnosed as localized and about 30% are regional.