IPU
Volume 12

International Perspectives In Urology

John A. Libertino, M.D.
series editor

Bladder Cancer

Edited by
Javadpour

International Perspectives In Urology

Volume 12

John A. Libertino, M.D.
series editor

Bladder Cancer

Edited by

Nasser Javadpour, M.D., F.A.C.S.
Professor and Director of Urologic Oncology
University of Maryland School of Medicine
Baltimore, Maryland
Consultant, National Naval Hospital
Bethesda, Maryland

WILLIAMS & WILKINS
Baltimore/London

Editor: James L. Sangston
Associate Editor: Jonathan W. Pine, Jr.
Copy Editor: Caral Shields Nolley
Design: Bert Smith
Production: Anne G. Seitz

Made in the United States of America

Library of Congress Cataloging in Publication Data

Main entry under title:

Bladder cancer.

(International perspectives in urology ; v. 12)
Includes index.
1. Bladder—Cancer. I. Javadpour, N. 1937–
II. Series. [DNLM: 1. Bladder neoplasms.
W1 IN827K v. 12 /WJ 504 B6311]
RC280.B5B63 1984 616.99'462 84-2223
ISBN 0-683-04356-0

Composed and printed at the
Waverly Press, Inc.

Bladder Cancer

THIS VOLUME IS ONE OF A SERIES

International Perspectives In Urology

EDITED BY
John A. Libertino, M.D.

CURRENT AND FORTHCOMING TITLES

McDougal and Persky
TRAUMATIC INJURIES OF THE GENITOURINARY SYSTEM

Javadpour
RECENT ADVANCES IN UROLOGIC CANCER

Jacobi and Hohenfellner
PROSTATE CANCER

deVere White
ASPECTS OF MALE INFERTILITY

Bennett
MANAGEMENT OF MALE IMPOTENCE

Roth and Finlayson
STONES: CLINICAL MANAGEMENT OF UROLITHIASIS

Donohue
TESTIS TUMORS

Marberger and Dreikorn
RENAL PRESERVATION

Lang
CURRENT CONCEPTS OF URORADIOLOGY

Johnston
MANAGEMENT OF VESICOURETERIC REFLUX

McGuire
CLINICAL EVALUATION AND TREATMENT OF NEUROGENIC VESICAL DYSFUNCTION

Series Editor's Foreword

Cancer of the urinary bladder represents a formidable cause of cancer-related deaths annually. Although 75% of the 35,000 new tumors diagnosed annually in the United States are localized to the bladder, 10,000 people will succumb to this disease on an annual basis. Even though the majority of patients present with localized disease, the age-adjusted death rate has remained virtually the same since 1930. Clearly, advances have been made in the management of bladder cancer, it is reasonable for us from time to time to look at where we are and where we need to go with the management of any disease process.

With this in mind, Dr. Javadpour, Professor and Director of Urologic Oncology at the University of Maryland School of Medicine and consultant at the National Naval Hospital, has brought together the world's most outstanding international authorities on bladder cancer. Together they have provided us with a contemporary overview of bladder cancer, the epidemiologic considerations, pathology, natural history, and the clinical management of superficial and invasive bladder cancer.

This book represents the state of the art in terms of the diagnosis and treatment of bladder cancer. It is a reflection of Dr. Javadpour's commitment to uro-oncology and his dedication to the academic pursuit of our specialty. This textbook on bladder cancer represents the culmination of a great deal of effort on the part of Dr. Javadpour and the contributors, and we hope that it will stimulate others in our field to improve the longevity and quality of life of patients suffering from bladder cancer.

JOHN LIBERTINO

Preface

Cancer of the urinary bladder is a heterogenous disease involving several environmental factors and multistage processes. This disease has contributed to the understanding of carcinogenesis in human and laboratory animals. The first observation in gene-transferring technique was demonstrated in a line of bladder cancer. Also, the advent of cell surface isoantigens, T antigen, chromosomal banding, flow cytometry and utilization of cytology have improved the diagnosis and management of this cancer. In spite of some progress, a number of problems, including role of cystectomy, radiotherapy and finding effective chemotherapeutic regimen, remain unsolved. This book consists of two sections. The first section will review the progress in epidemiology, carcinogenesis, histopathology, cell markers, immunobiology, cytology, diagnosis and staging of bladder cancer. The second section will discuss surgery, radiotherapy, chemotherapy, combination therapy, management of superficial tumors, and clinical and experimental investigations in bladder cancer. A brief synopsis of an overview discusses the progress, problems and state of the art of the disease. This monograph is a part of a series, *International Perspective in Urology*. Its publication would have not been possible without the advice of John Libertino, M.D. of the Lahey Clinic and James Sangston, Senior Editor of Williams & Wilkins.

NASSER JAVADPOUR, M.D.

Contributors

Fernando Algaba, M.D.
Assistant Professor of Pathology
Autonomous University of Barcelona
Barcelona, Spain

Anwer Halim, Ph.D., F.R.C.S.
Senior Urologist
Tawam Hospital
Whittaker Corporation
Al Ain
United Arab Emirates

R. Marian Hicks, Ph.D., D.S.c., F.R.C.Path.
School of Pathology
Middlesex Hospital Medical School
London, England

Gerry B. Hill, M.B., Ch.B., F.R.C.P.(C)
Director, Department of Epidemiology
Alberta Cancer Board
Edmonton, Alberta, Canada

I. Hussain, M.B., F.R.C.S.
Senior Consultant and Head
Department of Urology
Central Hospital
Abu Dahbi
United Arab Emirates

Giovan Battista Ingargiola, M.D.
Institute of Urology
University of Palermo
Polyclinic Hospital
Palermo, Italy

Nasser Javadpour, M.D., F.A.C.S.
Professor and Director of Urologic Oncology
University of Maryland School of Medicine
Baltimore, Maryland
Consultant, National Naval Hospital
Bethesda, Maryland

Alexander W. Miller, M.D.
Associate Director of Laboratory Services
Rush Presbyterian-St. Luke's Hospital
Chicago, Illinois

Alvaro Morales, M.D., F.R.C.S.(C), F.A.C.S.
Professor and Chairman
Department of Urology
Queens University
Kingston, Ontario, Canada

William M. Murphy, M.D.
Pathologist, Baptist Memorial Hospital
Professor of Pathology and Urology
University of Tennessee
Center for the Health Sciences
Memphis, Tennessee

Kevin J. O'Connell, M.D.
Chairman, Department of Urology
National Naval Medical Center
Associate Professor of Surgery, Urology
Uniformed Services University of the Health Sciences
Bethesda, Maryland

Carlo Pavone, M.D.
Institute of Urology
University of Palermo
Polyclinic Hospital
Palermo, Italy

Michele Pavone-Macaluso, M.D.
Institute of Urology
University of Palermo
Polyclinic Hospital
Palermo, Italy

Howard M. Radwin, M.D.
Professor and Chairman
Division of Urology
The University of Texas Health Science Center
San Antonio, Texas

Sameer Rafla, M.D., Ph.D.
Director and Chief of Radiation Therapy
The Methodist Hospital of Brooklyn
Lutheran Medical Center
Maimonides Medical Center
Clinical Professor of Radiation Oncology
State University of New York
College of Medicine
New York, New York

Jerome P. Richie, M.D.
Chief of Urologic Oncology
Departments of Surgery/Urology and Radiation Therapy
Brigham and Women's Hospital and Joint Center for Radiation Therapy
Harvard Medical School
Boston, Massachusetts

Francisco Solé-Balcells, M.D.
Associate Professor of Urology
Autonomous University of Barcelona
Barcelona, Spain

Myron Tannenbaum, M.D., Ph.D.
Chief of Surgical Pathology and Cytopathology
Bronx Veterans Administration Medical Center
Bronx, New York
Professor of Pathology
Mt. Sinai School of Medicine
New York, New York

Maria Tripi, M.D.
Institute of Urology
University of Palermo
Polyclinic Hospital
Palermo, Italy

José Vicente, M.D.
Institute of Urology, Nephrology and Andrology
Fundacion Puigvert
Barcelona, Spain

Ralph R. Weichselbaum, M.D.
Departments of Surgery/Urology and Radiation Therapy
Brigham and Women's Hospital and Joint Center for Radiation Therapy
Harvard Medical School
Boston, Massachusetts

Ezzat Youssef, M.D.
Attending Radiotherapist
The Methodist Hospital of Brooklyn
Lutheran Medical Center
Maimonides Medical Center
Instructor, Downstate Medical Center
New York, New York

Eduardo Zungri, M.D.
Institute of Urology, Nephrology and Andrology
Fundacion Puigvert
Barcelona, Spain

Contents

1

Overview of Bladder Cancer

Nasser Javadpour, M.D., F.A.C.S.

Cancer of the bladder is a heterogeneous disease with a strong environmental and geographic propensity. The epidemiologic studies have pointed to several environmental factors including occupation, diet, coffee drinking, cigarette smoking, certain medications and chronic bladder infections (Table 1.1). Bladder cancer is considered as an environmental model of carcinogenesis with multistage processes including initiating and promoting factors. A number of carcinogens have been shown to possess synergism in induction of bladder cancer such as saccharin and nitrosamines in rats. The most remarkable progress in the understanding of bladder cancer has been in the recognition of the role of carcinogens, initiators, and promoters in a complex setting producing a hetergenous cancer, causing 3000–7000 deaths/year in the United States (Fig. 1.1). The potentiality of the urothelium is shown in Figure 1.2.

Recent investigations utilizing gene transfer technique and hybridizations with normal cell DNA has demonstrated the capability of oncogenes causing uncontrolled cell divisions when transferred to normal cell DNA (Fig. 1.3). As a matter of fact, the initial attempts to demonstrate transforming activity in human tumor DNA resulted in the recognition of an activated cellular oncogene from a cell line of bladder cancer. This development has opened a new avenue for possible detection, diagnosis, and preparation of therapeutic strategies against these targets.[1,2]

PREDICTORS OF RISK

Over the past several years, the advent of cell surface isoantigens, T-antigen, chromosomal analysis, flow cytometry and cytology have improved the detection of high risk and low risk bladder cancer (Table 1.2). Utilizing these markers, we have recognized a high risk, superficial low grade bladder cancer with loss of cell surface isoantigens, chromosomal abnormalities, abnormal cytology and flow cytometry that invariably invade and metastasize, and the patient succumbs. Recognition of this group that does not lend itself to identification by the conventional histopathologic examination allows appropriate initial therapy.

Table 1.1.
Environmental and Occupational Hazards in Bladder Cancer

Carcinogens	Exposure
Nicotine and caffeine	Smoking and ? coffee drinking
Nitrosamines, bracken ferm	Diets
Sweetner, tryptophane	Foods
Phenacetin, chlornaphazine	Medications
Bilharzial cystitis	Egypt and certain other countries
Chronic bladder irritation	Bladder exstrophy, chronic infection
Benzidine, β-naphthylamine	Aniline dye workers
Aromatic residues	Petroleum workers
Benzidine	Laboratory workers
Dye	Leather, textile workers, hairdressers, and spray painters.

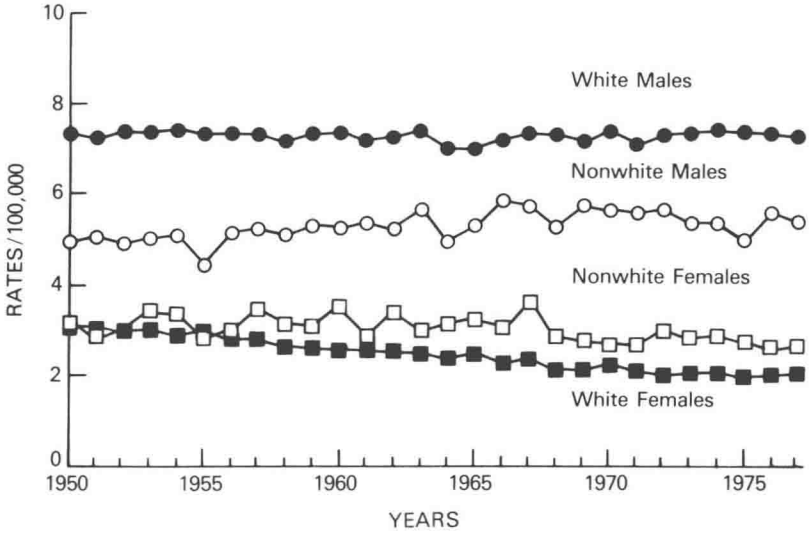


Figure 1.1. Age-adjusted mortality rates of bladder cancer.

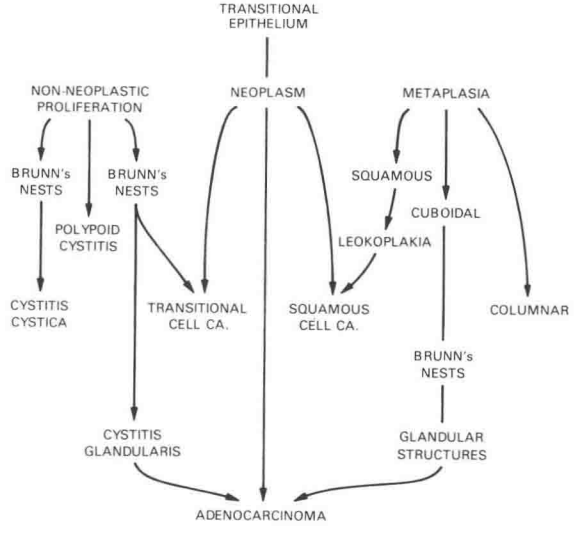


Figure 1.2. Potentialities of bladder epithelium. (From N. Javadpour, *Obstetrics and Gynecology* 35:600, 1970.)

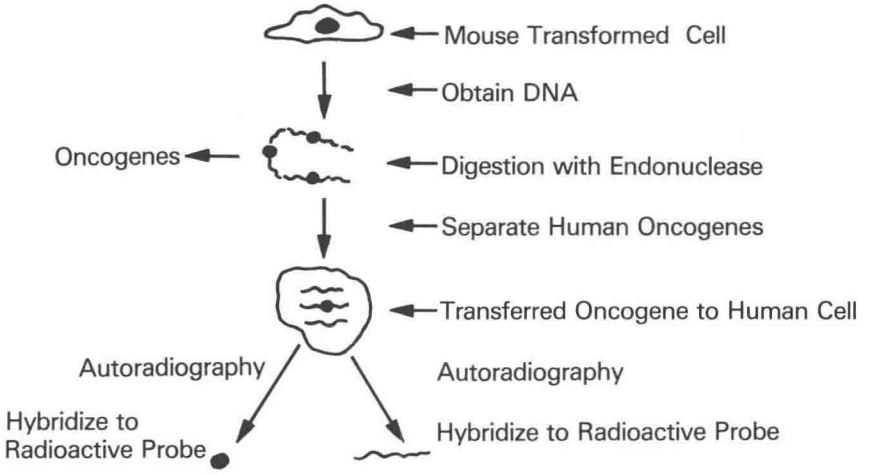


Figure 1.3. Transfer of oncogene and hybridization with DNA.

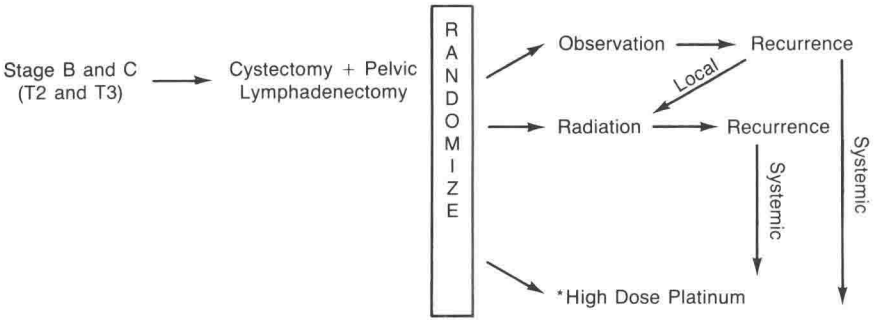
Table 1.2.
Factors Separating Low Risk and High Risk Groups of Bladder Cancer

Parameters	Low Risk	High Risk
Grades	I	III
Stages	0-A	B-D
ABO	Present	Absent
Chromosomes	Normal	Abnormal
Carcinoma *in situ*	Absent	Present
Recurrence	Less frequent	Frequent
Multiplicity	Less	More

tional histopathologic examination allows appropriate initial therapy. The improvements in immunocytochemical techniques, chromosomal banding technique and flow cytometry have made these procedures attractive and more reliable for clinical utilization.

DIAGNOSIS

Application of cytology, recognition of the natural history of carcinoma *in situ* and application of newer radioimaging techniques have improved the diagnosis and staging of these tumors. The use of fine needle aspirations of suspicious lymph nodes and utilization of computed tomograms have also been helpful. However, the clinical staging of the bladder cancer still needs improvement in reducing staging error. The pathology of carcinoma *in situ* has been better clarified. Mostofi has suggested designating carcinoma *in situ* as intraepithelial carcinoma, and grading them into three grades. Grade I represents less anaplastic (atypia), grade III represents more anaplastic (carcinoma *in situ*) and grade II will be an intermediate tumor (dysplasia). This classification is useful because it represents the degree of anaplasia, therefore, the natural history of the tumor. One may add cell surface antigen detection for grades I and II and predict the natural history and propensity for invasion; grade III already has an invasive natural history.



*200 mg/m^2 in 250 ml of 3% saline.

Figure 1.4. Randomized clinical trial with surgery, radiation and high dose platinum in invasive bladder cancer.

ADVANCES IN THERAPY

In treating bladder cancer, one should divide them into the high risk and low risk group based on grade, stage, multiplicity in time and space, cell markers, chromosome and other parameters. Although the low risk patient responds well with conservative endoscopic resection, the high risk group needs more intensive therapy such as radiation and/or cystectomy. Utilization of intravesical chemotherapy including doxorubicin, thiotepa and mitomycin have been shown effective in several controlled studies. The experience of European Organizations for Research and Treatment of Cancer (EORTC) have been reviewed in Chapter 14 on chemotherapy of the bladder cancer. However, doxorubicin, *cis*-platinum, and cytoxan appear to be effective in treatment of disseminated bladder cancer. The role of radiation and its timing is not clear. Randomized clinical trials are necessary to resolve these problems. The role of yttrium-aluminum-garnet (YAG) or Argon laser beam and hematoporphyrin-derivative phototherapy are currently under investigation. The role of immunotherapy, particularly utilization of BCG, has been discussed in a separate chapter. We are embarking on a protocol that randomized the infiltrative bladder cancer into cystectomy, cystectomy with radiation, and cystectomy with radiation and high dose *cis*-platinum. The completion of this protocol will establish the value of radiotherapy and high dose *cis*-platinum as adjuvant therapy in this disease (Fig. 1.4).

The role of clonogenic assay in bladder cancer, as in other cancers, is still experimental and the current technical problems and lack of controlled clinical trials precludes its clinical utilization. The future developments in radioimmunotherapy and chemoimmunotherapy may have potential in diagnosis and management of bladder cancer.

REFERENCES

1. Krontiris, T. G. The emerging genetics of human cancer. *N. Engl. J. Med. 307*:404, 1983.
2. Shih, C., Paddly L. C., Murray M., and Weinberg R. A. Transforming genes of carcinomas and neuroblastomas introduced into mouse fibroblasts. *Nature 290*:261, 1981.

2

Epidemiologic Considerations

Gerry B. Hill, M.B., Ch.B., F.R.C.P.(C)

Traditionally epidemiology has been defined as the study of the distribution of disease, and the determinants of disease, at the population level. The primary orientation of the discipline was always etiological, but it remained separate from other disciplines with similar aims, such as experimental pathology and toxicology. As knowledge concerning a particular group of diseases expands, and in particular when specific causal agents are identified, the relevant disciplines tend to merge.[1] Within this interdisciplinary activity the epidemiologist, although still concerned primarily with disease phenomena in humans, focuses his/her attention more often on small groups of special interest, and increasingly on the biochemical characteristics of such individuals. In addition the contribution of the epidemiologist is more often as a methodologist specializing in the design and interpretation of studies of disease in humans.

The group of diseases encompassed by the term "cancer" is an example of this interdisciplinary convergence. Although the precise mechanisms are not fully understood, a conceptual model in which malignant transformation is seen as a multistage process initiated by specific agents and promoted by others is generally accepted. The majority of tumors arise in the epithelial cells exposed to external carcinogens or to those present in excretions and secretions. The evidence for this hypothesis in relation to bladder cancer has been reviewed recently.[2]

Multidisciplinary research would look beyond etiology and include also the reaction of the host and the response to treatment. In the content of bladder cancer a coordinated multidisciplinary program of research has been described,[3] aimed at reducing the morbidity and mortality associated with the disease.

As part of the research effort underlying a rational program of cancer control, three separate but related roles for the epidemiologist emerge:

1. Quantifying the impact of the disease in terms of incidence, mobidity and mortality.
2. Quantifying the importance of known causal agents and identifying others.