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Bladder
Cancer



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Bladder Cancer

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AMERICAN UROLOGICAL ASSOCIATION
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Bladder Cancer

Preface

To urologists everywhere this volume offers the subject matter of a recent AUA Seminar on bladder cancer.

The on-site seminar participants, with a unique faculty, explored the subject in great depth through presentation and free discussion. We have tried to capture all of this. Additional authors round out the topics for a glimpse of future clinical urology.

We hope you find this material highly relevant to your own practice.

William W. Bonney

George R. Prout, Jr.

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ISSUES AND QUESTIONS:

A Reader's Guide

Like any coverage of a subject in depth, this symposium provided answers and new concepts but also raised a number of controversies and questions. This section is a guide to some of the controversial issues raised, to help follow the thread of each issue through the various chapters.

Origins of Transitional Carcinoma

Is bladder cancer caused by exogenous carcinogens?

Yes, probably. Various chemicals have been implicated (to date no viruses), and clinicians should watch for clues to the identification of specific agents.

| | |
|-----------|---------------|
| Chapter 1 | p. 5 |
| Chapter 2 | pp. 13-17, 20 |

Is bladder cancer multifocal in origin ("field change") or monoclonal with ready dissemination to other parts of the bladder?

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| The issue is outlined in Chapter 3. | p. 29 |
|-------------------------------------|-------|

| | | |
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| A multifocal change would be the expected outcome of repeated exposure to external factors. | Chapter 2 | p. 12 |
|---------------------------------------------------------------------------------------------|-----------|-------|

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| The field change concept finds support in data from serial mucosal biopsies, in mapping studies of CIS in cystectomy specimens, and in longitudinal studies of tumor recurrence. | Chapter 4 | p. 45 |
| | Chapter 13 | p. 153 |
| | Chapter 14 | p. 161 |

Does elevated residual urine volume predispose to bladder cancer?

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|---------------------------------------------------------------------|-----------|----------|
| Probably, if stepwise carcinogenesis requires a long exposure time. | Chapter 1 | p. 5 |
| | Chapter 2 | p. 18-20 |

| | | |
|-----------------------------------|------------|--------|
| The answer is not directly known. | Chapter 16 | p. 181 |
|-----------------------------------|------------|--------|

Intravesical Dissemination of Bladder Cancer

Is the cancer spread by tumor cell shedding and remote implantation?

| | | |
|------------------------------------------|------------|-------------|
| There is good evidence for this concept. | Chapter 3 | pp. 30-31 |
| | Chapter 13 | pp. 152-153 |
| | Chapter 16 | pp. 181-182 |

| | | |
|----------------------------------------------------------------------------------------------|------------|------------|
| An equally plausible, biopsy proven mode of spread is lateral intraepithelial spread of CIS. | Chapter 3 | pp. 29, 30 |
| | Chapter 14 | p. 161 |

Is it spread by transurethral prostatic biopsy?

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|----------------------------------------------------------------------------------------------|------------|-------------|
| Some consider such a biopsy mandatory in selected cases, but its safety has been questioned. | Chapter 16 | pp. 179-181 |
|----------------------------------------------------------------------------------------------|------------|-------------|

Are other endoscopic procedures implicated?

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| Irritation of normal bladder mucosa by cystoscopic irrigation fluid or an indwelling Foley catheter. | Chapter 3 | pp. 30-31 |
| | Chapter 16 | p. 182 |

Screening Program with Urinary Cytology

Is routine screening justifiable in high risk, clinically normal populations?

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|---------------------------------------------------------------------------------------------|------------|--------|
| Some yes on the basis of single center experience. | Chapter 10 | p. 114 |
| Others say no because to date no one has shown increased survival as a result of screening. | Chapter 10 | p. 115 |

Everyone agrees to repeated cytologies in known bladder cancer patients at high risk for recurrence or progression to invasive disease.

*Tumor Markers:
Blood Group Antigens*

What is the basis for this test?

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|-------------------------------------------------------------------------------------------------------------------------|-----------|-----------|
| The blood group antigens (BGAg's) are genetically determined and appear on the surface of normal and neoplastic cells. | Chapter 7 | p. 71 |
| Among morphologically similar superficial tumors, BGAg loss correlates with subsequent progression to invasive disease. | Chapter 7 | pp. 71-72 |

Is this a clinically useful test?

| | | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|------------|
| Current evidence suggests that BGAg loss can distinguish those patients who warrant potentially curable cystectomy from those who do not need it. | Chapter 16 | p. 199 |
| However, many feel that the assay still belongs in the research laboratory, that it is still too expensive and that technical refinements are needed to make it more sensitive with fewer false results. | Chapter 7 | pp. 73-750 |
| | Chapter 10 | p. 113 |
| | Chapter 16 | p. 196 |

Tumor Markers: Karyotype

What is the basis for TCC karyotype studies?

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|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------|
| Normal urothelial cells have a very constant chromosome number with normal chromosome morphology, whereas bladder cancer cells have much variation with frequent abnormal chromosomes. | Chapter 8 | pp. 87-88 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-----------|

Could karyotype studies help to stage our patients?

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| Potentially yes, because the above abnormalities correlate with invasive disease and suggest the need for aggressive treatment. | Chapter 8 | pp. 88-91 |
|---------------------------------------------------------------------------------------------------------------------------------|-----------|-----------|

Could it play a role in clinical management?

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|--------------------------------------------------------------------------------------------------------------------------------|------------|--------|
| Potentially yes, to establish the neoplastic potential of biopsy-proven CIS and to make urine cytology studies more sensitive. | Chapter 8 | p. 93 |
| Not at the present time, because these studies are expensive, time consuming and require absolutely fresh tumor tissue. | Chapter 10 | p. 113 |

Tumor Markers: Electron Microscopy (EM)

What is the basis for this study?

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|-------------|
| Under scanning EM there are pleomorphic microvilli on early animal tumors, on human TCC cells, and possibly in biopsies of adjacent normal mucosa. This may represent an early, irreversible commitment to neoplasia. | Chapter 9 | pp. 97-98 |
| These changes are not seen in normal, radiated, of inflamed biopsies and seem to correlate with a high risk for tumor recurrence in TCC patients. | Chapter 9 | pp. 101-103 |

Could it be used in screening?

| | | |
|-----------------------------------------------------------------------------------------------------------------------------|-----------|-----------------|
| These changes are present in cytological specimens, even in well differentiated tumors not detectable by standard cytology. | Chapter 9 | pp. 97-100, 105 |
|-----------------------------------------------------------------------------------------------------------------------------|-----------|-----------------|

Host Immune Response

What is the basis for an assay of host immunity?

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------|
| Histocompatibility antigens are genetically determined and occur on normal and neoplastic cells. Closely related tumor specific antigens are probably determined by the abnormal neoplastic genes and can stimulate a host immune response. | Chapter 11 | p. 126 |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------|

Is this useful for cancer diagnosis and treatment?

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|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-------------|
| Animal experiments prove that a host can reject a tumor and survive while control animals succumb. | Chapter 11 | pp. 122-123 |
| However, at the present time human tumor specific antigens have not been sufficiently well isolated. Tissue culture assays of immune response are difficult to interpret. There is no proof that a break-down of "immune surveillance" plays any role in the origin of TCC. | Chapter 11 | pp. 123-124 |

Pretreatment Evaluation of the Cancer Patient

How accurate is classification and staging as practiced today?

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| Not very accurate for patients with clinically localized invasive bladder cancer, in that many of these patients are not cured by radical cystectomy. | Chapter 12 | p. 140 |
| The new AJC classification helps to define the sources and quality of information and to clarify the patient's changing stage with disease progression. | Chapter 18 | pp. 237-240 |
| | Chapter 12 | pp. 133-146 |

At the time of clinical staging would it help to include additional, new factors?

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| Yes. Promising new predictors of stage include microscopic invasion of lymphatic vessels in the primary tumor. | Chapter 12 | pp. 141-142 |
| One can also determine the extent of superficial disease by prostatic urethral biopsies and by cytology of the upper urinary tract in appropriate situations. | Chapter 16 | pp. 179-180, 183, 185, 189-193, 195, 203-206 |

Recurrence and Progression of Superficial Disease

After apparently complete destruction, superficial cancer often recurs in the bladder. What factors can predict this recurrence?

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| Several features of the initial tumor: multiplicity, size, invasion of underlying tissue, histological grade, and positive biopsies in adjacent mucosa. | Chapter 4 | pp. 43-44 |
| | Chapter 12 | pp. 136-137 |
| | Chapter 14 | p. 160 |

What factors can predict progression of superficial bladder tumor to an invasive, metastatic type of disease?

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|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------------|
| There is some opinion that superficial disease (including CIS) is a separate entity that may vary histologically over time but will never progress to invasive disease. | Chapter 1 | p. 6 |
| | Chapter 16 | p. 189 |
| Others feel that both CIS and well differentiated papillary tumors do progress to invasive disease. | Chapter 12 | p. 136 |
| | Chapter 14 | pp. 160, 162 |
| Longitudinal studies suggest that progression to invasive disease, when it does occur, can be seen within 2 years. | Chapter 4 | p. 44 |
| Initial tumor predictive factors for invasion may include a higher histological grade, the presence of positive mucosal biopsies adjacent to known tumor, and invasion of the primary tumor into lymphatic vessels. | Chapter 4 | p. 44 |
| | Chapter 12 | pp. 136, 141 |
| | Chapter 14 | pp. 161-162 |
| In regard to the concept of progression from superficial to invasive disease, theoretical pro's and con's are presented. | Chapter 1 | pp. 3-11 |

Diagnosis of Superficial Disease

Why has CIS just now become so important?

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|------------------------------------------------------------------------------------------------------------------------------|------------|-------------|
| It was previously regarded as a premalignant condition only, but it may in fact be a separate disease with unique prognosis. | Chapter 16 | p. 197 |
| It is not always cystoscopically recognizable, and its diagnosis requires special procedures. | Chapter 14 | pp. 161-162 |
| | Chapter 16 | p. 182 |

Is cytology important to diagnose superficial disease?

Yes, positive cytology correlates closely with high histological grade. In cases where the known tumor is well differentiated, a positive cytology suggests the presence of higher grade, undetected CIS and therefore predicts recurrence following TUR.

Chapter 5 pp. 59–60
 Chapter 14 p. 162
 Chapter 16 pp. 176, 182

Upper tract TCC can best be demonstrated by catheterized urine cytology or brush biopsy.

Chapter 16 pp. 183, 185

Management of Superficial Disease

Do the conservative open surgical procedures (segmental resection or cystotomy with loop resection) have a legitimate place?

Most urologists would avoid opening the bladder for loop resection, although a thorough mucosal stripping might be combined with radiation therapy for severe disease if the patient refused cystectomy.

Chapter 16 p. 202

Segmental cystectomy should be considered only for solitary tumors high on the dome or lateral wall with mucosal biopsies all negative.

Chapter 16 pp. 183–184

Some would manage even the largest superficial tumors by TUR and would always avoid segmental resection, citing the high postoperative recurrence rate; while others have had good results with segmental resection, especially in combination with intravesical chemotherapy.

Chapter 16 pp. 184,
202–203

How about radiation therapy for superficial disease?

Preoperative radiation therapy is theoretically unnecessary because superficial disease does not invade or metastasize. Even the most extensive, diffuse tumor can be cured by cystectomy alone.

Chapter 16 p. 202

Where definitive radiation therapy is given, 50% of patients have residual tumor and become potential candidates for salvage cystectomy.

Chapter 16 pp. 201–202

When is total cystectomy indicated?

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|-------------------------------------------------------------------------------------------------------------------------|------------|-------------|
| When severe bladder symptoms, positive mucosal biopsies, and positive cytology persist after intravesical chemotherapy. | Chapter 16 | pp. 203-204 |
| Persistent local tumor after definitive radiation therapy. | Chapter 16 | p. 185 |
| Invasion of the tumor into the prostatic urethra, duct, and parenchyma. | Chapter 16 | pp. 189-196 |

In the asymptomatic patient with positive cytology or biopsies after intravesical chemotherapy, how long would you treat and follow the patient before considering total cystectomy?

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| On the basis of experience in single centers, 6-12 months. After the first series of instillations had failed, most would begin a second series before considering cystectomy. | Chapter 14 | p. 162 |
| | Chapter 16 | pp. 175-176, 187, 204 |

Topical (Intravesical) Chemotherapy

Has intravesical chemotherapy found its place in superficial bladder cancer treatment?

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|--------|
| Yes, in that most urologists agree on its use after an incomplete TUR and in bladders with multifocal tumors or diffuse CIS (predictors of high recurrence rate). | Chapter 14 | p. 160 |
| | Chapter 15 | p. 167 |
| No, because large questions remain unanswered regarding its effect on ultimate survival, subsequent metastatic disease, delayed toxicity, optimal dose, and cost effectiveness when given immediately after TUR. | Chapter 15 | p. 168 |

How about prophylatic (immediate post TUR) thiotepa—is it safe? Is it effective?

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|--------------------------------------------------------|-------------|--------|
| Many use it on a regular basis and have found it safe. | Chapter 16, | p. 178 |
|--------------------------------------------------------|-------------|--------|