CURRENT CLINICAL UROLOGY

ERIC A. KLEIN, MD, SERIES EDITOR

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This book is dedicated to William Joseph Amato, an individual who has contributed greatly to my personal and professional development. He is my friend, my confidant, and my husband.

We also dedicate this book to the memory of Dr. Saroja Adusumilli.
Preface

Bladder cancer continues to be a major disease affecting the healthcare system in the United States, consuming almost $3 billion annually. Patients at low risk for disease-related death require long-term surveillance because of high recurrence rates. Treatment of intermediate- and high-risk disease requires complex management that is often misapplied due to difficulties in tumor staging and uncertainty about the natural history of non–muscle-invasive cancers. Radical surgery for muscle-invasive disease is underutilized because of concerns about complications, surgical technique, altered quality of life, and diminished reimbursement. Neoadjuvant chemotherapy is rarely incorporated in the management of locally advanced tumors, despite mounting evidence that it offers a modest, but real, survival advantage. Metastatic disease remains a deadly condition, as systemic therapies are largely palliative and not curative. Taken together, there are many challenging hurdles for clinicians when managing patients with this disease. Unfortunately, real progress in improving life expectancy from the disease has been slow.

A fundamental lack of clinical research in the field, coupled with disproportionately low funding from federal and foundation sources, has limited advances in multidisciplinary bladder cancer care. As a result, our practice patterns in 2008 are surprisingly similar to those in 1988. In consideration of the major challenges facing patients and providers, we developed this text focused on clinical management. Within Bladder Cancer: Diagnosis, Therapeutics, and Management, a group of accomplished authors examine emerging techniques and strategies developed to address common clinical scenarios. Authors provide insight into obstacles to improved survival, discuss methods to advance the field, and review the related supporting evidence. Our intended goal in creating this text is not to create a summary of bladder cancer, but to spur innovative thoughts and approaches to common problems in the management of early and advanced stage of the disease.

The book consists of four parts addressing diagnostics, surgical technique, and multidisciplinary care. Part I is dedicated to bladder cancer staging, which continues to plague clinicians who unknowingly understage 40–60% of patients. Inaccurate staging greatly undermines therapeutic efficacy and often leaves the patient undertreated. This section particularly focuses on understaging of invasive bladder cancer as well as improved pelvic staging with updated imaging. Part II addresses optimization of treatment for localized disease. Novel approaches to intravesical therapy are discussed, as are specific surgical techniques used to ensure cancer control but also provide improved organ preservation and quality of life. Part III briefly reviews applications of existing systemic therapies in the treatment of locally advanced tumors and metastatic disease. Consideration is given to new types of systemic therapies used in combination with standard drugs to provide a synergistic effect. Finally, Part IV is devoted to a discussion of infrastructure needed to support the translational research efforts that will propel this field forward. Contributors in this and earlier sections represent a mix of seasoned veterans and junior scientists representing the next generation to embrace novel technologies and innovative practice strategies.

Ann Arbor, MI, USA Cheryl T. Lee
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Part I

Improving Bladder Cancer Staging
1

Approaches to Carcinoma In Situ (CIS)

J. Stephen Jones

Abstract Despite its traditional categorization as “superficial,” Carcinoma in situ (CIS) is a high grade, flat, noninvasive bladder cancer confined to the urothelium. Bladder biopsy is required to establish a diagnosis. Cytology to examine voided or bladder wash urine can allow identification of malignant cells, but failure to recognize such cells does not rule out CIS. Options to improve cystoscopic recognition of malignant areas such as fluorescence cystoscopy and narrow band imaging are promising developments. A number of tumor markers have been developed. Most have high sensitivity, but these tests have varying specificity. The urologist must understand the implications of a negative or positive test in order to successfully integrate these tests into clinical practice.

Keywords Carcinoma in situ, Cytology, Cystoscopy, Intravesical therapy, Surveillance

1. Introduction

Malignant urothelial tumors confined to the bladder mucosa are accurately termed nonmuscle invasive instead of being given the traditional “superficial” label (1, 2). The traditional term suggested that all such tumors shared the relatively benign course of low grade papillary tumors. In contrast, patients with highly malignant lesions, including carcinoma in situ (CIS), actually have a serious prognosis if not recognized and treated successfully. CIS is often
mischaracterized as “premalignant” (3), but by definition it is actually a flat, noninvasive high grade urothelial carcinoma (UC) (Figs. 1 and 2). CIS is regarded as a precursor lesion for the development of invasive high-grade cancer that has simply been identified prior to invasion of the lamina propria. These lesions comprise 10% of bladder cancer (4).

The presence of CIS is usually suspected by hematuria or irritative voiding symptoms. Patients with macroscopic (gross) hematuria have reported rates of bladder cancer of 13–34.5% (5, 6). Bladder cancer is identified in 0.5–10.5% of patients with microscopic hematuria (7–10). The presence of irritative voiding symptoms doubled the risk in one study (5 vs. 10.5%) (10). The Mayo Clinic reported that 80% of patients with CIS presented with irritative symptoms (11). In a large review of patients diagnosed with interstitial cystitis, 1% had a missed diagnosis of CIS or UC. Two-thirds of these patients did not have hematuria (12). The presence of irritative voiding symptoms has been associated with diffuse disease, invasion, and a compromised prognosis, but there is no consensus on this finding in the literature (1, 3). Thus, cystoscopy and upper tract imaging are indicated in patients with hematuria and/or unexplained irritative symptoms (13).

### 2. Pathology

The bladder has three histological layers: (1) urothelium, (2) suburothelial loose connective tissue (lamina propria), and (3) detrusor or muscularis propria. CIS is a flat, high-grade lesion confined to the lamina propria. The TNM staging system for nonmuscle invasive tumors is shown in Fig. 1.1.

CIS lesions are comprised of severely dysplastic urothelium, and in older series were often categorized as “severe dysplasia.” Disorderly histology with nuclear atypia characteristic of high-grade malignancy is microscopically diagnostic. Denudement of some or all of the mucosa due to loss of cellular cohesion is often identified. Most pathologists consider mild versions of dysplasia or atypia to be benign. However, lesions interpreted as severe dysplasia or severe atypia are now regarded as being the same entity as CIS (2). Precise communication between pathologist and urologist can minimize the risk for misinterpretation.

Between 40 and 83% of patients with CIS will develop muscle invasion if untreated, especially if associated with papillary tumors (14). Among patients believed to have CIS alone, as many as 20% who are treated with cystectomy are found to contain invasive...
solid tumors on final pathology (15). The presence of CIS in cystectomy specimens performed for presumed T1 tumors was associated with upstaging in over half of the patients, compared to 6% upstaging in patients without CIS, in a recent series (16). Multicentricity of CIS is especially prone to progression (17). In a large series, presence of CIS was the second most important prognostic factor after grade (18).

There is a substantial risk of underestimation of the probability of progression in some patients with presumed “superficial” disease, and the risk of underestimation of the disease status based on sampling errors as shown in Tables 1.1 and 1.2.

3. Endoscopic Diagnosis

The goal of endoscopic biopsy is to provide specimens for pathological examination, and to remove all visibly abnormal tissue. Due to its tendency for multifocality, complete endoscopic eradication is often not feasible. Excessive use of electrocautery causes cellular reorientation and creates difficulty in the interpretation the pathology, so “cold cup” biopsies are the mainstay of diagnosis. Sampling of erythematous or otherwise suspicious mucosa is occasionally the source of tissue diagnostics for CIS, but normal-appearing tissue in patients with positive or suspicious cytology is often the actual site of CIS as described below.

A number of “tumor markers” have been developed to assist in the management of these patients. Several are approved in the United States for surveillance in patients with known bladder cancer, but most are not approved for initial diagnosis or screening, so are considered below along with conventional urinary cytology in the section labeled “Surveillance Strategies.”

4. “Random” Biopsies

CIS can exist in normal-appearing urothelium, so some random biopsies are often performed to identify CIS in patients undergoing surgery for visible tumors, in patients with positive cytology, or in those following intravesical or surgical therapy. However, the value of doing so is largely unproved. Random biopsies in high-risk patients were positive in 12.4% in one report, and altered treatment in 7%, including 14 of 1,033 patients in whom the only positive tissue was in the random biopsy – not in the area appearing abnormal (19). However, even when velvety red patches were biopsied in one report, only 11.9% of samples were positive (20). Fujimoto et al. prospectively evaluated the role of random biopsies of normal-appearing
urothelium and found cancer in only 8 of 100 biopsies, five of which were CIS. They concluded that random biopsies are indicated only in the setting of multiple tumors or positive cytology (21). An EORTC retrospective review concluded that random biopsies were not warranted because only 10% were positive (3.5% CIS) (22). As a result, current consensus is that random biopsies are not indicated in low-risk patients, i.e., those with low-grade papillary tumors and negative cytology, but may be of value in high risk patients such as those with high grade or multiple tumors, especially in patients with a history of CIS. Random biopsies are always indicated in the setting of a positive urinary cytology in the absence of abnormal cystoscopic findings.

Prostatic urethral biopsy using the cutting loop will occasionally identify urethral CIS, but bleeding may be more common (23). The theoretical risk that random biopsies provide an exposed bed for tumor implantation must be weighed against the additional value of the information obtained (24–26).

5. Diagnostic Strategies Following Intravesical Therapy

American urologists use BCG by a 2:1 margin compared to intravesical chemotherapy, whereas European urologists favor chemotherapy. The initial tumor-free response rate is as high as 80% (27–30). Approximately 50% of the patients experience a durable response for a median period of 4 years. Over a 10-year period, approximately 30% of the patients remain free of tumor progression or recurrence, so diligent surveillance is mandatory. The majority of these occur within the first 5 years (31). Herr reported progression in 19% of initial responders at 5 years, but 95% in nonresponders – findings confirmed by other investigators (32, 33).

The necessity of biopsy to determine a BCG response is unclear, although it should be strongly considered in high risk patients to determine disease status at this key point in time. Urine cytology can be useful in this setting, as a positive result is in essence

Table 1.1. Estimates of disease progression in nonmuscle-invasive bladder cancer WHO/International society of Urological Pathology Consensus Classification (source: [102]).

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>% Relative frequency</th>
<th>% Progression</th>
<th>% Deaths</th>
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<tr>
<td>Noninvasive</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Papilloma</td>
<td>10</td>
<td>0–1</td>
<td>0</td>
</tr>
<tr>
<td>PUNLMP</td>
<td>20</td>
<td>3</td>
<td>0–1</td>
</tr>
<tr>
<td>Papillary cancer low grade (TaG1)</td>
<td>20</td>
<td>5–10</td>
<td>1–5</td>
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<tr>
<td>Papillary cancer high grade (TaG3)</td>
<td>30</td>
<td>15–40</td>
<td>10–25</td>
</tr>
<tr>
<td>Invasive</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Papillary cancer (T1G3)</td>
<td>20</td>
<td>30–50</td>
<td>33</td>
</tr>
<tr>
<td>CIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td>10</td>
<td>&gt;50</td>
<td>–</td>
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<tr>
<td>Secondary</td>
<td>90</td>
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Table 1.2. Risk of understaging when cystectomy is performed for presumed nonmuscle-invasive disease (source: [103]).

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<th>Institution</th>
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<th>Risk (%) of understaging</th>
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<td>Urology and Nephrology Center Mansoura, Egypt</td>
<td>1997</td>
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<td>Stein et al.</td>
<td>USC</td>
<td>2000</td>
<td>39</td>
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<tr>
<td>Dutta et al.</td>
<td>Vanderbilt</td>
<td>2001</td>
<td>40</td>
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<td>Bianco et al.</td>
<td>Wayne State University</td>
<td>2004</td>
<td>27</td>
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<tr>
<td>Bayraktar</td>
<td>Vakif Gureba Hospital Urology Department</td>
<td>2004</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Aksaray-Istanbul, Turkey</td>
<td></td>
<td></td>
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<tr>
<td>Huguet et al.</td>
<td>Servicio de Urologia, Fundacion Puigvert Barcelona</td>
<td>2005</td>
<td>27</td>
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<tr>
<td>Ficarra et al.</td>
<td>University of Verona, Italy</td>
<td>2005</td>
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1. Approaches to Carcinoma In Situ (CIS)

a positive biopsy of the shed urothelium. Dalbagni reported minimal utility in routine biopsy following BCG if cystoscopy and urinary cytology were both negative. Whereas 5/11 patients with erythematous bladder mucosa and positive cytology had positive bladder biopsies, none of 37 with erythematous lesions and negative cytology was positive, and only 1/13 patients with a normal mucosa had positive biopsies (34). Other studies have suggested that the value of routine post-BCG biopsy is limited (35).

UroVysion FISH (Abbott Molecular, Chicago IL. See below) conversion from positive to negative has been shown to correlate with BCG response in a single-center study (36).

Declaring failure may take up to 6 months, as the response rate for patients with high grade bladder cancer treated with BCG rose from 57 to 80% between 3 and 6 months after therapy. Tumoricidal activity clearly continues for some period after cessation of therapy. This has obvious implications not only for declaring BCG failure and the need for subsequent therapy, but also for the interpretation of success rates of salvage protocols if administered soon after therapy (37).

6. Fluorescence Cystoscopy

Endoscopically, urologists suspect CIS on the basis of the presence of visible changes such as mucosal edema, denudement or “red spots.” However, CIS often creates no visible abnormalities, and it appears likely that the classic visible changes may be due solely to an inflammatory reaction and not to the actual CIS. A multicenter study found that 37% of the biopsies performed on the basis of suspicious endoscopic findings resulted in false negative biopsy (38). The failure of cystoscopy to identify all tumor for removal potentially explains the high rate of cancer recurrence soon after complete removal of all visible tumors (tumor cell implantation also contributing as described above). The most complete consideration of such issues has been in studies of fluorescence cystoscopy as described in the following chapter.

7. Molecular Aspects of CIS

Like most malignancies, CIS is a genetic disease. Chromosomal alterations caused by oxidative DNA damage create genetic abnormalities in tissues of the affected organ. There appear to be two separate genetic pathways leading to the development of urothelial carcinoma (39, 40). One leads to noninvasive, papillary tumors that tend to recur frequently, but rarely progress. These cancers usually follow an indolent course unless they convert to the second pathway, which occurs in less than 5% of cases (41). The second pathway leads to the development of CIS and ultimately to its natural outcome of invasive high-grade cancer.

Such genetic alterations can be evaluated using karyotyping, microsatellite analysis for allelic imbalance (42), comparative genomic hybridization (43), DNA ploidy analysis by flow cytometry (44), or fluorescence in situ hybridization (FISH) of probes or labels to site-specific chromosomal abnormalities (45). These technologies have allowed for the discovery that noninvasive papillary tumors tend to demonstrate relatively few chromosomal abnormalities, primarily involving loss of all or part of chromosome 9 and its p16 tumor suppressor gene at the 9p21 locus. In contrast, high-grade tumors (whether CIS, T1, or invasive) tend to have numerous and greatly variable chromosomal gains and losses. In addition to their relatively predictable aneuploidy, high-grade tumors also often have loss of all or part of chromosome 9 as the initial step in malignant degeneration (46).

Currently there is no known molecular marker to accurately predict progression from CIS to invasive disease. However, p53, pRb, or other molecular markers have been proposed as potential predictors of prognosis. Patients with p53-negative lesions progress 25% of the time, compared to the 75% progression rate for p53 positive lesions. Ten-year survival is 60% in patients with p53-positive lesions, and 88% in patients with p53-negative lesions (54). Nuclear p53 overexpression before BCG therapy has not been shown to predict response to therapy, but posttherapy p53 overexpression suggests a high likelihood of the disease progression (55, 56).

Other studies have failed to find a clear role for p53 status, so the role of p53 for the prediction of tumor behavior and response to therapy remains unclear, but the subject of intense investigation (57).
Multiple investigators are pursuing molecular markers to predict progression as well as markers to provide therapeutic targets.

8. Surveillance Strategies

According to the Agency for Health Care Policy and Research, annual expenditures are $2.2 billion for bladder cancer vs. $1.4 billion for prostate cancer (Donat 2003, 58 (102)). A significant portion of this cost is due to the potential need for lifelong surveillance, especially in high risk patients such as those with CIS (58).

Despite these financial resources, in an era of high-technology medical diagnostics, UC surveillance remains dominated by subjective modalities that rely on phenotypic alterations significant enough for the interpreter to differentiate the malignant from the normal structure (cystoscopy) or histology (conventional urinary cytology). Most protocols include this combination every 3 months for 18–24 months after the initial diagnosis, then every 6 months for the following 2 years, and then annually, resetting the clock with each newly identified tumor (59). Their traditional presumed status as the “gold standard” has been widely accepted despite evidence that both suffer from accuracy limitations (60). In addition, only 40% of patients fully comply with a standard surveillance protocol (61).

General guidelines for bladder cancer surveillance are shown in Table 1.3.

9. Cystoscopic Surveillance

Cystoscopy is a rapid, relatively painless method to visualize the urothelium in the office setting. The endoscopic appearance of CIS is classically described as a velvety red mucosal patch, although this finding has been shown to be unreliable as discussed above. The role of cystoscopy as a “gold standard” in cancer detection has come under scrutiny with the emergence of tumor markers and the development of newer endoscopic technology, including fluorescence cystoscopy (62).

Most lesions believed to be malignant are proven so pathologically, although the classic description of CIS is often absent (63, 64). Flexible fiberoptic cystoscopes are almost as sensitive, and are markedly more comfortable for men compared to rigid rod lens systems (65, 66), although there is no clear advantage to their use in women due to the short, relatively straight female urethra. Phase II studies reportedly show that flexible office-based fluorescence cystoscopy can improve the detection of CIS (67, 68). Moreover, the use of Narrow Band Imaging or NBI (Olympus Surgical, USA) in order to define differences in tissue vascularization has allowed identification of CIS in areas that appear normal by white light cystoscopy (unpublished data). This technology is under consideration for approval by the U.S. Food and Drug Administration (FDA) based on previous and ongoing investigations at our institution.

The vast majority of both men and women tolerate office-based cystoscopy with minimal discomfort.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Tumor status</th>
<th>Cystoscopy schedule</th>
<th>Upper tract imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Solitary TaG1</td>
<td>3 months following initial resection</td>
<td>Not necessary unless hematuria present</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annually beginning 9 months after initial</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>surveillance if no recurrence</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider cessation at 5 or more years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider cytology or tumor markers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>Q 3 months for 1–2 years</td>
<td>Consider imaging, especially for recurrence</td>
</tr>
<tr>
<td></td>
<td>Multiple TaG1</td>
<td>Semiannual or annual after 2 years</td>
<td>Imaging for hematuria</td>
</tr>
<tr>
<td></td>
<td>Large tumor</td>
<td>Consider cytology or tumor markers</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence at 3 months</td>
<td>Restart clock with each recurrence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>Q 3 months for 2 years</td>
<td>Imaging annually for 2 years, then consider lengthening interval</td>
</tr>
<tr>
<td></td>
<td>Any High Grade (inc. CIS)</td>
<td>Semiannual for 2 years</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annually for lifetime</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cytology at same schedule</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider tumor markers</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Restart clock with each recurrence</td>
<td></td>
</tr>
</tbody>
</table>
Most studies have failed to identify benefit to intrarethral lidocaine injection (69, 70), and recent studies actually found that the experience of pain was higher with the use of local anesthetics than in patients cystoscoped using aqueous lubricant alone (71–73). Use of a video monitor allows the patient to see and understand the findings, theoretically distracting them from discomfort. Men who are unable to do so experience almost twice as much pain (14.1 vs. 22.9 $p < 0.01$) as those who can see their findings on the monitor. This has not been found to be of significant benefit in women for unclear reasons (74).

10. Urine Cytology

Urinary cytology is not a laboratory test. Rather, it is a pathologist’s interpretation of the morphological features of dislodged urothelial cells. Poor cellular cohesion in CIS enhances the yield of cytology (Figs. 1.3 and 1.4). Its very high specificity is the strongest feature of cytology, because a positive reading even in the absence of cystoscopic or radiographic findings suggests the existence of malignancy in the vast majority of patients. Patients with a negative workup (cystoscopy and upper tract imaging) and a persistently positive cytology are found to have genitourinary cancer within 24 months (mean 5.6 months) in 40% of the cases (75).

Bladder irrigation (or barbotage) dislodges cells with poor cellular cohesion, which is common in CIS. This increases the cellularity available for evaluation compared to voided urine. Nevertheless, Murphy et al. showed that urine collected cystoscopically prior to obtaining a bladder wash provided additional diagnostic information. Bladder washings had a higher yield in their study of 313 patients, but 13.1% of cancers would have been missed in bladder washings alone. Moreover, mechanical trauma has the potential to create cellular alterations that might interfere with the interpretation (76). Radiographic contrast has also been implicated in creating fragmentation, nuclear pyknosis, cellular shrinkage, and cytoplasmic vacuolization that might lead to a false positive reading, especially when injected for retrograde pyelography (77). This appears to be less likely with low osmolar ionic as well as nonionic contrast media (78).

Recent studies fail to support the traditional reputation of cytology as being highly accurate for high grade lesions such as CIS. The Mayo Clinic recently observed that only 58% of bladder tumors were identified using cytology. Its sensitivity was not limited to low-grade tumors, as only 71% of high-grade cancers were identified. They reviewed the literature and found that series published after 1990 reported that cytology only identified 11% of grade 1, 31% of grade 2, and 60% of grade 3 tumors (79). These recent findings were well below those reported prior to 1990, when their review found that the
sensitivity of cytology was 94% for grade 3 tumors in published reports. The authors identified no explanation for this deterioration. A change in the stringency of cytological criteria for determining a case as positive was ruled out, as the very high specificity for studies before and after 1990 was not significantly different and was consistent with specificity in their own laboratory. These findings are consistent with numerous other studies, most strikingly by a recent multicenter study involving several institutions noted for bladder cancer expertise that found cytology had an overall sensitivity of 15.8% (80).

Thus, cytology has very high specificity, but low sensitivity for both high-grade and low-grade tumors, including CIS, in recently published reports (Fig. 1.5).

11. Tumor Markers

Based on the limitations of cytology, several biomarkers have been developed for diagnosis or surveillance. Most have adequate sensitivity but poor specificity and costs usually exceeding that for cytology. The most significant issue limiting widespread adoption of tumor markers is the lack of prospective data to support their impact on prognosis or disease management (81). Moreover, incomplete understanding of the significance of positive or negative marker results based on unclear levels of positive predictive value and negative predictive value create a scenario where clinicians often receive test results that do not clarify whether the patient is likely or unlikely to have bladder cancer. The economic impact of a false-positive cancer test in a screening population was calculated to be $1,024 for women and $1,171 for men, so tests with low specificity can lead to significant negative consequence even in the absence of malignancy (82). Despite continuing advances including those described herein, the above issues will limit the role of tumor markers in the foreseeable future.

Tumor markers can either be point-of-care tests (performed in the office) or laboratory based. These tests identify factors at different levels of cancer cell evolution, including tumor-associated antigens, blood group antigens, growth factors, cell cycle/apoptosis, and extracellular matrix proteins.

The qualitative point-of-care test, BTA stat® (Polymedco, Inc., Cortlandt Manor, NY, USA), and the quantitative BTA TRAK® (Polymedco) assays detect the human complement factor H-related protein. The sensitivity of these tests ranges from 50 to 80%, with a specificity of 50–75%. These tests are more sensitive than cytology, but can be falsely positive in patients with inflammation, infection, caffeine, nicotine, acetaminophen, acetyl salicylic acid or hematuria (83, 84). They are approved by the FDA for UC surveillance.

ImmunoCyt™ (DiagnoCure, Inc., Saint Foy, Canada) is a hybrid of cytology and an immunofluorescence assay. Three fluorescent-labeled monoclonal antibodies are targeted at a UC variant of CEA and two bladder mucins. Sensitivity and specificity are reported to be 86 and 79%, respectively. It has not been shown to be significantly affected by benign conditions, but adoption has been limited because interpretation is complex and requires a highly trained laboratory technician at this time (85, 86). This test is approved for UC surveillance.

The NMP22® BladderChek Test® (Matritech, Inc., Newton, MA, USA) is based on the detection of nuclear matrix protein 22, part of the mitotic apparatus released from urothelial nuclei upon cellular apoptosis. The protein is elevated in bladder cancer, but it is also released from the dead and dying urothelial cells. Benign conditions such as stones, infection, inflammation, hematuria, and cystoscopy can cause a false positive reading. Both a laboratory-based, quantitative immunoassay and a qualitative point-of-care test are available. The sensitivities and specificities range from 68.5 to 88.5% for sensitivity and from 65.2 to 91.3% for specificity (84). A multi-institutional trial involving 1,331 patients showed that the NMP22 was
more sensitive but less specific than cytology. Overall sensitivity was 55.7%. Overall specificity was higher for cytology at 99.2% compared with NMP22 at 85.7%. Combining NMP22 with cystoscopy increased sensitivity from 88.6 to 93.7% (79).

UroVysion® (Abbott Molecular, Chicago IL) is not truly a tumor marker, but is rather a cytology-based test that uses fluorescent in situ hybridization (FISH) of DNA probes or “labels” specific to certain chromosomal foci. Probes to identify centromeres to chromosomes 3, 7, and 17 are combined with a probe to the 9p21 locus. FISH probes can be developed to identify essentially any locus, but this combination has been shown to have the best combination of sensitivity and specificity (78). Cumulative data from comparative studies show sensitivity of 19 vs. 58% for grade 1, 50 vs. 77% for grade 2, and 71 vs. 96% for grade 3 for cytology compared to FISH. Similar findings occurred by stage where the sensitivity for cytology compared to FISH was 35 vs. 64% for Ta, 66 vs. 83% for T1, and 76 vs. 94% for muscle invasive carcinoma (74).

Notably, cytology detected only 67% of the cases with CIS vs. 100% detection by FISH in a review of all comparative studies published as of 2005. UroVysion has a specificity approaching that of cytology (74), but it will sometimes detect chromosomal changes before the development of phenotypic expression of malignancy, so leads to an “anticipatory positive” reading in some patients. Such readings will lead to identification of clinical tumors within 3–15 months in the majority of cases (37). This may allow identification of patients at risk of recurrence vs. those unlikely to recur in order to individualize surveillance protocols.

UroVysion has also been shown to clarify equivocal findings in patients with atypical or negative cytology (87). It is not affected by hematuria, inflammation, or other factors that can cause false positive readings with some tumor markers, so appears to be useful as a marker of CIS response to BCG (35).

Determining the utility of tumor markers and the choice of which one to use is not clear at this point in time. For example, if indication for biopsy in the operating room is the desired, then high specificity is preferred to limit the number of anesthetics and negative biopsies. Conversely, if increasing the interval of cystoscopic surveillance is the endpoint, then high sensitivity, particularly for high-grade tumors, is desired. Defining that a patient has a low likelihood of recurrence within the following year can allow individualism of surveillance protocols (Table 1.4, Fig. 1.6).

12. Investigational Markers

The Accu-Dx® (Intracel Corp, Rockville, Maryland, USA) point-of-care immunoassay is based on the higher level of VEGF that increases the permeability of the blood vessels to serum proteins, including plasminogen, fibrinogen, and the members of the clotting cascade in bladder cancer patients. This test detects fibrin and its degradation products. Its sensitivity and specificity is 68 and 86%, respectively, but it can also be falsely positive in patients with hematuria (88, 89). The test is currently not commercially available, but has been approved by the FDA.

The telomerase assay has shown high specificity but suboptimal sensitivity. Telomerase is a protein/RNA complex involved in extension of telomeres during cell cycle DNA replication, so is elevated in malignant cells. The stability of telomerase RNA is variable, yielding reports with unpredictable reproducibility (90, 91).

Hyaluronic acid is a nonsulphated glycosaminoglycan in the basement membrane that is degraded by

<table>
<thead>
<tr>
<th>Commercially available markers</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean%</td>
<td>Range%</td>
</tr>
<tr>
<td>Cytology</td>
<td>48</td>
<td>16–89</td>
</tr>
<tr>
<td>Hematuria dipstick</td>
<td>68</td>
<td>40–93</td>
</tr>
<tr>
<td>NMP22®</td>
<td>75</td>
<td>32–92</td>
</tr>
<tr>
<td>NMP22 BladderChek®</td>
<td>55.7</td>
<td></td>
</tr>
<tr>
<td>BTA stat®</td>
<td>68</td>
<td>53–89</td>
</tr>
<tr>
<td>BTA TRAK®</td>
<td>61</td>
<td>17–78</td>
</tr>
<tr>
<td>ImmunoCyt®</td>
<td>74</td>
<td>39–100</td>
</tr>
<tr>
<td>UroVysion®</td>
<td>77</td>
<td>73–81</td>
</tr>
</tbody>
</table>
hyaluronidase. The sensitivity and specificity for this test is between 80 and 85%, respectively. Cytokeratins 18, 19, and 20 are highly expressed in bladder cancer. However, all 3 are also induced with infections. The test for cytokeratin 8 and 18 is the UBC™ II ELISA (84).

Miscellaneous proteins with promise are BLCA4, a nuclear matrix bladder cancer protein; mucin 7, a glycoprotein that is mainly found in invasive and CIS bladder cancer; survivin, an antiapoptotic protein; Lewis X, found mainly in low-grade cancer; and CD44, a metastatic/invasive protein marker (84).

13. Management of Tumor Marker Results

Because most of the above tumor markers have low positive predictive value, a positive test is often associated with a benign condition. As long as the clinician recognizes this fact, simple diligence in assuring that malignancy is ruled out may be sufficient to address this situation. All tumor markers have a higher sensitivity than cytology, so are often positive in the presence of visible tumor despite a negative cytology. This is offset in many clinical scenarios by the disadvantage of excessive false positives in patients without malignancy. In addition, UroVysion is uniquely associated with the potential for “anticipatory positive” results due to the detection of chromosomal changes prior to phenotypic expression of those findings. Close surveillance and a low threshold to biopsy the bladder and image the extravesical urothelium is in order.

The negative predictive value of these tests is greatly variable. The highest NPV appears to occur with UroVysion. Our experience is that patients with a negative cystoscopy and negative UroVysion have a 5% chance of tumor recurrence within 2 years, compared to 62% with negative cystoscopy and positive UroVysion (92). Tests with a high negative predictive value may be useful for individualizing surveillance protocols in patients with low grade cancer, but this approach should be used with caution in patients with CIS.

Although conventional cytology is associated with a woefully low negative predictive value (NPV), its positive predictive value (PPV) is very high. Therefore, cytology can serve as a useful adjunct to tumor markers and their low PPV. For example, a screening tumor marker such as BTA stat or NMP-22 might be positive in the setting of a negative cystoscopy. A positive cytology at that point in time would automatically warrant biopsy. Conversely, the high NPV of UroVysion might preclude automatic biopsy in the same setting if it and cytology were negative.

14. Extravesical Surveillance

The likelihood of patients developing upper tract CIS or invasive UC after the diagnosis and treatment of nonmuscle-invasive disease has been reported as 0.002–2.4% over surveillance intervals of 5–13 years (93–96), although the risk increases substantially over time to as high as 18% in very high risk populations (97). Most reviews have concluded that patients with CIS should undergo upper tract imaging.

In a review of 591 patients with a median follow-up of 86 months, upper tract recurrence was 2.2% in patients at intermediate risk (recurrent or multifocal
disease), and 9.8% in high-risk patients, including intravesical chemotherapy failures (98).

Excretory urography is the traditional choice for upper tract imaging, but gives limited information about renal parenchyma and can miss small tumors. Retrograde pyelography requires instrumentation. CT urography is a promising technology for the evaluation of hematuria, but its role in the evaluation of patients with CIS has not been reported (99).

The synchronous or metachronous appearance of upper tract disease is associated with mortality rates of 40–70%. Patients with high-risk disease treated with BCG experience upper tract recurrence risk of 13–18% (97, 100). The risk for recurrence appears greatest over the first 5 years after treatment, yet persists for at least 15 years.

Selective cytology of the upper tract may increase the yield, but, in the presence of a bladder tumor, selective upper tract cytology may be falsely positive and is not recommended for most patients (96, 101). Bilateral ureteroscopy is often employed, but data on its yield are lacking. Nevertheless, patients with positive cytologies and a negative cystoscopic and radiographic evaluation may warrant bilateral flexible ureteroscopy. Although selective collection of tumor markers is logical, there is no evidence to date to support this practice.

15. Conclusion

Despite its traditional categorization as “superficial,” CIS is a high grade, flat, noninvasive bladder cancer confined to the urothelium. Bladder biopsy is required to establish a diagnosis. Cytology to examine voided or bladder wash urine can allow identification of malignant cells, but failure to recognize such cells does not rule out CIS. Options to improve cystoscopic recognition of malignant areas such as fluorescence cystoscopy and narrow band imaging are promising developments that have not received FDA approval in the United States at the time of this writing. A number of tumor markers have been developed. Most have high sensitivity, but these tests have varying specificity. The urologist must understand the implications of a negative or positive test in order to successfully integrate these tests into clinical practice.

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Fluorescence Cytoscopy

Philippe E. Spiess and H. Barton Grossman

Abstract Conventional diagnostic strategies for bladder cancer have consisted of white light cystoscopy and urine markers. It is recognized that white light cystoscopy can fail to detect carcinoma in situ (CIS). Furthermore, recent experiences with fluorescence cystoscopy demonstrate that white light cystoscopy can fail to detect papillary tumors as well. Several fluorescence agents have been used for photodynamic detection of bladder cancer, including 5-aminolevulinic acid, hexylester aminolevulinate, and hypericin. These novel agents can be applied intravesically from one to several hours prior to cystoscopy with no reported systemic toxicity, resulting in improved bladder cancer detection rates, particularly for CIS.

Recent phase III trials have demonstrated that transurethral resection of bladder tumors using fluorescence reduces short-term recurrence rates. Fluorescence cystoscopy is starting to play an increasing role in our diagnostic and therapeutic armamentarium for non-muscle invasive bladder cancer.

Keywords Bladder cancer, Fluorescence cystoscopy, Diagnosis, Carcinoma in situ, Treatment

1. Introduction

Bladder cancer represents the fifth most common malignancy in the United States, with an estimated 13,180 disease-specific deaths in this past year (1, 2). The diagnosis and surveillance of nonmuscle invasive bladder cancer produces a significant cost in healthcare resulting in part from frequent surveillance by cystoscopy and urinary marker evaluation. Regular surveillance is employed because up to 75% of the people with bladder cancer superficial to the muscularis propria will develop recurrent disease (3). Up to now, most practicing urologists have utilized white light cystoscopy and a urine marker as their diagnostic tools of choice for this disease. However, carcinoma in situ (CIS) and small papillary tumors can be difficult to visualize under white light cystoscopy. Failure to detect these cancers puts patients at risk of overt tumor recurrence and disease progression (4–6). A variety of alternative or adjunctive diagnostic strategies have been investigated in an effort to minimize this risk (5). Jocham et al. were the first to investigate the potential role of the fluorescence agent 5-aminolevulinic acid for bladder cancer.
(ALA) as a compound that could be applied intravesically and potentially improve bladder cancer detection (7). Since this preliminary report, the technology of fluorescence cystoscopy has improved significantly with the development of newer fluorescence agents such as hexylester aminolevulinate (HAL) and hypericin.

In this chapter, we review the principles of fluorescence cystoscopy with these agents and discuss the recent literature, which suggest that it has great potential as an adjunctive tool in the diagnosis and management of nonmuscle invasive bladder cancer.

2. Fluorescence Agents

Prior to the advent of modern fluorescence agents, compounds such as tetracycline were evaluated as potential diagnostic markers for bladder cancer. However, these agents lacked sufficient cancer detection capabilities (4, 5). Currently used fluorescence agents have been shown to enhance bladder cancer diagnosis and have minimal side-effects, which in most cases consist of lower urinary tract symptoms (i.e., urgency, frequency, and dysuria) indistinguishable from the expected side-effects associated with cystoscopy and biopsy (8–11). The reported sensitivity and specificity of these fluorescence agents in bladder cancer detection are summarized in Table 2.1 (11–17).

### 2.1. ALA

ALA is the first drug developed for clinical photodynamic detection of bladder cancer. Intravesical instillation of this agent results in its uptake by bladder tumors, which can be subsequently visualized using a specially designed light source (4, 6, 18). ALA fluorescence occurs because the agent is a heme precursor, and it causes protoporphyrin IX to amass within bladder cancer cells, which can be visualized as red fluorescence upon exposure to light of the appropriate wavelength. Several theories have been proposed to explain protoporphyrin accumulation in bladder cancer cells, including metabolic changes, unique chemical and structural properties, and rapid proliferation of cancer cells compared to the rest of the bladder urothelium (6, 18). The optimal dosing and duration of instillation of ALA has not been standardized. However, most urologists instill 1.5 g intravesically between 2 and 3 h before fluorescence cystoscopy. One of the major hindrances to fluorescence cystoscopy using this agent results from its net positive electrical charge, which impairs its intravesical absorption resulting in the requirement for long drug exposure.

### 2.2. HAL

In an attempt to improve intravesical uptake, ALA has been esterified forming the novel compound HAL. HAL is more lipophilic than ALA, facilitating its ability to cross the cell membrane and resulting in twice as rapid an absorption rate with 20 times lower concentrations required (5). Furthermore, HAL generates 2–4 times stronger fluorescence signal intensity than ALA, optimizing its bladder cancer detection. Typically, 50 ml of HAL (8 mmole/L) is instilled intravesically 1 h prior to cystoscopic evaluation (19). On 2nd March 2005, the European Union approved the use of the HAL agent Hexvix® (PhotoCure ASA) to enhance the detection of early stage bladder cancer (4, 20, 21).

### 2.3. Hypericin

D’Hallevin et al. were the first to report the application of hypericin as a novel agent for fluorescence cystoscopy (22). Hypericin has unique chemical and structural properties, that are quite distinct from those of ALA and HAL. Hypericin is derived from the plant extract of Hypericum perforatum and consists of a hydroxylated quinone compound (23). Upon excitation by fluorescence light, hypericin releases singlet oxygen molecules resulting in a bright red fluorescent signal (4, 24). Typically, hypericin is instilled at a concentration of 8 µmole/L between 1 and 2 h prior to fluorescence cystoscopy.

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**Table 2.1. Overall sensitivity and specificity of fluorescence cystoscopy agents.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Agent used</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zaak et al. (12)</td>
<td>1414</td>
<td>ALA</td>
<td>97</td>
<td>65</td>
</tr>
<tr>
<td>Grimbergen et al. (13)</td>
<td>160</td>
<td>ALA</td>
<td>97</td>
<td>49</td>
</tr>
<tr>
<td>Kriegmair et al. (14)</td>
<td>104</td>
<td>ALA</td>
<td>97</td>
<td>67</td>
</tr>
<tr>
<td>Schmidbauer et al. (15)</td>
<td>211</td>
<td>HAL</td>
<td>97</td>
<td>NA</td>
</tr>
<tr>
<td>Jichlinski et al. (11)</td>
<td>52</td>
<td>HAL</td>
<td>96</td>
<td>52</td>
</tr>
<tr>
<td>D’Hallevin et al. (16)</td>
<td>87</td>
<td>Hypericin</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Sim et al. (17)</td>
<td>41</td>
<td>Hypericin</td>
<td>82</td>
<td>91</td>
</tr>
</tbody>
</table>

ALA 5-aminolevulinic acid; HAL hexylester aminolevulinate; NA not available.
3. Fluorescence Cytoscopy

3.1. Rigid Cystoscopy Using Fluorescence Agents

Currently, fluorescence cystoscopy is considered an adjunctive tool to conventional white light cystoscopy for both the diagnosis and treatment of nonmuscle invasive bladder cancer. Typically, the fluorescence agent is intravesically administered via a urethral catheter 1 to several hours prior to the procedure, with the dosage and duration of instillation varying, depending on the specific agent being used. The patient is subsequently taken to the cystoscopy suite. Until recently, fluorescence cystoscopy was only conducted using rigid cystoscopes. The light source for fluorescence cystoscopy consists of a xenon lamp equipped with a light filter emitting light with frequencies between 375 and 440 nm. This fluorescence light can be activated on currently available cystoscopes via either a button on the cystoscope or by a foot pad (5). Under fluorescence cystoscopy, bladder tumors appear red, with the remaining normal urothelium having a dark blue appearance.

3.2. Flexible Cystoscopy Using Fluorescence Agents

Recently, flexible cystoscopic technology has been developed for use with fluorescence agents. Loidl et al. published a prospective study of 45 patients undergoing fluorescence cystoscopy using HAL as well as rigid cystoscopy using white light and HAL (25). Forty-one patients (91%) had exophytic papillary tumors, with 39 (95.1%) identified by HAL flexible cystoscopy and 40 (97.5%) by HAL rigid cystoscopy. In addition, CIS was identified in 17 patients, with 15 (88.2%) identified by HAL flexible cystoscopy, 15 (88.2%) by HAL rigid cystoscopy, 11 (64.7%) by white light flexible cystoscopy, and 13 (76.7%) by white light rigid cystoscopy. A phase II study by Witjes et al. similarly compared the performance of HAL flexible fluorescence cystoscopy to rigid fluorescence and white light cystoscopy (4, 26). Twenty patients participated in this study, and 27 histologically confirmed bladder tumors were detected among 19 patients. The bladder cancer detection rates for these 19 patients were 74% (N = 14) with HAL flexible cystoscopy, 89% (N = 17) with HAL rigid cystoscopy, and 79% (N = 15) with white light rigid cystoscopy. Overall, the fluorescence signal intensity of HAL flexible cystoscopy was 76% (30–147%) of that seen with fluorescence rigid cystoscopy. These preliminary findings suggest that the performance of flexible fluorescence cystoscopy is slightly inferior to that of rigid fluorescence cystoscopy. Future improvements in instrumentation may narrow this difference. As pointed out by Zlotta in a recent editorial, most diagnostic and surveillance cystoscopies performed today are conducted using flexible cystoscopes (27). Therefore, for fluorescence cystoscopy to be an attractive adjunctive tool in outpatient clinical practice, its merits must be demonstrated with flexible cystoscopy.

3.3. Pitfalls of Fluorescence Cytoscopy

One of the major concerns regarding fluorescence cystoscopy is its false-positive rate, which has been reported to be as high as 40% (4, 6, 13). When conducting fluorescence cystoscopy, it is essential to keep the excitation light perpendicular to the bladder urothelium. Tangential light can result in autofluorescence unrelated to bladder cancer. The experience of the surgeon and proper application of fluorescence cystoscopy can dramatically impact the performance of this test. Other causes for a false-positive test include the presence of urothelial inflammation, hyperplasia/dysplasia, and recent intravesical therapy.

4. Detection of CIS Using Fluorescence Cytoscopy

The merits of fluorescence cystoscopy are particularly evident in the detection of CIS, as illustrated in Table 2.2. As recently reported in a review by Jichlinski et al., fluorescence cystoscopy using ALA or HAL has a detection rate for CIS exceeding 90%, favoring its integration as a standard tool for the diagnosis and management of nonmuscle invasive bladder cancer (28). In a study by Zaak et al., 605 patients underwent 1,012 ALA fluorescence and white light cystoscopies as part of the diagnosis and surveillance of bladder cancer (8). Of the 142 fluorescence cystoscopies in which CIS was detected, 88 (62%) were detected on both white light and fluorescence cystoscopy, and 50 (35%) were detected solely on fluorescence cystoscopy. The remaining four cases (3%) were detected on white light cystoscopy alone. Fluorescence cystoscopy detects most CIS lesions and outperforms white light cystoscopy. In a study by Koenig et al., 55 patients with suspected cancer of the bladder underwent white light and fluorescence cystoscopy using ALA, with biopsies taken from suspected bladder lesions (29). The incorporation of fluorescence cystoscopy into their diagnostic strategy detected cancer of the bladder in six patients, two of whom had CIS. The authors concluded that fluorescence cystoscopy improved the overall diagnosis of malignant/dysplastic...