Bladder Cancer: Imperatives for Personalized Medicine

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Wide variations in the care of early bladder cancer exist, and among high–treatment intensity urology providers, overall survival is unchanged while rates of transition to major surgery are actually increasing. It has been said that for bladder tumors, it is time for a paradigm shift. We believe that the time is overdue.

Introduction

It has been estimated that 2.7 million people worldwide have a history of bladder cancer and that approximately 145,000 die every year from the disease.[1] In the United States, urothelial carcinoma of the bladder (UC) accounts for 95% of bladder cancers. Cigarette smoking accounts for at least 50% of UC in men and 35% in women.[2,3] It is less certain that UC in nonsmokers is related to environmental tobacco smoke exposures. Aromatic amines, polycyclic aromatic and chlorinated hydrocarbons, arsenic-laced drinking water, aristolochic acid, cyclophosphamide exposure, and a range of industrial chemicals have been implicated in urothelial carcinogenesis. Marked variation in individual susceptibility despite seemingly equal carcinogen exposures has been explained by genetic polymorphisms regulating varied detoxification mechanisms.[3,4] Familial bladder cancer is rare, and viral pathogenesis remains unproven. Although chronic inflammation is strongly implicated in the pathogenesis of squamous carcinomas of the bladder, its role in the pathogenesis of UC is unproven.[5] Prior use of nonsteroidal anti-inflammatory drugs, but not aspirin, is associated with a lowered risk of UC among nonsmokers alone.[6] Ninety percent of UC occurs in persons older than 55 years, with the highest risk in those aged 75 to 85 years.[7]

The multipronged approach to control of *Schistosoma hematobium* infections in Egypt that was followed by steep declines in mortality from associated squamous carcinomas of the bladder is a remarkable public health success story.[8] However, aging among rising world populations and a shift in the tobacco epidemic to rapidly industrializing nations with less stringent environmental protections portend a major increase in the global incidence of and mortality from UC. The periodic cystoscopies employed in the treatment and monitoring of bladder cancer place a significant burden on existing healthcare resources; in a 1995 survey of five solid tumors in the elderly, Medicare payments from diagnosis to death were highest for bladder cancer.[9] Cost-effective paradigms for controlling the global scale and impact of the disease are needed.

A Survey of Existing Management Paradigms and Challenges in Bladder Cancer

Transparently, the most effective single method for preventing and reducing deaths from bladder cancer would be the eradication of cigarette smoking. A more vigorous role for the oncology community in efforts to achieve this goal is strongly recommended.[3,10] Given that no more than a quarter of bladder tumors have lethal potential, it would be extremely difficult for a population-based screening test to demonstrate reduction in bladder cancer–specific mortality. For the diagnosis of UC, a highly sensitive and specific biomarker for malignancy that performs better than urine cytology and radiographic and endoscopic evaluation has not been identified. Education of patients and physicians with regard to the importance of prompt evaluation of macroscopic hematuria can make a difference in preventing deaths from the disease.[11] Microscopic hematuria carries far less specificity for cancer. There is insufficient evidence for an evidence-based algorithm for the investigation of hematuria.[12] Cystoscopy and upper tract evaluation are recommended in all patients with microscopic or macroscopic hematuria, particularly in the absence of infection or stones. Irritative voiding symptoms may imply carcinoma in situ and should also be evaluated with cystoscopy. Urine cytology has high specificity and positive predictive value for high-grade disease and carcinoma in situ but low sensitivity for low-grade lesions. Other
studies that are available—eg, the Nuclear Matrix Protein 22 (NMP22) test, fluorescence in situ hybridization (FISH), while often used, have yet to make an impact on the diagnosis and management of UC.

Non-muscle-invasive bladder cancer (NMIBC)

Tumors staged as Ta, T1, or carcinoma in situ (CIS) are grouped as NMIBC and account for 75% to 85% of bladder cancers. The terms "superficial" or "NMIBC" may serve to conceal the lethal biology contained within these entities. Guidelines for the management of NMIBC have been developed by the American Urological Association (AUA)[13] and the European Association of Urology (EAU); these are continually updated at www.uroweb.org.[14] The guidelines emphasize the importance of careful cystoscopic evaluation and a complete and correct transurethral resection (TUR) to making the correct diagnosis and facilitating removal of all visible tumors. Pathology reports should specify lesion grade, depth of invasion into the bladder wall, and whether lamina propria and muscle cells are present in the specimen.

A risk-adapted approach to perioperative or postoperative adjunctive intravesical chemotherapy or immunotherapy with bacille Calmette-Gurin (BCG) is presented in the EAU guidelines. Risk stratification is determined by assigning weights to the number of tumors, tumor diameter, prior recurrence history, Ta vs T1 disease, presence or absence of CIS, and grade (according to the 1973 World Health Organization classification); these weighted factors are used to generate total scores for recurrence (0 to 17) and progression (0 to 23). Patients are then stratified on the basis of their scores as low-, intermediate-, or high-risk for recurrence and progression at 5 years; each of these risk groups has its own correlative treatment and surveillance recommendations.

For example, in patients at low risk for recurrence and progression, a single postoperative instillation of chemotherapy (eg, mitomycin C) is recommended, with follow-up cystoscopy at 3 months—and if cystoscopy results are negative, again at 9 months and then yearly for 5 years. By contrast, for patients with a high risk of progression, the recommendations call for induction BCG (weekly × 6) followed by maintenance therapy as tolerated for at least 12 months—or immediate cystectomy. The US guidelines are similar: a single perioperative instillation of chemotherapy (mitomycin) is recommended for all patients undergoing transurethral resection of bladder tumor (TURBT), with the addition of adjuvant intravesical BCG induction and maintenance (3 weekly instillations at 3 and 6 months and then every 6 months) for high-grade tumors.

Although the risk of disease progression is reduced with intravesical BCG, because of the inclusion of low-risk NMIBC lesions in randomized trials, as well as the short follow-up time when the results of these trials are reported, it has been difficult to demonstrate an overall survival benefit.[15] Furthermore, the chronicity of UC mandates lifelong follow-up of patients; thus, studies likely underestimate the true impact of disease recurrence and progression after bladder-sparing strategies. It is unlikely that a randomized trial will be performed comparing survival and quality of life outcomes of immediate cystectomy vs intravesical BCG therapy with or without salvage cystectomy for high-risk NMIBC. There are no intravesical therapies for high-risk disease that have clearly improved outcomes over those achievable with BCG induction and maintenance therapy. While maintenance BCG reduces recurrence and progression rates, there is no consensus on the optimal dose, schedule, and duration of therapy (beyond 1 year). Early identification of BCG failure and subsequent transition to cystectomy is critically necessary to prevent deaths from progression to metastatic disease.[16,17] It has been estimated that between 30% and 45% of bladder cancer deaths could be avoided by earlier implementation of cystectomy in surgically fit patients with NMIBC.[18] This remarkable estimate, if accurate, is far in excess of the absolute survival benefit of 5% that neoadjuvant chemotherapy provides for muscle-invasive disease (MIBC).

BCG failure is inconsistently defined in the literature; a consensus definition has been proposed.[19] Persistent disease at 3 months following induction BCG therapy in high-risk NMIBC or failure to achieve disease-free status at 6 months following initial BCG therapy with either maintenance or retreatment at 3 months should prompt consideration of immediate cystectomy. To facilitate better treatment choices, molecular predictors of BCG outcome require elucidation and incorporation into clinically useful predictive tools. Preliminary data suggest that the urinary cytokine response to BCG may predict response to BCG.

Among surgically unfit patients, definitive studies that establish the efficacy of intravesical chemotherapy or other modalities as standard of care are awaited. Patients with micropapillary histology,[20] evidence of lymphovascular invasion, or prostatic urethral involvement may be better served by immediate cystectomy. The presence of multiple or high-risk tumors is associated with a higher risk of upper tract recurrences. Persistent urine cytology positivity in association with
negative cystoscopic findings warrants a search in upper tracts, with prostatic, urethral, and random bladder biopsies. There is limited evidence to suggest that smoking cessation following a diagnosis of NMIBC reduces the risk of recurrence and progression of disease.[21] However, neither the AUA[13] nor the EAU guidelines[14] cite smoking cessation as a management goal in NMIBC.

**Muscle-invasive bladder cancer (MIBC)**

There are two large randomized prospective phase III trials that demonstrate the benefit of neoadjuvant chemotherapy in MIBC. The European Organisation for the Treatment and Cure of Cancer (EORTC) study of treatment of MIBC with cisplatin, methotrexate, and vinblastine[22] and the Southwest Oncology Group (SWOG) study of methotrexate, vinblastine, Adriamycin (doxorubicin), and cisplatin (MVAC)[23] demonstrated that neoadjuvant therapy resulted in a 10-year absolute survival benefit of approximately 5% (number needed to treat [NNT] = 20). Pathological complete remissions with neoadjuvant therapy are associated with 85% long-term survival; conversely, pathological node involvement following neoadjuvant chemotherapy portends a high frequency of lethal disease progression.[24]

In contrast to neoadjuvant studies, the randomized adjuvant chemotherapy trials have been repeatedly criticized as underpowered and flawed, and two recent trials were closed due to poor accrual. A randomized comparison of 5 cycles of post-cystectomy MVAC chemotherapy (n = 70) vs 2 cycles of neoadjuvant and 3 cycles of adjuvant MVAC (n = 70) estimated that there were no major differences in survival outcomes between the two arms despite better tolerance of neoadjuvant MVAC.[24] Similar drop-out rates (10%) were observed when patients proceeded from neoadjuvant chemotherapy to surgery or proceeded from surgery to chemotherapy.

By contrast, in a large retrospective study, one-third of patients with MIBC were judged unfit to receive adjuvant chemotherapy following cystectomy as a result of the high rate of postoperative complications.[25] Patients with extravesical or pN+ MIBC who have recovered quickly from cystectomy should be considered for adjuvant chemotherapy, preferably on a clinical trial. While the optimum number of adjunctive cycles of chemotherapy is undefined, a minimum of 3 cycles should be targeted for completion. Currently, the use of gemcitabine (Gemzar)-cisplatin or dose-intense MVAC regimens has been transposed to the adjunctive therapy of MIBC, given the therapeutic equivalence and lesser toxicity of these regimens compared with traditional MVAC in metastatic disease.[26,27]

Despite level 1 evidence to support its use, it has been estimated that ≤ 12% of patients with MIBC receive neoadjuvant chemotherapy;[28] it is likely that physician, patient, and institutional barriers contribute to this statistic. The attitude, skill, and knowledge variables that account for these barriers require better understanding.

Organ-confined micropapillary UC, squamous carcinomas, and adenocarcinomas of the bladder are best managed with early cystectomy, while neoadjuvant etoposide-cisplatin-based chemotherapy is preferred in small-cell carcinomas. In patients with ≥ T3 or N+ small-cell carcinoma, prophylactic cranial irradiation should be considered, as the brain is often the exclusive site of relapse.[29] In UC with mixed glandular and squamous features, there is evidence of a persistent survival benefit with neoadjuvant chemotherapy.

Given the quality of life consequences of removal of the bladder and the prevalence of MIBC among the surgically unfit, there is abiding interest in advancing organ-conservation through the integration of TUR, chemotherapy, and radiation therapy. There are no direct comparisons of surgery and radiotherapy in the management of MIBC. Patient selection and the availability of salvage surgery contribute to disease-specific and overall survival outcomes. Following chemotherapy, a third of patients will harbor residual MIBC despite negative cystoscopies and biopsies, and organ preservation is thus not recommended. Current guidelines for MIBC recommend that radiation-based bladder conservation attempts be reserved for the medically unfit.[30]

**Metastatic bladder cancer (MBC)**

Chemotherapy remains the mainstay of management in MBC, and while advances in this area have long since reached a plateau, the development of less-toxic regimens, including gemcitabine-cisplatin and dose-dense MVAC,[26,27] has facilitated the design of novel combination strategies. Among subgroups of patients with metastatic disease who have a favorable risk profile (minimally symptomatic, no visceral metastases), long-term survival with cisplatin-based chemotherapy may be seen in up to 25% of patients, whereas the median survival of patients with poor risk profiles (symptomatic, visceral metastases) is 9 months.[31] These data demonstrate the importance of risk stratification for the design and interpretation of clinical trials in MBC. The
integrated biomarkers into prognostic and predictive models has the potential to further enhance the accuracy of clinical trial design and therapy planning. In the second-line setting, although response rates are low, vinflunine has been shown to modestly improve survival over best supportive care[32] and is available in Europe.

Metastatic bladder cancer remains the major testing ground for novel therapeutics, and while to date novel agents, including angiogenesis inhibitors and signal transduction inhibitors, have not yielded significant single-agent activity in MBC, a range of combination strategies are being pursued in single-arm and randomized studies. The challenge of linking accurate biological information with drug design and/or treatment strategy is key to the success of these efforts.

**Molecular and Cellular Pathogenesis of Bladder Cancer: The Road to Translation**

Clinicopathological phenotyping of bladder cancer has yielded a fascinating Janus-like molecular portrait of UC.[33,34] The vast majority (80%) of UCs are genetically stable low-grade papillary tumors (Ta) with a propensity for multifocality and post-resection recurrence, very limited invasion potential (≤ 5% risk of progression to muscle invasion), and high (90%) long-term disease-specific survival. Conversely, the remaining lesions represent genetically unstable tumors that have arisen de novo or from high-grade CIS lesions and that carry lethal potential, with a 50% risk of progression and 50% disease-specific survival following surgery for muscle-invasive disease.

Among noninvasive, low-grade papillary tumors, the most common genetic lesions are deletions of chromosome 9 and point mutations in the fibroblast growth factor receptor 3 gene (FGFR3) and in the alpha catalytic subunit of phosphatidylinositol 3-kinase (PIK3CA). More than half of bladder tumors of all stages and grades show chromosome 9 alterations and loss of heterozygosity (LOH).

Several candidate tumor suppressors on 9p (eg, CDKN2A encoding p16 and p14) and 9q (eg, PCH1, DBC1, TSC1) have been identified, but given the observed complexities, a multigenic model of inactivation may be required in order to link genotype to phenotype. Activating FGFR3 mutations are found in 80% of low-grade Ta lesions and are the most common genetic alteration in bladder cancer. FGFR3 mutations are also found in 75% of benign nondysplastic urothelial papillomas and are rarely associated with CIS and TP53 mutations. The most common FGFR3 mutations—S249C in exon 7 (67%) and S375C in exon 10 (20%)—result in ligand-independent receptor dimerization, while the exon 15 mutation (3%) in the kinase domain predicts constitutive activation via altered protein conformation. Papillary tumors with concomitant CIS are generally FGFR3 wild-type, with patterns of chromosomal changes and gene expression signatures that are different from those seen in FGFR3-mutated tumors. While it appears that for the most part FGFR3 mutations do not play a significant role in invasive progression, invasive and metastatic tumors that carry activating mutations paradoxically behave in a more aggressive fashion. Current molecular studies have also suggested that NMIBC lesions might be better categorized on the basis of their FGFR3 status than by traditional grade and stage, and that such a categorization might improve current prognostic models.[35]

The early identification of HRAS mutations in bladder cancer is a historic landmark in cancer research. Mutations in RAS genes (HRAS, NARAS, and KRA52) have been identified in UC with more variable and lesser frequency than FGFR3 mutations, and with no association with tumor grade or stage. RAS and FGFR3 mutations appear to be mutually exclusive in Ta lesions, a finding that supports observations that oncogenic effects of mutationally activated FGFR3 are mediated by the Ras signaling pathway and that constitutional activation of the receptor tyrosine kinase–Ras signaling pathway is responsible for the genesis of an overwhelming majority of Ta lesions. RAS mutations are equally frequent in Ta and invasive subgroups, however, raising the possibility that a subset of invasive cancers may have evolved from a low-grade papillary lesion. Synchronous and metachronous multifocal Ta tumors share genetic alterations, indicating genomic stability and a clonal origin. Interestingly, Ta tumors with more complex genetic alterations can appear earlier than their clonal counterparts with shared but less complex alterations, a phenomenon that indicates growth-advantaged evolution in the former lesions.

To date, the most compelling differences between low-grade noninvasive lesions and invasive, high-grade tumors are alterations in the p53 and Rb tumor suppressor pathways. Multiple TP53 mutations, overexpression of HD2M, loss of p21 expression, and stabilized p53 expression, all of which carry an adverse prognosis in non-mutated tumors, have been identified. LOH in RB1 has been identified in over 50% of invasive tumors, and together with p53 status, Rb expression has been demonstrated to have prognostic significance. Additionally, E2F3 transcription factor overexpression...
associated with a 6p22 amplicon occurs exclusively in about 10% of invasive tumors, along with a high proliferation index and loss of Rb or p16 expression.

LOH at the PTEN locus on chromosome 10q, observed exclusively in invasive tumors, has implicated the PI3-kinase pathway in the progressive phenotype of UC. Other genes in the PI3-kinase pathway, including TSC1 and PIK3CA, are found in bladder tumors of all stages and grades, and the different roles of this pathway may therefore contribute to different phenotypes of disease.

ERBB2 amplification is seen in 10% to 14% of UC and is associated with higher grade and stage of disease. The association of more frequently observed ErbB2 overexpression with clinicopathological features is less certain. Additional insights into the contribution of ErbB2, along with other ErbB family members—EGFR, ErbB3, and ErbB4 (also overexpressed in UC)—to the two pathways of urothelial tumorigenesis are required. To date, amplification or point mutations of EGFR have not been reported, and this likely explains the lack of clinical activity of EGFR inhibitors in UC.

Recently, epigenetic silencing by histone methylation and hypoacetylation within seven stretches of contiguous genes, referred to as multiple regional epigenetic silencing (MRES), was reported in 26 of 57 bladder cancers (Ta, T1-T4).[36] The MRES phenotype was tightly associated with a CIS gene expression signature,[37] with absence of FGFR3 mutations, and with muscle-invasive disease, thus extending the two-pathway model of bladder cancer pathogenesis.

Tissue-specific transgenic murine models of bladder cancer have been generated,[38] and the models generated thus far indicate that oncogene cooperativity is necessary to generate invasive and metastatic tumor—eg, p53 and Rb family gene inactivation by SV40 T-antigen[39] or PTEN and p53 disruption.[40] By contrast, mutant HRAS transgenic models generate mainly hyperplastic lesions with very slow development of non-invasive phenotypes resembling their human counterparts. FGFR3-mutant models have not been reported.

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**Therapeutic Agents Mentioned in This Article**

Adriamycin (doxorubicin)

Bacille Calmette-Gurin

Bevacizumab (Avastin)

Cetuximab (Erbitux)

Cisplatin

Docetaxel

Donvitinib (TKI258)

Etoposide
Trastuzumab (Herceptin)

Vinblastine

Vinflunine

Unfortunately, we currently have inadequate insight into the genetic or epigenetic changes that may direct transformation of low-grade noninvasive tumors into high-grade invasive ones. Identification and clinical validation of predictive markers that reliably distinguish divergent pathways of behavior are required to advance real-world personalization of surgical and medical management of these tumors. Examples of existing challenges include inconsistencies in the data with respect to the prognostic value of p53 and Rb status, the relevance of low-frequency FGFR3 mutations in invasive cancers, and identification of alternative disease pathways for the 50% of high-grade invasive tumors that do not possess p53 or Rb defects.

Recent insights into the spatially restricted organization of the bladder epithelium and the cellular origins of transitional carcinomas promise to enrich the early genetic insights offered by the two-pathway carcinogenesis model. A p53 homologue—p63—has been shown to be critical for normal transitional epithelium development. Basal and intermediate layers of epithelium express p63, several high-molecular weight cytokeratins, and mature A/B blood group antigens—whereas apical umbrella cells express specific low–molecular weight cytokeratins and Lewis X determinant and are p63-negative. The bladder epithelium in TP63-null mice comprises a single layer of cells that resembles an umbrella-cell phenotype, suggesting the possibility of independent derivation from basal/intermediate cells. The prognosis of muscle-invasive tumors with a basal-cell phenotype appears to be inferior to that of tumors with a luminal phenotype.[41] In xenograft studies, bladder cancer cells with basal-cell phenotypes account for tumor repopulation capacity, possess distinctive gene expression signatures that regulate invasion and metastasis, and define a population of NMIBC with adverse prognosis.[42,43]

The integration of cellular signatures with the genetic data from the two-pathway model is likely to further strengthen our understanding of the significant heterogeneity of UC, develop prognostic and predictive biomarkers for prospective validation, and identify high-value therapeutic targets. A molecular distinction between carcinogen-related and non–carcinogen-related cancers is required for a deeper understanding of pathogenesis. Extension of molecular (genetic and epigenetic) and cellular studies to other histological variants of bladder cancer, including squamous carcinomas, adenocarcinomas, small-cell carcinomas, and carcinosarcomas, will be critical to a fuller explanation of bladder neoplasia.

**Molecular Therapeutics**

As with prostate, lung, hematological, and other cancers, an arsenal of genomic strategies is being utilized to identify novel gene fusions and other cryptic drivers of bladder cancer progression that may be drug targets. Innovative strategies to discover compounds or targets for induction of synthetic lethality in p53, Rb, and RAS-mutated backgrounds[44] are relevant to at least 50% of MIBC. A significant fraction (31%) of upper tract urothelial carcinomas demonstrate microsatellite instability reminiscent of Lynch type 2 lesions[45] and may be biologically distinct from bladder urothelial carcinoma. Whether a subset of these upper tract tumors will be amenable to synthetic lethal approaches now under study for tumors with DNA mismatch–repair defects remains to be seen.[46] Gene expression models have allowed prediction of chemotherapy sensitivity in the United States National Cancer Institute’s Developmental Therapeutics Program (NCI-DTP) NCI-60 Human Tumor Cell Line Screen (which does not include bladder cancer lines). Use of this paradigm has been explored in urothelial carcinoma, and adoption of these principles for drug discovery and identification of synthetic lethal targets in bladder cancer lines may pave the way for individualized prediction of drug sensitivity and therapy design in MBC.[47] Further insights into epithelial-stromal
interactions—e.g., interactions mediated by c-met[48]; the downregulation of immune response by infiltrating myeloid cells[49]; the role of T-lymphocyte subsets in regulating UC[50]; and the interactive role of VEGF, FGF, and other cytokines in driving bladder-specific angiogenesis and lymphangiogenesis—will broaden our understanding of how the UC tumor microenvironment is reshaped to confer lethal progression. The epithelial and stromal components of the UC microenvironment represent therapeutic targets, and the challenge for translation is to synthesize an integrated, feasible, and effective strategy.

### Table 1

A Cross-Section of Molecular Therapeutics in Clinical Trials in Bladder Cancer

The pre-operative setting of localized NMIBC and MIBC offers an experimental platform for translational explorations with novel agents—e.g., the study of gene signatures predictive of therapy-induced complete pathological response, validation of therapy targeting, insights into drug resistance, reconciliation of preclinical observations, and development of surrogate predictive markers. The risk of adverse outcomes with novel agents in a potentially curable setting must be balanced with the imperative to improve outcomes for individual patients. Pre-operative experimental therapy offers a complementary view to that of parallel trials in metastatic disease in which distant organ colonization by MBC cells may generate biology distinct from that seen in the bladder environment. A cross-section of clinical trials with molecular therapeutics and related targets implicated in the biology of bladder cancer is shown in Table 1. To date, no single agent (including EGFR family inhibitors, angiogenesis inhibitors, signal transduction inhibitors) has demonstrated significant clinical activity. High-quality targets—or multiple pathway-based targets—for therapy are needed for major advances in the field.

### The Imperatives for Personalized Medicine in Bladder Cancer

### Table 2

A Short List of Bladder Cancer Priorities

It has been rightly lamented that only a small minority of bladder cancer patients are enrolled in clinical trials. Robust collaborative clinical care and research partnerships among multidisciplinary groups within and among institutions are required to drive progress in the field. An enhanced portfolio of novel therapeutics[7] tethered to well-annotated tissue repositories and underpinned by strong translational science has the potential to change the therapeutic landscape meaningfully and to enhance organ-preservation options in localized disease. A short list of research priorities in bladder cancer, reflecting the imperatives for individualized management of the disease, is shown in
Table 2. In addition, the special needs of the elderly[51] and the increasing pressures on resource-constrained environments within and outside the developed world must be confronted. The cost of cancer care in the United States is projected to rise by nearly 40% between 2010 and 2020, to an annual cost of $173 billion.[52]

These are formidable challenges, and Benjamin Franklin's adage, "an ounce of prevention is worth a pound of cure," cannot be more relevant given today's research funding shortfalls. Wide variations in the care of early bladder cancer exist, and among high–treatment intensity urology providers, overall survival is unchanged while rates of transition to major surgery are actually increasing.[53] It has been said that for bladder tumors, it is time for a paradigm shift.[54] We believe that the time is overdue.

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