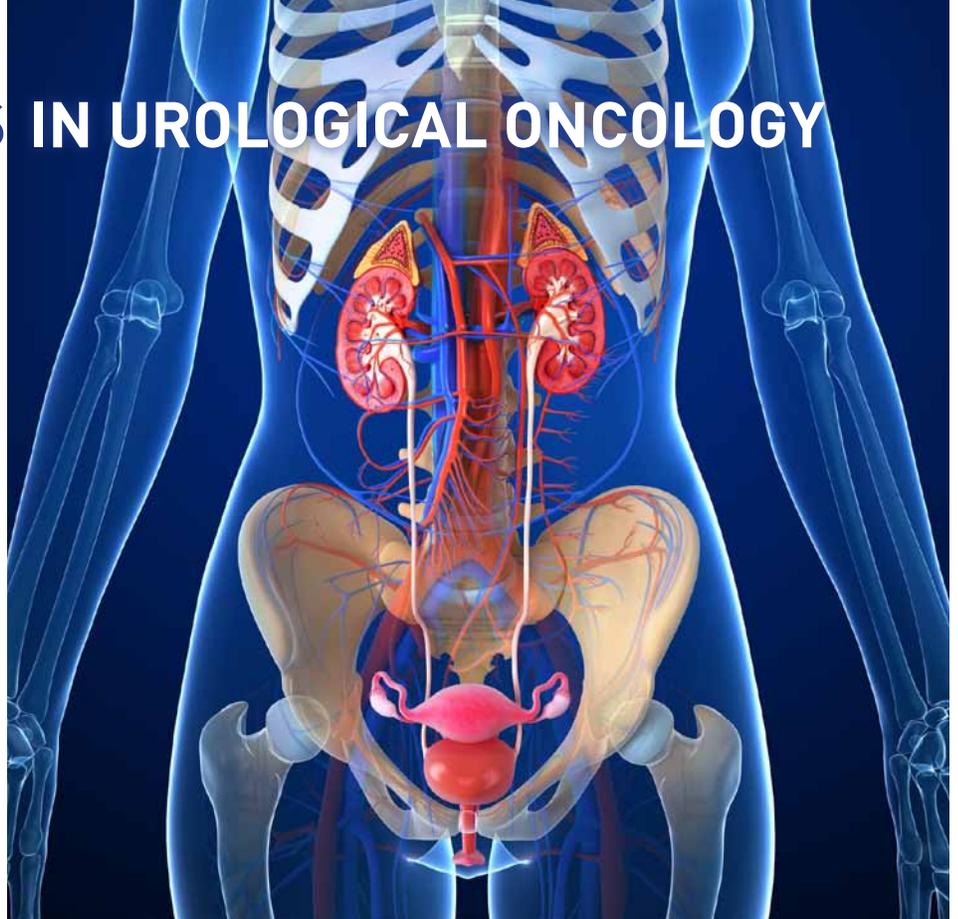


ADVANCEMENTS IN UROLOGICAL ONCOLOGY

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Urologic Oncology in the Department of Urology at the Weill Medical College of Cornell University has been quite active over the last decade. Both clinical and scientific research has grown enormously. Dr. Scherr, the Clinical Director of Urologic Oncology and the Ronald Stanton Clinical Scholar in Urology, Associate Professor of Urology has played an active role in both clinical and research activities.

A robust and clinically active service has evolved over the last decade. In particular, we have one of the largest robotic oncology practices in the world. Both prostate and bladder cancer can be treated with the use of robotic technology. This form of minimally invasive surgery allows for precision oncological control while maximizing functional outcomes including sexual function and urinary control. We are now able to perform complete nerve sparing bladder reconstructive surgery that allows both men and women to achieve complete urinary control and normal sexual function following bladder cancer surgery.

Bladder cancer has become a large focus in the Division of Urologic Oncology at Weill Medical College of Cornell University. The

American Cancer Society estimated that 70,980 new cases of bladder cancer were diagnosed in 2009 in the United States alone, accounting for 14,330 deaths¹. Bladder cancer ranks as the fourth and the eighth most common malignancy in men and women, respectively, in the Western world². The urothelium is the dominant type of epithelium lining the urinary bladder, ureters, and renal pelvis,³ and more than 90% of bladder cancers are urothelial carcinomas⁴. Approximately 70% of newly diagnosed cases of bladder cancer represent superficial disease, whereas the remaining 30% are more aggressive, and invade the muscular layers of the bladder wall⁵ (see Figure 1 for a brief overview of the bladder mucosa organization). Current standard practice dictates that transurethral bladder surgery and bladder biopsies be done in a hospital setting, adding to cost and patient anxiety. Reasons include risks of complications, including bleeding, infection, and for a small proportion, bladder perforation, requiring open surgical intervention in the operating room to repair the bladder. Also, patients require a foley catheter for a mean period of 1.7 days post-procedure.

One of the greatest problems with the clinical management of non-muscle invasive bladder cancer is the very high recurrence rate (31-78% at 5 years)⁶. Consequently, it is necessary to maintain patients on lifelong surveillance, which includes periodic cystoscopic evaluations along with urinary cytology assessments as well as periodic CT imaging to assess the urothelium of the upper urinary tracts. It is estimated that over 4 million cystoscopies are performed each year and that approximately \$4 billion per year is spent on bladder cancer surveillance, making bladder cancer **the most expensive cancer over the lifetime of a patient**⁷, with ~60% of the costs attributable to treatment of recurrences⁸.

CURRENT CHALLENGES IN BLADDER CANCER MANAGEMENT

In contemporary clinical practice, any suspected neoplastic lesion (irrespective of grade) found during a cystoscopic procedure is completely resected, whereas lesions representing reactive changes are typically left untreated. Patients having high-grade lesions are further treated with intravesical adjuvant therapy. The most

significant current challenges of bladder cancer management are three-fold.

(1) Inability of the urologist, using the 10-12x magnification of a typical cystoscope, to adequately distinguish carcinoma from benign reactive changes (e.g., inflammation).

In case of papillary or pseudo-papillary lesions, this represents a large number of unnecessary biopsies that turn out to be benign upon histopathologic examination, and typically warrant nothing more than continued surveillance. This is especially a concern in the case of carcinoma in situ (CIS), which is a superficial and flat but high-grade lesion, whose presence has been identified as an important prognostic factor for the recurrence and/or progression of bladder cancer⁹. A recent estimate suggests that conventional white light cystoscopy is apt to miss up to 42% of the CIS¹⁰. Part of the problem is that CIS and benign inflammation appear quite similar under a regular cystoscope (irregular erythematous flat lesions), and it is often impossible to biopsy all suspicious lesions due to considerations of patient safety and cost.

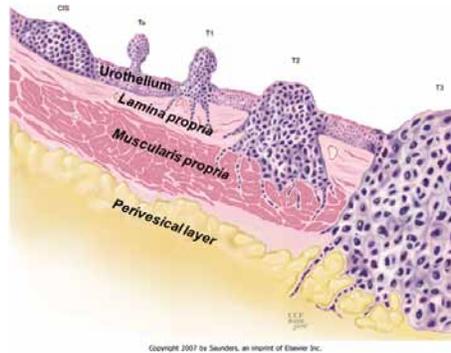
(2) Inability of the urologist to assess the areas surrounding the biopsy sites for neoplastic changes.

A study investigating the source of “recurrences” of urothelial carcinoma on repeat cystoscopy found that up to ~50% of the apparent recurrences were in fact pre-existing tumors that were missed during the first cystoscopy¹¹. Currently, standard white light cystoscopy does not allow visualization of tissue substructures and cellular features in the vicinity of the biopsy/resection sites.

(3) Inability of the urologist to ensure that biopsies removed for subsequent histopathologic diagnosis are of adequate quality.

One of the major goals of cystoscopic procedures, in addition to local control of disease via tumor resections, is obtaining biopsies of suspicious lesions for subsequent histopathologic diagnosis and staging. This diagnosis typically includes the

following categories: (a) benign/malignant; (b) low-grade/high-grade (grading); and (c) invasive/noninvasive (staging). In order to be able to do this, the biopsies have to be of adequate quality, which includes: (a) no cautery artifacts in the regions of interest, so cellular features are clearly visible for grading; and (b) presence of muscularis propria in the specimen to ensure correct staging, since muscle-invasive bladder cancer is highly aggressive and is typically no longer eligible for superficial resection and surveillance, but rather, is treated with radical cystectomy. It is crucial for the pathologists to be able to accurately stage and grade tumors, since



the treatment modalities are distinct for high-grade vs. low-grade disease, and for noninvasive vs. muscle-invasive disease. Currently, standard white light cystoscopy does not allow visualization of tissue substructures and cellular features.

For many decades, scientists and clinicians alike have been wrestling with the dilemma of studying the process of carcinogenesis. Both in vitro and in vivo experimentation has been utilized to dissect out molecular mechanisms in an attempt to further understand the transformation from a normal to a malignant phenotype. Toward this goal, there has been a continuous interplay between technology and scientific and clinical questioning. Clinical inquiries have driven technical developments and technology has certainly impacted the questions being asked. This co-dependent relationship between scientific inquiry and technological achievement is represented in no better way than in the development of multi-photon imaging. Thus, the field of non-linear laser excitation has evolved and at

its center is the phenomenon of multi-photon microscopy (MPM). MPM has now been used throughout the biosciences and has become the standard form of in vivo fluorescence microscopy in laboratory animals. Two and three photon fluorescence imaging allows for real time observation of cellular events in live tissue. It has already been utilized in several areas of molecular biology and cancer therapeutics. In particular, it has been used to image gene expression, track cell populations and image patterns of cellular migration, monitor molecular therapeutics, quantify tumor angiogenesis, among others. We feel that multi-photon imaging is prepared to help us further understand the molecular mechanisms of carcinogenesis and move forward to human, in vivo trials as both a diagnostic tool as well as a real-time measure of cancer therapeutics in human malignancies.

Human transitional cell carcinoma of the bladder is a realistic starting point for the application of multi-photon imaging to human cancer treatment. Several points make this clear. First, a prerequisite to the application of any external imaging device is the ability to apply the device directly to the tumor. The fact that bladder cancer is easily accessible through the male or female urethra makes the application of two-photon imaging realistic inside the bladder. Second, the current necessity for frequent biopsy in bladder cancer for pathology provides immediate access to tissue for MPM inspection to establish its effectiveness. Third, at the Weill Medical College New York Presbyterian Hospital, we see over 300 new cases of bladder cancer per year and therefore have the capacity of applying MPM in a rapid and efficient manner. Fourth, we have well developed orthotopic bladder tumor models in laboratory animals as well as several transgenic strains that allow for the application of MPM in the study of transitional cell carcinoma. Finally, we have several therapeutic interventions for bladder cancer that focus either on specific molecular targets or involve immune manipulation that we feel can be better studied with the use of MPM.