Session II: Bladder

Prevention, detection, and management of urothelial cancer: Where is better imaging needed?

Edward M. Messing
University of Rochester Medical Center, Rochester, NY 14642, USA

Bladder cancer, primarily urothelial cancer, is the fifth most commonly diagnosed non-cutaneous malignancy in the US and the second most prevalent malignancy in middle-aged and elderly males. Our exploration of bladder cancer includes its epidemiology, clinical presentation, and how it is currently managed from a clinical and population-based perspective.

Imaging may be of assistance in the prevention, diagnosis, and clinical management of bladder cancer, through such methodologies as CT diagnosis of bladder cancer; fluorescence cystoscopy for superficial bladder cancer therapy and prevention of recurrences (Dr. Grossman), improved staging using ferromagnetic nanoparticles (Dr. Harisinghani), and spectroscopic diagnosis with elastic light scattering (Dr. Bigio).

Preclinical models have generated data germane to bladder cancer including prevention using flat panel detector cone beam CT imaging, identification of sentinal lymph nodes using intravesical indocyanine green (ICG) and near infrared fluorescence, and reduction of morbidity by identifying cavernosal nerves using ICG near infrared fluorescence. Some of these new technologies are in late-stage clinical testing, while others are still under development in preclinical models.

Fluorescence cystoscopy: Improving detection and outcome of bladder cancer

H. Barton Grossman
University of Texas MD Anderson Cancer Center, Department of Urology, Houston, TX 77030, USA

Endoscopic visualization (cystoscopy) and transurethral resection are effective, well tolerated techniques for diagnosis and treatment of bladder cancer. However, it is widely recognized that cystoscopy can miss biologically important lesions such as carcinoma *in situ*. Attempts to improve the effectiveness of cystoscopy are not new, but initial methods were impractical and had limited efficacy. Fluorescence cystoscopy became feasible with the discovery that intravesical administration of aminolevulinic acid (ALA) made bladder cancers fluoresce when exposed to blue light. More recently, the creation of a hexyl ester of ALA, HAL, made this technique practical because it reduced the amount of time needed for drug exposure prior to cystoscopy to one hour.

Not surprisingly, fluorescence cystoscopy can reveal carcinoma *in situ* that is visually occult with conventional (white light) cystoscopy. Unexpectedly, fluorescence cystoscopy also enhanced the detection of papillary tumors. While increased detection is laudable, patient benefit has not been demonstrated. Using European Association of Urology bladder cancer guidelines, fluorescence cystoscopy with HAL resulted in a change in therapy in 17% of patients. Furthermore, several studies with ALA have shown that resection of bladder cancer with fluorescence results in improved disease-free survival compared to conventional resection with white light. An ongoing international study is testing the ability of resection with HAL to decrease the rate of tumor recurrence.

Fluorescence cystoscopy improves bladder cancer detection and enables more complete resection with increased tumor free survival.

Nanoparticles in bladder cancer

Mukesh Harisinghani
Massachusetts General Hospital, Abdominal Imaging/Interventional Radiology, Boston, MA 02114, USA

Cancer of the urinary bladder is one of the most common malignant tumors of the urinary tract; definitive therapy and prognosis depend on depth of tumor infiltration and extent of metastatic lymph nodes. Current cross-sectional imaging modalities like computed tomography (CT) and magnetic resonance imaging (MRI) rely predominantly on nodal size for detecting metastases and hence have limited accuracy, due to considerable overlap between size of benign and malignant nodes. Gadolinium enhancement is not very useful for detecting nodal metastases, as both normal sized metastatic nodes and non-metastatic nodes may show similar enhancement. The role of ^{18}F-fluorodeoxyglucose (FDG) whole-body positron emission tomography (PET) for nodal staging is limited, as FDG accumulates as part of the physiologic process in the urinary bladder and thus obscures PET positive nodes; also, FDG uptake in bladder cancer is low. Thus, in order to detect metastasis in normal-size lymph nodes, it is necessary to obtain a differential enhancement between normal lymph node tissue and metastases. Previously published studies using ultrasmall superparamagnetic iron-oxide (feru-moxtran) nanoparticles have found that normal nodal tissue shows contrast uptake and selective decrease in signal intensity on T2- or T2*-weighed images, whereas nodal areas infiltrated with metastases lack ferumoxtran uptake and retain their high-signal intensity on the post-ferumoxtran MR images. In exploring the limitations of existing imaging techniques, clinical examples show the advantages of nanoparticle-enhanced MRI in improved nodal staging in bladder cancer. Improved sensitivity and specificity of nodal detection on therapy and prognosis may impact treatment of bladder cancer.

Spectroscopic diagnosis of bladder cancer with elastic light scattering

Irving J. Bigio
Boston University, Departments of Biomedical Engineering, Electrical and Computer Engineering and Physics, Boston, MA 02115, USA

Noninvasive optical tissue diagnosis, often called "optical biopsy," utilizing various types of optical spectroscopy and typically mediated by optical fibers, has become a major component of the growing field of biomedical optics. The most common approach has been based on UV-light-induced fluorescence spectroscopy, although Raman spectroscopy and reflectance spectroscopy have also been investigated. Our group at Boston University (continuing earlier work by Bigio and colleagues started at Los Alamos National Laboratory) has developed elastic scattering spectroscopy (ESS), a point spectroscopic measurement technique. Performed using appropriate fiberoptic geometry, the technique is sensitive to morphological changes at the cellular and subcellular level. These include size and hyperchromaticity of cell nuclei, chromatin granularity, nuclear crowding, and changes in the size/density of mitochondria and other cellular organelles. ESS spectra derive from wavelength-dependent optical scattering efficiency caused by optical index gradients (due to cellular and subcellular structures). The ESS method senses those morphology changes in a semi-quantitative manner, without actually imaging the microscopic structure.

For bladder cancer, the intent is not to replace conventional biopsy/histopathology with ESS as the primary diagnostic method, but rather to use it to provide guidance for more selective biopsy with the goal of significantly reducing the number of unnecessary biopsies (increased specificity), while, nonetheless increasing the yield (sensitivity). Guided treatment is also enabled by this modality, as the treatment of choice for recurrent bladder disease is removal or ablation of suspicious lesions under endoscopy. ESS can identify tissue requiring ablation and can determine disease margins. This approach will have more immediate acceptance by the medical community, with commensurate rapid commercial potential. An early clinical study has yielded promising statistics, although the sample size was small.