



8th Annual Bladder Cancer Think Tank

Collaborating to Move Research Forward

On August 8-10, 2013, more than 120 leading clinicians, researchers, patient advocates, and industry representatives convened in Snowmass Village, Colorado, for the 8th Annual Bladder Cancer Advocacy Network Think Tank. Being the only bladder cancer-specific annual meeting in North America, this year's Think Tank engaged participants representing more than 60 institutions, coming from across the United States and Canada. Bladder cancer is the sixth most common cancer in the United States with an estimated 72,500 new cases and over 15,000 deaths projected for 2013. With no major changes in these statistics over the past 30 years, there continues to be a tremendous need for more bladder cancer research. Since 2006, the Think Tank meeting has focused on creating collaborative opportunities for basic scientists, practitioners, advocates and industry partners to move the field forward.

To set the tone for the meeting, Dr. Harvey V. Fineberg was invited to present the Keynote Address, "Cancer Care for the Whole Patient." Dr. Fineberg, President of the Institute of Medicine, emphasized the importance of patient-centered care, including psychosocial health needs, which are often not adequately addressed. Many clinicians don't understand their patients' psychosocial needs, are unaware of psychosocial health care resources and fail to recognize, treat or refer patients to appropriate psychosocial services. Dr. Fineberg highlighted the IOM committee's standard of care and suggestions for implementing the best care practices more broadly. He stressed that attending to psychosocial needs is an integral part of high-quality cancer care and every patient should have the right to receive care with appropriate psychosocial health services.

With the theme of "Collaborating to Move Research Forward," the Think Tank panel presentations and interactive discussions focused on three main areas in bladder cancer: gender disparities, sexual dysfunction, and targeting novel pathways. In addition, throughout the meeting, participants worked in smaller groups to identify projects for the upcoming year focusing on areas such as improving enrollment and quality of clinical trials, collecting data from multiple institutions for future research, evaluating patterns of care for non-muscle invasive bladder cancer, improving the delivery of care for muscle-invasive disease, improving the quality of life for survivors, addressing upper tract disease, and examining the impact of health policy changes on bladder cancer. The Think Tank also featured young researchers presenting on significant topics related to the disease.

The meeting concluded with a renewed commitment by all participants to continue this collaboration of exploring new ideas, sharing the latest research and examining multidisciplinary approaches to advancing the diagnosis, treatment and quality of life care for patients with bladder cancer.

Session One: Understanding Gender Disparities in Bladder Cancer

“Impact of Gender on Diagnosis and Outcomes of Bladder Cancer”

Yair Lotan, MD, UT Southwestern, Chair

“Bladder Cancer: Experimental Evidence that Sex Matters”

Edward Messing, MD, University of Rochester

“Life after Cystectomy: The Role of Gender in Functional Outcomes”

Angela Smith, MD, University of North Carolina, Chapel Hill

Panel Discussion

Eila Skinner, MD, Stanford University

The role of gender has not been fully explored in terms of bladder cancer diagnosis, outcomes, experimental evidence, and quality of life following bladder removal surgery. There are statistics available on incidence and diagnosis but there remains a lack of understanding regarding why these differences in gender exist. The goal of the panel was to generate discussion and inspire more work in this area. Men are three times as likely as women to be diagnosed with bladder cancer, and this higher incidence is not well explained by exposure to tobacco or occupational carcinogens. Women often experience a delay in diagnosis and are less likely to be immediately referred to a urologist if they have blood in their urine. This impacts the stage of diagnosis. Furthermore, women also have a higher mortality rate than men and experience worse outcomes per stage of diagnosis despite receiving similar treatment. The higher incidence rate of bladder cancer among men is supported in animal experimental data with male rodents having higher rates of incidence than female rodents. Studies are being conducted to look at expression of hormone receptors in bladder cancer patients. Women also have different outcomes in quality of life as well as urinary, sexual and bowel function following bladder removal surgery. Using nerve-sparing and gynecologic organ-sparing surgical techniques may be connected to improvements in urinary function including hypercontinence in women with neobladders, and sexual function. There is a lack of research on sexual function following radical cystectomy among men and women separately and evaluating bowel function following radical cystectomy in women. There is a significant need for further investigation into gender disparities in bladder cancer. Further research could help determine the impact of gender on diagnosis, provide a better understanding of underlying causes of bladder cancer and help improve quality of life.

Session Two: Sexual Dysfunction in Bladder Cancer: Expanding the Conversation

David Latini, PhD, Baylor College of Medicine, U.S. Department of Veterans Affairs, Co-chair

Cheryl Lee, MD, University of Michigan, Co-chair

“Sexual Reintegration: The Patient Perspective”

Pat Boumansour, Survivor

Randy Layne, Survivor

“Beginning the Conversation: Office-based Tools”

John Mulhall, MD, Memorial Sloan-Kettering Cancer Center

“Nurturing Healthy Relationships: Coping with Psychosocial Challenges in Sexual Health”

Daniela Wittmann, PhD, LMSW, CST, University of Michigan

Sexual dysfunction following bladder removal and reconstruction is a topic that has been insufficiently addressed. Patients, physicians and social workers shared their perspectives during the session. The patients on the panel reported that they were focused on surviving bladder cancer and hadn't considered sexual function issues before the surgery. In retrospect patients wished they had been fully informed by their doctor about the topic prior to surgery. Other speakers highlighted the importance of talking about sexual function before and after surgery, addressed barriers to discussing the issue for patients and physicians and tactics to improve outcomes. Studies have found that patients often want the physician to initiate the conversation about sexual function while physicians are waiting for the patient to bring up the topic with the result being that it is not discussed. It was emphasized that the physician's goal is to achieve a cancer cure while maintaining the patient's quality of life. The speakers discussed that returning to normal may not be a reasonable goal. A better objective is “to facilitate the return of the patient (and the couple where one exists) to satisfactory sexual relations.” Physicians need to know

about the available options, set realistic expectations, refer patients to a sex therapist when necessary, and ensure there is a champion for addressing sexual function issues at their medical institution. Understanding how chemotherapy, radiation and surgery can impact sexual function is also important. Additionally, it is essential to know that self-image and self-esteem are components of a patient's sexuality.

Session Three: Targeting Novel Pathways in Bladder Cancer

Andrea Apolo, MD, National Cancer Institute, Co-chair

Jonathan Rosenberg, MD, Memorial Sloan-Kettering Cancer Center, Co-chair

"Therapeutic Targets and Pathways in Bladder Cancer"

Margaret Knowles, PhD, University of Leeds

"Treatment Selection and Predictive Biomarkers in Bladder Cancer"

Dan Theodorescu, MD, PhD, University of Colorado

"The Bladder Cancer Genome: Significance and Limitations"

Bogdan Czerniak, MD, PhD, MD Anderson Cancer Center

"Radiotherapy Biomarkers in Bladder Cancer"

Jason Efstathiou, MD, PhD, Massachusetts General Hospital, Harvard Medical School

"Understanding the Immunologic Effect of BCG on Tumor Growth and Development"

Matthew Albert, MD, PhD, Institut Pasteur

There are many areas of research that offer promising insight into targeting new ways to fight bladder cancer. Areas that were discussed in this session include fibroblast growth factor receptor 3 (FGFR3), the potential of individualized medicine in bladder cancer with prognostic and predictive markers, understanding the bladder cancer genome, bladder preservation with chemotherapy and radiation, and understanding immunologic effects of BCG therapy. Dr. Margaret Knowles spoke about targeting a specific gene for novel treatment, FGFR3. There are many therapeutic agents in development and clinical trials that target FGFR3 receptors. Dr. Knowles discussed the potential for investigating this gene in bladder cancer. Dr. Dan Theodorescu also spoke about gene expression and biomarkers. He explained that individualized cancer medicine offers the opportunity to use gene expression and mutation to tailor treatment plans to each patient using prognostic and predictive markers. Prognostic markers look at "disease aggressiveness", for example predicting progression from non-muscle invasive bladder cancer to muscle invasive disease, or cancer recurrence after bladder removal surgery. Predictive markers may indicate the likelihood that a patient's cancer will respond to specific treatments. These two types of markers can improve outcomes by predicting which patients would be more likely to benefit from different therapies. Dr. Bogdan Czerniak expanded the discussion to the bladder cancer genome, which can offer insights into pathways and genetic and epigenetic events leading to the development of disease. For example, looking at molecular pathways involved in the development of bladder cancer, there are many pathways involved, so it makes sense that a tumor might not respond to a single agent if there are alternate pathways. This approach can provide information about early events in bladder cancer development at the genomic level which will generate risk factors, detection markers, therapeutic targets and preventive targets. The limitations are that these discoveries and pathways are still virtual and need to be verified using molecular biology. Dr. Jason Efstathiou turned the discussion to gene expression and biomarkers related to radiation therapy for bladder cancer. Researchers are finding that having higher levels of expression of certain genes is associated with a better response to radiation and chemotherapy while the reverse is true with other genes. In this way, radiation and chemotherapy treatment for bladder cancer also can be enhanced using biomarkers. Biomarkers can be used to predict outcomes and select subsets of patients with muscle-invasive bladder cancer who will have better outcomes with the treatment. Lastly, Dr. Matthew Albert explored how a patient's immune system responds to Bacille Calmette-Guerin (BCG) treatment for non-muscle invasive bladder cancer. Examining how the immune system responds to BCG therapy could allow for improving response rates in bladder cancer patients or even applying the concept to other diseases. BCG is typically administered to patients with non-muscle invasive bladder cancer in six weekly instillations, often with maintenance therapy following the initial six weeks. There was a small inflammatory response following the first instillation of BCG. However, after the third weekly instillation there was a much bigger inflammatory response. This is an indication of priming the immune system for a larger response. A single instillation of BCG is capable of

achieving t-cell priming, but those T-cells don't move into the bladder. It's necessary to have repeated instillations of BCG to move T-cells into the bladder micro-environment.

Supporting Young Investigators

Four young investigators were awarded John Quale Travel Fellowships to present their research at the 2013 Think Tank Meeting:

Richard Bambury, MB, BCh, BAO, Memorial Sloan-Kettering Cancer Center, presented on the genomic characterization of metastatic urothelial carcinoma.

Sima Porten, MD, MPH, MD Anderson Cancer Center, discussed the biology of bladder cancer metastases.

Srinivas Vourganti, MD, National Cancer Institute, talked about precision medicine in the treatment of urothelial carcinoma.

Daniel Willis, MD, MD Anderson Cancer Center, presented on micropapillary bladder cancer.

Ami Bhatt, MD, PhD, an early career translational investigator at the Dana-Farber Cancer Institute, was the recipient of BCAN's 2012 **Raymond and Maria Floyd Award for Bladder Cancer Research** and presented on her results. With the help of the award, Dr. Bhatt conducted research on next-generation sequencing to identify bladder cancer-associated pathogens. Within her dataset she did not find viruses in the primary bladder cancer tumors or metastases. However, she discovered that gene expression of primary bladder cancer tumors and metastases were fairly similar and that primary tumors and metastases were more similar to primary tumors and metastases in other patients than they were to normal bladder tissue from which they had evolved. This finding has also been demonstrated in breast cancer research. Her next steps are to continue her research including whole exome sequencing and further investigation of pathogens in different types of bladder cancer.

Ongoing Collaboration

Attendees at the 2013 Think Tank participated in seven different working groups including one newly-formed group. The working groups met in small group sessions to discuss ongoing projects and to develop plans for the coming year. Each group presented on their activities to the full Think Tank.

Enhancing Enrollment and Design of Bladder Cancer Clinical Trials

This working group is focusing on how to improve clinical trial design and enrollment. Entering its third year, the working group continued efforts to improve quality of clinical trials as well as coordination among investigators by working with BCAN to develop an online dashboard to serve as a central repository of open bladder cancer trials, available to researchers and the general public. The clinical trials dashboard will include patient, physician and clinical investigator portals.

Translational Science

As it enters its third year, this working group's goal is to set up a marketplace of ideas, research questions, unique assessment tools and bladder cancer tissue resources. Last year the group focused on micropapillary bladder cancer (MPBC), a sub-type of urothelial carcinoma seen in up to 2-5% of all bladder cancers. Overall prognosis is poor and response to BCG and systemic chemotherapy is generally seen as less effective. The group conducted a survey among medical professionals regarding treatment for MPBC. The next steps are to finalize data agreements between participating institutions, have a group of pathologists confirm the MPBC cases and share the data from collaborating institutions. The group will focus on global characterization of MPBC and pathology projects.

Non-Muscle Invasive Bladder Cancer

This working group is in its second year and is focusing on evaluating patterns of care for non-muscle invasive disease and identifying potential improvements. Group members are working on many projects, including a prospective study on cystoscopy and surveillance patterns; a prospective pilot study comparing non-muscle invasive bladder cancer surveillance guidelines from the European Association of Urology (EAU) and American Urological Association (AUA); and a study looking at high grade non-muscle invasive bladder cancer tumors, including secondary treatments given, progression to muscle invasive disease, and other treatment options.

Standardization of Care

As it enters its fifth year, this working group's goals are to identify current practice patterns for evaluation and treatment of muscle invasive disease and work towards developing a standardized approach. Ongoing projects include a Quality of Care Initiative which analyzed chemotherapy use at 16 academic medical centers before and after surgery, and found substantial differences among the institutions. The group is proceeding with a survey on patient understanding and satisfaction of their treatment for muscle invasive bladder cancer. New efforts include standardizing pathology reporting for cystectomy and TURBT, utilizing a multidisciplinary clinic in treating bladder cancer, standardizing the approach to common issues in bladder cancer care, publishing a handbook for managing bladder cancer, and standardizing quality of life reporting.

Survivorship

Since 2009, this working group has focused on identifying the needs of bladder cancer survivors and designing tools to help address those needs. The working group has developed a Bladder Cancer Survivorship Care Plan, which provides a record for providers and patients of all treatments received, doctors seen, and available treatment resources. The plan has been pilot tested in multiple institutions and the results are being analyzed. The group has also developed a Patient Tool Kit that is available on the BCAN website and features topics such as cystoscopy, transurethral resection of a bladder tumor (TURBT), BCG, radical cystectomy, and urinary diversions. New efforts include working with BCAN on urinary diversion informational videos for patients, peer support training, developing a tip sheet on dietary modification after bladder removal surgery, creating a tip sheet on sexual health, raising awareness through articles in lay and medical professional publications, and giving medical professionals education regarding how to talk to patients when breaking bad news and making difficult decisions.

Patient-Centered Outcomes and Policy (formerly Health Services Research / Health Policy)

In its second year, this working group is focused on health policy, quality of care, and comparative effectiveness research issues in bladder cancer. The group's efforts include looking at the provisions in the Affordable Care Act for coverage of patients enrolled in clinical trials, performance measurement involving developing condition-specific genitourinary measures and the American Taxpayer Relief Act of 2013 provision to opt out of the Physician Quality Reporting System with participation in a "qualified clinical registry", and bundled payment demonstration projects. They are investigating qualified clinical registries to make sure they provide adequate information regarding bladder cancer data. Lastly, they are looking at Patient Centered Outcomes Research (PCOR) related to bladder cancer.

Upper Tract Disease

In its first year, this working group's goals are to design studies to allow for improved diagnosis and clinical staging of upper tract urothelial carcinoma (UTUC). The group identified gaps in knowledge about neoadjuvant chemotherapy and the role of lymphadenectomy and is collaborating to create clinical trials to address these issues.

BCAN gratefully acknowledges that the 2013 Think Tank was supported by unrestricted educational grants from:

Abbott Molecular, Inc.; Dendreon Corporation; OncoGenex Pharmaceuticals; and Photocure.