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Summary of the 8th Annual Bladder Cancer Think Tank: Collaborating to move research forward

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Abstract

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Objectives: The 8th Annual Bladder Cancer Think Tank (BCAN-TT) brought together a multidisciplinary group of clinicians, researchers, and patient advocates in an effort to advance bladder cancer research.

Methods and Materials: With the theme of "Collaborating to Move Research Forward," the meeting included three panel presentations and seven small working groups.

Results: The panel presentations and interactive discussions focused on three main areas: gender disparities, sexual dysfunction, and targeting novel pathways in bladder cancer. Small working groups also met to identify projects for the upcoming year, including: (1) improving enrollment and quality of clinical trials; (2) collecting data from multiple institutions for future research; (3) evaluating patterns of care for non-muscle-invasive bladder cancer; (4) improving delivery of care for muscle-invasive disease; (5) improving quality of life for survivors; (6) addressing upper tract disease; and (7) examining the impact of health policy changes on research and treatment of bladder cancer.

Conclusions: The goal of the BCAN-TT is to advance the care of patients with bladder cancer and to promote collaborative research throughout the year. The meeting provided ample opportunities for collaboration among clinicians from multiple disciplines, patients and patient advocates, and industry representatives.

Keywords

Bladder cancer; BCAN; Think Tank; Targeted therapies; Sexual dysfunction; Gender disparities; Working groups

1. Introduction

From August 8 to 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 (BCAN-TT). This year's meeting engaged participants representing more than 60 institutions from across the United States, Canada, and Europe. Bladder cancer is the sixth most common cancer in the United States. In 2013, there were an estimated 72,500 new cases and more than 15,000 deaths from this malignancy [1]. 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 BCAN-TT has focused on creating collaborative opportunities for researchers, practitioners, advocates, and industry partners to move the field forward.

Dr. Harvey V. Fineberg, president of the Institute of Medicine, set the tone for the meeting in his keynote address, "Cancer Care for the Whole Patient." Fineberg emphasized the importance of patient-centered care, including patients' psychosocial needs, which are often inadequately addressed. Many clinicians do not understand their patients' psychosocial needs and thus fail to recognize and treat them, or are unaware of the psychosocial health care resources available for referral. Fineberg highlighted the Institute of Medicine 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 that every patient has a right to appropriate psychosocial health care services.

BCAN-TT panel presentations and interactive discussions focused on 3 main areas: sex disparities, sexual dysfunction, and targeting novel pathways in bladder cancer. Small groups of participants also met to identify projects for the upcoming year, which included the following: (1) improving enrollment in and quality of clinical trials, (2) collecting data from multiple institutions for future research, (3) evaluating patterns of care for non–muscle-invasive bladder cancer (NMIBC), (4) improving delivery of care for MIBC, (5) improving quality of life for survivors, (6) addressing upper tract disease, and (7) examining the effect of health policy changes on research and treatment of bladder cancer. The BCAN-TT also featured young researchers who presented on significant topics related to the disease.

The meeting concluded with all participants renewing their commitment to collaboratively explore new ideas, share the latest research, and examine multidisciplinary approaches to advancing the diagnosis, treatment, and care of patients with bladder cancer.

2. Understanding sex disparities in bladder cancer

2.1. Cochairs: Yair Lotan, Edward Messing, Angela Smith, and Eila Skinner

The role of sex in bladder cancer diagnosis, outcomes, experimental evidence, and quality of life following cystectomy has not been fully explored. Men are 3 times more likely to develop bladder cancer in their lifetime than women are, which has been attributed to higher exposure to tobacco and occupational carcinogens in men [1–3]. Previous studies found that the population attributable risk owing to smoking was 50% to 65% in men and 20% to 30% in women, though recent studies have demonstrated a more balanced population attributable risk of approximately 50% for both sexes because of increased rates of smoking in women [4]. A very large cohort study that included 281,394 men and 186,134 women found that current smokers who smoked more than 40 cigarettes/d had a 4-fold (men) and 5-fold (women) higher risk of bladder cancer than never smokers of the same sex [4]. Population attributable risks explain what proportion of bladder cancer is attributable to a risk factor such as smoking; however, they do not explain differences in the incidence rates of bladder cancer in men and women with similarly high exposures to tobacco. Data from the National Bladder Cancer Study found that, when adjusted for age, men had a bladder cancer incidence of 27.5/100,000 person-years vs. 7.0/100,000 person-years for women [5]. These data were based on bladder cancer incidence in 1978, when men smoked much more frequently than women.

Over the past 20 to 30 years, rates of smoking among women have increased. A similar incidence of bladder cancer among heavy smokers of both sexes might thus be expected, as smoking is the number 1 risk factor for developing bladder cancer [4]. Although it is evident that smoking is associated with an increased risk of bladder cancer for both sexes, it does not explain the sex differences in incidence. Data from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial found that men had significantly higher rates of bladder cancer than women, despite similar intensity of smoking [6,7].

The second most common cause of bladder cancer is occupational exposure, primarily to aromatic amines [3]. A study of bladder cancer incidence in the United Kingdom found that the overall risk for bladder cancer owing to occupational exposure was only marginally higher in men than in women (7.06% in men vs. 1.89% in women) [2]. Similar findings were seen in the National Bladder Cancer Study where, in the absence of exposure to cigarettes, occupational hazards, or urinary tract infection, the sex disparity in risk for bladder cancer persisted (11 vs. 4.1/100,000 person-years in men and women, respectively) [5].

Bladder cancer is far less common in women than in men, and these sex differences in incidence have remained constant over the past 20 to 30 years, despite females smoking relatively more and entering male workplaces, so that carcinogen exposure should favor a narrowing of these incidence differences. As this has not occurred, other explanations may exist. Several laboratory investigations have focused on sex hormones and their receptors to explain these differences. Overall, 2 animal models have primarily been used: carcinogen-induced urothelial carcinoma using N-butyl-N (4-hydroxybutyl) nitrosamine and transgenic models using SV-40 large T antigen linked to the urothelium-specific uroplakin II promoter. In both models, hormonally intact males develop more tumors, and more quickly, than females [8–10]. Castrated males develop tumors at the female incidence rate [8–11]. Androgen receptor-knockout (AR-KO) males develop far fewer bladder tumors, and females without ARs develop none [8]. Male AR-KO mice given testosterone develop more tumors, but far fewer than wildtype males who receive testosterone [8]. Urothelial-specific AR-KO male mice do not develop N-butyl-N (4-hydroxybutyl) nitrosamine–induced bladder cancers, indicating the importance of AR in the urothelium [12]. Estrogens and estrogen receptor α inhibit bladder cancer formation in these models, but estrogen receptor β promotes it. Downstream effector molecules of the AR include cytochrome p450 4p1 (activates carcinogens) [13], urothelial uridine diphosphate glucuronosyltransferase (detoxifies carcinogens), CD24 [14,15], MMP9, COX-2 [16] (all up-regulated by AR), and TSP-1 [10] (down-regulated by AR). All of these molecules favor bladder cancer growth. These laboratory investigations have provided preliminary evidence that may explain some of the sex disparities in bladder cancer incidence, but much work remains to further elucidate the causes of these differences.

Another area of sex disparity is functional outcomes after cystectomy. In women, functional outcomes following radical cystectomy include urinary, sexual, and bowel functions, as well as overall quality of life. Urinary functional outcomes related to the orthotopic neobladder are different among women and men. Overall, rates of both incontinence and hypercontinence are higher in women than in men [17,18]. Anatomic hypotheses for achieving successful functional outcomes include preservation of the nervous system through nerve-sparing cystectomy [19] and establishing posterior support for the neobladder through gynecologic organ preservation [20]. A handful of studies of gynecologic organ preservation reveal improved hypercontinence rates compared with anterior exenteration [21,22]. A further argument for gynecologic organ preservation is that estrogen deprivation and vaginal resection may further contribute to female sexual dysfunction. No specific studies address bowel dysfunction in women. General studies suggest that bowel dysfunction does occur [23], but more research is necessary to identify the causes. Finally,

quality of life represents a combination of all 3 functional outcomes, but few studies evaluate female- specific quality of life following cystectomy. In summary, more research on functional outcomes in women following radical cystectomy for bladder cancer is urgently needed.

3. Sexual dysfunction in bladder cancer: Expanding the conversation

3.1. Cochairs: David M. Latini, Cheryl T. Lee, John Mulhall, and Daniela Wittmann

Sexual dysfunction following bladder removal and reconstruction has been insufficiently addressed. Patients, physicians, and social workers shared their perspectives during this session. Patients on the panel reported that before surgery they were focused on surviving bladder cancer and thus did not consider issues of sexual function. In retrospect, however, patients wished they had been fully informed by their doctor about this topic before surgery. Other speakers highlighted the importance of talking about sexual function before and after surgery, barriers to discussing the issue for patients and physicians, and tactics for improving outcomes. John Mulhall, M.D., director of Sexual and Reproductive Medicine at Memorial Sloan-Kettering Cancer Center, spoke on the importance of frank discussions with patients about sexual health and sexual outcomes. After cancer cure, the next most important goal is to facilitate the return of satisfactory sexual relations and intimacy, not just sexual intercourse, between partners. Daniela Wittmann, Ph.D., a social worker, sex therapist, and assistant professor of urology at the University of Michigan, discussed the importance of the grief and loss process for cancer survivors, who frequently experience changes in body image and sense of self because of changes in their sexual function. Sex therapists are uniquely qualified to educate survivors and their partners about accommodating to a new sexual reality and to address changes in the patient and intimate relationships brought on by bladder cancer.

Studies have found that patients often want the physician to initiate the conversation about sexual function, whereas physicians wait for the patient to bring up the topic, with the result that it is often not discussed [24]. Speakers emphasized that the physician's goal is to achieve a cancer cure while maintaining the patient's quality of life, and 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 available options, set realistic expectations, refer patients to a sex therapist when necessary, and ensure the presence of an advocate to address sexual function issues at the patient's medical institution. Understanding how chemotherapy, radiation, and surgery can affect sexual function, and that self-image and self-esteem are components of a patient's sexuality, is essential. This session was truly instructive and provided the impetus for BCAN's first video segment in the new online series entitled "Conversations About Bladder Cancer," which features members of the Survivorship Working Group (SWG) [25].

4. Targeting novel pathways in bladder cancer

4.1. Cochairs: Andrea Apolo and Jonathan Rosenberg

The 8th Annual BCAN-TT convened an expert panel to discuss “Targeting Novel Pathways in Bladder Cancer.” The panel (Margaret Knowles, Ph.D., from the University of Leeds; Dan Theodorescu, M.D., Ph.D., from the University of Colorado; Bogdan Czerniak, M.D., Ph.D., from MD Anderson Cancer Center; Jason Efstathiou, M.D., D.Phil., from Massachusetts General Hospital, Harvard Medical School; and Matthew Albert, M.D., Ph.D., from the Institut Pasteur/Inserm) drew on their expertise in predictive biomarkers, cancer genomics, immunotherapy, and signaling pathways to highlight factors driving the variable biology of bladder cancer.

Dr. Knowles discussed therapeutic targets and pathways in bladder cancer, with a focus on the fibroblast growth factor receptor 3 (FGFR3). FGFR3 is an oncogenic driver of bladder cancer and a promising therapeutic target [26,27]. Although it is most commonly activated by mutation in low-grade noninvasive bladder tumors (>70%), a significant number of invasive tumors also exhibit this mutation (~ 15%), and 40% to 50% of these show up-regulated expression of nonmutant protein. Generation of FGFR3 fusion proteins has recently been identified as an additional mechanism by which FGFR3 can be activated in bladder cancer. These fusion proteins are most commonly generated by genomic rearrangements on chromosome 4 that fuse the major part of *FGFR3* (exons 1–18) to the nearby gene *TACC3*. Functional work has demonstrated that these fusions are highly activated oncogenic proteins that are constitutively dimerized and signal in the absence of FGF ligands. Strikingly, bladder tumor cell lines containing FGFR3 fusions are extremely sensitive to small molecules and antibodies that target FGFR3. Taken together, preclinical studies indicate that the presence of point mutations in *FGFR3*, up-regulated expression of nonmutant protein, or the presence of a fusion protein may be useful biomarkers for predicting sensitivity to FGFR inhibitors. However, recent evidence from an RNA interference screen indicates that inhibition of FGFR3 can be rescued by epidermal growth factor receptor (EGFR) signaling [28]. Conversely, inhibition of EGFR signaling leads to up-regulated expression of FGFR3. Thus, in some tumor cells cultured in vitro and in xenografts in vivo, optimum cell killing was achieved only when both receptors were inhibited. Although FGFR3 is a potential therapeutic target in advanced bladder cancer, careful assessment of several biomarkers will be required to allow selection of patients for therapy, and this may require assessing the status of EGFR expression or activation [29]. The recent finding of EGFR-FGFR3 feedback should encourage development of trials involving combinations of EGFR and FGFR as a valid approach to the treatment of advanced bladder cancer.

Dr. Czerniak expanded the discussion to the bladder cancer genome, which can offer insights into pathways as well as genetic and epigenetic events leading to the development of disease [30]. His laboratory is credited with developing a unique strategy that combines whole-organ topographic histologic and molecular mapping [31]. This approach was extended to the genome profiling platforms and has provided unique information on the chronology of events in the evolution of the cancer genome from occult field effects to

invasive disease. This strategy is particularly powerful in disclosing the initiating cancer events associated with the development of so-called field effects. Czerniak has provided evidence for the existence of a novel class of genes, termed forerunner genes, which contribute to the early expansion of intra-urothelial neoplasia [30,32]. These genes appear to control several important oncogenic pathways involved in activating the basal stem–like transcriptional programs. Overall, this approach provides insights into early events in bladder cancer development on a genomic scale, which can in turn be useful for the development of novel risk factors, detection markers, and therapeutic and preventive targets [33,34].

Dr. Theodorescu discussed some of the challenges in developing molecular profiles, or gene expression markers (GEMs), that can predict tumor prognosis and response to therapy [35]. Few prognostic biomarkers are approved for clinical use, primarily because their initial performance cannot be repeated in independent data sets. Theodorescu posited that robust biomarkers could be obtained by identifying deregulated biological processes shared among tumor types having a common etiology. To test this hypothesis, Theodorescu and his team performed a gene set enrichment analysis of publicly available gene expression data sets comprising 1,968 patients who had one of the 3 most common tobacco-related cancers (lung, bladder, and head and neck). The team identified cell cycle–related genes as the most consistently prognostic class of biomarkers in bladder cancer and lung adenocarcinoma [68]. Next, the team developed a 12-gene cell cycle signature and found it was predictive of outcome in an independent cohort. This work characterizes the importance of cell cycle–related genes in prognostic signatures for bladder cancer and lung adenocarcinoma, and identifies a specific signature likely to survive additional validation. The use of molecular profiles to predict treatment outcomes requires a training data set to identify the profile and a second independent clinical trial to validate it. This strategy is promising but time-consuming, expensive, and not amenable to the rapid development of biomarkers for regimens that include new drugs before clinical studies are carried out. Theodorescu's group recently proposed a new strategy that extrapolates in vitro drug response data to make in vivo predictions based on the gene expression profiles common to both. This approach, called coexpression extrapolation (COXEN), uses expression microarray data as a "Rosetta Stone" for translating between drug activities in a cancer cell line panel to drug activities in a set of clinical tumors. It represents a "correlation of correlations," bridging in vitro cell sensitivity data with the relevant gene expression of a particular patient population [35]. The COXEN algorithm proceeds through 6 discrete steps [36]. The Southwest Oncology Group 1,314 study (A Randomized Phase II Study of COXEN with Neoadjuvant Chemotherapy for Localized, Muscle-Invasive Bladder Cancer), proposed for activation by the National Cancer Institute via the cooperative group mechanism, will specifically test the COXEN combination GEMs for gemcitabine and cisplatin, and for methotrexate, vinblastine, doxorubicin, and cisplatin. It will additionally provide prospectively gathered clinical outcomes with standardized gene expression data for the entire cohort, which will be useful in any future validation of new GEMs in this clinical setting.

Dr. Efstathiou focused on biomarkers of response to bladder-sparing radiation or chemoradiation. In MIBC, combined modality therapy (transurethral resection of bladder tumor + chemoradiation) achieves a complete response and preserves the native bladder in ~

70% of patients, while offering long-term survival rates comparable to contemporary radical cystectomy series [37,38]. Quality-of-life studies have demonstrated that the retained native bladder generally functions well, and that long-term toxicity of chemoradiation to pelvic organs is relatively low [39,40]. These results support the use of modern bladder-sparing trimodality therapy for selected patients as an alternative to frontline cystectomy and may be a potentially curative therapy for elderly patients who are not surgical candidates [41]. The optimal regimen of combined chemoradiation, as well as the addition of rational molecular targeted therapy and personalized treatment selection, is still under investigation. Promising biomarkers of response and outcome to bladder-sparing radiation-based therapy involved in DNA repair, apoptosis, proliferation, angiogenesis, and hypoxia, such as high MRE11, normal HER2, low ERCC1, high XRCC1/APE1, and low vascular endothelial growth factor-B, need further validation [42–47]. The contribution of selective bladder-sparing therapy to patients' quality of life offers a unique opportunity for urologic surgeons, radiation oncologists, medical oncologists, pathologists, and translational scientists to cooperate in a truly multidisciplinary effort.

Lastly, Dr. Albert presented results from his laboratory's exploration of how a patient's immune system responds to Bacille Calmette-Guérin (BCG) treatment for NMIBC [48,49]. Examining how the immune system responds to BCG therapy has defined strategies that may help improve response rates in patients with bladder cancer, and perhaps permit extension of this successful immunotherapeutic strategy to other malignancies. BCG is typically administered to patients with NMIBC in 6 weekly instillations, often followed by maintenance therapy. There is typically a modest inflammatory response following the first instillation of BCG, despite the administration of live bacteria harboring high concentrations of toll-like receptor agonists. After the third weekly instillation, however, there is a robust inflammatory response marked by high numbers of neutrophils and mononuclear cells, as well as induction of inflammatory cytokines and chemokines. Recent discoveries have established that this increased inflammatory response is owing to the priming of BCG-specific T cells. Using an experimental mouse model, it was shown that depletion of T cells before the third BCG instillation abrogated the inflammatory response. Moreover, vaccinating animals intradermally 3 weeks before initiating intravesical therapy induced a strong intrabladder response after a single BCG instillation. Retrospective analyses of patient data have confirmed these results, showing in a population of European patients who received childhood BCG vaccination that those who maintain a purified protein derivative (PPD) response (PPD+) had a better clinical outcome as compared with PPD-negative (PPD–) patients. There are plans to initiate interventional clinical trials to determine if the priming of BCG-specific T cells by intradermal vaccination, before intravesical therapy, can result in improved clinical response to bladder cancer immunotherapy.

5. Working Groups

Attendees at the 2013 BCAN-TT participated in 7 different working groups, one of which was newly formed. In small group sessions, participants discussed ongoing projects and plans for the coming year. Each group presented on their activities to the full BCAN-TT.

6. Clinical Trials Working Group

6.1. Cochairs: Jonathan Rosenberg and Matthew Galsky

The Clinical Trials Working Group (CTWG), established in 2011 to address the relative lack of highly effective trials in urothelial cancer, published a position article titled, “Critical analysis of contemporary clinical research in muscle-invasive and metastatic urothelial cancer: a report from the Bladder Cancer Advocacy Network Clinical Trials Working Group” [50]. This article highlighted the fact that most contemporary clinical trials in muscle-invasive and advanced urothelial carcinoma are small, nonrandomized phase II trials involving 2 or 3 centers. Therefore, the CTWG set a goal to develop a clinical trials “dashboard” and a clearinghouse for clinical trials in development. The dashboard would allow patients to identify trials they might participate in, help investigators understand current protocol accrual, and highlight areas of opportunity and development to foster more collaborative relationships. This dashboard will be available online in 2014. To complement the dashboard, the CTWG is currently considering developing a database of therapeutic targets relevant to urothelial cancer, along with a comprehensive listing of associated therapies, their stage in preclinical and clinical development, and sponsoring pharmaceutical companies. This may serve to facilitate collaborations with the Translational Science Working Group (TSWG) and foster a concerted strategy to promote clinical drug development in urothelial cancer.

7. Translational Science Working Group

7.1. Cochairs: Donna Hansel, Ashish Kamat, and Thomas Flaig

During the past year, TSWG focused on micropapillary bladder cancer (MPBC), a rare clinical entity that might benefit from a multicenter approach that would foster the development of subsequent projects in pathology and clinical management. The group developed and distributed a survey assessing clinicians’ views and practice patterns concerning MPBC. Findings from this survey are being prepared for publication.

The TSWG identified short- and long-term goals for a multicenter project involving institutions doing work in bladder cancer. In the short term, each of the participating sites is cataloging cases of MPBC. Working with an existing bladder cancer clinical database from one of the BCAN sites, a similar database has been tested and is being finalized for use by all participating sites.

With this infrastructure in place, a series of short-term actions has been outlined: (1) A pathology subgroup of the TSWG will start to examine the cataloged cases of MPBC to morphologically confirm diagnoses with a consensus panel. (2) The clinical database will then be used to gather correlative clinical data on confirmed MPBC cases. (3) Initial clinical outcomes will be analyzed, examining areas of uncertainty highlighted in the survey results, with the aid of the compiled multicenter pathology and clinical database information. Questions to be addressed could include the following: What is the response rate to intravesical BCG in confirmed MPBC cases, and how durable are those responses? What is the response rate to cisplatin-based combination chemotherapy in MPBC, and should it be used in the neoadjuvant setting?

In the medium term, participating sites will work with the BCAN-TT to pursue other objectives that arise from the assembly of a centralized MPBC tissue bank, such as investigating molecular findings believed to be associated with MPBC, validating markers of aggressive disease, and investigating potential molecular targets, including HER2 and FGFR3.

The TSWG has laid the foundation for a multicenter team that can correlate clinical and pathological features for the benefit of the bladder cancer community. Its initial focus has been on MPBC, but the tools being developed will facilitate the investigation of other rare bladder cancers from a multicenter perspective.

8. NMIBC Working Group

8.1. Chair: Yair Lotan

This second-year working group focuses on evaluating patterns of care for NMIBC and identifying potential improvements. Projects include a prospective study on cystoscopy and surveillance patterns; a prospective pilot study comparing NMIBC surveillance guidelines from the European Association of Urology (EAU) and the American Urological Association (AUA); and a study looking at secondary treatments for high-grade NMIBC tumors, progression to MIBC, and other treatment options.

A plethora of questions arise in the management of NMIBC. Bladder cancer encompasses a heterogeneous group of diseases with different biologic behaviors. The majority (75%–80%) are non-muscle-invasive urothelial carcinomas that frequently recur (>50%) and progress to an invasive phenotype in 10% to 15% of patients but seldom metastasize [51]. Historically, patients with category Ta (papillary) disease have recurrence rates at 1, 2, and 3 years after transurethral resection of 36%, 45%, and 48%, respectively, whereas recurrence rates for stage T1 disease are 50%, 64%, and 70%, respectively [52]. Risk stratification has been used to determine risk of recurrence and progression, using factors such as stage, grade, tumor size, number of lesions, and number of previous recurrences.

A prospective study is seeking to assess clinical practice patterns of urologists, as there is considerable variability in frequency of surveillance and use of cystoscopy and urine-based tumor markers [53]. Another study of surveillance patterns is randomizing patients with low-risk bladder cancer based on AUA and EUA guidelines [54,55]. AUA surveillance guidelines for patients with NMIBC indicate that patients should undergo cystoscopy every 3 months for the first 2 years after diagnosis, then every 6 months for the next 2 years, and then yearly; the EAU recommends less frequent follow-up. These surveillance approaches have never been prospectively assessed, even though the EAU approach of examining patients less frequently could considerably reduce follow-up costs and inconvenience to patients.

Currently, the primary treatment for high-grade NMIBC is BCG, but use of early cystectomy, especially for BCG failure, is increasing. Questions remain concerning the optimal timing of cystectomy, optimal use of BCG, and alternative treatments following BCG failure. The working group plans to retrospectively assess practice patterns in patients with high-grade NMIBC and then develop a prospective database.

9. Standardization of Care Working Group

9.1. Cochairs: Andrea B. Apolo, Matthew G. Kaag, and Srikala S. Sridhar

The Standardization of Care Working Group (SOCWG) promotes standardized, multidisciplinary care for patients with bladder cancer. The SOCWG reported on 3 ongoing projects and discussed 2 new projects at this year's BCAN-TT.

The ongoing quality of care initiative (QCI) was designed to evaluate the use of perioperative chemotherapy for patients with MIBC. The retrospective phase of this study evaluated the use of chemotherapy at 16 academic medical centers and included data on 4,450 patients [56]. Despite level 1 evidence demonstrating a survival benefit for patients receiving neoadjuvant chemotherapy before cystectomy, the rate of perioperative chemotherapy use was only 34%, with significant variation among institutions (12%–58%). The prospective phase of the QCI used a Web-based tool to examine participating institutions regarding 4 predetermined quality indicators: (1) whether the patient was referred to medical oncology, (2) whether perioperative chemotherapy was recommended, (3) whether the patient received at least 3 cycles of cisplatin-based chemotherapy, and (4) whether a bilateral pelvic lymph node dissection was performed, including at least the external iliac, hypogastric, and obturator lymph nodes. Initial data gathered from the prospective portion of the study suggest significant increase in the use of perioperative chemotherapy over time. Currently, study enrollment is complete, and data analysis is ongoing.

SOCWG has also examined disparities in the use of perioperative chemotherapy. A project stemming from the QCI aims to understand the rationale behind medical oncologists' use of cisplatin-based chemotherapy regimens in the perioperative setting. A 26-question survey was distributed electronically to 92 oncologists. Although the majority of surveyed oncologists offer perioperative chemotherapy, overall referral rates are low, and non–cisplatin-based regimens continue to be used, despite evidence suggesting that they are less effective [69]. In a third ongoing project, the SOCWG is using a web-based survey, developed in collaboration with the SWG, to evaluate patient understanding of, and satisfaction with, their treatment for MIBC. Since being posted on the BCAN website, the survey has received 180 responses.

At the 2013 BCAN-TT, 3 new projects were initiated. The first will look at barriers to standardized pathology reporting for radical cystectomy and transurethral resection. In the near future, a questionnaire will be circulated to urologists and allied pathologists via the AUA to assess basic provider demographics and the use of standardized pathology reporting. Detailed questions regarding the inclusion of various elements of the pathology report will be asked, with the aim of assessing both academic and community practices. The second phase of this project will assess ways to disseminate information on accepted standards of pathology reporting to urologists and allied pathologists.

The second new project for the coming year addresses the multidisciplinary clinic as a potential standard of care in the management of MIBC. The study will investigate the role of the multidisciplinary clinic in the timely provision of perioperative chemotherapy and

radical cystectomy. The first part of the project will better define the various multidisciplinary paradigms used in the academic and community settings, ranging from tumor boards alone to fully integrated clinics with physicians and supporting staff from surgical, medical, and radiation oncology. Questionnaires will be circulated to AUA members to assess the use of multidisciplinary clinics, as well as perceived barriers to their use. We will then examine the relationship between the degree of multidisciplinary integration and patient outcome–related variables.

The final new project for the coming year is an effort to provide practitioners with a reference source containing evidence-based material to guide the management of patients with bladder cancer. The SOCWG will rely on the expertise of BCAN-TT participants to compile and disseminate a compendium of evidence-based best practice summaries with commentary by leaders in the field of bladder cancer, as a means of improving the use of established standards of care.

10. Survivorship Working Group

10.1 Cochairs: Cheryl T. Lee and David M. Latini

The mission of the SWG is to develop programs that improve quality of life for bladder cancer survivors, caregivers, and family through educational programs, research, and advocacy. The group includes bladder cancer survivors, physicians, nurses, social workers, and other social scientists.

During the 2013 BCAN-TT, the SWG focused mainly on continuing education for health care providers and the survivor community. Meeting activities were a natural extension of several ongoing or recently completed initiatives. Over the past year, the SWG worked with BCAN staff to revise the pamphlet entitled “Bladder Cancer Basics for the Newly Diagnosed” to make it more accessible to patients with low health literacy and to develop a Spanish-language version. The SWG strategized about methods to enhance available resources for the bladder cancer community, particularly online materials. During the meeting and shortly thereafter, SWG members participated in 2 webinars that addressed the concerns of bladder cancer survivors [57,58] and created 2 video modules to be included in BCAN’s upcoming video series on urinary diversion.

To promote the development of interdisciplinary strategies to enhance bladder cancer awareness, the SWG diversified its membership with colleagues from nursing and social work, strengthening our expertise in wound and ostomy care and behavioral sex therapy. SWG members drafted 2 articles, one targeted to the general population and the other to wound and ostomy nurses, to raise bladder cancer awareness across health disciplines.

An ongoing project of the SWG has been developing and testing a new survivorship care plan for both early- and late-stage disease. The draft care plan was developed with input from an expert panel of urologists, medical oncologists, nurses, and social scientists. Overall, 2 focus groups were conducted with survivors separated by sex. Moreover, 2 additional focus groups were conducted with physician providers and nonphysician providers. All 4 groups were asked to provide feedback on the content of the care plan,

including its readability and usefulness as a communication tool for providers and survivors. Recently, 2 abstracts describing preliminary results of the focus groups were presented at the annual meeting of the Society of Behavioral Medicine [59]. SWG members and other members of the BCAN-TT also conducted a multicenter pilot study of the new care plan in the ambulatory setting in both academic and community practices. Data from this pilot study will support applications for external funding for a larger trial of the care plan. The SWG held detailed discussions of possible funding opportunities, patient and provider outcomes, the role of survivor-members as advisors on study design, selection of relevant patient outcomes, and grant review.

A major emphasis of the SWG is quality of life—helping survivors and their families live healthier and happier lives despite the physical and psychosocial transformation that accompanies the diagnosis and treatment of bladder cancer. A recent collaborative SWG study discusses bladder cancer burden and the unmet needs of the survivors [60]. The 2013 BCAN-TT provided an opportunity to address sexual dysfunction, an important topic that is routinely overlooked in the survivorship community [25]. As part of a multidisciplinary session, bladder cancer survivors Patricia Boumansour and Randy Layne discussed their own experience with changes in sexual function after surgical treatment. Both reported they were more focused on surviving bladder cancer than on potential changes in sexual function after treatment. However, they both stressed the importance of asking questions before treatment to fully understand potential long-term changes in quality of life.

In the coming year, the SWG will develop new patient education tools on nutrition for cystectomy patients and the use of intravesical BCG. Building on the 2013 BCAN-TT survivorship session, SWG members will develop a list of frequently asked questions about sexual dysfunction and ways to improve physical function and personal relationships. Lastly, the SWG will create learning opportunities for patient advocates and volunteers, the frontline of support for new and returning visitors to BCAN's online community. Members of the SWG plan to provide on-site training for peer counselors at the BCAN-TT 2014 meeting, using an adaptation of an existing training program at the University of Michigan. We believe this will enhance volunteers' peer support skills and reduce volunteer stress and burnout.

11. Patient-Centered Outcomes and Policy Working Group (formerly Health Services Research and Health Policy Working Group)

11.1 Cochairs: Seth Strope and John Gore

The urologists, oncologists, and advocates who comprise the Patient-Centered Outcomes and Policy Working Group (PCOPWG) aim to (1) identify, disseminate, and act on policy-relevant issues pertinent to bladder cancer; (2) develop concepts for translational health services research that maximize the health outcomes of patients with bladder cancer; and (3) place BCAN-TT members in health policy-relevant roles within national organizations.

As the Affordable Care Act is implemented, we will continue to learn more about its effect on bladder cancer care. We have previously discussed the potential role of bundle payment

programs on bladder cancer care, specifically on cystectomy care, which has a high-cost index admission and high readmission rates after discharge. In the past year, the PCOPWG has been synthesizing the evidence for clinical implementation of cystectomy care based on the Enhanced Recovery After Surgery protocols used in colorectal surgery. At select health centers, use of the Enhanced Recovery After Surgery cystectomy protocol has reduced lengths of stay and readmission rates. We created a conceptual model of preoperative, intraoperative, inpatient, and convalescent cystectomy care and a hierarchy for examining literature on cystectomy, colorectal surgery, pelvic surgery, and abdominal surgery. The goal of this project is to identify best practices for postoperative cystectomy and areas where more evidence is needed to inform optimal algorithms of cystectomy care.

Goals for the next year include (1) developing a new collaborative research project, (2) generating and testing performance measures for bladder cancer care, (3) evaluating available instruments for measuring quality of life for patients with NMIBC, (4) developing patient-centered resources for bladder cancer care, and (5) cataloging data resources available to BCAN-TT participants.

Members of the PCOPWG hold policy-relevant positions within the AUA and other national organizations, including Young Urologists liaison to the AUA Health Policy Council, membership on the AUA Quality Improvement and Patient Safety Committee, and AUA representative to the National Quality Forum.

12. Upper Tract Disease Working Group

12.1 Cochairs: Surena Matin and Vitaly Margulis

This working group met for the first time in 2013. Before the meeting, working group leaders made a preliminary list of goals for improving the understanding and treatment of upper tract disease, including the following:

(1) Prospectively validating the benefit of neoadjuvant chemotherapy

(2) Evaluating and quantifying the role of lymphadenectomy

(3) Improving clinical risk stratification

(4) Determining the optimal type of bladder cuff management

(5) Improving detection and staging after cystectomy

(6) Increasing recognition of Lynch syndrome by urologists and providing recommendations for optimal screening procedures

(7) Increasing national and global collaboration for this disease

This list was further elaborated and accepted by the working group as a whole. Although not all items were addressed, a few priority items were discussed and further developed, as described later.

Retrospective data suggest that in high-risk patients, neoadjuvant chemotherapy is associated with a complete remission rate of approximately 15% [61]. A recent analysis, also based on

retrospective data, showed improvement in 5-year disease-specific survival of 92% for patients receiving neoadjuvant chemotherapy vs. 64% for matched historical controls [62]. Remaining challenges include the need for prospective validation, clarification of patient selection, and a practical clinical trial design that allows for broad enrollment to extrapolate findings to most patients. The latter is particularly relevant for patients with renal insufficiency and for setting an ideal glomerular filtration rate threshold for cisplatin chemotherapy eligibility. The group also addressed the ethics of denying chemotherapy for high-risk patients, which is now standard practice at some institutions. Also discussed were chemotherapy regimens and a design for kidney-sparing lead-in therapy.

Regarding lymphadenectomy, the group discussed putative templates, patient selection, and determining benefit. There are sparse data in the literature for all of these issues. Japanese studies have preliminarily identified landing zones depending on the location of the upper tract tumor (renal pelvis, proximal ureter, midureter, and distal ureter) [63]. Retrospective work by the Japanese investigators suggests a possible therapeutic value for patients with non–organ-confined disease who have more than 7 lymph nodes removed [63]. Further data from an international collaboration involving 95 patients suggested that the number of lymph nodes removed was an independent predictor of disease-free survival, as long as at least 8 nodes were removed [64,65]. The working group suggested a singlearm safety and feasibility trial that would provide preliminary recurrence and survival data to inform a future phase II trial. The initial templates would be based on the Japanese studies, as well as a multicenter North American study currently underway.

A novel concept introduced by the working group was to improve the effect of single-dose chemotherapy instillation to prevent disease recurrence by administering it intra-operatively. This concept was based on 2 recent randomized prospective trials that showed a benefit for patients who received intravesical chemotherapy after nephroureterectomy [66,67]. The group presented a preliminary design for a single-arm phase II study based on historical data showing a 30% recurrence rate with 40% to 50% reduction with treatment, and secondarily measuring quality-of-life core correlatives.

The University of North Carolina is developing an upper tract Research Electronic Data Capture database to improve international collaborations. The database will be tested at a few centers initially, then opened to multiple international centers with the goal of creating the largest prospectively designed and updated international database on upper tract disease. Data mining, study ideas, and authorship of generated articles will be subject to a transparent standard operating procedure to ensure fairness and scientific integrity.

Finally, the group discussed ways to improve recognition of Lynch syndrome. Current efforts include a consensus panel statement recommending screening guidelines to improve urologists ability to recognize the syndrome. It was agreed that modifying the current upper tract Research Electronic Data Capture database and enrolling patients with Lynch syndrome in clinical trials should be a major priority.

13. Conclusions

The goal of the BCAN-TT is to advance the care of patients with bladder cancer and to promote collaborative research throughout the year. With the theme of "Collaborating to Move Research Forward," the 2013 BCAN-TT addressed sex disparities, sexual dysfunction, and novel therapeutics, 3 major topics in bladder cancer research. The meeting provided ample opportunities for collaboration among clinicians from multiple disciplines, patients and patient advocates, and industry representatives.

Acknowledgments

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Appendix

2013 Bladder Cancer Think Tank Attendees' names, institutions

Dr. Rosalyn Adam, Boston Children's Hospital

Dr. Piyush Agarwal, National Cancer Institute

Dr. Hikmat Al-Ahmadie, Memorial Sloan-Kettering Cancer Center

Dr. Matthew Albert, Institut Pasteur

Dr. Ajjai Alva, University of Michigan

Dr. Gilad Amiel, Baylor College of Medicine

Dr. Andrea Apolo, National Cancer Institute

Dr. Jessie Au, Optimum Therapeutics, Inc

Dr. Arjun Balar, New York University Cancer Center

Dr. Jeffrey Bassett, Vanderbilt University Rick Bangs, Patient Advocate Ambaw Bellette, Photocure

Dr. Ami Bhatt, Dana-Farber Cancer Center

Dr. Trinity Bivalaqua, Johns Hopkins University Pat Boumansour, Patient Advocate

Dr. Earle Burgess, Carolinas Health Care

Dr. Daniel Canter, Urologic Institute of Southeastern Pennsylvania

Dr. Karim Chamie, University of California, Los Angeles

Dr. Ronald Chen, University of North Carolina, Chapel Hill Dr. David Chen, Fox Chase Cancer Center

Dr. Arnold Chin, University of California, Los Angeles

Dr. Jessica Clement, University of Connecticut Marge Coffin, Patient Advocate

Dr. John Colberg, Yale University School of Medicine

Dr. Bogdan Czerniak, MD, Anderson Cancer Center

Dr. Sia Daneshmand, Keck USC Institute of Urology

Dr. Colin Dinney, MD Anderson Cancer Center

Dr. Tracy Downs, University of Wisconsin

Dr. Robert Dreicer, Cleveland Clinic Mary Dunn, N.P., O.C.N., University of North Carolina, Chapel Hill

Dr. Jason Efstathiou, Massachusetts General Hospital, Harvard Medical School

Dr. Harvey Fineberg, Institute of Medicine

Dr. Thomas Flaig, University of Colorado, Denver

Dr. Michael Freeman, Cedars-Sinai Medical Center Karen Godfrey, Patient Advocate

Dr. Jeffrey Gingrich, University of Pittsburgh Jocelyn Goffney, R.N., M.S.N., C.W.O.C.N., Methodist Hospital

Dr. Heather Goltz, University of Houston-Downtown

Dr. John Gore, University of Washington

Dr. Robert Grubb III, Washington University

Dr. Elizabeth Guancial, University of Rochester

Dr. Amit Gupta, University of Iowa

Dr. Khurshid Guru, Roswell Park Cancer Center

Dr. Noah Hahn, Indiana University

Dr. Donna Hansel, University of California, San Diego

Dr. Lauren Harshman, Dana-Farber Cancer Insitute

Deborah Hensley, B.S.N., R.N., C.U.R.N., UT Southwestern Vanessa Hoffman, M.P.H., R.D., BCAN Dr. Jean Hoffman-Censits, Thomas Jefferson University

Dr. M’Liss Hudson, Ochsner Medical Center Veronica Hunter, BCAN Dr. Molly Ingersoll, Institut Pasteur

Dr. Brant Inman, Duke University

Dr. Gopa Iyer, Memorial Sloan-Kettering Cancer Center

Dr. Cindy Jacobs, OncoGenex

Dr. Susan Jewell, Abbott Molecular Dr. Matthew Kaag, Penn State Hershey

Dr. Ashish Kamat, MD Anderson Cancer Center

Dr. Lawrence Karsh, The Urology Center of Colorado

Dr. Wassim Kassouf, McGill University

Dr. William Kim, University of North Carolina, Chapel Hill Dr. Margaret Knowles, University of Leeds

Dr. Theresa Koppie, Oregon Health & Science University Prem Kumar, M.Sc., Photocure

Dr. Donald Lamm, BCG Oncology

Dr. David Latini, Baylor College of Medicine, U.S. Department of Veterans Affairs

Randy Layne, Patient Advocate

Dr. Eugene Lee, MD Anderson Cancer Center

Dr. Cheryl Lee, University of Michigan

Dr. Seth Lerner, Baylor College of Medicine

Dr. Michael Locker, Dendreon

Dr. Yair Lotan, UT Southwestern

Dr. Vitaly Margulis, UT Southwestern

Dr. Surena Matin, MD Anderson Cancer Center Gerald McNamara, M.B.A., BCAN Board of Directors

Dr. David McConkey, MD Anderson Cancer Center

Dr. Maxwell Meng, University of California, San Francisco

Dr. Edward Messing, University of Rochester

Dr. Matthew Milowsky, University of North Carolina, Chapel Hill

Dr. Nihal Mohamed, Mount Sinai Hospital

Dr. John Mulhall, Memorial Sloan-Kettering Cancer Center Dr. Kenneth Nepple, University of Iowa Health Care

Dr. Matthew Nielsen, University of North Carolina, Chapel Hill

Dr. Michael O'Donnell, University of Iowa

Dr. Peter O'Donnell, University of Chicago Nancy Parrish, Patient Advocate

Dr. Elizabeth Plimack, Fox Chase Cancer Center

Dr. Michael Porter, University of Washington David Pulver, BCAN Board of Directors Diane Zipursky Quale, BCAN Board of Directors

Dr. Vandana Rajakumar, Abbott Molecular

Dr. Stephen Riggs, Carolinas Medical Center

Dr. Jonathan Rosenberg, Memorial Sloan-Kettering Cancer Center

Dr. Arlene Siefker-Radtke, MD Anderson Cancer Center

Dr. Eila Skinner, Stanford University

Dr. Marc Smaldone, Fox Chase Cancer Center

Dr. Angela Smith, University of North Carolina, Chapel Hill

Dr. Kala Sridhar, Princess Margaret Hospital

Dr. Walter Stadler, University of Chicago

Dr. Gary Steinberg, University of Chicago

Dr. Jeff Steinberg, Dendreon

Dr. Seth Strope, Washington University

Dr. Robert Svatek, UT Health Science Center Dr. Jennifer Taylor, Memorial Sloan-Kettering Cancer Center

Dr. Dan Theodorescu, University of Colorado, Denver Yngvil Thomas, M.Sc., Photocure

Dr. Edouard Trabulsi, Thomas Jefferson University

Dr. Daniel Vaena, University of Iowa Jake Vinson, M.H.A., Memorial Sloan-Kettering Cancer Center

Dr. K. David Weidner, Capital City Consulting

Dr. Daniela Wittmann, University of Michigan

Dr. Steven Wong, University of California, Los Angeles

Dr. Yu-Ning Wong, Fox Chase Cancer Center

Dr. Jonathan Wright, University of Washington

2013 John Quale Travel Fellowship Attendees

Dr. Richard Bambury, Memorial Sloan-Kettering Cancer Center

Dr. Sima Porten, MD Anderson Cancer Center

Dr. Srinivas Vourganti, National Cancer Institute

Dr. Daniel Willis, MD Anderson Cancer Center

2013 John Quale Travel Fellowship Awardees

2013 Patient Advocates

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