AUA2013 in San Diego was successful beyond my expectations, and yet as I reflect on it, I become aware of things we could have done differently or perhaps better. The comments I received from attendees were insightful and sometimes emotional. I heard them all and will consider them when planning AUA2014. I wish to share with you my view from this year’s Podium.

The Board of Directors met on Thursday as many of the members wanted the opportunity to participate in the programs on Friday. A new initiative was introduced on Friday as the AUA joined partners in programming with the Society of Urologic Oncology, Society of Basic Urologic Research, National Cancer Institute, and National Institute of Diabetes and Digestive and Kidney Diseases. The research session on cancer and benign disease as well as the residents programs had excellent speakers. Standing in the back of the packed room, it was a joy to witness attendees engaged in the programs. The Research Scholar Reception was a cheerful event. Perhaps the sunlit atrium area was too bright and too large, dampening the sound of the speakers.

The Live Surgery program on Saturday morning once again “filled the house.” The opening bell of the Residents Bowl brought many people to the Science and Technology Hall. The Southeastern Section won the championship and Dr. Ray Leveillee, Section President, made sure everyone at the meeting saw him carry the cup.

The Saturday Spanish Urology Program, choreographed by Dr. Shlomo Raz and the Confederación Americana de Urología (CAU)

--- Continued on page 6 ---
ZYTIGA® is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). 

FOR PATIENTS WITH mCRPC WHO HAVE PROGRESSED ON ADT* 

IMPORTANT SAFETY INFORMATION

- **Contraindications**—ZYTIGA® is not indicated for use in women. ZYTIGA® can cause fetal harm (Pregnancy Category X) when administered to a pregnant woman and is contraindicated in women who are or may become pregnant.

- **Hypertension, Hypokalemia, and Fluid Retention Due to Mineralocorticoid Excess**—Use with caution in patients with a history of cardiovascular disease or with medical conditions that might be compromised by increases in blood pressure, hypokalemia, or fluid retention. ZYTIGA® may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition. Safety has not been established in patients with LVEF < 50% or New York Heart Association (NYHA) Class III or IV heart failure (in study 1) or NYHA Class II to IV heart failure (in study 2) because these patients were excluded from these randomized clinical trials. Control hypertension and correct hypokalemia before and during treatment. Monitor blood pressure, serum potassium, and symptoms of fluid retention at least monthly.

- **Adrenocortical Insufficiency (AI)**—AI was reported in patients receiving ZYTIGA® in combination with prednisone, after an interruption of daily steroids and/or with concurrent infection or stress. Use caution and monitor for symptoms and signs of AI if prednisone is stopped or withdrawn, if prednisone dose is reduced, or if the patient experiences unusual stress. Symptoms and signs of AI may be masked by adverse reactions associated with mineralocorticoid excess seen in patients treated with ZYTIGA®. Perform appropriate tests, if indicated, to confirm AI. Increased dosages of corticosteroids may be used before, during, and after stressful situations.

- **Hepatotoxicity**—Monitor liver function and modify, withhold, or discontinue ZYTIGA® dosing as recommended (see Prescribing Information for more information). Measure serum transaminases [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] and bilirubin levels prior to starting treatment with ZYTIGA®, every two weeks for the first three months of treatment, and monthly thereafter. Promptly measure serum total bilirubin, AST, and ALT if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline should prompt more frequent monitoring. If at any time AST or ALT rise above five times the upper limit of normal (ULN) or the bilirubin rises above three times the ULN, interrupt ZYTIGA® treatment and closely monitor liver function.

- **Increased ZYTIGA® Exposures With Food**—ZYTIGA® must be taken on an empty stomach. No food should be eaten for at least two hours before the dose of ZYTIGA® is taken and for at least one hour after the dose of ZYTIGA® is taken. Abiraterone Cmax and AUC0-infinity (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state.

For more information, please visit [www.zytigahcp.com](http://www.zytigahcp.com).
**ADVERSE REACTIONS**—The most common adverse reactions (≥10%) are fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection, and contusion.

The most common laboratory abnormalities (≥20%) are anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT, and hypokalemia.

**DRUG INTERACTIONS**—ZYTIGA® is an inhibitor of the hepatic drug-metabolizing enzyme CYP2D6. Avoid co-administration with CYP2D6 substrates that have a narrow therapeutic index. If an alternative cannot be used, exercise caution and consider a dose reduction of the CYP2D6 substrate. In vitro, ZYTIGA® inhibits CYP2C8. There are no clinical data on its use with drugs that are substrates of CYP2C8. Patients should be monitored closely for signs of toxicity related to the CYP2C8 substrate if used concomitantly with abiraterone acetate.

Based on in vitro data, ZYTIGA® is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution during treatment with ZYTIGA®.

**USE IN SPECIFIC POPULATIONS**—Do not use ZYTIGA® in patients with baseline severe hepatic impairment (Child-Pugh Class C).

*Study Design: ZYTIGA®, in combination with prednisone, was evaluated in a Phase 3, randomized, double-blind, placebo-controlled, multicenter trial in patients with mCRPC who had not received prior chemotherapy (N = 1,088). Patients were using a luteinizing hormone-releasing hormone (LHRH) agonist or were previously treated with orchiectomy. In the ZYTIGA® arm, patients received ZYTIGA® 1,000 mg orally once daily + prednisone 5 mg orally twice daily. In the placebo arm, patients received placebo orally once daily + prednisone 5 mg orally twice daily. In this study, the coprimary efficacy endpoints were overall survival and radiographic progression-free survival.

†Local therapy = radiation and/or surgery.

‡For many patients with mCRPC, gonadotropin-releasing hormone (GnRH) agonist therapy typically continues throughout the disease course, and is used concomitantly with other mCRPC treatments, including ZYTIGA®. This illustration is not intended to suggest that ZYTIGA® is the only treatment option following androgen-deprivation therapy (ADT).

§Primary endpoint.

||Secondary endpoint.

Please see brief summary of full Prescribing Information on adjacent pages.
ZYTIGA® (abiraterone acetate) Tablets
Brief Summary of Prescribing Information.

INDICATIONS AND USAGE
ZYTIGA® is a CYP17 inhibitor indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer.

CONTRAINDICATIONS
• Pregnancy: ZYTIGA can cause fetal harm when administered to a pregnant woman. ZYTIGA is not indicated for use in women. ZYTIGA is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss (see Use in Specific Populations).
• Hypersensitivity, Hypokalemia and Fluid Retention Due to Mineralocorticoid Excess: ZYTIGA may cause hyper- tension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Clinical Pharmacology (12.3) in full Prescribing Information). In the two randomized clinical trials, grade 3 or 4 hypertension occurred in 2% of patients, grade 3 or 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA (see Adverse Reactions).

WARNINGS AND PRECAUTIONS
• Hypertension, Hypokalemia and Fluid Retention: ZYTIGA may cause hypertension, hypokalemia, and fluid retention as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Clinical Pharmacology (12.3) in full Prescribing Information). In the two randomized clinical trials, grade 3 or 4 hypertension occurred in 2% of patients, grade 3 or 4 hypokalemia in 4% of patients, and grade 3 to 4 edema in 1% of patients treated with ZYTIGA (see Adverse Reactions).
• Co-administration of a corticosteroid suppresses adrenocorticotropic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Use caution when treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia. Use ZYTIGA with caution in patients with a history of cardiovascular disease. The safety of ZYTIGA in patients with left ventricular ejection fraction <50% or New York Heart Association (NYHA) Class III or IV heart failure (in Study 1) or NYHA Class II to IV heart failure (in Study 2) was not established because these patients were excluded from these randomized clinical trials (see Clinical Studies (14) in full Prescribing Information). Monitor patients for hypertension, hypokalemia, and fluid retention at least once a month. Control hypertension and correct hypokalemia before and during treatment with ZYTIGA.

Adrenocortical Insufficiency: Adrenal insufficiency occurred in the two randomized controlled studies in 0.5% of patients taking ZYTIGA and in 0.2% of patients taking placebo. Adrenocortical insufficiency was reported in patients receiving ZYTIGA in combination with prednisone following withdrawal of daily steroids and/or concurrent infection or stress. Use caution and monitor for signs and symptoms of adrenocortical insufficiency, particularly if patients are withdrawn from prednisone, have prednisone dose reductions, or experience unusual stress. Symptoms and signs of adrenocortical insufficiency may be masked by adverse reactions and/or changes in mineralocorticoid excess seen in patients treated with ZYTIGA. It clinically indicated, perform appropriate tests to confirm the diagnosis of adrenocortical insufficiency. Increased dosage of corticosteroids may be indicated before, during and after stressful situations.

Hepatotoxicity: In the two randomized clinical trials, grade 3 or 4 ALT or AST increases (at least 5X ULN) were reported in 4% of patients who received ZYTIGA, typically during the first 3 months after starting treatment. Patients whose baseline ALT or AST were elevated were more likely to experience liver test elevation than those with normal values. Treatment discontinuation due to liver enzyme increases occurred in 1% of patients taking ZYTIGA. No deaths clearly related to ZYTIGA were reported due to hepatotoxicity events.

Measure serum transaminases (ALT and AST) and bilirubin levels prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. In patients with baseline moderate hepatic impairment receiving a reduced ZYTIGA dose of 350 mg, measure ALT, AST, and bilirubin prior to the start of treatment, every week for the first month, every two weeks for the following two months of treatment and monthly thereafter. Promptly measure serum total bilirubin, ALT, and AST if clinical symptoms or signs suggestive of hepatotoxicity develop. Elevations of AST, ALT, or bilirubin from the patient’s baseline and ALT >5X ULN may prompt more frequent laboratory monitoring. If at any time AST or ALT rise above five times the ULN, or the bilirubin rises above three times the ULN, interrupt ZYTIGA treatment and closely monitor liver function. Re-treatment with ZYTIGA at a reduced dose level may take place only after return of liver function tests to the patient’s baseline or to AST and ALT less than or equal to 2.5X ULN and total bilirubin less than or equal to 1.5X ULN (see Doseage and Administration (2.2) in full Prescribing Information).

The safety of ZYTIGA re-treatment of patients who develop AST or ALT greater than or equal to 20X ULN and/or bilirubin greater than or equal to 10X ULN is unknown.

Increased ZYTIGA Exposures with Food: ZYTIGA must be taken on an empty stomach. No food should be consumed for at least two hours before the dose of ZYTIGA is taken and for at least one hour after the dose of ZYTIGA is taken. Abiraterone Cmax and AUC0-24 (exposure) were increased up to 17- and 10-fold higher, respectively, when a single dose of abiraterone acetate was administered with a meal compared to a fasted state. The safety of these increased exposures when multiple doses of abiraterone acetate are taken with food has not been assessed (see Doseage and Administration (2.2) and Clinical Pharmacology (12.3) in full Prescribing Information).

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
• Hypertension, Hypokalemia, and Fluid Retention: Due to Mineralocorticoid Excess (see Warnings and Precautions).
• Adrenocortical Insufficiency (see Warnings and Precautions).
• Hypokalemia (see Warnings and Precautions).
• Increased ZYTIGA Exposures with Food (see Warnings and Precautions).

Clinical Trial Experience: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Two randomized placebo-controlled, multicenter clinical trials enrolled patients who had metastatic castration-resistant prostate cancer who were using a gonadotropin-releasing hormone (GnRH) agonist or were previously treated with orchectomy. In both Study 1 and Study 2 ZYTIGA was administered at a dose of 1,000 mg daily in combination with prednisone 5 mg twice daily in the active treatment arms. Placebo plus prednisone 5 mg twice daily was given to control patients.

The most common adverse drug reactions (≥10%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were fatigue, joint swelling or discomfort, edema, hot flush, diarrhea, vomiting, cough, hypertension, dyspnea, urinary tract infection and infection. The most common laboratory abnormalities (≥2%) reported in the two randomized clinical trials that occurred more commonly (≥2%) in the abiraterone acetate arm were anemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycemia, elevated AST, hypophosphatemia, elevated ALT and hypokalemia.

Table 1: Adverse Reactions due to ZYTIGA in Study 1

Table 2: Laboratory Abnormalities of Interest in Study 1

Study 2: Metastatic CRPC Prior to Chemotherapy
Study 2 enrolled 1,195 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy. Patients eligible if AST and ALT > 2.5X ULN and patients were excluded if they had abnormal metastases. Table 3 shows adverse reactions on the ZYTIGA arm in Study 2 that occurred with a ≥2% increase in frequency compared to placebo. The median duration of treatment with ZYTIGA was 13.8 months.

Table 3: Adverse Reactions in ≥5% of Patients on the ZYTIGA Arm in Study 2

ZYTIGA® (abiraterone acetate) Tablets

Table 1: Adverse Reactions due to ZYTIGA in Study 1

Table 2: Laboratory Abnormalities of Interest in Study 1
Cardiovascular Adverse Reactions: In the combined data for studies 1 and 2, cardiac failure occurred more commonly in patients treated with ZYTIGA compared to patients on the placebo arm (2.1% versus 0.7%). Grade 3-4 cardiac failure occurred in 1.8% of patients taking ZYTIGA and led to 5 treatment discontinuations and 2 deaths. Grade 3-4 cardiac failure occurred in 0.2% of patients taking placebo. There were no treatment discontinuations and one death due to cardiac failure in the placebo group.

In Study 1 and 2, the majority of arrhythmias were grade 1 or 2. There was one death associated with arrhythmia and one patient with sudden death in the ZYTIGA arms and no deaths in the placebo arms. There were 7 (0.5%) deaths due to cardiorenal torsades de pointes in the ZYTIGA arms and 3 (0.3%) deaths in the placebo arms. Myocardial ischemia or myocardial infarction led to death in 3 patients in the placebo arms and 2 deaths in the ZYTIGA arms.

DRUG INTERACTIONS
Effects of Abiraterone on Drug Metabolizing Enzymes: ZYTIGA is an inhibitor of the hepatic drug-metabolizing enzyme CYP2C8. In a CYP2D6 drug-drug interaction study, the Cmax and AUC of dextromethorphan (CYP2D6 substrate) were increased 2.8- and 2.9-fold, respectively, when dextromethorphan was given with abiraterone acetate 1,000 mg daily and prednisone 5 mg twice daily. Avoid co-administration of abiraterone acetate with substrates of CYP3A4 with a narrow therapeutic index (e.g., thiourea). If alternative treatments cannot be used, exercise caution and consider a dose reduction of the concomitant CYP3A4 substrate drug [see Clinical Pharmacology (12.3) in full Prescribing Information].

In vitro, ZYTIGA inhibits CYP3A4. There are no clinical data on the use of ZYTIGA with drugs that are substrates of CYP3A4. However, patients should be monitored closely for signs of toxicity related to the CYP3A4 substrate if used concomitantly with abiraterone acetate.

Drugs that Inhibit or Induce CYP3A4 Enzymes: Based on in vitro data, ZYTIGA is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, azithromycin, nefazodone, seconadine, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, in vivo. Avoid or use with caution, strong inhibitors and inducers of CYP3A4 during ZYTIGA treatment [see Clinical Pharmacology (12.3) in full Prescribing Information].

USE IN SPECIFIC POPULATIONS
Pregnancy: Category X [see Contraindications]: ZYTIGA can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. While there are no adequate and well-controlled studies with ZYTIGA in pregnant women and ZYTIGA is not indicated for use in women, it is important to know that maternal use of a CYP19 inhibitor could affect development of the fetus. Abiraterone acetate caused developmental toxicity in pregnant rats at exposures that were lower than in patients receiving the recommended dose. ZYTIGA is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with ZYTIGA.

In an embryo-fetal developmental toxicity study in rats, abiraterone acetate caused developmental toxicity when administered at oral doses of 10, 30 or 100 mg/kg/day throughout the period of organogenesis (gestational days 6-17). Findings included embryo-fetal lethality (increased post implantation loss and resorptions and decreased number of live fetuses), fetal developmental delay (skeletal effects) and urogenital effects (bilateral ureter dilation) at doses ≥10 mg/kg/day. Decreased fetal body weight at 100 mg/kg/day, and decreased fetal body weight at 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 0.03, 0.1 and 0.3 times, respectively, the AUC in patients.

Nursing Mothers: ZYTIGA is not indicated for use in women. It is not known if abiraterone acetate is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from ZYTIGA, a decision should be made to either discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness of ZYTIGA in pediatric patients have not been established.

Geriatric Use: Of the total number of patients receiving ZYTIGA in phase 3 trials, 73% of patients were 65 years and over and 30% were 75 years and over. No overall differences in safety or effectiveness were observed between these elderly patients and younger patients. Older reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Patients with HEPATIC IMPAIRMENT: The pharmacokinetics of abiraterone were examined in subjects with baseline mild (N = 8) or moderate (N = 8) hepatic impairment (Child-Pugh Class A and B, respectively) and in 8 healthy control subjects with normal hepatic function. The systemic exposure (AUC) of abiraterone after a single oral 1,000 mg dose of ZYTIGA increased by approximately 1.1-fold and 3.6-fold in subjects with mild and moderate baseline hepatic impairment, respectively compared to subjects with normal hepatic function. No dosage adjustment is necessary for patients with baseline mild hepatic impairment. In patients with baseline moderate hepatic impairment (Child-Pugh Class B), reduce the recommended dose of ZYTIGA to 250 mg once daily. If elevations in ALT or AST >5X ULN or total bilirubin >3X ULN occur in patients with baseline moderate hepatic impairment, discontinue ZYTIGA treatment [see Dosage and Administration (2.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

The safety of ZYTIGA in patients with baseline severe hepatic impairment has not been studied. These patients should not receive ZYTIGA.
AUA News

July 2013
Volume 18–Number 7

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Dr. Ralph Clayman. Having a NASA engineer along with the Department of Defense, ethicists, economists and the “Urology Doc Stars” on the same platform was a treat.

The Live Surgery images at the Plenary session on Wednesday were spectacular, and I am anxious for feedback from attendees as to the quality of this program. Dr. Marston Linehan, Chief of Urologic Surgery and the Urologic Oncology Branch, Center for Cancer Research at the National Cancer Institute, gave the Ramon Guzı́ras lecture after the “soul-baring” Presidential Address by Dr. Dennis Pessis.

The rain Sunday morning and afternoon assured us of filled meeting rooms throughout the day, but then it stopped just in time for the sold-out Welcoming Reception abroad the USS Midway. At the Presidents’ Reception on Tuesday, 41 international leaders were recognized along with scores of exchange faculty.

A total of 114 countries, representing 55% of the attendance at this year’s AUA meeting, provided me the opportunity to meet with a number of international delegates, as well as sign memorandums of understanding with the Republic of Korea, Sociedade Brasileira de Urologia and CAU.

The Global Philanthropic Committee, a joint effort of AUA, European Association of Urology, Société Internationale d’Urologie, Pan African Urological Surgeons’ Association, CAU, Caribbean and other multinational associations, was joined this year by the Endourology Society. The Committee honored Dr. Robert Flanigan for his vision and thanked him for serving as the International Education Consultant. Laborie and Olympus are gratefully acknowledged for their donations of equipment to this effort.

Running each day along the beautiful San Diego bay gave me new energy. Being on the boat with the Indian American Urological Association on Monday evening was a special treat.

Perhaps not all are happy with the AUA, as I spent considerable time dispelling erroneous information about AUA initiatives. I understand I need to do a better job of getting information out to you, and plan to do so in future issues of AUA News. ◆

“Praise and criticism seem to me to operate exactly on the same level. If you get a great review, it’s really thrilling for about ten minutes. If you get a bad review, it’s really crushing for ten minutes. Either way, you go on.”

—Ann Patchett

Case of Month Series

Continued from page 1

leadership, grows each year. The hallway outside the room was as full as the meeting room.

It was a delight to kick-off the Plenary program on Sunday with medical student Jeffrey Pearl from Northwestern University presenting one of 10 best abstracts awarded this year. New this year, the abstract review team leaders voted for the best abstract in their category, and the winning authors were invited to open the Plenary session each day of the meeting. Also on Sunday, the 1st annual AUA National Chief Resident debate was held. The quality of these debates was outstanding, making it too bad someone had to lose!

The Plenary sessions were filled to near capacity each day. In fact, the AUA guidelines session on Monday was so popular that we ran out of space. The technology of Twitter feed allowed us to recognize the needs of the audience, and so we decided on the spot to repeat the session on Tuesday. The ability of the staff and faculty to add this session on such short notice and dissipate the information to the audience was remarkable.

The Town Hall program on the future of robots was coordinated by Dr. Kevin Loughlin, Kevin Prankoff and David Green were inadvertently omitted from this article and appear below.

CORRECTION

Volume 18, Issue 6 (June 2013), Page 33: The photographs of Drs. Kevin Loughlin, Kevin Prankoff and David Green were inadvertently omitted from this article and appear below.

Dr. Kevin Loughlin Dr. Kevin Prankoff Dr. David Green

and, thus, broaden their educational horizons.

An attractive aspect of this program is that it addresses an important and often overlooked issue particular to this era, namely that of information overload. Each case essentially condenses 8 to 10 pages of Campbell-Walsh Urology or similar source material into a readily digestible item, extracting and illustrating the essentials, and presenting them in a concise and clinically relevant manner.

We have now produced more than 180 of these cases, with a long-term goal of approximately 350 to 400. These cases will cover well over 80% to 90% of what a urologist needs to know to function well in day-to-day practice in addition to most of the fundamentals of subspecialty practice.

In the long term we envision an electronic library that will be available 24-7 and prove to be a great resource for routine practice. For instance, if you were consulted about a case of priapism in the emergency room, you could rapidly access a related case and refresh your memory about potential etiologies, relevant examination findings and which agents are preferred for management as well as the fundamentals of safe administration.

This program was developed in collaboration with our colleagues at University Hospitals Urology Institute and Rainbow Babies & Children’s Hospital. Dr. Jonathan Ross serves as an Associate Editor and oversees the Pediatric Urology components of the program, and Drs. David Goldfarb and Howard Goldman from the Cleveland Clinic also serve as Associate Editors. ◆
Prostate Cancer

Prostate cancer had a robust presence at the 2013 AUA Annual Meeting with more than 500 abstracts presented in 27 poster or podium sessions. Accompanying these presentations were well constructed plenary sessions as well as 3 new clinical guidelines including the Early Detection of Prostate Cancer.

Epidemiology and Natural History

Active surveillance (AS) regimens continued to be underused in the United States in the last decade (220). Such observations are contrasted by findings from a Swedish population based study emphasizing that more than 50% of patients with low risk disease are successfully maintained on AS (661). In addition, at a 10-year median followup only 54% of patients on AS experienced disease progression with less than 1% cancer specific mortality (CSM) (223).

In 3,013 patients the metabolic syndrome was associated with prostate cancer (OR 1.44) as well as high grade histology (OR 1.58) at prostate needle biopsy (PNBx) (341).

Detection and Screening

At a median followup of 12.8 years the Rotterdam section of the ERSPC (European Randomized Study of Screening for Prostate Cancer) reported a 32% risk reduction in CSM among screened men 55 to 69 years old but no benefit in men 70 years old or older (1932).

The grade D recommendation assigned to prostate specific antigen (PSA) screening by the U.S. Preventive Services Task Force has translated to a decrease in the number of men screened as determined by patients presenting with an increased PSA or those undergoing PNBx (1233, 2061).

The prolonged impact of PNBx on erectile function and urinary symptoms (1927) and the increased risk of infectious complications with repeat biopsies (1244, 1246) highlight the need to improve biopsy accuracy. Novel techniques such as magnetic resonance imaging (MRI)/transrectal ultrasound fusion may be valuable given their ability to improve the detection of high grade tumors while reducing the number of cores needed for diagnosis (2218, 2219).

Markers

Epigenetic field effects can aid in the diagnosis of prostate cancer at PNBx. In particular, variations in the methylation patterns of the EVX1 and FGF1 genes in tumor negative biopsy tissue differentiate between patients with and without prostate cancer (negative predictive value 0.909, AUC 0.774) (2132).

In patients with adverse pathological features at prostatectomy genomic classifier systems are able to identify patients at greatest risk for disease progression and disease specific mortality (2130, 2229, 2230, 2243). Such tools can help tailor individual patient followup regimens as well as the decision making process regarding adjuvant therapy.

Staging

Preoperative MRI may aid surgical planning before prostatectomy. In a series of 335 patients undergoing robotic assisted laparoscopic prostatectomy (RALP), preoperative MRI had a positive and negative predictive value of 59% and 80%, respectively, for the detection of extraprostatic extension (239). Furthermore, a nomogram combining MRI findings with biopsy data (percent ipsilateral positive cores) improved the detection of side specific extracapsular extension (AUC 0.871) (237). Classification of pT3a cancers into focal vs established demonstrated prognostic significance when evaluating 10-year disease-free survival among men with a low risk of distant metastasis (2130, 2229, 2230, 2243).

RADIOLOGY Corner

Evaluating Testicular Nodules with Sonoelastography: An Emerging Technology

A 30-year-old man presented to the office after 1 year of infertility despite regular intercourse with his 29-year-old wife. On examination he had a normal bilateral testis, epididymides, vas deferens and a grade I palpable left varicocele. Scrotal ultrasound confirmed left varicocele and demonstrated multiple subcentimeter hypoechoic lesions in the right testis with color Doppler showing blood flow (fig. 1). Blood work revealed normal testosterone, luteinizing hormone, follicle-stimulating hormone and tumor markers (human chorionic gonadotropin, α-fetoprotein, lactate dehydrogenase), and 2 semen analyses showed oligoasthenospermia. What would be your next step?
survival after prostatectomy (367).

**Localized Disease**

Of approximately 5,500 patients undergoing minimally invasive radical prostatectomy those undergoing laparoscopic radical prostatectomy had a higher rate of overall complications as well as high grade (Clavien III/IV) complications than those undergoing RALP (676).

In a SEER (Surveillance, Epidemiology and End Results)-Medicare based study of nearly 10,000 patients undergoing prostatectomy incisional hernias were significantly more common after minimally invasive radical prostatectomy (HR 3.2) (1347).

Two reports addressed the therapeutic impact of nodal yield at prostatectomy, and neither extended lymphadenectomy during robotic prostatectomy (359) nor higher overall nodal yield (358) impacted the risk of biochemical recurrence (BCR).

**Advanced Disease**

A report on 1,088 chemotherapy naïve patients with metastatic castration resistant prostate cancer (CRPC) randomized to abiraterone acetate or placebo indicated delayed time to disease progression in the abiraterone acetate cohort (713).

The alpha-emitting radiopharmaceutical radium-223 dichloride was shown to reduce pain and opiate use as well as improve quality of life in patients with CRPC and bone metastases (714).

Between 1992 and 2007 the use of chemotherapy in men with metastatic prostate cancer increased from 12% to 31% (779). However, accompanying this greater use of chemotherapy was a 50% hospital readmission rate from therapy, highlighting the morbidity associated with metastatic prostate cancer and resultant treatment.

In a retrospective review of 292 patients with pT3N+M0 prostate cancer, adjuvant hormone therapy improved BCR-free survival vs adjuvant radiotherapy or observation alone, but had no impact on cancer specific survival or overall survival (718).

The optimal timing to initiate salvage radiation therapy (SRT) for BCR after prostatectomy was addressed in a review of the SEARCH (Shared Equal Access Regional Cancer Hospital) database (719). A pre-SRT PSA of 1 ng/ml or less versus 1 ng/ml was associated with a lower failure rate, although there were no observed differences in failure rates among stratified pre-SRT PSA values less than 1 ng/ml.

**Basic Research**

Several groups explored the impact of diet on prostate tumorigenesis. A low fat fish oil diet was associated with decreased pro-inflammatory eicosanoids and prostate cancer cell cycle progression score compared to Western diet in a cohort of men undergoing prostatectomy (315).

A prostate cancer mouse xenograft model suggested that compared to other fat sources (olive oil, corn oil or other saturated fats), only fish oil was associated with slowed tumor growth and improved survival (316). A high fat diet resulted in larger tumor size and significant alternations in microRNA expression, particularly miR-15a down-regulation, in a prostate cancer mouse xenograft model (314). Such microRNA changes may underlie high fat diet induced prostate tumorigenesis.

Overall the Annual Meeting highlighted the wealth of work being done to better understand the biology, therapy and natural history of prostate cancer. Such knowledge will be increasingly important given the changing landscape of prostate cancer detection.

**Infection/Inflammation**

Dr. Jeannette Potts  
Palo Alto, California

This brief summary will highlight a few of the most compelling presentations, including observations (lessons learned) and discoveries (stay tuned).

The incidence of urinary tract infections (UTIs) and urosepsis continues to increase at alarming rates. A review of national databases informs us that nearly 5,000 new cases of urosepsis are diagnosed every day in the United States (1055). The cost of care has increased sevenfold from 2000 to 2010 while other hospital costs have increased only 37%. Nevertheless, urosepsis carries a 15% mortality rate, which is 8 times higher than that of other diagnoses.

A contributing factor may be the increasing rate of catheter related UTIs, which are associated with increased length of hospital stay (LOS), sepsis and mortality. Increased mortality was associated with the inability to identify the culpable organism and the acquisition of the infection during hospitalization (both of which imply the added dangers of nosocomial infection), as well as patient age and severity of other illnesses (1054). These observations were corroborated by other reviews demonstrating the expected risk factors for mortality such as advanced age, black race and being uninsured (1056). However, a rather shocking observation was the significantly higher mortality rate for patients 45 to 64 years old (9% vs 3% to 4%) after controlling for comorbid conditions. The researchers suspect this was caused by a possible delay in medical attention or higher rates of resistant organisms.

Sepsis associated with obstructive stones is another high risk scenario in which early intervention is paramount. Researchers demonstrated the value of knowing one’s biogram. Escherichia coli was the most commonly identified pathogen (1057). However, 40% of the isolates were resistant to fluoroquinolones (FQs). The overall resistance rate was 25% for all organisms and 16% were resistant to FQs. History of antibiotic resistance was the only predictive factor among the patients. However, the resistance rates correlated with the institution’s biogram, which helped guide (and improve) therapy.

Another valuable caveat applies to the use of regional biograms, as they are becoming increasingly available and may be more helpful for those practicing at large referral centers.

In what might be classified as a call to action, researchers proved with shocking economic calculations the need for UTI management outside the emergency department setting. Using the Nationwide Emergency Department Sample 10.8 million cases (2006 to 2009) were reviewed (1062). Treat and release cases represented 80% of these emergency visits at an average cost of $1,992 (vs $122 to $172 for outpatient office and laboratory fees). If we could use strategies to improve outpatient access for UTIs, this could translate to a $4 billion savings.

Prophylaxis must not be taken lightly as shown in what is to my knowledge the first study of its kind correlating urological procedures to subsequent infective endocarditis (IE) (1169). A chart review spanning 12 years revealed 384 patients with IE, of whom 111 had enterococcal IE and a history of a urological procedure within 1 year of IE diagnosis.

“A review of national databases informs us that nearly 5,000 new cases of urosepsis are diagnosed every day in the United States (1055).”

As we are well aware FQ resistance is a growing concern with prophylaxis and the treatment of patients undergoing prostate biopsy. Culturing the rectum to identify resistant organisms may be one way to improve prophylaxis. Other studies have demonstrated a 93% concordance between the specimens obtained at biopsy and those obtained at an earlier consultation (1163). In another study infection complication after biopsy in 238 men previously empirically treated for an increased PSA was twice as likely (5%) as in 277 untreated men (2.5%) (1164).

Empirical antibiotics should be avoided. Period. And yet in another example, state-of-the-art microbial identification techniques were used to study 257 patients with the urological chronic pelvic pain syndrome (UCPPS) and 261 controls, of whom 60% were male in both groups (1147). No significant differences were found between the symptomatic patients and the controls.

Do not empirically treat chronic prostatitis or interstitial cystitis/bladder pain syndrome (IC/BPS) with antibiotics. In addition, do not look for glomerulations to corroborate the...
Take Home Messages

Separated from page 8

Minimally Invasive Surgery

Dr. James A. Brown
Iowa City, Iowa

Robotic assisted cystectomy is no better than open radical cystectomy (RC). The plenary session featured a late breaking news presentation on the interim analysis of a 123 patient prospective, randomized trial. Robotic cystectomy was 2 hours longer, resulted in 155 ml less estimated blood loss (EBL) but otherwise provided equivalent outcomes. These findings plus other reports of similar clinical, pathological and quality of life outcomes put live robotic cystectomy surgeries and courses in perspective (1624, 1625).

Endoscopic inguinal lymphadenectomy nearly eliminates wound complications. A much lower complication rate (7% vs 56%, largely wound and lymphedema) was reported compared to the open approach (940). The 28 endoscopic procedures took an average of 34 minutes longer to perform (fig. 1).

In fact, “LESS ain’t much more.” Laparoendoscopic single site (LESS) surgery provides renal and adrenal surgical results equivalent to those of standard laparoscopy (51, 834, 835, 836, 844, 1555, 2111) but with a frequent need for extra trocars and a limited cosmetic benefit (46). Magnetic tracking technology was used to demonstrate suboptimal joint ergonomics for LESS (879). In a plenary session on reconstructive procedures micro-laparoscopy was presented as a better way to go and deserving of further study.

The long-term benefit of zero ischemia robotic/laparoscopic partial nephrectomy (PN) is probably zero. While some investigators reported the benefit of improved short-term renal function (1192, 1193), others importantly found no long-term renal function improvement when patients were followed for more than 14 months (1195, 1461).

Near infrared fluorescence (NIRF) with indocyanine green is a fairly dazzling tool. There was an approximately 80% agreement between histology and NIRF (625, 851). NIRF also works to display ureteral structures (863), is a thousandfold better in a 10% milk solution (847) and can identify implanted prostate specific membrane antigen positive cells during porcine laparoscopic surgery (1319). However, its true value needs to be proven (fig. 2).

For the small renal mass (SRM), robotic PN has passed laparoscopic and is gaining on open surgery. Assessment of the Nationwide Inpatient Sample revealed that the relative use of robotic PN was up to 29% in the Midwest and 26% in adults younger than age 50 years (1305, 1645).

Prior radiation, morbid obesity, and taking aspirin with or without Plavix® pose no problems for robot-assisted radical prostatectomy (RARP). Salvage RARP outcomes were comparable to those of open surgery without the need for open conversion (1218). In another study men with a body mass index greater than 40 kg/m² undergoing RARP had outcomes similar to those of normal weight men but with an operative time 20 minutes longer (1219).

Others found that RARP could be safely performed in men taking acetaminophen acid and/or clopidogrel, but with a longer hospital stay (7.3 vs 5.7 days) and a slightly greater transfusion rate (5% vs 4%) (858, 1011).

In terms of biochemical recurrence after RARP, a positive surgical margin (PSM) greater than 3 mm may cause recurrence and pelvic lymph node dissection (PLND) may prevent it. A PSM 3 mm or longer or multifocality was an independent predictor of BCR (1000), and the first report of biochemical control in patients with positive lymph nodes undergoing RARP with PLND was presented (864).

For incontinence after RARP, beware prior transurethral prostate resection (TURP) and the long case. Prior TURP in 53 men resulted in a 10% greater PSM rate (29.4% vs 19.6%), worse 1 month urinary leakage and weaker urinary stream at 1 year (860). The same group reported that in a single surgeon, 2639 case experience at 18 months after surgery, EPIC (Expanded Prostate Cancer Index Composite for Clinical Practice) continence outcomes were negatively associated with operative time. However, erectile function measured by the Sexual Health Inventory for Men score was not associated with operative time or EBL (859).

“Empirical antibiotics should be avoided. Period.”
Second-line therapy for your adult overactive bladder (OAB) patients

After the prescription you write

Turn to one you perform.

To learn more about BOTOX® visit
www.botoxforoab.com/hcp
If you would like to be contacted by a BOTOX® representative, please call 1-800-44-BOTOX, Option 1

Indication
Overactive Bladder
BOTOX® for injection is indicated for the treatment of overactive bladder with symptoms of urge urinary incontinence, urgency, and frequency, in adults who have an inadequate response to or are intolerant of an anticholinergic medication.

IMPORTANT SAFETY INFORMATION, INCLUDING BOXED WARNING

Warning: Distant Spread of Toxin Effect
Postmarketing reports indicate that the effects of BOTOX® and all botulinum toxin products may spread from the area of injection to produce symptoms consistent with botulinum toxin effects. These may include asthenia, generalized muscle weakness, diplopia, ptosis, dysphagia, dysphonia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening, and there have been reports of death. The risk of symptoms is probably greatest in children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions, particularly in those patients who have an underlying condition that would predispose them to these symptoms. In unapproved uses, including spasticity in children, and in approved indications, cases of spread of effect have been reported at doses comparable to those used to treat cervical dystonia and at lower doses.

Please see the adjacent page for additional Important Safety Information.
IMPORTANT SAFETY INFORMATION (cont.)

CONTRAINDICATIONS

BOTOX® (onabotulinumtoxinA) is contraindicated in the presence of infection at the proposed injection site[s] and in individuals with known hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation.

Intradetrusor injection of BOTOX® is contraindicated in patients with overactive bladder who have a urinary tract infection (UTI), in patients with urinary retention, and in patients with post-void residual (PVR) urine volume >200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability Between Botulinum Toxin Products

The potency Units of BOTOX® are specific to the preparation and assay method utilized. They are not interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity of BOTOX® cannot be compared to nor converted into units of any other botulinum toxin products assessed with any other specific assay method.

Spread of Toxin Effect

See Boxed Warning.

Injections in or Near Vulnerable Anatomic Structures

Care should be taken when injectiing in or near vulnerable anatomic structures. Serious adverse events including fatal outcomes have been reported in patients who had received BOTOX® injected directly into salivary glands, the oro-lingual-pharyngeal region, esophagus and stomach. Some patients had pre-existing dysphagia or significant debility. (Safety and effectiveness have not been established for indications pertaining to these injection sites.) Pneumothorax associated with injection procedure has been reported following the administration of BOTOX® near the thorax. Caution is warranted when injecting in proximity to the lung, particularly the apices.

Hypersensitivity Reactions

Serious and/or immediate hypersensitivity reactions have been reported. These reactions include anaphylaxis, serum sickness, urticaria, skin and underlying tissue edema, and dyspnea. If such a reaction occurs, further injection of BOTOX® should be discontinued and appropriate medical therapy immediately instituted. One fatal case of anaphylaxis has been reported in which lidocaine was used as the diluent, and consequently the causal agent cannot be reliably determined.

Pre-existing Neuromuscular Disorders

Individuals with peripheral motor neuropathic diseases, amyotrophic lateral sclerosis, or neuromuscular junctional disorders (eg, myasthenia gravis or Lambert-Eaton syndrome) should be monitored particularly closely when given botulinum toxin. Patients with neuromuscular disorders may be at increased risk of clinically significant effects including severe dysphagia and respiratory compromise from therapeutic doses of BOTOX®.

Urinary Tract Infections in Patients With Overactive Bladder

BOTOX® increases the incidence of urinary tract infection. Clinical trials for overactive bladder excluded patients with more than 2 UTIs in the past 6 months and those taking antibiotics chronically due to recurrent UTIs. Use of BOTOX® for the treatment of overactive bladder in such patients and in patients with multiple recurrent UTIs during treatment should only be considered when the benefit is likely to outweigh the potential risk.

Urinary Retention in Patients Treated for Overactive Bladder

Due to the risk of urinary retention, treat only patients who are willing and able to initiate catheterization post-treatment, if required, for urinary retention.

In patients who are not catheterizing, post-void residual (PVR) urine volume should be assessed within 2 weeks post-treatment and periodically as medically appropriate up to 12 weeks, particularly in patients with multiple sclerosis or diabetes mellitus. Depending on patient symptoms, institute catheterization if PVR urine volume exceeds 200 mL and continue until PVR falls below 200 mL. Instruct patients to contact their physician if they experience difficulty in voiding as catheterization may be required.

In clinical trials, 6.5% of patients (36/552) initiated clean intermittent catheterization for urinary retention following treatment with BOTOX® (onabotulinumtoxinA) 100 Units as compared to 0.4% of patients (2/542) treated with placebo. For patients treated with BOTOX® 100 Units was 63 days (minimum 1 day to maximum 214 days) as compared to a median duration 11 days (minimum 3 days to maximum 18 days) for patients receiving placebo.

Patients with diabetes mellitus treated with BOTOX® were more likely to develop urinary retention than non-diabetics. In clinical trials, 12.3% of patients with diabetes (10/81) developed urinary retention following treatment with BOTOX® 100 Units as compared to 0% of patients (0/69) treated with placebo. In patients without diabetes, 6.3% of patients (33/526) developed urinary retention following treatment with BOTOX® 100 Units as compared to 0.6% of patients (3/516) treated with placebo.

Human Albumin and Transmission of Viral Diseases

This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) is also considered extremely remote. No cases of transmission of viral diseases or CJD have ever been reported for albumin.

ADVERSE REACTIONS

The following adverse reactions to BOTOX® for injection are discussed in greater detail in the following sections: Spread of Toxin Effect (see Boxed Warning), Hypersensitivity Reactions (see Contraindications and Warnings and Precautions), and Urinary Retention in Patients treated for Overactive Bladder (see Warnings and Precautions).

The most frequently reported adverse reactions for overactive bladder occurring within 12 weeks of injection include urinary tract infection (BOTOX® 18%, placebo 6%), dysuria (BOTOX® 9%, placebo 7%), urinary retention (BOTOX® 6%, placebo 0%), bacteriuria (BOTOX® 4%, placebo 2%), and residual urine volume (BOTOX® 3%, placebo 0%). A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX® 100 Units and placebo than non-diabetics.

The incidence of UTI increased in patients who experienced a maximum post-void residual (PVR) urine volume ≥200 mL following BOTOX® injection compared to those with a maximum PVR <200 mL following BOTOX® injection, 44% versus 23%, respectively.

Post Marketing Experience

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin. There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Co-administration of BOTOX® and aminoglycosides or other agents interfering with neuromuscular transmission (eg, curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated. Use of anticholinergic drugs after administration of BOTOX® may potentiate systemic anticholinergic effects. The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin. Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX®.

For more information on BOTOX®, please see brief summary of Prescribing Information on the following pages.
BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION
BOTOX® (onabotulinumtoxinA) for injection for intradetrusor use

INDICATIONS AND USAGE

Overactive Bladder
BOTOX (onabotulinumtoxinA) is indicated for the treatment of overactive bladder with symptoms of
urinary urgency, frequency, and urge incontinence in adults who have inadequate response or are
intolerant of an anticholinergic medication.

CONTRAINDICATIONS

Known Hypersensitivity to Botulinum Toxin
BOTOX is contraindicated in patients with a hypersensitivity to any botulinum toxin preparation or to any of
the components in the formulation [see Warnings and Precautions].

Infection at the Injection Site(s)
BOTOX is contraindicated in the presence of infection at the proposed injection site(s).

Urinary Tract Infection or Urinary Retention
Intraderm injection of BOTOX is contraindicated in patients with overactive bladder who have a urinary tract
infection. Intraderm injection of BOTOX is also contraindicated in patients with urinary retention and in
patients with post-vacc residual urine volume ≥200 mL who are not routinely performing clean intermittent self-catheterization (CIC).

WARNINGS AND PRECAUTIONS

Lack of Interchangeability between Botulinum Toxin Products
The potency units of BOTOX are specific to the preparation and assay method utilized. They are not
interchangeable with other preparations of botulinum toxin products and, therefore, units of biological activity
of BOTOX cannot be compared to nor converted into units of any other botulinum toxin products assessed
with any other specific assay method.

Spread of Toxin Effect
Postmarketing safety data from BOTOX and other approved botulinum toxins suggest that botulinum toxin
effects may, in some cases, be observed beyond the site of local injection. The symptoms are consistent with
the mechanism of action of botulinum toxin and may include asthenia, generalized muscle weakness, diplopia,
ptosis, ophthalmoplegia, dysphagia, dysarthria, urinary incontinence, and breathing difficulties. These symptoms
have been reported hours to weeks after injection. Swallowing and breathing difficulties can be life threatening and
there have been reports of death related to spread of toxin effects. The risk of such symptoms is probably greatest in
children treated for spasticity but symptoms can also occur in adults treated for spasticity and other conditions,
and particularly in those patients who have an underlying condition that would predispose them to these symptoms.
In unapproved uses, including spasticity, dysphagia, and/ or aspiration pneumonia, the symptoms are
transient, may have a duration of several months or longer. Localized pain, infection, inflammation, tenosynovitis,
swelling, erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or
anxiety may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin.
However, weakness of nearby muscles may also occur due to spread of toxin [see Warnings and Precautions].

Overactive Bladder
Table 1 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials
for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 1: Proportion of Patients Catherizing for Urinary Retention and Duration of Catherization following an
injection in double-blind, placebo-controlled clinical trials in OAB

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Proportion of Patients Catherizing for Urinary Retention</th>
<th>Duration of Catherization for Urinary Retention (Days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>66%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0, 1, 214</td>
<td>3, 18</td>
</tr>
</tbody>
</table>

Patients with diabetes mellitus treated with BOTOX were more likely to develop urinary retention than those
without diabetes, as shown in Table 2.

Table 2: Proportion of Patients Experiencing Urinary Retention following an injection in double-blind,
placebo-controlled clinical trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units</td>
<td>Placebo</td>
</tr>
<tr>
<td>(N=525)</td>
<td>(N=542)</td>
</tr>
<tr>
<td>(N=526)</td>
<td>(N=516)</td>
</tr>
</tbody>
</table>

Human Albumin and Transmission of Viral Diseases
This product contains albumin, a derivative of human blood. Based on effective donor screening and testing
manufacturing processes, this product carries a low risk of transmission of viral diseases. However, the risk of
transmission of viral diseases cannot be excluded.

ADVERSE REACTIONS

The following adverse reactions to BOTOX (onabotulinumtoxinA) for injection are discussed in greater detail in
other sections of the labeling:

• Spread of Toxin Effects [see Warnings and Precautions]
• Hypersensitivity [see Warnings and Precautions]
• Urinary Retention in Patients Treated for Bladder Dysfunction [see Warnings and Precautions]

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in
the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not
reflect the rates observed in clinical practice.

BOTOX and BOTOX Cosmetic contain the same active ingredient in the same formulation, but with different
tablets of impurities and dosage. Therefore, adverse reactions observed with the use of BOTOX cosmetic also
have the potential to be observed with the use of BOTOX.

In general, adverse reactions occur within the first week following injection of BOTOX and while generally
transient, may have a duration of several months or longer. Localized pain, inflammation, tenosynovitis, swelling,
erythema, and/or bleeding/bruising may be associated with the injection. Needle-related pain and/or anxiety
may result in vasovagal responses (including e.g., syncope, hypotension), which may require appropriate medical therapy.

Local weakness of the injected muscle(s) represents the expected pharmacological action of botulinum toxin.
However, weakness of nearby muscles may also occur due to spread of toxin [see Warnings and Precautions].

Overactive Bladder

Table 3 presents the most frequently reported adverse reactions in double-blind, placebo-controlled clinical trials
for overactive bladder occurring within 12 weeks of the first BOTOX treatment.

Table 3: Adverse Reactions Reported by ≥2% of BOTOX treated Patients and More Often than in Placebo

<table>
<thead>
<tr>
<th>Patients Treated Within the First 12 Weeks after Intraderm Injection, in Double-blind, Placebo-controlled Clinical Trials in Patients with OAB</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=525)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Dysuria</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Bacteruria</td>
</tr>
<tr>
<td>Residual urine volume*</td>
</tr>
</tbody>
</table>

*Reduced PVR not requiring catherization. Catherization was required for PVR ≥350 mL regardless of symptoms, and for PVR <200 mL to <350 mL with symptoms (e.g., voiding difficulty).

A higher incidence of urinary tract infection was observed in patients with diabetes mellitus treated with BOTOX 100 units and placebo in patients with diabetes, as shown in Table 4.

Table 4: Proportion of Patients Experiencing Urinary Tract Infection following an injection in Double-blind,
Placebo-controlled Clinical Trials in OAB according to history of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Patients with Diabetes</th>
<th>Patients without Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units</td>
<td>Placebo</td>
</tr>
<tr>
<td>(N=51)</td>
<td>(N=52)</td>
</tr>
<tr>
<td>(N=56)</td>
<td>(N=56)</td>
</tr>
<tr>
<td>Urinary tract infection (UTI)</td>
<td>25% (31%)</td>
</tr>
</tbody>
</table>

The incidence of UTI increased in patients who experienced a maximum post-vacc residual (PVR) urine volume ≥200 mL following BOTOX injection compared to those with a maximum PVR <200 mL following BOTOX injection, 44% versus 23%, respectively. No change was observed in the overall safety profile with repeat dosing during an open-label, uncontrolled extension trial.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. Formation of neutralizing antibodies to
dolium toxin type A may reduce the effectiveness of BOTOX treatment by inactivating the biological activity of the
toxin.

In a long-term, open-label study evaluating 326 cervical dystonia patients treated for an average of 9 treatment
sessions with the current formulation of BOTOX, 4 (1.2%) patients had positive antibody tests. All 4 of these patients
had pre-existing dysphagia or significant debility. These symptoms have been reported hours to weeks after injection.

The incidence and duration of urinary retention is described below for patients with overactive bladder who
received BOTOX or placebo injections.

Overactive Bladder

In double-blind, placebo-controlled trials in patients with OAB, the proportion of subjects who initiated
catheterization following injection (CIC) for urinary retention following treatment with BOTOX or placebo is shown
in Table 1. The duration of post-injection catherization for those who developed urinary retention is also shown.
The critical factors for neutralizing antibody formation have not been well characterized. The results from some studies suggest that BOTOX injections at more frequent intervals or at higher doses may lead to greater incidence of antibody formation. The potential for antibody formation may be minimized by injecting with the lowest effective dose given at the longest feasible intervals between injections.

Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of BOTOX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These reactions include: abdominal pain; alopecia, including madarosis; anorexia; aspiration pneumonia; brachial plexopathy; denervation/muscle atrophy; diarrhea; dry mouth; dysarthria; dysphagia; facial palsy; facial paresis; hyperhidrosis; hypoaesthesia; localized numbness; malaise; muscle weakness; myalgia; myasthenia gravis; nausea; paresthesia; peripheral neuropathy; pruritus; pyrexia; radiculopathy; respiratory depression and/or respiratory failure; skin rash (including erythema multiforme, dermatitis psoriasiform, and psoriasis-like eruption); strabismus; syncope; tinnitus; vertigo; vision blurred; visual disturbances; and vomiting.

There have been spontaneous reports of death, sometimes associated with dysphagia, pneumonia, and/or other significant debility or anaphylaxis, after treatment with botulinum toxin [see Warnings and Precautions].

There have also been reports of adverse events involving the cardiovascular system, including arrhythmia and myocardial infarction, some with fatal outcomes. Some of these patients had risk factors including cardiovascular disease. The exact relationship of these events to the botulinum toxin injection has not been established. New onset or recurrent seizures have also been reported, typically in patients who are predisposed to experiencing these events. The exact relationship of these events to the botulinum toxin injection has not been established.

DRUG INTERACTIONS

Aminoglycosides and Other Agents Interfering with Neuromuscular Transmission

Co-administration of BOTOX and aminoglycosides or other agents interfering with neuromuscular transmission (e.g., curare-like compounds) should only be performed with caution as the effect of the toxin may be potentiated.

Anticholinergic Drugs

Use of anticholinergic drugs after administration of BOTOX may potentiate systemic anticholinergic effects.

Other Botulinum Neurotoxin Products

The effect of administering different botulinum neurotoxin products at the same time or within several months of each other is unknown. Excessive neuromuscular weakness may be exacerbated by administration of another botulinum toxin prior to the resolution of the effects of a previously administered botulinum toxin.

Muscle Relaxants

Excessive weakness may also be exaggerated by administration of a muscle relaxant before or after administration of BOTOX.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C.

There are no adequate and well-controlled studies in pregnant women. BOTOX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

When BOTOX (4, 8, or 16 Units/kg) was administered intramuscularly to pregnant mice or rats two times during the period of organogenesis (on gestation days 5 and 13), reductions in fetal body weight and decreased fetal skeletal ossification were observed at the two highest doses. The no-effect dose for developmental toxicity in these studies (4 Units/kg) is approximately 0.7 times the average high human dose for upper limb spasticity of 360 Units on a body weight basis (Units/kg).

When BOTOX was administered intramuscularly to pregnant rats (0.125, 0.25, 0.5, 1, 4, or 8 Units/kg) or rabbits (0.063, 0.125, 0.25, or 0.5 Units/kg) daily during the period of organogenesis (total of 12 doses in rats, 13 doses in rabbits), reduced fetal body weights and decreased fetal skeletal ossification were observed at the two highest doses in rats and at the highest dose in rabbits. These doses were also associated with significant maternal toxicity, including abortions, early deliveries, and maternal death. The developmental no-effect doses in these studies of 1 Unit/kg in rats and 0.25 Units/kg in rabbits are less than the average high human dose based on Units/kg.

When pregnant rats received single intramuscular injections (1, 4, or 16 Units/kg) at three different periods of development (prior to implantation, implantation, or organogenesis), no adverse effects on fetal development were observed. The developmental no-effect level for a single maternal dose in rats (16 Units/kg) is approximately 3 times the average high human dose based on Units/kg.

Nursing Mothers

It is not known whether BOTOX is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when BOTOX is administered to a nursing woman.

Pediatric Use

Bladder Dysfunction

Safety and effectiveness in patients below the age of 18 years have not been established.

Geriatric Use

Overall, with the exception of Overactive Bladder (see below), clinical studies of BOTOX did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. There were too few patients over the age of 75 to enable any comparisons. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Overactive Bladder

Of 1242 overactive bladder patients in placebo-controlled clinical studies of BOTOX, 41.4% (n=514) were 65 years of age or older, and 14.7% (n=182) were 75 years of age or older. Adverse reactions of UTI and urinary retention were more common in patients 65 years of age or older in both placebo and BOTOX groups compared to younger patients (see Table 5). Otherwise, there were no overall differences in the safety profile following BOTOX treatment between patients aged 65 years and older compared to younger patients in these studies.

Table 5. Incidence of Urinary Tract Infection and Urinary Retention according to Age Group during First Placebo-controlled Treatment, Placebo-controlled Clinical Trials in Patients with OAB

<table>
<thead>
<tr>
<th>Age Group</th>
<th>≤65 Years</th>
<th>65 to 74 Years</th>
<th>≥75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>BOTOX 100 Units (N=344)</td>
<td>73 (21%)</td>
<td>51 (30%)</td>
<td>36 (38%)</td>
</tr>
<tr>
<td>Placebo (N=348)</td>
<td>23 (7%)</td>
<td>20 (13%)</td>
<td>16 (19%)</td>
</tr>
<tr>
<td>BOTOX 100 Units (N=169)</td>
<td>21 (6%)</td>
<td>14 (8%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Placebo (N=151)</td>
<td>2 (0.6%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

Observed effectiveness was comparable between these age groups in placebo-controlled clinical studies.

OVERDOSAGE

Excessive doses of BOTOX (onabotulinumtoxinA) for injection may be expected to produce neuromuscular weakness with a variety of symptoms.

Symptoms of overdose are likely not to be present immediately following injection. Should accidental injection or oral ingestion occur or overdose be suspected, the person should be medically supervised for several weeks for signs and symptoms of systemic muscular weakness which could be local, or distant from the site of injection [see Boxed Warning and Warnings and Precautions].

These patients should be considered for further medical evaluation and appropriate medical therapy immediately instituted, which may include hospitalization.

If the musculature of the oropharynx and esophagus are affected, aspiration may occur which may lead to development of aspiration pneumonia. If the respiratory muscles become paralyzed or sufficiently weakened, intubation and assisted respiration may be necessary until recovery takes place. Supportive care should involve the need for a tracheostomy and/or prolonged mechanical ventilation, in addition to other general supportive care.

In the event of overdose, antitoxin raising against botulinum toxin is available from the Centers for Disease Control and Prevention (CDC) in Atlanta, GA. However, the antitoxin will not reverse any botulinum toxin-induced effects already apparent by the time of antitoxin administration. In the event of suspected or actual cases of botulinum toxin poisoning, please contact your local or state Health Department to process a request for antitoxin through the CDC. If you do not receive a response within 20 minutes, please contact the CDC directly at 1-770-488-7100. More information can be obtained at http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5232a6.htm.

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Based on 72309US13, 72312US13, and 72511US10. APC12TF13
Take Home Messages

To improve continence after RARP, is hypothermia or electrograftomy (EMG) stimulation the answer? In a report on 36 patients treated with RARP with hypothermia the localized neutrophil count decreased 50% in the postrolateral periurethral tissue (p=0.03) and hypothermia was associated with shorter time to no pad use (26 vs 69 days, p=0.08) (849). Intraoperative identification of the nerves innervating the levator ani using EMG stimulation was feasible and was associated with improved 8-week postoperative EPIC continence scores (852).

Counterintuitively a urethral Foley catheter was tolerated as well as a suprapubic tube (SPT) after RARP. In a prospective, randomized trial comparing urethral catheter removal on postoperative day 1 (with SPT indwelling) vs postoperative day 7, investigators found similar pain, catheter related bother and treatment related satisfaction in the perioperative period (1408). Importantly the authors now no longer routinely offer SPT with early urethral catheter removal.

In terms of robotic momentum, did RARP get ahead of itself? In a comparison of RARP publications and surgeries (as a percentage of minimally invasive plus open), in 2008 RARP surgery markedly outpaced publications, raising concern that RARP adoption outpaced the robustness of evidence based literature (131).

Additionally, in a review of the SEER database from 2004 to 2007, intensity modulated radiotherapy and RARP increased in use from 43% to 50% in low risk patients, from 48% to 59% in men with a low probability of living 10 years and from 27% to 36% for men with both characteristics (125).

In a report on the robot’s dark side, that of adverse events, the Food and Drug Administration MAUDE (Manufacturer and User Facility Device Experience) database (2009 to 2010) showed a 0.1% overall adverse event rate, but this was for a significantly greater severity of the event observed than was expected for the type of device used (855). Others found a 6.6% positioning injury rate including shoulder pain, hand/thigh paresthesia and arm weakness (853). Of the injuries 59% resolved within 1 month, 18% resolved within 1 to 6 months and 23% persisted beyond 6 months. Operative time, arm on board away from trunk, ASA (American Society of Anesthesiologists) score and amount of intravenous fluid infused were associated factors.

Finally, we have the robot and laparoscope simulator we have been waiting for. The TELELAP Alf-X® system, a novel telesurgical system, was reported to provide haptic sensation (1405, 1412). A patient specific simulator allows computerized tomography (CT) volume data to be entered into a model generating system (877). Three surgeons performing transperitoneal (4) and retroperitoneal (9) renal surgeries rated it well in terms of anatomical integrity, efficacy of simulation and sense of security during the subsequent operation (figs. 3 and 4).

Outcomes Analysis

Interest in outcomes analysis in the field of urology continues to grow, with 105 abstracts presented at this year’s meeting. We highlight those presentations addressing how best to use evidence-based medicine to create sustained improvements in population health.

Several abstracts effectively highlighted the potential impact of changing demographics and epidemiology on the incidence of urolithiasis. While the association between diabetes and urolithiasis is well established, NHANES (National Health and Nutrition Examination Survey) data were used to demonstrate that the likelihood of kidney stone formation is greater with increasing severity of diabetes (66). Patients with pre-diabetic range hemoglobin A1C levels had a 1.68 OR for stone formation, whereas those with diabetic range hemoglobin A1C levels had an OR for stone disease of 2.82.

Data from the Women’s Health Initiative demonstrated that increasing body mass index, low physical activity level and high caloric intake were each independently associated with an increased risk of stone formation (67). Such studies might ultimately be useful in risk stratifying patients as well as targeting screening and metabolic interventions toward those with the highest risk of stone formation.

Identifying best practices was another common theme. The results of a randomized trial comparing robotic and open cystectomy were presented as late breaking news in the plenary session. The investigators found no differences in complications, oncologic outcomes or LOS between the 2 procedures and, thus, closed the study early. The results of the trial call into question the usefulness of robotic cystectomy and highlight the importance of comparative effectiveness studies before the dissemination of new technologies.

While new guidelines for the treatment of metastatic CRPC were presented, one group examined the cost-effectiveness of such strategies which use expensive new drugs to treat this condition (128). When estimating societal willingness to pay a threshold of $100,000 per year of life saved, there were no cost-effective strategies for the treatment of metastatic CRPC, with the closest being docetaxel monotherapy at $102,000 per life-year. Such analyses are currently used in other countries to determine drug coverage and will likely become more common in the United States as policy makers continue to determine value in health care spending.

Several groups studied the evolution of existing practice patterns. Treatment decision making was analyzed among patients from the PCOS (Prostate Cancer Outcomes Study), enrolling men from 1994 to 1995, and CEASAR (Comparative Effectiveness Analysis of Surgery and Radiation for prostate cancer), enrolling men from 2011 to 2012 (136). While race was associated with a decreased likelihood of receiving definitive treatment in the PCOS, this no longer held true in the CEASAR. Meanwhile, age and baseline health remained associated with treatment choice in both cohorts.
community groups has increased the general awareness of this problem. However, a systematic review of all randomized controlled trials on prostate cancer between 2002 and 2011 showed that only 22% of trials enrolled black men (59). The United States had the highest proportion of black men enrolled (44%) compared to the rest of the world, where only 8% of enrollees were black. More concerning was the fact that these estimates have not changed with time.

Another example of practice not following evidence is in the use of imaging to stage prostate cancer. While rates of inappropriate use of imaging remain high in the United States, some suggest a possible roadmap for change (130). Based on the Swedish data there was a decrease in inappropriate imaging from 45% to 3% associated with a national effort to improve imaging practices. Disappointingly the appropriate use of imaging also decreased, although to a much smaller extent. Such findings can help guide United States policy efforts such as the Choosing Wisely® campaign.

Several presentations focused on quality measurement. In an assessment of the quality of care of women with urinary incontinence performance on several quality metrics was widely variable and inadequate across different clinical settings (152). Others looked at quality measures, studying the effect of performance feedback and educational intervention on improving the use of immediate intravesical chemotherapy for nonmuscle invasive bladder cancer (NMIBC) (56). This group found little change in practice patterns after intervention and suggested a possible ceiling effect, making it challenging to demonstrate improved care where care is already of relatively high quality. Such studies might ultimately help decide the types of quality measures most suitable to be linked with payment incentives and physician/practice quality measures.

Another type of quality measure gaining popularity is the patient experience survey. Patient satisfaction with the surgeon was analyzed along the 5 constructs of the Surgical CAHPS (Consumer Assessment of Healthcare Providers and Systems) survey (71). Postoperative office visit communication was most strongly correlated to satisfaction with the surgeon, and experience with postoperative care correlated more strongly to overall satisfaction than did preoperative care or patient interaction with the reception staff.

Finally, site of service delivery has become increasingly important to reduce the costs associated with unnecessary hospital admissions. Medicare data were used to study how the opening of an ambulatory surgery center (ASC) affected the local hospital volume of urological surgeries and outcomes (62). Markets where ASCs opened had corresponding decreases in rates of hospital based urological outpatient surgeries from 59 per hospital service area (HSA) at baseline to 39 per HSA 4 years later.

"Another example of practice not following evidence is in the use of imaging to stage prostate cancer."
suggest that the program may have been a policy success.

In summary, there is a tremendous amount of actionable research occurring in urology. Such efforts, in particular those focusing on cost, quality and implementation, are likely to prove useful in the coming years with increasing efforts to measure and reward high value health care. Ultimately such information should be used to help direct policy and ideally improve patient care.

Kidney Cancer

Dr. Andrew Wagner
Boston, Massachusetts

There were more than 220 kidney cancer abstracts accepted for presentation at the Annual Meeting. Among the various topics abundant work was presented in several general categories such as improving prognostication in localized and advanced disease, assessing surgical quality, and evaluating chronic kidney disease (CKD) and medical morbidity after radical nephrectomy (RN) and PN.

Improving Prognostication

Several groups presented work on tumor markers that might help indicate aggressive disease, including the total number of DNA aberrations (623), platelet derived growth factor-b receptor (1795), fibrinogen (731), C-reactive protein (744, 1921) and the cytoplasmic localization of hypoxia inducible factor-2a (1071). One or more of these markers may become useful adjuncts of risk stratification nomograms.

The impact of lymphovascular invasion (LVI) on pathology analysis is unclear. Patients with low stage renal cell carcinoma (RCC) and LVI had cancer specific survival similar to that of patients with high stage RCC (1075). Moreover, LVI was a predictor of late recurrence after nephrectomy (742). However, clinical lymph node invasion is not always associated with metastatic disease. Up to 60% of patients showing preoperatively suspicious nodes on imaging had negative findings on final pathology (743).

Renal biopsy can be helpful for evaluating SRMs for resection. However, there is a 22% nondiagnostic rate, and biopsy was not recommended for masses smaller than 1.5 cm or those with cystic qualities (1065).

“Patients with low stage renal cell carcinoma (RCC) and LVI had cancer specific survival similar to that of patients with high stage RCC (1075).”

In addition, surveillance should be considered for older patients with SRMs. One group developed a scoring system that, if validated, could assist in identifying patients suitable for surveillance (1067). Another retrospective study showed that patients 75 years old or older might not in fact benefit from PN (1634). In the years to come we will find ourselves continuing to temper the use of surgery for SRMs in this age group.

Surgical Quality

With pay for performance changes on the horizon, quality control in surgery is a hot topic. After evaluating more than 1,200 patients undergoing PN using the NSQIP (National Surgical Quality Improvement Program) database, more patients had superficial wound infections, organ space infections, UTIs and transfusions after open surgery than did those after undergoing minimally invasive PN (1187). Another group used the NSQIP to demonstrate that PN cases involving junior residents had higher complication rates than those performed by postgraduate year 6 residents or fellows, indicating a need for prospective analysis and perhaps improvements in surgical simulation (733).

Whether complex surgical cases should be directed toward tertiary centers remains controversial. Using the Nationwide Inpatient Sample database more than 48,000 nephrectomy cases were analyzed for complications. Patients treated at low volume hospitals were (up to) 28% more likely to have an adverse outcome (1635).

Warm Ischemia Time and CKD

The effect of warm ischemia time (WIT) on ultimate renal function after PN continues to foster intense discussion. Two groups found that parenchymal volume preservation was more important than WIT for kidney function (1191, 1460).

Several groups evaluated the usefulness of robot-assisted zero ischemia partial nephrectomy. The cases appeared to be longer than standard clamped PN, but at early followup there was a smaller decrease in estimated glomerular filtration rate (eGFR) (1192). However, others demonstrated equivalent long-term renal functional outcomes when comparing zero ischemia to standard clamped PN (1458, 1195).

The prospective, randomized EORTC (European Organisation for Research and Treatment of Cancer) trial 30904 evaluated renal function up to 15 years after surgery, and showed that average creatinine remained stable in the PN arm and there was a slight upward trend of 0.25 mg/dl in the patients treated with RN (1186). These data continue to be in contradistinction to those of large retrospective series showing an eightfold higher risk of eGFR less than 45 ml/min/m² for RN vs PN and a lower rate of death per year for PN vs RN (1304).

RCC and Lipid Metabolism

Evaluation of the normal parenchyma may offer some clues about the development of CKD after kidney surgery. Vascular sclerosis in the noncancerous parenchyma of nephrectomy specimens may be associated with future stage III and IV CKD (1804). In addition, nephrosclerosis was present in 68% of patients treated with nephrectomy compared to 30% of age-matched healthy patients (1462). Furthermore, patients undergoing RN had a higher incidence of de novo hyperlipidemia compared to those undergoing PN (1303, 1465).

“Vascular sclerosis in the noncancerous parenchyma of nephrectomy specimens may be associated with future stage III and IV CKD (1804).”

Finally, the use of statins was independently associated with improved overall and disease-free survival in a retrospective study (1646), suggesting that the treatment of hyperlipidemia may be an important adjunct for patients with RCC.

In summary, much new and important information was presented on kidney cancer at this year’s AUA meeting. Improvements in tumor markers, biopsy technique and surveillance algorithms will allow us to better predict the natural history of large and small kidney tumors. In addition, prospective evaluations of volume and training effects of surgical quality in kidney surgery are needed. Long-term renal function after PN may depend less on WIT and more on functional renal volume lost during surgery. Finally, patients with RCC may be at risk for altered lipid metabolism, setting them up for deleterious vascular changes.

Bladder Cancer

Dr. Edmund Chiong
Singapore

There were more than 230 presentations on bladder cancer (BC) at this year’s meeting with interesting findings.

External beam radiation therapy with or without brachytherapy for uterine cancer involved an increased risk of BC and death of 1.7 and 2.3-fold, respectively (1284).

Heavy smokers (history of more than 30 pack-years), especially men, were more likely to have higher grade BC, with a more advanced stage and an increased risk of muscle invasion at initial presentation (1291).

A prospective randomized study of 362 patients with NMIBC showed that fluorescence cystoscopy (FC) had a significantly improved detection rate and a lower recurrence rate for up to 4 years compared to white light cystoscopy (WLC) (40.8% vs 58.8%) (1279). A meta-analysis revealed that FC plus WLC significantly increased tumor detection and reduced recurrence rates at 12 months compared to WLC alone (34.5% vs 45.4%) (1293).

A prospective, randomized study of narrow band imaging cystoscopy and bipolar plasma vaporization demonstrated significantly improved diagnostic accuracy, increased detection rates (94.9% vs 84.3%), decreased repeat residual tumor transurethral resection (TUR) rates and reduced 3-year recurrence rates (16.3% vs 33.3%) compared to WLC and monopolar TUR (1280).

Repeat TUR before the initiation of intravesical bacillus Calmette-Guérin (BCG) significantly decreased recurrence rates at 3, 6 and

Continued on page 20

Take Home Messages ▼ Continued from page 15
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radium Ra 223 dichloride injection

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Important Safety Information

- **Contraindications:** Xofigo is contraindicated in women who are or may become pregnant. Xofigo can cause fetal harm when administered to a pregnant woman.

- **Bone Marrow Suppression:** In the randomized trial, 2% of patients in the Xofigo arm experienced bone marrow failure or ongoing pancytopenia, compared to no patients treated with placebo. There were two deaths due to bone marrow failure. For 7 of 13 patients treated with Xofigo bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients in the Xofigo arm and 2% in the placebo arm permanently discontinued therapy due to bone marrow suppression. In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.3% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) was similar for patients treated with Xofigo and placebo. Myelosuppression—namely thrombocytopenia, neutropenia, pancytopenia, and leukopenia—has been reported in patients treated with Xofigo.

Monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

- **Hematological Evaluation:** Monitor blood counts at baseline and prior to every dose of Xofigo. Prior to first administering Xofigo, the absolute neutrophil count (ANC) should be ≥1.5 × 10^9/L, the platelet count ≥100 × 10^9/L, and hemoglobin ≥10 g/dL. Prior to subsequent administrations, the ANC should be ≥1 × 10^9/L and the platelet count ≥50 × 10^9/L. Discontinue Xofigo if hematologic values do not recover within 6 to 8 weeks after the last administration despite receiving supportive care.

- **Concomitant Use With Chemotherapy:** Safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use of Xofigo in patients on chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes, or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

- **Administration and Radiation Protection:** Xofigo should be received, used, and administered only by authorized persons in designated clinical settings. The administration of Xofigo is associated with potential risks to other persons from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

- **Adverse Reactions:** The most common adverse reactions (≥10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema. Grade 3 and 4 adverse events were reported in 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia.

Please see following pages for brief summary of full Prescribing Information.
Xofigo (radium Ra 223 dichloride) Injection, for intravenous use

Initial U.S. Approval: 2013

BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xofigo™ is indicated for the treatment of patients with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

2 DOSAGE AND ADMINISTRATION

2.3 Instructions for Use/Handling

General warning

Xofigo (an alpha particle-emitting pharmaceutical) should be received, used and administered only by authorized persons in designated clinical settings. The receipt, storage, use, transfer and disposal Xofigo are subject to the regulations and/or appropriate licenses of the competent official organization.

Xofigo should be handled by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

Radiation protection

The administration of Xofigo is associated with potential risks to other persons (e.g., medical staff, caregivers and patient’s household members) from radiation or contamination from spills of bodily fluids such as urine, feces, or vomit. Therefore, radiation protection precautions must be taken in accordance with national and local regulations.

For drug handling

Follow the normal working procedures for the handling of radiopharmaceuticals and use universal precautions for handling and administration such as gloves and barrier gowns when handling blood and bodily fluids for radiation or contamination. In case of contact with skin or eyes, the affected area should be flushed immediately with water. In the event of spillage of Xofigo, the local radiation safety officer should be contacted immediately to initiate the necessary measurements and required procedures to decontaminate the area. A complexing agent such as 0.01 M ethylene-diamine- tetraacetic acid (EDTA) solution is recommended to remove contamination.

For patient care

Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. When handling bodily fluids, simply wearing gloves and hand washing will protect caregivers. Clothing soiled with Xofigo or patient fecal matter or urine should be washed promptly and separately from other clothing.

Radium-223 is primarily an alpha emitter, with a 95.3% fraction of energy emitted as alpha-particles. The fraction emitted as beta-particles is 3.6%, and the fraction emitted as gamma-radiation is 1.1%. The external radiation exposure associated with handling of patient doses is expected to be low, because the typical treatment activity will be below 8000 kBq (216 microcurie). In keeping with the As Low As Reasonably Achievable (ALARA) principle for minimization of radiation exposure, it is recommended to minimize the time spent in radiation areas, to maximize the distance from radiation sources, and to use adequate shielding. Any unused product or materials used in connection with the preparation or administration are to be treated as radioactive waste and should be disposed of in accordance with local regulations.

The gamma radiation associated with the decay of radium-223 and its daughters allows for the radiosensitivity measurement of Xofigo and the detection of contamination with standard instruments.

4 CONTRAINDICATIONS

Xofigo is contraindicated in pregnancy.

Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. Xofigo is not indicated for use in women. Xofigo is contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus [see Use in Specific Populations (8.1)].

5 WARNINGS AND PRECAUTIONS

5.1 Bone Marrow Suppression

In the randomized trial, 2% of patients on the Xofigo arm experienced bone marrow failure or ongoing pancytopenia compared to no patients treated with placebo. There were two deaths due to bone marrow failure and for 7 of 13 patients treated with Xofigo, bone marrow failure was ongoing at the time of death. Among the 13 patients who experienced bone marrow failure, 54% required blood transfusions. Four percent (4%) of patients on the Xofigo arm and 2% on the placebo arm permanently discontinued therapy due to bone marrow suppression.

In the randomized trial, deaths related to vascular hemorrhage in association with myelosuppression were observed in 1% of Xofigo-treated patients compared to 0.5% of patients treated with placebo. The incidence of infection-related deaths (2%), serious infections (10%), and febrile neutropenia (<1%) were similar for patients treated with Xofigo and placebo. Myelosuppression; notably thrombocytopenia, neutropenia, pancytopenia, and leukopenia; has been reported in patients treated with Xofigo. In the randomized trial, complete blood counts (CBCs) were obtained every 4 weeks prior to each dose and the nadir CBCs and times of recovery were not well characterized. In a separate single-dose phase 1 study of Xofigo, neutrophil and platelet count nadirs occurred 2 to 3 weeks after Xofigo administration at doses that were up to 1 to 5 times the recommended dose, and most patients recovered approximately 6 to 8 weeks after administration [see Adverse Reactions (6)].

Hematologic evaluation of patients must be performed at baseline and prior to every dose of Xofigo. Before the first administration of Xofigo, the absolute neutrophil count (ANC) should be ≥ 1.5 x 10^9/L, the platelet count ≥ 100 x 10^9/L and hemoglobin ≥ 10 g/dL. Before subsequent administrations of Xofigo, the ANC should be ≥ 1.0 x 10^9/L and the platelet count ≥ 50 x 10^9/L. If there is no recovery to these values within 6 to 8 weeks after the last administration of Xofigo, despite receiving supportive care, further treatment with Xofigo should be discontinued. Patients with evidence of compromised bone marrow reserve should be monitored closely and provided with supportive care measures when clinically indicated. Discontinue Xofigo in patients who experience life-threatening complications despite supportive care for bone marrow failure.

The safety and efficacy of concomitant chemotherapy with Xofigo have not been established. Outside of a clinical trial, concomitant use with chemotherapy is not recommended due to the potential for additive myelosuppression. If chemotherapy, other systemic radioisotopes or hemibody external radiotherapy are administered during the treatment period, Xofigo should be discontinued.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in another section of the label:

• Bone Marrow Suppression [see Warnings and Precautions (5.1)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In the randomized clinical trial in patients with metastatic castration-resistant prostate cancer with bone metastases, 600 patients received intravenous injections of 50 kBq/kg (1.35 microcurie/kg) of Xofigo and best standard of care and 301 patients received placebo and best standard of care once every 4 weeks for up to 6 injections. Prior to randomization, 58% and 57% of patients had received docetaxel in the Xofigo and placebo arms, respectively. The median duration of treatment was 20 weeks (6 cycles) for Xofigo and 18 weeks (5 cycles) for placebo.

The most common adverse reactions (≥ 10%) in patients receiving Xofigo were nausea, diarrhea, vomiting, and peripheral edema (Table 3). Grade 3 and 4 adverse events were reported among 57% of Xofigo-treated patients and 63% of placebo-treated patients. The most common hematologic laboratory abnormalities in Xofigo-treated patients (≥ 10%) were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (Table 4).

Treatment discontinuations due to adverse events occurred in 17% of patients who received Xofigo and 21% of patients who received placebo. The most common hematologic laboratory abnormalities leading to discontinuation for Xofigo were anemia (2%) and thrombocytopenia (2%).

Table 3 shows adverse reactions occurring in ≥ 2% of patients and for which the incidence for Xofigo exceeds the incidence for placebo.

Table 3: Adverse Reactions in the Randomized Trial

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Xofigo (n=600)</th>
<th>Placebo (n=301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancytopenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>36</td>
<td>35</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>13</td>
<td>10</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal failure and impairment</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Laboratory Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic Laboratory Abnormalities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>93</td>
<td>68</td>
</tr>
<tr>
<td>Lymphocytopenia</td>
<td>72</td>
<td>53</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>31</td>
<td>22</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>5</td>
</tr>
</tbody>
</table>

Laboratory values were obtained at baseline and prior to each 4-week cycle.

As an adverse reaction, grade 3-4 thrombocytopenia was reported in 6% of patients on Xofigo and in 2% of patients on placebo. Among patients who received Xofigo, the laboratory abnormality grade 3-4 thrombocytopenia occurred in 1% of docetaxel naïve patients and in 4% of patients who had received prior docetaxel. Grade 3-4 neutropenia occurred in 1% of docetaxel naïve patients and in 3% of patients who have received prior docetaxel.

Fluid Status

Dehydration occurred in 3% of patients on Xofigo and 1% of patients on placebo. Xofigo increases the incidence of dehydration as diarrhea, nausea, and vomiting which may result in dehydration. Monitor patients’ oral intake and fluid status carefully and promptly treat patients who display signs or symptoms of dehydration or hypovolemia.

Injection Site Reactions

Erythema, pain, and edema at the injection site were reported in 1% of patients on Xofigo.

Secondary Malignant Neoplasms

Xofigo contributes to a patient’s overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure may be associated with an increased risk of cancer and hereditary cancer risks. Due to its mechanism of action and neoplastic changes, including osteosarcomas, in rats following administration of radium-223 dichloride, Xofigo may increase the risk of osteosarcoma or other secondary malignant neoplasms [see Nonclinical Toxicology (13.1)]. However, the overall incidence of new malignancies in the randomized trial was lower on the Xofigo arm compared to placebo (<1% vs. 2%, respectively), but the expected latency period for the development of secondary malignancies exceeds the duration of exposure for patients on the trial.

Subsequent Treatment with Cytotoxic Chemotherapy

In the randomized clinical trial, 16% patients in the Xofigo group and 18% patients in the placebo group received cytotoxic chemotherapy after completion of study treatments. Adequate safety monitoring and laboratory testing was not performed to assess how patients treated with Xofigo will tolerate subsequent cytotoxic chemotherapy.
7 DRUG INTERACTIONS
No formal clinical drug interaction studies have been performed. Subgroup analyses indicated that the concurrent use of bisphosphonates or calcium channel blockers did not affect the safety and efficacy of Xofigo in the randomized clinical trial.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Category X [see Contraindications (4)]
Xofigo can cause fetal harm when administered to a pregnant woman based on its mechanism of action. While there are no human or animal data on the use of Xofigo in pregnancy and Xofigo is not indicated for use in women, maternal use of a radioactive therapeutic agent could affect development of a fetus. Xofigo is contraindicated in women who are or may become pregnant while receiving the drug. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, apprise the patient of the potential hazard to the fetus and the potential risk for pregnancy loss. Advise females of reproductive potential to avoid becoming pregnant during treatment with Xofigo.

8.3 Nursing Mothers
Xofigo is not indicated for use in women. It is not known whether radium-223 dichloride is excreted in human milk. Because many drugs are excreted in human milk, and because of potential for serious adverse reactions in nursing infants from Xofigo, a decision should be made whether to discontinue nursing, or discontinue the drug taking into account the importance of the drug to the mother.

8.4 Pediatric Use
The safety and efficacy of Xofigo in pediatric patients have not been established.

In single- and repeat-dose toxicity studies in rats, findings in the bones (depletion of osteocyes, osteoblasts, osteoclasts, fibro-osseous lesions, disruption/disorganization of the physis/growth line) and teeth (missing, irregular growth, fibro-osseous lesions in bone socket) correlated with a reduction of osteogenesis that occurred at clinically relevant doses beginning in the range of 20–80 kBq (0.541–2.16 microcurie) per kg body weight.

8.5 Geriatric Use
Of the 600 patients treated with Xofigo in the randomized trial, 75% were 65 years of age and over and while 33% were 75 years of age and over. No dosage adjustment is considered necessary in elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Patients with Hepatic Impairment
No dedicated hepatic impairment trial for Xofigo has been conducted. Since radium-223 is neither metabolized by the liver nor eliminated via the bile, hepatic impairment is unlikely to affect the pharmacokinetics of radium-223 dichloride [see Clinical Pharmacology (12.3)]. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with mild hepatic impairment. No dose adjustments can be recommended for patients with moderate or severe hepatic impairment due to lack of clinical data.

8.7 Patients with Renal Impairment
No dedicated renal impairment trial for Xofigo has been conducted. Based on subgroup analyses in the randomized clinical trial, dose adjustment is not needed in patients with existing mild (creatinine clearance [CrCl] 60 to 89 mL/min) or moderate (CrCl 30 to 59 mL/min) renal impairment. No dose adjustment can be recommended for patients with severe renal impairment (CrCl less than 30 mL/min) due to limited data available (n = 2) [see Clinical Pharmacology (12.3)].

8.8 Males of Reproductive Potential
Contraception
Because of potential effects on spermatogenesis associated with radiation, advise men who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective contraceptive method during and for 6 months after completing treatment with Xofigo.

Infertility
There are no data on the effects of Xofigo on human fertility. There is a potential risk that radiation by Xofigo could impair human fertility [see Nonclinical Toxicology (13.1)].

10 OVERDOSAGE
There have been no reports of inadvertent overdosing of Xofigo during clinical studies. There is no specific antidote. In the event of an inadvertent overdose of Xofigo, utilize general supportive measures, including monitoring for potential hematological and gastrointestinal toxicity, and consider using medical countermeasures such as aluminum hydroxide, barium sulfate, calcium carbonate, calcium gluconate, calcium phosphate, or sodium alginate. Single Xofigo doses up to 250 kBq (6.76 microcurie) per kg body weight were evaluated in a phase 1 clinical trial and no dose-limiting toxicities were observed.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
Animal studies have not been conducted to evaluate the carcinogenic potential of radium-223 dichloride. However, in repeat-dose toxicity studies in rats, osteosarcomas, a known effect of bone-seeking radionuclides, were observed at clinically relevant doses 7 to 12 months after the start of treatment. The presence of other neoplastic changes, including lymphoma and mammary gland carcinoma, was also reported in 12- to 15-month repeat-dose toxicity studies in rats. Genetic toxicology studies have not been conducted with radium-223 dichloride. However, the mechanism of action of radium-223 dichloride involves induction of double-strand DNA breaks, which is a known effect of radiation.
Animal studies have not been conducted to evaluate the effects of radium-223 dichloride on male or female fertility or reproductive function. Xofigo may impair fertility and reproductive function in humans based on its mechanism of action.

17 PATIENT COUNSELING INFORMATION
Advise patients:
- To be compliant with blood cell count monitoring appointments while receiving Xofigo. Explain the importance of routine blood cell counts. Instruct patients to report signs of bleeding or infections.
- To stay well hydrated and to monitor oral intake, fluid status, and urine output while being treated with Xofigo. Instruct patients to report signs of dehydration, hypovolemia, urinary retention, or renal failure / insufficiency.
- There are no restrictions regarding contact with other people after receiving Xofigo. Follow good hygiene practices while receiving Xofigo and for at least 1 week after the last injection in order to minimize radiation exposure from bodily fluids to household members and caregivers. Whenever possible, patients should use a toilet and the toilet should be flushed several times after each use. Clothing soiled with patient fecal matter or urine should be washed promptly and separately from other clothing. Caregivers should use universal precautions for patient care such as gloves and barrier gowns when handling bodily fluids to avoid contamination. When handling bodily fluids, wearing gloves and hand washing will protect caregivers.
- Who are sexually active to use condoms and their female partners of reproductive potential to use a highly effective method of birth control during treatment and for 6 months following completion of Xofigo treatment.

Manufactured for:
Bayer HealthCare Pharmaceuticals Inc.
Wayne, NJ 07470
Manufactured in Norway
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Revised: 05/2013
6708400BS
In a double-blind, randomized trial of 166 patients who underwent open RC with urinary diversion restrictive intraoperative fluid management (low volume crystalloid infusion combined with norepinephrine) decreased the incidence of intraoperative blood loss (800 vs 1,200 ml), the need for blood transfusion (intraoperative 8% vs 31%, postoperative 28% vs 48%), LOS (15 vs 17 days) and 90-day complication rate (52% vs 73%) compared to standard intraoperative hydration (1254). "

A retrospective study of 1,506 patients indicated that cigarette smoking was associated with worse prognosis after RC for bladder cancer, and its effects were abrogated by more than 10 years of smoking cessation (1445).

Complete debulking TUR before neoadjuvant chemotherapy (NAC) was strongly associated with pT0 status at RC (1443). Extranodal extension and lymph node density were also reported as strong predictors of outcome in patients with node positive disease after RC (1874).

In an evaluation of 891 patients who underwent RC, comorbidity status incorporating Charlson comorbidity index, ASA score, Elschauser index and Eastern Cooperative Oncology Group performance status improved the prediction of 5-year all cause mortality, and only Charlson comorbidity index was associated with 5-year CSM (1614).

A prospective study indicated a high concordance rate of cell cycle and proliferation related marker status (p53, p21, p27, Ki67 and cyclin E1) between TUR and RC specimens which could guide clinical decision making for NAC and radical cystectomy (394).

The expression and cellular localization of epidermal growth factor receptor and its mediators (PIKfyve and USP2a) in bladder specimens were also reported to predict chemosensitivity and disease recurrence in patients with muscle invasive bladder cancer (1871).

One study described an enhanced recovery after surgery (ERAS) protocol comprising various preoperative, intraoperative and postoperative measures, which focuses on avoiding bowel preparation and nasogastric tubes, early feeding, nonnarcotic pain management, use of μ-opioid antagonists and early ambulation (514). The ERAS protocol was shown to enhance bowel function recovery and decrease LOS (4 vs 8 days) after RC compared to no ERAS without any significant increase in early complication or hospital readmission rates.

In a retrospective study sarcopenia, measured by psoas muscle area (body surface area adjusted) on preoperative CT as an easily obtained objective measure of frailty was associated with longer LOS and greater 90-day complication rates among patients undergoing RC (1633).

In a retrospective study sarcomenia, measured by psoas muscle area (body surface area adjusted) on preoperative CT as an easily obtained objective measure of frailty was associated with longer LOS and greater 90-day complication rates among patients undergoing RC (1633).

A prospective randomized trial (109 patients) presented as late breaking news in the plenary showed no difference in 90-day morbidity rates between open and robotic RC with extracorporeal urinary diversion.

Another prospective, single center, randomized trial (60 patients, median followup 19 months) of open, robotic and laparoscopic RC showed that open RC was associated with greater EBL (650 vs 350 vs 300 ml), longer LOS (13 vs 10 vs 9 days) and delayed bowel recovery (7.5 vs 4 vs 4 days) but shorter operating time (277.5 vs 367.5 vs 300 minutes) than robotic and laparoscopic RC (1624).

In a multicenter retrospective study (3,661 patients) robotic RC was safe and yielded acceptable pathological outcomes compared to open RC (1764). Robotic RC data from 2 institutions (181 patients) were comparable to those of open RC in terms of health related quality of life outcomes using the validated Bladder Cancer Index and EORTC body image scale questionnaires (1625).

According to the SEER database only a minority of patients underwent all evaluations required for an initial diagnosis of BC (525). Decreased adherence to such guidelines could affect patient survival.

Many groups reported findings from the National Cancer Data Base. Patients (53.2%) undergoing RC for cT2 or cT3 bladder cancer (7,843 from 1998 to 2010) did not undergo adequate PLND (1619). Access related predictors of inadequate PLND included median income, distance from hospital and geographic location.

Many patients (53.5%) younger than 65 years did not undergo RC for cT2 or cT3 bladder cancer (4,027 from 1998 to 2010) (1631). The predictors of nontherapy included gender, race, insurance status, distance from hospital and geographic location.
Dietary Modifications to Reduce Pediatric Nephrolithiasis

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Recent studies have reported an increasing incidence of nephrolithiasis in children. Sas et al found that symptomatic stones increased from 7.9/100,000 in 1996 to 18.5/100,000 in 2007. Adolescents 14 to 18 years old have a tenfold greater risk of symptomatic kidney stones than children age 0 to 3 years. Pediatric stone disease is more common in females and in non-Hispanic white children.

The exact reason for the increasing incidence of pediatric nephrolithiasis is unclear. The most popular explanations for the increase in pediatric stone disease are obesity plus changes in dietary habits such as decreased dairy intake, decreased calcium intake, decreased water intake and possibly increased fructose intake. In adults these dietary factors have a major role in the development of stone disease. Obesity has been linked to the development of kidney stones, and decreases in fluid and calcium intake have increased the risk of stone development. Increased oxalate consumption can promote stone formation, whereas decreased dietary intake of sodium and animal protein is beneficial in stone prevention.

There have been clear dietary changes in the pediatric population during the last 30 years with an ever increasing rate of obesity. In 2005 to 2006, 11% to 17.8% of children in the United States were deemed overweight. Globally more than 40 million children younger than 5 years are overweight. Obesity is associated with insulin resistance and recent studies have shown that pediatric patients with type 1 diabetes and metabolic acidosis have an increased risk of urolithiasis. Metabolic acidosis promotes low urine pH, hypercalciuria and hypocitraturia, all of which have a role in the development of stone disease. While the exact association between obesity and the development of kidney stones in children is currently unconfirmed, children should remain active and parents should be encouraged to provide nutritional diets.

Dietary sodium intake has substantially increased and it is estimated that children consume 1.6 to 6.8 gm sodium per day due to the increased consumption of salt loaded processed foods. High sodium intake increases the urinary excretion of calcium and may result in urinary hypocitraturia. In addition, increased sodium chloride intake influences systemic acid-base status.

With the increased consumption of animal protein, high dietary consumption of sodium chloride induces metabolic acidosis. To compensate for the acid load the kidneys conserve anions, including urinary citrate, which contributes to hypocitraturia. A reduction in the dietary intake of sodium and an increase in potassium intake may benefit stone formers.

In the pediatric population daily sodium intake should be less than 3 gm. The addition of fruits and vegetables provides magnesium, potassium and citrate, all of which protect against stone formation. Excessive protein should be avoided in pediatric stone formers, with intake limited to 100% of the recommended daily allowance. In addition, children with hypocitraturia may benefit from the consumption of citrate rich juices such as lemonade.

Since the 1970s the mean intake of milk has decreased for children and adolescents. Poor intake is most likely due to the increased consumption of sugar based drinks. Decreased dietary calcium intake is associated with an increased risk of stone formation.

While counterintuitive, low calcium diets are less effective in the treatment of calcium stone disease compared to diets containing normal amounts of calcium with limited amounts of sodium and animal protein. Low sodium, low protein diets reduce urinary calcium and oxalate excretion. Children with stone disease should avoid excess calcium intake. However, children require calcium for bone development and recommendations for daily intake vary by age. Therefore, calcium restriction in children is contraindicated.

Studies have shown that up to 66% of children start the day in a hydration deficient state and that the degree of hydration deficiency is dependent on water intake. Adequate fluid intake is the cornerstone of stone prevention, although the exact amount required for children is undetermined. Most physicians recommend fluid intake at least equal to calculated maintenance rates in children and no less than 2 to 2.5 L in adolescent stone formers. During the summer months and with increases in activity levels this amount should be increased. For children with metabolic risk factors such as cystinuria or severe stone disease, further increases in fluid intake are required.

Fructose consumption has increased substantially since the 1970s. The estimated average daily intake of fructose is 55 gm (range 38 to 78). Consumption of fructose is highest among adolescents. Fructose consumption has been directly related to the occurrence of uric acid nephrolithiasis. However, the effects of high fructose diets and the role of fructose in calcium stone disease are controversial.

Small studies have suggested that high fructose diets may alter urinary constituents important in stone formation. Fructose has been significantly enhanced BC progression (1130). These investigators also identified an EDIL-3 tumor associated protein contained in urothelial carcinoma exosomes that was associated with tumor migration.
Supporting our Future Urologists

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As new urology residents across the nation begin their residency programs this month, they are provided the opportunity to practice their knowledge, skills and bedside manner to become the physicians they have always aspired to be. With more than 2,000 domestic and international urology resident members in 114 residency programs across the United States, the American Urological Association supports the residents by providing them with evidence-based education and research, as well as student enrichment and resident support programs.

Our residents have access to training at some of the best facilities in the country and the advances in basic science research, technology and patient care make now an exceptional time to study urology. It is within the context of these possibilities, coupled with the changes we expect from the health care reform movement, that the AUA seeks to further guide our residents through a new millennium. We hope you will take time to learn more about the many resources, some of which are briefly described below, that the AUA provides to residents, program directors and coordinators.

Urology Residency Match Program (https://www.auanet.org/education/urology-and-specialties-matches.cfm)
For more than 25 years, AUA has administered in early January the Urology Residency Match Program. Urology is one of the few specialties that participate in a match other than the Main Residency MatchSM of the National Resident Matching Program® administered in March. Each year approximately 550 applicants apply for nearly 235 positions, thereby making urology one of the most competitive specialties to enter. This summer medical students from around the country will start the process to participate in the 2014 Match.

Residents Committee (http://www.auanet.org/about/committees.cfm)
The AUA Residents Committee is comprised of residents from each of the 8 AUA Sections, which provides residents the opportunity for Section representation designed especially to meet their needs. The Residents Committee not only provides a unified voice about their concerns, but also plays a vital role in their education and career development.

International Resident Scholar Program (http://www.auanet.org/international/resident-programs.cfm)
The AUA International Resident Scholar Program is a unique opportunity for residents from Brazil, China, India and Japan to visit the United States, attend the AUA Annual Meeting and participate in cutting-edge science on a broad range of urological topics.

Resident Research Awards (http://www.auanet.org/research/urology-care-foundation-funded-research-74.cfm)
Since 1975 the AUA has funded research opportunities for and provided support to young men and women who are interested in pursuing a career in urological research. The Resident Research Award is designed to fund an outstanding urology resident for 1 year while he or she fulfills their obligation for research training. The AUA Board of Directors recently approved additional funds to support resident research awards.

Residents Forum
The Residents Forum is the single best opportunity for urology residents to learn how to navigate job searches, personal and practice finances, job related legal issues and the trade-offs of specialty training versus private practice positions. This event is held each year at the AUA Annual Meeting. More information regarding the 2014 Forum will be available in the coming months.

National Urology Residents Preceptorship Program (http://www.auanet.org/research/urology-residency-preceptorship-139.cfm)
Recently introduced at AUA2013, the National Urology Residents Preceptorship Program is focused on aligning talented investigators with urology research departments, and to assist in preparing them for a strong career path as a surgeon-scientist.

Residents Bowl
Designed to foster a friendly competitive spirit, the National Residents Bowl matches residents in an ultimate battle of the brains. The 8 AUA Sections send 4 residents each year to compete in an ultimate brain bender. Residents Bowl matches residents in an ultimate battle of the brains. Residents Forum is the single best opportunity for urology residents to learn how to navigate job searches, personal and practice finances, job related legal issues and the trade-offs of specialty training versus private practice positions. This event is held each year at the AUA Annual Meeting. More information regarding the 2014 Forum will be available in the coming months.

National Chief Resident Debate
Conceived to encourage a spirit of camaraderie and the art of persuasion among chief residents from each AUA Section, the National Chief Resident Debate examines select topics from different fields of interest. Chief residents from AUA Sections deliberate about topics during 15-minute debates moderated by recognized experts in specific fields.

Examination Resources (http://www.auanet.org/education/examination-resources.cfm)
The Self-Assessment Study Program (SASP) is the AUA’s most popular study tool for the American Board of Urology exam preparation. This 150-question, multiple choice practice examination addresses the core curriculum of medical knowledge and latest advances in patient care. Four convenient formats are now available to support a candidate’s learning preference.

In addition to providing quality, evidence-based urological education and a sense of community to its resident members, AUA also provides a variety of resources for program directors designed to keep them abreast of important deadlines, educational events and other information of interest to residents.

For information about these resources visit Grant Programs: http://www.auanet.org/education/grant-programs.cfm; Program Vacancy Information: http://www.auanet.org/education/residency/program-vacancies.cfm; AUA Residency Connection and the AUA International Residency Connection Newsletters: http://www.auanet.org/education/residents-enewsletters.cfm;
The Evolution of Multidisciplinary Research

Dr. Johannes Vieweg
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Health care is changing right in front of our eyes. New directions toward population based medicine, the ever increasing influence of managed care, the consolidation of health services and our nation’s push to make health care more affordable have undoubtedly impacted research directions and policy. Such trends should come as no surprise since health economists and political stakeholders predicted imminent and fundamental changes to our health care system in the late 1990s.1 These predictions included an explosion of clinical service demands for physicians due to decreased financial margins and the need to provide high quality care at a reduced cost. With these socioeconomic challenges, protected research time for many clinical and translational researchers is rapidly disappearing, as is the time devoted to the research mission of academic institutions.

Most of you may recall Dr. Elias Zerhouni, the 15th director of the National Institutes of Health (NIH), who was appointed by President George W. Bush in May 2002. Soon after his appointment Dr. Zerhouni convened a series of meetings to chart a Roadmap for Medical Research in the 21st century.2 The purpose of these meetings was to identify major opportunities and gaps in biomedical research, and determine how to make the biggest impact on the progress of biomedical research.

Zerhouni’s NIH Roadmap identified major opportunities in the 5 main areas of new pathways to discovery, research teams of the future and reengineering the clinical research enterprise. Generally the Roadmap challenged the prevailing directions and conduct of NIH funded research at that time, and indicated major changes to expedite the transition from academic discovery to societal benefit.

The Roadmap announced new priority areas such as genetics or precision medicine, a new team based approach to science, and consolidation and better integration of research support environments. In response to the NIH Roadmap, in 2004 Congress authorized the funding of innovative and cross-cutting research programs through the NIH Common Fund. Overseen by the director’s office, this fund was designated to support cross-cutting programs that involve the participation of at least 2 of NIH’s 27 Institutes and Centers, or programs that would otherwise benefit from better oversight and/or coordination. To date, the Common Fund has been used to support a series of short-term, exceptionally high impact trans-NIH programs, including the NIH Pioneer and New Innovator awards.

In terms of research policy, a new full-spectrum translational research model was introduced at that time that spans discovery research (T1, bench) to early phase clinical trials (T2) to outcomes research (T3-T4, bedside). The major objective of this new translational model was to allow the rapid transition of scientific discovery into clinical trials, eventually resulting in improved health care in our communities.

The launch of these new initiatives coupled with the new translational research model fundamentally changed the way research is conducted. Today we see a major shift toward collaborative research in genetics, pathway driven investigations and a preponderance of health services research, all following the themes of disease prediction, precision medicine and cost-effectiveness research.

A second major change in modern science is based on the realization that complex scientific problems are best addressed through interdisciplinary research teams.3 Studies have shown that diverse teams develop new ideas connectively and that such connective thinking leads to a higher rate of breakthroughs than science performed at the individual level.4 Therefore, substantial investments in multidisciplinary team science projects have commenced and have been funded by the NIH and other research support organizations in the last 2 decades.

However, implementing team science, particularly across disparate geographic locations, has proven challenging, and research organizations today are exposed to a higher degree of scrutiny before issuing an award to ensure the availability/presence of transformational leadership and an appropriate infrastructure conducive to team science. In addition, not all researchers are well suited to cross disciplinary collaboration. Matching investigators, research infrastructures and intended innovations effectively has become a challenging task for team science leadership.

One approach that science and health care can synergize was recently proposed by current NIH Director Dr. Francis Collins and his team. They described an organizational research model consisting of a network of collaborating research sites, data and health care centers that integrate research and clinical data sets, and a coordinating center that manages the interactions, all overseen by NIH staff, a scientific advisory board and special expert groups.5 This integrated network model is not unique as it has been used in one way or another by several NIH institutes, for example, through the U54 specialized center cooperative agreements mechanism.

For the urology research community it will be important to better understand and follow NIH supported directions so that we can remain competitive as a specialty when it comes to larger scale collaborative research and training programs. As public and private investments in team science initiatives have grown substantially, several adjustments will be necessary to successfully participate in complex disease research.

Reorganization of urological research centers into collaborative teams and consolidation of research resources are major trends that can no longer be ignored. Moreover, we will have to broaden our thinking and skill sets, collaborating with and learning from other disciplines such as sociology, economics, law and the humanities. In the end success in urology research will depend on our ability to adapt to the present challenges and our willingness to collaborate.


Diet and Pediatric Nephrolithiasis

Continued from page 21

associated with insulin resistance and the metabolic syndrome,6 both of which are associated with stone formation in adults.6–8 Currently there are no recommendations for daily fructose intake in children.

Stone development is multifactorial. In pediatric stone formers close attention to the dietary intake of sodium and calcium is required. Fluid consumption is important and efforts to maintain the recommended levels of fluid intake should be a main focus in children with stone disease. More studies are needed to better understand how obesity, diet, exercise and environmental factors influence the development of stones in children. A better understanding of how these factors contribute to the development of stone disease in children will allow more focused preventive efforts.  


Two subjects of major surgical interest to the urologist, pelvic organ prolapse (POP) repair and the treatment of localized prostate cancer, were reported in articles reviewed this month along with editorials.


This article from the National Institutes of Health (NIH) supported Pelvic Floor Disorders Network reports the long-term results of the CARE (Colpopsy and Urinary Reduction Efforts) trial of open mesh sacrocolpexy (SCP) in 322 women with POP without stress urinary incontinence (SUI) randomized to simultaneous Burch urethropexy (to prevent SUI due to POP repair) or no urethropexy. The original study showed greater than 90% cure of POP at 2 years and prevention of SUI in 68% of patients treated with Burch vs 55% without.

The present extended CARE trial was limited to a smaller group of women (215) because of decreased NIH funding, with further losses to followup such that 7-year outcomes were determined in only 126 women. Of these women 90 were examined with extensive measurements of anatomical success vs failure of POP repair plus standardized quality of life (QOL) questionnaires administered by trained professionals, with 36 evaluated using QOL questionnaires alone.

On anatomical examination cases were characterized as anatomical failures according to agreed upon measurement criteria. Symptomatic failure (sensing a bulge on Pelvic Floor Distress Inventory, resorting to the use of a pessary or undergoing repeat POP surgery) could be evaluated in all women. Composite outcomes combined symptomatic and anatomical determinations.

In the final cohort of 126 women reported on at 7 years, symptomatic failure was estimated to occur in 29% who underwent SCP with Burch and 24% treated with SCP alone. The anatomical failure rate was estimated to be 27% with Burch vs 22% without, and composite failure was estimated at 48% of women who underwent both procedures vs 34% treated with SCP alone.

If Burch urethropexy was performed in addition to SCP, the development of SUI was estimated to be decreased to 62% vs 77% with SCP alone but overall incontinence was about equal (75% vs 81%). Mesh erosions did occur and by year 2 of the original 322 women 17 had experienced erosion with 6 more cases reported through year 7. Of the 23 women (equally split between those with vs without Burch operations) 15 required formal operative removal (13 per vagina and 2 abdominal), 4 were treated with estrogen cream and 4 were asymptomatic. Seven women with SCP plus Burch and 13 in the SCP alone group received some form of treatment directed toward control of SUI by year 7.

The authors reported being “surprised by the magnitude of treatment failures” after SCP. However, this reviewer is mostly surprised by the fact that despite the high composite failure rates estimated in both groups (48% and 54%), only 11 women underwent repeat POP surgery. A similar point was made by Iglesia in the accompanying editorial. Are some criteria for failure in the extended CARE trial overblown?

Finally, the mesh erosion rate of 10% at 7 years is not nearly as common as lay press articles and legal advertisements might suggest. However, it is clear that this possible complication should be discussed extensively with women seeking POP repair (presently amounting to 225,000 operations annually in the United States).


There will never be a randomized, controlled trial of radical prostatectomy (RP) vs radiotherapy (RT) reporting survival data, and this study is likely the closest we will ever see. The authors used the PCOS (Prostate Cancer Outcomes Study) population to address survival outcomes. The PCOS identified all men in 6 SEER (Surveillance, Epidemiology and End Results) regions with newly detected prostate cancer between October 1, 1994 and October 31, 1995.

The original number of men (11,000) was reduced randomly at first and then by agreement to participate, and further by age at diagnosis (55 to 74 years old) of those treated with RP or RT during the first year after diagnosis to a final of 1,655 men, of whom 1,164 underwent RP and 491 initially received RT.

Overall mortality (OM) and prostate cancer specific mortality (PCSM) were reported. Because selection bias always favors RP candidates with fewer comorbidities, propensity score methodology was used to reduce this selection bias, as was studying subgroups by propensity score quintiles and comparing propensity score matched samples. During the 15-year followup ending at patient death or end of study (December 31, 2010) there were 568 deaths overall including 104 from prostate cancer.

OM and PCSM rates were statistically lower among patients who underwent RP vs RT (HR 0.60 and 0.35, respectively, both p <0.0001). This dual advantage was shared by men in each propensity quintile and by those grouped by age at treatment (55 to 64 and 65 to 74 years old).

When focusing on low risk prostate cancer, there was a continued advantage of RP in terms of overall mortality, but PCSM differences lost statistical significance. Comparing a subgroup of 437 men treated with RP vs RT plus androgen deprivation therapy (ADT) showed an advantage for RP in overall and prostate cancer specific mortality (HR 0.65 and 0.36, respectively). Similarly, subgroup analyses of men with no reported comorbidities showed the same dual advantage for RP vs RT.

The authors recognize the potential pitfalls of their study, including 1) higher prostate cancer directed RT doses today vs 1994/95, 2) the advent of 3-dimensional conformal RT and intensity modulated radiation therapy since that time, 3) longer term adjunctive ADT today and 4) the possible contamination of the RT cohort with the inclusion of cases of abandoned RP (such cases were excluded from final analyses).

Nevertheless, the article leaves one with the conclusion that there is residual selection bias in this report or “a true survival advantage for RP.”

In the editorial Madan et al were somewhat more skeptical, citing the current use of prolonged ADT for high risk disease as well as the fact that improvements in the target delivery of radiation “render data from nearly 20 years ago increasingly irrelevant.” The authors continue by noting that prostate cancer is the only solid tumor for which radiation alone is routinely used for patients in whom surgery is possible, suggesting that initial surgery be performed in all those with localized disease, with adjunctive RT used when pathology findings demand. The article actually stated that some patients in the PCOS population had adjunctive or salvage RT after RP or vice versa. Might the article conclusions be altered by analyzing these data?
The ability to assess pathology by palpation has long been a key part of the physician's physical examination, with firmness of a lesion as a sign of worrisome pathology. With new high resolution ultrasound systems, lesions smaller than 1 cm are being detected despite the inability to palpate the abnormality on examination.

Sonoelastography, tissue elasticity imaging, is an evolving ultrasound modality which adds the ability to evaluate the stiffness of biological tissues. This technology provides a representation, using color, of the softness or hardness of the tissue of interest. Elastography has been studied for the assessment of breast, thyroid and prostate lesions.1-3

Two recent studies have used real-time elastography to differentiate benign from malignant testicular lesions. Goddi et al assessed 88 testes with 144 lesions, and found a 93% positive predictive value, 96% negative predictive value and 96% accuracy in differentiating benign from malignant lesions.4 Similarly Aigner et al assessed 50 lesions, and found a 92% positive predictive value, 100% negative predictive value and 94% accuracy.5

The patient in this case underwent ultrasound with elastography demonstrating multiple soft lesions (fig. 2). Ultrasound guided biopsy revealed that the lesions represented benign Sertoli cell nodules. The elastography findings of a hard lesion (nonseminomatous germ cell tumor [NSGCT]) and an intermediate lesion (testicular sarcoidosis) are shown in figures 3 and 4, respectively.

Real-time tissue elastography is an exciting innovation in assessing abnormalities on scrotal ultrasound examination. Further investigation is needed but this emerging technology may be used in the future to avoid surgical intervention for benign lesions found to be soft on elastography.6


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**Radiology Corner**

Continued from page 7

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**Fig. 1.** Testicular ultrasound of right testis with multiple solid hypoechoic lesions

**Fig. 2.** Sonoelastography with elastography (A) and gray-scale imaging (B). Note softness of lesions based on color bar.

**Fig. 3.** Sonoelastography with elastography (A) and gray-scale imaging (B) of hard lesion, and pathology revealed NSGCT.

**Fig. 4.** Sonoelastography with elastography (A) and gray-scale imaging (B) showing intermediate elastography pattern in testicular sarcoidosis.

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AUA Content Review: What it is and Why it Matters

Dr. J. Kellogg Parsons
Chair, AUA Educational Council Content Review Working Group
La Jolla, California

The AUA Office of Education content review process, administered by the Content Review Working Group, has an integral role in the planning of AUA educational courses. Developed in 2006, the review process oversees AUA sponsored educational activities associated with continuing medical education (CME) credit, including lectures, courses, publications and audiovisual materials.

CME activities accredited by the Accreditation Council for Continuing Medical Education (ACCME) provide physicians with the opportunity to increase their knowledge base, performance and skills to provide better care for their patients. The AUA content review process is essential in the production of accurate and reliable educational content. The review process resolves potential conflicts of interest and ensures that CME activities meet the requirements for educational content that is scientifically valid, based on the best available evidence, unbiased and free of the proprietary interests of commercial entities.

The review process is simple, straightforward and transparent. The Content Review Working Group reviews all topics for all CME associated AUA activities in advance. If the Working Group determines that a presentation is high risk, meaning the topic carries substantial potential for perceived commercial bias, the Working Group obtains the complete presentation and assigns a peer reviewer with specific expertise in the subject.

The Working Group manages a select group of expert peer reviewers who serve 4-year terms and represent a wide range of expertise covering all domains in urology. The reviewer assesses the course materials and submits a formal report to the Working Group. Based on the reviews, the chair and co-chair of the Working Group determine a plan of action.

Most educational activities are approved. However, some materials raise concerns, including but not necessarily limited to the use of brand names instead of generic equivalents, failure of the presenter to disclose relevant financial relationships with commercial entities, claims of uncertain scientific validity, an unbalanced perspective on treatment options, a paucity of robust medical evidence and nondisclosure of non-Food and Drug Administration approved drug indications.

If a presentation does not meet AUA Office of Education standards, then the Working Group requests specific revisions to the content and resubmission of the course materials to the Working Group for repeat review and approval.

Since its inception, the Working Group has successfully monitored CME associated AUA educational activities and maintained high standards in accordance with national CME accreditation standards. Under the direction of the chair and co-chair, the Working Group vigorously pursues a policy of continuing performance improvement and quality assurance in the execution of the review process.

Peer reviewers are regularly assessed with respect to the quality and timeliness of their reviews. New technology and system upgrades have improved the efficiency, accuracy and rigor of the review process. Notably there was a 77% increase in the number of content items selected for review for the 2013 Annual Meeting compared to the previous year, a workload increase that the Working Group managed effectively with these improvements and enhancements.

In summary, AUA content review raises the bar for enhancing medical education for AUA members. It serves as the necessary mechanism to resolve any conflicts of interest while maintaining the value of the learning experience. The Office of Education is dedicated to providing the highest quality CME to its members. This dedication has allowed the AUA to be awarded Accreditation with Commendation by the ACCME, the highest achievable rating.

### CALENDAR of Events

#### JULY 2013

**July 18**
AUA Hands-on Urologic Ultrasound
Destin, Florida
Sandestin Golf & Beach Resort
800-908-9414
registration@auanet.org
[www.auanet.org/content/courses/HOU134/](http://www.auanet.org/content/courses/HOU134/)

**July 19–21**
Gulf Coast Urology Seminar
Destin, Florida
Sandestin Golf & Beach Resort
[www.urologyseminar.org/UABWF/](http://www.urologyseminar.org/UABWF/)

**July 25–26**
ABU Qualifying Exam (Part I)
434-979-0059

#### AUGUST 2013

**August 11–13**
Highlights of AUA2013
Cariari, San Jose, Costa Rica
Hotel DoubleTree by Hilton
[www.annier.com](http://www.annier.com)

**August 23–25**
AUA/Urological Society of India Annual Review Course and Exam
Hyderabad, India
[www.auanet.org/education/education-calendar.cfm](http://www.auanet.org/education/education-calendar.cfm)
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**ANN ARBOR AREA:** Hospital employed joining two Urologists in well-established practice with 113 bed hospital. 1-3 call. Excellent salary, bonus, benefit packages. SURGICAL SEARCH, 800-831-5475, surgicalsrch@aol.com.

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References: