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KEY LEADERS' OPINION ON ANDROLOGY AND UROLOGY

EDITORS: QIAN ZHANG, BENJAMIN N. BREYER, XIONGBING ZU

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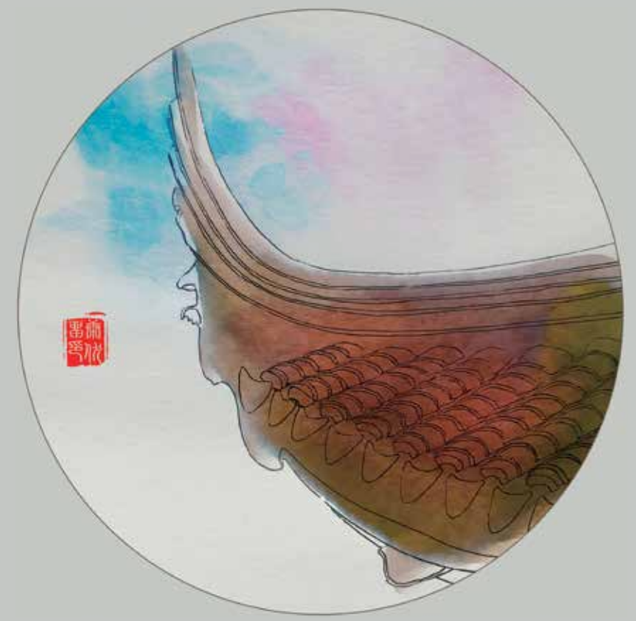

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Contributors

Laura Agostinelli
Polythecnic University of Marche, Department of Gastroenterology, Ancona, Italy

Michael R. Abern
Division of Urology, Department of Surgery, Duke Cancer Institute, Durham, NC, USA

Emmanuel S. Antonarakis
Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Bunting-Blaustein Cancer Research Building, 1650 Orleans St - Room 1M45, Baltimore, MD 21231, USA

Stéphane Bolduc
Centre de Recherche en Organogénèse Expérimentale/ LOEX, Division of Regenerative Medicine, CHU de Québec Research Center/FRQS, Québec City, QC, Canada; Department of Surgery, Faculty of Medicine, Laval University, Quebec City, QC, Canada

Helen Boyle
Medical Oncology Department, Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon cedex 08, France

William O. Brant
Department of Surgery (Urology), Center for Reconstructive Urology and Men's Health, University of Utah, Salt Lake City, USA

Benjamin N. Breyer
University of California San Francisco, California, USA

James D. Brooks
Department of Urology, Stanford University, Stanford, CA 94305, USA

Jorge Camarero
Pharmacology and Clinical Assessment Division, Spanish Medicines Agency, Campezo 1 - Edi cio 8, 28022 - Madrid, Spain

Peter R. Carroll
UCSF Helen Diller Family Comprehensive Cancer Center, Department of Urology, University of California San Francisco, San Francisco, CA 94143, USA

Toby C. Chai
University of Maryland School of Medicine, Division of Urology, 29 S. Greene St., Suite 500, Baltimore, MD 21201, USA

Thomas Chi
Department of Urology, University of California, San Francisco, California, USA

Zara Risoldi Cochrane
Department of Pharmacy Practice, Creighton University, School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, NE 68178, USA

Nathalie Cools
Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, B-2610 Antwerp, Belgium

Robert Crescentini
University of South Florida College of Medicine, Medical Oncology & Hematology Fellow, Florida, USA

Ingrid M.E. Desar
Departments of Medical Oncology, Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands

Gregory Diorio
Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

Mostafa M. Elhilali
Department of Surgery, Division of Urology, McGill University, Montreal, QC, Canada

Mohamed A. Elkoushy
Department of Surgery, Division of Urology, McGill University, Montreal, QC, Canada; Department of Urology, Suez Canal University, Ismailia, Egypt

Ferry ALM Eskens
Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, the Netherlands

Masatoshi Eto
Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Mayer Fishman
H. Lee Moffitt Cancer Center & Research Institute, Department of Genitourinary Oncology, Florida,USA

Keong Tatt Foo
Department of Urology, Singapore General Hospital, Yong Loo Lin School of Medicine, National University of Singapore, and DUKE-NUS Graduate Medical School, Singapore

Carlo Ganini
Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy; Italian Nephro-Oncology Group/Gruppo Italiano di Oncologia Nefrologica (G.I.O.N.), Pavia, Italy

Maurice Garcia
Department of Urology, University of California, San Francisco, USA

Saeid Ghorbian
Department of Biology, Bonab Branch, Islamic Azad University, Bonab, Iran

Kirsten L. Greene
UCSF Helen Diller Family Comprehensive Cancer Center, Department of Urology, University of California San Francisco, San Francisco, CA 94143, USA

Marine Gross-Goupil
Saint-André Hospital, University Hospital, Bordeaux, France

Liang-Jun Gu
Peking Union Medical College Press. Beijing 100730, China

Shilpa Gupta
H. Lee Moffitt Cancer Center & Research Institute, Department of Genitourinary Oncology, Florida,USA

Balázs Győrffy
Research Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences-Semmelweis University, Hungary

Brigitte Haberkorn
Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, the Netherlands

Matthias M. Heck
Department of Urology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany

Luca Incrocci
Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Katherine L. Ji
Managing Editor, Translational Andrology and Urology, Beijing 100730, China

Tracey L. Krupski
University of Virginia Department of Urology, Charlottesville, Virginia

Alexandre Langlois
Centre de Recherche en Organogénèse Expérimentale/ LOEX, Division of Regenerative Medicine, CHU de Québec Research Center/FRQS, Québec City, QC, Canada

Andrew Leone
Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

Louise Lim
Experiment Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, UK

Tom F. Lue
Department of Urology, University of California, San Francisco, USA

Jules P. Manger
University of Virginia Department of Urology, Charlottesville, Virginia

Jack W. McAninch
University of California San Francisco, California, USA

Zsuzsanna Mihály
Research Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences-Semmelweis University, Hungary

Sasja F. Mulder
Departments of Medical Oncology, Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands

Peter F.A. Mulders
Departments of Medical Urology, Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands

Masahiro Nozawa
Department of Urology, Kinki University Faculty of Medicine, Japan

Carsten-Henning Ohlmann
Department of Urology, Saarland University, Homburg/Saar, Germany

Chiara Paglino
Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy; Italian Nephro-Oncology Group/Gruppo Italiano di Oncologia Nefrologica (G.I.O.N.), Pavia, Italy

Alexisz Panajotu
Research Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences-Semmelweis University, Hungary

Amy M. Pick
Department of Pharmacy Practice, Creighton University, School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, NE 68178, USA

Thomas J. Polascik
Division of Urology, Department of Surgery, Duke Cancer Institute, Durham, NC, USA

Camillo Porta
Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy; Italian Nephro-Oncology Group/Gruppo Italiano di Oncologia Nefrologica (G.I.O.N.), Pavia, Italy

Sima Porten
Department of Urology, University of California, San Francisco, USA

Tom Powles
Experiment Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, UK

Jacob Rajfer
UCLA School of Medicine, Division of Urology, Harbor-UCLA Medical Center, Torrance, CA 90509, USA

Sophie Ramsay
Centre de Recherche en Organogénèse Expérimentale/LOEX, Division of Regenerative Medicine, CHU de Québec Research Center/FRQS, Québec City, QC, Canada; Department of Surgery, Faculty of Medicine, Laval University, Quebec City, QC, Canada

Vicki Ratner
Interstitial Cystitis Association of America (ICA), McLean, Virginia, USA

Alain Ravaud
Saint-André Hospital, University Hospital, Bordeaux, France; Université Bordeaux 2, Victor Segalen, Bordeaux, France

Amanda Reed-Maldonado
Department of Urology, University of California, San Francisco, USA

Margitta Retz
Department of Urology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany

Cassandra Ringuette-Goulet
Centre de Recherche en Organogénèse Expérimentale/LOEX, Division of Regenerative Medicine, CHU de Québec Research Center/FRQS, Québec City, QC, Canada

Sol Ruiz
Biotechnology and Advanced Therapies, Spanish Medicines Agency, Campezo 1 - Edi cio 8, 28022 - Madrid, Spain

Melissa T. Sanford
UCSF Helen Diller Family Comprehensive Cancer Center, Department of Urology, University of California San Francisco, San Francisco, CA 94143, USA

Hans-Peter Schmid
Kantonsspital St. Gallen, St. Gallen, Switzerland

Dorien M. Schrijvers
Laboratory of Physiopharmacology, University of Antwerp, B-2610 Antwerp, Belgium

Roland Seiler
Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada

Sergey Shikanov
1709 Pontiac trail, Ann Arbor, MI 48105, USA

Ariana L. Smith
Division of Urology, University of Pennsylvania, Philadelphia, PA 19106, USA

Philippe E. Spiess
Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

Marshall L. Stoller
Department of Urology, University of California, San Francisco, California, USA

Wataru Takahashi
Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Emil A. Tanagho
Department of Urology, University of California, San Francisco Medical Center, San Francisco, California, USA

Kenichiro Tanoue
Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Eric Taylor
Department of Urology, University of California, San Francisco, California, USA

Matvey Tsivian
Division of Urology, Department of Surgery, Duke Cancer Institute, Durham, NC, USA

Hirotsugu Uemura
Department of Urology, Kinki University Faculty of Medicine,377-2 Ohno-higashi, Osaka-sayama, 589-8511, Japan

Ilse Van Brussel
Laboratory of Pharmacology, University of Antwerp, B-2610 Antwerp, Belgium

Amaryllis H. Van Craenenbroeck
Division of Nephrology-Hypertension, Antwerp University Hospital, B-2650 Edegem, Antwerp, Belgium

Carla M.L. van Herpen
Departments of Medical Oncology, Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands

Yoshihiro Wada
Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Alan J. Wein
Division of Urology, University of Pennsylvania, Philadelphia, PA 19106, USA

Aviva E. Weinberg
Department of Urology, Stanford University, Stanford, CA 94305, USA

Johannes M. Wolff
AKH Viersen, Viersen, Germany

Alex K. Wu
Department of Urology, University of California, San Francisco, USA

Kamran Zargar-Shoshtari
Department of Genitourinary Oncology, Mof tt Cancer Center, Tampa, FL, USA

Cover Image Illustrator:

Kang Fu, Shanghai, China

Executive Typesetting Editor

Maple S. Zhu, AME Publishing Company

Will scholarly journals perish?

Will scholarly journals perish? This is a question that has puzzled me for years.

The introduction of online journals results in the inevitable recession of print journals. The uprise of the open access journals has been changing the structure of scholarly journals ceaselessly. What keeps me thinking is the open access of clinical trials data. What would be the bigger picture if open access to clinical trials data becomes the mainstream?

It is interesting that with the primary bottleneck lying in the availability of open data, the Big-data Clinical Trial (BCT) seems to stay where it was in spite of the increasingly popularity of "Big Data" among scientists. It has to be the fact that without open data, a statistical analysis is restricted to a particular area (or several areas). Even with big enough data, the study can only be termed as "research with big data sets" rather than "big data research", which are totally different concepts. Big Data is constituted by a plurality of dimensions. On one hand, for an individual (e.g., a patient), the relevant data covering his/her disease course is big enough; on the other hand, for the entire population, as more as individuals (e.g., patients) are expected to be included, to contains all the elements just like the "universe set" in set theory; by doing so, scientists expect to carry out the so-called clinical studies in real-world settings.

Why do the real-world-based clinical trials so appealing? It is understandable that the results and conclusions are likely to be altered in studies targeting the same issue using the same research method with sample size changed. In addition, the probability of such a "likely" is quite high. In many top journals, it is a common phenomenon that some authors tend to validate the results of one study in another population using the same research method. However, if the results are "validated" in one population, it only means that they are "repeatable". Will the results also be repeatable in the second, third, and more populations? If the attempts are not continuing, which should be, the "validation" is equivalent to "self-deception" in a sense.

When clinical research data is open accessed, we can easily integrate data from multiple centers for statistical analysis and meanwhile "validate" the results in multiple populations. If this is the case, then another question arise: can everyone easily publish his/her results/papers in high-profile journals such as the *New England Journal of Medicine*? My answer is NO.

When the open access to clinical research data becomes mainstream, we can easily find the constant update of database on the Internet. Simply by clicking on a button, we obtain the statistical results of the most current data. A further button click would display the validation results based on a specific population. The database would be updated at a certain period of time (e.g., 1 month or 1 day), and the statistical results would "likely" also be changed accordingly. At that time, the questions may change to "would any researchers publish their findings in a journal?" Well, even if someone is still keen to write such articles, journals may be reluctant to publish them because of the indefiniteness of the findings with the risk of being overturned at anytime.

Eventually here it comes the serious question: will scholarly journals perish? My answer is still NO. Then in what way the scholarly journals would probably lead to?

During my Business Administration course, my teacher distributed to us an article from the Case Study column of the *Harvard Business Review*. In this highly respected journal, articles in this column often present one case first, followed by the comments from two experts. These comments could either support or oppose each other. My teacher asked us to study the case, read through the comments and then form our own point of views on the case. He encouraged us to interpret the case from different perspectives independently in what form that I found pretty practical.

The course brought a possible answer to me. When the open access to clinical research data becomes mainstream, the entire publishing industry, especially the publication of "scholarly journals", would eventually experience revolutionary change. It may no longer focus on the rigid and cold outcomes but it would definitely cares more about the reflection on the problems, update of insights, and integration of science and arts.

AME Medical Review Series is a production of the above thinking. As an attempt, we decided to invite experts internationally to provide their views on a specific topic to share their insights with more clinicians and thus benefit more patients. The first chosen topic for the series is the currently controversial one: conventional surgery versus stereotactic body radiotherapy for

the early stage lung cancer. As the first book to the series, we hope it would give you a glance at the coming changes.

The book series will be written by a group of individual experts who are willing to contribute medical reviews and comments to individuals who are interested in clinical research and medical reviews specifically. The book in your hand may possibly be on a heavy subject but we do hope it is presented in an easier way. It will be more than great if it brings you some thoughts and inspire you in some way.

Stephen D. Wang
Founder and CEO,
AME Publishing Company

Preface

How lucky are we as physicians today to have the entire medical literature at our fingertips? On the other hand, how unlucky are we that we simply do not have the time to read, dissect and discuss in detail each report or manuscript that we review. One of the ways physicians attempt to solve this dilemma is by attending conferences, lectures, etc. Another possible way is to read in short but succinct reports the thoughts and opinions of recognized experts in their respective areas. It is in this vein that this tome was conceived. The editors and publisher have come together to put in print a series of expert opinions covering many of the subspecialties of Urology that would normally not be on the radar for most Urologists. Ranging from stone disease, urodynamics, erectile dysfunction, oncology, tissue engineering and BPH, this potpourri of chosen papers expound not only on what many of us may have learned in our training but many of the authors of these chosen manuscripts pitch to their audience a number of "out of the box" ideas and suggestions that one would only obtain from a one on one interaction with the author. It goes without saying that it was only the size of this tome that limited the inclusion of many equally worthy ideas and suggestions that have been penned by our Andrology and Urology colleagues.

We are indeed indebted to our three guest editors who had the responsibility for choosing the contents of this book: Drs. Benjamin N. Breyer from the University of California San Francisco in the United States, and Dr. Qian Zhang from the First Hospital of Peking University and Dr. Xiong-bing Zu from the Central South University (CSU) in China. As such, publication will be bilingual in Chinese and English. Finally, all of editors owe a token of gratitude to Amy Liu, the senior editor of *Translational Andrology and Urology*, a division of the AME Publishing group, the publisher of this book, who was the driving force behind the concept and publication of this compendium of expert opinions.

Jacob Rajfer, MD
Distinguished Professor Emeritus of Urology UCLA School of Medicine Los Angeles, CA, USA
(Email: jrajfer@ucla.edu)

Preface

This book represents a compendium of articles written by international thought leaders. These articles have been previously published in the journal *Translational Andrology and Urology*. However, by condensing these key articles into a single book, the reader can go to a single source and read about the newest ideas and important findings in andrology and urology. The reader will be able to efficiently acquire information about developments in all key areas without having to go to multiple different volumes. A diverse array of topics, from benign to neoplastic conditions, from basic to clinical science, from the kidneys, all the way down to the urethra, is covered. Each article is authored by authoritative and influential internationally renowned investigators in their fields. This volume is a valuable resource to all those who are curious and want to be better educated in andrology and urology.

Toby C. Chai, MD

Department of Urology, Yale University School of Medicine, New Haven, CT 06519-8058, USA

(Email: toby.chai@yale.edu)

Preface

You are about to read a comprehensive book covering many aspects of urology and andrology. A total of 54 chapters cover expert insights on disease mechanisms and progress in treatment including new techniques. Prognosis research is also covered, as well as special cases analyses. Last but not least cost effective management is being addressed.

The book represents a comprehensive overview on developments, controversies and important current knowledge and the authors address relevant clinical questions within the field of urology and andrology by providing practical recommendations on the basis of contemporary evidence.

The editors hope very much that this book will not only serve as a free-standing textbook, but also as a valuable resource in daily clinical practice.

I want to applaud all of those who worked so diligently in this project and as for the readers, enjoy this excellent book.

Monique J. Roobol

Monique J. Roobol, PhD, MSc
Professor, Decision making in Urology,
Erasmus University Medical Center,
Rotterdam, The Netherlands

Preface

Urologic diseases can affect men, women and children at any age as they all related to urinary tracts, as well as reproductive organs in male. It is well known that erectile dysfunction, incontinence, urinary tract infection, prostatitis, enlarged prostate, infertility, Peyronie's disease, kidney cancer, bladder cancer, kidney stones and vasectomy are the most common urology problems affecting men. As different urologic diseases encompass different conditions, the management of them varies depending on the nature of specific issue. This book *Key Leaders' Opinion on Andrology and Urology*, therefore, aim to capture the full range of distinguished expert thinking on common andrologic and urologic diseases.

The book opens with introductory chapters covering the mechanism and treatment progress that consolidate our understanding of pathogenesis and current study situation of those common urologic diseases. On the second half of the book, it aims to view the future challenges in this field and provide some special cases for analysis. The last two chapters are devoted principally to the cost effective management of nephrolithiasis and urinary stone disease.

We sincerely hope that this very comprehensive compilation will provide the urologists with fresh new insights into the management of urologic diseases.

Qian Zhang

Qian Zhang, MD, PhD
Institute of Urology, Peking University;
Department of Urology, Peking University First Hospital,
Beijing, China

Preface

Translational Andrology and Urology (*TAU*) is an open access journal that publishes focused issues on critical topics in Andrology and Urology. The journal is indexed on PubMed, does not charge publication fees and boasts many leading urologists and scientists as authors. Most of the manuscripts from the journal are expert commentaries, editorials and critical reviews. This book is composed of articles selected by the *TAU* staff from previously published work. The articles they have assembled are organized as mechanism, treatment progress, new techniques, and cost effective management. The articles included are informative and enjoyable on a diverse group of topics with many written on nephrolithiasis and sexual medicine.

Benjamin N. Breyer MD, MAS, FACS
Associate Professor in Residence,
Departments of Urology and Epidemiology and Biostatistics,
University of California, *San Francisco*, *USA*
(Email: benjamin.breyer@ucsf.edu)

Preface

In the past few decades, experts get to know more about urologic diseases and the treatment of it has become more and more matured. It is inspiring to witness the fast development in the field of andrology and urology. However, limited by current knowledge, there are still many unknowns.

Keeping that in mind, we are pleased to launch this book *Key Leaders' Opinion on Andrology and Urology* to provide the interested readers with more cutting-edge information of urologic diseases. In the book, we carefully collected a series of excellent articles on andrology and urology that cover the mechanism, treatment progress, new technique, prognosis, special case analysis and cost effective management of bladder cancer, urinary stone disease, prostate cancer, erectile dysfunction, renal cell carcinoma, urological trauma, Peyronie's disease, etc.

This book is an amalgamation of excellent articles from distinguished urologists all around the world. Hopefully the book will become a valuable manual to urologists in clinical practice.

Xiongbing Zu

Xiongbing Zu, MD, PhD
Department of Urology, Xiangya Hospital,
Central South University,
Changsha, China

Preface

It is with great pride that I served as one of the Associate Editors to present this unique collection of articles written by leaders across the subspecialties field of urology. These articles have previously been published at the journal of *Translational Andrology and Urology* and provides state-of-art knowledge on the ever-increasing and complex topics faced by many urologists. Under the editorships of Drs. Qian Zhang, Benjamin Breyer and Xiong-bing Zu, together with honorary editorial supervision by Drs. Jacob Rajfer, Toby Chai and Monique J. Roobol, I'm sure this book will serve as an invaluable source of refences on various urology and andrology topics to urologists in training as well as those in practice.

Eric Chung

Eric Chung

Andro Urology Centre, Brisbane, Australia

Professor of Surgery, University of Queensland, Princess Alexandra Hospital

(Email: ericchg@hotmail.com)

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Coining a new term-Urovesicology: advancing towards a mechanistic understanding of bladder symptoms

Toby C. Chai

University of Maryland School of Medicine, Division of Urology, 29 S. Greene St., Suite 500, Baltimore, MD 21201, USA

Correspondence to: Toby C. Chai, MD. University of Maryland School of Medicine, Division of Urology, 29 S. Greene St., Suite 500, Baltimore, MD 21201, USA. Email: tchai@smail.umaryland.edu.

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Introduction

When patients present with lower urinary tract symptoms (urgency, frequency, nocturia, slow stream, hesitancy, sense of incomplete emptying, post-void dribbling), urinary incontinence (stress and urge), urinary retention, dysuria, and/or bladder pain, the urologist would be the most appropriate specialist to evaluate and treat these patients. These symptoms will be collectively labeled as "urovesicologic" symptoms, the reason which will become apparent. Because these symptoms usually have no known cause, empiric (trial-and-error) treatments directed at ameliorating symptoms, but not at the underlying pathophysiology, are the usual recourse.

Within the field of urology, there are numerous appellations given to those who treat urovesicologic symptoms. These appellations, to date, include female urologist, female pelvic medicine and reconstructive surgeon, urogynecologist, neurourologist, urodynamicist, and probably a few more. Why so many? Of course, there are specific reasons. Labels with the words "female" or "gyn" imply that these subspecialists focus only on female patients. The use of the words "medicine" and "surgeon" imply that the physician has both intellectual and technical skills. The label "neuro" implies expertise in treating urologic issues in patients with concomitant neurologic diagnoses such as spinal cord injury, multiple sclerosis, post-cerebrovascular accident (stroke), Parkinsons, and Alzheimers, which can adversely affect bladder function. The term "urodynamicist" implies an expert in urodynamics with the further implication that urodynamics can objectively determine the etiology of the urovesicologic symptoms and/or prognosticate treatment outcomes.

Ultimately, how do these numerous labels help patients with these urovesicologic symptoms? Do we even need these many labels? The critical issue is the lack of understanding of how physiologic function/dysfunction translates into symptoms. We should not be so focused on a specific gender, treatment modalities (medicine versus surgery), distinct concomitant disease (neurogenic versus non-neurogenic) or ability to do specialized testing (urodynamics). The urologists should be the specialty that seeks knowledge about the pathophysiologic mechanisms underlying urovesiciologic symptoms.

Therefore, I propose a new term, "urovesicology" (uro=urine + vesic=bladder + ology=study of) which would be a discipline that studies basic pathophysiologic mechanisms that lead to bladder symptoms. Urovesicology will not be limited to mechanisms based on a gender (male or female), a specific treatment method (medical or surgical), a specific cause (neurologic injury or degeneration) nor a specific testing modality (urodynamics), but rather, urovesicology would be defined by development and implementation of new treatments and/or diagnostic tests for urovesicologic symptoms based on ability to measure, detect, and/or quantify specific pathophysiologic mechanisms. Future treatments will therefore be driven by mechanistic principles rather than the current paradigm of empirical symptoms-based treatment. This editorial will present what the future in urovesicology might hold.

Future of urovesicology research from the neurophysiologic level

Current treatments for urovesicologic symptoms that target the nervous system include: (I) Implantable sacral neuromodulation (1,2) (II) Posterior tibial nerve stimulation

(3,4) (III) Onabotulinumtoxin A detrusor injection (5,6). These therapies impact the neurophysiologic control of bladder function. Electrostimulation of the sacral 3rd nerve root and posterior tibial nerve may work through modulation of central organization of afferent signals to impart symptomatic relief. Functional positron emission tomography (PET) data show that the blood flow patterns (surrogate marker for neural activity) to certain areas in the brain are altered in the patients with idiopathic urge incontinence and furthermore are altered during InterStim treatment (7). Other studies using functional MRI (fMRI) in normal and urge incontinent subjects suggest that urge incontinence is associated with measureable changes in brain activities (8,9). fMRI might be useful as a diagnostic test in order to stratify patients to treatment options. By understanding brain function and its relationship to urovesicologic symptoms, future treatments might be able to target these central neural projections, although treatments targeting the central nervous system (CNS) would likely have to clear a high bar in terms of safety.

Intradetrusor injections of onabotulinum toxin A prevent the release of acetylcholine by the pre-junctional motor nerve terminals thereby preventing contraction of detrusor muscle. The USA Food and Drug Administration (FDA) just recently approved the use of intradetrusor injections of onabotulinum toxin A (BoTox™) for neurogenic detrusor overactivity incontinence secondary to multiple sclerosis and spinal cord injury (5). Therefore, this is the first approved use of pharmacologic neuromodulation (as opposed to electrical neuromodulation) for treatment of a urovesicologic symptom related to neurologic diagnoses. Additionally, there is evidence that this toxin is efficacious for non-neurogenic (i.e. idiopathic) urgency urinary incontinence and urinary frequency (6).

A better understanding of bladder afferent signaling mechanisms may also bear fruit. Understanding chronic bladder pain (aka interstitial cystitis/painful bladder syndrome) as form of central nervous system sensitization (10) may unlock mechanistic processes that can be therapeutically targeted. Another related issue is how pelvic organ cross-innervation can modulate afferent signals from different pelvic organs (11,12) leading to various pelvic symptoms. Urinary urgency, frequency and bladder pain are sensory problems and therefore, a better understanding of the afferent mechanisms will lead to more efficacious treatments. Measurement of bladder afferent function using current perception thresholds (CPT) in asymptomatic women have been published (13). Interestingly, bladder CPT testing showed that a change in bladder sensation was not correlated with occurrence of detrusor overactivity detected on urodynamics (14) suggesting that detrusor overactivity may not necessarily be related to the sensation of urgency.

Non-obstructive urnary retention is a poorly understood clinical problem. Whether this is from neurogenic and/or myogenic failure is unknown. For patients with urinary retention secondary to neural compromise from spinal dysraphism, nerve re-routing (somatic-to-autonomic motor connection) has been described to normalize bladder motor function although this therapy has engendered controversies (15,16). Whether or not nerve re-routing can be applied to patients without neurologic defects (idiopathic non-obstructive urinary retention) would depend on whether the cause of the retention is primarily neurogenic or myogenic failure.

Urovesicologic symptoms secondary to spinal cord injury (SCI) is a major issue in long-term care. Philosophically, it can be argued that the best approach to addressing all of SCI-related problems is to discover how to regenerate spinal cord neurons so that SCI-patients can be cured of their injury. The use of embryonic stem cells injected intrathecally to regenerate neurons has been studied in animal models of SCI (17). The first clinical trial for use of human embryonic stem cells in treating acute spinal cord injury was recently stopped after 4 SCI patients were enrolled due to entrepreneurial economic reasons (18). Whether stem cell therapy in SCI would also normalize bladder function remains unknown.

Socially acceptable bladder control is a behavioral and cognitive event that occurs during toilet training age. The strong connections between the brain and bladder have led some to equate bladder behavior with emotions and the soul (19). Along this paradigm, it has been suggested that corticotropin releasing factor (CRF) has a role as a mediator of emotional influences on bladder function (20). This association has been born out in animal studies of voiding behavior in social stress situations. There were changes in electrical activity of neurons in the locus coeruleus in the brain (21) and bladder wall remodeling (22) which are under the control of CRF (23). Whether CRF can be used for urovesicologic symptoms remains to be seen.

In the future, will we ultimately be able to detect an abnormal neurophysiologic signal in patients with urovesicologic symptoms who currently have no measureable neurologic deficits? How will this signal be measured? Will we have a treatment that normalizes this signal? Where in the CNS will this signal be – the peripheral or central nervous system? The answers will come with continued research.

Future of urovesicology research at the bladder level

The main method to study bladder physiology for many years has been to focus on bladder (detrusor) smooth muscle. Much of the work has been to explore mechanisms to block unwanted detrusor contractions that presumably underlie the pathophysiology of urgency urinary incontinence. Fewer studies have addressed molecular causes of smooth muscle contractile failure and whether idiopathic non-obstructive urinary retention could be related to these mechanisms. This traditional research paradigm on blocking contractility led to oral antimuscarinics in treating urinary frequency, urgency, nocturia and urge incontinence. So while antimuscarinics represent a viable treatment option, they are not uniformly effective and have bothersome side effects. Patients do not stay on these medications long term. As in almost all treatments for urovesicologic symptoms, use of antimuscarinics requires no detailed understanding of pathophysiology underlying symptoms in an individual patient.

A new paradigm for the function of the bladder urothelium is its role in regulation of bladder function (24). Investigators have suggested that the bladder urothelium may be a key regulator of bladder afferent signaling through crosstalk with suburothelial and intra-urethral sensory nerve fibers. This is opposed to the notion that bladder afferent signaling arise only from the afferent nerves. Bladder urothelial cells are known to release neurotransmitters in response to stretch and also express receptors that are typically found on neurons. Some have proposed that the site of action of antimuscarinics may not only be on detrusor smooth muscle, but also on the urothelium. Suburothelial myofibroblasts, which are located just underneath the urothelium, are specialized cells which are thought to regulate spontaneous detrusor contractions (25,26). Can future therapies target the bladder urothelium to specifically reverse a urothelial physiologic abnormality? Can cystoscopy in the future incorporate new imaging techniques to be able to visualize urothelial abnormalities to help in diagnosis in patients with urovesiologic symptoms? The answers will depend on whether the new paradigm of urothelial function is true or not.

The urothelium also plays a key role in preventing bacterial invasion of the underlying stroma. While many researchers are interested in bacterial virulence factors, fewer are interested in host defense factors which the bladder urothelial cells play a central role. For example, the host response to bacterial pathogens is initiated by bacterial lipopolysaccharide (LPS) interaction with the Toll-like receptor 4 (TLR4) on the bladder urothelial cell. Activation of TLR4 stimulates cytokine release from bladder urothelial cells which can lead to activation of the immune system resulting in a robust host defense against the offending bacteria (27). Understanding host urothelial responses would be critical in being able to leverage this understanding in reducing urinary tract infection (UTI) perhaps without antibiotics.

The future of bladder specific therapies depends on whether urovesicologic symptoms arise directly from the bladder compartments (urothelium, suburothelium, nerves, smooth muscle) or whether symptoms arise secondarily from other conditions and diseases such as neurologic diseases (e.g., SCI, multiple sclerosis, stroke, etc.), metabolic syndrome (see later section), bladder outlet obstruction, and/or urethral/pelvic floor (bladder outlet) pathology (see later section).

Future of urovesicology from the urethra/pelvic floor level

The urethra, urethral sphincteric complex and pelvic floor muscles comprise the bladder outlet. The motor function of the bladder and the urethra/pelvic floor must act in opposite fashions. During storage, bladder is relaxed whereas the urethra/pelvic floor is contracted, during emptying, bladder is contracted whereas the urethra/pelvic floor is relaxed. The knowledge of urethral and pelvic floor function is even less than the knowledge of bladder function. Perhaps the urovesicologic condition that best exemplifies our lack of understanding of basic urethral function is female stress urinary incontinence (fSUI). We have been treating fSUI for many years and yet our treatment is still not directed at reversing urethral sphincter pathophysiology. Furthermore, we have no tools to identify specific mechanisms that underlie urethral pathology leading to fSUI. Whether fSUI is caused by an anatomic lack of support of the urethra (i.e. urethral hypermobility) versus lack of intrinsic urethral function (i.e. lack of neuromuscular function, lack of vascularity, lack of urethral coaptation) has been argued for decades. It is argued that intrinsic urethral function, not loss of anatomic support, is the primary basis of fSUI (28). A recent study suggests that fSUI is due to a neuromuscular defect, as measured by EMG, of the female urethral sphincter (29). Furthermore, duloxetine, an agent that can increase urethral sphincteric tone via increased efferent activity from Onuf's nucleus, was found to be efficacious in fSUI (30). Despite these and other findings, our current treatment is still based on an anatomic-based treatment

(midurethral sling) which partially obstructs the bladder outlet. It is conceivable that the sling could correct the neuromuscular function of the urethra, but the mechanical advantage (e.g., backboard or hammock effect) of the sling is likely the primary reason for its beneficial effect.

While detrusor overactivity has been traditionally described as the pathophysiology of overactive bladder (OAB), investigators have wondered whether urethral sensory dysfunction plays a role in OAB. What is interesting is that urethral sensation appears to be decreased in OAB and furthermore, the sensation in the urethra increased after treatment with tolterodine (31). The concept that the female urethral physiologic disturbances may play a role in urovesicologic symptoms is not new, especially with the previous nomenclature of "female urethral syndrome" (32). We will also require a better understanding of the role of the pelvic floor musculature in bladder function. Studies have framed urovesicologic symptoms in the context of pelvic floor myofascial disorders, both in males and females (33-35). Treatments to relax pelvic muscles have resulted in reduction of urovesicologic symptoms.

The interesting, yet potentially difficult, aspect of treating urovesicologic symptoms is the ying-yang relationship between the bladder and its outlet (urethra/pelvic floor) from the motor (efferent) perspective. Normal functioning of the lower urinary tract requires complementary yet opposite functions of the muscles comprising the bladder and urethra/pelvic floor. During urinary storage, there should be no urinary incontinence with the bladder relaxed, and the urethra contracted. During micturition, the bladder contracts while the urethra relaxes resulting in maximum emptying efficiency. Therefore treatments directed at the motor function of the urethra and pelvic floor have to take into account this inverse relationship with the bladder. However, while motor functions of the bladder and urethra are necessarily contradictory, the sensory (afferent) functions of the bladder and urethra/pelvic floor are not, with constant sensory signals from the lower urinary tract flowing into to the central nervous system. Leveraging our understanding of the mechanisms underlying urethral/pelvic floor sensation into viable treatment options for urovesicologic symptoms will be important in the future.

Future of urovesicology from genomics/proteomics and biomarkers level

For diseases in which the pathophysiologic mechanisms are poorly understood, genomics and proteomics technologies allow researchers to probe for possible etiologies. Genetic investigational tools such as genome-wide association study (GWAS) can localize potential gene loci related to cause of urovesicologic symptoms by comparing symptomatic versus non-symptomatic (control) patients. However, several difficulties lie with this type of approach. First, accuracy of GWAS requires a homogenous afflicted population (phenotype). Phenotyping patients who have urovesicologic symptoms are neither uniform nor completely objective. Patients often have more than one type of lower urinary tract symptoms and there is high degree of overlap of symptoms making a "pure" phenotype difficult. Second, the interaction of many genes complicates the ability to detect a clean signal; none of the urovesicologic symptoms is thought to be due to a single-gene defect. Third, finding a significant association between a disease and loci within the genome does not mean that the gene products and/or function of the gene products within these loci will be known. Another approach would be to compare the genome of responders versus non-responders (or poor-responders) to a particular therapy in hopes of finding a genetic signal that underlies response to treatment. This approach would not require a specific phenotype for the cases and may still shed light on the pathophysiologic mechanisms underlying the cases.

As genetic tools advance and statistical abilities to analyze large datasets improve, genetics-based research may pay off. It is hoped that the end result of these approaches is a mechanistic based treatment for urovesicologic symptoms. While peer-reviewed original research in this area is sparse, a recent review of what the future holds for genetic studies for urovesicology has been published (36).

Proteomics examines the entire protein expression profile using high throughput technologies such as mass spectroscopy. A pilot study of urinary proteomics in interstitial cystitis/painful bladder syndrome (IC/PBS) has been published; this study showed differences in urinary protein expression profiles between cases (IC/PBS) and controls (37). Taking a different approach, another investigative group has examined proteomics at a cellular level by examining the effects of the putative causal factor for IC/PBS, antiproliferative factor (APF) (38). These investigators mapped out protein increases/decreases that APF induced within a cell. Based on bioinformatic network analyses of APF-induced protein changes, the authors identified the β-catenin network as a central pathway regulated by APF (39) suggesting a mechanism of action for APF. How will urinary proteomics change urovesicology in the future? It is uncertain, but a PubMed review of the terms "urinary proteomics and bladder cancer" revealed

95 publications suggesting that urinary proteomics is on its way to becoming an integral part in bladder cancer management. Given the rapid advances in technology, both in terms of throughput analysis (e.g., mass spectroscopy) and data analyses algorithms (e.g., statistical methodologies coupled with computing speed), urinary proteomics could be easily applied to urovesicology to elucidate pathophysiologic mechanisms underlying urovesicologic symptoms which would lead to novel treatments.

Proteomics should eventually identify candidate proteins of interest. However, one urinary protein, nerve growth factor (NGF), which was not identified with proteomics, has been studied by extensively by one research group as a possible biomarker for OAB (40). The origin of the increased NGF in the urine from OAB patients is not known; it can be from the urothelium, nerves or even perhaps the upper urinary tract. It was shown that bladder urothelial tissue levels of NGF was similar between subjects with detrusor overactivity versus those without detrusor overactivity (although all subjects had OAB symptoms) (41) suggesting that the source of urinary NGF might not be the bladder urothelium. On the other hand, there is a transgenic mouse model of conditional NGF knock-in where NGF overexpression is restricted to bladder urothelium. These transgenic animals had significantly increased voiding frequency, increased mast cells in bladder wall, and increased pelvic hypersensitivity (42). A monoclonal antibody to NGF (tanezumab) has been tested for IC/PBS (ClinicalTrials.gov identifier NCT00999518), but the results have not been published. Urinary NGF changes has also been correlated with treatment outcomes (43) suggesting decreased urinary NGF with successful treatment of urinary symptoms with antimuscarinic therapy. Similarly, urinary NGF was decreased after successful treatment of IC/PBS (44).

Another set of urinary biomarkers under investigation is that of epidermal growth factor (EGF), heparin-binding epidermal growth factor-like growth factor (HB-EGF) and APF in IC/PBS. These 3 markers have been found to be the most useful in delineating the phenotype of IC/PBS (45). However, these urinary markers have not been associated with other pathologic findings from bladder biopsies, presence of ulcers on cystoscopy (46) or response to treatment (albeit it a negative treatment trial) (47).

The future of urovesicology will parallel other clinical disciplines if urologic investigators apply the rapidly advancing technologic tools of genetics, proteomics and biomarkers. Personalized medicine, based on each individual's genomic sequence, may one day help predict biologic responses to treatment, and/or identify risk factors associated with treatment failure. Discovery of biomarkers that help diagnose, prognosticate response to treatments, and/or help with treatment selection will brighten the future of uroveiscology.

Future of urovesicology from tissue engineering/ stem cell level

The promise of stem cells in urovesicology is exemplified by the use of striated-muscle derived stem cell injections into urethral sphincter for treatment of fSUI (48,49). However, no FDA-approved stem cell therapy for fSUI exists today. A recent review of this topic suggests that there are roadblocks to overcome including validity of animal models and multilineage differentiation of the injected stem cells (50).

Tissue engineering, where a biological neobladder was grown in laboratory and successfully augmented into neurogenic bladder patients, has attracted much attention (51). The goal of developing a total bladder replacement however, is complicated by the fact that there is no afferent and efferent neural connection to the tissue engineered bladder. Therefore, there would not be the normal sensation of fullness (afferent signaling) nor contraction (efferent signaling) of the tissue engineered bladder. A more realistic goal is the development of a tissue engineered ileal conduit, where afferent/efferent signaling would not be required. This neoconduit would spare the use of native ileum. This technology is being currently developed by Tengion as the Neo-Urinary Conduit™ (www.tengion.com). It involves the removal of autologous fat from the patient which is processed in the laboratory so that adipose stem cells differentiate into urothelial and smooth muscle cells on a biodegradable scaffold.

Stem cells and tissue engineering continue to fascinate both the scientific community and public. It remains to be seen whether these technologies will be successfully implemented in urovesicology. Tissue engineering and stem cells approach problems in urovesicology from a different perspective in that knowledge of symptoms pathophysiology is not as important. Because these technologies are designed to augment or replace normal function of the bladder or urethra, the pursuit of why the bladder or urethra does not properly function becomes less critical. However, a close collaboration between tissue engineers/stem cell biologists with the physiologists could result in not just biologically compatible tissue, but tissue with true function.

Future of urovesicology from the metabolic syndrome level

Epidemiologic studies have found strong associations between urovesicologic symptoms and metabolic syndrome (insulin resistance, dyslipidemia, central obesity and hypertension) in men (52,53). More recently, similar associations were described in women (54). To strengthen these associations, researchers have found that weight loss decreased urovesicologic symptoms in both genders (55,56). However, a study on Chinese male population did not find significant associations between uroveiscologic symptoms with metabolic syndrome (57).

The cause of metabolic syndrome is multifactorial. Several theories exist of how metabolic syndrome relate to urovesicologic symptoms. One possibility is the increased autonomic activity seen in metabolic syndrome. Spontaneously hypertensive rats (SHR), due to increased autonomic activity from noradrenergic hyperinnervation, have bladder overactivity (58), thereby providing a proof-of-concept link between hyperautonomic activity and bladder overactivity. This link was studied and confirmed in a large study of men with urovesicologic symptoms (59). Other potential causal links include the pro-inflammatory state in metabolic syndrome and findings of inflammation in prostate of men with urovesicologic symptoms (60,61). The molecular link between metabolic syndrome and BPH may be PPARγ (peroxisome proliferator-activated receptor gamma or glitazone receptor) (62). PPARγ regulates inflammation and insulin resistance and thus sits at the crossroads between these two conditions, thereby potentially regulating both of these processes. These and other studies in the literature are starting to provide a picture that some of the urovesicologic symptoms may be part of a systemic disease rather than a primary lower urinary tract disease. Since a treatment directed at the metabolic syndrome (weight loss) resulted in lessening of urovesicologic symptoms, some could argue that addressing the systemic issue first, before treating the urovesicologic issues, could be a better strategy. However, it is likely that combination treatments for both conditions will be required in some patients. Also, more research into the causal links could potentially unlock novel targets that could treat both conditions.

Conclusions

Diagnosis and treatment of urovesicologic symptoms are imperfect. A primary reason is a lack of mechanistic understanding of why these symptoms occur and therefore, a lack of targeted treatments. A broad based research approach utilizing knowledge and technologies from other disciplines will help advance the field of urovesicology more quickly towards a better understanding of pathophysiology. Collaboration with researchers in other disciplines will accelerate discoveries resulting in a higher translational impact. The ultimate goal is to bring effective treatments to the many who suffer from urovesicologic symptoms. The future for urovesicology looks brighter than ever.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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Mechanism

The aging penis: what is it trying to tell us?

Jacob Rajfer

UCLA School of Medicine, Division of Urology, Harbor-UCLA Medical Center, Torrance, CA 90509, USA

Correspondence to: Jacob Rajfer, MD. Chief, Professor of Urology, UCLA School of Medicine, Division of Urology, Harbor-UCLA Medical Center. Torrance, CA 90509, USA. Email: jrajfer@ucla.edu.

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Aging is the price we all pay for living long. While the alternative to aging is a less attractive option, what clinically affect us most during this aging process are the detrimental effects aging has on the smooth muscle throughout our body. Those of us, who have been fortunate enough to enter middle age or better yet, senescence, know how true this is. Consider during this time period the onset of maladies such as essential hypertension, GERD, overactive bladder, farsightedness, constipation, bladder outlet obstruction and the most feared of all aging related symptoms that can afflict any man, erectile dysfunction. All of these conditions have essentially one thing in common-the smooth muscle in that tissue does not function optimally. The main reason for these aging associated dysfunctions is that the smooth muscle mass, at least part of it, within each of these tissues has begun to undergo apoptosis with replenishment by fibrous tissue.

The timing of when this aging related apoptosis of the smooth muscle begins to occur in an individual, specifically in the penis, is assumed to be genetically predetermined. In some men, it can occur in the 3rd to 4th decades of life whereas in others it may not manifest itself until later on in life. It can be extrapolated from data from the massachusetts male aging study (MMAS) that 20% of men in their 20's have some form of erectile dysfunction and this prevalence increases about 10% per decade such that a 50 year-old man has about a 50% chance of having some problem with his erectile function while a 70 year old will have about a 70% chance (1). The major culprit of this aging related apoptosis seems to be oxidative stress. Oxidative stress is primarily a byproduct of metabolism and since we all "live" by the process of metabolism, oxidation will always win out in the end despite the presence of all the anti-oxidative pathways within the mitochondria and despite all the anti-oxidants that we can throw at the cell. This explains why decreasing caloric intake which essentially decreases metabolism is the only known mechanism that has been shown to increase longevity (2).

However, from experimental studies performed in aging animals, specifically within the corpora of the penis, another previously unrecognized anti-oxidant pathway has recently been identified. This pathway involves the production of nitric oxide (NO) within the cell which, until this NO producing pathway was identified within the smooth muscle cells of the aging corpora (3), NO was only known to be produced in the vascular endothelium, neural tissue, Kupffer cells and the macrophages. NO as a molecule has many functions including being a quencher of reactive oxygen species (ROS) and as such, NO can ameliorate oxidative stress by combining with ROS, for example, to form peroxynitrite. Besides the corpora, this recently recognized NO producing pathway in the corporal tissue is also upregulated during the aging process in a number of other tissues including the peripheral arteries (4).

This begs the question as to how and why NO produced in this specific manner came to be chosen as one of the molecules assigned to such a task as combating oxidative stress. The answer may simply lie in availability. In that time period 1 to 2 billions of years ago when life as we know it today first formed presumably as the result of an increase in oxygen within the atmosphere about a half billion years earlier, there were basically in the atmosphere only three molecules-carbon, oxygen and nitrogen-available for most any task within the cell. These three chemicals obviously offered very few combinations, the most obvious being NO and carbon monoxide (CO). Since the late 1980s, we have become aware of the importance of NO in a multitude of cellular functions including immunity, communication and cell survival. Thus, on the surface, it appears as if NO has been chosen over CO at least by mammalian cells to be involved with most cellular functions other than basic metabolism. That is not to say that cells abandoned CO completely. Although CO in high concentration is known to be toxic to cells, it has recently been discovered that CO

may also possess anti-inflammatory, anti-apoptotic and anti-oxidative effects, and like NO, CO is also known to possess vasodilatory activity (5).

As life evolved and single cells merged to become multicellular organisms, three avenues of NO production, each with its own genetic control and specific translation and transcription, have also evolved. Of these three isoforms of the enzyme, nitric oxide synthase (NOS), that make NO, the one that is primarily committed to fighting for cell survival is the inducible nitric oxide synthase (iNOS) isoform. The gene that regulates this iNOS enzyme is located on chromosome 17 and, as mentioned above, is normally active only in the macrophages and Kupffer cells. iNOS stays inactive in every other cell unless that cell is exposed to specific stimuli that can upregulate its production and NO producing activity. One example of such a stimulus to iNOS is endotoxin. Another appears to be the aging process which is characterized within tissues by apoptosis of the parenchymal cells and an increase in tissue fibrosis. Whether this upregulation of the iNOS gene with aging is simply a response to the increased oxidative stress associated with aging or is the result of some other as yet unknown process associated with aging remains to be determined.

Oxidation, the byproduct of metabolism that causes the smooth muscle cells to undergo apoptosis and fibrosis, will of course impact the function of that smooth muscle. In the penis, this reduced muscle mass may lead to inadequate vasorelaxation of the corporal smooth muscle which in turn does not allow the subtunical veins to be completely compressed against the underside of the tunica albuginea of the corporal bodies. The clinical result is an inability to maintain an erection, so called venous leakage or cavernosal veno-occlusive dysfunction (CVOD). There are some experimental data to suggest that in the human the loss of about 15% of this muscle mass in the penis results in clinical CVOD (6). The earliest sign of this condition occurring in man is the recognized increase in the refractory period that many potent men begin to experience usually sometime around or during their 3rd to 4th decades of life (7).

When evaluated, CVOD turns out to be the most common cause of ED such that up to two-thirds of men who initially present with ED have this as the primary cause of their ED (8). When vascular tests are performed such as dynamic infusion cavernosometry and cavernosography, it is evident that CVOD as a cause of ED is much more prevalent than a pure arteriogenic cause. Today, we categorize patients who have CVOD as having a vasculogenic cause for their ED mainly because the smooth muscle of the cavernosal tissue is embryologically, morphologically and physiologically similar to that of the smooth muscle within the media of the peripheral arterial system and as such this cavernosal tissue which consists of both the smooth muscle and the cavernosal sinusoids including its endothelium is considered part of the vascular system of the penis. This underlies the statement as to why the penis is considered an outpouching of the peripheral vascular system and indeed, it was this relationship that ultimately led to the hypothesis that whatever causes the peripheral vascular system to dilate-at that time called endothelial derived relaxing factor-must be the same as in the penis. We now know that this erectogenic chemical within the penis is NO that is derived from neuronal NOS (nNOS) and it initiates the series of events that ultimately leads to vasodilatation in the corporal tissue. In the vascular system, the major vasodilator is the endothelial derived NO. Each of these tissues, the endothelium and nerve, has its own isoform of NOS (eNOS and nNOS, respectively), each controlled by its own genome.

If one adheres to the concept that the media of the peripheral arterial system is similar to the smooth muscle within the cavernosa, it makes sense that any systemic disorder that afflicts the cavernosal smooth muscle may also afflict the media of the arterial system or vice versa. With respect to aging, if the cavernosal smooth muscle begins to undergo aging related changes i.e. apoptosis and fibrosis of the trabecular tissue of the cavernosa, it follows that this may also occur within the media of the arterial system (4). When the media of the arterial system undergoes such changes i.e. loss of smooth muscle with an increase in fibrosis, the artery is considered to be arteriosclerotic (not atherosclerotic) and such a process leads to its inability to vasodilate efficiently. Clinically, this arteriosclerosis or stiffness of the peripheral vascular system is the hallmark of hypertension and we have proposed that this aging related change in the peripheral vasculature is most likely the cause of essential hypertension. In fact, based on this observation, our research group believes from a histological point of view that ED is essential hypertension of the penis and, similarly, essential hypertension is ED of the peripheral vascular system. Clinical data to support this assumption that ED and essential hypertension is the same disease albeit in two different tissues may be gleaned from the results of both the National High Blood Pressure Education Program and the MMAS where the aging related prevalence of hypertension in men (9) appears to be exactly the same as the prevalence of ED as reported in the MMAS (1).

The recognition that NO is a potent quencher of reactive oxygen species and that iNOS is upregulated in the cavernosa of the aging penis suggested to us that we may be able to take advantage of this observation to curb the negative effects of aging i.e. smooth muscle loss and increase in fibrosis within the cavernosal tissue. In other words, could we delay or even prevent the onset of aging related CVOD? Since the PDE5

inhibitors are known to upregulate the effects of NO by inhibiting the degradation of its second messenger, cGMP, we initially tested this hypothesis in aged animals and found that continuous PDE5 inhibition, presumably enhancing the upregulation and function of iNOS, not only prevented or delayed the onset of aging related apoptosis and fibrosis, but even suggested that this treatment may simultaneously increase SMC production within the penis (10). Further evidence to support this anti-apoptotic and anti-fibrotic role of the PDE5 inhibitors can be gleaned from the study of Schwartz *et al.* where chronic PDE5 inhibitor treatment to men undergoing radical prostatectomy demonstrated that the PDE5 inhibitor therapy not only prevented the loss of smooth muscle within the cavernosa but, as in our animal model, tended in some patients to increase the amount of smooth muscle within the cavernosa (11). This anti-fibrotic effect of the PDE5 inhibitors has also been extended to patients who have had prolonged periods of priapism where chronic treatment with these PDE5 inhibitors seem, at least observationally, to minimize the known fibrosis and scarring within the cavernosa that occurs after prolonged priapism (12).

In conclusion, it was the aging penis in the early 1990s that bore witness to one of the major discoveries in urology i.e. the role of the NO molecule in the erectile response (13). Today, two decades later, again via another cellular pathway for synthesizing NO, the aging penis is now providing us with evidence of how the body attempts to fight the aging process. The recognition that chronic treatment with drugs that upregulate the effects of NO from this iNOS pathway may have a beneficial effect on either slowing or reversing the aging changes within the penis has opened up new avenues of investigation to try to possibly halt, prevent or delay the onset of ED. Since it appears that what occurs within the aging penis does not stay within the aging penis, it is our belief that the aging penis will continue to provide us with insight into how we may be able to prevent or delay the onset or progression of other aging related maladies such as essential hypertension, congestive heart failure, overactive bladder, certain forms of bladder outlet obstruction and other aging related muscular dysfunctions.

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Mechanism

Micro-RNAs, next-generation molecular markers in male infertility field

Saeid Ghorbian

Department of Biology, Bonab Branch, Islamic Azad University, Bonab, Iran

Correspondence to: Saeid Ghorbian, Ph.D. Department of Biology, Bonab Branch, Islamic Azad University, Bonab, Iran.
Email: ghorbian20@yahoo.com or saeid.ghorbian@bonabiau.ac.ir.

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The prevalence of male infertility appraised 10-15% in worldwide. Male infertility is frequently coupled to deficient in sperm development and production (1). Of note, in principle of the number of sperm cells in seminal fluid, has been categorised in azoospermia, severe oligozoospermia and mild oligozoospermia. In azoospermia condition, a sperm cell counts approximately $\leq 5\times10^6$ cells/mL, and in severe oligozoospermia and mild oligozoospermia, sperm cell counts $>5\times10^6$ cells/mL and $<20\times10^6$ cells/mL respectively (2). Male infertility is a multi-factorial syndrome accompanied a broad category of disorders. Moreover, until several decades, investigators endeavor to reveal the molecular procedures of male infertility, although the most aspects remain a clinical obstacle. Interestingly, the cause of infertility in more than 50% of infertile men is undiscovered. In generally, the known causes of male infertility are categories in genetic and environmental conditions. The genetic abnormalities are involving, numerical and structural chromosomal in sufferers for oligozoospermia and azoospermia (3,4). Routinely; the diagnosis of male infertility can be supported by assessment of microdeletions that occurred in the long arm of the Y chromosome (Yq) especially in azoospermia factor (AZF) regions (5,6). As previously an investigation in this filed revealed that, the frequency of these microdeletions in azoospermia and severe oligozoospermia men are approximately 13% and 1-7% respectively (7). Notwithstanding, the Y chromosome microdeletions consideration can be customarily be proposed to each of men with azoospermia and severe oligozoospermia. Although in more than cases, they are not powerful tolls to explore all of factors that leading to infertility. Furthermore, we need to introduce a new biomolecular marker for consideration of infertile men with the cause of unexplained. Currently, the results of several investigators have been suggesting that with providing of miRNAs expression patterns, it possibly that a benefit to reveal of causes of the infertile men unexplained. However, the results of authors revealed that miRNAs play strictly roles in post-transcriptional and post-translational regulatory in several biological procedures (8). The miRNAs are involvement in several of reproductive processes such as embryogenesis, oogenesis, and spermatogenesis (9,10). Here, I summarize a short overview in recent studies revealed that dysregulation in miRNAs expression's patterns, leading to defective sperm production (11-16) (*Table 1*). In generally, in mammalian spermatogenesis, miRNAs plays an important impact in development of spermatozoa, particularly in germ cells and somatic cells (17). However, It is conceivable that for any up-regulation and down-regulation in miRNAs expression patterns, significantly affecting in spermatogenesis pathways and leading to several types of reproduction abnormalities (18,19). Importantly, the spermatogenetic disturbance is the most common feature of male-factor infertility, but it is not complete explained of causes. Furthermore, with considering the important role of miRNAs in spermatogenesis, it has potential to provide and development expression profile of miRNAs in different conditionals of infertility. Finally, it is possible that using of the measurement expression pattern's of these molecules in the seminal fluids; introduce as a novel biomolecular marker for consideration and determination of idiopathic infertility patients.

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Table 1 The short overview of recent studies that worked on patterns miRNAs dysregulation in azoospermic or idiopathic infertile patients

Abnormality type	Locations	Up-regulation	Ref	Down-regulation	Locations	Ref
Azoermia/ Idiopathic infertile men	4q25	hsa-mir-302a	(12)	hsa-mir-34c-5p	11q23.1	(13,16)
	9p21.3	hsa-mir-491-3p		hsa-mir-122	18q21.31	
				hsa-mir-146b-5p	10q24.32	
				hsa-mir-509-5p	Xq27.3	
	4	hsa-mir-574-5p	(15)	hsa-mir-29c	1q32.2	(12)
	4q25	hsa-mir-297		hsa-mir-34b	11q23.1	
	18q21.31	hsa-mir-122		hsa-mir-520d-3p	19	
	6	hsa-mir-1275		hsa-mir-383	8p22	
	19q13.42	hsa-mir-373				
	22q11.21	hsa-mir-185		hsa-mir-383	8p22	(11)
	16p13.12	hsa-mir-193b				
				hsa-mir-100	11q24.1	
				hsa-mir-512-3p	19q13.42	
	13q31.3	miR-19b	(14)	hsa-mir-16	16p12-p11.2	(15)
	-	let-7a		hsa-mir-23b	9q22.32	
				hsa-mir-26a-1	3p22.2	

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Mechanism

Treating the cystine stone former presents a singular clinical challenge

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Cystinuria represents a relatively rare hereditary condition leading to impairment of the renal proximal tubule's dibasic amino acid transporter. The only manifestation of this disease is calculi formation. Unlike other nephrolithiasis disease processes, cystine stone formation is due directly to supersaturation of an insoluble solute precipitating out of the urinary milieu. The genes responsible for this are SLC3A1 and SLC7A9 which encode for the protein heterodimer that is responsible for reabsorption of filtered dibasic amino acids. While the International Cystinuria Consortium recently revised its categorization of cystine patients into type A and type B where type A patients have mutations in both alleles of SLC3A1 and type B in SLC7A9, from a clinical perspective, genotyping offers little clinical benefit and does not alter patient treatment or give insight to disease penetrance. Although both of these genes and their protein products have been characterized, the stone forming tendency of cystinurics is not fully understood and further genetic mutations may exist as well. Cystinuria is most easily diagnosed with a stone analysis revealing the classic hexagonal-shaped cystine crystal, but a positive family history of cystinuria, a urine sample with elevated cystine (often >400 mg/day), or a positive sodium nitroprusside test can also make the diagnoses (1).

Treatment of these patients typically includes urinary alkalization, typically with potassium citrate, increased hydration, and decreased sodium and animal protein intake. If these fail, then cystine binding thiol medications are initiated. Patients' tolerance of these medications is debatable and their availability can be problematic as well. Anyone that has cared for these patients can attest to the frustration that both the patient and clinician experience in trying to prevent future calculi formation. While these patients represent a relatively small proportion of stone formers, the impact of their morbidity is significant. Fortunately, new drug development continues, utilizing new techniques with computer modeling as well as atomic force microscopy. These and other novel techniques will hopefully lead to better characterization of the disease penetrance and its medical treatment.

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Mechanism

Making sense of dietary calcium and urinary stone disease

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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The regulation of dietary and supplemental calcium intake in relation to urinary stone disease is not well understood (1). For instance, why do most patients with primary hyperparathyroidism with markedly increased serum and urinary calcium not have a history of urinary stone disease? There must be other factors involved in stone formation. Calcium stone formers have traditionally been classified by their 24-hour urine collections to be hypercalciuric (>4 mg/kg), hyperuricosurics (>600 mg for women; >750 mg/24 h urine for men), hyperoxaluric (>40 mg/24 h urine) and/or hypocitraturic (<320 mg/24 h urine). These defects can occur by themselves or as a part of a constellation of abnormalities. Generalized dietary stone recommendations include a low sodium intake, limiting high sodium-containing foods, limiting the frequency of eating out, including and especially at fast food restaurants, limiting many frozen foods and the salt shaker at the table. Additionally, patients should drink adequate volumes to ensure that they void 1.5-2.0 liters per day. Calcium intake on the other hand is not well understood by many urologists, primary care physicians, and the lay press. It is assumed that if one has a calcium-based stone one should decrease their calcium intake. It is now well studied that stone formers with the lowest dietary calcium intake have the highest stone recurrence rates. Calcium stone formers in general should not decrease their dietary calcium intake. This should be the standard recommendation for our calcium stone formers.

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Mechanism

Alexander Randall may have had it right after all

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Several theories exist regarding the pathogenesis of urinary calculi, and the early incipient events leading to calculus formation remain the most controversial. The authors detail a theory by which microscopic Randall plaques (RP) lead to calcium oxalate calculi in idiopathic calcium oxalate stone formers (1). Outlined is a process by which RP form in the basement membrane of the loops of Henle and spread through the interstitium through mineral deposition in an organic matrix, eventually eroding through the urothelium. Once exposed to the urinary milieu, precipitation of minerals and organic substances occurs based on urinary constituents. The process leading to RP formation is not yet fully defined, but one must consider an alternative theory based on a more vascular process. In short, formation may be RP due to a process similar to how atherosclerotic lesions form in arteries as the vasa recta that surround the tubules have turbulent flow, relative hypoxia, and hyperosmolarity which is an ideal environment for vascular injury and a calcifying process. The early events leading to RP and calcium oxalate stone formation has yet to be determined, but is likely multifactorial and represents an area of research fit for collaboration beyond our fellow urologic colleagues.

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Mechanism

Reactive oxygen species may unite many mechanisms by which calcium oxalate stones form

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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The pathogenesis of calcium oxalate nephrolithiasis remains a mystery, but the suggestion that it is simply due to perturbations in urinary super saturations remains an inadequate explanation (1). It is likely due to much more complex and nuanced mechanisms that incorporate inorganic and organic components. How these components propagate into Randall plaques or calculi or even where these stone-forming events occur (vasa recta, collecting ducts, or the basement membrane of the loops of Henle) is debatable. Metabolic derangements leading to uncontrolled reactive oxygen species (ROS) generation or a reduced antioxidant capacity to alleviate oxidative stresses may play a role in Randall plaque formation through tissue damage and/or ROS-induced altered gene expression. Markers of oxidative stress/damage (e.g., N-acetyl-β-glucoseaminidase, malondialdehyde, or β-galactosidase) have been detected in animal models with calcium oxalate nephrolithiasis. Further supporting this hypothesis, medications (angiotensin converting enzyme inhibitors or statins) known to reduce oxidative stresses or diets high in antioxidants have been shown to decrease nephrolithiasis in experimental models. The mechanism by which increased oxidative stress/damage leads to Randall plaquess is unclear, but likely represents some combination of altered gene expression, tissue remodeling, biomineralization, and inflammation. Even the mechanistic timing is unknown as to whether the oxidative damage occurs first and then leads to Randall plaque formation or vice versa. This represents an area of promise and continued research is needed across several intersecting disease processes (hypertension, hyperlipidemia, diabetes mellitus, obesity, nephrolithiasis, etc) that likely have a shared mechanism/metabolic abnormality.

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Mechanism

The link between metabolic syndrome and nephrolithiasis: a white whale for understanding urinary stone disease

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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The incidence of nephrolithiasis has risen steadily over recent decades, as has the rates of the metabolic syndrome. Several factors have contributed to this, including the increased incidence of obesity; more than 30% of Americans have a body mass index (BMI) >30. The etiologies for both are complex and multifactorial, but a consistently demonstrable relationship does exist between the two. Patients with either affliction are prone to the other, with the highest incidence of stones found in those with several factors leading to the metabolic syndrome (1). Furthermore, several of the disease process (hypertension, atherosclerosis, diabetes mellitus, or dyslipidemia) related to the metabolic syndrome each are associated with an increased risk of nephrolithiasis. The reason for this is unclear, and likely goes beyond just poor dietary factors leading to serum and urine chemistries ideal for renal calculus formation. No underlying mechanism has yet been identified correlating these processes to one another. Continued basic and translational research is needed to understand how these diseases are linked. While a growing body of epidemiologic data supports these associations, they only serve to highlight the importance of further research to truly understand the underlying mechanisms driving these links. As translational research continues to expand in the field of nephrolithiasis, newly generated knowledge will fill the gaps brought to light by these epidemiologic data.

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Mechanism

Moderation may be the best fad diet for urinary stone disease

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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With recent increases in obesity throughout the United States and other industrialized nations, fad diets continue to gain in popularity. Although little formal research has been undertaken regarding the health impact of these fads, each has its own questionable health benefits as well as potential health risks, including lithogenic effects (1). Furthermore, many are simply iterations of the same core fad diet tenet. For instance, several fad diets focus on low carbohydrates (Dukan, Atkins, or zone diets) which are often accomplished through increased intake of animal protein. Although little data exists regarding each diet type, one could reasonably expect an increased metabolic acid load from the animal protein leading to decreased urinary citrate and increased urinary calcium. The opposite problem can also exist. When not balanced with adequate calcium intake with meals, other diets focusing on the complete omission of animal protein, namely veganism, potentially have an increased lithogenic effect through increased uric acid and oxalate consumption. Regarding oxalate, it is often difficult for patients to identify high oxalate foods and successfully reduce them. Therefore, for patients with hyperoxaluria we recommend that these patients focus on consuming calcium with their meals through either a dairy product or oral, chewable calcium tablets (like calcium carbonate). This dietary calcium will bind the dietary oxalate and prevent its gastrointestinal absorption and subsequent renal excretion. Unlike most fad diets, a popular diet that likely does exert a protective effect on nephrolithiasis is the traditional Mediterranean diet. This, as with most balanced diets, focuses on moderation and overall healthy eating habits.

Dietary advice is the first line prevention of nephrolithiasis and a healthy stone sensitive diet with low sodium, moderate protein, moderate calcium, and good oral fluid intake is likely to offer a greater medical and weight loss benefit than most current popular fad diets.

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Mechanism

Mast cell activation syndrome

Vicki Ratner

Interstitial Cystitis Association of America (ICA), McLean, Virginia, USA

Correspondence to: Vicki Ratner, M.D. Founder and President Emeritus, Interstitial Cystitis Association of America (ICA), 1760 Old Meadow Road, suite 500, McLean, VA 22102, USA. Email: VRatner@aol.com.

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It has been over 30 years since the Interstitial Cystitis Association of America (ICA) was established in 1984. Although a great deal more is understood about interstitial cystitis/bladder pain syndrome (IC/BPS), the cause and cure of this condition remains unknown. One hypothesis regarding etiology that appears to have been overlooked or dismissed is a theory that involves mast cells. It is worthwhile taking a second look.

Mast cell activation syndrome (MCAS)

Mast cells are found in all tissues of the body and are typically in close proximity to blood vessels and nerves. "The clinical presentation of MCAS is very diverse, due to both the widespread distribution of mast cells and a great heterogeneity of aberrant mediator expression patterns, (therefore) symptoms can occur in virtually all organs and tissue" (1). When mast cells degranulate, there are a wide range of inflammatory mediators released in various combinations. These include histamine, heparin, proteases, tryptase, cytokines such as TNF alpha, certain prostaglandins, leukotrienes and many others (1-4). In fact, there are over 200 inflammatory mediators that have been identified thus far. MCAS is distinct from mastocytosis in that it does not include the entire body, but may involve a specific organ, such as the bladder or GI tract. It is a condition of inappropriately activated mast cells (5). If MCAS does play a role in IC/BPS, the number of mast cells on bladder biopsy may be increased in IC/BPS patients or the mast cell population may not be increased, but may be hyper-responsive and degranulate more frequently in response to a trigger stimuli. It is also possible that mast cells may release inflammatory mediators without degranulation of the mast cell (1-3). Genetic abnormality is likely to play a role as well (5).

To date, I am not aware of any large-scale study that compares the number of mast cells in the bladder biopsy of IC/BPS patients versus the number of mast cells in patients with a normal bladder biopsy using up-to-date staining techniques. H&E staining is the typical stain used in the pathology lab, which is not adequate to identify the correct number of mast cells on biopsy. Some urologists request the use of tryptase or toluidine blue, and while this improves accuracy, the most sensitive and accurate stain available today is CD-117 (2).

In the bladder, mast cells are in close proximity to neurons, as they are in all areas of the body. They all communicate with each other. Mast cells can both degranulate as well as transgranulate via the formation of filipodia (thin, finger-like projections) that attach directly to the neuronal membrane (6). The inflammatory mediators, once released into the bladder could initiate urgency, frequency, supra-pubic pressure and pain of varying degrees. This would depend on the number of mast cells that degranulate, those that release inflammatory mediators without degranulation, the type of inflammatory mediators released, and/or mast cells that are normal in number but are hyper-responsive and degranulate more frequently. Transgranulation has already been shown to occur in the normal bladder *in vivo* (7). Via transgranulation, mast cell inflammatory mediators are taken up directly by the nerve via endocytosis and released into the cytoplasm of the nerve, or found in membrane-bound organelles within the nerve (6). This could trigger pain fibers in the bladder and the electrical impulses would then travel via the ascending pain pathway from the bladder to the spinal cord and on to the central nervous system (CNS), targeting the limbic system, thalamus and cortex.

In the CNS, transgranulation has been shown to

occur as well (6), but what role the mast cell fragments play within the CNS is unclear (8). The phenomenon of transgranulation in the CNS has been found in both normal and diseased states. (6,8). This could be the case in other organs as well. However, we are primarily looking at mast cells in the bladder and mast cell degranulation in this case, with transgranulation providing a pain pathway to the CNS from local symptoms in the bladder.

Mast cells and mast cell degranulation may provide a useful way of evaluating patients who likely have IC/BPS. Products of mast cell degranulation in the urine, for example histamine, N-methylhistamine and others, can be extremely difficult to measure because of their short half-lives. This may contribute to false negative results. However, accurate testing of many urinary inflammatory mediators have been successfully measured (3) and objective findings could yield results that might:

(I) Explain the etiology or an etiology of IC/BPS;
(II) Provide diagnostic testing, and/or a marker for the condition;
(III) Provide treatment directed at the specific inflammatory mediators found to be abnormally high;
(IV) Reduce the amount of time to diagnosis, and possibly categorize the disease.

Measuring the number of mast cells in the biopsies of IC/BPS patients and controls using the stain CD-117 is a relatively simple trial that could be easily undertaken. Inflammatory mediators should then be measured in the urine of both IC/BPS patients and controls to further evaluate the potential differences between these two groups. If there appears to be no difference between the two groups, next steps should include use of an electron microscopy using time lapse photography on bladder biopsies from IC/BPS patients and controls to see if the mast cells in the biopsies of IC/BPS patients are degranulating at a more frequent rate, or releasing inflammatory mediators without degranulating compared to the control group.

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Diagnosis and treatment of benign prostate hyperplasia in Asia

Keong Tatt Foo

Department of Urology, Singapore General Hospital, Yong Loo Lin School of Medicine, National University of Singapore, and DUKE-NUS Graduate Medical School, Singapore

Correspondence to: Dr. Keong Tatt Foo, MBBS, FRCS. Department of urology, Singapore General Hospital, 20 College Road, Academia, Singapore 169856, Singapore. Email: keongtatt@gmail.com.

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Introduction

Benign prostatic hyperplasia (BPH) is a common disease, not only in Asia but worldwide. The spectrum of disease may vary in differently region, but the basic pathophysiology is the same. To manage the disease, we need to define what it is, before the diagnosis. Management would be according to the basic fundamentals of good clinical practice. That is, whatever we do is for the benefit of the patient that we should manage the patient as a whole, as taught by Professor Jieping Wu, a pioneer of modern Urology in China.

Definition of BPH

Clinical BPH has been defined as benign prostatic enlargement (BPE) (1), but in our practice and clinical observation, many patients with smaller prostates less than 20 grams may still cause obstruction and symptoms. In our study to characterize normal prostate on transabdominal ultrasound (TAUS) on patients who presented with asymptomatic microscopic haematuria who had flexible cystoscopy done, we could find only four normal patients out of 77 patients studied (2). Many patients with small prostate can still have obstruction, if not symptoms due to prostate adenoma, and this may be the cause of the microscopic haematuria. The adenoma causes obstruction by virtual of where it is sited, rather than its size. An adenoma siting at the strategic bladder outlet would cause more obstruction than one sited in the lateral lobe of the prostate. When it arises from the middle and protrudes into the bladder, it forms the classical median lobe obstruction due to the ball valve effect (3). If it is sited beneath the bladder neck, in the subcervical region, it would lift the bladder neck high and causes obstruction. Thus the previously described bladder neck obstruction, in relatively young patients is not due to primary bladder neck pathology, but is essentially a variant of BPH. Bladder neck dyskinesia, as a primary diagnosis is rare.

In transurethral enucleation and resection of prostate, the adenoma can be separated from the false capsule, and often the adenoma coalesces together to form multiple adenomata and cause obstruction. This can be seen on histology of the BPH, which is described as nodular BPH by the pathologist.

The adenoma is essentially similar to that of the fibroadenoma of the breast, except that the prostate is sited at the bladder outlet and causes varying degree of obstruction, and may further progress.

Thus we can define clinical BPH, simply as a prostate adenoma or adenomata, irrespective of size, causing obstruction to the bladder outlet, with or without symptoms.

Diagnosis of BPH

With the above definition, BPH can be diagnosed with some confidence using transabdominal or transrectal ultrasound (TRUS) and estimating the urinary flow rate. TAUS is less invasive than TRUS. In Asian region patients has lower body mass index (BMI) and imaging the prostate with some accuracy is seldom a problem, as in obese patients. TAUS can easily be repeated.

As BPH can present with or without symptoms, therefore relying on the International Prostate Symptoms Score (IPSS) solely, to decide on treatment is not reliable. Digital rectal examination (DRE) is inaccurate; estimation

of size is inaccurate especially if big. Further, a seemingly small prostate can also cause obstruction and symptoms. The DRE is mainly to assess the consistency of the prostate to detect possible carcinoma.

Although lower urinary tract symptoms (LUTS) is the commonest presentation of BPH, it is not diagnostic as there are many other causes of LUTS, ranging from bladder dysfunctions due to diabetes and age, neurogenic bladders and urethral strictures. BPH can also present with acute retention of urine (AUR) without previous history of LUTS. In our study on AUR in Singapore, 50% denied any history of LUTS before the acute episode (4). A more serious complication is that of chronic retention of urine which is often seen in less developed part of Asia. This would result in significant obstruction leading to back pressure changes with severe hydronephrosis and chronic renal impairment. In a report from Sri Langka, 30 patients with chronic retention of urine were seen within a period of 1 year, presenting with nocturnal enuresis (5). With the advent of using prostate specific antigen (PSA) as a marker for detecting possible prostate cancer, many asymptomatic patients present with elevated PSA. In a most recent report of TRUS biopsy for elevated PSA in Taiwan, out of 12,968 patients biopsied, 36% of patients were positive (6). Presumably the rest is mainly due to BPH or BPH with chronic prostatitis.

Thus, after taking a detailed history and physical examination, a clinic ultrasound would be useful. In fact, it is essential in the proper diagnosis of BPH to differentiate it from the many other pathologies. The ultrasound machine need not be sophisticated, and often an old machine from the diagnostic radiology would suffice, for the measurement of the size (PV) and shape, looking at the intravesical prostatic protrusion (IPP). It can also be used for estimation of the postvoid residual urine (PVR).

IPP is the distance measured from the inner most tip of the prostate to the base, at the circumference of the bladder, seen on the sagittal view of the prostate ultrasound (3). The measurement is done in patient with a comfortably full bladder (7). Normal prostate with no BPH, is inverted similar to the female bladder neck and the flow rate would also be normal. IPP has 100% specificity and positive predictive value in the diagnosis of BPH (2), Therefore patients with LUTS but no BPH can easily be differentiated in the clinic, and other possible causes of LUTS, such as over active bladder or nocturnal polyuria can then be suspected and managed accordingly.

The urinary flow rate can be determined with the simple uroflow machine. If not available, the average flow rate can be done easily with a measuring jar and using a timing device (the stop watch or the smart phone) which is readily available, even in the remotest part of Asia.

Predicting obstruction and progression of BPH

Patients with IPP can further be graded according to the degree of IPP to predict obstruction. It has been established that the greater the IPP the more the obstruction on pressure flow studies (8). Of 200 patients studied, for grade 1 IPP ≤5 mm, 79% of patients are not obstructed, whereas for grade 3 IPP more than 10 mm, almost 94% of the patients are obstructed urodynamically. IPP has also been found to be a good predictor of success in trial off catheter after episode of AUR in a study of 100 patients (6). For patients with grade 1 IPP, 36% failed trail off, while 67% failed if there is a grade 3 IPP.

As IPP is related to obstruction, it is also related to the progression of the disease BPH. Our studies showed that of 259 patients with a mean follow-up of 32 months, for grade 1 IPP, 6% progressed in terms of the need for surgery and complications. Whereas if it is a grade 3 IPP, 44% of patients will progress (9).

However, patients should not be treated just on the findings of IPP alone, even though with grade 3 IPP, 44% of patients will progress with deterioration of symptoms, increased PVR or retention of urine, 56% of them do not progress. Therefore, for a more balanced decision making, treatment of BPH should be according to the severity of the disease as a whole.

Classifying the severity of BPH

Fundamentally the prostate adenoma (clinical BPH) causes obstruction and symptoms. Obstruction is more important than symptoms, as obstruction if not relieved, would progress and cause organs dysfunctions.

Therefore, the severity of BPH can be classified according to the obstruction and symptoms. The symptoms can be quantified with the IPSS, and the quality of life index (QOL). There is poor co relation between IPSS and obstruction and therefore the symptoms score should not be used as the sole parameter in the decision making on further treatment (10). Also the IPSS is not related to QOL, which depends on patients' life style and occupation. A retiree with nocturia 4 times may not be bothered while a young executive with a score of nocturia 2 times, may be

Table 1 Staging of BPH

Stage	Significant obstruction	Bothersome symptoms	Treatment
I	Absent	Absent	Watch & counsel
II	Absent	Present	Medical treatment
III	Present	Irrespective	Surgical options
IV	Complications of BPH		Surgery

Significant obstruction, PVR >100 mLs, or max voided volume <100 mLs; bothersome symptoms, QOL ≥3; BPH, benign prostatic hyperplasia; PVR, postvoid residual urine; QOL, quality of life.

bothered. Therefore QOL is more important than IPSS in the assessment of symptoms.

Prostate adenoma (PA) causes varying degree of obstruction. Obstruction would be significant when there is organ dysfunction. The two main functions of the bladder are storage and emptying. When the emptying function is affected patient would develop persistent high residual urine. When the storage function is affected the maximum voided urinary volume would be low, and this can easily be measured. Thus significant obstruction can be defined as when there is persistent residual more than 100 mL and/or maximum voided volume less than 100 mL (10,11). With these cut off and definitions, the severity of BPH can be classified accordingly:

(I) Stage I would be a patient with no significant obstruction, and no bothersome symptoms;
(II) Stage II would be a patient with bothersome symptoms but no significant obstruction;
(III) Stage III would be a patient with significant obstruction, irrespective of symptoms;
(IV) Stage IV would be a patient with complications of BPH such as retention of urine, recurrent gross haematuria, urinary infection and bladder stones formation.

Generally, there is good concordance between the grade and stage of the disease. Stage I patients can be treated conservatively with advised on proper fluid intake and healthy life style. Stage I Grade 1 can be reassured and discharge from follow-up, while the stage I grade 2 or 3 patients need to be followed up at 6 months to 1 year interval as it is predicted that they are more likely to progress. Stage II patients can be treated with medication, while, Stage III grade 3 patients would be advised more aggressive treatment with surgery as an option. Stage IV patients would generally require surgical treatment (*Table 1*).

There would be some patients with persistently high residual urine (suspected staged III) but low grade IPP, and these patients would require flexible cystoscopy and/or urodynamics studies to detect hypo active bladder.

For Asian region, it is more practical to have flexible cystoscopies available, rather than investing in the urodynamic set up which is far more expensive and not specific. Often, the pressure flow study would show equivocal obstruction, or in patients with more severe obstruction with no IPP, they would not be able to void, and pressure flow study cannot be done. Some of these patients had been mistakenly treated as for hypocontractile or neuropathic bladder with long-term catheterization. A flexible cystoscopy would help in diagnosing mechanical bladder outlet obstruction in the 21% of patients who are still obstructed in spite of a low IPP (9).

Modalities of treatment

The natural history of BPH is that it is a slow progressive disease. The majority of patients will do well even without any active treatment. In one study on the 5-year follow-up of 107 patients with prostatism, presumably due to BPH, 32% improve, 52% remained stable and only 16% deteriorated and 9% required surgery (12).

These 16% who are going to deteriorate, can now be more confidently identified for more active treatment with our grading and staging of BPH (13). In that study of 408 patients, 59% of patients was treated conservatively, 32% with medications and 9% had TURP done, approximating the natural history closely.

The majority of patients do well or stable even without treatment, therefore conservative management should be the main stay in the treatment of BPH.

Conservative management

This would consist of reassurance and advice on fluid intake and healthy life style, such as regular exercise with walking, qigong, yoga or tai chi. These can help in reducing symptoms for patients with mild BPH, especially the low grade and low stage disease.

The concern of most patients who come to see the family doctor or the urologist, are whether they have cancer or whether they will develop kidney problems. With normal PSA and DRE, prostate cancer is less lightly. If there is no

persistent PVR more than 100 mL, most patients could be reassured, even though they may have some LUTS and bothersome symptoms. Advising more fresh fruits and vegetables in the diet and less red meat would be appropriate.

Medical treatment

There are two main groups of medications for treating BPH:

(I) The alpha blockers which relieve symptoms by blocking the sympathetic nerve endings at the bladder neck. They have not been shown to prevent progression of the disease (14). Therefore alpha blockers should be given only to patients who are bothered by their symptoms and not just symptoms score alone. Most literatures report the efficacy of the medication by the improvement in average reduction in symptom scores. How many patients are actually relieved of their bother, and whether the symptoms returned without the alpha blockers are not reported. It had been shown that patients with high grade IPP do not response as well to alpha blockers (15). This is due probably to the distorted bladder neck. If they are still bothered and developing bladder instability with deteriorating symptoms, surgery should be advised early.

Also patient should be informed of the efficacy of the medication and its possible side effects, that of hypotension, giddiness and possibility of falls. The final decision whether to take the medication or not should be that of the patient.

Patients who opted for the alpha blocker treatment should be given a trial of medication first for not more than 2 to 4 weeks to assess the effectiveness and the side effects. Only if patients are satisfied with the results, then they would be considered for long-term medication. Even then, patients should be advised that they may take the medications on when needed basis. In this way it would be more cost effective. Those patients with high grade IPP 2 to 3 should be followed up more closely at 6 to 12 months to monitor their progression.

For patients with prostate more than 30 to 40 grams, 5 alpha reductase inhibitors (5 ARI's) can be added.

(II) 5 ARI's: the two main 5 ARI's used in Asia are finasteride (proscar) and dutasteride (avodart). They act by preventing the conversion of testosterone to 5 hydroxytestosterone which stimulate the growth of BPH.

They have been shown to be effective only in patients with large prostate more than 40 grams, and not effective in patients with small prostate less than 30 grams, or with PSA less than 1.5 ug/L.

5 ARI's are expensive, considering the need for long-term treatment. Even though in some Asian countries, the cheaper generic versions are available, the side effects of the drugs are that of sexual dysfunctions with loss of libido and ejaculation failure and erectile dysfunction. Therefore the drug should be prescribed to patients only with large prostate and high stage disease, at risk of developing voiding or storage problems.

5 ARI's help to reduce the need for surgery for many patients, especially the older patients and those with co morbidities. However, not all patients with large prostate response to the 5 ARI's as the medication can shrink the size, but cannot alter the shape of the adenoma. In the flow dynamics of obstruction, the middle lobe distorts the flow, while the lateral compress the flow and distortion is more obstructive than compression. So even though the 5 ARI's may shrink the prostate, it cannot change the shape. Some patients, with protruding lobes may still continue to progress and this may lead to surgical intervention (16).

Surgical treatment

Surgery would ideally restore the prostate to normal shape (normal anatomy) to achieve normal functions. For that the best procedure would be the enucleation of the prostate adenoma/adenomata, be it by open method, laparoscopic or transurethral.

With understanding of the basic pathology, that BPH is not diffused enlargement, but nodular hyperplastic adenoma, to remove the pathology completely should be the goal of any surgical procedure. Incomplete removal would lead to recurrent symptoms and obstruction due to the progression of the residual adenoma.

Because of the irregularity of the adenomata, the problem with conventional TURP is that often, adenomatous tissue is left behind. To remove the tissue completely may lead to resecting too deep, and cause perforation of the false capsule leading to bleeding. To avoid this, varying amount of adenoma would be left behind leading to recurrent

problems, often many years later.

Therefore, retrograde enucleation of the adenoma would be the procedure of choice to remove the pathology tissue more completely. Also there would be less bleeding as the perforating vessels are diathermised at source, instead of being resected repeatedly (17).

Holmium laser enucleation of prostate (HoLEP) had been shown to have good long-term results, but for Asian countries, transurethral enucleation and resection of prostate (TUERP) would be more practical and more cost effective. This had been pioneered by Liu *et al.* in China, with good results (18). No extra instrument is needed. The prostate is enucleated in a retrograde fashion and with the lobe attached at the bladder neck; it can then be rapidly resected. Compared to conventional TURP, TUERP is better, as evidence by the fact that the flow rate is better and that the PSA, as a surrogate measure of prostate volume is statistically less than after TURP (19).

The incidence of post-operative incontinence is higher in the enucleation of prostate but often the incontinence is temporary. With better experience and technique of marking out the distal margin of the apical lobe and preventing tearing of the membranous urethra, the incidence of temporary incontinence can be reduced.

Currently, at the last EAU meeting in Madrid 2015, TURP is still considered as the gold standard for significantly obstructing prostate. The problem with TURP is the retreatment rate of 3-14.5% after 5 years (20) presumably due mainly to recurrent/remnant adenoma.

Apart from recurrent LUTS, another common presentation is that of painless gross haematuria, due to the congested neovascularity on the recurrent/remnant adenomatous tissue.

TUERP would help to reduce this problem.

The vaporization procedure, using various types of laser (KTP green light laser, etc.) and electrodes, though result in less bleeding than TURP, often also leave residual adenoma post procedure, and long-term results are not favorable compared to standard TURP (21).

Thus for Asian countries, TUERP with bipolar resection, using saline would be the way forward for the significantly obstructing prostate.

Comments

Clinic ultrasound is essential in diagnosing BPH.

The machine is also useful for assessing other urological problems such as urinary stone and haematuria and urinary infections. In Asia, an ultrasound machine in the clinic should have priority to the urodynamic unit which is far more expensive.

The phosphodiesterase type 5 inhibitor (PDE 5), tadalafil for medical treatment should be reserved for those who present mainly with erectile dysfunction and LUTS. It is probably effective only for patients with minimal BPH, small gland with minimal protrusion and obstruction.

The anticholinergics for patients with over active bladders, having frequency and urgency should be reserved for patients mainly with bladder problem and minimal BPH, with low grade IPP and low PV. It should be prescribed with caution in patients with high grade IPP as it may result in worsening of PVR and retention of urine.

The aim of surgery should be complete removal of the adenoma to minimized recurrent problem. Less minimally invasive procedures such as transurethral microwave thermotherapy, transurethral needle ablation, do not address the fundamental problem and do not have good long-term results.

Conclusions

BPH can be defined as prostate adenoma causing obstruction and can be diagnosed confidently with non-invasive transabdominal ultrasound in the clinic. The disease can then be graded according to the IPP on TAUS for predicting the obstruction and progression. Treatment can then be tailored to the severity of obstruction and symptoms. In this way, by considering the whole picture, BPH as a common disease, can be treated more cost effectively, avoiding overtreatment and under treatment.

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Footnote

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Treatment Progress

Erectile dysfunction: Doctors' perspectives on patients' concerns

Katherine L. Ji[1], Liang-Jun Gu[2]

[1]Managing Editor, Translational Andrology and Urology; [2]Peking Union Medical College Press. Beijing 100730, China

Correspondence to: Katherine L. Ji. Managing Editor, Translational Andrology and Urology. Email: tau@amepc.org.

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Erectile dysfunction is a problem which has become increasingly prevalent in modern societies. Although typically not life-threatening, it is of special concern because it can dramatically lower the quality of life and cause mental/social problems. In recent years, many new drugs and equipment have been developed for the management of ED. However, the proper application of these interventions is highly depended on the knowledge, awareness and attitudes toward of clinicians towards ED.

Recently, a questionnaire-based survey was conducted targeting clinicians during the Fifth Great Wall Translational Andro-Urology Forum (GTAUF2012) in conjunction with the launch of the new journal Translational Andrology and Urology (TAU) held in Hainan International Conference and Exhibition Center, Haikou, China on March 8-12, 2012. A total of 147 clinicians responded to the survey, although not all the questions listed in the form were answered and the quality of a small proportion of the feedbacks might be questionable.

According to the data obtained from the survey, most respondents reported that less than 200 ED patients visited their outpatient departments every month (<100 visits, n=71 (48.30%); 100-200 visits, n=48 (32.65%)]. Twenty clinicians (13.61%) reported that their monthly outpatient ED visits reached 200-500 and only seven respondents (5%) had to manage more than 500 patients every month, which may be explained by the specialties of their institutions and by the possibility that the questionnaires were not filled in by professionals in this field (*Figure 1A*).

For the age distribution, ED was most common in the 40-50 year age group (n=62.5, 42.52%), followed by 30-40 year age group (n=45.5, 30.95%). Patients aged 50 years or higher accounted for 21.09%, whereas those younger than 30 years were least (n=8, 5.44%) (*Figure 1B*). The most common cause of ED in men was stress (n=74, 50.34%), followed by underlying diseases (n=51, 34.69%) such as diabetes. Less than 10% of ED patients visited their doctors due to trauma (*Figure 1C*). The main complaint evoked by the patients was "ED affects sexual life (not for birth)" (which accounted for about 47.21%). About one fourth (n=25.8, 25.92%) of the patients visited their doctors because they felt "ED takes away their feeling of being a man". About 17.55% (n=25.8) of the patients felt "mental stress due to various reasons" (*Figure 1D*). The majority of ED patients spent 1000-5000 RMB yuan for the treatment of their disease: 5000-1000 RMB yuan accounted for 52.38% (n=77) and 1000-5000 RMB yuan 31.97% (n=47) (*Figure 1E*). For severe cases, surgical treatment would be accepted under two conditions: "medical treatment and other therapies have failed" (n=67, 45.58%) and "huge mental stress due to conditions such as divorce" (n=56.5, 38.44%). Only 15 patients (10%) might seek surgical treatment due to severe congenital conditions (*Figure 1F*). The major factor that may affect the acceptance of surgical treatment was the effectiveness and side effects of a specific surgery (n=94, 63.95%), although the previous success cases (n=30, 20.41%) and costs (n=20, 13.61%) could also affect decisions in a few patients (*Figure 1G*).

In summary, quite a few mid-aged ED patients may visit their doctors due to the impaired quality of life and other mental/social problems. Although most patients would prefer medical treatment costing 1,000-10,000 RMB yuan, quite a few severe ED patients may accept surgical treatment, with their main concerns on the effectiveness and side effects rather than costs. Since ED is caused by diverse causes and currently available drugs have many limitations, surgical treatment based on more sophisticated equipment and procedures may provide more promising solutions.

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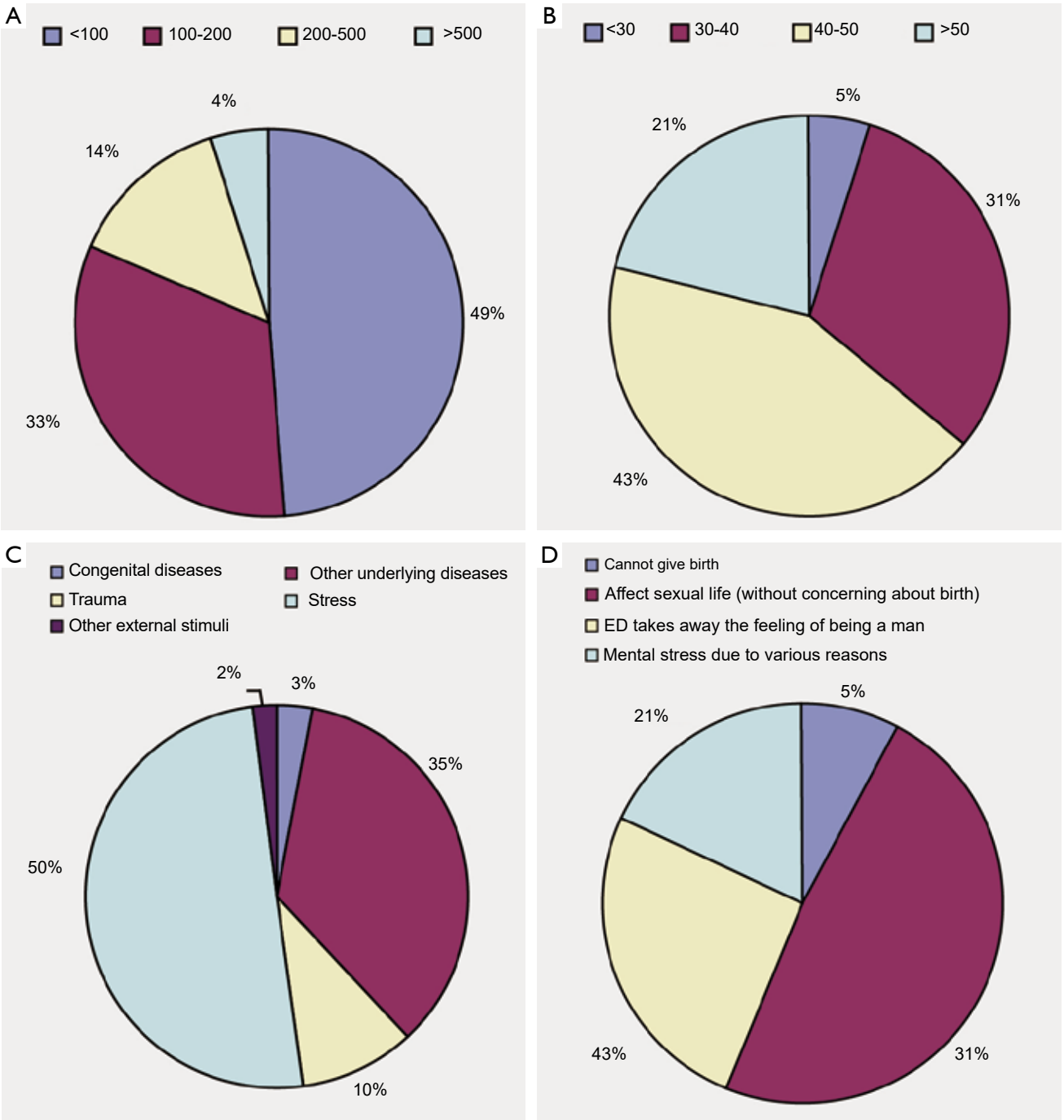

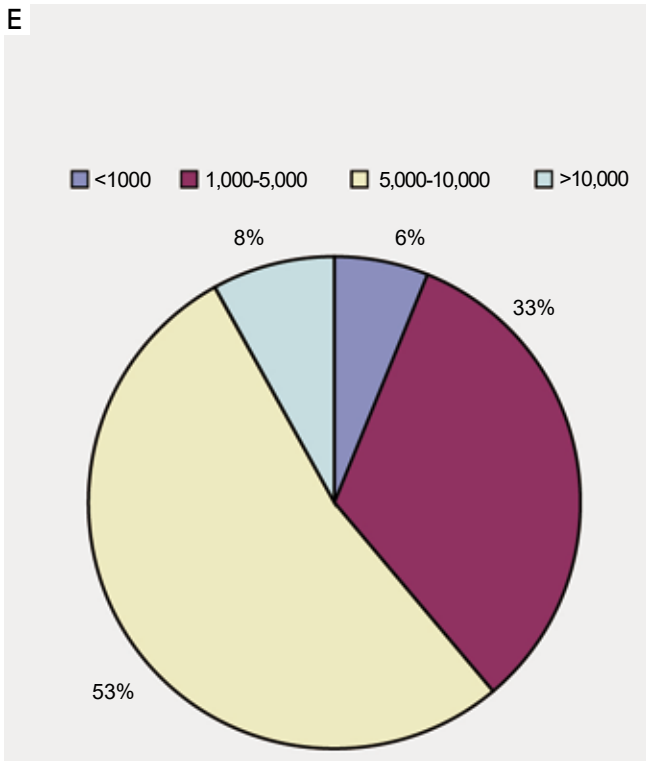

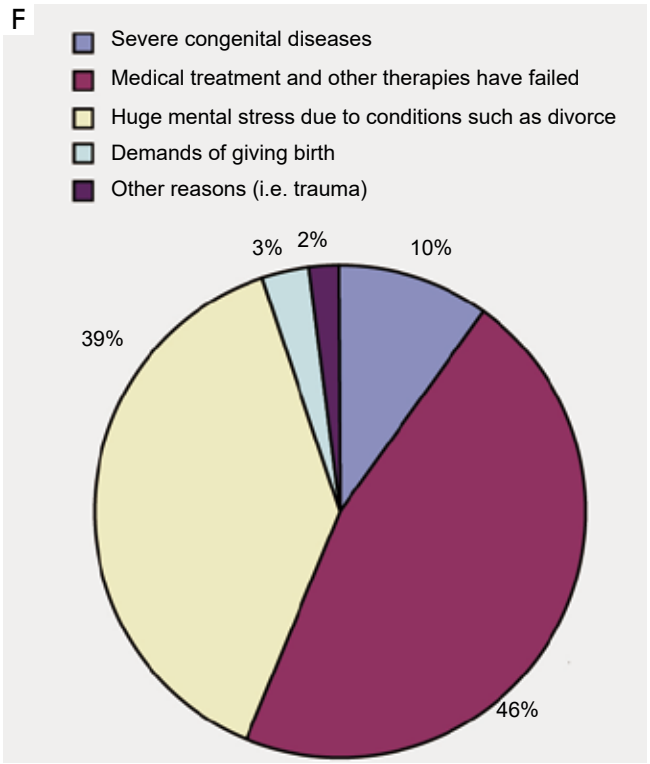

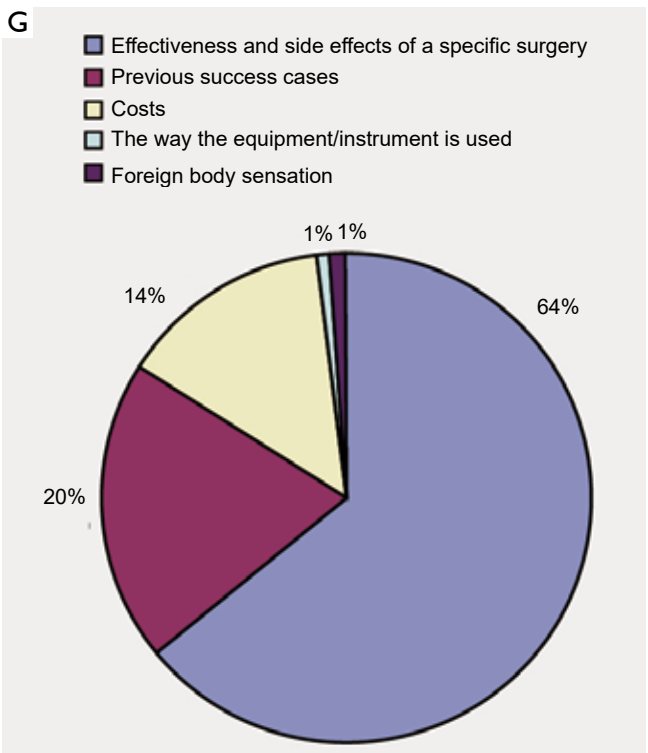

Figure 1 A: Outpatient ED visits per month; B: Age distribution of ED patients; C: Causes of ED; D: Main complaints of ED patients; E: Costs of ED treatment; F: Under which condition will an ED patient accept a surgery; G: Factor that may affect the acceptance of surgical treatment

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Treatment Progress

Continuous or intermittent? On the dosing schedule of sunitinib for advanced renal cell carcinoma

Masahiro Nozawa, Hirotsugu Uemura

Department of Urology, Kinki University Faculty of Medicine, Japan

Correspondence to: Masahiro Nozawa, MD, PhD. 377-2 Ohno-Higashi, Osaka-Sayama, 589-8511, Japan. Email: nozawa06@med.kindai.ac.jp.

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Sunitinib is globally approved for treatment of advanced renal cell carcinoma (RCC) at a dosage of 50 mg/day with four weeks on treatment and two weeks off, based on a randomized phase III trial in which its superiority over interferon alpha was established as first-line therapy for patients with metastatic RCC (1). On the other hand, continuous daily dosing of sunitinib at a dosage of 37.5 mg/day may be expected to provide consistent antitumor activity with a better safety profile compared with the 50 mg/day intermittent schedule according to two phase II trials (2,3). The recently published paper reported the result of a very interesting randomized phase II study called "Renal EFFECT Trial", in which the efficacy and safety of sunitinib was directly compared between the 50 mg/day intermittent schedule and the continuous 37.5 mg/day as first-line therapy for patients with advanced RCC (4).

In this study, patients with treatment-naïve, clear cell advanced RCC were randomly assigned in a 1:1 ratio to receive sunitinib 50 mg/day with four weeks on treatment and two weeks off (schedule 4/2) or 37.5 mg/day on a continuous daily dosing schedule (CDD), with 146 patients in each arm. The primary end point was time to tumor progression (TTP). As a result, although statistically not significant, a longer TTP and progression-free survival (PFS) was observed with the 4/2 schedule. Median TTP in the 4/2 schedule and CDD arms was 9.9 months (95% CI, 7.0 to 13.4 months) and 7.1 months (95% CI, 6.8 to 9.7 months), respectively (hazard ratio [HR], 0.77; 95% CI, 0.57 to 1.04; P=0.090). Median PFS was 8.5 months (95% CI, 6.9 to 11.1 months) and 7.0 months (95% CI, 6.0 to 8.7 months) in the schedule 4/2 and CDD arms, respectively (HR, 0.77; 95% CI, 0.58 to 1.02; P=0.070). No significant difference between the schedule 4/2 and CDD arms was observed in objective response rate (32% and 28%, respectively), stable disease rate (43% and 49%, respectively), or overall survival (median, 23.1 and 23.5 months, respectively).

Patient baseline characteristics were similar between both arms, although a slightly higher number of patients had a lower Karnofsky performance status, MSKCC poor risk disease, and liver metastases in the CDD arm compared with the schedule 4/2 arm. When analyzed by the MSKCC risk criteria, however, the relative increase in TTP with the 4/2 schedule was most pronouncedly shown in the favorable-risk (HR, 0.56; 95% CI, 0.29 to 1.07; P=0.075) rather than in the intermediate or poor-risk group. Moreover, in the multivariable analysis which assessed an independent relationship for each variable studied among a range of pretreatment clinical features, the trend for longer TTP (HR, 0.74; 95% CI, 0.53 to 1.01; P=0.061) and PFS (HR, 0.75; 95% CI, 0.55 to 1.02; P=0.071) with schedule 4/2 was observed. Predictors for TTP were baseline lung or bone metastases within the multivariable analysis.

What about safety and tolerability? Median treatment duration was five months (range, <1 to 26 months) and six months (range, <1 to 25 months) in the 4/2 schedule and CDD arms, respectively. There were no significant differences between both arms in incidence of commonly reported treatment-related adverse evens of any grade or grades 3 to 4. Eleven percent and 15% of patients discontinued treatment because of adverse events, 65% and 62% had at least one dose interruption, and 36% and 43% had a dose reduction in the 4/2 schedule and CDD arms, respectively. However, the median relative dose intensity

of sunitinib was higher with the 4/2 schedule (91%) than CDD (78%), which suggests that maintaining the dose may be more difficult in the continuous dosing regimen rather than in the intermittent. The presence of a certain off-treatment period in the regimen may be of value to maintaining the dose. This hypothesis may be sustained by the observation that patients on the 4/2 schedule showed a reversible on/off effect of self-reported fatigue and other symptoms, whereby the symptom scores were better at the beginning of each treatment cycle following the two-week break compared with scores of day 28. Finally, the 4/2 schedule was statistically superior to the CDD regimen in time to deterioration, a composite end point comprising death, progression, or disease-related symptoms (HR, 0.77; 95% CI, 0.60 to 0.98; P=0.034).

In conclusion, there was no benefit in efficacy or safety for 37.5 mg/day continuous dosing of sunitinib compared with 50 mg/day with four weeks on treatment and two weeks off. This paper emphasizes the importance of assessing new dosing strategies in randomized studies before implementing them in clinical practice.

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Footnote

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Treatment Progress

Modifying sunitinib schedule in advanced kidney cancer patients: Reflections from the renal EFFECT trial

Camillo Porta, Carlo Ganini, Chiara Paglino

Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Pavia, Italy, and Italian Nephro-Oncology Group/Gruppo Italiano di Oncologia Nefrologica (G.I.O.N.), Pavia, Italy

Correspondence to: Camillo Porta, MD. Medical Oncology, I.R.C.C.S. San Matteo University Hospital Foundation, Piazzale C. Golgi, 19, 27100 Pavia, Italy. Tel: +39-0382-501355; Fax: +39-0382-525240. Email: c.porta@smatteo.pv.it.

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On March 19th 2012, the results of the Renal EFFECT trial were finally published ahead of print by the authoritative *Journal of Clinical Oncology* (1).

The Renal EFFECT trial was a randomized phase II trial of sunitinib given to advanced renal cell carcinoma (RCC) patients, either according to the standard schedule (50 mg daily, 4 weeks on, 2 weeks off) or according to a modified schedule, with sunitinib given continuously at the reduced dose of 37.5 mg daily.

Even though the declared primary end-point of the study was time to progression (TTP), and despite authors claimed that "*this trial was not designed to be either a superiority or a noninferiority trial*" (1), in practical terms the study was supposed to answer a completely different question, i.e., is the continuous dosing schedule equieffective, but safer, as compared to the standard schedule?

Let's start to analyze the results of this study in terms of efficacy.

Median TTP was 9.9 months for the classical schedule *vs*. 7.1 months for the continuous daily dose schedule; consistent with the TTP analysis, a longer progression-free survival (PFS) was observed in patients treated with the classical schedule: 8.5 *vs*. 7.0 months; overall survival, on the other hand, was almost superimposible between the two treatment arms (23.1 *vs*. 23.5 months) (1).

As a whole, the observed better performance in terms of efficacy outcome measures (TTP and PFS) of the classical schedule is someway in agreement with a recent pharmacokinetic/pharmacodynamic meta-analysis aimed at investigating the relationship between sunitinib exposure and efficacy and tolerability endpoints (2); according to such meta-analysis, the importance of maintaining patients on a 50 mg dose of sunitinib and striving to avoid unscheduled dose titrations (as well as unscheduled treatment interruptions) during treatment, clearly emerged (2). Indeed, patients with the highest exposure to sunitinib displayed longer TTP, longer OS, a higher probability of a response, and greater tumor size decreases (2).

Despite that, the absolute PFS values observed in the two treatment arms of the renal EFFECT trial (1) were someway disappointing; no one would infact consider the 8.5 months of PFS achieved by the standard arm a satisfactory outcome for first line sunitinib, irrespective of any statistical consideration.

And indeed, all the efficacy figures reported in the renal EFFECT trial were lower than those accomplished by sunitinib (given according to the standard schedule) within the pivotal registration trial, as summarized in *Table 1* (3).

These results, however, are probably relatively easy to explain. Indeed, we agree with study investigators that "*… is not an unusual observation, when progressing from more highly selective pivotal phase III efficacy trials to subsequent effectiveness studies with broader elegibility criteria …*", to sometime observe a relevant drop in efficacy measures (1).

Furthermore, as again stressed by the authors in their discussion, at the time of the conduction of this trial, a range of treatment options were already available, inevitably leading to a selection bias, not to take into account the possible temptation to switch therapy early (1), instead of trying to optimize treatment adequately, and aggresively managing adverse events to keep patients on treatment.

The safety profile of the two schedules is a completely

Table 1 Phase II Renal EFFECT trial: Comparison with sunitinib registration phase III study

	Renal EFFECT study (1)		Phase III trial *vs*. Interferon (3)
	Sunitinib 50 mg daily, 4 weeks on, 2 weeks off (n=146)	Sunitinib 37.5 mg daily, continuous dosing (n=146)	Sunitinib 50 mg daily, 4 weeks on, 2 weeks off (n=375)
Previous nephrectomy	80%	77%	91%
MSKCC risk score			
Good	29%	26%	38%
Intermediate	62%	60%	56%
Poor	8%	14%	6%
Median relative dose-intensity	90.8%	77.5%	n.r.
Median TTP (months)	9.9	7.1	n.r.
Median PFS (months)	8.5	7.0	11.0
Median OS (months)	23.1	23.5	26.4
ORR	32.2%	28.1%	31%

MSKCC: Memorial Sloan-Kettering Cancer Center; TTP: time to progression; PFS: progression-free survival; OS: overall survival; ORR: objective response rate

different, and more complex, issue.

Indeed, the study showed no significant between-arm differences in the incidence of any grade 3 or 4 adverse events, or of any grade 3 or 4 laboratory abnormalities; furthermore, as far as the rate of treatment discontinuations due to adverse events, it was 11% and 15% in the classical and continuous dosing schedule, respectively, another surprising (and someway unexpected) finding (1). Finally, a superiority of the standard schedule over the modified one in time to deterioration (i.e., a composite end-point of death, progression and disease-related symptoms) was observed (1).

For sure, the lack of the two weeks' rest in the modified schedule have played a role, not allowing an adequate recovery from sunitinib-related adverse events. Furthermore, as already clearly evidenced from everyday clinical practice, multiple and prolonged nonsevere toxicities may lead to a more deleterious impact on patients' quality of life, than a single, severe, but short-term, toxicity.

At this point, a key question remains unanswered: how to ameliorate the safety profile of sunitinib, to reduce unnecessary (and possibly detrimental) dose reductions and treatment interruptions?

A population pharmacokinetic analysis of data from studies performed in healthy volunteers and patients with cancer treated with sunitinib clearly showed a high inter-patient variability in pharmacokinetics, with coefficients of variation in the range of 40-60%, meaning that certain patients in a given population treated with the same dose/schedule may experience increased exposure to sunitinib. For example, it has been calculated that approximately 8% of patients given sunitinib 50 mg QD would have at least as much exposure (AUC) as a typical individual receiving a 75 mg QD dose (4). Furthermore, this population pharmacokinetic analysis identified female gender and low body weight as covariates that significantly increase exposure to sunitinib (4).

An interesting report from a Dutch group already raised the issue that sunitinib dosing schedule (the classical 50 mg daily, 4 weeks on, 2 weeks off) could be suboptimal for unselected mRCC patients; indeed, a number of patients are initially overtreated resulting in unnecessary adverse events, while other patients who do not experience any toxicity may be undertreated (5). With the use of the fixed dosing regimen, similarly to the population pharmacokinetic study addressed above, the authors found a highly significant correlation between severe sunitinib-related toxicity and patient characteristics such as BSA, female gender, and high age (5).

We cannot but agree with the authors' conclusions that attempts to optimise the dosing schedule of sunitinib in unselected metastatic RCC patients are warranted (5).

As a whole, all the above data clearly suggest that the modified schedule used in the renal effective trial did not achieve the goal of being better tolerated and equieffective,

as compared to the standard schedule, and that the idea itself of giving sunitinib (and perhalps also all the other targeted agents presently used in RCC) at a fixed dose makes little sense, if any.

Indeed, alterntive schedules and dosing (e.g., on the basis of BSA) should be pursued, but will it be so?

Probably not, unfortunately, thus leaving patients experiencing unnecessary toxicities and detrimental dose reductions and treatment discontinuations.

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Treatment Progress

The complexity of sunitinib dosing in renal cell cancer patients

Ingrid M.E. Desar[1], Sasja F. Mulder[1], Peter F.A. Mulders[2], Carla M.L. van Herpen[1]

Departments of Medical Oncology[1] and Urology[2], Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands
Correspondence to: Ingrid M.E. Desar. Departments of Medical Oncology, Radboud University Nijmegen Medical Center, PO box 9101, 6500 HB Nijmegen, the Netherlands. Tel: +31 24 3610353; Fax: +31 24 3540788. Email: i.desar@aig.umcn.nl

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Sunitinib is an oral multityrosine kinase inhibitor, targeting - among others - vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). Sunitinib is one of the first so called targeted therapies which is approved as first line treatment for metastatic renal cell carcinoma (mRCC), and for second line in Gastro intestinal stromal tumors (GIST) and Pancreatic neuroendocrine tumors (PNET). Its introduction in 2006 introduced a new era in the treatment of mRCC, but also raised a lot of clinical relevant questions. One of these is which dosing schedule is most efficient with the lowest toxicicity and the best quality of life. The approved schedule for sunitinib is 50 mig oid in the so called "4 weeks on and two weeks off" (4/2 schedule). This is a remarkable schedule against the background of the Von Hipple Lindau (VHL) mutation induced overexpression of angiogenic vascular endothelial growth factor (VEGF) in clear cell RCC, which is the main target of sunitinib. Furthermore, in GIST it has been showed that during the two weeks off period the intratumoural metabolic activity as measured by FDG-PET can increase (1).

Motzer *et al*. addressed this question in The *Journal of Clinical Oncology* (2) by publishing a phase II randomised study comparing the approved daily 50 mg dose oid 4/2 schedule with a continuous daily dose (CDD) schedule of 37.5 mg oid in 292 treatment naïve clear cell mRCC patients. No significant difference in median time to progression (TTP, defined as time between random assignment and documented progression) or median progression free survival (PFS), median overall survival (OS) and objective response rate (ORR 4/2 *vs*. CDD; 32% *vs*. 28%) was found, although a trend towards a longer TTP in the 4/2 schedule patients was mentioned [9.9 *vs*. 7.1 months, Hazard Ratio (HR) 0.77, P=0.09].

Although randomisation was stratified according to their MSKCC risk category, more patients in the CDD group were classified as poor risk (14% *vs*. 8%), with worse clinical condition (Karnofsky score 70 12% *vs*. 3%) and presence of liver metastases (25% *vs*. 16%). Both univariable and multivariable analyses did not show independent relationships, although again a trend towards longer TTP was confirmed. Time to deterioration, one of the secondary endpoints assessed in a post hoc analysis, which was a composite endpoint of death, progression and self reported disease-related symptoms was longer with the 4/2 schedule than with the CDD schedule. (HR 0.77, P=0.034, median time to the composite end point 4.0 *vs*. 2.9 months). This secondary endpoint is not frequently reported and it's clinical relevance above the commonly reported endpoints as OS, PFS and quality of life is unclear. Since treatment with sunitinib and its analogues can be maintained for years, adequate treatment of adverse events and care for quality of life is essential. The self reported disease-related symptoms are interesting, but quality of life data are unfortunately missing.

Three other non-randomised phase II studies on continuous sunitinib dosing have been published, including more than three hundred patients in total (3-5). The ORR varied between 20-35%, median PFS from 8.2 to 13 months and median OS from 19.8 to 25 months, all comparable to the current study of Motzer *et al*. (2) and also to the keystone study of 4/2 sunitinib *vs*. interferon-α (ORR 31%, median PFS 11 months and med OS 26 months) (6,7). In conclusion, CDD or the 4/2 schedule do not really differ in terms of efficacy.

When no difference in efficacy can be claimed, perhaps a difference in safety and tolerability, or quality of life, can be a reason to have a preference for one of both

schedules. However, the toxicity profile of both schedules was comparable as was the amount of patients who discontinued sunitinib because of adverse events (4/2 *vs.* CDD; 11% and 15%). Interesting to see is the high amount of patients needing drug interruptions (4/2 *vs.* CDD; 65% *vs.* 62% of which 29% and 13% for more than 7 days) or dose reductions (4/2 *vs.* CDD; 36% *vs.* 43%). The dose intensity was 91% in the 4/2 group and only 78% in the CDD group. Also interesting is the, clinically recognisable, pattern in self reported outcomes in the 4/2 group. Patients report rising amounts of adverse events during the 4 weeks on part of the schedule, and recovery during the 2 weeks off. In the other phase II CDD studies (3-5) 43-50% of the patients needed dose reductions and 10-16% of the patients discontinued treatment due to adverse events which is again comparable to the current Motzer study (2). In conclusion, no preference for either 4/2 or CDD can be given based on the reported toxicity in this study.

What should be also taken in account when trying to get the maximum benefit from sunitinib treatment? Houk *et al.* showed that higher exposure of sunitinib (measured as area under the curve during steady state, AUCss) significantly correlates with a higher probability of ORR and with longer TTP or OS, but also with increased risk of adverse events (8). Two frequently occurring adverse events of sunitinib, hypertension and hypothyroidism, are associated with better clinical outcome and suggested as efficacy biomarkers (9,10). In case of hypertension which needs multidrug treatment, a CDD schedule can be helpful in reaching a stable blood pressure, because the risk of hypotension within the 2 weeks of period, and the, sometimes big, changes in blood pressure. There is also a suggestion that a third adverse event, the hand foot syndrome (HFS) is a potential biomarker of efficacy. On the ASCO GU 2011 a retrospective study in 770 patients was presented, in which HFS was significantly and independently associated with improved ORR, PFS and OS (abstract 320).

Furthermore, in a subset of patients treated with sunitinib, a flare up syndrome occurs after discontinuation of treatment. This syndrome consists of tumour related complaints which can occur within days after stop of treatment (11,12). Reintroduction of even the same tyrosine kinase inhibitor can treat the flare up phenomenon. The pathobiology of the syndrome is not well understood. Patients in the 4/2 schedule can experience this flare up syndrome during the 2 weeks off period. These patients should turn over to a CDD schedule.

An alternative treatment strategy would be intrapatient dose escalation until reaching one of the clinical efficacy biomarkers, e.g., hypertension or hypothyroidism, for as far as tolerated. This would fit in the data of exposure - response relationship and the well known high interpatient variability of both treatment response as well as experienced toxicity. This strategy needs more research and pharmacokinetic as well as molecular imaging research may be helpful in this.

All together, this illustrates the complexity of adequate sunitinib treatment in individual patients. The choice for a 4/2 or CDD schedule has to be based on the individual patient. In terms of PFS or OS efficacy, no significant difference between the both schedules has been shown. The combination of the exposure related ORR chance results of Houk *et al.* and the somewhat lower ORR in part of the CDD phase II studies suggests that the 50 mg 4/2 schedule perhaps is better for the patient subset needing a rapid volume response, for example in case of obstruction, pain or neo-adjuvant treatment. On the other side, a CDD schedule can be more helpful in patients with severe hypertension or flare up syndrome after discontinuation.

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Footnote

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Towards new treatment options for renal cell carcinoma: development and clinical results of tivozanib, a selective VEGFR tyrosine kinase inhibitor

Ferry ALM Eskens, Brigitte Haberkorn

Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, the Netherlands

Correspondence to: Ferry ALM Eskens, MD, PhD. Department of Medical Oncology, room HE 120, Erasmus University Medical Center. PO Box 2040, 3000 CA Rotterdam, the Netherlands. Email: f.eskens@erasmusmc.nl.

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Clear cell renal cancer (RCC) is the tumor in which the treatment paradigm of locally advanced and metastatic disease has almost completely shifted away from immunotherapy/cytokine treatment towards antiangiogenic therapies.

Apart from a very few selected cases where either interferon-α or (high dose) interleukin-2 is applied, most patients with RCC are nowadays treated with any of the currently registered oral VEGF receptor (VEGFR) tyrosine kinase inhibitors. The rationale to pursue treatment with these VEGF inhibiting agents is found in the biology of RCC where increased Hypoxia Inducible Factor (HIF)1-α leads to increased levels of VEGF ligands, making RCC a predominant angiogenesis driven tumor.

Even though initial clinical studies have demonstrated meaningful antitumor activity of bevacizumab in RCC at the end of the previous millennium, its registration for the treatment of RCC only in combination with interferon-α has somewhat hampered clinical acceptability. Nowadays, and based upon a large randomized phase III clinical study demonstrating superior activity and increased overall survival when compared to interferon-α in fist line treatment, the VEGFR tyrosine kinase inhibitor sunitinib is a global drug of choice for the first line treatment of advanced RCC.

Following the obvious success of sunitinib, many new VEGFR tyrosine kinase inhibitors have been developed. Amongst these new tyrosine kinase inhibitors that have been tested in RCC, most notably sorafenib, pazopanib and axitinib, tivozanib is the latest development.

Tivozanib is a potent and selective VEGFR tyrosine kinase inhibitor with an IC_{50} of 0.21, 0.16, and 0.24 nmol/L for VEGFR-1, -2 and -3 respectively, that inhibits angiogenesis and vascular permeability in tumor tissues and has demonstrated antitumor effects in a wide range of cancer types. Tivozanib is currently being tested in combination with various cytotoxic drug regimens for various indications, but is also, as could be expected, considered to be of interest for the treatment of RCC. Its high selectivity for VEGFR tyrosine kinases could probably mean that apart from activity, tolerability and safety could be an advantage when compared to other, more broad spectrum tyrosine kinase inhibitors, such as sunitinib or sorafenib, both registered for the treatment of RCC.

In the current study (1), Nosov *et al.* applied a randomized discontinuation design which allows for proper activity assessment and a good assessment of safety and tolerability.

Patients with RCC not amenable to surgery were allowed to have received previous systemic therapy, albeit that previous exposure to VEGF- pathway targeted therapy was not allowed. Based upon the data presented in their manuscript, it is clear that the antitumor activity of Tivozanib looks promising, with an absolute increase in Progression Free Survival (PFS) of 7 months (P=0.01) in the randomized double blinded treatment part of this study and an overall median PFS of 11.7 months. Of note is that of the 272 initially enrolled patients, 78 (28%) showed such benefit (response ≥25%) from open-label tivozanib treatment, that they were allowed to continue open label treatment following the first antitumor assessment, whereas only 50 patients (18%) showed disease progression (≥25%) and had to be taken off treatment following the

first antitumor assessment. This observed response rate of tivozanib seems to be comparable with response rates observed in the pivotal phase 3 trial of sunitinib and the (randomized discontinuation) trials performed with sorafenib, pazopanib and axitinib (2-5).

The observed safety profile of tivozanib in this study is well in line with that of the other VEGFR tyrosine kinase inhibitors mentioned and confirms the overall good safety profile observed in the phase I trial of tivozanib with predominantly on-target side effects such as hypertension (6). Cumbersome side effects such as gastrointestinal toxicities and hand-foot skin syndrome and side effects suggestive for increased thromboembolic tendency occurred only infrequently, as did rade 3 or 4 haematological toxicity.

With regard to the 'final' position that tivozanib might reach within the crowded field of VEGFR tyrosine kinase inhibitors available for the treatment of advanced RCC, randomized trials comparing progression free and overall survival are mandatory; if these trials are to be designed for superiority, probably large numbers of patients will be needed when considering the fact that all VEGFR tyrosine kinases discussed here have shown biological and clinical activity. In studies designed to demonstrate non-inferiority, thorough assessment of patient reported outcomes and/or Quality of Life doubtlessly have to be an integral and crucial endpoint. While awaiting the results of the randomized study NCT00720941 comparing first line efficacy of sunitinib *vs.* pazopanib, it is currenly too early to forecast a dramatic shift in the first line treatment preference of advanced RCC.

The fact that some patients cannot tolerate a given VEGFR tyrosine kinase inhibitor, while showing good tolerability for another compound, allows oncologists and patients to make in the very near future an even larger choice between several active compounds now that tivozanib is likely too to find a place and become registered within the armamentarium of VEGFR tyrosine kinase inhibitors available for the treatment of advanced RCC.

Results of the randomized phase 3 trial comparing tivozanib to sorafenib in first line VEGF pathway directed therapy in subjects with advanced RCC (TIVO-1) have been presented at the 2012 ASCO meeting (7).

In conclusion, this phase II randomized discontinuation trial has shown that tivozanib is an active VEGFR tyrosine kinase inhibitor for the treatment of advanced RCC.

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Footnote

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Milestones for development of tivozanib for kidney cancer therapy

Robert Crescentini[1], Shilpa Gupta[2], Mayer Fishman[2]

[1]University of South Florida College of Medicine, Medical Oncology & Hematology Fellow, Florida, USA; [2]H. Lee Moffitt Cancer Center & Research Institute, Department of Genitourinary Oncology, Florida,USA

Correspondence to: Mayer Fishman, MD, PhD. H. Lee Moffitt Cancer Center & Research Institute, Department of Genitourinary Oncology, USA. Email: mayer.fishman@moffitt.org.

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In the May 10, 2012 issue of the *Journal of Clinical Oncology*, Nosov and colleagues report on a company-sponsored (AVEO), phase II randomized discontinuation trial (RDT) of tivozanib therapy for metastatic kidney cancer (1). This trial is part of a development of tivozanib seeking to expand the growing list of active medical treatment options blocking the vascular endothelial growth factor (VEGF) pathway, besides drugs with mammalian target of rapamycin (mTOR) pathway inhibition, and treatments using immune mechanisms. Among the VEGF pathway approaches, small molecule tyrosine kinase (TKI) inhibitors already approved for use in metastatic renal cell carcinoma include sunitinib, sorafenib, pazopanib, and most recently axitinib; bevacizumab is an antibody that binds plasma VEGF, so that the VEGF receptor remains without this ligand. Tivozanib is distinguished from the other small molecule VEGFR TKI by a more potent inhibition of VEGF receptors 1, 2 and 3 (half-maximal inhibition at 0.24 nmol/L or lower), and a long half-life (reported here at 87.0±27.9 hours) (1). The high potency is reflected in the relatively lower daily dose, 1.5 mg daily, versus daily doses of 10-800 mg for the others. Additionally, the relative potency for VEGFR1, VEGFR2 and VEGFR3 versus the inhibition of kinases that are not VEGF receptors is over 10 fold, which is higher than for other members of the group. This feature may decrease off-target inhibition, impacting side effects or therapeutic effects (1,2).

The randomized discontinuation trial (RDT) format for cancer therapy evaluations was introduced to kidney cancer therapeutics during the development of sorafenib (3). The method allocates those with major responses to continue on treatment, and those with progression or intolerance to stop treatment; the middle group, with nominally stable disease at a landmark time point, are randomized to continue on treatment or to stop, through the next evaluation time point. The strength of the method is to address the known heterogeneity of rates of progression as is typically observed in the population with metastatic kidney cancer, and to emphasize progression-free survival (PFS), among those initially achieving a major response. In the sorafenib RDT trial 65 patients who had stable disease at the landmark were randomized to continue sorafenib or receive placebo, and median PFS of 24 *vs.* 6 weeks (P=0.0087) favored sorafenib (3). The subsequent randomized pivotal phase III trial of sorafenib *vs.* placebo confirmed superiority of sorafenib for PFS endpoint, (5.5 *vs.* 2.8 months, P<0.01), and overall survival improvement was observed as well (19.3 *vs.* 15.9 months, P=0.02; this P-value was not significant by the prespecified boundary rules) (4).

In the report here, 306 worldwide patients were assessed for eligibility over about 10 months in 2007-2008, and 272 were treated. By the 16 week time point, 78 of had tumor size decreases of >25%, qualifying for continuation on open-label drug, and 76 were discontinued from the trial, for progressive disease or other reasons. The primary endpoint of overall response rate at the 16 week point was 18% (95% CI: 14-23%), and counting responses qualifying after further therapy, 24% (95% CI: 19-30%). Among 118 patients allocated to double-blind randomization for 12 weeks of treatment, 61 were assigned to tivozanib and 57 to placebo. After progression during the 12 weeks double-blind treatment, 24 of the placebo group were switched to open-label tivozanib. The median PFS (counted from the point of random assignment) significantly favored continuation of tivozanib, 10.3 *vs.* 3.3 months, P=0.010). The majority of patients enrolled had clear cell histology

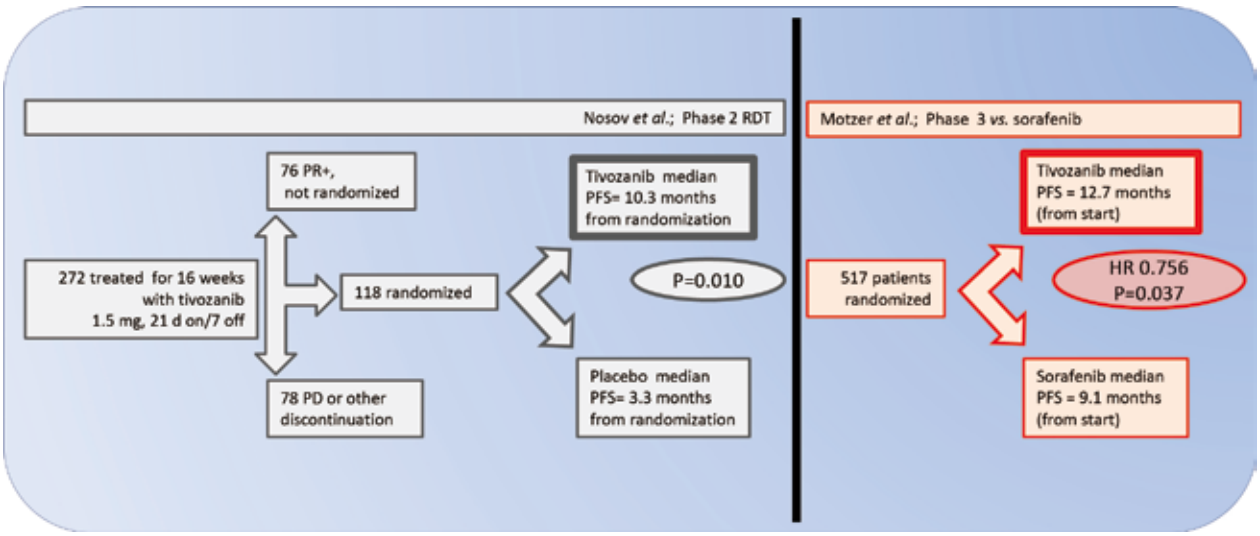

Figure 1 Highlights of PFS results in international randomized trials

and had undergone nephrectomy, approximately half were treatment naïve. A subset with greater benefit was those with clear cell histology and prior nephrectomy (ORR 32%, median PFS 14.8 months) (1). Most common reported adverse events reported were hypertension and dysphonia, which may be considered "on-target" related with respect VEGFR-TKI inhibition (1,2).

In June 2012 at the ASCO annual meeting in Chicago, the pivotal trial of tivozanib *vs.* sorafenib [NCT01030783], a direct comparison between two active agents, was presented by Motzer and colleagues. The meeting report describes the 517 patient trial in patients with metastatic kidney cancer who had undergone nephrectomy, who were either treatment naïve or had received one prior systemic therapy excluding VEGF or mTOR directed therapy. Patients were randomized to receive tivozanib 1.5 mg daily for three weeks followed by 1 week off therapy [the same as in (1)] or sorafenib given continuously at 400 mg twice daily. Results show the positive finding of a median PFS in the tivozanib arm of 12.7 months compared to 9.1 months in sorafenib arm (HR 0.756, 95% CI: 0.580-0.985, P=0.037). In the treatment-naïve subset, the results were similar (5). Overall survival data were not mature, but contemporary availability of many second-line approaches can be anticipated to attenuate the power to observe a difference.

Although the relative frequency of side effects was not the primary endpoint of the trial, they are of interest in this direct comparison. This serves to address the hypothesis that tivozanib and axitinib have more relative specificity for the VEGFR TKI, thus being different from sorafenib, sunitinib or pazopanib, which also have significant inhibition of the activity of proteins such as B-raf, C-kit, or FGFR1. Hypertension, dysphonia and back pain were seen at higher frequency with tivozanib, while diarrhea, palmar-plantar erythrodysesthesia and alopecia were seen more frequently with sorafenib.

With over 500 clear cell kidney cancer patients treated with tivozanib, observed major responses, statistically significant improvement of PFS in the RDT format trial, and statistically significant improved PFS in direct comparison to sorafenib, there is little doubt that tivozanib is a new drug that is practical for use and can impact the disease course for a significant fraction of kidney cancer patients (*Figure 1*). The challenges remaining for drug development and market introduction in an indication of metastatic kidney cancer will be to see to what extent differences of side effects, cost, convenience and the capacity for synergistic combination may matter, potentially to make tivozanib a better choice for some patients.

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Could tivozanib be a new potent pan-VEGF inhibitor in RCC therapy?

Zsuzsanna Mihály, Alexisz Panajotu, Balázs Győrffy

Research Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences-Semmelweis University, Hungary

Correspondence to: Zsuzsanna Mihály, MD. 1st Dept. of Pediatrics, Research Laboratory for Pediatrics and Nephrology, Hungarian Academy of Sciences – Semmelweis University, Hungary. Email: zsmihi@msn.com.

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In the course of the last decade the therapy of renal cell carcinoma (RCC) stepped into a new era as targeted therapies changed protocols and the prognosis of patients as well. Could this successful start with sunitinib and sorafenib be continued by more potent agents? Because objective response rates (ORR) are still far from ideal (none of them reach 50%), other targeted molecular approaches need to be developed. Consequently, a number of currently ongoing trials focus on confirming potential new agents for the systemic therapy of metastatic RCC (mRCC). One of these, tivozanib is a tyrosine kinase inhibitor blocking all three VEGF receptors (pan-VEGF inhibitor), thus it potentially possesses all the indications of the currently recommended Sorafenib, Pazopanib and Axitinib.

Currently used agents in second-line therapy after cytokine treatment are sorafenib and pazopanib. Sorafenib increases overall survival by 7.5 to 35 months, PFS by 5.4 to 12 months beside an ORR of 46%. For pazopanib the trials demonstrate 9.3 months progression-free survival (PFS) instead of PFS and an ORR of 20% to 32 % (1).

In a recent report in the *Journal of Clinical Oncology* by Nosov and his colleagues describe the latest results of a phase II randomized trial of tivozanib (2). The primary end points were safety, the ORR at 16 weeks, and the percentage of progression free survival of randomly assigned patients after 12 weeks of tivozanib treatment compared to a placebo treated control group. The secondary end points comprised PFS. Earlier, tivozanib activity was observed in a phase I study in which RCC patients experienced clinical benefit from treatment.

The patients (n=272) were administered tivozanib 1.5 mg/d orally for 16 weeks. Then, patients with less than 25% change in tumor size (n=118) were randomly assigned to receive either tivozanib (n=61) or placebo (n=57) for the next 12 weeks in a double-blind manner. Patients with partial response (n=78) or more than 25% tumor shrinkage could continue the open label tivozanib therapy. The remaining 76 patients discontinued the study, mainly due to progressive disease (n=51).

The ORR after 16 weeks was only 18%, but all patients had partial response (PR). Throughout the entire study though, the ORR was 24% (19% to 30%). The PFS after 12 weeks (measured from random assignment) was significantly (P=0.01) longer among patients with tivozanib treatment (10.3 months; 8.1 to 21.2 months) compared to patients receiving placebo (3.3 months; 1.8 to 8.0 months). It has to be mentioned that of the 57 patients in the placebo arm 24 completed the arm without progression, 24 patients switched to the open label tivozanib due to progressive disease and 9 patients discontinued the trial. The median PFS in all treated patients was 11.7 months (8.3 to 14.3 months) excluding the placebo arm. The study results show that in RCC patients after nephrectomy tivozanib demonstrates improved antitumor activity with an ORR of 30% (23% to 37%) and median PFS of 14.8 months (10.3 to 19.2 months) compared to patients without nephrectomy.

The 15 deaths throughout the trial were mostly the consequences of disease progression, and none of them was treatment related. The most common adverse events (AE) were hypertension (45%), dysphonia (22%), diarrhea (12%), asthenia (10%) and certain laboratory abnormalities. Although 22 patients ended the trial due to AE, side effects in grade 3 and 4 were infrequent.

We must also draw the attention to some of the

limitations of the study. The 272 enrolled patients did not come from a homogenous group (83% had clear-cell histology, 73% of the patients had nephrectomy, and 54% of the patients were treatment naive). Pharmacokinetic samples were collected from only 21 patients to measure the concentration of tivozanib. Finally, out of those who completed the double-blind trial, in the placebo arm 26 patients progressed out of 50 cases while in the tivozanib arm 23 patients progressed out of 58 - the difference between the two cohorts is only marginally significant by a chi-square test (P=0.0498, not reported by the authors).

How could we identify RCC patients gaining the most in terms of progression free survival after tivozanib treatment? In an ongoing phase III trial tivozanib and sorafenib are compared to evaluate their efficacy and safety in 517 patients with advanced RCC. The results show statistically significant improvement in PFS with a median PFS of 12.7 months in case of tivozanib compared to a median PFS of 9.1 months with sorafenib in treatment-naïve patients (3).

Could the lower prevalence of adverse events in tivozanib-treated patients be a benefit providing superiority over the currently used agents? As today more patients are being treated for longer periods of time, the management of the associated AEs is gaining importance. Eisen and his colleagues suggest an alternative solution to this issue by using improved strategies to monitor and manage patients with side effects (4) .

In conclusion, the results of the tivozanib phase II trial are so far encouraging but the final data gathered during a phase III trial must settle the debate if it could become one of the recommended agents for RCC therapy.

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Treatment Progress

Tivozanib: is total VEGFR inhibition the way to success in terms of tolerability and efficacy in advanced kidney cancer?

Marine Gross-Goupil[1], Alain Ravaud[1,2]

[1]Saint-André Hospital, University Hospital, Bordeaux, France ; [2]Université Bordeaux 2, Victor Segalen, Bordeaux, France
Correspondence to: Marine Gross-Goupil, MD, PhD. Saint-André Hospital, University Hospital, Bordeaux, France.
Email: marine.gross-goupil@chu-bordeaux.fr.

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The family of tyrosine kinase inhibitors is still growing. After sunitinib, sorafenib and more recently pazopanib, and axitinib, we probably now should count on tivozanib (1). This pan-VEGFR inhibitor (VEGF-R1,-R2,-R3) is more selective and potent *in vitro* than previous known TK inhibitors. Tivozanib was tested in a phase II trial reported by Nosov *et al.* (1) Tivozanib was administered at a daily dose of 1.5 mg, for 3 weeks followed by a break of 1 week. Of the 272 patients treated during the first period of 16 weeks, 78, who presented tumour shrinkage of at least 25%, were maintained on tivozanib. All of the 118 patients who presented less than 25% change in the tumour, were randomized between placebo and tivozanib, during the next 12 weeks. Finally, 76 patients discontinued the treatment and were excluded from the analysis, mainly due to progressive disease (50/76). The main clinical characteristics include clear cell histology (83%), and prior nephrectomy (73%) with no previous treatment (54%). Considering all the patients, the median progression-free survival (PFS) and objective response rate (ORR) were 11.7 and 24% respectively. Results may be considered according to the two sequential periods of treatment. The ORR during the sixteen week open-label period reached 18% (95%CI, 14-23%), with 66% of stable disease (SD). At the end of the second double-blind period, significantly more patients in the tivozanib arm (49%, n=30) were progression-free, compared with the placebo-arm (21%, n=12), (P=0,001); median progression-free survival was also statistically longer in the tivozanib arm compared to placebo, 11.9 months (9.3-14.7 months) and 9.1 (7.3-9.5) respectively, HR=0.797, P=0.042. The ORR were 33% and 23% in the two groups respectively, P=0.014.

In terms of toxicity, the hypothesis suggesting that the specificity of the target would permit a decrease in off-targeted toxicity was confirmed with less adverse events apart from hypertension, a class effect. The two more frequent adverse effects of any grade reported were: hypertension (45%), and dysphonia (22%). Other toxicities, frequently reported with other TKIs, such as asthenia, diarrhea, stomatitis or hand-foot syndrome, were reported in 10%, 12%, 4% and 4% respectively, all grades. Dose-reduction concerned only 8% of the patients, and interruptions 4% (n=11). According to the data, the authors concluded that tivozanib demonstrated promising activity and an acceptable safety and tolerability profile.

Furthermore, these results are in accordance with the data presented by Robert Motzer at the ASCO 2012 meeting concerning a phase III trial, comparing tivozanib and sorafenib in the first-line setting (2). The same schedule of tivozanib was compared to 400 mg, twice daily of sorafenib continuously. The trial demonstrated a statistically significant benefit in progression-free survival in the 260 patients treated with tivozanib compared to the sorafenib group (n=257): 11.9 months (9.3-14.7 months) and 9.1 months (7.3-9.5 months) respectively, HR=0.797, P=0.042. The toxicity profile was as expected according to the results of this phase II trial, with 26% of grade 3/4 hypertension, and 21% of grade 3/4 dysphonia. The incidence of hypertension should be interpreted along with previous data reporting this effect, as a biomarker of pharmacological activity. Furthermore, its predictive role of a therapeutic effect, with sunitinib and more recently with axitinib has also been reported (3,4). Lastly, the safer toxicity profile may allow better exposure of the patient to

the drug. However, the recent titration data concerning axitinib has begun to shed light on the question of the fixed pre-defined dose of tyrosine kinase agents.

In conclusion, tivozanib is really a new anti-angiogenic drug in the landscape of treatment in RCC and not only a me-too drug as sunitinib, sorafenib and pazopanib are. The next challenge is the position in 1st line between tivozanib and axitinib, waiting for forthcoming planned trials.

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Tivozanib: a novel VGFR inhibitor for kidney cancer

Helen Boyle

Medical Oncology Department, Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon cedex 08, France

Correspondence to: Helen Boyle, MD. Medical Oncology Department, Centre Léon Bérard, 28 rue Laënnec, 69373 Lyon cedex 08, France. Email: helen.boyle@lyon.unicancer.fr.

Abstract: Treatment of kidney cancer has changed over the past 10 years with the approval of several targeted agents. These drugs are given on a long term base and toxicity is an issue for most patients. Despite improvement compared to immunotherapy, most patients will progress on these drugs. There is a need for more portent and better tolerated drugs. Tivozanib is a potent pan VEGR specific inhibitor. In this phase II trial it gave interesting results with an overall median PFS throughout the study of 11.7 months (95% CI: 8.3-14.3 months) and an overall objective response rate of 24% (95% CI: 19-30%). "Off"-target toxicity was mild.

Keywords: Tivozanib; VGFR inhibitor; kidney cancer

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Treatment of metastatic kidney cancer is based on targeting the VEGF pathway. Most renal cell carcinomas are clear cell and present a somatic mutation in VHL, leading to the accumulation of HIF and the transcription of HIF inducible genes for instance VEGF (1). Several VEGF tyrosine kinase inhibitors are approved for renal cell carcinoma: sunitinib, pazopanib, sorafenib and axitinib based on data from randomised phase III trials (2-6). However sunitinib, pazopanib and sorafenib are multitarget TKIs that interact with other pathways and therefore have off-target side effects, that impact the tolerance of these treatments (diarrhoea, hand-foot syndrome, haematological toxicity···).

Tivozanib is a selective, potent, pan VEGFR inhibitor that blocks VEGFR1, VEGFR2 and VEGFR3 at picomolar concentrations. It is administered orally.

Nosov et al report here on a phase II randomized trial of discontinuation (7). Patients received 1.5 mg of tivozanib daily for 3 weeks followed by a 1-week break. Tumour assessments were performed every 2 cycles. Patients who had more than a 25% tumour shrinkage at 16 weeks continued on tivozanib, patients who had an increase of 25% or more in tumour size stopped treatment. Patients, who didn't meet either of these criteria, were randomized between receiving 12 weeks of placebo or 12 weeks of tivozanib. Tumour status was assessed at every cycle during this phase. Patients who progressed during this phase were unblinded. If they were on placebo they were started again on tivozanib. For the other patients, treatment was stopped.

After 12 weeks, all patients were unblinded and patients could continue on tivozanib. Primary objectives were safety, objective response rates at 16 weeks and the percentage of patients who remained progression free after 12 weeks with placebo or tivozanib.

Two hundred and seventy two patients were enrolled. Most patients had clear cell carcinomas (83%), 73% had had a prior nephrectomy. About half of the patients were treatment naive (54%). No prior VEGF pathway targeted therapy was allowed.

At 16 weeks, 29% of patients had tumour shrinkage of ≥25%. Seventy six patients had stopped treatment: 50 because of disease progression and 26 for other causes. A hundred and eighteen patients were randomized between receiving tivozanib (n=61) and placebo (n=57).

The objective response rate at 16 weeks was 18% (95% CI: 14-23%), all were partial responses. Sixty six percent of patients had stable disease as best response.

In the blinded phase, progression free rates were significantly higher in the patients who continued tivozanib

than in those who switched to placebo [49% (95% CI: 36-63%) *vs.* 21% (95% CI: 11-34%); P=0.001]. Median PFS (from randomization) was 10.3months (95% CI: 8.1-21.2 months) in the tivozanib arm versus 3.3 months (95% CI: 1.8-8months) in the placebo arm (P=0.01). Forty eight patients out of the 57 patients in the placebo arm were restarted on tivozanib: 24 because they progressed on placebo and 24 at the end of the blinded phase as they hadn't progressed on placebo. Ninety four percent of patients who had progressed on placebo had disease control when restarting tivozanib (objective response or stable disease).

The overall median PFS throughout the study was 11.7 months (95% CI: 8.3-14.3 months) (patients on placebo were censored at the time of randomization). The overall objective response rate was 24% (95% CI: 19-30%).

Patients who had clear cell carcinoma and who had undergone previous nephrectomy had better ORR and longer PFS.

The most frequent toxicity was, as expected, hypertension (45%; grade 3-4:12%). Other frequent side effects were dysphonia (22%; no grade 3-4). Diarrhoea occurred only in 12% of patients and asthenia in 10%. Liver toxicity was mild (1% of grade 3-4 elevation of ASAT and ALATs respectively). Lymphopenia (6%), hypokalemia (6%), increased gamma-glutamyl transpeptidase (17%) and increased uric acid (7%) were the most frequent grade 3-4 lab anomalies. Severe adverse events occurred in 13% of patients.

Eight percent of patients required dose reduction due to side effects, 4% had treatment interruptions and 9% stopped treatment because of them. Fifteen patients died on study: 8 because of disease progression and 6 from cardiovascular events. None of these deaths were considered to be treatment related.

This phase II trial shows good results with this selective and potent VEGFR inhibitor. Tolerance was good with less "off-target" side effects, than what is usually seen with less selective VEGFR inhibitors.

These interesting results with tivozanib were confirmed with the first results from a phase III trial presented at ASCO (8).

Tivozanib was compared to sorafenib in a phase III trial that enrolled 517 patients with advanced renal cell carcinoma and prior nephrectomy. Patients were treatment naive or had received no more than 1 prior systemic therapy for metastatic disease. No prior VEGF- or mTOR-targeted therapy was allowed. Primary endpoint was PFS according to independent review. Patients who progressed on sorafenib were crossed over to tivozanib in a specific trial.

Median PFS was longer in the tivozanib arm: 11.9 months versus 9.1 months in the sorafenib arm (HR=0.797, 95% CI: 0.639-0.993; P=0.042).

In the treatment-naive stratum (70% of patients enrolled in each arm), the median PFS was 12.7 months with tivozanib versus 9.1 months with sorafenib (HR: 0.756, 95% CI: 0.580-0.985; P=0.037). More patients had an objective response with tivozanib than with sorafenib [ORR=33% *vs.* 23%; (P=0.014)]. Hypertension (44%, grade 3-4: 24%), dysphonia (21%) and back pain (14%) were more frequent with tivozanib than sorafenib. Diarrhoea, hand-foot syndrome and alopecia were significantly more frequent with sorafenib.

These progression free survival data and favorable toxicity profile may allow tivozanib to become an option for the 1st line treatment of patients with metastatic renal cell carcinoma.

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Treatment Progress

Enzalutamide (formerly MDV3100) prolongs survival in docetaxel-pretreated castration-resistant prostate cancer patients

Matthias M. Heck, Jürgen E. Gschwend, Margitta Retz

Department of Urology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany
Correspondence to: Matthias Michael Heck, MD. Department of Urology, Technische Universität München, Klinikum rechts der Isar, Ismaninger Str. 22, 81675 München, Germany. Email: m.heck@lrz.tum.de.

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Until lately, castration-resistant prostate cancer (CRPC) patients who progressed following docetaxel chemotherapy had no treatment alternative with proven survival benefit. This changed with a series of recently published phase III trials that lead to approval of several new, life-prolonging agents by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

In 2010, cabazitaxel, a second-generation taxane that inhibits cell division by blocking the depolymerisation of microtubuli, was shown to have a survival benefit of 2.4 months post-docetaxel in a randomized trial (TROPIC) (1). In 2011, abiraterone acetate, a steroidal androgen biosynthesis inhibitor that leads to suppression of androgen synthesis in testicular tissue, adrenal cortex and tumor tissue itself, demonstrated a survival benefit of 4.6 months post-docetaxel in a double-blinded, randomized trial (COU-AA-301) (2,3).

Enzalutamide (formerly called MDV3100) now joins the list of drugs that were shown to prolong suvival following docetaxel chemotherapy. In August 2012, results of a double-blinded, randomized trial comparing enzalutamide with placebo in 1,199 CRPC men were reported (AFFIRM) (4). Enzalutamide is an androgen-receptor antagonist that blocks androgens from binding to the androgen receptor, prevents nuclear translocation of the androgen receptor and inhibits the androgen receptor from associating with DNA to induce transcription of target genes (5). In the AFFIRM-trial patients were randomized 2:1 in a verum-arm treated with 160 mg enzalutamide daily (800 patients) or a placebo-arm (399 patients).

The trial was stopped early following an interim analysis at the time of 520 deaths that revealed a survival benefit of 4.8 months (median overall survival of 18.4 months in the enzalutamide group versus 13.6 months in the placebo group) and a 37% reduction in the risk of death (P<0.001) in patients treated with enzalutamide. As a result, the study was unblinded and enzalutamide was offered to patients of the placebo-group.

The overall survival benefit was consistent across all subgroups, including age, baseline pain intensity, geographic region and type of disease progression at entry. Furthermore, superiority of enzalutamide was achieved for all secondary end points, including PSA-level response rate (54% *vs.* 2%, P<0.001), soft-tissue response rate (29% *vs.* 4%, P<0.001), quality-of-life response (43% *vs.* 18%, P<0.001), the time to PSA progression (8.3 *vs.* 3.0 months, P<0.001), radiographic progression-free survival (8.3 *vs.* 2.9 months, P<0.001) and the time to the first skeletal-related event (16.7 *vs.* 13.3 months, P<0.001).

Noteworthy, the enzalutamide group had a lower incidence of adverse events of grade 3 or above (45.3% *vs.* 53.1% in the placebo group). The most common adverse events that were reported more frequently in the enzalutamide group included fatigue, diarrhea and hot flashes. Seizures were reported in 5 of 800 (0.6%) patients treated with enzalutamide versus none (0%) in the placebo group. Therefore, the investigators suggested that enzalutamide should be used with caution in patients with a history of seizure, with predisposing factors, e.g., brain injury, stroke, brain metastases, alcoholism or with concomitant medication that may lower the seizure threshold.

In conclusion, the androgen-receptor antagonist enzalutamide prolongs survival in docetaxel-pretreated

CRPC patients and has an excellent safety profile that compares favourably to other agents such as cabazitaxel with a risk of neutropenia and abiraterone acetate with a risk of mineralocorticoid side-effects. Enzalutamide has been approved by the FDA in August 2012 for CRPC patients following docetaxel-chemotherapy. It is marketed under the name Xtandi by Medivation and Astellas.

For a future assessment of the optimal position of enzalutamide in the treatment sequence in CRPC, important pending results on a randomized phase III trial with enzalutamide in chemo-naïve patients are yet to be awaited (PREVAIL).

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Treatment Progress

Enzalutamide: the emperor of all anti-androgens

Emmanuel S. Antonarakis

Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Bunting-Blaustein Cancer Research Building, 1650 Orleans St - Room 1M45, Baltimore, MD 21231, USA

Correspondence to: Emmanuel S. Antonarakis, M.D. Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Bunting-Blaustein Cancer Research Building, 1650 Orleans St - Room 1M45, Baltimore, MD 21231, USA. Email: eantona1@jhmi.edu.

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In the last few years, there has been a rekindled interest in the androgen receptor (AR) and AR signaling as valid therapeutic targets in prostate cancer. While the primary goal of therapy for recurrent or advanced prostate cancer has long been to reduce circulating and intratumoral androgen levels, recent laboratory and clinical data have shown that AR signaling remains active (and continues to drive tumor growth) even in the castration-resistant state (1). In addition, while first-generation AR blockers (e.g., flutamide, bicalutamide, nilutamide) have been used clinically with some success, none of these secondary hormonal manipulations have demonstrated an unequivocal survival benefit in men with prostate cancer. These anti-androgens have several shortcomings, including that they are only weak antagonists of the AR and that they may also function as partial AR agonists (especially with prolonged use).

Enzalutamide (Xtandi®, Medivation Inc. and Astellas Inc), previously known as MDV3100, is a next-generation anti-androgen that has at least 3 separate activities: it functions as a potent and irreversible inhibitor of the AR, it impairs translocation of the AR from the cell cytosol into the nucleus, and it blocks the interaction of the AR with DNA androgen-response elements at the transcription complex. For these reasons, enzalutamide has also been described as an AR signaling inhibitor. In a recent issue of the *New England Journal of Medicine*, Scher and colleagues (2) report the mature results of the AFFIRM study, a multinational phase III randomized trial of enzalutamide versus placebo in men with metastatic castration-resistant prostate cancer who had developed disease progression despite docetaxel chemotherapy. A total of 1,199 men were randomized (2:1) to receive either oral enzalutamide 160 mg daily (800 patients) or placebo (399 patients). The primary endpoint was overall survival, and the trial was halted early after a planned interim analysis which revealed a significant prolongation of median survival in the enzalutamide arm compared to the placebo arm (18.4 months versus 13.6 months, hazard ratio 0.63, P<0.001). In addition, enzalutamide showed overwhelming evidence of clinical benefit with respect to all pre-planned secondary endpoints, proving superior to placebo in terms of radiographic progression-free survival (8.3 versus 2.9 months, hazard ratio 0.40, P<0.001), PSA response rate (54% versus 2%, P<0.001), time to PSA progression (8.3 versus 3.0 months, hazard ratio 0.25, P<0.001), radiographic response rate (29% versus 4%, P<0.001), and time to first skeletal-related event (16.7 versus 13.3 months, hazard ratio 0.69, P<0.001). In addition, data presented at the 2012 Annual ASCO meeting revealed that enzalutamide produced improvements in several quality-of-life measures including pain palliation, physical wellbeing, functional wellbeing, social wellbeing, and emotional wellbeing (3). Enzalutamide was generally very well tolerated, with the most common adverse events being fatigue (34%), diarrhea (21%), hot flashes (20%), and headache (12%). Notably, about 1% of patients receiving enzalutamide experienced a seizure (compared to 0% in the placebo arm), necessitating discontinuation of the study drug. The results of this trial led to the FDA approval of enzalutamide on August 31, 2012 for the treatment of men with metastatic docetaxel-pretreated castration-resistant prostate cancer.

The current study is important because it provides a proof-of-principle that a continued assault on the AR can be a fruitful therapeutic endeavor even in men with castration-resistant prostate cancer who have progressed

despite multiple additional lines of hormonal therapy. It also validates the AR as a *bona fide* therapeutic target in castration-resistant prostate cancer. However, many intriguing questions remain: what is the predominant mechanism of resistance to enzalutamide? Should enzalutamide be used in patients who have not received prior chemotherapy? Will enzalutamide be effective in men who have previously received novel androgen-synthesis inhibitors such as abiraterone? The last question is especially relevant, because all patients on the AFFIRM study were abiraterone-naïve due to the trial's eligibility criteria. An additional intriguing observation is that a substantial number of patients who progressed on enzalutamide showed evidence of PSA elevations after an initial decline in PSA. Because PSA itself is an AR-regulated protein, it can be hypothesized that AR signaling still remains active even after enzalutamide resistance develops. To this end, preclinical experiments have shown that one potential mechanism of enzalutamide resistance may be an increased expression of truncated AR splice variants that lack the androgen-binding domain but remain constitutively active (4). Because enzalutamide acts at the ligand-binding domain, such truncated AR variants would not be expected to be inhibited by this drug, although novel small molecules that target the AR splice variants are on the horizon (5).

A potentially concerning adverse effect of enzalutamide is the occurrence of seizures. Convulsions are a known dose-dependent toxicity of enzalutamide when given at supratherapeutic levels in animal models, and the mechanism of seizures is thought to be related to inhibition of gamma-aminobutyric acid (GABA) receptors in the brain. Although the incidence of seizures in the AFFIRM trial was small (approximately 1%), it should be remembered that eligible patients were required to have a low seizure risk at the time of enrolment (i.e. no prior seizures, no brain metastases, no recent stroke, no concomitant medications known to lower the seizure threshold), suggesting that the true incidence of seizures in an unselected patient population may be even higher. The presence of a seizure would generally necessitate discontinuation of enzalutamide.

In conclusion, enzalutamide is the first AR blocker to demonstrate an unequivocal survival benefit in men with castration-resistant prostate cancer, and has been hailed by some as the "emperor of all anti-androgens". While the benefits of enzalutamide in chemotherapy-refractory patients are now confirmed, it remains to be seen if this drug will prove equally effective in a broader range of men with castration-resistant prostate cancer. In addition, the use of enzalutamide in earlier disease settings (*i.e.* the non-castrate PSA-recurrent state) is an exciting possibility of the future.

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Footnote

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Denosumab: Delay of bone metastasis in men with nonmetastatic castrate-resistant prostate cancer

Jules P. Manger, Tracey L. Krupski

University of Virginia Department of Urology, Charlottesville, Virginia

Correspondence to: Jules P. Manger, MD. University of Virginia Health System, Department of Urology. Tel: 434-924-2224; Fax: 434 243 6878. Email: jmanger@virginia.edu.

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In a large multicenter phase 3 randomized controlled trial published in *Lancet*, Smith and colleagues highlight a potential new indication for denosumab for patients with hormone refractory prostate cancer (1). Already approved for prevention of skeletal-related events in the setting of bone metastases in solid tumors (Xgeva) and prevention of androgen deprivation therapy (ADT) induced bone loss (Prolia), the authors theorized that denosumab administered prior to bone metastasis might stabilize the bone microenvironment thus delaying time to first bone metastasis. Men with castrate-resistant nonmetastatic prostate cancer treated with denosumab showed improved bone-metastasis-free survival and delayed time to first bone metastasis compared to those dosed with placebo.

Denosumab is a fully human monoclonal antibody that selectively binds and neutralizes receptor activator of nuclear factor kappa-B ligand (RANKL). This inhibits RANKL activation of osteoclasts in the vicious cycle of bone turnover. While the FDA-approved indications of denosumab fit intuitively into this mechanism, the delay of onset of bone metastasis with denosumab is rooted in the "seed and soil" hypothesis of metastasis of Paget and Fuchs. Denosumab demonstrates antitumor and antimetastatic properties independent of its osteoclast inhibition. In a mouse xenograft model of prostate cancer, Fc-RANK (a RANKL inhibitor) delays bone metastasis, inhibits osteolysis, and preserves bone architecture with decreased bony tumor burden (2). Similarly, in a mouse mammary cancer model, RANKL inhibition delays non-osseous metastasis and decreases metastatic tumor burden (3).

In the *Lancet* article, investigators performed a placebo-controlled, randomized trial in 319 centers in 30 countries. They enrolled 1,432 men with castration-resistant prostate cancer defined as three consecutive PSA rises despite castrate testosterone. Men with metastatic disease or recent antiresorptive therapy were excluded from this study. Based on premature study closure due to low event rate in similar intravenous bisphosphonate studies (4), this study targeted high risk prostate cancer. PSA of 8 ng/dL or greater and/or PSA doubling time of 10 months or less was deemed high risk for bone metastasis. The study was open label to any chemotherapeutic agents. A centralized computer randomization maintained allocation concealment. Patients were randomized to 120 mg denosumab subcutaneously monthly versus saline placebo. Patients, investigators, and radiologists were all blinded to treatment intervention. Bone scans, and confrirmatory studies based on suspicious bone scans, were obtained every 4 months to assess for bone metastasis with central radiology review. Results were analyzed by intention to treat for efficacy outcomes and per protocol for safety outcomes (four patients in the control group were accidentally dosed with denosumab). The primary endpoint was bone-metastasis-free survival. Secondary outcomes included time to bone metastasis, symptomatic bone metastasis, and overall survival (OS).

The enrollees were overwhelmingly white heptagenarians with good functional status. Half of the men had undergone local therapy with prostatectomy, radiation or both. The study group found an improvement in bone-metastasis-free survival from 25.2 months in the placebo group to 29.5 months in the denosumab cohort for a 4.2 month improvement and a similar delay in time to first bone metastasis. There was a greater rate of symptomatic bone metastases in the placebo cohort than those treated with

denosumab, 13% versus 10%.

With regards to safety, there was no significant difference in study discontinuation due to adverse event or grade 3 or higher adverse events as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 3. Hypocalcemia was rare in both groups and symptomatic hypocalcemia only occurred in one patient randomized to denosumab who was not taking his supplemental calcium and vitamin D. Osteonecrosis of the jaw (ONJ) occurred exclusively in the denosumab cohort in 33 men (5%). The majority of these men had risk factors such as dentures or poor dentition. Two-thirds of men who developed ONJ required at least minor debridement for treatment. The percentage of patients ONJ is higher in this than in other studies evaluating denosumab in cancer metastatic to bone; nevertheless the length of treatment and follow up is longer in this study making the incidence in line with prior studies. This rate of ONJ was worrisome to the food and Drug Administration. In February 2012, the FDA's Oncologic Drugs Advisory Committee voted 12-1 to deny an expanded indication for denosumab in preventing bone metastasis. In part, the committee stated that the 5% risk of ONJ did not justify a four-month potential delay in prostate cancer metastasis (5).

Bony metastasis is a dreaded yet inevitable consequence of castrate-resistant prostate cancer that is costly in terms of patient quality of life and societal economic burden. Similar to the controversy of when to initiate ADT in the setting of recurrence after local treatment, this study calls into question when to initiate denosumab in the setting of castrate-resistant prostate cancer. Is it best to initiate therapy in the setting of impending bony metastasis to prolong bone-metastasis-free survival or better to stabilize the bone to minimize skeletal related events with denosumab once clinical or radiographic bone disease develops? The FDA felt this study was insufficient to justify approval of denosumab for this indication. They were concerned about the clinical relevance of the endpoint of bone-metastasis-free survival or time to first bone metastasis. Additionally, they were underwhelmed with the magnitude of the effect of 4.2 months, optimistically expecting results in the 6 to 12 month range. They felt a better study design would focus on outcomes of SRE and OS in castrate-resistant prostate cancer patients treated in an early (prior to bony metastasis) versus delayed (after imaging confirmation of metastasis) strategy (5). Certainly, 4 month overall survival advantage has been robust enough to justify approval of other prostate cancer drugs such as abiraterone and sipuleucel-T.

Manipulation of the bone microenvironment in the clinical scenario of high-risk nonmetastatic castrate-resistant prostate cancer has the potential to improve not only quality of life but overall survival. Innovative agents, such as selective estrogen receptor modulators (SERMs), or new combinations of existing agents will continue to be vigorously pursued.

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Footnote

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Treatment Progress

Prevention of bone metatasis in prostate cancer by denosumab: Unneeded endpoint or unmet need?

Carsten-Henning Ohlmann

Department of Urology, Saarland University, Homburg/Saar, Germany

Correspondence to: Carsten-Henning Ohlmann. Dept. of Urology, Saarland University, Kirrbergerstr. 1, 66421 Homburg/Saar, Germany. Tel: +49-6841-16-24700; Fax: +49-6841-16-24795. Email: Carsten.Ohlmann@uks.eu.

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Targeting bone metastases in prostate cancer (PCa) is a major goal since bone metastases are present in >90% of advanced PCa patients causing significant morbidity and mortality (1). Treatment strategies used for "bone targeted" therapies including bisphosphonates and radionuclides mainly focused on the treatment of existing bone metastases and were not deemed to delay the development and formation of new bone metastases. Preclinical evidence suggests that the RANK-Ligand plays an important role for the development of bone metastasis by influencing cell migration and the tissue-specific metastatic behavior of cancer cells. Targeting the RANK-Ligand may therefore be effective in preventing the development of new bone metastases in prostate cancer patients (2). Denosumab is a monoclonal antibody that binds the RANK-Ligand thereby inhibiting interaction with its receptor on the cell surface of osteoclasts and prostate cancer cells. After demonstrating efficacy in the prevention of treatment induced bone loss and prevention of skeletal related events, denosumab has already been licensed for the treatment of prostate cancer patients (3,4). Most recently, the results of a phase-III clinical trial investigating the effects of denosumab on the development of bone metastases have been published (5). The trial recruited 1,432 patients to randomly receive either denosumab (120 mg s.c. 4-weekly) or placebo. Patients with castration-resistant prostate cancer and a high risk of developing bone metastases (i.e. PSA >8 ng/mL and/or PSA doubling time <10 months) were included into the trial. Treatment was continued until occurrence of bone metastases as evidenced by bone scan that was confirmed by a second imaging modality (CT, MRI or plain radiography). Patients were then taken off study and treated per investigator discretion to receive standard treatment for bone metastasis.

Primary endpoint of the trial was bone-metastasis-free survival, as determined by time to first occurrence of bone metastasis (symptomatic or asymptomatic) or death from any cause. Secondary endpoints included time to first bone metastasis and overall survival. The results showed that denosumab significantly improved bone-metastasis-free survival by 4.2 months compared to placebo [HR 0.85 (95% CI: 0.73-0.98), P=0.028]. Median time to first bone metastasis was 29.5 (95% CI: 25.4-33.3) and 25.2 (95% CI: 22.2-29.5) months with denosumab and placebo, resulting in a risk reduction of 15% [HR 0.85, (95% CI: 0.73-0.98), P=0.028] for the development of bone metastasis (*Figure 1*). Furthermore time to first bone metastasis improved significantly (33.2 *vs.* 29.5 months, HR 0.84 with P=0.032) and denosumab led to a 33% reduction in the risk to develop symptomatic bone metastasis (HR 0.67, P=0.01). There was no difference in the time to overall prostate cancer progression (22.4 *vs.* 21.9 months, P=0.13) and median overall survival (43.9 *vs.* 44.8 months, P=0.91) between treatment groups. Overall toxicity and the rate of serious adverse events did not differ significantly, although patients receiving denosumab showed a higher incidence for osteonecrosis of the jaw (5%, any grade) and hypocalcemia (2%, any grade).

By meeting its primary endpoint, denosumab can be regarded as the first "bone targeted" agent that prevents the development of bone metastasis in patients with PCa. This clearly demonstrates the role of RANK and its ligand for the process of bone metastasis formation and leads the way for new treatment strategies in PCa. Despite the positive results of the trial the FDA (food and drug administration) did not agree to expand the indication of XGEVA for the prevention of bone metastasis. The FDA assessed overall

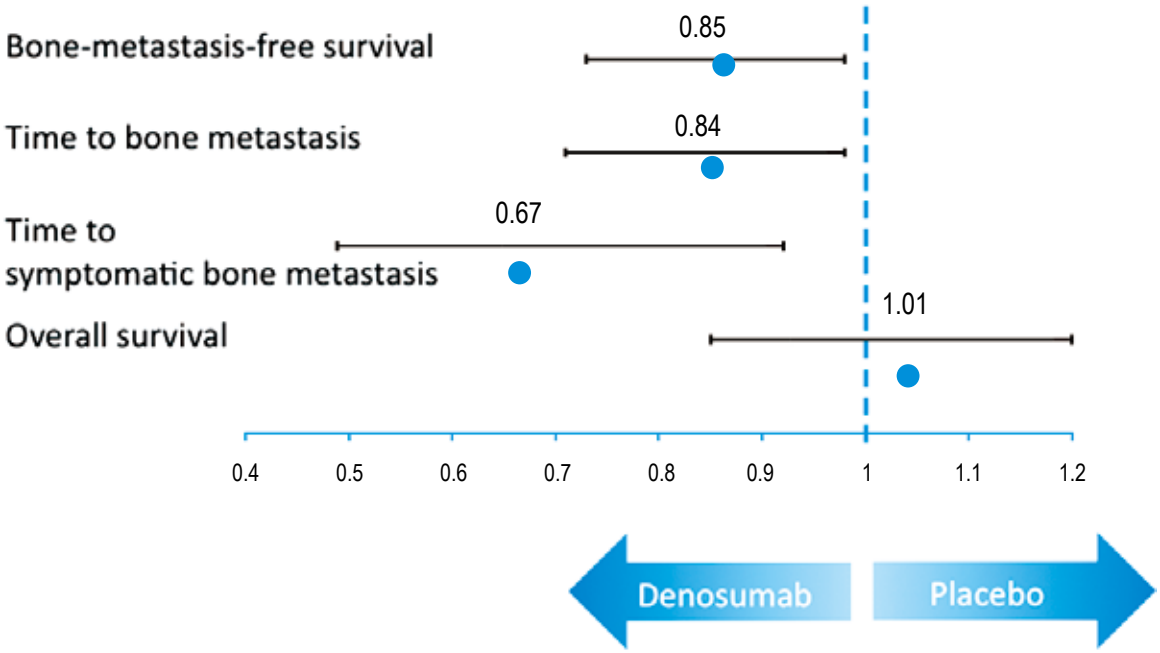

Figure 1 Hazard Ratios (HR, CI 95%) of the primary (bone-metastasis-free survival), secondary (time to bone metastasis, overall survival) and exploratory endpoints (time to symptomatic bone metastasis)

survival, patterns of metastases, and the development of symptomatic metastases as important review issues prior to the initiation of the trial. Time to symptomatic bone metastasis was evaluated in the trial by a *post-hoc* analysis and the FDA therefore considered this endpoint of little value. Furthermore overall survival did not show a difference between groups. Given the fact that denosumab had to be stopped at the time of first bone metastasis and the various subsequent treatments it seems not surprising that an overall survival benefit was not shown for denosumab. The FDA further questions whether time to first bone metastasis is a clinically relevant endpoint given the fact that denosumab showed efficacy in prevention skeletal related events in the metastatic setting with a similar delay. These seemingly limitations of the trial and its results lead to an underestimation of the clinical benefit of denosumab rather than provoking a too optimistic interpretation. It would be not surprising if a delay in the development of bone metastasis as the leading cause of morbidity and death from prostate cancer has an impact on the clinical course and survival of the patients. Even if not proven by the results of this trial it will hopefully prompt further investigations of therapies directed against the development and formation of bone metastasis. Unfortunately the trial of denosumab *vs.* zoledronic acid in metastatic PCa patients did not report on the prevention of subsequent bone metastasis since is seems unlikely that the development of the first bone metastasis abrogates the preventative effect of denosumab. Apart from the new insights in androgen signaling and the integration of the new anti-hormonal into modern therapeutic strategies, treatments targeting bone metastases will clearly have the capability of improving the prognosis of patients with prostate cancer.

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Extension of the therapeutic spectrum in castration-resistant prostate cancer: Osteoclast inhibition with denosumab

Johannes M. Wolff[1], Hans-Peter Schmid[2]

[1]AKH Viersen, Viersen, Germany; [2]Kantonsspital St. Gallen, St. Gallen, Switzerland

Correspondence to: Johannes M. Wolff, MD. Professor and Chairman, Department of Urology, Cornelius Hospital, Heesstrasse 2-10, D-41751 Viersen, Germany. Tel: +492162-4821271; Fax: +492162-4821248. Email: wolff@akh-viersen.de.

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Denosumab is a human monoclonal antibody (IgG2) that binds to RANK ligand (RANKL). It reduces osteoclasts and thereby decreases bone resorption and cancer-induced bone destruction.

A randomized, double-blind, placebo-controlled phase-3 study evaluated the effect of denosumab on bone metastasis-free survival in men with castration-resistant prostate cancer (CRPC) (1). They were at high risk for the development of bone metastases. This was defined as a prostate-specific antigen (PSA) value of ≥8 ng/mL and/or a PSA doubling time of ≤10 months. Patients were randomized 1:1 to receive denosumab 120 mg subcutaneously (SC) every 4 weeks (Q4W; n=716) or placebo SC Q4W (n=716). The main exclusion criteria included evidence of radiographically detectable bone metastases, evidence of viszeral metastases (except lymph nodes), intravenous bisphosphonate use, and history or evidence of osteonecrosis of the jaw. Patients were recommended to supplement calcium ≥500 mg and vitamin D≥400 IU. The primary endpoint of the study was bone metastasis-free survival; this was determined by the time from randomization to the first occurrence of bone metastasis or death. Secondary endpoints were time to first bone metastasis and overall survival. Patients were exposed to denosumab for a median of 19 months and to placebo for a median of 18 months; patients remained on study for a median of 20.2 and 19.0 months, respectively.

The median bone metastasis-free survival was significantly increased by 4.2 months in the denosumab arm compared to the placebo arm [(29.5 versus 25.2 months; hazard ratio (HR): 0.85; P=0.028]. The median time to first bone metastasis was also significantly increased in the denosumab arm compared to the placebo arm (33.2 versus 29.5 months; HR: 0.84; P=0.032). Symptomatic bone metastases were reported in 69 (10%) and 96 (13%) patients in the denosumab and placebo arms, respectively (P=0.03), and the time to a symptomatic bone metastasis was significantly delayed in the denosumab arm compared to the placebo arm (HR=0.67; P=0.01). No differences in OS (HR=1.01; P=0.91) or progression-free survival (HR=0.89; P=0.09) were reported between the two arms.

Results are summarized in *Table 1*.

Adverse events were reported similiarly in both arms, except for osteonecrosis of the jaw: 94% of patients in the denosumab arm and 93% of patients in the placebo arm. The results are summarized in *Table 2*.

This study demonstrates that in patients with CRPC a bone-targeted therapy can delay the time to bone metastasis.

Table 1 Results for patients with castration-resistant prostate cancer

Endpoint, (mo)	Denusomab	Placebo	Hazard Ratio	Risk Reduction	P value
BMFS (median)	29.5	25.2	HR=0.85	15%	P=0.028
Time to first bone metastasis (median)	33.2	29.5	HR=0.84	16%	P=0.032
Overall survival (median)	43.9	44.8	HR=1.01	ns	P=0.91
Progression-free survival (median)	21.7	19.3	HR=0.89	ns	P=0.09

BMFS = bone metastasis-free survival; HR = hazard ratio; NS = not significant

Table 2 Safety results

Event, n (%)	Denosumab (n=720)	Placebo (n=705)
Overall AEs	676 (93.9)	655 (92.9)
Most common AEs:		
- Back pain	168 (23.3)	156 (22.1)
- Constipation	127 (17.6)	119 (16.9)
- Arthralgia	123 (17.1)	112 (15.9)
- Diarrhea	111 (15.4)	102 (14.5)
- Urinary-tract infections	108 (15)	96 (13.6)
Grade 3, 4, or 5 AEs	381 (53)	353 (50)
ONJ (cumulative incidence)	33 (4.6)	0
Hypocalcemia	12 (1.7)	2 (0.3)

ONJ=osteonecrosis of the jaw

Already in 1889 Stephen Paget proposed the seed and soil hypothesis between tumour cells and host microenvironment to explain the spread to different anatomic sites of different cancers. A vicious cycle of complex interactions between prostate cancer cells and bone microenvironment is suggested.

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Therefore the study highlights the important role of bone microenvironment and RANKL signalling in the development of bone metastases in men with CRPC.

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Footnote

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Treatment Progress

Identification of biomarkers in pazopanib treated patients with renal cell carcinoma

Amy M. Pick, Zara Risoldi Cochrane

Department of Pharmacy Practice, Creighton University, School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, NE 68178, USA
Correspondence to: Amy M. Pick, PharmD, BCOP, Associate Professor. Department of Pharmacy Practice, Creighton University, School of Pharmacy and Health Professions, 2500 California Plaza, Omaha, NE 68178, USA. Email: apick@creighton.edu.

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Targeted therapy has become the mainstay in the treatment of renal cell carcinoma (RCC). That being said, it is difficult to predict which patients will respond to targeted therapy. A recent article published in *The Lancet Oncology* attempts to identify biomarkers in patients receiving pazopanib that may be helpful in the clinical management of renal cell carcinoma.

Tran and colleagues performed an investigation of prognostic or predictive biomarkers in metastatic RCC patients treated with pazopanib (1). Using a retrospective design in three phases, the authors screened, confirmed, and validated prospective cytokines and angiogenic factor (CAF) biomarkers using previously published data from an open-label phase 2 trial and a randomized, placebo-controlled phase 3 study. From all patients enrolled in the phase 2 trial, 129 samples were selected for initial screening because these individuals had the greatest or least change in tumor length from baselines. The initial screening phase tested for 17 potentially valuable CAFs, although the authors' inclusion criteria for which biomarkers to assess are unclear. During the confirmation phase, the investigators tested promising CAFs in the complete sample of patients from the same phase 2 trial (n=215). Finally, the validation phase used available samples from the phase 3 trial and analyzed pre-treatment levels of 7 CAFs for their relationship to progression-free survival (PFS): interleukin 6, interleukin 8, osteopontin, VEGF, hepatocyte growth factor (HGF), tissue inhibitor of metalloproteinases-1 (TIMP-1), and E-selectin. Of the 435 patients enrolled in the phase 3 trial, 344 (79%) samples were obtained by Tran et al for validation.

After these three phases of analysis, 4 CAFs were found to interact significantly with PFS in metastatic renal-cell cancer patients who received pazopanib treatment. High (relative to median) pre-treatment plasma concentrations of interleukin 8, HGF, osteopontin, and TIMP-1 were correlated with statistically significant reductions in PFS. Median decreases in PFS ranged from 16-17.8 weeks in patients with high concentrations of these biomarkers, compared to patients with low concentrations. In addition, the study authors found that higher levels of interleukin-6, interleukin-8, and osteopontin were stronger negative prognostic markers than standard clinical classifications, including Eastern Clinical Oncology Group, Memorial Sloan Kettering Cancer Center, and Heng methods. Attempts to investigate the relationship of CAFs to overall survival were confounded by the high proportion of patients (55%) in the phase 3 trial who were randomized to receive placebo but were switched to pazopanib therapy upon disease progression.

Renal cell carcinoma is a biologically diverse cancer accounting for approximately 4% of all new cancer diagnoses in the United States (2). Mutations of the von Hippel-Lindau (VHL) gene are involved in most cases of hereditary and sporadic RCC, leading to overexpression of interleukin-8, VEGF and PDGF (1,3). Numerous targeted agents have been approved for use in renal cell carcinoma, including tyrosine kinase inhibitors and mTOR inhibitors. Pazopanib is one of four tyrosine kinase inhibitors used in the treatment of RCC targeting both VEGF and PDGF.

Past research has been done to identify factors that would be useful in guiding a personalized treatment approach to RCC. These factors have focused on clinical features, histology, immunohistochemistry, VEGF levels, gene mutation status and cell cycle and proliferation markers (4). Although there are numerous biomarkers mentioned in the literature, there is currently no standard biomarker routinely

used in the therapy management of RCC. As new drugs emerge, it would helpful for practitioners to have guidance on which therapy would be appropriate for an individual patient.

While high-quality prospective trials remain the gold standard for predictive biomarker validation, retrospective analyses of clinical studies represent a more feasible and cost-effective alternative when designed and conducted appropriately. Strengths of the Tran et al study include the prospectively declared techniques and study population, and its use of data from two separate peer-reviewed randomized controlled trials for the identification and validation of CAFs. However, the potential for selection bias of the study samples remains since not all patients from the phase 3 trial were included in the validation phase. In addition, no clear sample size or power calculations were described by the investigators, leaving doubt as to whether the analyses were adequately powered to detect all predictive or prognostic biomarkers.

The authors found a high correlation between the three platforms tested (ELISA, protein array, and multiplex assay), suggesting that results were independent of the CAF testing method. However, concentration cutoffs established on one platform could not be applied to other tests. Therefore, verifiable cutoffs must be established before these results can be applied widely.

The study by Tran and colleagues was a well-designed trial that provides evidence for the use of certain CAF biomarkers in the prediction of outcomes in patients treated with pazopanib. Future research needs to expand on this information in order to identify clinically relevant biomarkers that can be generalized to the entire RCC population.

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Treatment Progress

Proposal of "cyclic therapy", a novel treatment strategy with targeted agents for advanced renal cell carcinoma

Masahiro Nozawa, Hirotsugu Uemura

Department of Urology, Kinki University Faculty of Medicine,377-2 Ohno-higashi, Osaka-sayama, 589-8511, Japan
Correspondence to: Masahiro Nozawa, MD, PhD. Department of Urology, Kinki University Faculty of Medicine, 377-2 Ohno-Higashi, Osaka-Sayama, Osaka 589-8511, Japan. Email: nozawa06@med.kindai.ac.jp.

Abstract: The number of molecular targeted agents for advanced renal cell carcinoma (RCC) has gradually increased, but evidence on the optimal order of selection for such agents has not yet caught up with this trend. In addition, timing of switching molecular targeted drugs may also become an important issue for controlling the disease as types of these drugs grow in number. Based on the fact that the efficacy of a rechallenge of the drug previously used suggests the recovery of the sensitivity, a cyclic therapy in which drugs are changed before exacerbation to repeatedly administer several drugs in a rotated manner, may also be an effective sequential therapy.

Keywords: Cyclic therapy; sequential therapy; rechallenge; renal cell carcinoma (RCC); targeted therapy

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Current status and challenges of sequential therapy in advanced renal cell carcinoma

At present, it is evident that complete remission of metastatic renal cell carcinoma (mRCC) can be hardly expected through administration of an existing molecular targeted agent alone (1-10). On the other hand, simultaneous combination therapy with multiple molecular targeted agents may not be realistic in terms of tolerance (11-14). Therefore, the goal of current medical treatment for advanced RCC should be to aim for maximal extension of survival by sequentially administering individual drugs, while maintaining as high quality of life (QOL) as possible. For this purpose, recommended drugs for each setting have been proposed in various guidelines based on evidence obtained (15,16).

Unfortunately, valuable evidence on which drug selection for conducting sequential therapy can be absolutely defined has not been fully collected. For example, when sunitinib is used in a patient as first-line therapy, everolimus or axitinib is usually considered as the option for the second-line therapy after the patient develops resistance to sunitinib. However, there has been no evidence demonstrating which of these two drugs is superior to the other.

In addition, even when superiority of either drug is shown, drug efficacy from the third-line treatment and thereafter may be reversed, or no difference may be observed in the final overall survival (OS). In fact, in the AXIS trial, although superiority of axitinib to sorafenib as the second-line therapy was shown from the viewpoint of progression-free survival (PFS), there was no significant difference in OS between the two groups (2). These results suggest that, because there are other effective agents that can be administered at or after the third-line therapy, the final treatment outcome may become almost constant regardless of the order of drugs used, when full use of these alternative drugs can be skillfully made. In other words, a proposition is raised: how meaningful is it, from the viewpoint of OS, true benefit for the patients, to determine the order of drugs used by comparing PFS for individual drugs?

Currently, only for the first-line therapy, at least three treatment effective options, sunitinib, pazopanib, and a combined therapy of bevacizumab/IFN, are present for favorable- and intermediate-prognosis patients. When possible drug combinations for sequential treatment as the second-, third-, or fourth-line therapy are considered,

conducting clinical trials to determine merits and demerits of all the drug combinations is not feasible, because the patterns of combination therapy increase at an exponential rate. Eventually, it may be almost impossible to build up high-quality evidence to establish the most effective sequential therapy when OS is used as the primary endpoint.

The meaning of the efficacy of rechallenge

We have already reported an outcome of rechallenge with sorafenib in our institute (17). In the study, patients were administered with first sorafenib with a median PFS of 5.7 months. Subsequently, these patients experienced treatments with sunitinib and everolimus, and after a 7.6-month median interval from the initial sorafenib challenge, they were rechallenged with sorafenib. The median PFS on the rechallenge was 5.4 months. Thus, the outcome of the sorafenib rechallenge was comparable to that of the first with sorafenib. For sunitinib, the effect of rechallenge was similarly investigated (18). These results suggest the presence of a mechanism in which, at least for sorafenib and sunitinib, sensitivity to these drugs can be regained by providing a given period of time without treatment, even after resistance to these two drugs has developed. If the mechanism can be universally applied to other targeted agents, it will further broaden options to select drugs used in sequential treatment.

Unlike the era in which only sorafenib and sunitinib were available soon after the approval of these first molecular targeted drugs, in the current situation, in which seven molecular targeted agents can be used, there may possibly be doubts on the importance of rechallenge therapy. However, in actual clinical settings, drugs should be selected based not only on prognostic factors and previous history of treatment shown in algorithms in guidelines, but also patient's age, performance status, functions of various organs, as well as concomitant diseases and profiles of adverse events for the drugs should be fully considered. Therefore, although seven drug options are potentially available for the patient, drugs that can actually be administered to an individual patient for a long time may be limited in many cases, depending on comorbidity and/or development of adverse events. In these cases, the following sequential therapy can be applied: a drug mainly used in the treatment should be rechallenged, while other drugs are not administered more than necessary for a prolonged period, and used as a relief during the period between the first challenge and rechallenge with the main drug. Therefore, an implication suggested by the efficacy of rechallenge was that it proposed a rationale for discussion of the timing of switching drugs for advanced RCC.

Timing of switching drugs

It has been reported that clear cell carcinoma, which accounts for approximately 80% of RCC, has heterogeneous genetic background depending on primary or metastatic focus, or site within a primary focus (19,20). Differences in genetic background suggest that sensitivity to drugs may be also varied. It is not a rare case in which responsiveness to a drug is significantly different between primary and metastatic foci, or a metastatic focus tends to shrink while other foci inversely show a trend to enlargement. One of the reasons for these phenomena may be the heterogeneity of gene mutation in these cancer cells. In that case, it is expected that simultaneous combination therapy with multiple drugs that target different molecules would show excellent anti-cancer effect, but this is unfortunately not realistic, at least in terms of tolerance to combined therapy with existing molecular targeted drugs. Consequently, there is no other way but to use several drugs by sequentially switching them. However, if a patient deteriorates instead of achieving complete remission, it means that the tumor was initially sensitive to a drug used but later developed resistance to the drug during treatment. In other words, in the course of therapy with continuous administration of a single drug, sensitivity of the tumor to the drug may be gradually decreased as a whole.

On the other hand, the efficacy of rechallenge suggests that no exposure to the drug during a given period of time may cause regaining of tumor sensitivity to the drug. When hypothesizing that some sensitivity can be restored by introducing a non-exposure period, additional anti-tumor effect can be expected by divided treatment with non-exposure periods through drug interruption, compared to continuous administration of the drug until sensitivity is lost. We will simulate a sequential therapy by applying this hypothesis. Treatment regimen 1 is a conventional sequential switch therapy in which three drugs are administered until the sensitivity of each drug is decreased to zero. By contrast, in treatment regimen 2, a drug is administered over divided dose periods by shortening single dosing duration and inserting other drugs to the non-exposure period. The latter method can not only add anti-tumor effect as sensitivity is regained, but also maintain sensitivity of the tumor to each

drug, showing a potential for continuous treatment. In addition, in the latter regimen, no non-treatment period for cancer is present, because other drugs are administered during the non-exposure period of the main drug, which would otherwise be a non-treatment period if a single drug were used. It can be said that this dosing regimen works only in today's treatments of RCC, where a relatively long prognosis is expected because many effective drugs are available.

Proposal of "cyclic therapy"

An ideal drug selection would of course be a tailor-made treatment based on biological characteristics of a patient and his/her tumor. However, predictive markers of therapeutic effects to determine the optimal drug for the cancer in a patient before treatment have not yet established. In addition, under present circumstances, even the evidence necessary to determine an order of administration of drugs is insufficient, as mentioned above.

Seven different drugs are now available for RCC, after approval of axitinib. It is highly possible that more new drugs will be developed in the future. In a sequential therapy, it may be difficult to administer all drugs to be used in the natural course of cancer if each of these drugs is continued until disease deterioration. In other words, there may be drugs that are not administered to the patient before end of treatment. In that case, the possibility cannot be denied that drugs that were sixth or seventh on a waiting list could have been the most beneficial agent for the patient. To avoid such a misfortune, the dosing regimen described above would be useful. For example, drugs could be evaluated based on the following criteria at the stage after administering all the drugs within the first treatment cycle: I. the most beneficial drug; II. drugs with excellent anti-tumor effect but poor tolerance; III. drugs with intermediate anti-tumor effect and tolerance; IV. drugs showing some anti-tumor effect but leading to unacceptable adverse event(s); and V. drugs not showing any anti-tumor effect. Based on the preliminary evaluation, drugs that met criteria IV and V are withdrawn from treatment, and only drugs that met criteria I, II, and III are used from the second cycle: Drug I is mainly used, and a non-exposure period is set after a certain treatment period with Drug I. Drugs II and III are inserted between the first treatment and rechallenge with Drug I. This "cyclic therapy" with these three different drugs would be repeated. Apart from whether this model is an ideal sequential therapy or not, it may be an idea worth considering as a method to achieve a therapeutic goal for advanced RCC aiming to maximally extend survival while maintaining as high QOL as possible.

Conclusions

New drugs effective for RCC could be continuously developed in the future. Evidence cannot always indicate all the answers to the many questions in drug selection. Although a tailor-made therapy based on biological characteristics of a patient and his/her tumor would be ideal, no markers for predicting effects of treatment have been discovered to date. In this context, we must always explore treatment methods that can lead to as much benefit for patients as possible. Evidently, our goal is not to seek a means to continuously administer a single agent for as long as possible. We should play a role in making full use of the treatment modalities currently available and considering and devising ways to obtain the optimal outcome.

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Footnote

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Does patient-tailored immunotherapy pave the way for new renal cell carcinoma treatment perspectives?

Ilse Van Brussel[1], Amaryllis H. Van Craenenbroeck[2], Dorien M. Schrijvers[3], Nathalie Cools[4]

[1]Laboratory of Pharmacology, University of Antwerp, B-2610 Antwerp, Belgium; [2]Division of Nephrology-Hypertension, Antwerp University Hospital, B-2650 Edegem, Antwerp, Belgium; [3]Laboratory of Physiopharmacology, University of Antwerp, B-2610 Antwerp, Belgium; [4]Laboratory of Experimental Hematology, Vaccine and Infectious Disease Institute (VAXINFECTIO), University of Antwerp, B-2610 Antwerp, Belgium

Correspondence to: Ilse Van Brussel. Laboratory of Pharmacology, Faculty of Medicine and Health Sciences, University of Antwerp, Universiteitsplein 1, B-2610 Antwerp, Belgium. Email: ilse.vanbrussel@ua.ac.be.

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Renal cell carcinoma (RCC) constitutes 80 to 85 percent of primary renal neoplasms in adults (1). Although surgical resection can be curative in localized disease, many patients eventually recur. Patients with locally advanced or metastatic disease have a poor prognosis, with a 5-year survival rate of less than 15%. Because RCC is highly resistant to both chemotherapy and radiation therapy (2), immunotherapy might have the highest potential as a novel treatment for RCC (3). Accumulating evidence indeed shows that effector cells of the immune system play an important role in the recognition and elimination of neoplastic cells. Particularly in RCC, experimental data suggest that the immune system might be extremely important in controlling the disease *in situ* (4). For example, in RCC, major T cell infiltrates can be demonstrated in the tumor. The presence of antigen-specific T cell clones has been shown in both primary lesions and draining lymph nodes, and these clones are able to lyse renal carcinoma cells *in vitro* (5,6). Unfortunately, in the long term, the immune response against RCC fails to limit disease progression.

To date, several immunotherapeutic approaches have been proposed to treat RCC (3,7), particularly since different RCC-related tumor antigens have been identified that can be targeted, processed and presented by immune effector cells (8). It is well known that of these immune effector cells, dendritic cells (DCs) play an orchestrating role in regulating T cell responses, partly due to their potent antigen-presenting capacity (9). The attractive concept of autologous monocyte-derived DC-based tumor vaccination resulted in an increasing number of phase I/II trials with different approaches regarding the vaccine composition, including the nature of the antigen(s) (7). Synthetic peptides are commonly used to load DCs in DC-based vaccination trials, but are mostly HLA-A*0201-restricted which limits their clinical use. The use of tumor lysate circumvents this restriction and has the advantage of inducing a polyclonal immune response. Similarly, the use of total renal tumor RNA-transfected DCs has proven to induce T cell activities directed against a broad set of renal tumor-associated antigens (10). In the AGS-003 strategy, autologous DCs co-electroporated with the patients' amplified tumor mRNA and synthetic CD40L RNA are employed (11). Although encouraging results are reported upon administration of this vaccine with regard to immune response as well as survival (12), results from the phase III trial have not been published yet (http://clinicaltrials.gov/ct2/show/NCT01582672).

Recently, the first autologous DC-based therapy was approved by the Food and Drug Administration (FDA) for treatment of patients with asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (mCRPC). Sipuleucel-T (known by the trade name, "Provenge") is a cellular vaccine which is created upon collection of patient's white blood cells and subsequent *in vitro* incubation of these cells with a fusion protein that combines prostate acid phosphatase (PAP) with recombinant granulocyte-macrophage colony-stimulating factor (GM-CSF). Upon re-infusion of this cell product into the patient, sipuleucel-T stimulates the patient's own immune system to specifically recognize and combat his cancer. As was published in the New England Journal of Medicine, sipuleucel-T prolonged median survival by 4.1 months

compared with results in placebo-treated patients (13). In summary, the advantage of DC-based immunotherapeutic strategies is good tolerability and observed survival benefit. Unfortunately, these patient-tailored therapeutics are very time-consuming and costly. As an alternative, targeting DCs *in vivo* may be more attractive from a cost-effectiveness perspective, since this approach would omit tailor-made *ex vivo* culturing. Indeed, such off-the-shelf therapeutic vaccines have shown preliminary evidence of efficacy (13), providing hope that improvements in patient outcomes with this modality may lead to therapeutic options that are less resource-intense. Walter *et al.* (14) developed IMA901, a peptide vaccine for RCC, consisting of nine HLA-A*02-restricted tumor-associated peptides (TUMAPs) and one HLA-DR-restricted TUMAP in combination with administration of GM-CSF. GM-CSF is used to stimulate antigen-presenting cells (APCs), including DCs (15), *in vivo*. Subsequently, TUMAPs bind to major histocompatibility complex (MHC) molecules on the cell surface of APCs, and in turn the activated APCs facilitate *in vivo* priming of T cells. Hence, the designated purpose of IMA901 is to elicit a therapeutic immune response to antigens expressed by cancer cells. The authors report stabilization of the disease or a partial response to therapy in 43% of the 28 patients that received eight intradermal IMA901 vaccinations. In the remainder 57% of subjects, RCC progressed (14). Furthermore, subjects that responded to multiple TUMAPs were significantly more likely to experience disease control than subjects that responded to only one TUMAP or showed no response (14), indicating that the enhancement of the breadth of immune responses targeted to antigens introduced by the vaccine is of great consequence.

Strong and broad T cell responses will prevent immune escape by certain cancer cells that have altered their cell surface expression of certain HLA molecule(s). Although Walter *et al.* have not addressed the added value of inclusion of the HLA-DR-restricted TUMAP, others have demonstrated the importance of $CD4^+$ T cell help in the stimulation of such strong and effective cellular immune responses. $CD4^+$ T helper cells deliver help for $CD8^+$ cytotoxic T cells by fully activating DCs through the CD40-CD40 ligand signaling pathway as well as by the secretion of interleukin-2 (16). Pan HLA-DR epitope (PADRE) peptides, that are capable of binding to different MHC class II molecules with high-affinity (17), have been used in conjunction with other forms of vaccines to enhance vaccine potency in preclinical models (18,19) and they have also been used in clinical trials with minimal toxicity (20). Alternatively, $CD4^+$ T cell help can be achieved by using synthetic long peptides (SLPs) (21). Following *in vivo* uptake by DCs, a proportion of the SLPs is processed and loaded into MHC class II molecules, allowing fragment presentation to $CD4^+$ T helper cells. Another part of the ingested SLPs is digested by the proteasome in the cytosol and the endoplasmatic reticulum. This is followed by loading of 8-10 amino acid-long peptides into MHC class I molecules, which allows fragment presentation to $CD8^+$ cytotoxic T cells (22).

Nevertheless, the increase in median overall survival in the patients treated with IMA901 was not associated with standard measures of efficacy, including changes in size and volume of measurable lesions. This uncoupling effect on survival and disease progression appears to be a common property of immunotherapy, and is designated as a delayed treatment effect. Indeed, biological effects of cancer vaccines are not related to their pharmacokinetics, and effectiveness may take weeks or months to become apparent (23). Hence, effectiveness as measured by tumor regression at traditionally early time points may fail to demonstrate any measurable potentially beneficial effect. For this, studies are intensified to develop new, non-invasive diagnostic tests, e.g., biomarkers, to carefully monitor the effect of the vaccination strategy on the tumor. The feasibility and value of a comprehensive biomarker program has been underscored by Walter *et al.*, as indicated by the identification of two biomarkers, APOA1 and CCL17, that are potentially predictive for vaccine-induced immunity and overall survival.

Furthermore, studies that improve or refine immunotherapeutic outcomes in the clinic are warranted. Simple methods that are likely to increase efficacy include (I) administration of boost vaccinations in order to extend the response; (II) treating patients earlier in their disease course; (III) and combination strategies with agents that are known to activate, accelerate, and augment immune responses (24). These include adjuvants (IL-7, IL-12, IL-15, and monophosphoryl lipid) to augment T cell responses, and antagonists of negative regulators of T cell activation [anti-CTL-associated receptor 4 (CTLA-4) and anti-programmed death 1 (PD1) receptors], as well as agents to neutralize immunosuppressive cytokines (anti-IL-10 and anti-TGF-β) that are important in winding down immune responses. Walter and colleagues (14) improved the efficacy of the IMA901 vaccination by means of a single-dose cyclophosphamide. Indeed, the median overall survival of the patients treated with IMA901 and cyclophosphamide was 23.5 months compared to 14.8 months in the patients

treated without cyclophosphamide. It has been postulated that this immunomodulator counteracts the regulatory mechanisms that oppose successful immunotherapy, e.g., by reducing the numbers of regulatory T cells (Tregs) (25).

In conclusion, it remains to be established from ongoing phase III trials whether the DC-based vaccine AGS-003 or the peptide vaccine IMA901 results in the best treatment for advanced renal cell carcinoma with the highest overall survival benefit. However, it is likely that vaccination approaches will become part of the armamentarium of nephrologists, urologists and medical oncologists who manage and care for renal cancer patients.

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Footnote

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Treatment Progress

Immunotherapy in renal cell cancer: the more the merrier?

Jorge Camarero[1], Sol Ruiz[2]

[1]Pharmacology and Clinical Assessment Division, [2]Biotechnology and Advanced Therapies, Spanish Medicines Agency, Campezo 1 - Edificio 8, 28022 - Madrid, Spain

Correspondence to: Jorge Camarero. Pharmacology and Clinical Assessment Division, Spanish Medicines Agency, Campezo 1 - Edificio 8, 28022 - Madrid, Spain. Email: jcamarero@aemps.es.

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Renal cell carcinoma (RCC) is the most common primary malignancy affecting the kidney and considered a disease refractory to systemic therapy beyond cytokine therapy (the use of interferon alfa and interleukin 2 was limited when targeted therapies became available) (1). Currently, eight drugs are approved in the European Union (EU) for the treatment of advanced RCC, including IL-2, IFN-α, sorafenib, sunitinib, everolimus, temsirolimus, bevacizumab in combination with IFN-α, and pazopanib.

Despite the increasing availability of treatment options, a number of clinical trials are ongoing to identify and develop new therapeutic alternatives. Active immunotherapy has become an attractive option for the treatment of different types of cancer (2).

Due to the immunogenic nature of RCC, immunotherapy approaches are being developed but a number of factors have hampered their development, such as lack of defined antigens, selection of optimal dose and schedule, tumor escape from immune recognition (including loss or downregulation of HLA class I antigens) or tumor mediated suppression of immunity (involving regulatory T cells -Tregs-), increased oxidative stress, or recruitment of myeloid-derived suppressor cells (3). Indeed Steffen Walter and coauthors (4) have tried to target and investigate several of these mechanisms with a new immunotherapy for patients with RCC. Interestingly, their study has also pursued the identification of predictive biomarkers of immune response and efficacy of the "cancer vaccine".

Immune recognition of tumor-associated antigens by self-HLA (human leukocyte antigen) class I-restricted CD8+ cells is a key feature in detection and destruction of tumor cells. This is the main rationale Steffen Walter *et al*. have used for their approach, i.e. selection of HLA class I tumor-associated multiple peptides (TUMAPs) to try to stimulate an effective immune response against the tumor. The success of this treatment would require a normal expression of HLA class I genes (5) and, therefore, any regulatory or irreversible/structural defects underlying HLA class I loss may be a potential limitation for this approach. The second aim of the study was to identify an agent that reduced the number of Tregs in order to improve the clinical benefit of the vaccine. The role of Treg cells in cancer development and progression is not clear. Tregs may facilitate immune evasion through suppression on anti-tumor immune responses resulting in tumor growth (6). This is another basis for the rationale for IMA901 development. However, recent data indicate that the role of Tregs in other types of cancer, such as colorectal carcinoma, may be beneficial for the host by suppressing bacteria driven inflammation which, in the end, would promote carcinogenesis. Therefore, Tregs appear to play a dual role in cancer, sometimes being associated with a poor prognosis and others with more favourable prospects (7).

As a third aim the authors have also addressed a very interesting objective for this immunotherapy product, i.e. identification of biomarkers for a good clinical response.

From a point of view of product design, the advantages of this product are its simplicity and quite straightforward characterization as this is a mixture of 10 synthetic peptides. From the results published, the authors are presenting outcomes from a phase I and a phase II studies. For the phase I trial, 28 HLA-A*02+ subjects with RCC were recruited, 15 of them were treated with IMA901 as first line therapy, whereas 13 out of 28 had been previously treated up to three lines of treatment; 11 subjects achieved stable disease and one patient had a partial response.

In the phase II trial of Walter *et al*. 68 patients with metastatic RCC previously treated were randomised 1:1 to receive either cyclophosphamide (Cy; one single infusion administrated as an immunomodulator) together with IMA901 and GM-CSF or only IMA901 plus GM-CSF. Patients were stratified according to risk factors from Memorial Sloan-Kettering Cancer Center, (MSKCC) favourable or intermediate risk and previous treatment [cytokine or tyrosine kinase inhibitor (TKI)]. The primary endpoint was Disease Control Rate (DCR; percentage of subjects with complete or partial response or stable disease according to RECIST) after 6 months. Main secondary endpoints were Progression Free Survival (PFS), Overall Survival (OS), immunogenicity and safety. Results from this study showed a better DCR for those patients previously treated with cytokines than those receiving TKIs (31% *vs*. 14%). Focusing on the PFS and OS outcomes, no differences were observed between the two groups of study in terms of PFS, though OS was increased in the Cy+ arm [23.5 months for Cy+ compared with 14.8 months for Cy-, hazard ratio (HR) =0.57, P=0.090]. Several subgroup post-hoc analyses were carried out, showing positive results in immune responders. Of note, the median OS was not reached after 33.1 months in those patients previously treated with cytokines.

All these results seem to be pointing out to a promising treatment in metastatic RCC, although the design and sample size hamper the ability to draw firm conclusions. Indeed, results from the primary endpoint in both arms of the phase II study are unknown. Data from PFS did not show any differences between groups, and OS outcomes only appear to be outstanding in the subgroup which received previous cytokine treatment. In this way, subjects treated with cytokines could obtain a higher benefit of being treated with the cancer vaccine IMA901, whereas those patients with a TKIs front line treatment would not obtain better benefit than patients under either sorafenib or everolimus administration in second line. In fact, the median PFS for everolimus has been reported close to 4 months (RECORD-1 study) (8), albeit most of the patients in this study were heavily pre-treated; in other words, most likely patients with poorer prognosis. This apparent lower activity of the immunotherapy treatment in the TKIs pre-treated patients may indicate an unknown cross resistance mechanism, which could eventually reduce the clinical applicability for patients in second line, since the first line therapy currently used is based on TKIs and not on cytokines.

In addition, the analyses of the results, mainly PFS and OS, were carried out in the per protocol population (PP) (31 and 33 patients *vs*. 68 subjects for the ITT population). This latter caveat, methodologically speaking, goes further into subgroup analysis, with sample sizes of 17, 13, 22 or 9 patients. Interestingly, no results are shown regarding the other stratification factor, risk factor according to the MSKCC.

Taken together, these results should be considered as hypothesis generating and indeed a phase III trial is ongoing to investigate whether IMA901 can prolong OS in patients with metastatic and/or locally advanced RCC when added to standard first-line therapy with sunitinib.

In summary, the benefits of this new immunotherapy treatment seem to indicate that life expectancy for patients with metastatic and/or locally advanced RCC could be increased. However, the outcome appears to be solely outstanding in the subset of patients previously treated with cytokines, which is not deemed the standard first line therapy anymore. Despite this fact, a phase III trial will test IMA901 in combination with sunitinib, assessing OS as a primary endpoint, which is encouraging, since, as a whole, when oncologists prescribe a treatment without any expectations for full recovery, the control of the symptoms and patients' overall quality of life are the goal of the treatment. Certainly, these premises are usually sought in terms of PFS, especially from a regulatory view. However, the ongoing phase III study is ambitious and challenging, given that only temsirolimus (9) has demonstrated an increase in OS in first line for RCC patients.

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Footnote

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The argument for palliative care in prostate cancer

Melissa T. Sanford, Kirsten L. Greene, Peter R. Carroll

UCSF Helen Diller Family Comprehensive Cancer Center, Department of Urology, University of California San Francisco, San Francisco, CA 94143, USA

Correspondence to: Melissa T. Sanford, MD. Department of Urology, University of California San Francisco, 400 Parnassus Ave Suite 610, San Francisco, CA 94143, USA. Email: sanfordm@urology.ucsf.edu.

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Palliative care uses a team approach to improve the quality of life of patients and families faced with long-term and progressive illnesses through prevention and relief of suffering with symptom management. Palliative care focuses on three main realms to achieve these goals: morbidities associated with the disease, morbidities associated with the treatment, and quality of life of the patient. Oncology guidelines suggest initiating palliative care "early in the course of illness in conjunction with other therapies that are intended to prolong life, including chemotherapy and radiation" (1). Possibly due to the association with end of life care, palliative care is under-utilized for prostate cancer despite evidence showing benefit in several patient populations.

Prostate cancer is particularly amenable to palliative symptom management because of its long disease course and, often, non-lethal progressive nature. It is the most common cancer diagnosis in American males and there are expected to be almost 240,000 American men diagnosed with prostate cancer in 2013 (2). Of those staged at diagnosis, 80% will have localized disease, 12% will have regional disease, and 4% will have metastatic disease (3). Disease specific morbidity worsens as prostate cancer progresses and can include bony metastases, spinal cord compression, lymphedema, urinary obstruction, fatigue, anemia, and significant psychological effects including depression, anxiety, poor coping ability, altered view of self and future, lack of empowerment, and disrupted partner intimacy (4). The treatments for prostate cancer vary by stage but all may be associated with morbidity. Localized treatment with surgery and/or radiation is associated with side effects including pain, erectile dysfunction, incontinence, bowel dysfunction, fatigue, dysuria, gross hematuria, and urethral stricture development (5). Men who develop biochemical recurrence after localized therapy and men who are diagnosed with regional or metastatic disease may be treated with androgen deprivation which can cause side effects including nausea, vomiting, diarrhea, hot flashes, loss of libido, gynecomastia, insomnia, gastric ulceration, immune suppression, psychiatric effects, myalgias, weight gain, osteoporosis, and lower urinary tract symptoms (6). A number of novel therapies including chemotherapies, targeted-hormonal therapies, and immunotherapies have been developed for castrate-resistant prostate cancer in recent years that can prolong survival on average two to four months, however they may be associated with a number of severe side-effects (*Table 1*). In light of the significant disease and treatment morbidities associated with prostate cancer it is not surprising that Torvinen *et al.* found markedly worsened quality of life across the three realms of palliative care as prostate cancer progressed from localized to metastatic disease (7).

The literature overwhelmingly supports the utilization of palliative care in both long-term illness and various forms of cancer. Multiple randomized trials have demonstrated significantly improved quality of life, decreased symptom intensity, improved patient satisfaction, longer hospice stays, lower health care costs, and less aggressive end-of-life care (8,9). One of the most widely discussed and intriguing trials by Temel *et al.* showed significantly longer median survival (11.6 *vs.* 8.9 months, $P<0.02$) after implementation of palliative care for patients with non-small-cell lung cancer (10). The limited data examining palliative care specifically in prostate cancer also supports its use. A retrospective review at MD Anderson found that the most common symptoms reported by men with advanced prostate cancer included fatigue, drowsiness and pain.

Table 1 Castrate resistant prostate cancer treatment side effects

Drug	Median OS (months)	S/E
Mitoxantrone	No improvement, but improved symptom palliation	Dyspnea, mucositis, cytopenias, cardiac dysfunction
Docetaxel	2.9 (mitoxantrone/prednisone)	Neutropenia, neuropathy, fatigue, N/V, alopecia, diarrhea, dyspnea, tearing, peripheral edema, nose bleeds
Sipuleucel-T	4.1 (placebo/prednisone)	Chills, HA, fever
Abiraterone	4.6 (post-docetaxel, placebo/prednisone)	Fatigue, arthralgia, peripheral edema, anemia, back pain, bone pain, hypokalemia
Cabazitaxel	2.4 (post-docetaxel, mitoxantrone/prednisone)	Neutropenia, diarrhea, N/V
Enzalutamide	4.8 (post-docetaxel, placebo/prednisone)	Fatigue, diarrhea, hot flashes, seizures
Radium-223 dichloride	2.8 (placebo)	Nausea, vomiting, peripheral edema

OS, overall survival; S/E, side effects; N/V, nausea, vomiting; HA, headache.

After palliative care intervention patients had statistically significant improvement in those symptoms as well as sleep, well-being, anxiety and depression (11). Rabow *et al*. found that men with prostate cancer undergoing palliative care in addition to their oncologic or surgical management had significant improvements in fatigue (P=0.02), anxiety (P<0.01), depression (P<0.01), quality of life (P<0.01) and spiritual well-being (P<0.01) (12).

However, referrals to palliative care typically occur late in the disease process because of its inappropriate association with end-of-life care and failure to recognize that symptom management can be utilized throughout the course of a disease. Dalal *et al*. found that one barrier to care was the name "palliative care" itself. After changing their group's name from "palliative care" to "supportive care" they received an increase in consultations and shorter duration from the time of diagnosis to consultation (13). Similar to the change in terminology from "watchful waiting" to "active surveillance" indicating use in different patient populations and treatment interventions, perhaps palliative care would benefit from a name change to broaden its recognition and allow patients with non-life-threatening disease to benefit from its incorporation into routine care.

Palliative care used in conjunction with prostate cancer treatment can significantly improve patient quality of life however it is rarely implemented early in the disease process. With nearly 38,000 men expected to be diagnosed with regional or metastatic prostate cancer this year and an expected 30,000 deaths from prostate cancer in 2013 it is imperative that we begin to follow the guidelines and initiate symptom-modifying palliative care along with disease-modifying therapies.

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Footnote

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Treatment Progress

Greenlight laser vaporization versus transurethral resection of the prostate for the treatment of benign prostatic obstruction: evidence from randomized controlled studies

Mostafa M. Elhilali[1], Mohamed A. Elkoushy[1,2]

[1]Department of Surgery, Division of Urology, McGill University, Montreal, QC, Canada; [2]Department of Urology, Suez Canal University, Ismailia, Egypt

Correspondence to: Mostafa M. Elhilali. Department of Surgery, Division of Urology, McGill University, Montreal, QC, Canada.
Email: mostafa.elhilali@muhc.mcgill.ca.

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Transurethral resection of the prostate (TURP) is almost always regarded as the standard in the surgical treatment for benign prostatic obstruction (BPO). However, TURP is not uncommonly associated with perioperative morbidities, which are directly related to prostate volume and surgically high-risk patients with associated comorbidity, including pacemakers, anticoagulant and platelet antiaggregant medications. The time-dependent absorption of electrolyte-free irrigating fluid leading to hyponatremia, usually limit the time to perform a safe monopolar TURP especially in large adenomas.

In the last decade, a variety of cost-effective transurethral laser technologies emerged as alternative minimally-invasive surgical options for management of BPO, including the Greenlight photoselective vaporization of the prostate (PVP). This is a side-firing laser technique, which has been refined from the 60 W system initially introduced by Malek *et al.* (1) to the currently available models in use with different maximum power output (80, 120, and 180 W) and different fiber design. Several randomized controlled trials (RCTs) have confirmed the efficacy and safety of these subsequent Greenlight generations in comparison to TURP. Unfortunately, systematic reviews and meta-analyses are limited by the heterogeneous reporting of data of these RCTs due to the combination of different generations of PVP into a single arm against which TURP was compared. Occasionally, the TURP cohort included mono and bipolar technology, adding another component of heterogeneity. Another limitation resides in the different follow-up times reported with a high attrition rate beyond 1-year follow-up. Thangasamy and colleagues included nine RCTs with 448 patients undergoing PVP (80 W in five trials and 120 W in four trials) and 441 undergoing TURP with a follow-up ranging from 6–36 months (2). Six studies found no difference between PVP and TURP, two favored TURP, and one favored PVP.

The Greenlight laser is a continuous wave laser which initially used a potassium titanyl phosphate (KTP) crystal to produce a light beam at a wavelength of 532 nm. This wavelength is selectively absorbed by oxyhemoglobin in prostatic tissue at a power level of 80 W, allowing for tissue photovaporization with a short depth of penetration. Although comparable functional outcomes had been found between KTP/80 W and TURP for relatively small prostates in a nonrandomized prospective study (3), early functional results of TURP were superior to PVP in patients with prostates larger than 70 mL in another RCT (4).

Replacing the previous KTP/80 W, the High Performance System (HPS) generates more collimated laser beams (8° *vs.* 15°) with a lithium triborate crystal, increasing the power generated to 120 W (5), with consequent improvement in the ablation efficacy. In a bovine model, HPS laser at 80 and 120 W respectively vaporized 50% and 100% more tissue than the KTP/80 W (6). Nevertheless, several challenges remained including hemostasis and fiber deterioration while larger prostates remain problematic. In one RCT with 36-month follow-up, TURP was associated with significantly higher transfusion rate (20% *vs.* 0%) and percent reduction in prostatic specific antigen while HPS/120 W was

associated with significantly higher reoperation (11% *vs.* 1.8%) (7). We have to keep in mind that the major handicap of minimally invasive surgery for BPO is the durability/reoperation rates. Another multicenter RCT failed to demonstrate the non-inferiority of HPS/120 W to TURP on prostate symptoms at 12-month, despite the shorter length of hospital stay associated with HPS (8). Unfortunately, this study has a questionable methodology in terms of sample size calculation and the non-inferiority margin of two IPSS points and/or a difference in length of stay of ≥1 day between the two techniques. Sample size calculated was apparently underpowered and the number of patients enrolled per each arm was inconsistent with what has been calculated while increased length of hospital stay may result from non-procedural causes.

Consequently, Greenlight XPS/180 W was introduced in 2011 to provide the fastest and most efficient prostate vaporization with a comparable safety profile to the former Greenlight devices. It increases operation time efficiency by providing more energy/time and potentially used for vapoenucleation. Furthermore, the latest MoXy liquid-cooled fiber demonstrates less significant degradation during vaporization, leading to a constant high-power output until the end of the procedure and better coagulation with pulsed Trucoag.

The recent GOLIATH study prospectively compared XPS/180 W to the conventional TURP for the treatment of BPO (9). The authors are commendable in their efforts to develop the largest prospective RCT comparing laser prostatectomy with TURP. The short-term comparable efficacy and safety outcomes between both procedures which were previously observed at 6 and 12 months were maintained at the recently reported 2-year follow-up. Unfortunately, methodological flaws have created a significant level of bias that presents challenges in accepting its conclusions.

Considering the non-inferiority design of the study, one should be cautious when interpreting its results as such study design has its own limitations and is uncommonly associated with valid conclusions, whatever the perfect data analysis was. A selection bias is also expected from combining monopolar and bipolar data in the TURP arm (58.6% *vs.* 41.4%). A recent meta-analysis showed better perioperative outcomes with bipolar TURP and PVP compared with monopolar TURP (10). Seven patients in the TURP arm were diagnosed to have prostate cancer, 5 of them (3.8%) were diagnosed incidentally. This is well known to happen and should not influence the outcome from a functional point of view. The authors suggested that this finding should be considered as an adverse event, which does not make any sense. On the other hand, PVP techniques hardly provide tissue for pathological examination, representing a pitfall of these devices which should be considered a handicap rather than an advantage. Furthermore, early postoperative re-intervention rate was three times higher after TURP, a finding which became comparable after 6 months between both arms and was maintained until the 2-year follow-up. However, the number of reoperated patients progressively increased over time in the PVP arm after 6 months to the most recent follow-up reported (10 *vs.* 3 patients), especially for bladder neck contracture, including four patients in the PVP arm who needed reoperation in the second year *vs.* only one patient in the TURP group. This highlights the necessity for longer follow-up to adequately address the issue of reoperation, which usually challenges the long-term outcome of any prostatic intervention, especially with increasing patients' life expectancy. This is important when considering the overall treatment burden as long-term adverse events may far outweigh any short-term advantage from an approach that is initially less morbid, even if the intervention is initially efficacious.

Furthermore, it would be interesting in the latter study to have a subgroup analysis characterizing reoperated patients in either group stratified by the prostate size and addressing the functional outcomes, as well, especially that 50% of patients in both groups have prostates smaller than 48 mL. While smaller prostate glands can be managed equally well with any technique, larger adenomas are more challenging and could potentially be better treated with XPS/180 W, particularly with the adoption of the vapoenucleation principle which proved itself as a possible competitor to other laser enucleation approaches (11). This principle was not utilized in the GOLIATH study.

Cost analysis is another crucial parameter which should be taken into consideration when comparing different surgical procedures for BPO. The XPS/180 W was found to be associated with a significant reduction in overall costs when compared to TURP in a multicenter study (12). Cost was significantly higher in the surgical phase with XPS but was significantly lower in the post-surgical phase due to a shorter length of hospital stay that offsets the cost of the new technology. Some authors have argued that PVP may also have the advantage over TURP of preserving sexual function such as retrograde ejaculation (13). Others found that ejaculation was the main sexual function affected

Table 1 Percent changes in functional outcomes and prostate size after 12-month follow-up in three RCTs comparing the different Greenlight laser generations with the holmium: YAG ablation/enucleation of the prostate

Parameter	IPSS*	QoL*	Q_{max}*	PVR*	PSA*	TRUS*	Redo (%)
Greenlight KTP (n=52)	55	58	188	69	56	35	1 (1.9)
HoLAP (n=59)	69	59	157	66	70	40	2 (3.5)
P value	0.22	0.81	0.66	0.92	0.008*	0.1200	0.39
Greenlight HPS (n=40)	87	80	195	87	60	52	2 (5.4)
HoLEP (n=40)	88	83	260	96	88	78	0
P value	0.50	0.40	0.02*	0.02*	0.040*	0.0001*	0.10
Greenlight XPS (n=53)	77	75	131	58	46	43.1	2 (3.7)
HoLEP (n=50)	81	76	315	69	83	74.3	0
P value	0.41	0.90	0.01*	0.10	0.010*	0.0010*	0.49

*, P<0.05. RCT, randomized controlled trial; IPSS, International Prostate Symptom Score; QoL, quality of life; Q_{max}, maximum flow rate; PVR, post-void residual urine; TRUS, transrectal ultrasound; KTP, potassium titanyl phosphate; HPS, High Performance System; XPS, Xcelerated Performance System; HoLAP, holmium laser ablation of prostate; HoLEP, holmium laser enucleation of prostate.

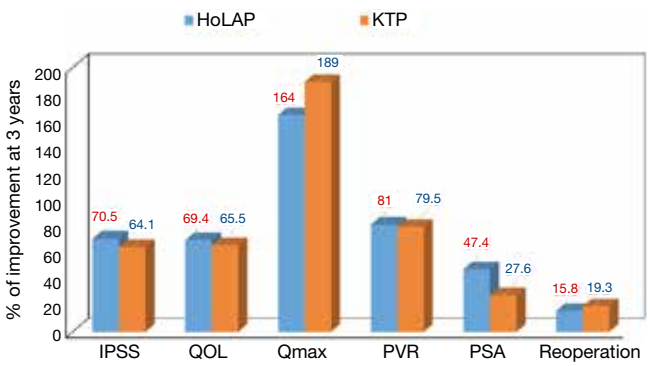

Figure 1 KTP *vs.* HoLAP after 3-year follow-up. *, for all comparison (P>0.05). IPSS, International Prostate Symptom Score; QoL, quality of life; Qmax, maximum flow rate; PVR, post-void residual urine; KTP, potassium titanyl phosphate; HoLAP, holmium laser ablation of prostate.

by PVP despite the significant improvement of sexual satisfaction and bother due to sexual symptoms (14). This may be due to the positive impact of relief of bothersome lower urinary tract symptoms.

Considering that patients presenting for BPO surgery became older, more morbid and had larger prostates (15), the comparison between PVP and TURP would have a different perspective, supporting the argumentation in favor of laser prostatectomy. Currently, the 532 nm laser is no longer used only for prostate vaporization but also for vapoenucleation techniques, encouraged by the introduction of the XPS system previously described. We at McGill University prospectively compared the three successive generations of Greenlight laser with the same old Holmium: YAG laser in three RCTs including 292 patients with BPO between March 2005 and April 2013 (*Table 1*) (11,16-18). For prostates <60 cc, functional outcomes were comparable between PVP using KTP/80W and Holmium laser ablation of the prostate (HoLAP) (16). However for prostates >60 cc, a significantly higher number of patients undergoing HPS/120W needed intraoperative conversion to monopolar TURP compared to Holmium laser enucleation of the prostate (HoLEP) (22% *vs.* 0%, P=0.001) (17). Nevertheless, Vapo-enucleation with XPS/180 W was not inferior to HoLEP in improving patients' symptoms (11), despite the finding that two patients (3.7%) in the XPS arm needed redo HoLEP within 12 months postoperatively and electrocautery was necessary for completion of the procedure in 8 (15%) patients undergoing XPS due to large prostate size which reached up to 150 mL in some patients (11). It seems that when KTP was compared to HoLAP for appropriately selected prostate size on a pure vaporization fundamental, the outcomes were comparable up to 3 years postoperatively, including retreatment rates (*Figure 1*) (18). However, with increasing the prostate size, PVP alone might be not sufficient and the vapoenucleation/enucleation principle needs to be adopted. Actually, the introduction of the XPS/180 W with the MoXy fibres encouraged the adoption of the enucleation principle,

making it a real contender to other laser enucleation techniques, including HoLEP in treating large adenomas.

In conclusion, Greenlight PVP has shown to be at least as effective as TURP and has the advantage of reducing perioperative complications and length of catheter time and hospital stay. Therefore, it was incorporated into both the American Urological Association (19) and the European Association of Urology (20) guidelines as an alternative to TURP. Nevertheless, some critical issues still need to be addressed such as the long-term functional outcomes and retreatment rates for XPS, adequate high level evidence addressing the results of PVP in coagulopathic patients, and sexual outcomes after PVP in terms of erection, ejaculation and sexual satisfaction.

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Footnote

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Comprehensive characterization of the perioperative morbidity of cytoreductive nephrectomy

Andrew Leone, Gregory Diorio, Kamran Zargar-Shoshtari, Philippe E. Spiess

Department of Genitourinary Oncology, Moffitt Cancer Center, Tampa, FL, USA

Correspondence to: Philippe E. Spiess, MD, MS, FRCS(C). Associate Member, Department of GU Oncology, Moffitt Cancer Center, 12902 USF Magnolia Drive, Tampa, FL 33618, USA. Email: philippe.spiess@moffitt.org.

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The authors report a single institution retrospective analysis of the reported complications and delay to initiation of systemic therapy in a cohort of 294 patients with metastatic renal cell carcinoma (1). This is the largest series evaluating this novel study question. There is presently no randomized controlled data in the era of targeted therapy demonstrating a survival benefit of upfront cytoreductive nephrectomy (CN). Despite this, CN is commonly utilized in well selected patients utilizing extrapolated data from the immunotherapy era. There is some evidence from the National Cancer Database, that adoption of CN from 2005–2008 (era of targeted therapy) actually has been decreasing with improvement in the effectiveness and enhanced reported toxicity profile of targeted therapy (2). Questions remain regarding which patients derive optimal benefit from CN.

The morbidity associated with upfront CN (previously reported as high as 37% with mortality as high as 6.6%) and may delay administration of targeted therapies (3). In the era of targeted therapy, evidence from NCDB analysis suggests that patients are increasing receiving systemic therapy after CN, however, less than 50% of eligible patients will receive systemic therapy (4).

There are currently two ongoing randomized trials examining CN with targeted therapies, CARMENA (NCT0093033) and SURTIME [NCT01099423 (5)]. Unfortunately, CARMENA, which randomized patients to CN + sunitinib *vs.* sunitinib alone will not be completed until 2018 and is limited by non-inferiority design and patient accrual issues. With the development of multiple targeted agents the study design will likely be obsolete by completion. The SURTIME trial aims to assess timing of CN relative to treatment with sunitinib. Both trials only include patients with high performance status (ECOG 0/1) patients and only clear cell type is included.

The authors of this study aimed to determine the effect of CN on administration of systemic therapy. They conclude found that only 11% of the cases who experienced a delay to systemic therapy greater than 60 days were secondary to surgical complications in patients who experienced delay to CN more than 60 days, only 11% of the cases were secondary to surgical complications whereas previous studies have suggested a higher rate of 19% (1,6). Factors in this study associated with perioperative complications were presence of liver metastases, intraoperative transfusion, and node positive disease. There are some limitations to the study. First, patients were excluded in the systemic therapy analysis if their medical oncologist did not treat with targeted therapy because of opting for surveillance. This raises the question of whether these patients were excluded for reasons related to ensuing postoperative complications. Second, there is an inherent selection bias in the patient population who underwent CN. Patient selection is critically important in deciding on treatment approach including implementation of CN and targeted therapy. Previous studies identified clinical/demographic factors associated with lack of survival benefit for CN. In patients with more than four negative prognostic factors: serum albumin below normal, lactate dehydrogenase above normal, clinical tumor stage of T3 or greater, presence of liver metastasis, symptoms at presentation resulting from a metastatic site, retroperitoneal lymphadenopathy, and supradiaphragmatic lymphadenopathy did not achieve a benefit from CN (7). Finally, the parameters included in the multivariate analysis are not robust and stage, a critical factor was excluded from one of models raising into

question its true clinical validity.

The largest study to date investigating the role of CN in metastatic RCC (mRCC) patients was published in 2014 (8). The study compared 982 patients who underwent CN to 676 patients who did not. CN was found to be of benefit in patients with less than four International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) prognostic factors: hemoglobin below lower limit of normal (LLN), corrected calcium greater than upper limit of normal (ULN), neutrophils above ULN, platelets greater than ULN, Karnofsky performance status <80%, and time from diagnosis to treatment <1 year. These studies suggest that many factors are necessary to consider in identifying patients garnering benefit from CN. Based on the confluence of patient clinical and demographic parameters, once patients are deemed appropriate candidates for CN questions remain regarding timing of CN.

Because of toxicity of immunotherapy, CN was traditionally performed prior to receiving systemic therapy. In this series, all patients received CN then targeted therapy. However, with a lower adverse effect burden, questions remain whether targeted therapy should be administered prior to CN. In an effort to reduce primary tumor size and therefore decrease associated perioperative morbidity, Abel *et al*. 2011 explored 168 patients treated with targeted agents prior to CN (9). The authors concluded that primary tumor response with 60 days after initiation of systemic therapy was an independent prognostic marker for survival. A handful of retrospective studies have investigated the safety of administering targeted therapy prior to CN (10,11). Complications within 30 days were no different; however one study which included bevacizumab demonstrated increased 90-day complication rate especially wound related infections.

The authors of this study included patients with poorer performance status (ECOG >1). Previous studies in the immunotherapy era only included good performance status patients (ECOG or Karnofsky performance status ≤1% or ≥80%, respectively) including EORTC 30947 and SWOG 8949 trials. Patients with poorer performance status are unlikely to have favorable overall survival, suggesting these patients may not benefit from CN. In those retrospective studies including patients with poor performance status there is not a benefit to survival with CN.

Finally, the authors include non-clear cell type RCC. However, only 10% of the patients were non-clear cell types including papillary and chromophobe. The optimal treatment approach to patients with mRCC and non-clear cell types remains undetermined. This is in part due to many trials excluding non-clear cell patients. Additionally, papillary RCC has a distinct molecular profile distinct from cc RCC (12). In conclusion, the role and timing of CN in the era of targeted therapy remains unknown and will require further research and studies until an answer is found.

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Treatment Progress

What's new in urological trauma? 2012 update

Benjamin N. Breyer, Jack W. McAninch

University of California San Francisco, California, USA

Correspondence to: Benjamin N. Breyer, MD. University of California San Francisco, 1001 Potrero Ave., Suite 3A20, San Francisco, California, USA. Email: bbreyer@urology.ucsf.edu.

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Urologic trauma continues to be a dynamic and evolving subspecialty of urology. This is evident by the trauma papers published this past year. Highlights of the 2011 literature include a needed revision of renal trauma grading, increased use of large population-based datasets and multiple papers examining the use of angioembolization.

Buckley and McAninch (1) revised the current American Association for the Surgery of Trauma Renal Injury Grading System producing a staging classification that is more clear and straightforward. Grade 1 (renal contusion), grade 2 (<1 cm laceration), grade 3 (>1 cm laceration without collecting system injury) remain unchanged. Grade 4 injuries now include all collecting system injuries. Grade 5 injuries denote major catastrophic vascular injury including main renal artery or vein laceration or avulsion of the main renal artery or vein thrombosis. This classification reflects that most injuries involving the renal parenchyma and segmental vessels can be managed conservatively while hilar injuries frequently will require surgery for salvage.

The majority of manuscripts related to urologic trauma this past year are case reports and case series which in part reflects the low volume of injuries seen at most centers worldwide. Management consensus and practice guidelines continue to be based on large, seminal case series from high volume urologic trauma centers. Increasingly, population-based data sets are being utilized to study urologic trauma epidemiology and outcomes. This trend should continue given the rise and availability of inexpensive, powerful statistical software and large publically accessible data sets. Urologic trauma has lagged other urologic subspecialties such as cancer in the utilization of such data sets.

The National Trauma Data Bank (NTDB) is a robust and publically available data repository. Managed by the American College of Surgeons, the NTDB contains trauma admissions of participating Level 1-5 trauma centers in the United States, totaling over 600,000 case records. Compared to case series, NTDB has the advantage of drawing from a large and diverse population from all regions of the country. Potential disadvantages include the reliance on administrative data and the inability to reexamine new variables in historical patients.

A number of groups have utilized this data set to study urologic trauma this past year. Bjurlin *et al*. examined over 16,000 bicycle injuries and found GU organs involved 2% of cases (2). The kidneys were the most commonly injured GU organ among bicycle accidents. Among patients who sustained a vertebral fracture, concurrent bladder/urethra (38%) or a renal injury (23%) were common. These bicycle related injuries represent the most severe type as these patients all required hospital admission to be included in the data set. The same group performed an analysis looking at geriatric urogenital trauma (3). They reported that penetrating GU injuries were less common among geriatric patients and that although geriatric patients have similar mean Injury Severity Scores as non-geriatric patients, they had significantly more comorbidities, hospital complications and higher mortality.

Another group used the NTDB to compare the operative and nonoperative management of bladder injury (4). They reported on over 8000 bladder injuries, 54% of which underwent bladder surgery. Of the bladder injuries 14% were intraperitoneal and 86% were extraperitoneal ruptures. Interestingly, only 76% of intraperitoneal bladder ruptures received operative management.

When to use angioembolization in the management of renal trauma has been (5) and continues to be a point of debate. A handful of studies examined the use of angioembolization to treat renal trauma. A group from

Seattle, Washington (6) used the NTDB to explore national practice patterns. Of 9002 renal injuries over a five-year period, only 165 patients (2%) underwent diagnostic angiography after renal injury with 77 undergoing angioembolization. Of concern, 30% of the patients who underwent angioembolization had grade 1 and 2 renal injuries. Strong evidence supports the use of conservative management for low-grade renal trauma. Increased collateral patient harm, renal damage and cost will be incurred with the use of angioembolization for low-grade renal injuries. Furthermore, they found the initial success rate for angioembolization to be low. 88% of patients required some type of secondary intervention, either surgery or repeated embolization. Interestingly, overall renal salvage of high-grade lesions was high with the use of successive angioembolization.

Sarani and colleagues reported on their single institution experience managing blunt renal trauma with either open surgical repair or angioembolization (7). They contend that patients with high-grade renal injuries without other indications for immediate abdominal operation benefit from arteriography and possible embolization. It should be noted that a third of their population had grade 3 injuries which in most cases could have been observed. Finally, a group from Germany reported on 19 patients who required angioembolization most of which were from iatrogenic causes (8). The initial failure rate was 37% with repeat embolization producing a similar failure rate.

We believe that embolization can effectively treat renal injuries that failed conservative management as evident by hypotension or the need for greater than 2 units of blood products. Embolization is not warranted when the patient is going to the operating room for repair of other injuries nor has a low-grade injury (grade 1-3) unless the previous criteria are met. High grade renal injuries that require intervention may be treated with similar success with embolization (most likely repeated) or surgery.

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Footnote

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Treatment Progress

Interpretation of PIVOT findings

Sergey Shikanov

1709 Pontiac trail, Ann Arbor, MI 48105, USA

Correspondence to: Sergey Shikanov, MD. 1709 Pontiac trail, Ann Arbor, MI 48105, USA. Email:sergeyshikanov@gmail.com.

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The results of the long awaited Prostate Cancer Intervention versus Observation Trial (PIVOT) have been recently published in the New England Journal of Medicine (1). The primary outcome of the trial was overall survival in men treated with radical prostatectomy (RP) or observation for clinically localized prostate cancer detected with PSA screening.

Seven hundred thirty one US veterans were randomized between 1994 and 2002 to RP or observation. Mean age of the cohort was 67 years, median PSA was 7.8 ng/mL, approximately half of patients had non-palpable disease, and same proportion had Gleason score ≤7. Overall survival was 2.9% higher and cancer specific survival was 2.6% higher in surgically treated patients at the10-year median survival mark. The most prominent overall survival benefit of 12.6% was observed in patients with intermediate-risk tumors by D'Amico criteria. The likelihood of bone metastases was twice lower in the RP arm of the trial. The authors concluded that RP does not reduce significantly overall and cancer specific survival in men diagnosed with PSA screening.

Does it mean that all men with clinically localized prostate cancer should not be offered RP or should PSA screened be abandoned if active treatment does not matter? Probably not.

First, prostate cancer, even detected with PSA screening and clinically localized, is a heterogeneous disease. There is plenty of evidence that low-grade small tumors may be treated expectantly while high proportion of aggressive tumors may present as pathologically extra-prostatic disease destined to recur despite surgery, not so for the middle of the spectrum. Indeed, in PIVOT study RP was mostly beneficial in the intermediate risk tumors. Unfortunately, due to low recruitment rates the study was underpowered to detect survival differences in the clinically relevant subgroups. In the retrospect, it is apparent that at the time of study design almost two decades ago the need to focus on particular risk group may not have been that obvious. Furthermore, the control of recruitment rate is beyond researches ability.

Second, by the randomized nature of the trial not all participants complied with the intended treatment. In the RP arm 15% chose observation, 7% chose radiation and in 2% surgery was abandoned, while in the observation arm 20% received RP. The inconsistent adherence to the assigned therapy results essentially in comparing '77% surgery' to '80% observation'. It may make sense epidemiologically to avoid bias by allowing the 'intention to treat' analysis, however may not apply clinically since for a particular patient treatment choice is 100%.

Third, the presence and magnitude of competing risks is of utmost importance. Simply put, if a significant proportion of study participants dies due to other causes there is no chance to find out whether they would succumb or not to prostate cancer. PIVOT investigators applied competing risks approach to survival analysis and used overall survival as an end-point to overcome this limitation. However, it may not be sufficient if the difference between the study cohort and general population is significant. Let's see how they compare. Overall, in the PIVOT cohort other-cause mortality (OCM) was about 35% at 12 years. This is significantly higher than 14% and 30% 10- and 15-year OCM in men treated with RP as estimated from SEER data in the same time period (2). There is even more striking difference when comparing with Scandinavian population data which showed 8% OCM at 10 years or Johns Hopkins cohort with 16% OCM at 15 years (3).

It is possible that 1/3 of PIVOT participants did not achieve the 10-year life expectancy as defined by recruiting criteria because of less than optimal general health of the VA population. In this context and considering constantly improving cardiovascular mortality in US (4) it will be

difficult to extrapolate PIVOT outcomes to future radical prostatectomy candidates.

In summary, PIVOT corroborates the concept that mostly men with intermediate risk prostate cancer may benefit from radical prostatectomy and that radical prostatectomy prevents bone metastases, an important clinical end-point. Its shortcomings suggest that benefit from radical prostatectomy should be more prominent in healthier population of men not subjected to significant competing risks of other-cause mortality. As an aside, this study is an example of how an accurately designed trial may loose some of its relevance due to suboptimal accrual and changes of target population over time. Another concern is that similarly to misinterpretation of PLCO and ERSPC trials by opponents of PSA screening, PIVOT will be misused by the opponents of radical prostatectomy.

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Refining treatment for the men who need it: lessons from the PIVOT trial

Michael R. Abern, Matvey Tsivian, Thomas J. Polascik

Division of Urology, Department of Surgery, Duke Cancer Institute, Durham, NC, USA

Correspondence to: Dr. Thomas J. Polascik, MD. Associate Professor of Urologic Surgery, 2301 Erwin Road, DUMC Box 2804, Durham, NC 27710, USA. Email: polas001@mc.duke.edu.

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Introduction

The diagnosis and management of asymptomatic prostate cancer (PC) are complex issues in the midst of several controversies and conflicting recommendations. Largely due to the results of two large PSA screening trials showing an unclear benefit of PSA screening on overall patient survival, the US PSTF has recommended against its routine use (1). If implemented, this policy would drastically reduce the number of organ-confined PC diagnosed. On the contrary, the NCCN recommends active surveillance for low-risk PC, and treatment for higher-risk disease (2). Therefore, we are faced with a dilemma: while decreased PSA testing may decrease detection of low-risk disease, one cannot risk-stratify and treat meaningful PC without screening-triggered biopsy and staging. Clearly, over-detection and over-treatment of PC are separate issues.

Drs. Wilt *et al.* helped to address the overtreatment question with the PIVOT trial, which sought to determine the overall and PC-specific survival in men randomized to watchful waiting versus radical prostatectomy (RP) (3). Importantly, the authors report a benefit in overall and PC -specific survival in men with intermediate-risk disease, but not low-risk (using the classification of d'Amico). The authors should be applauded for completing a randomized prospective trial as this has been historically difficult. However, due to an only 15% participation rate in eligible men, the sample sizes are modest for sub-group analysis leaving questions regarding the identification of groups of men that may derive the most benefit from treatment.

Need for better risk stratification

As shown in PIVOT trial, higher risk men will benefit from expedient radical treatment of PC as compared to watchful waiting. Recent data from our group corroborates this finding—men with d'Amico intermediate-risk disease who had RP delayed by as little as 9 months had inferior outcomes to those treated in 3 months or less (4). Although the biopsy strategy employed in the PIVOT trial was not reported, it can be assumed that a standard 6-12 core TRUS guided random biopsy, along with serum PSA and DRE were used to classify risk. Several studies have shown the limitations to this approach—with Gleason upgrading rates as high as 47% in men thought to be low-risk (5). In addition, there has been a Gleason grade migration since the PIVOT trial patients were enrolled—it is likely that some men classified as low-risk would now be intermediate-risk (6). This prime example of a history-effect threat to validity is a potential pitfall of any trial with long term outcomes, and could attenuate some of the survival benefit from RP demonstrated in the trial for intermediate-risk men (7). Clearly, refinements in risk stratification of PC are of interest as several studies, including PIVOT, demonstrate its importance in predicting PC outcomes.

Advances in prostate imaging and biopsy techniques provide future directions to improve the accuracy of PC risk stratification. Multi-parametric MRI improves the visualization of anterior prostate tumors that may be difficult to detect using standard TRUS biopsy schemes. In addition, endorectal coil contrast enhanced MRI with 1 mm slice thickness shows excellent sensitivity and specificity for extracapsular extension which can help identify tumors that are locally advanced and require treatment (8). Other investigational imaging technologies under development, such as acoustic radiation force imaging, may provide a low cost yet more detailed differentiation of PC from

normal tissue compared to standard TRUS (9). More thorough and systematic prostate biopsy approaches will also provide a more detailed assessment of a man's burden of PC. Transperineal 3-D mapping biopsies can sample the entire prostate gland including the anterior zone, and provide not only extent but location of PC foci commonly missed with standard TRUS biopsy (10). This is important because tumor volume has been shown to correlate with PC outcomes, yet is not accounted for in most of the widely adopted risk stratification schemes. Finally, the fusion of prostate imaging and biopsy allows targeted sampling of worrisome lesions that may pose significant risk if left undetected.

Treatment strategies

The PIVOT trial compared two treatment modalities that can be conceptualized as polar extremes: watchful waiting and palliation versus expedient radical treatment. Since the inception of the study, other management strategies have emerged between these extremes—specifically active surveillance (AS) and focal therapy (FT). Both of these aim to obviate or delay the need for potentially morbid radical treatment from men with localized disease. What lessons from the PIVOT trial can we apply to these approaches?

First, as shown by the authors, men with low-risk PC had no increase in overall or PC specific mortality when managed with watchful waiting. This is in line with a large body of literature that suggests that men with low-risk disease, especially those older than 65 years of age or with significant medical comorbidities, can be observed. However, in PIVOT, men under age 65 on watchful waiting had twice the number of PC deaths. FT may be an alternative for these men, as tumor foci may be identified and ablated providing oncological control of the disease while sparing the morbidity associated with radical treatment (11).

Second, higher risk men in the PIVOT trial did derive benefit from RP. There is little debate over the need for treatment of high-risk PC in most men. However, there is some debate regarding intermediate-risk disease. In the AS literature, one large center enrolling intermediate-risk men has shown more progression to radical treatment compared to low-risk men (12). Another report, however, has not shown this to be the case (13). Most would agree that intermediate-risk men would not be ideal candidates for AS. FT may be better suited to these men: intermediate-risk index lesions can be ablated without the urinary or erectile morbidity of radical therapy.

Conclusions

The PIVOT trial is important in that it provides high-level evidence that low-risk PC generally does not require immediate radical treatment, while higher-risk disease does. This calls into focus the importance of risk-stratified approaches to PC management. Continued advances in prostate imaging and biopsy techniques, as well as better biomarkers, are still needed to determine which men need radical treatment. FT provides an attractive option other than observation and radical treatment for young, healthy men with low-risk disease or intermediate-risk disease. Future trials are needed that compare AS, FT, and watchful waiting with regard to not only mortality outcomes but quality of life.

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Footnote

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Treatment Progress

PIVOT and the challenges of localized prostate cancer care

Aviva E. Weinberg, James D. Brooks

Department of Urology, Stanford University, Stanford, CA 94305, USA

Correspondence to: James D. Brooks, M.D. Department of Urology, Room S287, Stanford University School of Medicine, 300 Pasteur Drive, Stanford, CA 94305-5118, USA. Email: jdbrooks@stanford.edu.

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Putting it mildly, prostate cancer screening and treatment has been a contentious issue over the past year. With the recent US Preventative Services Task Force grade D recommendation to abandon routine PSA screening, pressing questions regarding the utility of population-wide PSA screening and the harms of overdiagnosis and overtreatment have continued to make national headlines. Determining whether PSA screening and subsequent treatment provides a survival benefit, in particular for men with low risk disease, has become of paramount concern to patients and urologists.

While the issues surrounding PSA screening and overtreatment have been known to the urologic community for many years, the controversy came into public focus with the publication of the results of the Prostate, Lung, Colon and Ovarian (PLCO) Screening trial showing no benefit to PSA or digital rectal exam screening (1). This study has been justly criticized for heavy prescreening of the study population, significant contamination of the control group, and poor compliance in the screening arm. Besides, the European Randomized Study of Screening for Prostate Cancer (ERSPC), in many ways a superior trial, did show a 21% *relative* risk reduction in prostate-specific mortality in PSA screened men (2). This result was reassuring in many ways, although the number of men that needed to be screened and treated, and the lack of benefit on all-cause mortality has been held up as evidence of overtreatment and the lack of benefit of screening. In support of detection and treatment of localized disease is the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4), a randomized trial comparing radical prostatectomy to watchful waiting, which demonstrated significant reductions in all-cause mortality, prostate-specific mortality, and the risks of metastatic disease in men treated with radical prostatectomy versus watchful waiting (3). While many of the patients in this study had intermediate and high-risk disease, long-term follow-up showed significant benefit in men with low risk prostate cancer, who were similar to patients with low risk disease detected in the PSA-era.

Now adding to the controversy is the PIVOT study, published in a recent issue of the New England Journal of Medicine (4). PIVOT is a prospective randomized trial designed to address whether radical prostatectomy, as compared to observation, improved overall survival and prostate cancer-specific survival in men diagnosed with prostate cancer during the PSA era. Initially designed to randomize 2,000 men, the study recruited only 731 men, which was compensated for by lengthening follow-up. At a median follow-up of 10 years, there was no difference in either overall or prostate-cancer specific mortality among the two treatment arms. Multivariate analysis showed that the effect of treatment on mortality did not vary according to age, race, performance status, or comorbid conditions. Subgroup analysis found no benefit of surgery for men with low-risk disease; however, radical prostatectomy reduced all cause mortality in men with PSA values greater than 10 ng/mL, and approached significance in those with intermediate and high-risk tumors. Notably, there was a statistically significant reduction in bone metastases in patients treated by radical prostatectomy (4.7%) versus expectant management (10.6%), which became more robust in patients with PSA >10 ng/mL and in those with intermediate and high-risk disease.

Despite portrayals in the media, the PIVOT trial does not signal the end of PSA testing and treatment of localized disease. PIVOT must be viewed in the light of its limitations. When enrollment goals were not met, the power calculation for the study was redone such that the

length of follow-up on their 731 men was increased and the study was then projected to have 91% power to detect a 25% relative reduction in all cause mortality, a high bar indeed. Placing this endpoint in perspective, a meta-analysis by Yusuf *et al.* of 7 randomized trials of patients with stable coronary artery disease stratified to either early coronary artery bypass graft versus medical management, demonstrated only a 17% relative reduction in overall mortality (5). In a similar fashion, a systematic review of over 31 randomized trials examining the survival benefit of adjuvant chemotherapy in early breast cancer, showed only a 14% relative risk reduction in overall mortality (6). Additionally, as astutely pointed out by Thompson *et al.* in his accompanying editorial, the PIVOT study remained underpowered with their enrollment of only 731 patients, and would have required 1,200 patients to be adequately powered to detect a 25% relative reduction in overall mortality (7). Another shortcoming of the study is the large proportion of patients, nearly 20%, who were non-adherent to their assigned treatment group, thus even further diminishing the capacity to identify a treatment effect. Additionally, only 10% of the men in their study were under the age of 60, therefore leaving the question of surgical management in a younger, healthier cohort, unaddressed.

Despite assertions that the study population in PIVOT is representative of men in the general population who have received a diagnosis of prostate cancer, men in PIVOT appear to be sicker and therefore more likely to die of causes other than prostate cancer. More than 40% of their study population had Charlson comorbidity scores of 1 or more, with a high proportion of patients with congestive heart failure, chronic obstructive pulmonary disease and prior myocardial infarction and strokes. Given this high rate of comorbid illness, it is not surprising that the overall mortality rate was so high (47% and 49.9% in the surgery and observation arms). In stark contrast are the mortality estimates found in the SEER database, where men age >65 years undergoing prostatectomy for clinically localized prostate cancer were found to have only a 20.6% and 40.8% all-cause mortality rate at 10 and 15 years follow-up (8). Even more striking, are the more recent actuarial mortality rates after radical prostatectomy found in a recent study by Eifler *et al.* which found overall survival rates at 10 and 20-year of 92.6% and 69.2% (9). Perhaps the patients in the PIVOT trial simply didn't live long enough to document any survival benefit. Consequently, we have to be very cognizant of patient specific factors notable to the VA population, when attempting to make recommendations for population-wide prostate cancer care, especially when considering the most recent NCCN guidelines, which recommend directing care for patients with very low risk and low risk prostate cancer based on 20-year and 10-year life expectancies.

While the PIVOT trial adds to the current prostate cancer screening and treatment dilemma, it provides more questions than answers. The most pressing question is not whether we should diagnose and treat prostate cancer, but rather *who* should we be treating? Prostate cancer is a complex entity with a broad spectrum of disease, from those that are slow growing, asymptomatic, possibly non-fatal cancers to those that are high-grade, aggressive, and ultimately lethal if left untreated. Furthermore, prostate cancers diagnosed in the PSA era have been shown to be significantly different from those found in earlier eras; there has been a profound stage migration; the Gleason scores are lower, the volume of disease is smaller, and there is a lower proportion of metastatic disease at diagnosis. What we can learn from PIVOT, PLCO and ERSPC is that increasingly, patients with low risk prostate cancer should be managed initially with active surveillance. By uncoupling the diagnosis of prostate cancer from treatment, which active surveillance offers, the arguments against PSA screening and prostate cancer overtreatment become irrelevant. Results from several active surveillance studies show that active surveillance is safe in properly selected patients (10). Unfortunately, the portion of patients on active surveillance has not changed, even though an increasing number of men are diagnosed with low risk disease (11). Acceptance of active surveillance by patients and physicians will be facilitated by developing reliable biomarkers that will allow us to effectively identify clinically high risk disease so as to guide future appropriate and individualized care (12).

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Footnote

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Complete remission with tyrosine kinase inhibitors in renal cell carcinoma

Yoshihiro Wada, Kenichiro Tanoue, Wataru Takahashi, Masatoshi Eto

Department of Urology, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan

Correspondence to: Masatoshi Eto. Department of Urology, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Email: etom@kumamoto-u.ac.jp.

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In the era of cytokine therapy, although response rates of interleukin-2 (IL-2) in patients with metastatic renal cell carcinoma (m-RCC) were not satisfactory, a small percentage of complete remission (CR) was achieved (1). Recently, targeted therapy has replaced cytokine therapy. Sunitinib, a tyrosine kinase inhibitor (TKI), has been especially effective in tumor reduction but has rarely induced CR (1). Because of the unique and characteristic adverse effects (AEs) of targeted drugs, this study highlights the importance of maintaining therapy in patients who have achieved CR with TKIs. A multicenter study on m-RCC patients who achieved CR with either TKI (sorafenib, sunitinib) alone or in combination with local treatment (surgery, radiotherapy, radiofrequency ablation) was performed retrospectively. The subjects of the study were 64 patients who achieved CR: 36 were treated with TKI alone and 28 with TKI plus local treatment. The denominator of all patients treated with TKIs was not available, but the incidence of CR from a part of them was 1.7%. This rate is in line with data from other studies (1,2). The aim of this study is to characterize the patients, to assess the indication of discontinuing targeted therapy, and to define the subsequent therapeutic implications.

Because of the small number of patients involved, this study could not definitively answer any one of the above questions. However, their findings do suggest some specific benefits.

The patients' characteristics are shown in *Table 1*. The majority of patients who attained CR were of favorable or intermediate risk, but 3 patients with poor risk also obtained CR. The fact that the majority of patients had received sunitinib was in line with the fact that sunitinib, with an approximately 30% reduction rate, has been shown to be more effective than sorafenib for tumor reduction (1). *Table 2* compares the characteristics of patients who maintained CR with those who experienced disease relapse. None of the factors that predict a higher risk of relapse after discontinuation of TKIs was seen. In patients who achieved CR with TKI alone, the relapse rates varied: 44% for patients with TKI arrest at CR, 33% for patients with TKI arrest after further cycles of the same TKI, and 13% for those in which TKI administration was ongoing. Among them, there was no statistically significant difference. Similarly, in patients who achieved CR with TKI in combination with local treatment, the relapse rate for patients with TKI arrest at CR, for those with TKI arrest after further cycles of the same TKI, and for those with ongoing TKI administration were 52, 50, and 33%, respectively. Again, there was no statistically significant difference. These results may suggest a tendency for the relapse rate to decrease as the length of TKI therapy increases. Furthermore, in 14 of 26 patients, relapse occurred in a previously involved metastatic site. Considering the

Table 1 Patients characteristics

Characteristics		No. of patients	%
Histology	Clear cell	60	94
	Papillary	4	6
TKIs	Sunitinib	59	92
	Sorafenib	5	8
Prognostic group	Favorable	22	34
	Intermediate	39	61
	Poor	3	5

Table 2 Characteristics of patients maintaining CR *vs.* patients experiencing disease relapse

Characteristics		Patients stopped TKI after achieving CR with TKI alone, n=28		Patients stopped TKI after achieving CR with TKI plus local treatment, n=25	
		No. of patients with disease relapse, n=11	No. of patients with maintaining CR, n=17	No. of patients with disease relapse, n=13	No. of patients with maintaining CR, n=12
TKIs	Sunitinib	9	16	13	11
	Sorafenib	2	1	0	1
Prognostic group	Favorable	3	9	4	4
	Intermediate	8	6	9	8
	Poor	0	2	0	0
No. of metastatic sites	1	4	9	6	5
	2	6	4	5	5
	3	0	3	2	1
	>3	1	1	0	1
Presence of hepatic metastases		1	4	1	0
Median time from start of		480	255	688	322
Median follow-up, days treatment to CR, days		476	330	531	684

recurrence sites and the fact that all of the samples obtained by surgical resection included viable tumor-cells, (i.e. no patients achieved a pathological CR), it is suggested that tumors might arise where residual cancer cells have located.

On the other hand, although the overall response rate (ORR) of IL-2 treatment is approximately 15%, CR was attainable in up to 5% of m-RCC (1). Only 4 of 21 patients who achieved CR with IL-2 had a recurrence within four years (1). It is noted that IL-2 could induce such long term CR without additional administration. In this study, the median follow-up in maintaining the CR groups was short, 8-11 months; therefore the duration of CR cannot be discussed yet. However, CR obtained with targeted therapy seem to be essentially different from that obtained with immunotherapy. For example, targeted therapy directly inhibits tumor-growth signaling, whereas immunotherapy works indirectly via immune-cells, e.g., natural killer cells or cytotoxic T lymphocytes, and so on. As for achieving CR with immunotherapy, anti-cancer effects might be memorized by the immune-cells, and even after the cessation of treatment, those cells might continue to prevent disease recurrence.

On the other hand, as for achieving CR with targeted therapy, a rebound effect associated with the discontinuation of TKI might induce rapid re-growth and metastases by the residual cancer-cells (3). Moreover, the 1.7% of CR response rate for TKIs was evidently lower than that for IL-2 (1). Of the 64 patients, 28 had received TKI therapy and additional local treatment when they obtained the initial CR. Of the 26 patients, 11 patients received local treatment after recurrence. Furthermore, in this study, re-administration of TKIs did not induce any CR after recurrence.

Benefits arising from the discontinuation of therapy include a decrease in or absence of toxicity leading to the improvement of QOL, prevention of the development of resistance to drugs, and a reduction in the cost of treatment.

The fact that all patients in this study had previously undergone nephrectomy might have influenced the incidence of obtaining CR. Cytokine therapy significantly extended overall survival when nephrectomy was performed in the cytokine era (4). Therefore, we should always consider a multidisciplinary treatment, including surgery and radiotherapy, and not confine treatment to pharmacotherapy alone.

This study simply illustrates that TKIs can induce CR, either alone or in combination with local treatment. It also shows that CR was obtainable at every metastatic site and in every prognostic group. It does not clarify, however, whether or not discontinuation of therapy with TKIs after achieving CR is an acceptable strategy option. Further research is needed to determine that. Axitinib, a new TKI, is now in phase III

of clinical trial for patients at high risk of recurrent renal cell carcinoma following nephrectomy as an adjuvant setting (5). In that trial, first a radical resection of tumor is firstly performed, similar to the CR status. Then axitinib is administrated to examine whether or not it reduces the rate of recurrence.

Although the trial situation differs from that of this study, the results of the adjuvant trial might answer some of the questions that this study could not due to the small number of eligible CR patients.

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Treatment Progress

Neuromodulation and neurostimulation: overview and future potential

Emil A. Tanagho

Department of Urology, University of California, San Francisco Medical Center, San Francisco, California, USA
Correspondence to: Emil A. Tanagho, MD. Department of Urology, University of California, San Francisco Medical Center, 400 Parnassus Avenue, Suite A-610, San Francisco, CA 94143-0330, USA. Email: ETanagho@urology.ucsf.edu.

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Introduction

The history of neuromodulation and neurostimulation began after several important discoveries in the fields of neurophysiology and electricity. In 1811, Bell (1) was the first to conduct experiments on the spinal nerve roots. He reported that manipulation of the anterior sacral roots led to muscle contractions of the back, but not the posterior fibers of the spinal nerves. Magendie (1822) further recognized the anterior motor and the posterior sensory function of the roots (2). In 1833, Hall (3) uncovered the distinct function of the spinal cord and medulla oblongata and well as the reflex function. These were the pioneering discoveries that open the door for further examination of the somatic and autonomic nervous system. In the mid-19th century, Giannuzzi (4) (1863) stimulated the spinal cord in dogs and concluded that the hypo gastric and pelvic nerves are involved in regulating the bladder function. In 1872, Budge (5) postulated that there are two sets of nerves innervating the bladder: the motor fibers from the anterior roots of S1, 2, and 3, and the sensory fibers from the hypo gastric plexus. He postulated the presence of a micturition center in S2 to S4 in 1864 (6). The early 20th century saw the development of electric oscillators, stimulators, and amplifiers that greatly improved the understanding of nerve impulses, synaptic transmission, and function of the nervous system. Significant improvement was also achieved by radiofrequency induction that led Glen and his associates (7) to develop the totally implantable heart pacemaker, one of the first commercially available stimulators. In the ensuing years, stimulators for different organ systems were developed: a heart pacemaker, a diaphragmatic pacemaker, and a cochlear implant.

Modern interest in electrical control of bladder function began in the 1950s and 1960s. The most pressing question at that time was the best location for stimulation. Several groups attempted to initiate or prevent voiding by stimulating the pelvic floor, the detrusor muscle, the spinal cord or the pelvic sacral nerve roots. Even other parts of the body, such as the skin, were stimulated to influence bladder function.

McGuire (1955) (8) and Boyce (9) and his associates (1964), tried direct bladder stimulation using different forms of electrodes with limited success. In 1963, Bradley (10) and his associates published their experience with an implantable stimulator in a chronic dog model. However, when applied to humans, it induced bladder contractions, but no voiding. In the early 70's Nashold and Freedman (11,12) were the first to attempt to achieve micturition by direct spinal cord stimulation. They applied direct electrical activation of the micturition center in the sacral segment of the conus medullaris and reported that the region for optimum stimulation is S1 to S3. They compared the stimulation of the dorsal surface of the spinal cord at L5, S1, and S2 with depth stimulation (2-3 millimeters) at S1 and S2 in an acute and then in a chronic setting. They reported that only the depth electrode induced voiding. In 1975, Dr. Nashold (13,14) and his associates reported that eight patients with electrodes implanted in the sacral segment produced bladder contractions and bladder emptying when stimulated. Their success excited a great deal of interest in the neuroprothesis program at the NIH regarding the potential use of neurostimulation as a means of bladder control in paraplegic and quadriplegic patients. This prompted the leaders of this program,

Drs. Terry Hambrecht and Karl Frank, to reach out and visit us at UCSF. After a long day of discussions about the potential of this new approach, we were contracted by NIH to pursue the neuroprosthetic work and explore its potential. We started testing a varieties of electrodes in 1975 (15), including surface electrode, dorsal column electrodes, wrap around electrodes, in depth electrodes, as well as bipolar, tripolar, horizontal, vertical, and transverse designs. Regardless of the type of electrodes, the detrusor response to neurostimulation was similar. The wrap around surface electrode with the most extensive current spread gave the same results as the coaxial electrode with the least current spread, prompting us to theorize that current did not cross the midline of the spinal cord. Unfortunately, no real voiding was achieved. Besides the expected detrusor contractions there was also a strong sphincteric contraction. Nevertheless, small amount of voiding happened at the end of the stimulation- the so-called post-stimulus voiding (16). This result contrasted with the earlier work of Nashold and Freedman, inspired us to map the neuronal cell bodies in the spinal cord that differentially controls the detrusor and the sphincter. Using retrograde tracers, horseradish peroxidase, injected in various locations of the lower urinary tract, the existence of two separate groups of nuclei was delineated: the parasympathetic and the pudendal nucleus. Interestingly, the pudendal nucleus extends beyond the parasympathetic nucleus both caudally and cranially (17) and we realized that it is very difficult to stimulate the bladder nuclei without stimulating the sphincter nuclei at the spinal cord level even with very fine microelectrodes.

For these reasons, sacral root stimulation was investigated based on the hypothesis that different roots would carry different neuronal axons to different locations. We performed numerous experiments on a canine mode (18,19) as the anatomy of the bladder innervation is similar to the human's. After a dorsal lumber laminectomy, the sacral spinal roots were exposed and were stimulated either intradurally or extradurally, within the spinal canal. We developed several models: I. Unilateral stimulation of the intact sacral root at various levels; II. Simultaneous bilateral stimulation of the intact sacral root at various levels; III. Stimulation of the intact ventral and dorsal roots separately; IV. Stimulation of the proximal and distal cut ends of the divided dorsal and ventral roots. From these studies, it was evident that stimulating an intact root is the least effective and stimulating the ventral component is the most effective; while no difference was noted between right and left roots stimulation. We also noted that besides the detrusor contractions, stimulation caused some sphincter contraction, owing to the presence of both autonomic and somatic fibers in the ventral root. The study then continued with the addition of neurotomy to eliminate the afferent fibers. The dorsal fibers were separated and cut and only the ventral component was stimulated. These experiments showed that to achieve maximum specific detrusor contraction, the dorsal component must be separated from the ventral component and the somatic fibers of the root must be isolated and selectively cut. These studies also showed that stimulation with low frequency and low voltage can maintain adequate sphincteric activity (20,21). However, stimulation with high frequency and low voltage will fatigue the external sphincter and block its activity. When high frequency and low voltage stimulation is followed by high voltage stimulation, bladder contraction could be induced and voiding achieved (22,23). These findings, when combined together, showed that detrusor contractions could be activated separately from sphincteric activity.

Sacral roots were also evaluated by histologic and electronmicroscopic examination of chronic stimulated sacral roots, as compared to the contralateral non-stimulated roots. The studies revealed no damage to the neurons. We noted also that the responses to neurostimulation remained stable over several months, and the integrity and viability of the sacral root were maintained.

In 1974, Brindley (24) working on the baboons, isolated the sacral roots intradurally and placed them into slots of his implant. When he applied weak electrical stimulation, it resulted in activation only of the striated sphincter muscles. When he used continuous stimulation with high voltage, he obtained activation of both the detrusor muscles as well as the sphincter muscles. Knowing that the detrusor smooth muscles relax much slower than the prompt relaxation of the striated muscles, he achieved micturition by delivering bursts of stimulation for one second with stimulation/rest ratio of 2 to 1. The bladder contracted smoothly while the striated sphincteric relaxed in the off interval, and the female baboons consistently emptied the bladder. In 1977 (25), Brindley and his associates began implanting sacral anterior root stimulator in paraplegic patients with incontinence. In 1986 (26), they presented their experience with the first fifty cases of whom about thirty were completely continent and five were continent at night. Forty-three patients regularly used their implants for micturition. Twenty-six of thirty-eight male patients were able to produce penile erection under stimulation. In 1986, Sauerwein combined sacral anterior root stimulation with

sacral de-afferentiation in patients with spinal cord lesions to overcome reflex urinary incontinence (27,28). Rhizotomy of the posterior roots of S2 to S5 in forty-five patients resulted in diminished spasticity in 93% and secured continence in 91% of patients.

In 1982 and 1983, we developed a colony of paraplegic dogs in which we implanted newly designed spiral electrodes to minimize nerve damage on selected sacral roots (29). After dorsal root rhizotomy, usually S2 was selected for the electrode implant, which was secured in place to the sacral lamina to prevent any tension. Complete bladder evacuation was achieved with high frequency (200 Hz) low voltage stimulation followed by high voltage stimulation. This colony of dogs was maintained on this stimulation regiment for over eight months. After that, they were euthanized, and we performed histological evaluation of the stimulated sacral roots, which would reveal complete preservation of normal integrity. Based on these results, we embarked on human clinical trials through the 1980s. After several variations, we performed electrode implantation on the ventral root of S3 most of the time, rarely combining with S4. After doing extensive posterior rhizotomy and occasional selective peripheral neurotomy, we concluded that this model was the most successful combination to achieve continence and to promote bladder evacuation. In 1990 (30,31), we reported on the first thirty-five patients suffering from neuropathic voiding dysfunction caused by suprasegmental spinal cord lesions. Of the twenty-five patients that were available for follow up, 60% experienced restored reservoir function and restored continence with complete bladder evacuation.

In our continuing neuroanatomic studies, it was determined that the dorsal sacral neurotomies could be done more extensively and easier if performed intradurally rather than extradurally (32). Our previous studies have also shown the existence of a separate parasympathetic nucleus and a pudendal nucleus in the sacral segment. We noted that the ventral sacral roots emerged as numerous separate rootlets (33). The spatial orientation of these rootlets imply that each carries the axons of the closest neuronal cell group in the spinal cord and gathered in a few rootlets-the rootlets formed by axons emerging from the parasympathetic nuclei maintained their identity throughout the entire intra spinal course. The same arrangement was noted in those emerging from the pudendal nuclei. These rootlets grouped into bundles that later constitute the ventral root, which then exit the dura. The dissection of these rootlets throughout their entire intradural course showed that they maintained their identity until they exit from the dura. This suggests that the stimulation of the specific rootlet might be equivalent in its specificity and selectivity to micro stimulation of specific neuron groupings in the spinal cord itself. In addition, the fiber that might carry somatic fibers to the sphincter could be identified by stimulating these rootlets intradurally. They could be cut, and then electrode is placed extradurally on the entire ventral root, avoiding the activation of the striated sphincter. This could make the stimulation more selective, eliminating detrusor sphincter dyssynergia. As an outcome from this work, we can consider intradural dorsal rhitzomy, plus cutting selective anterior somatic rootlets that are mostly carrying somatic fibers, then extradural electrode placement on the intact selected sacral root.

In additional work (22), taking advantage of the knowledge that high frequency current can block large somatic fibers, electrical blockade of undesirable responses was tested to replace selective somatic neuroautomies. High frequency sinusoidal stimulation was effective in blocking external sphincteric activity. However, the sinusoidal wave form is not efficient. An alternate phase rectangular wave was more efficient and induced the same blockade. Alternating pulses of high frequency and low aptitude, followed by low frequency and high amplitude, were effective in inducing low pressure voiding without the need for somatic neurotimies. This approach has not yet been tried clinically, but it might prove to be the answer to the problem of the detrusor sphincter dyssynergia in electrically stimulated voiding.

Neuromodulation

The widely applied neuromodulation (34) in the management of voiding dysfunctions and pelvic pain is a small byproduct of this extensive work on the development of what we look at as a bladder pacemaker to restore bladder function in high spinal cord lesions. During our testing of the spinalized animal in which we had implanted electrodes in various segment of the sacral roots and while doing our urodynamic monitoring, we noted that when the bladder went into activity with any degree of filling, if we stimulated the sacral roots, we could immediately inhibit this activity. The bladder stayed quiet as long as the stimulation was maintained. The moment stimulation stopped, the bladder became overactive again. That took us by surprise initially, but after considering it, we realized that this is a normal natural reflex. If the bladder tends to overact, we can suppress it by overactivating a sacral root, which would have tightened the perineal muscles and that

inhibits detrusor activity. That was the first insight into the fact that driving the sacral roots can inhibit detrusor overactivity. We felt that if this could be accomplished in the full-blown overactive spastic neurogenic bladder, it would definitely be easier to accomplish the same under less severe conditions. There is a reflex inhibitory mechanism that exists between pelvic floor and detrusor activity. As it was noted, sphincteric contraction suppressed detrusor activity and also pudendal nerve blockade improved bladder capacity. Excluding mechanical obstruction, most voiding dysfunctions are related to the urinary bladder or the pelvic floor. To the latter group, they ascribed the severe urge and frequency to sphincteric instability and pelvic pain because of the constant pelvic floor hyperactivity. It became clear that whenever we diminished the uretheral sphincter and pelvic floor instability, it stabilized the entire micturition reflex mechanism. This is what initiated the concept of neuromodulation. Activation of the external sphincter by sacral root stimulation inhibited detrusor activity as a normal reflex, and this diminished detrusor instability. This however requires an intact sensory pathway. The stimulating parameters are too low to activate the autonomic component of the sacral root; however, it stimulates mainly the somatic component in both the afferent sensory fibers and efferent motor fibers. Intraspinal connections between the pudendal and the parasympathetic nuclei in the sacral segment are likely responsible for the modulation of the voiding reflex and detrusor activity. Having this knowledge and understanding, we started testing our patients. The first sacral root implant was actually done per cutaneously in 1981. We tested numerous patients with a variety of voiding and pelvic floor dysfunction with very encouraging results. With proper selection, this modality of neuromodulation became highly successful. This approach is now being used worldwide and becoming highly popular and successful and is being called interstim neuromodulation. The basic principle of it is the interaction between the pelvic floor and detrusor activity.

Neuromodulation, however, had a broader application as it is currently being tested and applied on a variety of other dysfunctions as fecal incontinence, spastic colon, dyssynergia interstitial cystitis, and other varieties of pelvis floor dysfunctions with varying degrees of success.

Future potential of neurostimulation and neuromodulation

Neurostimulation and neuromodulation are here to stay (35). They have already proven their effectiveness and their potential benefits. Considerable progress has been made during the last two decades in understanding the basic issues that are related to neurostimulation and its potential application, not only in the urinary tract and the pelvic organs, but also in other organs. Whenever there is an intact motor neuron system that can be isolated, it can be stimulated to drive the function it was intended for. Electrophrenic respirators are clear examples of the successful application of neurostimulation to drive the diaphragm in high quadriplegic patients. The auditory prosthesis is another successful application of neurostimulation to restore hearing loss.

Application of neurostimulation to lower and upper extremities for rehabilitation has been investigated widely and is highly promising of achieving mobility as well as restoring and maintaining function of either extremity. The optimum goal is to restore full function to make the individual capable of utilizing both upper and lower extremities. With the progress being made, this potential is likely achievable.

The nervous system is fortunately quite specific for its function, whether it is sensory or motor, whether it is somatic or autonomic. A knowledge of the precise anatomic connections and distributions open the door for reproducing specific function by tapping into the segments of the nervous system to do the job desired. A clear example of that is seen in the sacral roots, which we tapped into to control pelvic floor function. The complete root is considered in its two basic components, the sensory dorsal and the motor ventral components. Both roots are made out of several rootlets. These rootlets are derived from the spinal cord and from the adjacent neural cells with a certain degree of specificity for their function. This knowledge is raising the potential that we can identify precisely the neural unit that is responsible for a certain function to be stimulated and driven.

As discussed earlier, these are the basic knowledge and know how to develop a complete bladder pacemaker that can achieve restoration of the basic function of the urinary bladder, making it gain capacity as a reservoir and be able to empty completely and at the same time maintain continence. In spite of this knowledge, this has not yet been clinically applied. There are several reasons for this. Primarily, there is no prothesis available at the moment that can deliver the specific stimulation parameters required for the successful bladder pacemaker. It has not been developed because of its complexity, and the limited population in need of this kind of approach. In addition, the surgical

approach proposed is highly demanding.

The patient population for this approach, the complete bladder pacemaker, is primarily high paraplegic and quadriplegic patients as the result of spinal cord injury. The approach, as it stands today, does require certain neurotmesis, whether it is dorsal rhizotomy or selective somatic neurotomy of one kind or another. Those patients are usually adamant against any more nerve cutting or nerve damage. They already sustained extensive injury to their spinal cord, and they refuse any approach that will further interfere with the integrity of what is left of their nervous system. The most important is the approach itself, which is a quite demanding surgery. It needs the interested neurourologist, who should have the surgical capability close to that of a neurosurgeon or a neurosurgeon, who is deeply interested in neurourology to be encouraged to embark on such a highly demanding delicate surgical intervention. Either way, it will require extensive training before wide application and wide use of that knowledge and technology become available.

If we combine all of these factors together, we start to appreciate why this technology is not much widely used and properly applied for this needy population. Industries are less than enthusiastic to embark on the development of such a complex prostheses. There is a limited population. Compound that with the limited number of neurourologist, who care for them and who have learned this neurosurgical expertise to consider such an approach, coupled by a vast segment of discriminative population, who would not consent to any surgical intervention that would include further neurotmesis.

Technology and knowledge on how to develop the true perfect bladder pacemaker that can also be a bowel pacemaker as well as an erectile function pacemaker for the quadriplegic or the high paraplegic is with us. Further development in our understanding of electrical blockade of neural transmission might help in eliminating most if not all neurotmesis. That in itself would be a major step forward because a simplified surgical technique, and no neurotomy would be more acceptable to patients.

Neurostimulation for the control of the visceral organs has a long and arduous history. However, great progress has been made and knowledge has been expanded. What has been a dream is getting closer to becoming a reality.

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Footnote

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Treatment Progress

Gastric bypass surgery patients warrant special attention for preventing urinary stones

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Obesity rates have steadily risen throughout the industrialized world, with America leading the way. Currently more than 15 million Americans fall into the extreme categorization of morbid obesity, defined as body mass index (BMI) >40. Several weight reduction treatment options exist for these patients, with surgical intervention representing an effective and popular approach. Overall, surgical approaches are categorized as restrictive, malabsorptive, or a combination of the two. Fortunately, restrictive approaches, "lap banding" or sleeve gastrectomy, do not yield an increased risk for nephrolithiasis. The same cannot be said for malabsorptive approaches, with the Roux-en-Y gastric bypass (RYGB) representing the most popular of these. These have been clearly shown to lead to increases in urinary oxalate and calcium while leading to a decrease in urine volume and urinary citrate where the risk of a future calculus after RYGB is 2-3 fold greater. To combat these changes, both human and animal studies support the utilization of dietary modifications (reduction of oxalate and fatty foods, increased oral hydration, and supplementation with citric salts and calcium) to reduce the risk of nephrolithiasis formation (1). These dietary change recommendations, however, must be carefully made for patients, for whom changes in gut transit time and potentially hydration status and capacity to eat food may be drastically altered. For example, in these nephrolithiasis patients with a rapid gut transit time, we routinely recommend against restricted sodium intake, contrary to recommendations given to most stone formers. Additional routine recommendations we provide to stone-forming patients who are status post RYGB include increased oral hydration, calcium in the form of dairy of calcium tablets with all meals, and often times potassium citrate supplementation. These patients should have established, long term relationships with their dietary and stone specialists to prevent recurrence of stones.

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Treatment Progress

Ureteral stents are part of an ever-expanding technology horizon

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Although the concept of ureteral stenting has been around since the 1800s, it was not until the 1960s that the more modern version ureteral stents (at that time referred to as splints) were placed endoscopically. Many of the common problems with ureteral stents (irritative voiding symptoms, hematuria, encrustation, bacterial colonization, etc.) have persisted over the years, but several recent advances may abolish or drastically mitigate these problems. Recent attempts to address problems with bacterial colonization, encrustations, and biofilms have included gel-based hydrolyzed polyacrylonitrile, slow-release varnish coatings, and antimicrobial triclosan coatings (1). Unfortunately, many of these advances are not yet clinically available, and those that are, triclosan coated ureteral stents, have fallen out of mainstream clinical practice. Other attempts at addressing the irritative symptoms associated with ureteral stents continue to be an on-going process. The Percuflex™ Helical (Boston Scientific) stent was designed to better conform to the contour of the ureter, but no evidence exists yet regarding decreased stent-related symptoms. Several other novel stent designs are promising, but are still within the clinical trial phase as well. Although the authors include the Allium metal self-expanding ureteral stent within their discussion, at our institution, we have also utilized the metallic Resonance™ stent (Cook Medical) as a recent advance in ureteral stenting technology. The ability of metal stents to resist compressive forces combined with their approved dwelling time of 1 year is appealing, but the greatest drawback is likely the concern over increased lower urinary tract symptoms. Modern endourological ureteral stents have been in existence for nearly 50 years, and while several recent advances have taken place in ureteral stent technology which offer the promise increased comfort with decreased encrustation, unfortunately many of the latest designs are still within human clinical trial phases and their true utility is yet to be determined.

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Injection therapy for Peyronie's disease: pearls of wisdom

William O. Brant[1], Amanda Reed-Maldonado[2], Tom F. Lue[2]

[1]Department of Surgery (Urology), Center for Reconstructive Urology and Men's Health, University of Utah, Salt Lake City, USA; [2]Department of Urology, University of California, San Francisco, USA

Correspondence to: Tom F. Lue. Department of Urology, University of California, San Francisco, USA. Email: Tom.Lue@ucsf.edu.

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Peyronie's disease (PD) is a localized connective tissue disorder of the penis that may result in formation of plaque, penile deformity, pain, erectile dysfunction and emotional stress. It can affect the tunica albuginea, septum, or intracavernous struts leading to curvature, shortening, indentation, or hourglass deformity of the erect penis. Because it is a localized disease, a focal therapy seems to be the most rational approach. Additionally, patients are understandably hesitant to have surgery on the penis. This commentary summarizes the combined experience of verapamil and Xiaflex injection by the authors. Other practitioners use interferon and other medications. We do not use these and therefore have eliminated this from the discussion.

Verapamil injection

Although not FDA approved for use in PD, verapamil has been used commonly for many years (1-3). Verapamil is administered as 10 mg in 10 cc of NS, every 2 weeks. Our practice is to perform a penile block, use a 21 g needle to administer the medication, and to give six injections prior to reevaluation of the clinical situation. If there is good improvement but not quite enough, the patient may elect to have another six injections of 20 mg in 10 cc.

Although the number of patients receiving verapamil has decreased since the FDA approved Xiaflex, there still is a patient population that seems to benefit from this medication. Unlike Xiaflex, verapamil is given in a larger volume. In other studies, injection of saline alone has a good response rate, and it is unclear to us the relative role of the drug itself versus the hydro-distension effect of the large volume of saline.

Cost

Verapamil is substantially cheaper than Xiaflex, and thus may be used when insurance coverage or other financial considerations prohibit the use of Xiaflex.

Pain

Although Xiaflex is not uncomfortable to receive, some patients have significant pain for up to 48 hours after the injection, with rare patients having discomfort beyond this period. Verapamil is more painful to receive, likely due to the volume of fluid, but is not significantly painful thereafter. It hastens the resolution of PD-related pain. Although many studies have noted that resolution of pain is an eventuality in PD patients, it is often a considerable source of bother in those patients who have it, and resolution of pain as rapidly as possible is a very desirable outcome. We have found that Xiaflex may be extremely uncomfortable in patients in whom pain is a predominant symptom.

Non-curvature deformities

Verapamil seems to have a superior outcome for deformities that are not purely curvature in nature. These include waists, hourglass, and areas of instability or hinging. Although the deformity in these cases appears lateral, a lateral plaque is relatively uncommon and these defects usually are associated with a typical, dorsally located plaque. Our surgical experience has shown us that the area of indentation is a contracture, rather than an area of underlying corporal fibrosis. The dorsal plaque is associated

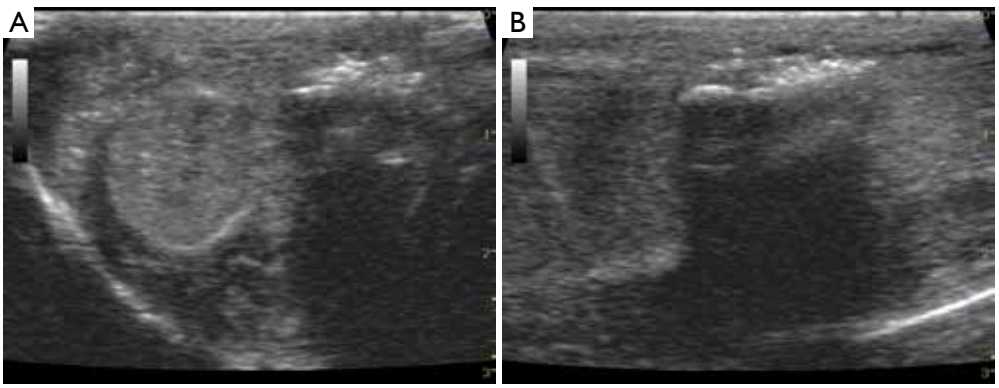

Figure 1 Penile ultrasound 5 minutes after Xiaflex injection into the plaque showing increased echogenicity from micro-bubbles in the plaque in (A) transverse view and (B) longitudinal view.

with abnormalities in the intracorporal struts, which causes local contracture. Our theory is that verapamil and/or the associated hydrodistension allows the struts to expand and thus corrects these types of abnormalities.

Stage of disease

With stable disease and heavy plaque calcification, verapamil seems to have much less efficacy than when used in the context of early disease and softer plaques. Overall, we prefer to use Xiaflex in the context of stable plaques.

Xiaflex (collagenase clostridium histolyticum) injection

The main difference between Xiaflex and other injectable therapy is Xiaflex's ability to dissolve the collagenous fibrous tissue within the plaque (4,5). However, Xiaflex also carries the risks of hematoma and penile fracture due to thinning/softening of the tunica albuginea. The modeling/stretching maneuver to expand/lengthen the contracture following Xiaflex injection is as important as the injection itself. Clinical trials have clearly shown that the combination of injection plus modeling has the best results in reduction of penile curvature.

Location of injection

Anatomically, the thinnest portions of the tunica albuginea are on the lateral aspect (3 and 9 o'clock positions) and between the corpus spongiosum and the cavernosa (6 o'clock position). At this time, the company does not recommend injection to the ventral plaque for fear of damaging the urethra. After more than 1,000 injections, we feel that the ventral plaque is not necessarily a contraindication as long as the plaque is clearly palpable, not calcified, and thick (>0.3 cm by ultrasound measurement). We have also found that ventral plaques respond, in these situations, as well as dorsal plaques. The urethra can always be spared as long as the plaque can be firmly pinched between the thumb and index finger. The injection should be directed to the 5 and 7 o'clock positions not 6 o'clock position. We have seen herniation, hematoma, and micro-rupture of the lateral tunica after injection of Xiaflex to the lateral aspect of the penis. Therefore, we do not recommend Xiaflex injection to lateral aspects of the penis for men with true lateral curvature. We have not injected Xiaflex to sites of intracavernous or septal fibrosis and therefore cannot recommend it at this time.

Injection technique

The instruction from the company is to insert the needle to the plaque and slowly withdraw while injecting Xiaflex solution. We feel that this may "waste" part of the injected Xiaflex because it is very difficult to be certain that the needle is still inside the plaque if one is injecting while withdrawing. Additionally, we have seen higher rates of ecchymosis and swelling, likely due to extravasation of Xiaflex outside of the plaque via the needle track. Instead, we prefer to forcefully inject Xiaflex to the plaque against the high resistance (*Figure 1A,B*). We also prefer to inject into at least two sites within the plaque to avoid rupturing the thin plaque with the total amount 0.25 mL. Of course, a large and thick plaque is not a problem with 0.25 mL.

Since the volume of Xiaflex is small, it is important to pick the best spot for injection. This can be done in several

Figure 2 Ecchymosis of penis and pubic area 3 days after Xiaflex injection.

Figure 3 Hematoma at dorso-lateral aspect of penis 7 days after Xiaflex injection.

ways, but we prefer to compare the palpable plaque with the patient's erection and choose the site that corresponds to the site of maximum deformity. One author prefers to have the patient mark this site with a permanent marker the day prior to the injection so he has the correspondence of the palpable plaque, the patient's subjective view of the area of maximum deformity, and the view of this area as seen on auto-photography. The other authors prefer to inject a vasodilator (most of time with 0.05 mL of phentolamine/papavarine solution) and self-stimulation to induce erection and mark it with a marker before giving the local anesthetic.

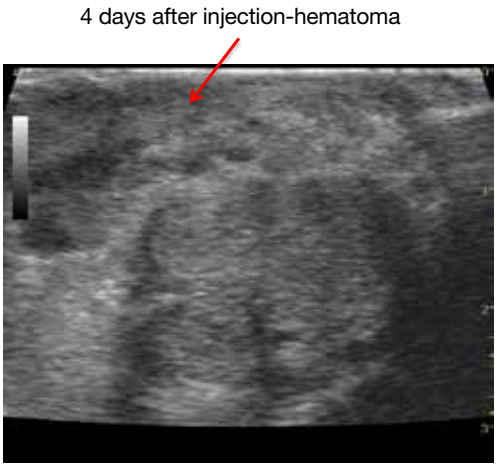

Figure 4 Penile ultrasound 4 days after Xiaflex injection in a patient with hematoma. No obvious rupture/disruption of the tunica albuginea is noted.

Patient taking anticoagulants

Discontinuation of an anticoagulant or antiplatelet medication for 5 days prior to injection is preferred. If contraindicated (e.g., cardiac stents that require aspirin), we teach the patient to apply a loose compressive dressing and change this daily for 2-3 days to prevent excessive ecchymosis.

To operate or not to operate

Bleeding during or after nocturnal erections can present with ecchymosis (bleeding within the subcutaneous tissue) (*Figure 2*) or hematoma (blood clots between Buck's fascia and tunica) (*Figure 3*). In both conditions, a penile ultrasound to confirm the diagnosis is all that needed (*Figure 4*). Ultrasound examination of the tunica is operator dependent, and such examinations should only be done if the examiner is comfortable with this. On the other hand, if ecchymosis /hematoma developed suddenly during or after sexual intercourse, penile fracture is the most likely diagnosis until proven otherwise. If penile ultrasound confirms a sizeable tunical rupture, surgical repair is recommended.

Hourglass deformity or unilateral indentation

If the plaque is palpable at the dorsal or ventral aspect, we have injected Xiaflex into the plaque followed by daily stretching with a vacuum erection device with reasonably good results. If only lateral plaque is palpable, we do not

recommend Xiaflex injection anymore because we have seen hematoma and herniation after Xiaflex injection in several cases.

Injection schedule

The package insert recommends two injections 1-3 days apart, followed by daily stretching and manipulation by the patient for 6 weeks. In some patients who developed severe skin edema and ecchymosis, we have waited up to 1 week to give the second injection. In some men with small plaque, we elected to give one Xiaflex injection followed by modeling to prevent potential tunical rupture.

Conclusions

If a patient is interested in the most definitive, rapid treatment of a stable Peyronie's deformity, surgical approaches continue to be the gold standard. However, most of our patients are understandably hesitant to pursue surgery and are willing to undergo the inconvenience of repeated injections to achieve a less invasive approach to their deformities. Our combined experience with over 1,000 patients receiving verapamil and over 400 patients receiving Xiaflex has shown us that these medications can be very successful and satisfying, but rely on (I) careful consideration of the patient's individual characteristics, (II) adherence to good techniques for injecting and (III) patient's willingness to comply with their at-home physical therapy. Verapamil is appropriate for less stable disease and in softer plaques, whereas we prefer Xiaflex for more stable disease and denser plaques. We avoid Xiaflex in true lateral plaques (which are very uncommon). For technique, a fanning technique is appropriate for verapamil, administered via a 21 g needle for maximum hydrodistention. For Xiaflex, the needle should remain within the densest portion of the plaque, corresponding the point of maximum deformity, in order to minimize extravasation and subsequent ecchymoses. The best results are seen when patients comply with manipulation of the plaque, via a combination of stretching, gentle bending of the erect penis in the opposite direction of the curve, and massage of the plaque.

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Looking beyond the guidelines for perioperative antibiotics in nephrolithiasis

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Establishing guidelines for the use of perioperatively antibiotics for patients being treated for urinary stone disease presents a particularly challenging clinical issue. Nephrolithiasis patients represent a variety of etiologies, from obstructive to infectious stones, and their treatment ranges from practically non-invasive in the form of extracorporeal shockwave therapy to relatively invasive with percutaneous approaches. In addition, within each procedure type, there is a large gradation in level of associated morbidity—a ureteroscopy with a basket stone extraction for a distal 5 mm stone likely represents a much different infectious risk compared to a ureteroscopy with laser lithotripsy for a proximal 1 cm ureteral stone requiring ureteral orifice dilation along with access sheath placement. Therefore, the application of guidelines to even one type of procedure may not encapsulate the complex diorama that embodies stone patients and their treatments. As the authors very nicely summarized (1), recommendations regarding antibiotic use for stone procedures reflect an extremely broad and varied number of practice patterns. What this points to is the pressing need for better research to understand markers to predict which patients will develop infection postoperatively and how to best apply appropriate antibiotics for these patients. Additionally, this highlights the need for a better biomarker for infection than traditional urine or even stone cultures in order for us all to more safely manage our nephrolithiasis patients.

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Treatment Progress

Should perioperative anticoagulation be an integral part of the priapism shunting procedure?

Tom F. Lue, Maurice Garcia

Department of Urology, University of California, San Francisco, USA

Correspondence to: Tom F. Lue, MD. Emil Tanagho Endowed Chair in Clinical Urology. Department of Urology, University of California, 400 Parnassus Ave. Suite A633, San Francisco, CA 94143-0738, USA. Email: TLue@urology.ucsf.edu.

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We propose that post-shunting recurrence of ischemic priapism is a postoperative thromboembolic complication, similar to cases of postoperative thrombosis of veins (femoral or popliteal) or arteries (cerebral or coronary). Therefore, perioperative anticoagulation should be given to men undergoing these shunting procedures to prevent this complication.

Two illustrative cases are presented herein.

Case 1

The patient is a 22-year-old man with a history of schizophrenia, controlled with oral medications (olanzapine and valproic acid). Over the past two years, he had eight episodes of ischemic priapism, lasting between 4-14 hours, which all resolved spontaneously.

The patient presented again to a local hospital with a chief complaint of painful erection for three days. The patient was immediately transferred to our center. A thorough history yielded only recent (and only intermittent) use of olanzapine as a possible causative factor for the ischemic priapism. He complained of severe, dull pain in his penis. On physical examination, his penis was rigid and tender. There were no signs of infection. His WBC count was normal.

He was taken to the operating room, as he declined bedside procedure in the emergency department. On exam, the tip of the rigid corporal body was easily palpable at a shallow depth from the surface of the glans. A marking pen was used to make two vertical incision lines about 1 cm long, 0.5 cm lateral to urethral meatus. Local anesthetic (0.25% bupivicaine) was injected into the subepithelial layer (not the underlying spongy tissue) of the glans overlying the planned, T-shunt sites (*Figure 1*). Bilateral T-shunts were then performed using a 10-blade scalpel, in quick succession. Bilateral corporal tunneling was performed using 22-Fr. straight urethral sounds as previously described (1-3). With the sound oriented slightly laterally, the sound was passed gently to the crura without injury to the urethra. After the sound was removed, there was immediate drainage, of thick dark viscous blood. The penis was milked until blood draining forth from the shunt sites turned into a bright-red color. The T-shunt sites were closed with running-locking 4-0 chromic sutures. Care was taken to place each suture shallowly within glans tissue, so as to minimize incorporation of deeper glans tissue at the shunt site. The penis was moderately edematous, but remained non-erect throughout a 10-minute observation period and through the end of the surgery. A Foley catheter was placed which drained clear yellow urine. Following transfer to the recovery room, the patient was discharged to the ward for observation.

The patient was found to have a partially erect phallus until the evening. However, the next morning, the patient awoke with a rigid erection. Based on our exam, the patient appeared to have early recurrence of ischemic priapism. He consented to our recommendation to return to the operating room for repeat T-shunt and tunneling. We also explained to him our recommendation of perioperative anticoagulation. He was given subcutaneous heparin 5,000 units pre-operatively. In the operating room, approximately 15 hours after his previous surgery, we removed the sutures on the glans. Upon doing so, a small clot immediately presented itself below the suture line on each side (*Figure 2*).

Figure 1 Sub-epithelial injection of local anesthetic prior to T-shunt procedure.

Figure 2 A clot at the previous T-shunt site on the glans is noted after the sutures were removed.

With repeat T-shunt and tunneling, there was drainage of very dark blood that was less viscous than what was drained at surgery 15 hours prior. There was no additional clot noted in the blood evacuated from the corporal bodies. As before, we milked the penis until the first return of fresh bright blood. We observed the penis for several minutes and noted no recurrence of priapism. We then proceeded to close the T-shunts with 4-0 chromic interrupted locking sutures. The penis remained moderately soft and not rigid through the end of the case. He was given 325 mg of aspirin and 40 mg of famotidine after recovering from anesthesia and instructed to take baby aspirin (81 mg) and famotidine (40 mg) daily for two weeks. One more subcutaneous heparin injection was given 12 hours after the initial dose.

For the next 24 hours, the penis remained partially erect, but not rigid. The patient reported no penile pain at rest, and was discharged approximately 30 hours after his second surgery. As numerous case reports have suggested that olanzapine can cause ischemic priapism, his psychiatrist was contacted before discharge. Close outpatient follow-up (within 24 hours) with his psychiatrist was arranged prior to discharge.

At follow-up 2-week later, the patient reported no recurrence of painful erection since discharge. He confirms that he continues to take aspirin 81 mg daily. He also confirms that he awakens each morning with a good erection (painless, about 90% rigidity, sufficient for penetration), and that these erections detumescence spontaneously. Erections recur intermittently during the day and evening. On exam, no gross swelling or ecchymosis was visible. His penis was fully engorged but soft and the mid-shaft could be easily compressed. Color duplex penile ultrasound was performed. Arterial flow was evident in each cavernous artery (*Figure 3*) and the glans-cavernosum shunt was patent with detectable flow (*Figure 4*).

Case 2

The second case is a 40-year-old politician who had suffered from anxiety and insomnia for several months

Figure 3 Arterial flow was visible in the cavernous artery shown in color duplex ultrasound.

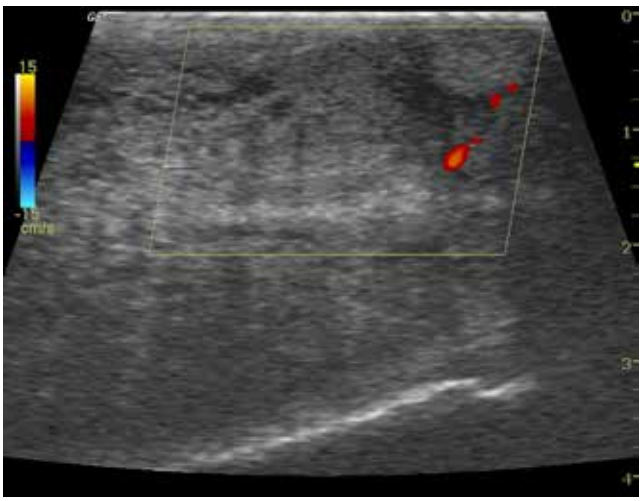

Figure 4 Flow from distal corpus cavernosum to the glans penis (right upper corner of the sonograph) was seen indicative of a patent shunt.

because of a personal financial problem. He was given trazodone for insomnia. After taking the first dose, he woke up the next morning with a rigid erection. He was well known in the community and was embarrassed to seek medical treatment. He presented to a local hospital about 48 hours later. Aspiration of old blood and injection of a diluted phenylephrine solution failed to resolve the priapism. A Winter's shunt was performed by a local urologist. The priapism was relieved only to recur about six hours later. He was taken to the operating room and a spongiosum-cavernosum shunt was performed. The penis became soft (but swollen) after the procedure. However, persistent painful erection occurred the next morning and he was referred to our emergency room for further management. Under local anesthesia a 10-blade scalpel was used to create a T-shunt bilaterally. This was followed by bilateral tunneling with a 22 Fr. straight female sound. The priapism subsided shortly after, and the patient was discharged home.

He returned the next day, again, with a rigid painful erection. We recommended our perioperative anticoagulation therapy and started him with 325 mg aspirin and subcutaneous injection of 5,000 units of heparin. He was brought to the operating room for a repeat T-shunt procedure. When the sutures on the glans were removed, blood clots were noted at the T-shunt site. Repeated T-shunt and tunneling was performed which resulted in a partial detumescence. Manual compression of the base of the penis dislodged a few blood clots followed by non-coagulated old blood. The penis remained at partial erection but compressible ten minutes after the wound on the glans was closed with continuous locking water-tight 4-0 chromic sutures to prevent postoperative bleeding. He was given one more dose of subcutaneous 5,000 units of heparin and instructed to take baby aspirin (81 mg) daily for two weeks after discharge. His partial erection decreased gradually and the penis was flaccid after about five days. He reported fully-regained erectile function without the need for phosphodiesterase-5 inhibitors about three months later.

Comments

In ischemic priapism that does not respond to alpha-adrenergic agonists, various shunting procedures have been developed to re-establish circulation of the corpora cavernosa and prevent necrosis of erectile tissues. However, early closure of the newly created shunt, resulting in recurrent priapism, is a common complication which leads to repeated shunting procedures, longer hospital stays, increased patient sufferings, and less than favorable outcomes. In fact, early recurrent priapism is the most common emergent phone consultation to our andrology clinic. In subsequent exploration/re-shunting, blood clots at the site of shunting can always be expelled, followed by un-coagulated "crank-case oil"-like old blood. It is well documented that the old blood inside the corpora cavernosa does not clot due to the abundance of endothelium-derived

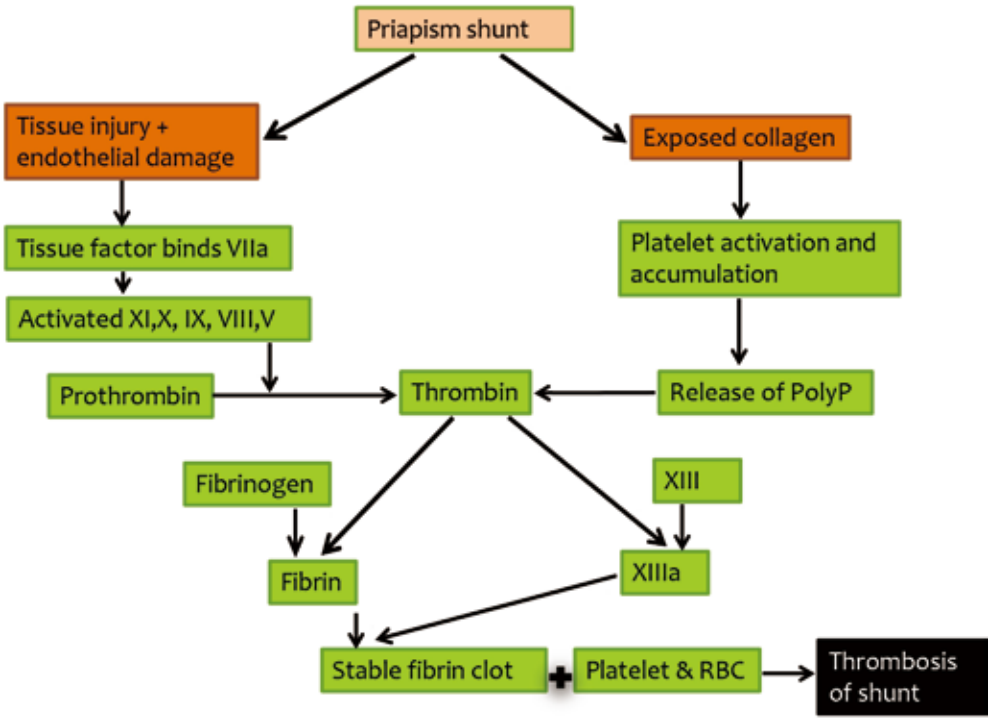

Figure 5 Proposed mechanism of clotting of shunt modified from the cell-based model of blood coagulation (5). Damage to the tunica albuginea and endothelial lining of the corpus cavernosum during creation of the shunt triggers the tissue factor to bind factor VIIa and activates the cascade of coagulation. In addition, exposed collagen of the tunica albuginea causes accumulation and activation of platelets and release of inorganic polyphosphate (PolyP), a powerful activator of thrombin. The final product is thrombosis of the shunt by blood clot made of a mixture of red blood cells (RBC), fibrin and platelets.

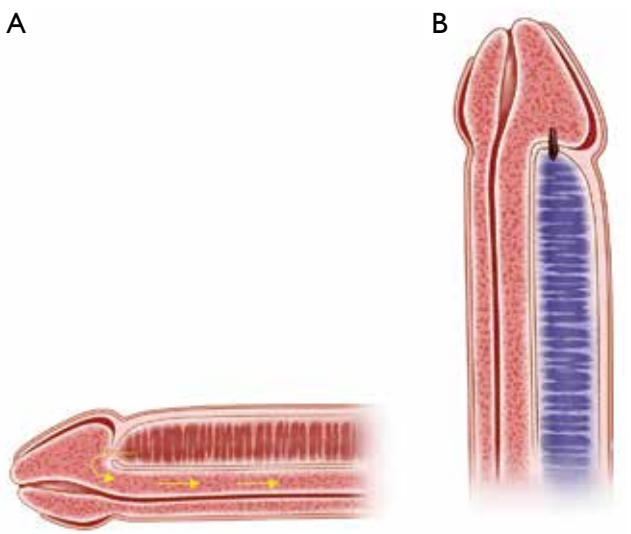

Figure 6 Diagram of cross sections of lateral longitudinal view of the penis showing complete thrombosis of a small glans-cavernosum shunt (A), and a wild-patent shunt in a penis received perioperative anticoagulation and a large caliber shunt (B).

anticoagulating and fibrinolytic factors within the corpora cavernosa (4). However, the newly created shunt is not lined and protected by endothelium. In fact, the shunt cuts a new wound through the collagen-rich tunica albuginea. The collagen-activated platelets and fibrin begin to form a clot within minutes to seal off the shunt in a similar fashion as a clot forming at the site of an injured blood vessel wall (5) (*Figure 5*).

Keeping the newly created shunt patent requires a continuous high blood flow through a large caliber shunt. When all goes well, the shunt remains open for hours to days (*Figure 6A*) until the smooth muscles of the corpora cavernosa and helicine arteries regain normal contractile capacity (6). Once the post-ischemic high blood flow is normalized, a larger clot will form and shunt will close spontaneously. Premature closure of the shunt from inadequate size and stagnant blood flow will enhance the adherence of platelets and fibrin to collagen, eventually forming a thrombus at the site of shunting and cause

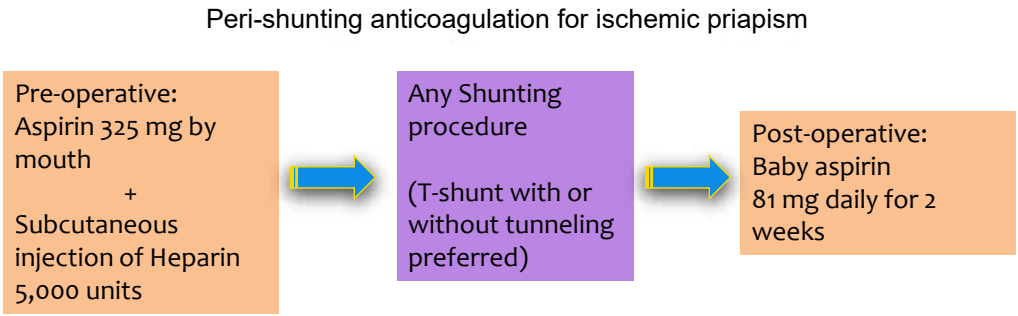

Figure 7 Perioperative anticoagulation for prevention of premature shunt closure in ischemic priapism.

early recurrence of priapism (*Figure 6B*). In essence, early postoperative shunt closure is a postoperative thrombotic complication, and its management/prevention should be incorporated into the future guidelines for treatment of ischemic priapism (*Figure 7*).

The risk of postoperative thrombo-embolic complications, such as femoral-popliteal venous thrombosis, pulmonary embolism, and cerebral and coronary arterial occlusion, is ever present, and each poses a major threat to a patient's life. Clinical guidelines have been established (and are constantly evolving) to prevent these complications in various surgeries. Likewise, premature closure of a priapism shunt is a postoperative thrombotic complication, and, given the resulting morbidity, deserves to be treated with the same precautions as other thrombo-embolic complications. Over time, we have witnessed many of these complications along with the resulting pain and suffering of our patients. However, in the past two years, we have also observed the success of perioperative anticoagulation therapy in preventing premature shunt closure, resulting in better outcomes. We, therefore, propose that perioperative anticoagulation should be an integral part of priapism shunting procedures.

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Footnote

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New Technique

Clinical challenges in tissue-engineered urethral reconstruction

Sophie Ramsay[1,2], Cassandra Ringuette-Goulet[1], Alexandre Langlois[1], Stéphane Bolduc[1,2]

[1]Centre de Recherche en Organogénèse Expérimentale/LOEX, Division of Regenerative Medicine, CHU de Québec Research Center/FRQS, Québec City, QC, Canada; [2]Department of Surgery, Faculty of Medicine, Laval University, Quebec City, QC, Canada

Correspondence to: Stéphane Bolduc, MD, FRCSC. Pediatric Urologist, Associate Professor, Clinician-Scientist, Division of Urology, CHU de Québec (CHUL), 2705, Boulevard Laurier, Bureau R-1742, Québec (Québec) G1V 4G2, Canada. Email: stephane.bolduc@fmed.ulaval.ca.

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Urologic patients often present with congenital and/or acquired tissue and organ dysfunctions requiring surgical reconstruction to re-establish normal genitourinary system function. The field has made tremendous use of limited resources, developing creative and effective ways to reconstruct or replace inadequate tissues. Urethral reconstruction continues to be a challenging area of expertise for urologists. Whilst for some conditions, only one or a few procedures are recognized as standard of treatment, over 300 techniques are known for urethral stricture and hypospadias repair. This diversity illustrates the complexity of these conditions and indicates the lack of a gold standard procedure. In addition to the surgeon's skills, successful outcomes of any procedure depend on the availability of appropriate tissues. A wide variety of tissues, such as (vascularized) skin grafts, and bladder and buccal mucosa, have been used in urethral repair. However, all of these substitutes have limitations compared to autologous urethral tissue, which can lead to complications (e.g., stricture formation, graft failure). Furthermore, the amount of tissue that can be harvested from a donor site is limited, which can be problematic, especially in the case of long defects. To overcome these difficulties, alternative methods for urethral reconstruction have been explored.

Traditional reconstructive surgery methods are associated with varying degrees of donor site morbidity as well as inherent notable complications. Tissue engineering (TE) is an emerging field offering the possibility of providing true biological substitutes with patient-specific properties to restore the structure and function of pathologically altered tissues. TE was full of hope and promise in its infancy in the late 20th century and has truly exploded in the first decade of the 21st. In 2010, over 4,000 articles were available on PubMed when searching for "tissue engineering" or "regenerative medicine," as compared to less than 400 in the year 2000 (1). Several groups have attempted tissue-engineered urethral substitution by using acellular and cellularized matrices (2). A major issue concerning acellular matrices, as shown in rabbits by Dorin *et al.* (3), is that urothelial regeneration in acellular graft is limited to 0.5 cm, which compromises success in more complex cases, such as long strictures. Tissue-engineered matrices containing autologous cells in addition to extracellular matrix are more promising. The main advantage of this method is that a large autologous-cell graft having the ability to grow *in vivo* without rejection can be created with only a limited amount of material, such as a piece of oral mucosa. Moreover, studies have reported that stem cells can simply be obtained from urine (4,5), making this approach even more attractive.

Despite significant progress in the urethral TE field, very few teams have proceeded to clinical trials and published their results to date. However, the four clinical trials so far conducted present encouraging results. Indeed, Engel *et al.* (6) have seeded oral keratinocytes on collagen-based matrices (MukoCell®) and grafted their substitutes in 10 patients with a success rate averaging 90%. Fossum *et al.* (7) rather used bladder urothelial cells seeded on decellularized dermal matrices to treat six patients and were 83% successful at a mean follow-up of 87 months. Bhargava *et al.* (8) chose the recellularized matrices approach by seeding oral keratinocytes and fibroblasts in donor dermal matrices that were then grafted in five patients. Within the first nine months of follow-up, two patients had graft complications. One patient had to undergo excision of the entire graft due to scarring, whereas another had to have partial excision due to graft hyperproliferation. In a recently

published update of their study commenting on long-term results with a mean follow-up of 111.8 months (9), they reported that of the original five patients, four had a normal-looking urethra and still retained their graft *in situ* nine years post-implantation. Finally, Raya-Rivera *et al.* (10) reported the success of performing an open-bladder biopsy to harvest 1 cm^2 of full thickness bladder tissue, which was then divided into urothelium and smooth muscle. Urothelial and smooth muscle cells were then grown separately in culture, and subsequently seeded on the luminal and outer surface of a tubularized polyglycolic acid mesh scaffold. Their constructs were prepared over the course of four weeks prior to being used as urethral replacement grafts for gaps of 4 to 6 cm in five pediatric patients aged 10 to 14 years who had a history of either a failed posterior urethral repair or complete posterior urethral disruption from pelvic trauma. They reported excellent success over a median follow-up of 71 months. These are outstanding results in a limited number of patients with long-segment and/or complex stricture disease. Although this is certainly far from an "off-the-shelf" alternative, with consistently reproducible outcomes, this could offer an alternative that would be superior to current approaches to long-segment urethral replacement.

On the other side, there is an increasing understanding of the complexity underlying the use of *in vitro* techniques and their translation into clinical studies with reliable and consistent outcomes that can be scaled to achieve true clinical successes (11-14). The extensive culture time required for TE models could limit their clinical application, but as reconstructive urethral surgeries are usually performed on an elective basis, this would be a minimal inconvenient. High cost of production and lack of off-the-shelf availability are the major disadvantages of the technique, but appropriate scientific development and careful commercialisation will help circumvent these aspects.

These and other limitations have been discussed in an editorial published by Barbagli and Lazzeri (15) in European Urology, in which they highlighted that "the gap between technical success in the laboratory or animal experiments and clinical application of tissue-engineered materials for the human bladder has been reported in the literature" and that "the same gap between investigative *in vitro* studies and clinical use of tissue-engineered materials in patients is evident for urethral reconstruction." The authors also mentioned that while there is a plethora of publications describing diversified TE products, solely three papers have reported clinical results on the use of these products in urethral stricture disease (16).

This triggered a letter to the editor by Osman *et al.* (17) in which they questioned various elements. First, they criticized Barbagli and Lazzeri for pointing out a recent publication as "the most important step in the clinical use of a tissue-engineered material for urethral reconstruction" as Barbagli is a coauthor of this specific paper and since it only includes preliminary data from work realised with the pharmaceutical company Urotiss. Secondly, referring to Barbagli and Lazzeri's inquiry about the future of TE urethral reconstruction when looking at if from a worldwide perspective, Osman *et al.* commented that currently, the main focus should be on the achievement of high-quality phase 1 and 2 studies and on long-term follow up, notably to avoid safety issues such as the recent saga with polypropylene mesh, rather than on commercialisation and globalization of a TE technique for urethral surgeries. They also noted that significant costs and expertise required for TE would add to the challenge of making it accessible to developing countries.

In their editorial, Barbagli and Lazzeri also wondered about what would be the optimal use of TE technology for different urethral conditions (simple *vs.* complex). At the present time, available TE models are promising, but in simple cases where local tissues or buccal mucosa are available, these less troublesome options should remain the gold standard. We agree that using TE models only in complex cases harbouring higher complication rates will place TE in a difficult position to prove itself, but these are the situations where patients can benefit the most from it and where the cost-effectiveness risks to be the greatest. Osman *et al.* believe that academic centers should ally and share the strengths of their regenerative scientists and clinicians to enhance even more the expertise on TE.

Barbagli and Lazzeri (18) replied to Osman *et al.* and suggested studying the "new world" of TE in simple cases. They concluded by asking for "tight collaboration, sharing experiences and knowledge among everyone working on and dedicating time to TE" and acknowledged that there is a "need to increase our efforts to conduct high-quality clinical trials for TE in urology." Those last two comments go along the same line. Undeniably, there should be more cooperation in urologic TE because the purpose of optimizing this technology is to improve patients' health and quality of life, and although the sphere has progressed remarkably in the last fifteen years, it is still not enough. Experts and leaders in the field should call for a focus

meeting on the subject to set objectives for the next 5 to 10 years. An upcoming European or American Urologic Association (EAU or AUA) meeting would be perfect for that!

Knowledge on TE in the field of urethral repair is expanding and still finding its way into clinical implementation. Although experience with differentiation of stem cells (either isolated from urine or from adipose tissue) towards different lineages is gaining ground, protocols with *in vitro* expansion of original tissues are better established at this moment. It is noteworthy that no research has yet been performed with pseudostratified urethral epithelium. Tissue-engineered buccal mucosa has been used in urethral reconstruction and good results have been obtained with this easily available cell source. In contrast to harvesting a full graft of buccal mucosa for reconstructive surgery, TE only requires a very small biopsy, making the harvest relatively non-invasive.

In conclusion, more studies are needed in urethral reconstruction to explore alternatives with respect to scaffolds and cell sources. Orabi *et al.* study (19) strongly supports that scaffolds without cells will not be appropriate for long-segment urethral strictures. Finally, Osman *et al.* (17) suggest that several options for scaffolds and stromal cells, and even epithelial cells, exist and merit investigation, with respect to clinical efficacy whilst considering safety issues and convenience to the patient in making any choices.

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New Technique

Predicting the future of urodynamics

Ariana L. Smith, Alan J. Wein

Division of Urology, University of Pennsylvania, Philadelphia, PA 19106, USA

Correspondence to: Ariana L. Smith.Division of Urology, University of Pennsylvania, Philadelphia, PA 19106, USA. Email: ariana.smith@uphs.upenn.edu.

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The clinical assessment of lower urinary tract dysfunction has been supported by objective measures obtained during urodynamics (UDS) for more than 30 years. Over this time, equipment has evolved with several technological advances, understanding has progressed with achievement of many milestones in UDS research, and access to care has improved with UDS equipment present in many health care centers throughout the developed world.

UDS testing began with the introduction of noninvasive uroflometry, followed by pressure flow studies, and more recently the additional use of fluoroscopy. Electromyography electrodes, air charged bladder and rectal catheters, and automated puller systems have added to the information gained at the time of study. Unfortunately, this has all come at a huge cost to the health care industry. Aside from equipment start up and maintenance fees, billing to Medicare is at a minimum is greater than $500 per study (1).

While the acquisition of more data from UDS cannot be contested, the translation to superior clinical outcomes can be. Recent data suggest UDS do not lead to superior outcomes in the setting of uncomplicated and demonstrable stress urinary incontinence (2). It is important that this data not be extrapolated to other urologic conditions or to more complicated or non-demonstrable stress incontinence. Several patient scenarios where UDS can offer diagnostic value can be supported; however, clinical trials data is limited. In order to justify the cost of this intervention, appropriately designed clinical trials documenting improvement in patient treatment outcome, including avoiding harm, should be employed. In the absence of this supporting data we can expect precertification and billing denials from insurance companies to increase and ultimately UDS utilization to drop significantly in upcoming years. Important sub-considerations include the circumstances under which simultaneous fluoroscopy (videourodynamics-VUDS) is necessary, as this adds considerably to cost, and whether the addition of electromyography has improved the diagnostic or prognostic worth of UDS or VUDS.

Patient comfort and dignity is certainly a major concern with a test that involves exposing and manipulating the urethral and anal orifices and requiring an "audience" (observer) for a typically private function. Sustained discomfort following the test has been reported, and sequelae of urinary tract infections are well documented (3). As imaging modalities improve and the sophistication of computer software to allow real time input and transmission of data evolve, at home ambulatory noninvasive methods of assessing bladder function will likely follow--much like the Holter monitor to study cardiac function. This technology will allow assessment of the patients bladder function in their usual day to day setting without the artifact of catheters and wires or the impact of observers to a usually solo activity. Cost will need to be contained with development and utilization of this emerging technology or widespread acceptance will be unlikely. In an aging population with a high anticipated prevalence of incontinence, accessible, affordable and comfortable testing will be in demand. Therefore, defined guidelines on the proper use of UDS perhaps through algorithms of care will likely be in use. For example, behavioral modifications and non-invasive conservative methods of treatment may be required prior to utilization of UDS. Undoubtedly, allocation of health care resources to an aging population will add new challenges to the treatment of urological conditions.

UDS of the future will need to balance cost effective health care with the temptation of utilizing state of the art

and emerging technology. Most important will be proving that UDS have the ability to improve patient treatment as measured by patient satisfaction scores and patient reported outcome measures. Regardless of the evolution of equipment and technology, the primary aims of UDS should remain the same: (I) to reproduce the patient's complaint during the study, and (II) to provide a pathophysiologic mechanism to explain the patient's complaint (4).

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Predicting response to neoadjuvant chemotherapy in bladder cancer: controversies remain with genomic DNA sequencing

Roland Seiler

Department of Urologic Sciences, University of British Columbia, Vancouver, BC, Canada
Correspondence to: Roland Seiler, MD. 2775 Laurel St., Vancouver, British Columbia V5Z 1M9, Canada. Email: r_seiler@gmx.ch.

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Neoadjuvant cisplatin-based chemotherapy (NAC) in muscle-invasive bladder cancer is an accepted standard of care (1,2). NAC improves patient outcomes quantified by a 5–8% higher 5-year overall survival (OS) and an increase of pathological downstaging of 10–15% (3-5). However, a considerable number of patients do not response to NAC. They are over treated and suffer from unnecessary adverse effects. This led biomarker researchers focus on the prediction of response to NAC (6-11), including the recently published study carried out by Plimack *et al*., which performed genomic DNA sequencing of pretreatment tumor tissue (12).

They used two independent cohorts, enrolled of clinical trials, for discovery (n=34) and validation (n=24). The NAC regimens were accelerated methotrexate, vinblastine, doxorubicin, and cisplatin (AMVAC) (13) in the discovery cohort and dose-dense gemcitabine and cisplatin (DDGC) (14) in the validation cohort. Of pretreatment tumor samples, DNA alterations in 278 cancer-related genes were determined. They discovered a decision tree based on alterations of three genes (ATM, RB1, and FANCC), which was able to predict pathologic downstaging (≤ pT1pN0cM0), complete response (pT0pN0cM0) as well as progression free survival (PFS) and OS. None of the nonresponders in the discovery cohort had an alteration in one of these genes. In the validation cohort, this decision tree was partially significant. About 64% patients with pathological downstaging and only 15% nonresponders had at least one alteration in one of these genes (P=0.033). Although, the Kaplan-Meier curves for RFS and OS looks discriminative, only the log-rank test for OS was almost significant (P=0.055). However, this cohort is smaller, the follow up shorter, the included patients older and with a higher ECOG, which questions RFS and OS as appropriate endpoints.

Intuitively, it seems evident that these DNA repair-associated genes (ATM, RB1, and FANCC) are related to the response to NAC. But DNA alterations do not necessarily reflect functional and structural changes of a given protein. To investigate the potential biological consequence of a given alteration, they used computed prediction models. Indeed the vast majority of alterations were predicted to be deleterious. However, only structural analysis of the proteins and the subsequent loss of their biological function may allow to prove the consequences of these genomic DNA alterations.

Recently two other groups investigated genomic DNA alterations of pretreatment tumor tissue and related their findings with likelihood of response to NAC (7,11). Van Allen *et al.* discovered that somatic mutations in ERCC2, a gene related to DNA-repair, were associated with favorable response (11). Interestingly, they proved their findings *in vitro* and showed that ERCC2-deficient cell lines failed to rescue cisplatin sensitivity. Groenendijk *et al.* found that only complete responders but none of the nonresponders showed missense mutations in ERBB2 (7). The trend for more missense mutations in ERCC2 in complete responders was not significant.

Interestingly, all groups identified different genomic DNA alterations. Several reasons could explain this inconsistency. The rather small cohorts (range, 24–71), differences in cohort enrolment and NAC regimens might influence the discovery. The clinical stages of these cohorts are comparable but there are differences in practice patterns. While NAC is considered in all patients with muscle-invasive bladder cancer in North America, this is less common in Europe where NAC is predominantly suggested for higher staged patients. Therefore, the rate of surgical downstaging may be different. Since surgically

down-staged tumors are indistinguishable from tumors that respond to chemotherapy, there is a higher risk in a North American patient cohort that biologically resistant tumors are erroneously classified as chemoresponsive. In addition, all studies used different criteria to define the response to NAC. Van Allen *et al.* did not consider lymph node positive cases as non-responders and Groenendijk *et al.* excluded patients with invasive organ confined residual tumors. Plimack *et al.* not only compared nonresponders with complete responders but also with those that had pathologic downstaging and they included survival as secondary endpoint. Finally, all studies used different sequencing methods. Van Allen *et al.* performed whole exome sequencing, whereas the two others (7,12) used targeted sequencing of cancer-related genes. Importantly, the panel used by the Plimack *et al.*, did not include ERCC2, what prevented a potential validation.

Two studies reported a common finding (11,12). Responders had a significantly higher rate of somatic mutations when compared with non-responders. In general, bladder cancer as well as other cancers induced by carcinogens such as tobacco smoke shows a higher rate of somatic mutations (15,16). A somehow ironic consequence may be that smokers respond better to NAC than nonsmokers. Only Van Allen *et al.* provided smoking status but this data did not show a trend that supports this hypothesis (11). However, this could be an interesting question for future studies investigating genomic DNA alterations in relation with response to NAC.

A definitive validation of these findings is still needed. Ideally, future cohorts should be larger, treated with a specific chemotherapy regimen, combined with a chemonaive cohort to define the biomarker as predictive rather than prognostic and include all genes of interest. Another open question is the appropriate study endpoint. The nature is rarely black or white and why should this be the case in response to NAC? I would suggest a three-graded system for example as follows: Complete, partial and non-responders. Patients without remaining tumor are obviously complete responders. Patients with urothelial in-situ carcinoma and non-invasive papillary tumors should also be categorized as complete responders. These tumors are rarely lethal, are not treated with cisplatin and have similar outcomes when compared with patients without residual tumors (17). Patients with extravesical extension of the remaining primary tumor and lymph node metastasis should be categorized as non-responders. But how would we categorize patients with invasive organ confined residual tumors? Several studies showed similar outcomes of patients with organ confined residual tumors invading into the submucosa and muscle, respectively (4,17,18). More importantly, patients with muscle-invasive organ confined disease had a significant better outcome than those with extravesical extension of residual tumors. Therefore, I would categorized those patients with invasive but organ confined residual tumors as partial responders. An advantage of the suggested three categories would be that surgical downstaging of nonresponders is very unlikely. We might also include other parameters, for example histological signs and regression in surgical specimens after NAC. Recently, we described these histological signs and suggested a tumor regression grade that categorizes response to NAC (19). But these findings need to be validated in larger datasets before being taken into account for newly defined categories. In addition, we might also be able to identify biomarkers assessed in residual tumors that define response to NAC. Eventually, a combination of pathological staging, histological assessment and biomarkers might be used to define new categories. Of course, these suggested categories are pure speculation. But the fact is that all three studies (7,11,12) used different patient categories with regard to response to NAC. This indicates that its definition suggested in the literature is not generally accepted. Therefore, a valid definition of response to NAC will be essential for future biomarker studies.

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New prognostic models in metastatic renal cancer

Louise Lim, Tom Powles

Experiment Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, UK

Correspondence to: Tom Powles. Experiment Cancer Medicine Centre, Barts Cancer Institute, Queen Mary University of London, EC1A7BE, UK. Email: Thomas.powles@bartshealth.nhs.uk.

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Currently 7 targeted therapies have been approved for the treatment of advanced RCC: sorafenib, sunitinib, temsirolimus, axitinib, bevacizumab in combination with interferon-α, everolimus and pazopanib (1). There is difficulty distinguishing between them due to lack of head to head studies. Therefore there are multiple treatment options for patients in the first and second line setting.

Due to clinical trial design, specifically cross-over and the influence of subsequent therapies, few of these drugs have proven overall survival benefit compared to the control arm (2,3). Despite this, the development of targeted therapy has increased survival in metastatic renal cancer approximately 2 fold (2,4).

There is huge variation in outcome to targeted therapy within the patient population. This is coupled with a lack of biomarkers to predict response and inadequate detail on the biological mechanisms of drug failure. Sophisticated imaging and biomarker analysis have not proved helpful in the identification of patients who might benefit from treatment (5). Therefore one could argue we have made very little progress in the drive towards personalized medicine and only identified new hurdles, such as tumour heterogeneity (6). Moreover evidence suggests that targeted therapy results in dynamic changes to the tumor which may partly explain why predictive markers from archived tissues may not be relevant in the relapsed setting (6).

The field may be becoming more complex as established endpoints such as response and even progression free survival may not correlate with overall survival. To illustrate this, the most recent 2nd line study, comparing VEGF TKI therapy with mTOR inhibition in sunitinib refractory RCC, shows that while there is no difference in progression free survival patients on mTORs had a shorter survival (7).

It is unlikely that this will become any more straight forward in the future, as the responses seen with newer immune therapies such as PD-1 appear unpredictable (8). It is conceivable that established benchmarks such as RECIST which is used to be used to measure progression may become redundant with these new agents.

Therefore the identification of new predictive markers is the next big step in renal cell carcinoma.

From this article recently published in Lancet Oncology (9), five candidate angiogenic factors were measured for their prognostic significance in patients with metastatic renal cancer treated with pazopanib. The randomization of patients against placebo allowed for the investigation of predictive markers as well as prognostic markers. They used a 3 step approach with a screening phase, conformation and validation phase. In the pazopanib treated group, high baseline levels of interleukin 8, osteponitin, hepatocyes growth factor (HCG) and tissue inhibitor of metalloproteinases (TIMP)-1 were associated with a shorted progression free survival. Further analysis showed different spectrum of prognostic plasma makers seen with placebo. These differences suggest that the targeted therapy is associated with distinct molecular profiles which are of prognostic relevance. In this manuscript, the prognosis of the cytokine expression appears more significant than other prognostic models such as Heng prognostic scores and is therefore a step in the right direction. Unlike standard clinical classifications, however some plasma markers were also predictive of greater relative benefit from pazopanib. For example patients with increased levels of cytokines especially interleukin 6 had a worse prognosis but a greater relative benefit from pazopanib. Although this study provides evidence that plasma markers can identify patients who receive greater relative benefit from pazopanib (as compared with placebo) it would indeed be interesting to

see whether these marker would predict benefit from other treatment types e.g., mTOR inhibitors.

The findings from these studies support the approach of the use of cytokine and angiogenic factor (CAF) profiling to define biologically distinct subgroups of patients with metastatic renal cell carcinoma whose tumours have a greater angiogenic drive. CAF profiling might also be particularly well suited for angiogenesis inhibitors and other drugs targeting the tumour micro-environment, in which both circulating host derived and tumour derived factors could affect response.

Another possibility is to investigate dynamic changes to cytokines from sequential plasma, as this may better define a responding population. Finally, the integration of these prognostic and predictive factors with other significant factors such as single nucleotide polymorphisms may increase the power of these models (10). Powerful models predicting which patients benefit from specific agents is likely to be more useful than the development of further similar VEGF TKI therapies.

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Is there a sexual life after treatment of cancer?

Luca Incrocci

Department of Radiation Oncology, Erasmus MC Cancer Institute, Rotterdam, The Netherlands

Correspondence to: Luca Incrocci, MD, PhD. Associate Professor, Department of Radiation Oncology, Erasmus MC Cancer Institute, PO Box 2040, Rotterdam 3000 CA, The Netherlands. Email: L.Incrocci@erasmusmc.nl.

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Cancer has surpassed heart disease as the leading cause of death in most western countries. The occurrence of cancer is increasing due to the growth and aging of the population, and to well-known risk factors (smoking, overweight, physical inactivity, urbanization) (1). Although there is a clear decrease in overall cancer mortality rates, mainly in developed countries, cancer still remains a major public health problem.

Due to modern surgical techniques, improved chemotherapeutical drugs and sophisticated radiation techniques cancer is slowly becoming a chronic disease. More people live longer or are cured. Therefore quality of life (QoL) in general and sexual functioning in particular have become very important for cancer patients. Several studies suggest that the patients' perception of their own health status may also provide independent prognostic information together with traditional biomedical data (2). Incorporating QoL measures and outcomes in cancer research to supplement the more traditional clinical endpoints has provided valuable information to guide clinical decision-making (2). If many years ago most of the protocols on cancer treatment did not incorporate QoL evaluation, at present clinical trial groups, such as the European Organisation for Research and Treatment of Cancer (EORTC), routinely include QoL assessment and sexual functioning into their protocols. With the introduction of sildenafil (Viagra®) in 1998, media attention to erectile and sexual dysfunction has made sexual problems in men more normative and has increased acceptance of help-seeking. Nevertheless, sexual functioning in cancer patients is not routinely addressed (3,4).

Biological factors such as anatomic alterations (rectum amputation, penile amputation), physiological changes due to hormonal status manipulations and secondary effects of medical intervention may preclude normal sexual functioning in both men and women even when sex desire is intact (4). Despite the life-threatening nature of cancer might result in the assumption that sexual activity is not important to patients and their partners this is not true (4). Side effects of the treatment such as nausea, vomiting, fatigue, hair loss together with disfiguring surgery can result in adverse effects on sexuality. Negative emotional states such as anxiety, depression, anger, often present in cancer patients, may disrupt sexual activity as well. The presence of a stoma poses further problems to the patient and the

Guest Editor Professor Luca Incrocci, MD, PhD.

partner. Anxieties about odour, stomal breaking and leaking, and potential discomfort all make this a difficult situation requiring empathy and specialised counselling. Training of stomal therapists in sexual counselling is mandatory to ensure good outcomes. Nurses have a dominant role in the delivery of acute cancer treatment and side effects management (5). However, sexual difficulties are frequently considered a late effect of treatment and there has been limited systematic research on late effects compared to the assessment and management of acute toxicity (6). As a result, the evidence base for clinical assessment and intervention for sexual difficulties in oncology is largely restricted to the pharmacological management of erectile dysfunction in men or the provision of dilators to prevent vaginal stenosis and shortening after pelvic radiotherapy in women (6). Nurses need to have a biophysiologic knowledge on the anatomy and physiology related to sexuality and about the effects of cancer and its related treatments on sexual functioning (5). Studies performed in both specialist cancer treatment centres and in primary care show consistently that there is lack of proactive communication on sexual matters, even although the doctors may have thought that the patients might experience a sexual problem (5,6). Sexuality in general, and in relation to cancer in particular, should be an integral part of training at undergraduate and postgraduate level (4). For the general public there are now many good publications and websites. This information should be readily available at all treatment centres. Cancer clinics may offer advantages when a specific consultation for sexual function and dysfunction in cancer patients is organized. At Erasmus MC Cancer Institute, Rotterdam, The Netherlands, we have set up in 2000 such a specific consultation where patients are counselled and, if needed, treated for their sexual dysfunctions. Its advantage is that it is settled in the same clinic where the patient receives the oncological treatment, and that the physician skilled in sexual counselling and treatment is also skilled in oncological treatments (4). Furthermore, there is a strict collaboration with other health care providers, including medical specialists, physiotherapists, psychologists, medical sexologists, nurses. Every stage of management, from initial diagnosis to treatment to the survivor stage has a variety of psychosocial stressors for the patient, partner, and other loved-ones (7). The cancer management team needs to continuously address, counsel, and educate about sexual function throughout the course of the cancer patient's life (7). The 3rd International Consultation on Sexual Medicine in 2009 appointed for the first time a committee on chronic illness (including cancer) and sexual medicine. The recommendations of the committee are very useful to help develop research programmes on oncology and sexual medicine (3). The International Society for Sexuality and Cancer (ISSC; www.issc.nu) was founded in 2002 to heighten awareness about sexuality in cancer patients by fostering research, encouraging training and increased service provision, and providing a forum at international meetings for discussion (4).

The papers in this issue deal with prostate cancer, gynaecological, rectal and breast cancer, broadening the interest from urologists to oncologists, psychologists, oncological nurses, gynaecologists, surgeons, and more. They provide evidence based information on the incidence, pathogenesis and extent of iatrogenic sexual dysfunctions following cancer treatments. Also pharmacologic, surgical, and psychological approaches to managing sexual dysfunctions in cancer survivors and their partners have been addressed. I am very grateful to *Translational Andrology and Urology*, and in particular to the Editor-in-Chief Prof. Lue, for giving me the possibility of addressing such an important topic and to dedicate an entire issue to it. The great majority of oncology professionals are scared to address sexuality and the great majority of sexological professionals are scared by cancer (4). It is time that cancer specialists and sexologists better understand each other. Cancer affects quantity and QoL. The challenge for physicians and other health care professionals is to address both components with compassion (4). If we accomplish this, the answer to the question "Is there a sexual life after treatment of cancer?" is definitely yes.

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Special Case Analysis

Commentary on refractory ischemic priapism

Maurice Garcia, Sima Porten, Tom F. Lue

Department of Urology, University of California, San Francisco, USA

Correspondence to: Tom F. Lue, MD. Emil Tanagho Endowed Chair in Clinical Urology Department of Urology, University of California, 400 Parnassus Ave, Suite A633, San Francisco, CA 94143-0738, USA. Email: TLue@urology.ucsf.edu.

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In our experience treating more than 100 cases of ischemic priapism, we noted that most with less than 24-hour duration responded well to aspiration/evacuation and injection of a diluted alpha-adrenergic agent (phenylephrine). In those of less than 48-hour duration, the majority could be reversed by a standard T-shunt with #10 blade. In those who failed T-shunt or had more than 48-hour duration, T-shunt with tunneling was effective for the vast majority of patients. However, there are always exceptions to any general rule. The following two educational cases represent an example where a repeat T-shunt with tunneling procedure was needed to reverse the priapism. The various comments below illustrate sub-optimal management by less experienced urologists and our recommendations for the same situations. This report will also introduce a new "Duration-directed Algorithm" (*Figure 1*), which we believe represents a more physiologic approach. In addition, we also propose a method to estimate ischemia time for standardize reporting of treatment outcome in clinical series.

Case presentation I

A 36 year-old man was referred to our urology service for management of ischemic priapism refractory to multiple medical and surgical treatments. The patient reported awakening one morning with a rigid erection, which, as the day progressed, became painful.

1st procedure: Forty-eight hours after onset, he presented to a local hospital complaining of severe penile pain, where he was managed initially with needle aspiration, injection of diluted phenylephrine (Comment 1), and application of an ice-pack. These treatments failed.

2nd procedure: Later on the same day, he underwent glans-cavernosum shunts with a needle. This too failed.

3rd procedure: The following morning (*Day 3*), he underwent bilateral glans-cavernosum T-shunt, using an 11-blade scalpel (Comment 2), which resulted in several hours of relief, but the painful, rigid erection returned.

4th procedure: The following morning (*Day 4*), the patient underwent a *Left* spongiosum-cavernosum shunt, at the peno-scrotal junction (Comment 3). The rigid, painful erect state soon returned. On the evening of *Day 5* the patient was transferred to our institution for further management.

The patient reported only two prior episodes of prolonged erections, both within the preceding two weeks. The first lasted 8 hours and spontaneously resolved, and the second lasted 10 hours and resolved only after needle aspiration.

He denied any history of use of erectogenic medications, drugs, or penile trauma. He denied any personal or family history of sickle–cell disease. The patient described his erectile function and penile sensation as normal and satisfactory for intercourse.

On initial exam, he was noted to have a rigid, painful erection. He was uncircumcised, and had phimosis due to significant foreskin swelling. The distal 2/3 of his penile skin was ecchymotic. A small eschar was present on the skin at the left-distal aspect of his penile shaft. A 16 Fr. Foley catheter was in place and draining faintly blood-tinged urine without clots. The patient was afebrile. Laboratory analyses were notable for a WBC of $11\times10^3/mm^3$ and urine analysis showed 11-20 RBC and <5 WBC per high power field.

5th procedure: After discussion of management options and the risks and benefits, the patient was taken to the operating room, where he underwent bilateral T-shunt

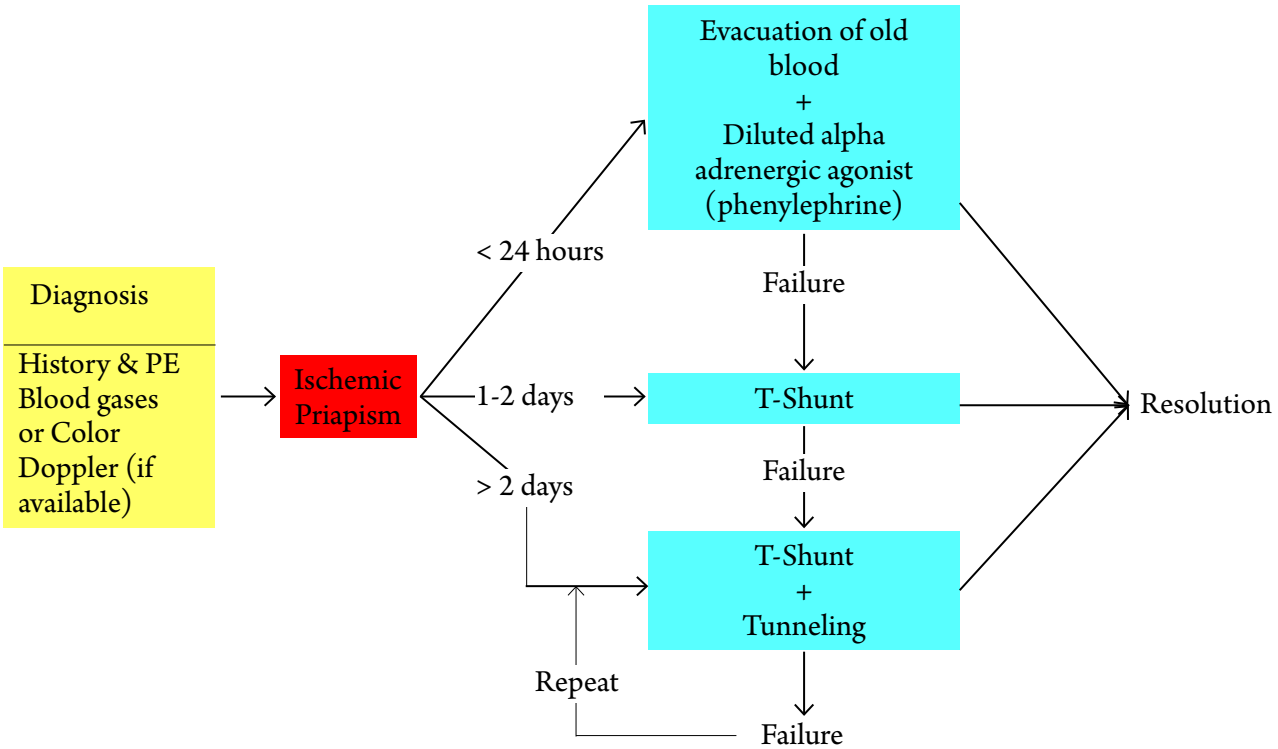

Figure 1 Duration-directed algorithm for ischemic priapism.

with a #10 blade scalpel, bilateral intracavernosal tunneling with a 22-Fr. straight urethral sound, which was advanced to the base of the penis. Dark ischemic blood was manually expressed from the penis until bright-red blood was visible. Circumcision was performed to prevent paraphimosis. At completion of surgery, the penis was partially erect but could be compressed easily. Given the presence of micro-hematuria and concern for an occult urethral injury, a new urethral catheter was inserted, and left this in place for 7 days (Comment 4).

Hospital course: Shortly after surgery, the patient reported significant reduction of the intense, constant, dull penile pain he experienced before surgery. He received intravenous (IV) Zosyn for 24-hour peri-operatively, and then was switched to an oral antibiotic (Cephalexin). His post-op urine analysis continued to show micro-hematuria. Urine culture remained negative. The morning after surgery, he was ambulating without assistance, tolerating a regular diet, and had adequate pain control with oral analgesics. He was discharged home on post-operative day #1 with prescriptions for 7 days of Cephalexin 500 mg QID (antibiotic), and Pentoxifylline 400 mg orally every 8 hours with meals ×6 months.

Follow-up: The patient reported complete resolution of the deep, dull penile pain which is characteristic of ischemic priapism pain within 36 hours after surgery. Discomfort at the sutured glans incision-sites resolved completely within 5 days after surgery. On exam, the incision sites were healing well, and ecchymosis was nearly entirely resolved. A cystourethroscopy was performed, and revealed a 4 mm × 3 mm. urethral injury at the 5 O'Clock position on the *left*, inferior-lateral aspect of the penile urethra, 5.5 cm from the urethral meatus. The patient was contacted by phone about 4 months after surgery. He reported return of nocturnal erections approximately 3 weeks after surgery, and return of normal erections (without the need for phosphodiesterase inhibitors) 6-weeks after surgery. At follow-up, his SHIM score was 25 (Comment 5).

Case presentation II

27 year-old otherwise healthy male with prior history of a 4-hour spontaneously resolving priapism approximately 4 months ago presented to ED with priapism for 36

hours. Patient denied inciting factors including drugs and medications.

1st procedure: Patient was seen at a community hospital where aspiration and injection of phenylephrine were attempted without success; he was subsequently sent to the emergency department of our hospital for further management.

2nd procedure: On admission, the patient was able to void without hematuria or dysuria. At that time 800 mL of blood was aspirated from the corpora at bedside (Comment 6), but the penis remained erect. Phenylephrine 500 mcg was injected into the corpora bilaterally at 3 min intervals, with a total of 20 mg. There was no evidence of detumescence following these procedures.

3rd procedure: Under local anesthesia, a bedside T-shunt was performed using an #11 blade scalpel (Comment 2), which was inserted dorsolaterally to the meatus on both sides, and rotated (blade-edge) 90-degrees laterally. This resulted in rapid detumescence. Therefore, the tunneling procedure was not performed. Approximately 200 mL of moderately dark blood was evacuated from glans wound sites. These were closed with interrupted 3-0 chromic sutures (Comment 7). The patient was started on oral Ciprofloxacin (twice daily) and pentoxyphylline (three times per day). UA and UCx were negative for blood or infection, respectively, and WBC was within normal range and remained stable after admission.

4th procedure: On hospital day #2, ischemic priapism returned and a color duplex penile ultrasound revealed no blood flow in the cavernous arteries. The patient was taken to the operating room for repeat T-shunt and bilateral tunneling. The sutures were removed and a #10 blade was used. Tunneling was performed with a 22F straight female sound, resulting in rapid detumescence. The patient reported pain relief after the procedure, however, his erection returned to 75% rigidity 8-10 hours after procedure. The antibiotic was changed to oral Keflex, 500 mg every 6 hours. On hospital day #3 the penis remained unchanged. Ketoconazole was started to reduce nocturnal erections and the urethral catheter was removed.

On hospital day #4, the penis was 100% erect. The patient continued to use on-demand IV analgesia, and oral ibuprofen, Percocet, Dilaudid, and oxycodone for additional pain control. However, he denied complete pain relief. At this time he was still able to urinate without a urethral catheter.

5th Procedure: On hospital day #6, there was no reduction in tumescence and edema. Bedside T-shunt with tunneling was again performed using a #10 blade scalpel. Intravenous Dilaudid, Ativan, and bupivicaine penile block were administered for pain relief and sedation. The previous shunts were clotted. Dark blood was expressed from the opened shunts. The patient tolerated the repeat procedure well. Aspirin (325 mg) and Pepcid (40 mg) daily were commenced. (Comment 8). He developed urinary retention that required insertion of a Foley urethral catheter.

Hospital day #7: The penis remained edematous and partially tumescent, but the patient reported decreased pain. On Hospital day #8 the penis was 90% detumesced, and edema had significantly improved. The urethral catheter was removed. The patient was discharged on Hospital day #10 with a prescription for aspirin (81 mg) and Pepcid (40 mg), each daily, for 2 weeks, Keflex antibiotic for 5 additional days, Ketoconazole for 2 more days (to reduce night-time erections), and Pentoxyfylline (to reduce intracorporal scarring) for 6 months. During the hospital course, the patient's hematocrit dropped from 36.2 to 26.1, but he remained asymptomatic. He returned to our clinic for follow-up evaluation 4 weeks later, and a color duplex ultrasound revealed excellent flow in both corpora cavernosa. He reported that nocturnal erections began to return 3 weeks after discharge from hospital. He reported normal penile sensation and denied pain with erections.

On follow-up evaluation at 6 weeks, the patient reported that erections of 70% rigidity (compared to baseline erectile function) returned 6 weeks after discharge home. These erections were described as sufficient for penetration, but of shorter duration as compared to baseline function. The patient had not yet tried oral PDE-5 inhibitors.

Expert opinions

Description of T-shunt and corporal tunneling surgical procedures

As described previously (1), the tips of the firm corporal bodies are palpated through the (normally) soft glans 1-2 mL of 0.25% Bupivicaine is injected subcutaneously (just blow the skin) on the glans. A circumferential block at the base of the penis is optional. A 10-blade scalpel is positioned vertically, inserted into the corpus cavernosum and advanced until the hub of the blade is at skin level. The sharp-edge of the blade is then rotated 90-degree *laterally*, and withdrawn.

Dark ischemic blood is expressed manually until the return is fresh and bright-red. The glans wound is closed

and the patient is observed for 15 minutes. If rigid erection returns, the same procedure is performed on the other side. If the dark ischemic blood drained out *slowly*, and the penis remained partially erect after expression of old blood (this usually occurs when priapism has lasted for >2-3 days), and severe edema of the intracavernous tissue is evident, bilateral tunneling via the same incisions should be performed. This is achieved with a 20- to 22-Fr. *straight* urethral sound. The surgeon should first estimate the length of the sound that will be inserted in order for the tip of the sound to reach the base of the penile shaft. The sound is held *parallel* to the long axis of the penis. It is inserted slowly and angled slightly laterally, so as to minimize risk of urethral injury. The base of the penis shaft is then grasped firmly, and dark (ischemic) blood is manually expressed from the incision site(s) until replaced by bright-red blood.

Incision site closure and Assessment

A 4-0 chromic suture is used to close the incision with running, locking sutures. Care taken to avoid placing the sutures too deeply, as deep closure can close the shunt. After closure, the penis is observed, to assess for resolution of the rigid state.

After 15 minutes, rigidity can be assessed by using the thumb and index fingers to squeeze the corporal bodies at mid-shaft. (For priapism events lasting greater than ~48 hours, it is normal for the penis shaft to be firm from local edema, even after the corporal bodies have been drained of trapped ischemic blood.) The shunt is considered open *if* the (awake) patient reports relief of constant dull ache within the penis (as is present in the rigid ischemic state), and if the penis is sufficiently soft that a 1-1.5 cm indentation can be made by the surgeon's fingers. If the penis returns to a rigid (priapism) state even after wound closure, we recommend repeating the tunneling once (bilaterally).

Wound dressing

The glans suture sites are dressed with antibiotic ointment for 5 days. The shaft should *never* be dressed with a restrictive dressing (e.g., Coband or other elastic bandages), as these may compress the dorsal vein and the corpus spongiosum, and thus close the shunts).

Comment 1: Although needle aspiration/drainage of ischemic blood, followed by injection/irrigation with diluted alpha adrenergic agent is generally successful for ischemic priapism of less than 24 hours duration, this approach is virtually "useless" for priapism of >48 hours duration, because of tissue edema, absence of intracorporal circulation, and the inability of cavernous smooth muscles to respond to medication. Our preferred approach is a T-shunt or T-shunt with tunneling.

Comment 2: Immediately after the ischemic state is corrected, a large amount of arterial flow rushes into the corpora cavernosa. This is due to "post-ischemic hyperemia" and it may last for hours to days. Without a large shunt to receive the excessive volume of inflow, the intracavernous pressure will soon rise and compress the tissue surrounding the outlet, effectively closing the shunt. The shunt created by a #11 blade is small and can easily close spontaneously. We prefer the larger incision offered by a #10 blade, and we rotate the blade 90-degrees laterally as it is withdrawn to make a "T-shaped" shunt, which ultimately serves to maximize the size of the shunt.

Comment 3: The purpose of a cavernosum-spongiosum shunt is to drain blood from the corpora cavernosa to the urethral bulb in the perineum. Anatomically, the spongy tissue that surrounds the male penile urethra is relatively thin. However, at the level of the bulbar urethra, the thickness of spongiosal tissue is several times greater. If a shunt is created at the level of the peno-scrotal junction, the thin layer of spongiosal tissue present is inadequate to drain the corporal body. Furthermore, the thin nature of the spongiosal tissue at this level increases the risk of urethral injury. The authors have seen several cases of cavernositis followed by caverno-urethral-cutaneous fistula and complete occlusion of the urethra, followed by subsequent severe cavernosal fibrosis, when a shunt is placed too distally. Given the simple technique and efficacy of the cavernosum-glans shunt with tunneling procedure we describe (1-4), we do not see a need for proximal shunting procedures.

Comment 4: The presence of hematuria and a history of recent spongiosum-cavernosum shunt should raise a red flag about urethral injury. To prevent the complications mentioned in Comment #3, it is important to place a urethral catheter and administer antibiotics for several days.

Comment 5: Currently, there is no standard definition of the "duration" of an ischemic priapism, and this may account for why it is difficult to interpret the efficacy and treatment outcomes reported in the literature. Theoretically, if no treatment is given after 5 days of ischemic priapism, the penile erectile tissue should be completely necrotic and any shunting procedure would fail to restore potency. In this case, although our T-shunt with tunneling procedure

(which reversed the priapism state) was performed 5 days after onset, the patient had already undergone multiple procedures (on days 3 and 4) to evacuate old blood and re-establish circulation, each of which resulted in temporary detumescence. During the brief period of detumescence, the ischemic state is interrupted, hypoxia is reversed, and tissues receive oxygenated blood flow. Blood flow helps to eliminate accumulated metabolic wastes. Therefore, in this patient, the longest continuous ischemia time was really only approximately 48 hours. We believe that both the patient's young age and the only 48-hour period of continuous ischemia can account for the return of erectile function we observed.

Comment 6: The purpose of aspiration/evacuation is to remove old, ischemic/acidotic blood and to facilitate return of fresh, oxygenated blood. Usually aspiration of 100-150 mL. is sufficient to achieve this. In our view, there is no need to drain more than 200 mL. of blood during aspiration.

Comment 7: Because of the rich blood supply of the glans, interrupted suture may not be able to achieve hemostasis. We recommend use of a running-locking suture.

Comment 8: Physiologically, the shunt will not close if the shunt is large enough to accommodate the reactive high arterial flow after the ischemia is reversed. This post-ischemic hyperemia, or "reactive high-flow state", usually lasts hours to days. A T-shunt created by a (smaller) #11 blade may not be adequate to drain high-volume arterial flow. The resulting build-up of high pressure is the likely cause of premature shunt closure in the two cases described above. The failure to maintain an open shunt after a #10 blade T-shunt in the second case may be due to severe local tissue edema, which can impede drainage across the shunt. For this reason, we gave the patient both aspirin (to prevent shunt clotting) and ketoconazole (to reduce nocturnal erections). Alternatively, a standard Al-Ghorab shunt (surgical excision of the tip of both corpora cavernosa) with tunneling can be performed (4). We prefer repeated T-shunt and tunneling because this can be performed at bedside, using only local anesthesia. Use of repeat #10-blade T-shunt with tunneling has been successful in reversing refractory priapism for all cases where initial use of T-shunt and tunneling failed.

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Footnote

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Special Case Analysis

Commentary on high flow, non-ischemic, priapism

Alex K. Wu, Tom F. Lue

Department of Urology, University of California, San Francisco, USA

Correspondence to: Tom F. Lue, MD, ScD (Hon), FACS. Emil Tanagho Endowed Chair in Clinical Urology Department of Urology, University of California, San Francisco. 400 Parnassus Ave. Suite A633, San Francisco, CA 94143-0738, USA. Email: TLue@urology.ucsf.edu.

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High-flow, non-ischemic priapism is a rare condition, with which many urologists and andrologists are unfamiliar. There are three types of high-flow priapism: traumatic, neurogenic and post-shunting. Traumatic high-flow priapism may arise from penetrating or blunt trauma to the penis resulting in rupture of the cavernous artery or its branches. Despite the unregulated large arterial flow, this does not result in rigid and painful erections, as seen in low-flow, ischemic priapism, because the venous channels are still competent. The neurogenic type is seen after irritation or injury to the central nervous system, and this is typically self-limiting. If this type persists, then it may change to ischemic priapism, and should be treated accordingly. Post-shunting high-flow priapism is a result of reactive hyperemia in response to the hypoxic and acidotic state of ischemicpriapism that lasts more than 24 hours. This condition will continue only if the shunt remains open. Once the hyperemic state subsides, the minimal flow in the flaccid penis will not be able to keep the shunt open leading to its spontaneous closure in most cases. In general, since blood circulation into and out of the corpora cavernosa is not impeded in cases of high-flow priapism, the condition is not painful, the penis is not completely rigid, and the prognosis is excellent if it is treated properly.

It is important to note that ALL ischemic priapism begins with increased arterial flow to the corpora cavernosa and a blood gas taken in the first few hours of priapism may not reflect the typical findings of hypoxia and acidosis seen in prolonged priapism (1). Moreover, after aspiration or evacuation of the old blood in ischemic priapism, one would see return of fresh blood and blood gases consistent with arterial blood. To mistake this condition for high-flow priapism is erroneous.

Case presentation 1

A 21-year-old man was referred to our clinic because of erectile dysfunction. Three years ago, he suffered from a blunt skate board injury to the perineum. The patient had no immediate sequelae from the injury except local tenderness, but the next morning he awoke with a partially erect penis (Comment 1). This was accompanied by difficulty attaining an erection sufficient for sexual intercourse (Comment 2). He was diagnosed elsewhere with high-flow priapism secondary to an arterial sinusoidal fistula. He underwent an embolization of the arterial sinusoidal fistula in January of 2007. He underwent two subsequent embolizations, which stopped his partial erections but his erectile dysfunction (ED) persisted. On physical exam, he had a normal-looking flaccid phallus with slight fullness. A color duplex ultrasound of his crura identified that hismain cavernous artery opened directly to a cystic cavity with large turbulent flow (Comment 3, *Figure 1 A*, *B*).

As he had already had 3 previous embolizations and persistent ED, he wished to have a more definitive therapy. He was taken to the operating room for open ligation of the ruptured right cavernous artery. An intraoperative ultrasound helped identify the depth and location of the cystic cavity that was surrounded by a thick fibrous sheath. Once the fibrous sheath was opened, a single arterial bleeder was identified along with several venous outlets within the cystic cavity. Several 4-0 Maxon sutures were used to suture-ligate these bleeders and to imbricate the cystic cavity. He was discharged with Ketoconazole 200 mg twice a day and prednisone 5 mg daily (Comment 4) for one month (2). Postoperative ultrasound 1 month later revealed complete resolution of the arterial sinusoidal fistula and cavity (*Figure 1 C*). The patient regained normal erectile function 3 months later.

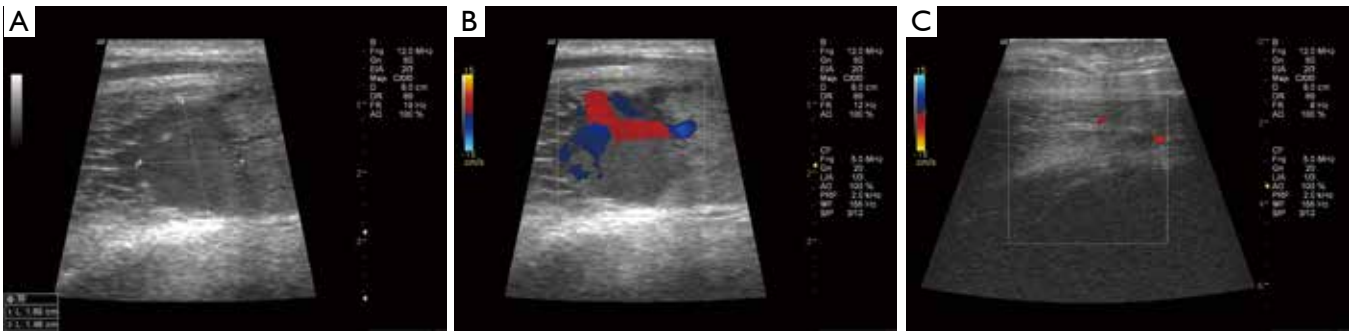

Figure 1 Longitudinal ultrasound scans of the crus of the penis. In A, the main cavernous artery can be seen opening directly into a cystic cavity of 1.65 cm × 1.48 cm in size. In B, color duplex ultrasound of the same area shows the dilated cavernous artery delivering large flow into the cystic cavity. The color duplex ultrasound in C was taken one month after surgery. The cystic cavity was no longer seen and small flow was seen in the same cavernous artery

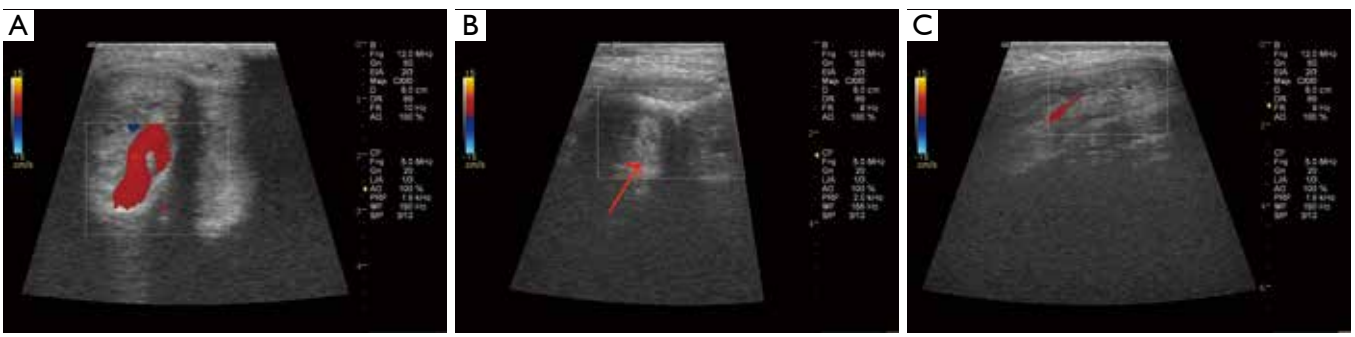

Figure 2 Transverse scans of the penile crura from the perineum. In A, the intact main cavernous artery is shown as a blue circular area, and the large irregular red area is the turbulent flow from an arterial-sinusoidal fistula (from a branch of he main cavernous artery). In untreated cases, this area will eventually become a cystic cavity once the damaged tissue is absorbed. In B, hyper-echoic lesion (arrow heads) seen within the right corpus cavernosum represents tissue reaction/fibrosis of the damaged erectile tissue. In C, the normal non-erect arterial flow in the main cavernous artery can be seen, 1 month after discontinuation of Ketoconazole

Case presentation 2

This is a 29-year-old man who suffered bruising and swelling to his scrotum and base of the penis after a motorcycle accident. Six days later, he came to the clinic because of a persistent partial erection that was not painful. Physical examination revealed a partial erection and tenderness at right base of the penis. A color duplex ultrasound revealed a well-defined main cavernous artery and turbulent flow in the surrounding area indicative of rupture of a branch of the cavernous artery (*Figure 2 A*). A diagnosis of high-flow, non-ischemic, priapism was made and he was treated with ketoconazole 200 mg twice per day, and prednisone 5 mg daily to suppress nocturnal erections (Comment 5). A follow up one month later revealed normal flaccidity of the penis, and color duplex ultrasound showed resolution of the arterial sinusoidal fistula. However, there was increased echogenicity in the erectile tissue suggestive of early fibrosis secondary to the tissue contusion (Comment 6). Ketoconazole was discontinued after 1 more month and the patient was given pentoxifylline 400 mg three times/day for 3 months to help resolve the fibrosis. Six months after injury, the patient had complete return of normal erectile function.

Case presentation 3

A 30-year-old man developed a painful rigid priapism after taking trazodone for insomnia. He underwent a successful Al Gohrab shunt about 36 hours later. The pain subsided, but the penis remained in a semi-erect

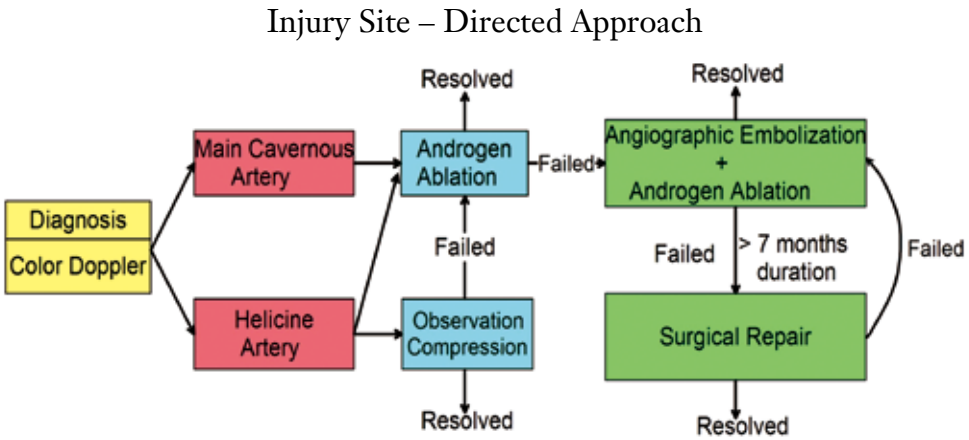

Figure 3 Proposed algorithm for the management of high-flow, non-ischemic, priapism

state with about 70% rigidity. Physical examination revealed a firm but compressible penis. A color duplex ultrasound sound performed by a radiologist was reported as "high-flow priapism" with peak flow velocity of more than 40 cm/second in both cavernous arteries. The urologist was alarmed by the report and requested embolization of bilateral penile arteries. The semi-rigid erection took three more weeks to subside. The patient never recovered erectile function. A color duplex ultrasound performed 1 year later revealed severe arterial insufficiency with peak flow velocity of 15 cm/second in both cavernous arteries.

Comments

Comment 1: The cavernous artery is well protected by the surrounding erectile tissue and the tunica albuginea. A blunt injury of enough strength may cause damage to the erectile tissue and cavernous artery or its branches. A typical straddle injury usually occurs while the penis is in the flaccid state and the cavernous artery is constricted. Therefore, no change of penile morphology or function is expected shortly after injury. A high-flow, non-ischemic priapism state typically occurs with the onset of nocturnal erections when the sudden increase of blood flow and pressure in the cavernous arteries "blows up" the injured portion of the artery, resulting in unregulated flow into the sinusoids, and a persistent partial erection.

Comment 2: This is a paradoxical condition because, with the high baseline blood flow to the corpora cavernosa, one would expect the patient to have better erections. Nevertheless, the majority of patients experience difficulty in achieving and maintaining erection. The cause is unknown but it may be due to the depletion of endothelial nitric oxide from continuing sheer stress on the sinusoidal endothelium.

Comment 3: In this case, the main cavernous artery opens directly to the cystic cavity. During erections, the cavernous artery can double its diameter and deliver more than 50 mL/min of blood flow to the penis in a young man. This large increase in diameter and flow during erections may re-open the thrombosed artery and explain the failure of the three previous embolizations.

Comment 4: Nocturnal penile erections are testosterone dependent (3) and therefore can be suppressed by androgen ablation therapy such as oral ketoconazole. Since the patient has failed three prior interventions, we feel that suppression of nocturnal erections after surgery should help decrease the chance of recurrence.

Comment 5: A small arterial bleeder may become thrombosed due to vasoconstriction or external compression. Elimination of nocturnal erections by androgen ablation therapy reduces the blood flow in the ruptured branch to a minimum and facilitates thrombosis at the ruptured site. This may not occur in case of main cavernous artery rupture.

Comment 6: The cavernous artery and its branches are protected by tunica albuginea and the erectile tissues. An external injury that is severe enough to damage the artery is expected to damage the surrounding erectile tissue too. Therefore, erectile function recovery usually takes several months and an antifibrotic agent such as pentoxifylline (4) is a useful adjunct after the unregulated bleeding has resolved.

Expert opinion

We reviewed our 30 years' experience and proposed a new approach to this rare condition (*Figure 3*). All cases suspected of high-flowpriapism should undergo color duplex ultrasound to confirm the diagnosis. The entire penis, including bilateral crura should be carefully scanned. Local compression with ice pack may cause spasm and thrombosis of the ruptured artery in the early stage especially if the injury involves a small branch of the cavernous artery. If the condition is bothersome (because of ED or persistent partial erection) and the patient wishes to receive treatment, androgen ablation therapy for 1-2 months is our choice. We recommend angiographic embolization only for those with rupture of the main cavernous artery. We would also place these patients on androgen ablation therapy for 1 month after embolization to prevent its recurrence. Surgical exploration and suture ligation of the ruptured artery is only indicated in those with a thick psudocapsule which may take 6 months or longer to develop. In high-flowpriapism, contusion of erectile tissue around the ruptured artery always occurs. Therefore, we recommend antifibrotic agents such as pentoxifylline for 3 months to reduce fibrosis after the high-flowpriapism is corrected.

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Footnote

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Special Case Analysis

Commentary on the myths of Peyronie's disease

Alex K Wu, Tom F Lue

Department of Urology, University of California, San Francisco, USA

Correspondence to: Alex K Wu. Department of Urology, University of California, San Francisco, 400 parnassus ave, San Francisco, CA 94143. Email: WuAK@urology.ucsf.edu.

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Peyronie's disease refers to an acquired curvature, narrowing or shortening of the penis. Prevalence rates of 0.4-20% have been published (1). Development of Peyronie's disease is likely related to minor injury to the tunica albuginea, septum or intracavernous struts. In some men, the resulting inflammation is trapped between layers of the collagen bundles and becomes progressive. This leads to an inflammatory mass (lump) formation in the early stage. Continuing inflammation produces profibrotic cytokines such as transforming growth factor beta and deposition of large amount of collagen fibers. The inflammation can also produce metalloproteinases that break the elastic fibers. The irregularly compacted collagen fibers and disrupted elastic fibers create an inelastic "plaque," the "incurable" component of Peyronie's disease. The loss of elasticity produces curvature, shortening, narrowing, distal flaccidity and erectile dysfunction depending on the location of the fibrotic process (2). In this article, we discuss the variable clinical presentation of and management of Peyronie's disease, illustrated by three cases. Up to now, Peyronie's disease has been considered an "incurable" disease because there is no medical treatment that can return the penis to its premorbid state. Nevertheless, we would like to revisit the anatomy of the disease, and propose a treatment to arrest the disease in its early stages. In more advanced stages, we recommend a combination of medication and physical force to restore penile anatomy, improve erectile function, and, thus, reduce the psychological devastation affecting the patient (3).

Case 1

A 60 year-old man presented to the Urology clinic with a complaint of three months of sudden onset painless penile deformity with curvature upwards and to the right. He denies any known history of trauma. He notes that he has 100% rigid erections, but is only able to penetrate 75% of the time due to his penile deformity (Comment 1). His past medical history includes depression, anxiety, herpes, and asthma. His surgical history includes orthopedic procedures to his right femur, and an appendectomy. He states that he is not in a stable relationship currently. He does not smoke or use any recreational drugs, and he drinks with moderation.

On physical examination, he had an uncircumcised phallus, and a normal meatus. His testicles were bilaterally descended, and normal in size. A dorsal firm plaque could be palpated, about 2 cm in length. Further evaluation with penile ultrasound (GE logiq P5 device, 12 MHz) revealed a dorsal, midline plaque measuring 2 cm × 1.5 cm with associated calcification measuring 1.3 cm × 0.9 cm (Comment 2). During examination, his penis was partially erect, and a 30 degree dorsal and rightward curvature was noted.

The patient was placed on pentoxifylline 400 mg PO TID. He did have some dyspepsia in response to this dose, and he was thus reduced to 400 mg PO BID. He continued on this dose for 8 months. Upon follow up, he noted improved curvature, from 30 degrees to 10 degrees. A dorsal plaque could still be palpated. Upon ultrasound evaluation of the penis, dorsal fibrosis was still evident, but the calcification had completely resolved (*Figure 1*).

Case 2

This is a 51 year-old man who presented with penile deformity and shortening. He recalled a minor penile injury during sexual intercourse about 1 year ago. There was no ecchymosis or urethral bleeding at that time (comment 3).

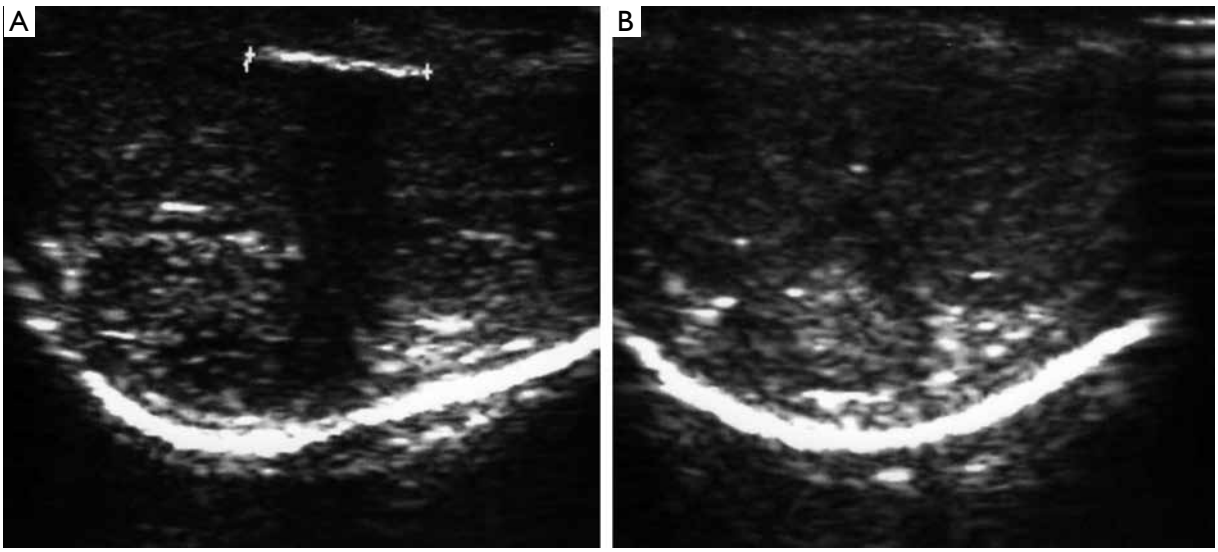

Figure 1 Ultrasound findings before and after 8 months of treatment with pentoxifylline. The calcification was no longer detectable on follow up. A. pre-treatment; B.post-treatment (8 months pentoxifylline)

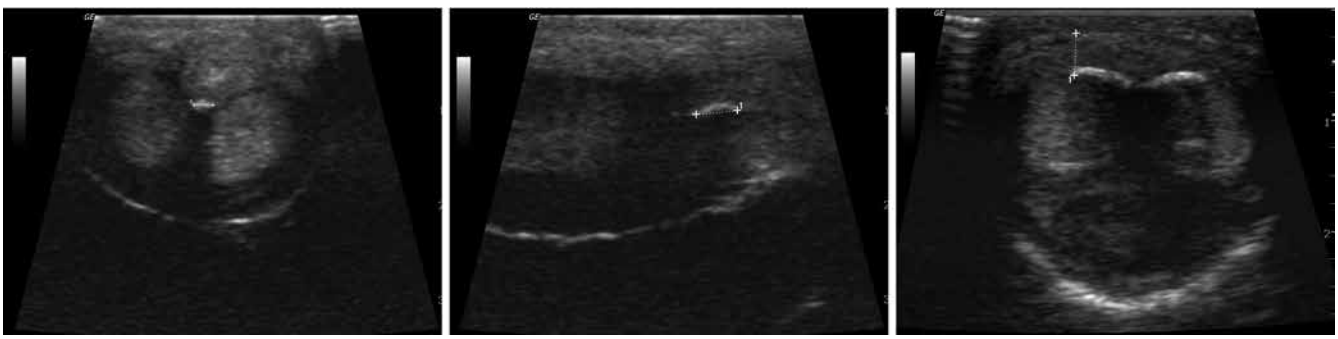

Figure 2 Penile ultrasound findings showing transverse and longitudinal views of a calcified ventral plaque (left and middle), and a dorsal calcified plaque (right). Note that the upper left sonogram is taken from the urethral side while the others are scanned from dorsal aspect

The pain subsided after a few hours. Shortly after, he noted a lump in the middle of his penis. Subsequently over the next several months, he developed progressive dorsal penile curvature and penile shortening with erections. Erections were also painful. Upon consultation with his local Urologist, he was told that he had Peyronie's disease and that this would resolve spontaneously. He was told to return in one year if the curvature persisted (Comment 4). However, the progressive shortening made sexual intercourse difficult and greatly affected his confidence, leading to cessation of intercourse with his female partner. About one year after his initial injury, he presented to our clinic, quite distressed about this issue, as is often seen in patients with Peyronie's disease (3). He noted that he had lost about 2 inches (5 cm) of length in the past year, and he provided a photograph confirming a 60 degree dorsal curvature. He was otherwise healthy and had not had any past surgeries.

On physical exam, he had an extensive palpable plaque along the dorsum of his penis. His testicles were normal in size, and were descended bilaterally. Penile ultrasound revealed a small ventral plaque and an extensive dorsal plaque with large calcification (*Figure 2*).

The patient underwent tunica-sparing excision of the ossified plaque (4), and a 16-dot plication (5) to correct the penile curvature. Post-operatively, he was given

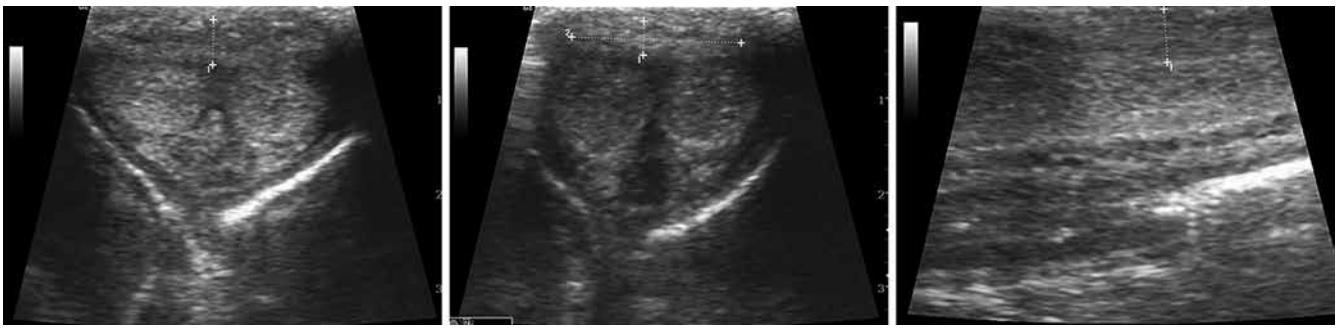

Figure 3 Penile ultrasound findings in a patient with a dorsal plaque (measured areas), thickened intracavernous struts (left figure), and distal flaccidity (right figure with higher echogenicity to the right of the figure)

pentoxifylline. Six weeks post-operatively, he was instructed to perform penile stretching with a vacuum device. Five months later, his painful erections and his erectile dysfunction resolved (comment 5). He was able to gain 1 inch (2.5 cm) in penile length after 6 months of stretching. At one year of follow up, the patient noted that while his erections were not as strong as before Peyronie's disease, he was able to have painless, regular, sexual intercourse without the need for phosphodiesterase 5 inhibitors, and his mood had significantly improved.

Case 3

A 55-year-old man presented with 18 months of progressive penile deformity and erectile dysfunction (ED). The patient did not recall history of penile injury. At the present, the penis curved upwards and to the left with erections. However, the patient also noted distal penile flaccidity, refractory to maximal dosages of phosphodiesterase 5 inhibitors. He was otherwise healthy and had not had any past surgeries.

Physical examination revealed extensive dorsal plaque and penile fibrosis, more severe on the left side. Penile ultrasound showed two dorsal plaques and distal intracavernous diffuse coarse echogenic spots consistent with fibrosis of the intracavernous struts (comment 6, *Figure 3*). An intracavernous injection test confirmed 45 degree dorsal, 30 degree left lateral curvature and distal flaccidity about 3 cm long (comment 7).

After extensive consultation regarding various medical and surgical options, the patient elected to under to implantation of an inflatable penile prosthesis. The penis became straight without the need for graft or plication sutures after dilation and implantation of the prosthesis (comment 8). He had an uneventful recovery and was able to resume sexual intercourse with a straight penis 5 weeks after surgery.

Case comments

I. Although the patient only began to notice penile deformity three months prior to presentation, it is likely that the process of inflammation and fibrosis began long before, given the finding of calcification.

II. In our experience, calcification occurs in about 31% of patients (6). If the calcification is less than 1.5 cm, 400-800 mg pentoxifylline tid has a more than 90% chance arresting or eliminating the calcification (7). Larger ones do not respond to pentoxifylline and surgical excision may be needed if the patient has persistent pain, severe shortening or curvature.

III. Ecchymosis occurs when blood escapes from the corpora cavernosa to the subcutaneous space through ruptured lateral or ventral tunica albuginea while urethral bleeding occurs if the tunica ruptures to the urethra. Since the dorsal tunica is much thicker, rupture rarely occurs. Instead, this type of injury often disrupts the junction between the septum and dorsal tunica, or septum itself, resulting in a dorsal plaque or septal fibrosis. No ecchymosis or urethral bleeding occured because the tunica albuginea was intact.

IV. Spontaneous resolution of Peyronie's disease occurs in less than 13% (8). Since no single "effective" medical treatment has been proven, patients are usually told to wait for a year and see if the disease resolves by itself. Unfortunately, for many patients, waiting results in more advanced disease, which has less response to medical therapy.

V. Surgical options for patients with large calcification/ossification include plication only, plaque excision with grafting, or subtunical ossified plaque excision and plication. Owing to the high incidence of ED after large plaque excision and grafting (9) as well as the patient's severe depression, we elected to perform subtunical ossified plaque excision and plication (4). Since neither neurovascular dissection nor grafting is needed, the chance of penile numbness and ED is reduced. For patients with penile shortening or narrowing, we recommend a combination of pentoxifylline and penile stretching with a vacuum device daily for 6 months, similar to regimens advised by Levine's group (10,11).

VI. The intracavernous fibrosis is most likely a result of thickening/fibrosis of the intracavernous struts because there is no reason for smooth muscle atrophy with intracavernous fibrosis in this case. Another typical finding is a smaller diameter of the corpus cavernosum from fibrosis of the struts.

VII. The senior author has good results in correcting hour glass deformities or localized indentations of less than 1 cm with grafts placed on the lateral aspect of the penis. However, most patients develop ED after placement of grafts to correct distal flaccidity of longer length. The authors suspect that the failure is likely due to the inability of tunica graft to correct the contracted intracavernous struts.

VIII. Most implant surgeons have observed the decrease in the curvature of the penis after corporal dilation and placement of penile prosthesis. Since, the length of the contracted tunica albuginea was not altered, the only explanation is the disruption of the contracted struts or disconnection of the struts from the tunica albuginea. This would then allow the inflatable penile prosthesis to inflate and lengthen/widen the corpora cavernosa.

Expert opinion

The non-surgical management of Peyronie's disease has significantly advanced, but despite multiple randomized trials and uncontrolled case series, one treatment alone has not been found to be definitively superior. Proposed oral therapy has included pentoxifylline, colchicine, and potassium para-aminobenzoate (12-14). In cases where the Peyronie's lesion is readily accessible, intralesional administration of Verapamil, Interferon, and Collagenase have all been tried with some success (15-17). In uncontrolled studies, traction devices and vacuum devices have been shown to result in some benefit to curvature (18,19).

The mechanisms of Peyronie's plaque formation have not been fully defined, but likely begins with an inflammatory process, possibly from trauma, which then leads to fibrosis, decreased elasticity and excess collagen deposition (20,21). Oral therapies, such as pentoxifylline may act on inflammation and early fibrosis. Indeed, pentoxifylline has been shown to inhibit fibrosis induced by Transforming Growth Factor (TGF) Beta-1 (22).

Intralesional therapies, such as interferon alpha-2b, may also limit inflammation and early fibrosis by decreasing fibroblast proliferation, extracellular matrix production, and collagen production from fibroblasts (17). Clostridial collagenase is a purified bacterial enzyme that selectively breaks up collagen, and thus may help further with late fibrotic scars, rich in collagen (16,23).

However, when working with intralesional therapies, it is important to be able to target the lesion. Thus, while plaques on the dorsum of the penis are readily accessible, patients with ventral plaques, intracorporal or septal fibrosis (*Figure 4*) and large calcifications may be less treatable with this method. Indeed, in a review of 891 men receiving penile ultrasonography for Peyronie's disease, Chung *et al.* found that 43% of patients had septal fibrosis (24).

The "incurable" component of the Peyronie's disease is the late dense fibrosis and "loss of elasticity" that is refractory to medical treatments including the most powerful therapy, the intralesional injection of collagenase. Dissolving or softening the plaque alone does not straighten the penis fully, as evidenced by recent clinical trials (8,23). The best results are in patients who have had a "modeling" procedure where the physician forcefully stretches the softened plaque after several injections of collagenase. Penile traction and vacuum erection devices help address the issue of loss in elasticity. These therapies will mechanically stretch the tunica to help straighten the penis. Levine's group has shown previously that therapy combining oral or intralesional therapy with penile traction provides both length and reduction in curvature (10).

Given the multiple components of Peyronie's disease (inflammation, fibrosis, and loss of elasticity), we typically recommend combination therapy for patients with moderate-to-severe curvatures or shortening, utilizing pentoxifylline and a vacuum device (*Table 1*). With vacuum therapy alone, inflammation from trauma would continue, and fibrosis would likely recur. In the case of more severe curvatures, pentoxifylline alone is unlikely to overcome the

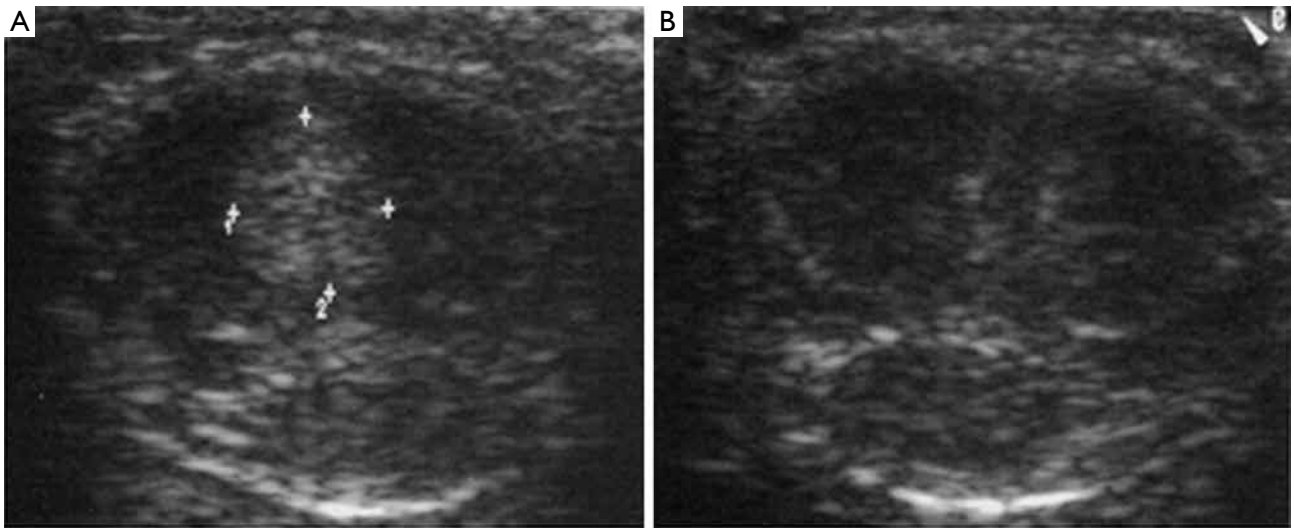

Figure 4 Normal ultrasound next to penile ultrasound showing septal. A.normal ultrasond; B. septal fibrosis

Table 1 Different therapies address different pathophysiologic aspects of Peyronie's disease

Pathology\Rx	Pentoxifylline/Colchicine	Verapamil/Interferon	Collagenase	Vacuum device/extender
Inflammation	+	+		
Early fibrosis	+	+		
Late fibrosis			+	
Lost elasticity				+

overall loss in elasticity, and thus minimal benefit will be seen with regards to straightening.

Decisions to pursue surgery should be patient centered. Indications to pursue surgical intervention include disease refractory to medical therapy alone, moderate-to-severe curvature. Curvature alone may typically be managed successfully with plication alone (25). Patients with hourglass deformities or large areas of calcification may benefit from tunical excision and grafting, but these patients must be counseled on the high risk of subsequent ED. Alternatively, a subtunical excision of ossified portion of plaque and plication may achieve the same goal with minimal risk of penile numbness and ED (4).

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Special Case Analysis

Randall plaque versus renal stone?

Thomas Chi, Joe Miller, Marshall L. Stoller

Department of Urology, University of California, San Francisco, USA

Correspondence to: Thomas Chi, MD. Department of Urology, University of California, 400 Parnassus Avenue, Box 0738, 6th Floor Urology Clinics, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu.

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A 43-year-old patient has just left the office. Her primary care physician had dutifully evaluated her recent complaint of vague abdominal pain with an abdominal ultrasound. The multiple, small, punctate hyperechoic lesions in the kidney were deemed concerning for renal calculi and an abdominal computed tomography (CT) scan was ordered to better delineate these "renal stones". The CT report revealed "*multiple bilateral punctate calcifications consistent with possible nephrolithiasis versus nephrocalcinosis*," and the patient was referred to urology clinic for further evaluation. In our clinic the patient was interviewed and examined and the scan was carefully reviewed. The patient denied symptoms of renal colic and physical examination demonstrated no costovertebral angle tenderness. No hydronephrosis or evidence of urinary obstruction could be seen on the scan, and we provided a diagnosis of Randall plaques and nephrocalcinosis. The patient was reassured that there were no stones to treat and there was no need for surgery. General lifestyle and dietary modification counseling for stone prevention were provided, and the patient was discharged from our clinic, happy with her benign diagnosis.

But is such a diagnosis benign?

Recent data suggests that a single CT scan may significantly increase a woman's lifetime risk of developing breast cancer. The repeated scanning that is often the mainstay of observation or conservative management of renal stones can result in a cumulative dose of radiation equivalent to that of survivors of Hiroshima's atom bomb. Furthermore, up to 2% of cancers in the United States today might be attributable to radiation related to CT scanning (1). We would argue that having a Randall plaque diagnosed as a renal stone is not so benign a designation and propose that it is time to redefine the delineation between the two. The core question can be simply put-what is the true difference between a Randall plaque and a renal stone, and how can we differentiate the two before patients are subjected to unnecessary diagnostic tests?

To frame the argument, consider the work of Alexander Randall and the ways in which data from his landmark findings could be exploited. In his original autopsy studies Randall noted that 17% of the nearly 500 kidneys had subepithelial plaques at the tip of the renal papilla (2). This knowledge can be used as a means to achieve a variety of ends, and these odds may seem quite attractive to patients seeking secondary gain from the diagnosis of a "renal stone". For example, a military reservist aiming to avoid deployment may seek out a CT scan and the subsequent diagnosis of a "renal stone", which would effectively render him non-deployable. Conversely, an airline pilot playing these same odds may go out of their way to get a kidney-ureter-bladder radiograph (KUB) rather than a CT scan, knowing that the low sensitivity for visualizing small calcifications of a KUB will help avoid being grounded with a diagnosis of a "renal stone".

As many as one-fifth of patients undergoing abdominal imaging have renal calcifications which may be diagnosed as "renal stones". But as we often see in our clinic, many of these calcifications are Randall plaques and not true renal stones. Over time, a subset of these Randall plaques will erode into the collecting system, become renal stones, and potentially cause pain. Additionally, although conventional wisdom holds that gross obstruction of the collecting system is the etiology of renal colic, it is theoretically possible that a Randall plaque could result in intraparenchymal obstruction of a duct of Bellini and cause pain (typically there are 12-15 ducts of Bellini in each papilla centrally located transporting

urine into the collecting system). So while a Randall plaque may be the precursor lesion to a renal stone, they are by no means equivalent. The line that differentiates the two remains an unexplored urologic frontier and the delineation carries broad implications for clinical practice and for patients.

A large part of the problem with defining this difference lies in the fact that Randall plaques and their role in stone formation remain poorly understood even though they have been under the proverbial microscope for over seventy years. In 1937 Alexander Randall first described a cream-colored lesion near the tip of the renal papilla. The lesion stained positive for calcium deposits and in many cases seemed to replace normal tubular structures. He theorized that these plaques eroded from the interstitium into the collecting system, effectively transitioning a plaque to a stone (2).

More recently, our group and others have examined this interface of the interstitium and collecting system using electron microscopy. Prominent ring-like structures, labeled calcified nanoparticles, have been discovered in this area and are thought to be the building blocks from which Randall plaques are formed (3-6). The composition of these small rings and what lies at the center of these particles remains to be defined. Lingeman's group analyzed Randall plaques with Fourier transform infrared spectroscopy and their data support plaques as a calcium phosphate-based phenomenon (7). Williams *et al.* later used micro-CT to analyze the interface between Randall plaques and growing calcifications at the papilla tip. Their findings demonstrated that calcium oxalate appears present at this junction (8), suggesting that apatite crystals of the plaque itself may aggregate calcium oxalate on top of a plaque and lead to erosion of stones into the collecting system.

These plaques may be more than simply subepithelial or superficial structures, however. High-resolution radiography with state-of-the-art mammography equipment revealed calcified spicules running deep into the papilla of ex vivo kidney specimens (*Figure 1*). This structural appearance has led our group to hypothesize that the origins of stone formation related to Randall plaques may in part be a vascular phenomenon (9). This hypothesis is based on the fact that the papilla contain only a few collecting ducts but hundreds of vasa recta. These tiny vessels are the continuation of the efferent arterioles as they flow down toward the tip of the papilla en route to return to the renal vein. For every one descending vasa recta there are four ascending ones, resulting in a unique location for potential vascular venous injury. Several aspects unique to renal physiology support this vascular hypothesis as an etiology for Randall plaque formation. First, laminar blood flow transitions to turbulent flow at the tip of the papilla as the vasa make their acute turn back toward the renal vein. In vascular plaque formation inflammation arises in areas of transition to turbulent flow. In the case of arterial plaques these locations include the bifurcation of the aorta and the iliac arteries, as well as the carotid arteries (10). The 180-degree turn creates a transition to turbulent flow in the vasa recta even more extreme than in the great vessels, predisposing the area to inflammatory changes and subsequent plaque formation. Second, there is a 10-fold increase in osmolality that occurs between the renal cortex and the tip of the papilla (11). This hyper-osmolar microenvironment supports a milieu of inflammatory cytokines and proteins where inflammation-related changes caused by vascular injury may be readily transformed into plaque aggregation. Lastly, from the renal cortex to the tip of the papilla, there is a decreasing gradient of oxygen carrying capacity, with medullary tissue demonstrating as little as one-half the carrying capacity of cortical tissue (12). In severe cases, as with diabetes mellitus, this can translate to events such as papillary necrosis and sloughed papilla that may obstruct the ureter. These three issues, a transition from laminar to turbulent blood flow, increased tissue osmolality, and relative hypoxia create the ideal setup for vascular calcification response to inflammation, which we theorize leads to Randall plaque formation.

To delineate the difference between Randall plaques and urinary stones, it is also important to understand the location of these plaques. But even the simple question of where these calcifications occur has no straightforward answer. There are the vasa recta and the collecting duct which lie next to each other. We have shown using electron microscopy that calcifications related to Randall plaques are closely connected to the vasa recta (6), while Lingeman *et al.* have shown they are closer to the collecting duct (13). These two domains are cell thicknesses apart and it is unclear if the initial events in stone formation are an intracellular or extracellular process. It is possible and likely that these events occur in between the two, outside the tubule but not actually in the duct itself. Mapping studies have demonstrated the Randall plaque to reside mostly at the tip of the papilla (14) which has been our experience as well. They can be seen endoscopically as a beige-color colored lesion underneath the urothelium with an unappreciated calcified network extending into the

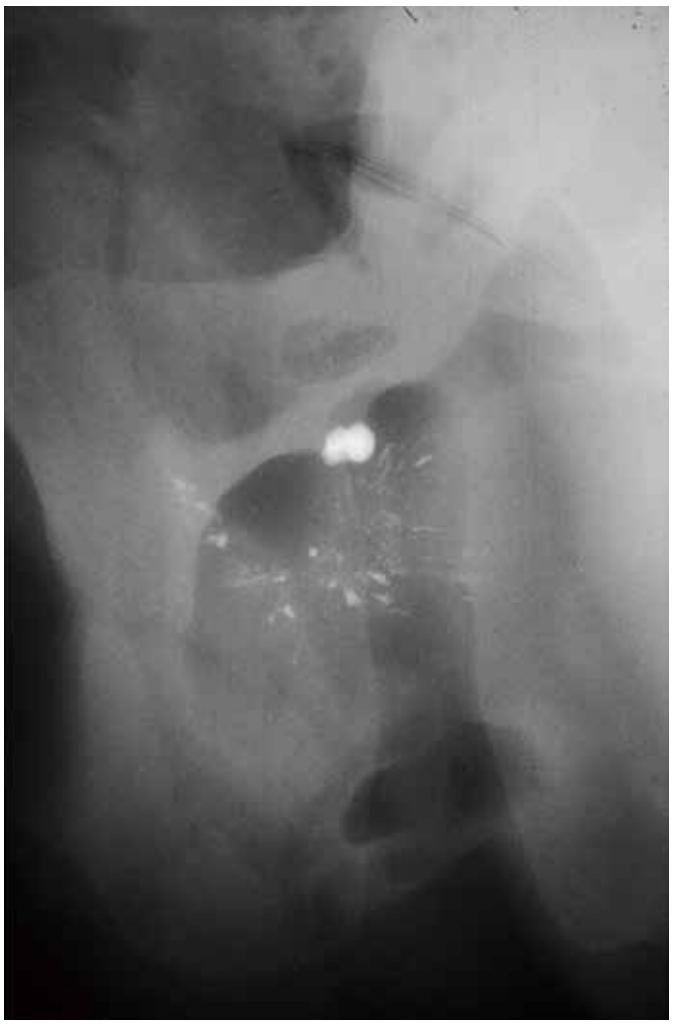

Figure 1 Mammography imaging of the kidney demonstrates a Randall plaque opacity at the center of the radiograph. Spiculated calcified tracks lead into the papillary tissue away from the plaque.

parenchyma, away from the calyx (*Figure 2*). Only when an inciting event occurs that causes the calcification to fall off does the calcification transition from Randall plaque to urinary stone. Therein lies the clinical challenge-how to differentiate the Randall plaque from the urinary stone before the patient buys themselves more unnecessary diagnostics and a trip to the urologist's office?

We propose that a renal stone is a free-floating calcification suspended within the urine of the collecting system. A Randall plaque on the other hand is an aggregate of a calcium compound intimately associated with and attached to the renal papilla.

Our proposed definition would require that on traditional CT Randall plaques are less than 2 millimeters in their greatest dimension, and at least one-half of the calcification in a Randall plaque is surrounded by renal parenchyma. On renal ultrasonography, small calcifications associated with postacoustic shadowing near the tip of the papilla without evidence of hydronephrosis should be labeled as Randall plaques in the absence of renal colic symptoms. On either imaging modality, if the calcification can be seen surrounded by urine in the collecting system, then this is likely a urinary stone that may warrant treatment. If more than 50% of the plaque is surrounded by parenchyma, this is a normal variant of renal anatomy and no intervention or further workup is required. While our definition for the how to differentiate a papillary Randall plaque from a urinary stone may not be universal, we propose that this should serve as a

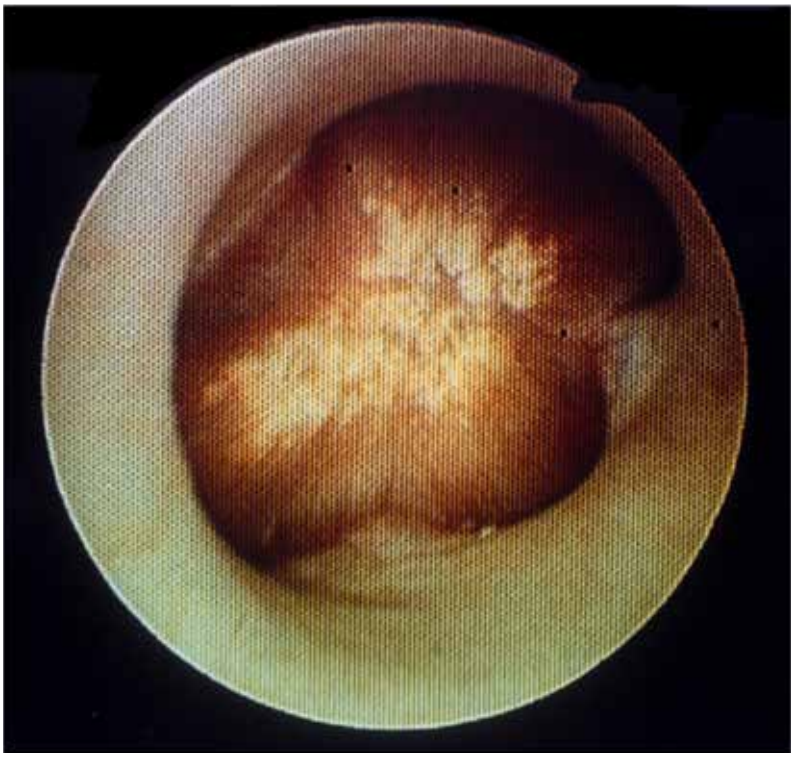

Figure 2 Endoscopic image of a renal papilla with the typical creamy appearance of a Randall plaque in the center portion of the papilla

starting point to standardize these diagnoses with the goal of foregoing unnecessary procedures for patients, whether diagnostic or therapeutic.

Randall plaques don't necessarily lead to renal stones and we would readily admit that we do not yet understand what triggers such transformation. But to keep patients out of harm's way, we do know that these could and should be diagnosed separately from urinary stones.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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The days of cost effective management for nephrolithiasis are already upon us

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Nephrolithiasis prevalence rates continue to rise globally and have nearly doubled within the United States over the last few decades. At the same time, health care costs have risen within the United States at an alarming rate. The economic burden of nephrolithiasis is estimated at greater than $5 billion annually. This estimate is based on direct cost related to healthcare delivery and indirect factors such as loss of productivity/work. Interestingly, medical expulsion therapy (MET) has been found to be more cost effective for ureteral stones than early endoscopic intervention, even when including increased emergency room visits for MET. A variety of medical and surgical options exist for symptomatic nephrolithiasis treatment. Unfortunately, concrete data is lacking as to the most cost effective surgical approach for nephrolithiasis. The issue of cost effectiveness quickly becomes more complex when the analysis begins to include stone size, location, cost of maintenance for endoscopes, laser fibers, etc. (1). Data is also limited as to the cost effectiveness of prevention of nephrolithiasis. Certainly the low upfront costs of general dietary recommendations (low salt diet, increased oral fluid intake, moderate protein intake, etc.) do not pose any great cost burden, but their effectiveness is unclear. Similarly, it is unclear as to the cost effectiveness of thiazides, potassium citrate, or other medications for the prevention of the various types of stone disease. With rising healthcare costs coupled with the rising prevalence of nephrolithiasis, not only is more research needed to provide greater clarity regarding the most cost effective approach to all types of nephrolithiasis, the importance of this type of research will only increase in the climate of increased scrutiny of healthcare expenditures.

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Balancing the utility of new technology against cost in urinary stone disease

Thomas Chi, Eric Taylor, Marshall L. Stoller

Department of Urology, University of California, San Francisco, California, USA

Correspondence to: Thomas Chi. Assistant Professor, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: tchi@urology.ucsf.edu; Marshall L. Stoller, M.D. Professor and Vice Chair, Department of Urology, University of California, 400 Parnassus Ave, 6th Floor Urology Clinics, Box 0638, San Francisco, CA 94143, USA. Email: MStoller@urology.ucsf.edu.

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Several advances in endourologic technology have allowed for a greater scope of care to be provided to urologic patients via a minimally invasive approach. The greatest of these is likely the current generation of flexible ureteroscopes which allow for a level of maneuverability, with or without active secondary deflection, that rarely prevent lower pole renal access via a retrograde approach. Other technical advances such as the development of ureteral access sheaths, hydrophilic working wires, laser fibers, and various basket and biopsy devices have also helped to advance our endourologic capabilities in treating complex upper tract calculus or oncologic disease. Most of these tools have been widely adopted, but advanced imaging capabilities such as narrow-band imaging (NBI) and photodynamic diagnosis (PDD) have yet to gain wide acceptance and utilization (1). One of the primary barriers to adoption of any of these technologies, including the flexible ureteroscope, is the cost associated with both acquisition and maintenance of these devices. The greatest benefit of these advanced technologies will come when their high cost declines allowing for more global access to these tools.

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