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Demystifying the ABU (and interpreting the alphabet soup of acronyms associated with it)

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The American Board of Urology (ABU) has a very distinct mission that is often misunderstood by urologists in the community. In addition, there is an enormous number of acronyms associated with the ABU. In this paper, I will attempt to explain the workings of the ABU and to define and explain the acronyms.
The mission of the ABU is to act for the benefit of the public to insure a high quality, safe, efficient, and ethical practice of urology by establishing and maintaining standards of certification for urologists. The ABU views that it truly serves the public, and decisions made by the ABU are measured against the public's best interests.

Key Words: American Board of Urology, ABU

The ABU was organized in 1934. It is a not-for-profit organization and is one of 24 medical specialty boards under the umbrella of the American Board of Medical Specialties (ABMS). Currently, the ABU has 12 trustees. Two new trustees are appointed each year to staggered, 6-year terms. New trustees are chosen by the current trustees of the ABU based on the nominations of a number of major urological organizations including the American Urological Association (AUA), the American Association of Genito-Urinary Surgeons (AAGUS), the American Association of Clinical Urologists (AACU), the American College of Surgeons (ACS), the Society of University Urologists (SUU), and the urology section of the American Academy of Pediatrics (AAP). ABU trustees are volunteers and are not paid for their services. The current ABU trustees are shown in Figure 1.

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The primary work of the board is to certify urologists. Certification is based on meeting standards of education, knowledge, skills, ethics, and practice patterns. Candidates who demonstrate that they meet the standards are awarded certificates by the board. The specific wording of the certificates has changed over time, but all certificates indicate that the candidate has met all the requisites of the board and is therefore a diplomate of the American Board of Urology. The wording also notes that the certificate must be maintained up to date and that it is revocable at any time by the board if the candidate no longer meets the ABU's standards.

Because the function of the ABU is often misunderstood, it is important to realize that its role is very limited. Although it works alongside and sometimes in concert with other organizations, its mission is relatively narrow. It is not a part of the AUA, an organization that exists primarily to support its members. In contrast, the ABU exists primarily to ensure the public that ABU diplomates are qualified urologists. The ABU is not involved in the training of urologists or in the development of residency training programs. That is primarily a function of the American College of Graduate Medical Education (ACGME) through their Residency Review Committee for urology. Similarly, the ABU is not involved with licensing. That is a function of state medical boards. In essence, the ABU does not in any direct way control or

Figure 1. American Board of Urology trustees, February 2008.
Upper row, from left: Gerald Jordan, Timothy Boone, Ralph Clayman, William Steers, Barry Kogan, Margaret Pearle (in-coming trustee), Paul Lange and Michael Koch.
Lower row, from left: Robert Bahnson (in-coming trustee), David Bloom (in-coming Vice President), Bedford Waters (in-coming President), Peter Carroll (out-going President), Howard Snyder (out-going Vice President), Stuart Howards (Executive Secretary), John Forrest.

limit the practice of urology. Its role in these areas is only highly indirect in that if the board feels an individual practitioner is violating the public trust, it may act to revoke that practitioner's certificate.

The ABU certification process is complex. In simple terms, the applicant must first document satisfactory completion of an approved urology residency training program. This is the primary method the ABU uses to assess the applicant's education. The applicant must then pass a written Qualifying Examination (QE), generally (but not always) at the completion of residency training. After passing the QE, the applicant, who must also have been practicing as a urologist for at least 16 months in one location, must undergo a clinical practice assessment. This is done primarily by a formal, written, peer-review process including a review of the candidate's practice, based on a 6-month billing log of all patient interactions. Finally, the candidate must pass an oral Certification Examination (CE). The candidate must complete this primary certification process within 5 years of having completed an approved residency training program.

The QE is a carefully designed, thoroughly tested assessment of urological knowledge and practice. The examination consists of 300 multiple choice questions. It is given in a testing center that specializes in computerized tests and offers excellent security for the ABU. The testing centers are generally quiet, comfortable, and reasonably close to home for most urologists. The examination is constructed by a committee of subject matter experts with experience in subspecialty areas of urology. Individuals on this committee write proposed new questions, usually in their subspecialty area. These are edited by a urologist with considerable experience in the qualifying examination. These questions are then scrutinized by fellow experts in the subspecialty area and by other experts without expertise in this subspecialty. If the questions are deemed to be valid ones on important concepts by all these experts at different levels of scrutiny, the questions are then placed on the qualifying examination as field test items. Field test items are not identifiable by candidates. Candidate responses to the field test items are used only for statistical purposes, and not to determine whether the candidate meets the criteria for board certification. Only after successful field test performance can the question be used on the QE for assessment of the candidate. Questions that test poorly are either revised and field tested again or they are discarded. The subject matter of the questions covers the entire field of urology and includes uroradiology, uropathology, and the six major competencies as defined by the ACGME.

The QE is scored using a Rausch model. This method is criterion referenced, meaning that the ABU sets a minimum benchmark for what knowledge a urologist must have in order to be certified. This differs from a percentile or population based scoring system in which each year, candidates who fail to reach a given percentile fail; for example, in some systems, candidates with scores that are 2 standard deviations below the mean would automatically fail. The ABU believes that the methodology of criterion referencing is fairer, gives each candidate a uniform opportunity to pass, and keeps the standards equal from year to year. There is no mandatory failure rate, so that if the candidates were extremely capable in a given year, 100% could pass. Table 1 shows the pass rates for the QE over the past 15 years. In general, the pass rate has been higher recently than it was 10 to 15 years ago, suggesting that candidates who are finishing residencies now are more capable or better prepared than those in previous years.

After successful completion of the QE and 16 months of urology practice in one location, candidates are eligible for the second phase of the certification process. They must have an unrestricted medical license and hospital privileges. They must have favorable peer reviews from physicians in their local area and a favorable review of acting in a professional

TABLE 1. **Pass rate for the American Board of Urology Qualifying Examination, 1994 - 2008**

Year	# Candidates	Pass rate (%)
1994	330	84
1995	337	82
1996	319	82
1997	336	76
1998	338	80
1999	336	82
2000	345	72
2001	454	83
2002	329	82
2003	307	82
2004	317	83
2005	299	90
2006	278	88
2007	285	91
2008	278	88

manner (for example, handling complications in a timely manner, and the absence of/reasonably explainable malpractice complaints). If a candidate meets these criteria, the ABU reviews a 6 month log of that individual's practice and compares this log to the candidate's peer group. Again, a benchmark is set that the applicant must exceed, and, in addition, practice patterns that are out of the ordinary can be uncovered. The size of an individual's office practice, office procedures, and surgical practice are readily compared to those of his or her peer group. Discrepancies are sometimes seen, but are often logically explained. For example, a urologist might have an office practice that is no larger than 25% of all urologists in his or her peer group, but might be performing more retroperitoneal ultrasounds than 95% of his or her peers. Such discrepancies are not considered inappropriate unless there is no reasonable explanation. The candidate is given an opportunity to explain discrepancies, by either providing an overall explanation and/or by explaining individual cases. In the example given, the candidate may have been doing ultrasounds for inappropriate indications, but it is also possible that he or she is the practice's resource person for ultrasounds and all the urologists in the group refer all their ultrasound patients to the candidate, giving him or her a disproportionate number of cases.

After successful completion of all the above reviews, the candidate may take the CE exam. This is an oral examination designed to test the candidate's ability to gather information relevant to a clinical problem, manage the problem effectively, react in a timely fashion to complications, and act in a professional manner. Trustees of the ABU construct the questions, and the questions are rigorously reviewed on multiple levels. Each candidate receives identical questions and is scored identically based on their responses. Each candidate receives three different test case scenarios from two different examiners (for a total of six cases per candidate). Each examiner is carefully selected based not only on their knowledge and expertise but also on their ability to be fair and consistent. The scoring system is designed to be as objective as possible. The scoring tendencies of examiners are evaluated and statistically corrected, so that a candidate is not penalized for having a "hard" examiner, nor is he or she more likely to pass with an "easy" examiner. As in the QE, scoring is based on a criterion reference system. There is a benchmark set by the ABU, and there is no required number of candidates who fail. As in the QE, if the candidates were able, 100% could pass. Table 2 shows the pass rates in recent years.

Initially the certificates had no time limits. However, by 1980, it became apparent that to ensure the public's trust, it would be necessary to periodically verify that

TABLE 2. **Pass rate for the American Board of Urology Oral Certification Examination, 1994 - 2008**

Year	# Candidates	Pass rate (%)
1994	327	80
1995	324	79
1996	326	77
1997	313	78
1998	316	83
1999	305	81
2000	337	86
2001	331	87
2002	277	95
2003	281	87
2004	280	91
2005	262	95
2006	227	93
2007	283	91
2008	271	92

a urologist still met appropriate standards. Hence the process of recertification was begun. All new certificates awarded after 1985 are limited to 10 years, and as a diplomate approaches the 10 year point, he or she applies for recertification. It was felt that the board could not legally force urologists who held certificates with no time limits to obtain recertification. Many older urologists have not voluntarily done so. Although the ABU would strongly prefer that all urologists renew their certification periodically (again, primarily to ensure the public that urologists continue to meet the standards of the ABU), it is not legally possible to enforce that policy. Moreover, the ABMS has recently viewed that recertification every 10 years is itself insufficient to ensure the public of ongoing quality practice, and they have mandated a continuous process of Maintenance of Certification (MOC).

The recertification process that takes place 10 years after certification mirrors the certification process in many respects. As noted above, however, recertification is being phased out in favor of MOC, hence nearly all urologists will be participating in MOC. MOC is a process put in place based on the mandate of the ABMS. The purpose again is to assure the public that urologists who are certified maintain their qualifications over time. In addition, MOC most likely will suffice as documentation for most state boards for Maintenance of Licensure (MOL). It will likely be required for hospital privileges and may well be a part of Pay for Performance (P4P).

Although the exact details of the MOC process in urology are still being determined, the general plan is known. Every diplomate will be required, every 2 years, to provide documentation of licensure and to do a structured patient management review of 5 of their own patients who have a common urological problem. Examples of common problems that will be acceptable are shown in Table 3. The diplomates are then required to compare their treatment with established guidelines and/or practice patterns. Every 4 years, there will be a review of their credentials, a peer review, and documentation of their continuing medical education credits (CME). Every 10 years, they will be required to submit complete 6 month billing logs as documentation of their activities. These logs will be reviewed as described previously. Finally, every 10 years, the certificate holder will be required to pass a computerized examination similar to that described above.

TABLE 3. **Patient management review topics**

Management of stage Ta, T1, and Tis bladder cancer
PSA screening
E & M of ureteral calculi
E & M of vesicoureteral reflux
E & M clinically localized prostate cancer
E & M of erectile dysfunction
E & M of varicocele
Prophylaxis of deep venous thrombosis
Antibiotic prophylaxis for urological procedures

The ABU takes its mission seriously. We believe that the urological community, for the most part, provides a very high level of urological care for the public. Yet, it is important both to assure the public of that, as well as to find those few practitioners who may not provide care at that level. Providing this service to the public is our mission. More information about the ABU can be found at www.abu.org.

Disclosure

None declared. □

Management of symptomatic benign prostatic hyperplasia-today

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Symptomatic benign prostatic hyperplasia (BPH) is one of the commonest causes of men presenting with lower urinary tract symptoms (LUTS). We can find this in 50% of men over the age of fifty. If BPH is not treated, then one can expect that the disease will progress in a significant number of individuals. What we need to do is try to predict, based on certain baseline parameters such as International Prostate Score (IPSS), prostate volume, prostate-specific antigen (PSA) and the degree of bother, those men to whom we should offer therapy. The other consideration is that combination therapy of a 5-alpha reductase inhibitor (5-ARI) and an alpha blocker, may provide the best results for the prevention of progression of the disease or ultimately, the need for surgery. The final considerations are "if", for "how long" and "for whom" should combination therapy be utilized.

Key Words: BPH, LUTs, alpha blocker, 5-alpha reductase inhibitor, combination therapy

Introduction

By age 50, over 50% of men will have some degree of benign prostatic hyperplasia (BPH) as a cause of their lower urinary tract symptoms (LUTS). As they get older, their symptoms will only increase and the disease will probably progress if untreated. BPH is the most common cause of reported LUTS that clinicians see today. There has been a dramatic change in the management of BPH symptoms in patients who have clinical signs of an enlarged prostate, over the last few years. The first step is to make the correct diagnosis of an enlarged prostate. Clinicians no longer rely only on results of a digital rectal examination (DRE). Rather, the patient's serum prostate-specific antigen (PSA) level has been proven and used as a surrogate marker in order to guarantee that the patient's prostate volume is at least 30 cc. Research has shown that having a prostate volume of at least 30 cc greatly increases a man's chances of responding to BPH therapy with a 5-alpha reductase inhibitor (5-ARI).

It is commonly believed that alpha blockers do not provide early and significant short term relief from LUTS and may not decrease BPH progression. Two important recent trials have demonstrated that compared to monotherapy with an alpha blocker alone, combination therapy with an alpha blocker and a 5-ARI can be very effective for treating men with an enlarged prostate. The combination can provide both early symptom relief, as well as prevent disease progression. The problem for clinicians is how to identify appropriate patients for combination therapy.

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The other patient management decision is whether combination therapy should be provided on a long term or even permanent basis.

This article based on a presentation at "Current Concepts of Men's Health" for the Urological Institute of Northeastern New York and the Albany Medical College, given in August 2008, addresses these issues.

Diagnosis

Today, most patients with BPH first present with complaints associated with an enlarged prostate. These complaints can range from a small amount of urinary frequency and nocturia to some hesitancy in urine flow, or even complete urinary retention. Sometimes the symptoms are new, but often they have been present for a very long time. Often it is the patient's partner who suggests that the man should see a physician. Sometimes urgency incontinence is associated with the progression of BPH. The difficulty in making a diagnosis is that these symptoms are somewhat vague. BPH is one cause of LUTS. It is important for physicians to rule out some of the more serious causes of LUTS.

As with most medical conditions, the physician needs to take an adequate patient history and perform an appropriate physical examination. In the case of suspected BPH, a questionnaire can help quantify the patient's reported symptom severity as well as help predict the risk of disease progression.

In taking the patient history, the physician seeks to determine if the patient has aggravating factors that can worsen bladder function and to find out when the problem started and how rapidly the symptoms have evolved.

The American Urological Association-Symptom Index (AUA-SI) for BPH developed a few years ago is a questionnaire that deals specifically with LUTS and is virtually identical to the International Prostate Symptom Score (IPSS).[1] By asking seven questions about a patient's voiding function, the clinician can obtain a symptom score to quantify BPH and obtain a prognosis. If a patient has a score of 8 or less out of a maximum score of 35 on the AUA-SI questionnaire, he is classed as having mild BPH symptoms; if his score is between 8 and 20, he is classed as having moderate BPH symptoms; and if his score is between 20 and 35, he is classed as having severe BPH symptoms.

A final question, question "eight", on the AUA-SI for BPH questionnaire is about "quality of life". The question asks, "If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?" The patient responds by choosing a number from 0 to 6, where 0 indicates feeling "delighted" and 6 indicates feeling "terrible." This score is also described as the "bothersome index." I like to call it, the "motivational index," since the degree that the symptoms bother the patient is an indication of how motivated the patient will be to agree to medical therapy.

Work-up

Besides taking an adequate patient history, it is important to carefully examine the patient. By doing this, the physician will be able to rule out other physical conditions that may mimic or contribute to symptoms of BPH. As well, the physician will be able to detect the presence or absence of signs of significant BPH progression such as a distended bladder, hydronephrotic kidneys, or potentially some neurological condition with symptoms that mimic LUTS.

It is very important for the clinician to perform a digital rectal examination (DRE), determine the patient's serum prostate-specific antigen (PSA) level and obtain results from a urinalysis, in order to rule out most other causes of LUTS. The DRE will allow the physician to identify any obvious signs of prostate cancer and estimate the prostate's volume. It has been shown that the finger is not very accurate in determining prostate volume. Consequently, the PSA test has been proposed as a surrogate marker for prostate volume. Many studies have shown that a serum PSA value of approximately 1.5 ng/ml consistently corresponds to a prostate volume of at least 30 cc,[2] an important number in the management of BPH. If a physician is not sure about the significance of the symptoms of BPH, then he or she can also suggest that a patient undergoes a uroflow study, a postvoid ultrasound, and possibly an abdominal ultrasound to rule out hydronephrosis. The severity of the patient's symptoms, the size of the prostate, significant signs of progression of an enlarged prostate, and finally, the patient's motivation all help the physician determine appropriate patient management and treatment options.

Treatment

In order to assess treatment options, patients are usually stratified according to their severity of symptoms and their prostate volume, as indicated in guidelines published in the Canadian Journal of Urology.[3] If the patient is suffering from recurrent gross hematuria, significant and recurrent febrile urinary tract infections, renal failure, hydronephrosis, or any signs of moderate to severe or complete urinary retention, then aggressive

therapy — usually with surgery — is indicated. If the patient's PSA value is elevated for his age, or his PSA velocity or PSA density are abnormal, a prostate biopsy should be performed to rule out prostate cancer as a cause of his symptoms. Once the physician is satisfied that there is no prostate cancer, that the patient's symptoms are only the result of BPH and there are no absolute indications for surgical intervention, then the patient can be offered medical therapy.

Surgery

The objective of surgery is to physically debulk the prostate or to perform incision/resection of any bladder neck contracture or spasming that may create the physical obstruction as a cause of the patient's symptoms. Different approaches to debulking of the prostate that have evolved for the last number of years range from standard transurethral resection of the prostate (TURP), to the use of microwaves, holmium laser enucleation or to most recently, green/white light laser vaporization of the prostate. The problem with these approaches to the treatment of the enlarged prostate is that they can also lead to long term side effects such as erectile dysfunction, urinary incontinence, or even the need for repeat/correctional surgery within 5 years.[4] Today, in most cases, these surgeries can be done as either outpatient or short stay procedures. If the patient has not reached the stage where surgery is indicated, then he can be offered medical therapy as a first line option.

Medical therapy

"Obstruction" in BPH can be classified as being "dynamic" or "fixed". The "fixed" component is related to the bulk of the prostate, that is, the enlargement of the prostate that is causing obstruction and a squeezing pressure on the urethra. The "dynamic" component of prostatic obstruction is believed to be caused by the stimulation of alpha receptors of the smooth muscle at the bladder neck and within the prostate capsule. Increasing the tone of these smooth muscle fibers causes spasming at the bladder neck or a tightness that can sometimes be corrected or alleviated by utilizing alpha blocker therapy.[5]

The first type of alpha blocker therapy that was used for BPH was a nonselective alpha blocker that had the significant side effect of severe orthostatic hypotension. The drug that most significantly exhibited this side effect was a phenoxybenzamine. The incidence of fainting and severe hypotension was so prevalent with this drug that it was discontinued for this indication.

Over the years, physicians have trialed newer, more uroselective alpha blocking agents that specifically impact the bladder neck and areas within the prostate capsule, rather than to contribute to orthostatic hypotension. Therapeutic agents have evolved from drugs such as terazosin (Hytrin, Abbott Laboratories) and doxazosin (Cardura, Pfizer), which were nonselective alpha blockers, to newer agents such as tamsulosin (Flomax, Boehringer Ingelheim Pharmaceuticals) and alfuzosin (Xatral, sanofi-aventis).[6] Although these newer drugs do not cause hypotension, they can lead to another side effect that is sometimes very disconcerting for the patient: decreased or absent ejaculation. This is usually due to decreased propulsion from the seminal vesicles rather than retrograde ejaculation. The alpha blockers do not elicit significant differences in terms of efficacy, but exhibit some differences in their side effect profiles. The attractive characteristic of alpha blockers is that patients' voiding symptoms resolve very quickly. A patient who has significant urinary hesitancy, urgency, or urinary frequency, or lacks a strong urinary stream can see a significant improvement within 24 hours or at the most within a week. In the short term, resolution of symptoms can be very satisfying for the patient; however, alpha blockers do not prevent the progression of BPH.[7] Although the patient has less urinary frequency, increased urinary flow, and decreased hesitancy and nocturia in the short term, with time, his prostate will continue to grow, his symptoms will increase, and his response to alpha blocker therapy will diminish. Ultimately, he may go into retention or need surgery to alleviate the obstruction from the prostate.

A serendipitous scientific discovery based on a congenital biochemical deficiency, lead to the development of another family of medications that has become very important in the management of BPH. These drugs, the 5-ARIs (5-alpha reductase inhibitors), act on the "static" component of prostatic obstruction.

Testosterone is converted to dihydroxytestosterone (DHT) within the prostate cells and it is DHT that causes the growth of prostate cells and the prostate itself. It was discovered that individuals who lacked the 5-alpha reductase enzyme developed ambiguous genitalia, but did not develop BPH. Researchers hypothesized that if they could inhibit the 5-alpha reductase enzyme and prevent the conversion of testosterone to DHT after puberty, this would not only prevent the growth of the prostate, but would actually shrink the prostate. This concept was proven for finasteride (Proscar, Merck Inc.), the first 5-ARI to be marketed, and for dutasteride (Avodart, GlaxoSmithKline), the second 5-ARI to be produced.[8]

After the development of finasteride it was determined that there are actually two types of 5-alpha reductase enzymes, type 1 and type 2. Finasteride inhibits the type 2 enzyme, whereas dutasteride inhibits both, type 1 and type 2 enzymes.[8] Inhibiting these enzymes prevents the conversion of testosterone to DHT, which can be measured biochemically. It has been shown that finasteride will cause about a 70% reduction of DHT levels within the prostate, in contrast to dutasteride which results in more than a 90% reduction of DHT levels.[9] In the only head-to-head trial comparing finasteride to dutasteride, after a 1 year comparison, there were no statistical differences in patients' response to either medication. The side effect profiles were virtually identical. It has been suggested that a longer trial might have demonstrated some differences.[10] The other question that has not been addressed is "How much DHT suppression is enough to control or decrease BPH?"

Early monotherapy trials with finasteride and dutasteride showed that monotherapy could shrink the prostate by 23% to 27%. The only drawback was that it took up to 6 months for most patients to experience any perceived clinical benefit based on shrinkage of the prostate.

The Proscar Long-term Efficacy and Safety Study (PLESS) showed that there was a significant patient response to monotherapy with finasteride.[11] Similar results were seen in the Avodart regulatory agency approval trials where dutasteride monotherapy was taken for 4 years to manage symptomatic BPH.[12] Patients in both trials achieved significant shrinkage of the prostate as well as a good reduction in symptoms and decreased disease progression compared to placebo.

The next question was whether combination therapy with an alpha blocker plus a 5-ARI could provide more immediate, improved symptoms in the short term, and, could also prevent disease progression (e.g., advent of urinary retention) and/or the need for surgery in the long term.

Trials were developed to compare monotherapy with an alpha blocker or a 5-ARI versus combination therapy with both agents; some trials also had a placebo arm.

Two important earlier short term trials included the Veterans Administrative Cooperative Study (VA-Coop) in the United States, which investigated the 5-ARI finasteride and terazosin (Hytrin), and the Prospective European Doxazosin and Combination Therapy (PREDICT) trial, which investigated the alpha blocker doxazosin and finasteride. Both studies lasted only 1 year. Their results suggested that in order to respond to 5-ARI therapy, a patient had to have a prostate with a minimum volume of 30 cc. In patients with small volume prostates, there appeared to be no difference in the clinical responses when comparing the placebo to the 5-ARI therapy (finasteride). Some clinicians have wondered whether a longer duration trial would have resulted in a more pronounced difference in the responses in each monotherapy arm.

A few years ago, the first results from the Medical Therapy of Prostate Symptoms (MTOPS) trial were reported. This was a very unique trial in that it was sponsored by the National Institutes of Health rather than industry, and it included only American patients. The trial compared doxazosin and finasteride monotherapy to either combination therapy with both agents or to placebo. To be included in the study, men had to have had no evidence of prostate cancer (i.e., a PSA level of less than 4 ng/ml and a negative DRE), as well as at least "mild" symptoms on the International Prostate Symptom Score (IPSS) scale (< 8). There was no prerequisite for a minimum PSA level or a prostate volume documented by transrectal ultrasound.

The MTOPS study showed that patients taking combination therapy had a 67% decreased risk of progression of prostate disease to: urinary retention or the need for surgery. Treatment responses in both monotherapy arms were similar, but symptom control with the alpha blocker appeared to be more effective compared to the 5-ARI alone, up to 5 years.[11]

The Combination of Avodart and Tamsulosin (CombAT) trial was developed to further investigate this same hypothesis. In this trial, monotherapy with dutasteride or tamsulosin was compared to combination therapy with both agents in "high risk" BPH patients. High risk of disease progression was defined as a patient with a prostate volume of at least 30 cc determined by transrectal ultrasound, a PSA of at least 1.5 ng/ml with an upper limit of 10 ng/ml, and an IPSS score of at least 12 signifying moderate symptoms of BPH. The study's ethical review board determined that since each monotherapy had been previously proven to be more effective than placebo in other trials, it would not be ethical to allow these high risk patients to receive only placebo for 4 years.

Currently, only the 2 year interim results from the CombAT trial are available. Again, patients in the combination arm had greater symptom reduction than patients in either monotherapy arm. Surprisingly, by 15 months into this study, the 5-ARI dutasteride appeared to be even more effective than the alpha blocker tamsulosin in reducing the AUA-SI. The average prostate volume of the patients in the CombAT trial was 54 cc, which was much higher than in the MTOPS trial.[13]

The 2 year results from the CombAT trial showed that compared to patients in the monotherapy arms, patients in the combination arm showed a marked improvement in quality of life, as measured by their responses to question 8 on the AUA-SI questionnaire as well as the BPH Impact Index.[14]

After a clinician has elected to treat his patient with combination therapy, the final question to ponder is: How long to maintain the combination therapy?

The profile of a patient who should be offered combination therapy is that of a man who has prostate enlargement greater than 30 cc, no evidence of prostate cancer, and moderate to severe symptoms of BPH disease. Assuming that the patient will achieve response to the 5-ARI by approximately 6 months and that the alpha blocker will not prevent progression of the disease, the physician must determine when and if to stop the alpha blocker.

This question was addressed in two recent studies: the Symptom Management After Reducing Therapy-1 (SMART-1) trial and the PRoscar and alpha blOcker combinAtion followed by disContinuation Trial (PROACT) study. In SMART-1, all patients were given a combination of dutasteride and tamsulosin for 6 months. Then in a blinded monotherapy with dutasteride. Both at 3 months and 6 months later, the patients were asked: "Do you feel the same, better, or worse compared to how you felt 3 months ago?" The SMART-1 trial concluded that approximately 77% of patients who continued with dutasteride alone after only 6 months of combination therapy were very happy with their symptom response and their voiding function.[15]

In the PROACT trial, if a patient was already on an alpha blocker, all that the investigator did was to add finasteride for 9 months. If the patient was not on an alpha blocker, he was given tamsulosin and finasteride for 9 months. At 3 months and 9 months after the initial 9 month combination therapy, patients were asked a similar question about their satisfaction with their present treatment regimen compared to how they felt before. The answer here as well, was that most patients felt quite comfortable after completing a total of 9 months of combination therapy.[16]

Regardless of absolute symptom response, both MTOPS and CombAT suggest that long term combination therapy will prevent progression of BPH symptoms, urinary retention, and the need for surgery to a greater extent than either monotherapy.

Possible side effects from the 5-ARIs include gynecomastia, decreased libido, and erectile dysfunction. The only surprise was that the incidence of ejaculatory dysfunction was "more than additive" in the combination arm compared to the specific incidences in either monotherapy arm. This could be a concern for some patients.

We await the 4 year data from the CombAT trial to see how its final numbers for progression, retention and surgery, in this "higher risk" population compare to the MTOPS final results.

Recently it has been shown that patients who are either receiving an alpha blocker alone or combination therapy with a 5-ARI may still exhibit symptoms of bladder irritation as manifested by complaints of frequency, urgency, and possibly urgency incontinence. Some studies have demonstrated that adding an anticholinergic medication will not give these patients a higher risk of developing urinary retention, but could offer them additional symptom improvement.[17,18]

Another proposal for an additional type of combination therapy arises from the hypothesis of a common pathway that stimulates BPH symptoms and erectile dysfunction. It appears that some men who have mild to moderate irritative symptoms of BPH such as frequency and urgency also develop erectile dysfunction. Some men who are treated for BPH with alpha blockers can have improved erectile function. Conversely, men who use type 5 phosphodiesterase inhibitors to manage erectile dysfunction can also show some improvement in voiding symptoms associated with BPH. A possible explanation for this might be that increased oxygenation through the nitric oxide pathway which is also critical in the development of erections, can stabilize the prostate. The interesting result is that although urinary symptoms might improve, uroflow rate does not change.[19]

Conclusions

What would I do if I had BPH?

If I had significant symptoms of frequency, urgency, obstructive symptoms and a prostate volume greater than 30 cc as demonstrated by either transrectal ultrasound or a PSA level greater than 1.5 ng/ml, I would accept combination therapy with a 5-ARI and an alpha blocker for about 9 months. If after taking combination therapy for 3 months I was still experiencing frequency and urgency symptoms, I would add an anticholinergic medication to my treatment regimen. At the end of 9 months, I would attempt to discontinue the alpha blocker and monitor my symptoms. If there were no changes, I would consider stopping the anticholinergic medication. If after another 1 month there were no changes in my symptoms, I would continue treatment with only the 5-ARI.

What we have seen is that simultaneous combination therapy with an alpha blocker and a 5-ARI is definitely more effective than either type of monotherapy to prevent progression of BPH symptoms as well as urinary retention and the need for surgery. In a number of patients, after 6 or 9 months of combination therapy it appears that we may be able to stop alpha blocker therapy, but maintain symptom response while still preventing progression. If the symptoms return, it is easy to reintroduce the alpha blocker. Other additional therapeutic agents can be offered in response to a patient's symptoms.

With the development of newer, more selective alpha blockers, as well as combination therapy with the 5-ARIs, we have changed our approach to the management of BPH. Today, compared to a number of years ago, the frequency of doing the "gold standard" TURP (transurethral resection of the prostate) has diminished significantly as more and more men initially attempt BPH management by using medical therapy. These men can enjoy a long term response without disease progression while sustaining mild and in most cases very tolerable side effects.

Disclosure

Dr. Jack Barkin is an active urologist and Chief of Staff at the Humber River Regional Hospital in Toronto. He sits on the medical advisory board for Abbott, GlaxoSmithKline, Merck Frosst, sanofi-aventis and Boeringer-Ingelheim. He has done the clinical research on Avodart, Flomax, Hytrin, Xatral and Proscar, both in monotherapy and combination. He has spoken all over the world for all of the companies outlined. □

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Use of anticholinergic therapy in men

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Lower urinary tract symptoms in men usually include symptoms of bladder overactivity such as urinary frequency, urgency or nocturia. These are often the initial presenting symptoms for men seeking medical attention for urinary dysfunction. The prevalence of overactive bladder in men is similar to women and increases with advancing age. While women with these symptoms are treated primarily with anticholinergic therapy, there is reluctance to use these agents in men due to concerns regarding worsening obstructive symptoms or urinary retention exacerbated by a large prostate. For men, alpha blocker monotherapy remains the primary therapy for lower urinary tract symptoms despite the fact that a larger fraction of men continue to experience symptoms of overactive bladder. There is emerging body of evidence that the use of anticholinergic agents may be safe and effective in men. We will discuss the rationale for the use of anticholinergic therapy in men with bladder overactivity, either alone, or in combination with alpha blockers. We will review the current literature on the topic and discuss potential future directions in the management of overactive bladder in men.

Key Words: overactive bladder, anticholinergic, combination therapy, men

Lower urinary tract symptoms (LUTS) are a constellation of both storage and voiding symptoms. The storage symptoms are frequency, urgency, nocturia and urgency incontinence. The voiding symptoms are hesitancy, poor flow, intermittency and straining to void.[1] In practice, the prevalence of obstructive symptoms is much higher, yet the patients are more bothered by their storage symptoms.[2] In this study by Peters et al, questionnaires were provided to 1271 men > 45 years old who presented to urology departments in 12 countries with symptoms of bladder outlet obstruction secondary to benign prostatic hypertrophy (BPH). The instrument contained 22 questions measuring 20 urinary symptoms plus seven condition specific quality of life questions and four questions concerning sexual function. The questionnaire was designed to determine both the prevalence of the symptoms and the degree to which the patient was bothered by the symptom. These men reported a high prevalence of the hallmark symptoms of overactive bladder (OAB), including urgency (75%), frequency (74%), and nocturia (74%), and a lesser prevalence of urge incontinence (48%), at least occasionally. Of those men reporting individual symptoms, those who reported some degree of bother by that symptom included urge incontinence (84%), urgency (80%), frequency (76%), and nocturia (74%). Overall, voiding symptoms were most prevalent, whereas storage symptoms (including those symptoms associated with OAB) were most bothersome. This is evident from the clinical observation that often the initial complaints

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from the patients presenting for evaluation of lower urinary tract function are related to urinary frequency, urgency or nocturia, and less often about decreased flow or hesitancy.

Overactive bladder may be defined as urinary frequency, urgency, nocturia, with or without urgency incontinence. It is equally prevalent in men and women, and in men, it often overlaps with conditions of the prostate. In a study of 5204 participants, Stewart et al noted that the prevalence of OAB symptoms for men was 16.0% and for women was 16.9%. The prevalence increased with age at a similar rate for both sexes.[3] Overactive bladder is a fairly common condition evaluated in the urology office in both men and women. While both men and women can have identical symptoms, women are initially treated with antimuscarinic therapy and men are more likely to be initially treated with alpha blockers alone for the same symptoms. Many men have persistent storage symptoms after treatment for BPH related voiding symptoms. When overactive bladder symptoms are evaluated it is very interesting to note that the prevalence is the same across all age groups in both men and women.[3]

Most men will exhibits symptoms of overactive bladder as well as obstructive symptoms and this is well delineated in the American Urological Association symptom score. Despite the data about similar prevalence, fewer men are treated with anticholinergics than women, a ratio of 80-20.[4] Published data show that many men are often not treated at all for their symptoms. If medical therapy is instituted, it is usually for treatment of obstructive symptoms alone, while a few men are treated for their overactive bladder alone and even fewer are treated with combination therapy. When treatment is focused primarily towards BPH and outlet obstruction, quite frequently the irritative symptoms are not relieved. As many as 65% of men treated for bladder outlet obstruction and lower urinary tract symptoms may not show symptomatic improvement.[5,6] It is instructive to note that even after a transurethral resection of prostate, overactive bladder symptoms may persist or recur in up to one third of the men.

Why is it that we treat men differently then woman when it comes to their bladder symptoms when the symptoms of overactive bladder are the same? This practice pattern likely stems from the fear that use of anticholinergic therapy may lead to worsening of voiding function and may result in urinary retention. Published pharmaceutical reports which will be described later in this review show that anticholinergics do not lead to increased risk of urinary retention.[4,7] We will highlight some of the current published reports with regard to the clinical utility of anticholinergic (or antimuscarinic) therapy in men. A safety study involving 220 men evaluated those who were urodynamically obstructed and determined the impact of utilization of an anticholinergic alone in this population. The study showed that there was no decrease in uroflow rates from baseline to 12 weeks for those receiving anticholinergics compared to those receiving placebo. Urodynamic evaluations from this trial also showed no change in detrusor contractions between the anticholinergic and placebo groups. The postvoid residual urine did show a slight increase in the anticholinergic group but this was not associated with a higher rate of adverse urinary effects.[8]

A trial of long acting tolterodine was performed by Kaplan et al in men who had failed initial alpha blocker therapy for benign prostatic hyperplasia. This was a small study of 43 men with a mean age of 61. All the men had failed alpha blocker therapy for at least 1 month and these men were given anticholinergic monotherapy for 6 months. The parameters studied were symptom score, voiding diaries, and adverse events. Men with a history of surgical or medical intervention for their BPH, and those with a PSA over 10 ng/ml were excluded. The study population had post void residual urine of 100 ml at the start of the study, a symptom score of 17 and uroflow rate in the obstructive range. Anticholinergic therapy resulted in an improvement in the symptom scores and uroflow rate (9.8 to 11.7), and a decrease in the postvoid residual volume (97 cc to 75 cc). The study also found a decrease in urinary frequency (9.8 to 6.3) and nocturia (4.1 to 2.9). Finally, none of these patients experienced urinary retention.[9]

Acute urinary retention has been reported in 2.4% to 2.9% of men receiving placebo in the Medical Therapy of Prostate Symptoms MTOPS and Veterans Administration Cooperative studies, respectively. It appears from open label as well as randomized trials that the use of anticholinergics does not increase the risk of acute urinary retention and appears to be safe in this regard.[8,10-12]

Lee et al studied the use of doxazosin with or without an antimuscarinic agent in men with both symptomatic BPH and overactive bladder. This was a prospective controlled study of 144 men and all had obstruction by urodynamics. The patients were subdivided into obstruction only or obstruction with detrusor over activity groups. Detrusor overactivity was defined as an involuntary detrusor contraction $\geq$ 10 cm H_2O. Symptomatic improvement was defined as > 3 point decrease in IPSS score. Mean age was 68,

symptom score was 25, prostate volume about 35 cc, bladder capacity of 304, uroflow rate in the obstructive range at 10.7 cc/sec, and modest postvoid residual of 42 cc. With alpha blocker therapy alone, only 35% of the patients demonstrated an improvement in the IPSS score. The remaining 65% who did not improve were given a combination of antimuscarinic agent and an alpha blocker. Of these, 73% noted an improvement with the addition of anticholinergic therapy.[13] The study also found that the combination of an anticholinergic agent with an alpha blocker did not increase the incidence of acute urinary retention.[13]

Another randomized study from evaluated the usefulness of combination therapy with alpha blocker with anticholinergic therapy versus alpha blocker alone. All men had urodynamics prior to the start of the study confirming mild to moderate bladder outlet obstruction. These men received 1 week of an alpha blocker and then were randomized to either the addition of an anticholinergic or continued on the alpha blocker alone. They all had urodynamic studies again at 12 weeks. Results from the combination group showed a slight decrease in detrusor contractions, an increase in flow rate, and no increase in residual volume.[14] This small study confirms the findings of previous studies that adding an anticholinergic agent in urodynamically proven obstruction is very safe and effective in relieving symptoms of obstruction and overactive bladder.

In 2006, the first large randomized, double blind, placebo controlled trial was reported which evaluated the effects of an anticholinergic (tolterodine) in addition to an alpha blocker (tamsulosin) in male patients with symptoms of overactive bladder and benign prostatic hypertrophy. The study included 800 men, but in this study, urodynamics were not performed. The inclusion criteria required that the patients be bothered by their symptoms, and have an IPSS $\geq$ 12, IPSS QOL $\geq$ 3, urinary frequency ($\geq$ 8 episodes/24 hrs), and urinary urgency ($\geq$ 3 episodes/24 hrs). Patients were treated with placebo, alpha blocker alone, anticholinergic alone, or combination anticholinergic and alpha blocker. A validated patient reported outcomes measure was used as the primary endpoint to evaluate patient perception of treatment benefit at the end of the 12 weeks. Results showed that most patients in the trial perceived a benefit from treatment. At 12 weeks, the combination therapy group had the best improvement with regard to frequency and urgency. Those patients with urge incontinence benefited with either monotherapy with the anticholinergic or combination therapy. Improvements in symptoms score were seen with alpha blocker alone or combination therapy. Either drug therapy was beneficial for urge incontinence. Improvements in IPSS score were seen with either alpha blocker or combination. To summarize, there was a significant improvement in the combination arm as a whole and combination was better than either monotherapy alone. For patient perceived outcomes, combination therapy was the best. Finally, there was no significant increase in postvoid residual or significant decrease in uroflow rate, or any increased risk of urinary retention with the use of anticholinergic therapy.[15]

At present, there are several anticholinergic agents in the market. Kaplan et al presented a study at the annual meeting of the American Urological Association in 2008 comparing three commonly used agents including solifenacin, darifenacin and tolterodine. All of the men in this study were on alpha blockers and had persistent frequency and/or urgency. Men were randomized to one of these three anticholinergics, in addition to the alpha blocker, and various outcome measures were analyzed. The results showed that darifenacin was not as effective as tolterodine or solifenacin with regard to urgency, IPSS storage symptoms and postvoid residual. Furthermore, nearly half the men receiving darifenacin experienced urinary retention in this trial. This study, albeit small, points out the possibility that not all anticholinergic agents are equivalent in treating men with LUTS and caution must be exercised before selecting any anticholinergic for a use in men.

At present, there are a few ongoing clinical trials to further elucidate the safety and efficacy of anticholinergics in men with LUTS. One of the limiting factors in the clinical use of anticholinergic drugs are the significant side effects. Using the active metabolite of the drug is thought to produce similar efficacy at a lower dose and with fewer side effects. There are studies examining the effects of 5HMP, which is the active metabolite of tolterodine. There are beta receptors present in the detrusor muscle of men with obstructive and irritative symptoms. Beta blockers have been shown to cause relaxation of the detrusor muscle, with minimal to no systemic side effects. Tachycardia is usually not noted, and since its mechanism of action is different than the anticholinergics, dry mouth is also not very common.[16-18] There is an ongoing trial of YM-178, a beta agonist, in men with LUTS.[18] These are just a few of the interesting directions that the treatment for overactive bladder may take in the future.

In conclusion, using anticholinergic agents in men with bladder overactivity is effective, safe and without any undue risk of incomplete emptying or urinary retention. These agents may be used as monotherapy

in men with mostly irritative and minimal obstructive symptoms. These agents also provide improved efficacy when used in combination with alpha blockers for men with persistently overactive bladder following monotherpay with an alpha blocker. The anticholinergic agents can be used safely in men without severe obstructive symptoms such as significantly diminished uroflow or very high postvoid residual volumes. In addition to the newer agents with improved efficacy and side effect profile, the role of various currently available anticholinergics in men with overactive bladder warrants further study.

Disclosure

None declared. □

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Screening for prostate cancer: an update

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SHARIAT SF, SCARDINO PT, LILJA H. Screening for prostate cancer: an update. The Canadian Journal of Urology. 2008;15(6):4363-4374.

The introduction of total prostate-specific antigen (tPSA) testing in serum has revolutionized the detection and management of men with prostate cancer. This review will highlight some of the exciting new developments in the field of prostate cancer screening in general and from our SPORE research program at Memorial-Sloan Kettering Cancer Center. First, it is important to understand that the inherent variability of tPSA levels affects the interpretation of any single results. Total variation in tPSA includes both analytical (i.e., pre-analytical sample handling, laboratory processing, assay performance, and standardization) and biological variation (i.e., metabolism, renal elimination, medication, physical and sexual activity, size and integrity of the prostate). Second, recent evidence demonstrates that no single tPSA cut-off separates men at high risk for prostate cancer from men at low risk or men with "significant" (high grade, high volume) cancer from those with low grade, indolent cancer. Taken together with a man's age, family history, ethnicity, and digital rectal exam results, tPSA levels add to the overall estimate of the risk of cancer, allowing men to share in the decision about a biopsy. Third, men who will eventually develop prostate cancer have increased tPSA levels years or decades before the cancer is diagnosed. These tPSA levels may reflect the long duration of prostate carcinogenesis and raise the question about a causal role for tPSA in prostate cancer development and progression. Total prostate-specific antigen measurements before age 50 could help risk stratify men for intensity of prostate cancer screening. Fourth, enhancing the diagnostic accuracy of tPSA, especially its specificity, is of particular importance, since higher specificity translates into fewer biopsies in men not affected by prostate cancer. While tPSA velocity has been shown to improve the specificity of tPSA, its sensitivity is too low to avoid prostate biopsy in a patient with an elevated tPSA level. Moreover, prospective screening studies have reported that tPSA velocity does not add diagnostic value beyond tPSA level. At this time, tPSA velocity appears most useful after diagnosis and after treatment, but its value in screening and prognostication remains to be shown. Finally, while free PSA molecular isoforms and human kallikrein-related peptidase 2 (hK2) hold the promise for detection, staging, prognosis, and monitoring of prostate cancer, evidence from large prospective clinical trials remain to be reported.

Key Words: prostate-specific antigen, human glandular kallikrein, prostate cancer, prognosis, detection

Introduction

Prostate cancer is the most commonly diagnosed cancer in American men and the second leading cause of cancer-related deaths. The wide availability of total prostate-specific antigen (tPSA) revolutionized prostate cancer screening and ushered in the tPSA era. This has resulted in earlier prostate cancer detection and an increase in incidence. However, it remains unclear whether screening for prostate cancer results in lower prostate cancer mortality. Indirect evidence from observational and case control studies is not consistent but does suggest the highly prevalent screening in this country has played a substantial role in the decrease in prostate cancer mortality in the United States.[1] Advocates of screening point to an increased rate of discovery of lower stage cancer, a decline in the incidence of metastatic disease, and a reduction in cancer related mortality after

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widespread tPSA screening. Critics of tPSA screening, on the other hand, point to high rates of over detection: the lifetime risk of diagnosis is currently ~18%, whereas that of death from prostate cancer is ~3%. A major problem with tPSA is its lack of cancer specificity. An elevated tPSA level can reflect the presence of cancer but can also be caused by benign prostatic hyperplasia (BPH), infection, and/or chronic inflammation. All prostate epithelial cells, whether normal, hyperplastic or cancerous, synthesize PSA. Neoplastic cells produce somewhat lower tissue levels of tPSA compared to BPH cells although both conditions cause tPSA elevation in the blood. Therefore, it has been suggested that tPSA should be considered as a marker of BPH related prostate volume, growth, and outcome rather than a reliable marker of prostate cancer.[2-4] In addition, there is continuing disagreement over the threshold level of tPSA that should indicate biopsy. Finally, tPSA levels do not directly correlate with the biological behavior of prostate cancer. This can lead to over detection and over treatment, resulting in increased cost, side effects, complications, and patient anxiety.

In addition to its use for early detection, use of tPSA testing has been found useful as an aid to predict prostate cancer risk and of treatment outcome. Indeed, tPSA is one of the key variables in pre and post treatment prognostic models for clinically localized prostate cancer.[5-7] However, Stamey et al have reported that for patients with a tPSA level of < 9 ng/ml, tPSA poorly reflected the risk of biochemical recurrence (BCR) after radical prostatectomy but was significantly correlated with the volume of the radical prostatectomy specimen, a direct reflection of the degree of BPH present.[8-10]

The purpose of this review is to discuss: 1) the inherent variability of serum tPSA levels, 2) the need to replace tPSA cut-offs with prediction tools that incorporate established risk factors, 3) the predictive value of tPSA in young man and the impact it could have on the age of onset and intensity of prostate cancer screening, 4) the controversies of tPSA velocity (tPSAV), and 5) the association of free PSA and its isoforms as well as human kallikrein-related peptidase 2 (hK2) with prostate cancer risk and outcomes.

PSA variability

It is important to consider the variability of tPSA and its derivatives in screening and monitoring of individuals over time. Total variation in tPSA includes analytical and biological variation. Analytical variation depends on assay performance, sample handling, and laboratory processing.[11,12] Biological variation relates to individual factors such as tPSA metabolism, renal elimination, and physical and sexual activity.[13,14]

First, transitory tPSA outliers, which may be due to infection, or following digital rectal examination (DRE) or prostate biopsies, may lead to non-cancer related higher tPSA value and result in a higher tPSA velocity (tPSAV). Oscillations up to 20%-30% in the tPSA range 0.1 ng/ml-20 ng/ml may be due to biological variation.[15,16]

Second, the use of different detection assays may be another important cause of variation. Differences in assay standardization can give an artificially high or low estimate of tPSA and tPSAV.[17-19] Assays are not interchangeable and caution should be exercised when comparing results from different commercial tPSA assays. Patients and physicians should be aware of which assay was used each time a tPSA measurement is performed, and an effort should be made to use the same assay at the next screening visit. In addition, studies of tPSA kinetics over time using different assays should be interpreted with caution.

Third, the effect of previous BPH treatment on tPSA remains mostly unpredictable. For example, the effect of commonly used 5-α-reductase inhibitors on the predictive value of tPSA kinetics for tumor progression is uncertain. Because 5-α-reductase inhibitors are known to decrease the PSA level with ~50% and mostly suppress the benign components of PSA secretion, they may enhance the utility of tPSA and tPSAV.[20] In addition, by shrinking the prostate gland, finasteride may increase the likelihood of detecting a small cancer on needle biopsy. It was initially implicated but recently refuted that finasteride also may induce the regression of low grade but not high grade prostate cancer.[21]

This large normal variability of tPSA requires larger changes between two consecutive measurements to distinguish pathological changes from changes resulting from analytical and biological variations. Nixon et al calculated the coefficient of variation (CV) over 2 weeks and demonstrated that a change between two tPSA measurements of approximately 25% indicated a significant change.[22,23] Bunting et al reported a critical difference, defined as the minimum percent change between two consecutive measurements that suggests a significant change beyond the normal variation, close to 60% over a time period of 1 year.[24] Bruun et al recently assessed the long term variability of the different forms of tPSA at several different tPSA levels in a randomly selected population of asymptomatic and apparently healthy men whose tPSA levels were < 2.0 ng/ml at the end of the 8 year observation period.[25] They found that the total intra-individual variation of tPSA was much less than that reported by Bunting et al[24] and somewhat

higher than the intra-individual variation for either free PSA or percent free PSA. This suggests that free PSA concentration in blood may vary less than complexed PSA concentration, which is the major contributor to tPSA. One explanation is that free PSA and complexed PSA may have different elimination pathways, and hence different elimination rates.[13,26-28]

Recently, Eastham et al evaluated the year-to-year fluctuations in tPSA levels over a period of 4 years in a cohort of men selected from a polyp-prevention trial study group.[29] Several cut-off points for tPSA were studied; 30% and 26% of the men with a tPSA level > 4 ng/ml and > 2.5 ng/ml, respectively, had a tPSA value below these cut-offs at the next tPSA-testing.

Optimal tPSA cut-off values

No single tPSA cut-off separates men at high risk for prostate cancer from men at low risk, nor men affected with high grade disease from those with low grade disease.

At a tPSA cut-off of ≥ 4 ng/ml, a significant cancers remain undetected[30] and intervention at lower tPSA levels has been proposed to improve patient outcomes.[31,32] Catalona et al found that 22% of men with a normal digital rectal examination and a serum tPSA level between 2.6 ng/ml and 4.0 ng/ml have prostate cancer, and 81% of them have organ confined disease.[33] Data from the Prostate Cancer Prevention Trial (PCPT) revealed that as many as 15% of men with normal digital rectal examination and a serum tPSA less than 4.0 ng/ml have prostate cancer.[30] Among men with tPSA levels ≤ 0.5, 0.6-1.0, 1.1-2.0, 2.1-3.0, and 3.1-4.0 ng/ml, prostate cancer was detected in 6.6%, 10.1%, 17.0%, 23.9%, and 26.9%, respectively. Moreover, approximately 25% of these men had a tumor with Gleason score of 7 or higher. These and other investigators demonstrated that increasing levels of tPSA are associated with increasing probability of prostate cancer risk within the 0-4.0 ng/ml interval.[30,34,35] There is no tPSA threshold at age 62-91 below which prostate cancer can be ruled out with high specificty.[30] No single tPSA cut-off separates men with "significant" (high grade, high volume) cancer from those with low grade, possibly insignificant cancer. Similar to the detection of prostate cancer, high grade cancer can also be found in men with low tPSA levels.

On the other hand, as of now, there is no evidence that lowering the tPSA threshold below 4 ng/ml improves the long term survival in men with prostate cancer while continuing to maintain the cost effectiveness of screening programs. Lowering the tPSA threshold combined with decreasing the age of tPSA screening may be beneficial for men who are at an increased risk for prostate cancer (i.e., strong family history of prostate cancer and/or African-American race). However, consideration must be given to the possibility that lowering the tPSA threshold could result in unnecessary biopsies and increased detection of indolent cancers. Finally, determination of the optimal, institution specific, and management guiding threshold involves not only clinical and epidemiologic features but should also consider the social and psychological implications of prostate biopsy and possible prostate cancer detection.

The difficulty in selecting a cut-off to define what constitutes an abnormal tPSA suggests that tPSA is most useful as a continuous variable, providing a spectrum of prostate cancer risk. Therefore, we prefer to include serum tPSA levels in an overall estimate of the risk of cancer, inform the patient of his particular risk, then make a shared decision about a biopsy.[7,30,34,36-40] Nam et al, for example, developed a model that predicts an individual's risk for prostate cancer in a cohort of 3108 men who underwent a prostate biopsy for the first time.[40] The model comprises factors that can be easily determined at the time of screening such as age, ethnicity, family history of prostate cancer, the presence of urinary symptoms, tPSA, percent free PSA, and digital rectal examination, Figure 1. Addition of all

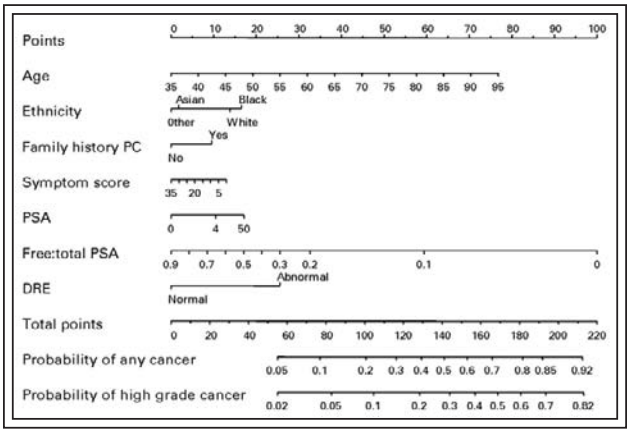

Figure 1. Nomogram prediction model for predicting prostate cancer at the time of biopsy. The nomogram is used by first locating a patient's position for each variable on its horizontal scale and then a point value is assigned according to the points scale (top axis) and summed for all variables. Total points correspond to a probability value for having prostate cancer or aggressive prostate cancer.
PSA = prostate-specific antigen; DRE = digital rectal examination.
Reproduced, with permission, from Nam RK et al. Assessing individual risk for prostate cancer. *J Clin Oncol* 2007;25(24):3582-3588.[40]

these risk factors improved the predictive accuracy of a base model from 0.62 to 0.74. The main advantage of this and other predictive tools[7] is that clinicians can assess prostate cancer risk on an individual basis and make management decisions. However, despite the reasonable accuracy, similar to all predictive tools, the exact probability cut-off for undergoing or foregoing a biopsy is left with the treating physician and patient and should be individualized.

Long term prediction of the future risk of prostate cancer using tPSA

Several studies have suggested that tPSA levels are associated with the risk of prostate cancer years, or even decades, before its diagnosis. The first long term prediction study, which reported that tPSA levels > 2.5 ng/ml predicted diagnosis of prostate cancer over the subsequent decade was limited by the small number of cancer cases (n = 44) and by the degradation of tPSA in archived serum samples.[41] In a prospective study involving a large number of cases, the lead time between tPSA levels ≥ 4 ng/ml and the subsequent clinical diagnosis of PCa was estimated at 5.5 years.[42] Similarly, Fang *et al* studied the risk of prostate cancer diagnosis in a cohort of 549 men following a baseline tPSA measurement at age 40-60 while providing a median follow-up of ~13 years.[43] They concluded a tPSA value above the age adjusted median carried a relative risk of subsequent cancer diagnosis of ~3.6.

Two larger studies extended prediction models to lower tPSA ranges and longer follow-up intervals. Loeb *et al* examined 1178 men in their 40s who had risk factors for prostate cancer.[44] The risk of subsequent prostate cancer diagnosis was 14.6-fold higher for men with a baseline tPSA level between 0.7 ng/ml and 2.5 ng/ml compared to men with tPSA < 0.7 ng/ml. Lilja *et al* assessed prostate cancer risk among 21,277 men younger than 50 years when they attended the Malmö Preventive Medicine study (MPM), a cardiovascular risk assessment study conducted between 1974 and 1986 in Malmö, Sweden.[45] The investigators measured tPSA levels in archived plasma obtained from 462 participants diagnosed with prostate cancer within a median of 18 years from start of the study and from 1222 matched controls. Of note, the attendance rate was high (74%) and the rate of tPSA testing in Sweden was low during most of the study period, leaving this study largely free of over detection or selection biases. the tPSA level at age 44-50 was very strongly associated with the likelihood of developing prostate cancer up to 25 years later, Figure 2. The odds ratio for a prostate cancer diagnosis at a tPSA value of 0.51 ng/ml-1.0 ng/ml was 2.51 compared to tPSA ≤ 0.50 ng/ml, which roughly corresponded to the population average. The odds ratio inreased to 7.02 for a tPSA of 1.0 ng/ml-1.5 ng/ml, and further up to 19.01 for a tPSA of 2.01 ng/ml-3.0 ng/ml compared to a tPSA ≤ 0.50 ng/ml. In a follow-up study, the authors have further shown that tPSA level at age 44-50 predicts the likelihood of developing advanced prostate cancer, defined as either locally advanced (clinical T3 or higher) or metastatic disease at the time of diagnosis.[46] In another analysis of the MPM study cohort, the value of PSA assessments in these younger men were compared with the blood taken from 1167 men of ages 59-61 years.[47] In this study, the prognostic accuracy of PSA (both tPSA and complexed PSA, described below) decreased with age. The authors hypothesized that these findings result from a greater prevalence of BPH

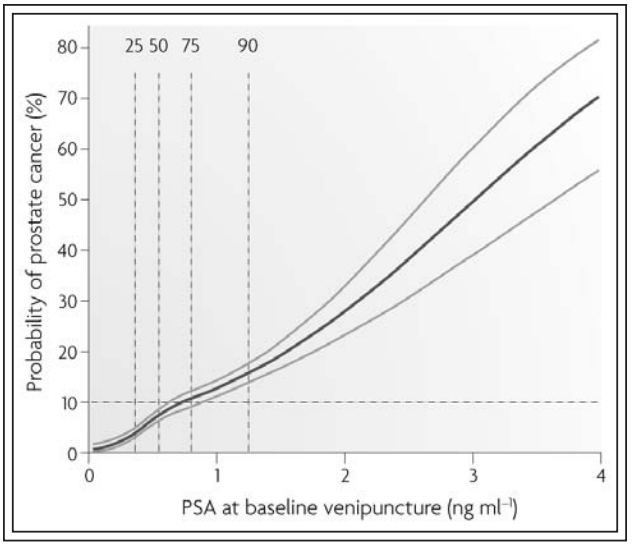

Figure 2. Early prediction of prostate cancer risk. The predicted probability of a prostate cancer diagnosis before the age of 75 years by total prostate-specific antigen (tPSA) measured at age 44-50 years, with 95% confidence intervals. The vertical lines represent the 25th, 50th, 75th and 90th percentiles of baseline tPSA, and the horizontal line represents the average lifetime risk (10%) of a prostate cancer diagnosis before the age of 75 years. Note that the tPSA levels reported from this study are approximately 13% lower than values derived from assays calibrated against the World Health Organization standard.
Reproduced, with permission, from Lilja H et al. Long-term prediction of prostate cancer up to 25 years before diagnosis of prostate cancer using prostate kallikreins measured at age 44 to 50 years. *J Clin Oncol* 2007;25:431-436.[45]

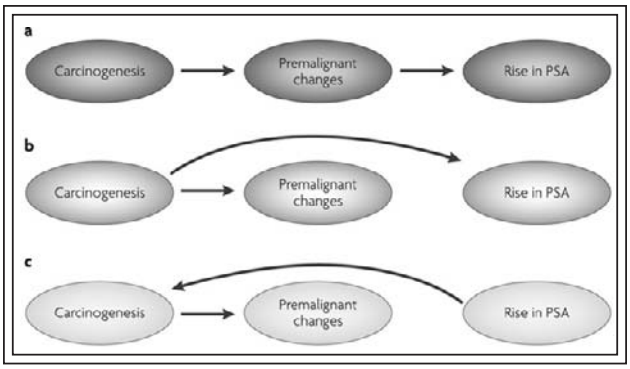

Figure 3. Three non-exclusive hypotheses to explain the association between total prostate-specific antigen (tPSA) level in younger men and prostate cancer diagnosed up to 25 years subsequently.
a) A carcinogenic process causes premalignant changes in prostate cells, which in turn increases leaking of PSA into the bloodstream.
b) A carcinogenic process causes premalignant changes in prostate cells. These changes are not sufficient to cause increased levels of serum PSA; however, carcinogenesis independently causes increased serum PSA by a separate process.
c) An unknown process causes an increase in serum PSA; extracellular PSA is causally influencing the carcinogenic process, which leads to premalignant changes in the prostate.
Reproduced, with permission, from Lilja H et al. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. *Nature Reviews Cancer* 2008;8:268-278.[48]

(and therefore of non cancer related tPSA increase) among older men.

In summary, these studies indicate that men who will eventually develop prostate cancer have increased tPSA levels years or decades before the cancer is diagnosed. These tPSA levels may reflect the long duration of prostate carcinogenesis or could reflect a causal role of tPSA in prostate cancer development and/or progression, Figure 3. A tPSA measurement before age 50 could help risk stratify men for frequency and/or type of later prostate cancer screening.

Approaches to enhance the diagnostic accuracy of tPSA for detecting prostate cancer

Enhancing the diagnostic accuracy of tPSA, particularly specificity, is critical, since higher specificity would reduce the number of biopsies performed in men not affected by prostate cancer. Several different strategies have been investigated, including the use of age-specific tPSA cut-offs, tPSA density, tPSA density of the transition zone, tPSA velocity (tPSAV), and the measurement of various molecular forms of PSA.[7,48-50] We will focus on tPSAV and the measurement of various molecular forms of PSA since they have the highest potential for improving our predictive accuracy.

Total PSA velocity

Total prostate-specific antigen velocity refers to the serial evaluation of serum tPSA concentration over time.[51,52] Different methods of calculating tPSAV are available (e.g., based on the first and the last measured values only or on a regression line through all available measurements, based on normal or logarithmic values), but only small differences in predictive value have been found among these derivatives. Connolly et al found that using all available PSA measurements in a linear regression analysis should be the method of choice for calculating tPSAV.[53] When using the first and last measurements only, these should at least be separated by a sufficiently long time period.

Carter et al showed that patients with BPH demonstrated a linear increase in tPSA levels over time, whereas patients with prostate cancer had an initial linear increase with a subsequent exponential rise that occurred approximately 5 years before cancer detection.[51] In men with an initial tPSA level between 4 ng/ml and 10 ng/ml, a tPSAV cut-off value of 0.75 ng/ml/year provided a sensitivity and specificity for prostate cancer of 79% and > 90%, respectively. If the initial tPSA concentration was less than 4 ng/ml, the specificity of remained > 90%, but the sensitivity dropped to an abysmal 11%. These results were questioned for using relatively short tPSA intervals of 1 and 2 years.[54] Subsequently, Carter et al showed that tPSAV values are useful if a minimum of three consecutive measurements are taken over a 2 year period.[55] While the specificity of tPSAV is high, its sensitivity is too low to advise against prostate biopsy in a patient with an elevated tPSA level who is otherwise healthy and a good candidate for curative therapy. Other limitations of tPSAV include imprecision due to biological and analytical intra-individual variability (see section on PSA variability) and tPSA stability. Moreover, to date, appropriate tPSAV cut-offs have not been determined for men with tPSA levels below 4 ng/ml. Finally, tPSAV may be of most use in patients whose serum tPSA concentration at initial screening is below 4 ng/ml to help predict who should be biopsied when they reach the 4 ng/ml threshold.[49,56-58]

Prospective screening studies have reported that tPSAV does not appear to add diagnostic value for prostate cancer detection beyond that of a single tPSA level. In an analysis of PCPT data, Thompson et al found that when tPSAV was used alone, it was an independent predictor of prostate cancer presence and aggressiveness.[36] However, when tPSAV was adjusted for the effect of tPSA and other standard variables, it lost independent predictive value. Similarly, the first two screening rounds of the Rotterdam section of the ERSPC found that tPSAV did not improve accuracy when combined with tPSA in the prospective setting.[57,58] Finally, a recent analysis from the Prostate, Lung, Colon, and Ovarian (PLCO) cancer screening trial showed that although tPSAV was an independent predictor of high grade disease, addition of tPSAV to tPSA only slightly increased its performance for prediction of high grade tumors.[59] Finally, using a large population based cohort of men in early middle age who were likely to have a low incidence of BPH, Ulmert et al found no benefit to calculating tPSAV or the velocity of any other PSA form over tPSA for long term prostate cancer prediction.[60] Of note, the predictive value of tPSAV alone was 0.712, while the predictive value of a single tPSA was higher (concordance index: 0.771) and the combined model including both PSA velocity and tPSA did not alter the predictive accuracy. The observed lack of additional predictive value for tPSAV indicates that tPSA levels do not increase sharply before prostate cancer diagnosis but rise gradually and slowly over many years, also in those men who later present with advanced cancer.

The most compelling support for the role of tPSAV in prostate cancer comes from prognostic studies. Several studies have shown that that a high pretreatment tPSAV is strongly associated with a poor disease specific survival following diagnosis and could help identify men with low tPSA values who are at increased risk of harboring a potentially lethal tumor.[61-64] Carter et al found a strong association between survival and higher tPSAV as early as 10-15 years before diagnosis in the Baltimore Longitudinal Study of Aging project.[64] Based on these findings, they proposed that a tPSAV threshold of 0.35 ng/ml/year be used in screening men with low tPSA levels to increase the detection of potentially lethal tumors still in the window of curability. These data have prompted debate as to whether this would suffice as evidence to warrant the National Comprehensive Cancer Network to recommend a prostate biopsy if the tPSAV is greater than 0.5 ng/ml/year.[65]

D'Amico et al reported that men with a preoperative tPSAV greater than 2.0 ng/ml/year had a 9.8-fold increased relative risk of death from prostate cancer than men with a lower tPSAV.[61] In a more recent study, these investigators reported that tPSAV was also significantly associated with the risk of cancer specific mortality following external beam radiation therapy.[62] Conversely, using data from 267 Scandinavian men with localized prostate cancer and baseline tPSA levels < 50 ng/ml, Fall and colleagues found that, although prognostically relevant, baseline tPSA levels and relative tPSAV in the first 2 years following diagnosis were not able to predict accurately which patients would have a lethal PCa outcome.[66] Nevertheless, there exists substantial evidence that tPSAV before treatment is associated with outcome, albeit, there is lack of evidence as to whether the predictive accuracy is improved by the combination of tPSAV and tPSA compared to a single tPSA alone.

This discrepancy between the prognostic and screening setting can be partially explained by the mode of detection, the lead time bias, and how tPSAV was measured. Due to the retrospective nature of these articles, there is no proof that the prospective use of tPSAV thresholds can identify men with an unfavorable prognosis at the time when curative treatment is still possible. The observation period necessary for obtaining a valid calculation of tPSAV that is not disturbed by considerable short term fluctuations may be too long, or the number of tPSA measurements may be too high for use in clinical practice. In addition, tPSAV may not correlate with early tumor progression, but could be a mere indicator of aggressive disease for which the window of curability has already closed. Furthermore, a quickly rising tPSA is more common in men with a high starting tPSA level.[67] This proportion of men is expected to be much smaller in a screened cohort than in a clinically diagnosed cohort. In the absence of better alternatives, tPSAV is an important and very practical parameter after diagnosis and/or treatment, but its value in screening and prognostication remains to be proven.

Free PSA

The serine protease, PSA, circulates in the serum in multiple molecular forms consisting of both free (unbound to other proteins) and complexed PSA (i.e. mainly bound to the protease inhibitor alpha-1-antichymotrypsin, ACT), Figures 4 and 5. The FDA has approved the use of percent free PSA testing [i.e., (free PSA/tPSA) x 100] as an adjunct to tPSA in men with a serum tPSA concentration between 4 and 10 ng/ml. While several studies have shown that

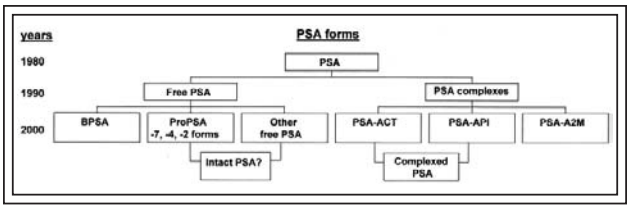

Figure 4. Time line for the discovery of various forms of PSA.
BPSA = benign or BPH-associated free PSA (fPSA); proPSA = precursor propeptide form of fPSA with an intact 7 amino acid-containing peptide leader sequence (-7proPSA) or with either a 3 amino acid peptide [leaving a 4 amino acid peptide remaining (-4proPSA)] or a 5 amino acid peptide (-2proPSA) clipped from the leader sequence of the parent pPSA molecule; other fPSA, refers to other truncated, enzymatically inactive forms of fPSA; intact PSA?, refers to other, as yet unidentified, intact enzymatically inactive forms of free PSA; PSA-ACT, PSA bound to alpha$_1$-antichymotrypsin; PSA-API, PSA bound to alpha$_1$-protease inhibitor; PSA-A2M, PSA bound to alpha$_2$-macroglobulin.
Reproduced, with permission, from Stephan C, Jung K, Diamandis EP, Rittenhouse HG, Lein M, Loening SA. Prostate-specific antigen, its molecular forms, and other kallikrein markers for detection of prostate cancer. *Urology* 2002;59:2-8.[95]

percent free PSA helps discriminate men with BPH from those with prostate cancer, the magnitude of this effect varies across populations.[68,69] Explanations for these inconsistencies may lie in the limited stability of free PSA in blood, particularly in stored sera.[12,70] In addition, prostate cancer patients with larger prostate volumes have higher percent free PSA thereby resulting in lower specificity due to the dilution effect.[71] Finally, the most appropriate percent free PSA cut-off value for clinical decision making remains controversial and percent free PSA may be more valuable as a continuous risk variable. Despite all these limitations, in a recent meta analysis of 66 studies, percent free PSA has been shown to outperform tPSA and complexed PSA as a predictor for biopsy outcome.[72]

Overall, percent free PSA might be less useful as a long term predictor of prostate cancer presence in younger men. Ulmert et al investigated the value of PSA isoforms in a retrospective study comprising a highly representative subset with over 4900 men aged ≤ 50 at the baseline blood draw from the MPM study cohort.[60] They found that among all men aged 44 to 50 years, the combination of tPSA, free PSA, percent free

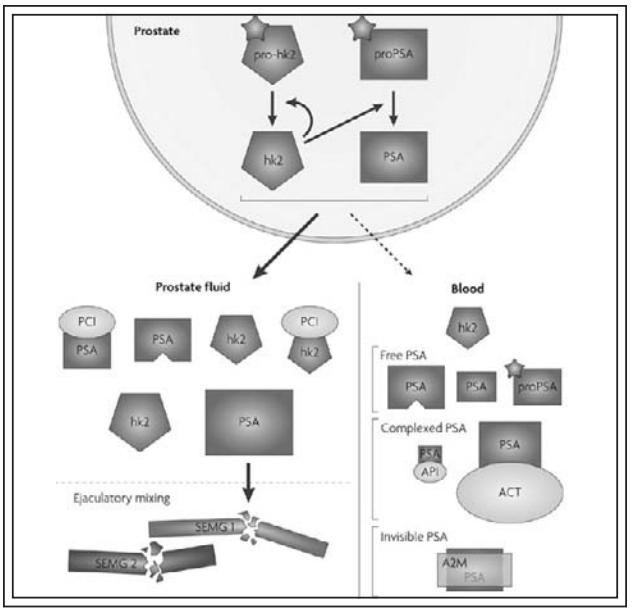

Figure 5. Prostate-specific antigen (PSA) subforms and interactions. Active forms of PSA and kallikrein-related peptidase 2 (hK2) and inactive forms are shown. In the prostate, propeptides are removed from proPSA and prohK2, leaving the mature, catalytic forms. hK2 might be one of the proteases responsible for these processing events. PSA and hK2 are released at high concentrations into prostatic fluid, then into seminal fluid, and at low concentrations into blood. PSA forms in prostatic fluid are active PSA, nicked PSA and PSA complexed with protein C inhibitor (PCI, encoded by SERPINA2), a protease inhibitor. The sizes in the figure indicate the relative abundances of the forms. In seminal fluid, active PSA is believed to be responsible for liquefaction of seminal fluid by proteolysing gel proteins (SEMG1 and SEMG2, which are secreted primarily by the seminal vesicles, though SEMG2 is also secreted in small amounts by the epididymis). Blood contains a variety of forms of PSA: free PSA forms (nicked, intact and proPSA) and complexed PSA. The most abundant form in blood is PSA complexed with α1-antichymotrypsin (ACT); complexes with α2-macroglobulin (A2M) or α1-protease inhibitor (API) are estimated to comprise only a 1-2% or lower proportion of PSA in blood. A2M envelopes PSA, masking the epitopes recognized by commercial PSA assays and thus rendering this form invisible to the assays. PSA levels in seminal fluid are 0.5°V3.0 mg/ml (~10^6-fold higher than in blood) and hk2 levels in seminal fluid are 2-12 microg/ml (~10^4-fold higher than in blood). (Reproduced, with permission, from Lilja, H. et al. Prostate-specific antigen and prostate cancer: prediction, detection and monitoring. Nature reviews cancer. 8, 268-278, 2008).[48]

PSA, did not improve the predictive power of tPSA alone, albeit enhancements were found for men with tPSA ≥ 1.2 ng/ml, and more notably in men with tPSA ≥ 2.0 ng/ml. In addition, Vickers et al showed that in men aged 59 to 61 years, the combination of percent free PSA, hK2 and tPSA was significantly superior to tPSA alone (AUC 0.819 versus 0.794, respectively), whereas third combination of markers was unable to enhance cancer risk predictions among men aged ≤ 50 at baseline. A hypothesis for this finding is that a shorter time delay between tPSA measurement and cancer diagnosis and increased frequency of BPH enhances the predictive value of both percent free PSA and hK2 among older men, whereas increased frequency of BPH decreases the predictive value of tPSA in older men.[47]

Measuring distinct subfractions of free PSA: proPSA, intact PSA, nicked PSA, and BPSA

The free PSA in the blood is (micro) heterogeneous and exists mainly as four distinctly defined subfractions, all of which are enzymatically inactive, Figure 5. Similar to most secreted peptide enzymes, PSA is initially produced as a 261 amino acid pre pro protein. Co-translational removal of an amino terminal leader generates a non catalytic zymogen (proPSA). Subsequent removal of the 7-residue propeptide generates the catalytically active mature form, a 237 residue single chain enzyme containing five intra chain disulphide bonds.

ProPSA

Compared to BPH associated transition zone epithelium, prostate cancer tissues have been found to contain higher levels of truncated versions of proPSA with either two (-2proPSA) or four (-4proPSA) extending N terminal of the mature 237 amino acid single chain sequence.[73] In a preliminary study of men with a tPSA value between 6 ng/ml and 24 ng/ml, the fraction of -2proPSA in the men with and without prostate cancer ranged from 25% to 95% and 6% to 19%, respectively.[73] In this study, -2proPSA was also reported to be a stable (i.e., not cleaved by either hK2 or trypsin), enzymatically inactive form of free PSA. In a follow-up study, Sokoll et al found that in men with tPSA levels between 2.5 ng/ml to 4.0 ng/ml, the percentage of proPSA to free PSA ratio was 50.1% in men with prostate cancer versus 35.5% in men with a negative prostate biopsy.[74] A higher percentage of proPSA to fPSA also has been associated with a higher risk for prostate cancer in men with tPSA levels between 4.0 ng/ml and 10 ng/ml.[75] Finally, a higher preoperative proPSA to free PSA ratio has been associated with higher Gleason grade, extracapsular tumor extension, and BCR after radical prostatectomy.[76-78] After validation in large, prospective studies, addition of preoperative proPSA to free PSA ratio measurements to standard preoperative predictive models may improve prediction of prostate cancer features and outcomes.

Intact PSA

Other assays recognizing distinctly different antigenic epitopes on free PSA have also been implicated to be useful tools to distinguish critical free PSA heterogeneity in blood as it measures only intact (i.e. both mature and proPSA single chain PSA), but does not recognize any nicked mutli chain PSA forms that are cleaved between Lys145 and Lys146. The level of intact PSA and the ratio of nicked to tPSA have shown potential for improving the discrimination of prostate cancer from BPH.[79,80] Similarly to free PSA, intact PSA levels degrade with freezing, storage, and thawing.[79]

Vickers et al evaluated whether a multivariable model including tPSA, free PSA, intact PSA, and hK2 predict the results of a prostate biopsy in previously unscreened men with elevated tPSA from the Göteborg cohort of the European Randomized study of Screening for Prostate Cancer screening (ERSPC).[70] They found that a statistical model including the four markers predicts the result of biopsy more accurately than a model incorporating tPSA and age alone. The area under the curve (AUC) for a predictive "base" model including age and tPSA was 0.680; incorporating the additional markers into the model significantly increased predictive accuracy to an AUC of 0.832. A similar significant increment in predictive accuracy was seen if the digital rectal exam was added to the base model. Moreover, decision analytic methods revealed that application of the model would lead to notably superior clinical outcomes than the current strategy of biopsying all men with elevated tPSA.

BPSA

Another distinct form of the multi chain cleaved free PSA, BPSA, forms through the clipping of intact single chain free PSA between amino acid residues Lys182 and Ser183 resulting in a neo-epitope. BPSA is present in prostatic tissue, blood, and seminal plasma.[73] BPSA expression has been localized to the nodular hyperplasia of the transition zone of men with BPH.[81] Serum levels of BPSA are higher in men with symptomatic BPH compared to men without lower urinary tract symptoms suggestive of BPH.[73]

Moreover, serum BPSA levels are almost undetectable in healthy men. Further studies have confirmed that serum levels of BPSA correlate with pathological nodular hyperplasia of the prostate.[82,83] Therefore, measurements of BPSA may hold most promise as a serum marker for BPH.

In summary, while assays capable of distinguishing distinct free PSA subfractions in the blood hold the promise of providing new tools for detection, staging, prognosticating, and monitoring of prostate cancer, independent replication of data from large prospective clinical trials remain to be reported. In addition, BPSA or nicked PSA, either alone or (quite likely) in combination with free or total PSA, may be useful in studying the development, clinical progression, and response to therapy of BPH.

Human kallikrein-related peptidase 2

Human kallikrein-related peptidase 2 (hK2) is a serine protease that shares 78% and 80% identity at the amino acid and DNA level with PSA. Moreover, both enzymes are mainly expressed in the prostate and are under androgen regulation. hK2 mRNA amounts to 10%-50% of the PSA mRNA in the prostate tissue but in serum and seminal plasma, hK2 concentration is only 1%-3% that of PSA. The low levels in serum pose analytical challenges for hK2 measurements but reliable assays are available in several research laboratories.

Some studies have suggested that tissue expression of hK2 may be more strongly associated with prostate cancer presence and progression than tPSA.[84,85] In addition, serum levels of hK2 and its ratios to free PSA and percent free PSA have been reported to outperform tPSA for prostate cancer detection.[85-88] Furthermore, preoperative serum hK2 has been suggested to be a stronger predictor of prostate cancer grade, stage, and volume in the prostatectomy specimens than tPSA or free PSA.[89-93] Recently, preoperative serum hK2 has also been shown to predict BCR with high accuracy.[93] In a cohort of 867 patients treated with radical prostatectomy for clinically localized disease, the predictive accuracy of hK2 for BCR after surgery was 0.721 (concordance index) versus 0.691 for tPSA. This difference in predictive accuracy was more pronounced in men with a tPSA < 10 ng/ml (0.739 for hK2 versus 0.599 for tPSA, $p < 0.0005$). Moreover, addition of hK2 significantly improved the predictive accuracy of a preoperative nomogram for prediction of BCR consisting of tPSA, clinical stage and biopsy Gleason grade.

In summary, hK2 seems to add statistically and clinically important information for prostate cancer detection and, more importantly, for prostate cancer prognostication, especially in the tPSA range below 10 ng/ml. This is particularly important, as most men diagnosed nowadays with prostate cancer have a tPSA below 10 ng/ml and this is the range where risk stratification using tPSA alone does not perform very well. Nevertheless, these findings need to be externally validated using independent large, well designed studies before hK2 can applied in clinical practice.

Decision analysis tools that integrate risk factors with markers to improve clinical decision making

In addition to tPSA and digital rectal examination findings, there are other risk factors of importance, such as age, family history of prostate cancer, ethnicity, other hereditary and environmental factors and attributes (e.g., diet, body mass index, supplement use), and a prior biopsy with negative results for cancer. Historically, physicians estimated a patient's risk based on clinical and anecdotal experience combined with an understanding of the medical literature, but such an approach is clearly biased.[7,37,94] Formal predictive/prognostic tools based on statistical models provide more accurate estimates and are widely available.[7,37,94] These models generally perform as well as or better than clinical judgment.[7,37,94] The estimates of risk and their potential consequences, the advantages and disadvantages of this knowledge, and subsequent treatment options can be discussed with the patient prior to undergoing biopsy or repeat biopsy.[7,37,94] Patients can then use their own priorities regarding disease, treatment and functional changes after treatment to decide whether to proceed with a biopsy. Ultimately, this counseling process will create a better-informed patient if a prostate biopsy is performed and cancer is detected.

Disclosure

Dr. Hans Lilja holds patents for free PSA and hK2 assays.

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Grant sponsor: National Institute of Health; T32 training grant (T32CA082088). □

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High risk prostate cancer: evolving definition and approach to management

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Advances in the early detection and treatment of prostate cancer have progressed far beyond our ability to identify patients with high risk prostate cancer. In general, designation of high risk prostate cancer implies the presence of disease that is likely become progressive or lethal if not managed aggressively. Without proper risk stratification, there is a significant likelihood of both overtreatments of men with low risk disease and undertreatment for men with high risk cancer. The major issues surrounding the clinical management of high risk prostate cancer revolve around the definition of high risk disease as well as the benefits of multiple modality therapy. Over the years, numerous attempts have been made to develop risk assessment tools such as risk categories, scoring systems and nomograms, but a widely accepted definition is yet to be determined. The benefits of routine clinical utility of these risk assessment tools remain somewhat difficult to ascertain. We will discuss several multimodality therapeutic approaches, especially in combination with androgen ablation, to improve the outlook for men with high risk or locally advanced prostate cancer. This review focuses on the potential limitations of the risk assessment tools available to the clinicians and the approach to management of high risk prostate cancer.

Key Words: prostate cancer, high risk, prostatectomy, androgen ablation

Introduction

Prostate cancer remains the most commonly diagnosed solid malignancy and the second leading cause of cancer related deaths for men in the United States.[1] In 2008, an estimated 186,320 men will suffer from newly diagnosed prostate cancer and 28,660 men will die of the disease. Clinical tools are needed to educate the patients about their disease, determine the prognosis and plan a course of action in order to change the natural history of the cancer. The debate regarding the true benefits of early detection and the best treatment modality is ongoing. However, it's mostly geared towards the increasing number of men with low risk prostate cancer because these men are likely to do well with any single therapeutic modality, including active surveillance.[2] The need and benefits of active treatment for high risk prostate cancer are less controversial.

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The issues surrounding the clinical management of high risk prostate cancer revolve around the definition (which determines the incidence) of the high risk disease as well as the additional benefits (and potential harms) from multiple modality therapy.

Several clinical scenarios may be categorized as "high risk" disease. This may include traditionally defined locally advanced prostate cancer (cT3-4)[3,4] at initial diagnosis or recurrent prostate cancer following initial treatment or the newly diagnosed prostate cancer which is likely to become progressive or lethal if not managed aggressively i.e. high grade, large volume disease. In this article, we will focus on only the clinically localized high risk prostate cancer.

Defining high risk prostate cancer

Prospective identification of patients with high risk prostate cancer should allow us to select those men whose cancer can be cured with a single modality treatment from those whose cancer is likely to be locally advanced, possibly with regional or distant micro metastases, hence necessitating multi modal therapy. A universally accepted definition of high risk prostate cancer does not exist. Despite two decades of PSA based screening, early detection and curative treatment of prostate cancer, the clinical parameters that are used to identify high risk cancer have remained unchanged i.e. PSA, Gleason score and clinical stage. Although terms such as locally advanced, cT3-4, high Gleason score or poorly differentiated cancer imply high risk disease, no single factor can reliable predict the response to treatment and subsequent failure.[5-7] Clinical stage based on DRE is notorious for interobserver variability and underestimating extra prostatic disease.[8] Gleason grading is also subject to interobserver variability and has been associated with significant over and under grading, especially depending upon the biopsy technique.[5,9] The PSA level, in the contemporary era, may be a reflection of benign prostatic hyperplasia (BPH) rather than cancer and many poorly differentiated cancers are associated with normal PSA levels.[10]

Multivariable assessment tools

Due to the limitations associated with the individual parameters mentioned above, these have been used in various combinations to develop numerous risk assessment tools including nomograms, categories, neural networks and guidelines. Medline search for "prostate cancer risk assessment tools" yields a dizzying array of published reports which claim to reliably predict the presence of high risk disease. A review and critical evaluation of some of these tools is warranted in order to understand the usefulness and limitations associated with incorporating these into routine clinical practice.

The American Urological Association Guidelines for the management of clinically localized prostate cancer used the risk assessment classification which is based on the D'Amico classification.[11,12] In these classifications, individual risk factors (PSA or Gleason grade or clinical stage) alone may potentially assign individual patients to the high risk category. This approach may overestimate the risk e.g. cT2c alone *or* a single focus of Gleason score 8 alone would be sufficient to classify the patient into high risk category, with potential for overtreatment. In an update of the initial D'Amico classification, the high risk cohort was classified as those men with any combination of Gleason score ≥ 7, PSA > 10 ng/ml, and clinical stage ≥ T2b. While this classification was an improvement, it still allowed overestimation of risk due to arbitrarily assigning equal weights and categorical cutoffs of various risk factors. For example, a patient with PSA of 11 and Gleason score 7 may potentially be assigned to the same risk category as a patient with cT3 and multifocal Gleason score 9 prostate cancer. This degree of overlap in risk assessment is clinically suboptimal as it may potentially lead to overtreatment for the former or undertreatment for the latter patient scenario mentioned above.

In order to minimize the heterogeneity associated within the risk groups, several multivariable risk assessment tools have been developed where the weight assigned to each variable in the model is proportional to its likely contribution to the risk of cancer recurrence. The most publicized of the multivariable risk assessment tools are the Kattan nomograms which were developed to predict outcome in both pretreatment and post treatment settings.[13] These nomograms utilize complex statistical calculations to assign proportionally weighted points to each variable. The initial preoperative model was based only on the PSA, Gleason grade and clinical stage, an updated version utilizes systematic biopsy information to enhance the ability to predict recurrence.[14] The UCSF Cancer of the Prostate Risk Assessment (CAPRA) score, which was based on the CaPSURE registry, utilizes additional clinical variables to predict the risk of recurrence.[15] The CAPRA score is calculated by assigning up to three points for Gleason score, up to four points for categorized PSA level, and one point each for age > 50, clinical stage T3a, and > 33% positive of biopsy cores. The CAPRA score ranges from 0 to 10, and every two point increase in CAPRA score roughly doubles the risk of biochemical recurrence following surgery.

Critical evaluation

Despite using multivariable approach for risk stratification, there are significant potential limitations associated with the clinical use of these models. Experienced urologists may find some of the assumptions and calculations made by the risk assessment tools difficult to reconcile, especially in certain clinical scenarios. For example, in the Kattan "preoperative" nomogram, a PSA 9 ng/ml is assigned a higher score than Gleason score 9, and in the prebrachytherapy nomogram, Gleason score 8 carries the same weight as PSA 3 ng/ml. In the CAPRA model, it is not clear why the age of 51years should carry the same score as clinical stage T3. Additional questions arise when one compares the ability of various assessment tools to predict survival after treatment. Mitchell et al applied the Kattan nomogram and the D'Amico risk categories to the CaPSURE registry and noted a significant difference in the predicted biochemical recurrence free survival.[16] In addition, the 95% CI for D'Amico model and the ranges for Kattan nomogram were quite wide, thus further limiting the clinical utility. Yossepowitch et al compared eight published definitions of high risk disease by analyzing the outcome of 4708 patients treated with radical prostatectomy. Based on the definition that was applied to their study cohort, 3%-38% of the patients could be classified in the high risk category.[17] Of the high risk subgroup (depending upon the definition) 22%-63% had organ confined disease and 41%-74% remained free of PSA recurrence for 10 years after surgery.

There are several potential reasons for the suboptimal performance of these tools including the fact that these, by design, are based on retrospective data, and the relative weights assigned to each clinical variable are based on historic data. While external cohort validation is often performed, most of the risk assessment tools have not undergone prospective validation, and the outcomes prediction of the contemporary patients is based on the assumption that the current clinical variables have similar implications as those from 10-15 years ago. This assumption is quite invalid, given our understanding of the shift in stage, tumor volume and Gleason grade which has taken place since the advent of PSA screening. Furthermore, most risk assessment tools do not utilize quantitative pathological information which has been shown to be predictive of outcome e.g. number of biopsy samples with high grade cancer, percent core with cancer etc. Another caveat to remember is that most of the prediction models are based on biochemical recurrence which may precede clinical recurrence, or metastases, or death by decades.

While several risk assessment tools have been developed, the clinical utility of these remains unclear due to the fact that often the range of predicted outcome is significantly wide and various tools yield disparate results. Inability to accurately predict high risk (and low risk) disease has significant implications for our patients as it may lead to overtreatment of those with lower risk disease or undertreatment for those with high risk disease. There are also broader implications for designing clinical trials. The definition or method used to assign high risk category will ultimately determine patient accrual and potential results. While significant advances have been made in the early detection and treatment of prostate cancer, our ability to predict high risk disease remain somewhat limited. This is quite evident from the fact that all of the risk assessment models today mostly depend on the same three variables that were used 20 years ago i.e. clinical stage, PSA and Gleason grade. Clearly, there is an urgent need to develop prediction tools that will incorporate novel molecular markers to enhance our ability to identify patients that are at high risk of disease progression and allow optimization of the therapeutic approach.

Management of high risk prostate cancer

Regardless of the definition used to signify the presence of high risk disease, it implies that local therapy alone may not cure or sufficiently control the cancer. In contrast to the localized low risk cancer, the standard approach to high risk cancer over the last 2 decades has been to employ systemic and/or combination therapy instead of local therapy alone. In an analysis of the CaPSURE registry for men with high risk prostate cancer (as defined by the CAPRA score), Cooperberg et al noted a steady decrease in the use of radical prostatectomy, brachytherapy and cryotherapy as the CAPRA score increased.[18] They also noted a corresponding increase in the use of luteinizing hormone releasing hormone (LHRH) alone or in combination with radiation therapy as the CAPRA score increased. Men in the highest risk group (CAPRA 8-10) were four times more likely to receive androgen ablation alone or with radiation therapy than any localized therapy alone, especially surgery. Analysis of Surveillance Epidemiology and End Results (SEER) database revealed that between 1995 and 2001, the number of men with localized T3 prostate cancer undergoing radical prostatectomy decreased by nearly 50%, with a corresponding increase in the use of XRT and/or androgen ablation.[19] Furthermore, nearly one quarter of patients under age 70 with T3 disease were not given any local therapy at all. Thus, it's long

been the standard practice to treat men with high risk disease with either a combination of systemic and local therapy (mostly radiation) or systemic therapy alone.

The primary reason for diverting patients with high risk cancer to androgen ablation alone or in conjunction with radiation therapy likely stems from the assumption that these men have incurable cancer. The increasing use of androgen ablation and/or radiation therapy is not necessarily due to any proven or perceived superiority in cancer control when compared to radical prostatectomy but rather from the complexity of the surgical procedure and high rates of incontinence and impotence. With the tremendous stage shift over the last 15 years due to early detection and improvements in the surgical technique, radical prostatectomy, either alone or with adjuvant therapy, may be a viable option for younger men with high risk prostate cancer.

Multimodality therapy

A review of literature for combination therapies for prostate cancer is striking for the large number of studies utilizing androgen ablation, radiation therapy, brachytherapy, prostatectomy and chemotherapy in every combination possible. A detailed analysis of the outcomes following the use of neoadjuvant and adjuvant androgen ablation therapy was outlined in a recent Cochrane review.[20] External beam radiation therapy along with concurrent, neoadjuvant and adjuvant androgen, androgen ablation was the most widely utilized combination therapy for high risk and/or locally advanced prostate cancer. Other less commonly utilized approaches included radical prostatectomy plus neoadjuvant androgen ablation or adjuvant radiation or androgen ablation. Neoadjuvant androgen ablation has also been utilized with brachytherapy, and at times in a trimodal approach using concomitant external radiation. A detailed discussion of each combination and the optimal duration of systemic therapy are beyond the scope of this review.

Neoadjuvant and concurrent androgen ablation for 3-8 months and radiation therapy demonstrated a significant improvement in biochemical disease free survival but did not reveal any improvements in overall survival.[10,21,22] Androgen ablation for 8 months was associated with a significant improvement in disease specific survival compared to only 3 months.[23] Neoadjuvant androgen ablation for 3-6 months prior to radical prostatectomy was associated with a significant downstaging and decrease in positive surgical margin rate but did not improve disease specific or overall survival.[24-26]

The use of concurrent and adjuvant androgen ablation (for up 3 years) with radiation therapy was evaluated in several studies.[27-29] All of these studies reported a benefit from hormonal ablation and increased disease free or biochemical recurrence free survival. However, there has been only one study that demonstrated a prolonged overall survival with the use of long term hormonal ablation.[27] A few studies of radical prostatectomy followed by adjuvant androgen ablation have been reported. Messing et al noted an increased overall survival in favor of hormonal ablation after surgery (in a randomized trial) whereas Wirth et al reported no such benefit, although both studies reported improved disease free survival.[30,31] The Early Prostate Cancer trial using antiandrogen following radical prostatectomy demonstrated an improvement in disease free survival, especially in the patients with locally advanced disease.[29]

Role of radical prostatectomy

In the early PSA era, most high risk patients presented with very high PSA levels and bulky stage T3 disease. Since then, there has been a trend favoring the use of hormonal ablation and/or radiation therapy and avoidance of radical prostatectomy for high risk or locally advanced prostate cancer due to fear of poor pathological outcomes and surgical complications. Previous studies of radical prostatectomy for high risk, poorly differentiated or locally advanced prostate cancer were associated with a high risk of positive surgical margins or lymph node metastases and low disease free survival.[6] Some centers have been strong proponents of wide surgical excision of locally advanced disease, along with adjuvant radiation or hormonal ablation.[7] These authors noted that clinical overstaging occurred in 24% of men who were thought to harbor cT3 disease, but had pT2 disease in the prostatectomy specimen. These patients required no additional therapy. Nearly two thirds of patients in this study required androgen ablation or radiation therapy at some point, yielding cancer specific and overall survival rates similar to those reported for radiation therapy and androgen ablation studies. However, this was not a randomized study and direct comparison between surgery and radiation is not possible.

In the contemporary, screening detected prostate cancer, the designation of high risk prostate cancer is often based on a single variable e.g. high Gleason score or PSA.[32,33] This, along with a better understanding of pelvic anatomy and the improvements made in surgical technique, may suggest that radical prostatectomy may be more feasible and effective in achieving adequate cancer control in the contemporary patients assigned to the high risk category.

Recent studies demonstrate encouraging pathological and disease free survival rates for men undergoing radical prostatectomy alone for poorly differentiated cancers. We and others have found that the cancer was confined to within the prostate in 26%-31% of the patients with high risk cancer defined as Gleason score 8-10.[34,35] Negative surgical margins or uninvolved seminal vesicles have been noted in as many as 50%-70% of men.[35-38] More importantly, the 5-year recurrence free survival, without any additional therapy, for these men with poorly differentiated cancer, ranges from 46%-71%, and 45%-82% in the subgroup with organ confined disease. It's clearly evident that surgical excision of high risk cancer is feasible and is associated with sufficient disease control in a large number of men with high risk disease treated with surgery alone. These men are able to avoid or safely postpone systemic therapies and the associated side effects from additional therapies.

Summary

Advances made in the early detection and active treatment of prostate cancer have progressed far beyond our ability to identify patients with high risk, potentially lethal cancers. Without proper risk stratification, there is a significant likelihood of both overtreatments of men with low risk disease and undertreatment for men with high risk cancer. Despite numerous attempts, the proper definition of high risk cancer remains elusive, and will likely remain so unless we are able to incorporate more sophisticated molecular markers in addition to the currently available clinical variables. Several multimodality therapeutic approaches have been utilized, especially in combination with androgen ablation, to improve the outlook for men with high risk or locally advanced prostate cancer. In addition, contemporary studies have highlighted the feasibility and efficacy of radical prostatectomy in the high risk cohort. Unfortunately, the heterogeneity of definitions, variations in inclusion criteria and the duration of systemic therapy preclude any meaningful or direct comparisons amongst various therapeutic modalities. Thus, the criteria for designation of high risk prostate cancer and defining the optimum treatment for this cohort remain fertile grounds for future research. □

Disclosure

None declared.

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Androgen deprivation therapy for advanced prostate cancer: why does it fail and can its effects be prolonged?

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SINGER EA, GOLIJANIN DJ, MESSING EM. Androgen deprivation therapy for advanced prostate cancer: why does it fail and can its effects be prolonged? The Canadian Journal of Urology. 2008;15(6):4381-4387.

Androgen deprivation therapy (ADT) has been the cornerstone of treatment for advanced prostate cancer for over 65 years. Although there can be worrisome side effects, data will be presented that for men with metastatic prostate cancer, immediate ADT can reduce the likelihood of developing the rare but catastrophic sequellae of metastatic disease, although it is unlikely to prolong survival compared with waiting for symptoms before initiating ADT. Additionally, for patients with extremely high risk prostate cancer that is not distantly metastatic (e.g. have a life expectancy from prostate cancer less than 10 years with all other available treatments except immediate ADT) and, whose life expectancy from non-prostate cancer diseases is excellent during this period, early ADT both alone and in conjunction with definitive local treatment prolongs survival. Moreover, ADT seems to be most effective when the cancer volume is low. However, eventually most men receiving ADT experience disease progression.

The biological mechanisms explaining how prostate cancer escapes from ADT's control include:

1) Alterations in the androgen receptor (AR) and in the AR co-factors (which modify the responsiveness of the AR to androgens) allow molecules and medications which are not normally AR agonists to act as agonists.

2) The human prostate gland, and particularly prostate cancer, may be able to synthesize androgens from both cholesterol and adrenal androgens. This may occur because prostate cancer tissue has higher concentrations of androgens than does the serum in patients receiving ADT. Thus, castrated men may not be starving their prostate cancers of androgens.

3) The AR in prostatic stroma far more strongly stimulates both malignant and benign prostatic epithelial growth than the epithelial AR does. Indeed, the epithelial AR, particularly in advanced prostate cancer, may have anti-proliferative and anti-tumor progression properties. That is, the AR in the prostatic epithelial cells, particularly malignant ones, may act as a tumor suppressor. Thus, by inhibiting the epithelial AR, its protective effects may be abrogated.

The controversial nature of these concepts, as well as the clinical and experimental data which support and question them, will be presented. Additionally, strategies for addressing each of these escape mechanisms, which may be able to prolong responsiveness to ADT, will be discussed.

Key Words: androgen deprivation, prostate cancer, androgen receptor, androgen independent, hormone therapy

Introduction

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy in the United States with 186,320 new cases and 28,660 deaths expected in 2008, making this the second leading cause of cancer-related mortality for American men.[1] Nearly all of the men who die from advanced prostate cancer will experience disease progression while receiving androgen deprivation therapy (ADT). Although ADT has been the cornerstone of treating advanced and metastatic prostate cancer for more than 65 years,[2] the optimal patient population, form of therapy, and timing of treatment are still being actively investigated and defined.

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Methods of ADT

ADT can be achieved via surgical or medical means, Table 1. Orchiectomy is one of simplest, fastest, and cost effective methods of achieving the castrate state.[3] Body image concerns, as well as its irreversibility, have made this option less appealing than medical approaches.[4] Medical castration can be administered orally (estrogens, steroidal or nonsteroidal antiandrogens) or via injections (luteinizing hormone receptor hormone

TABLE 1. **Methods of androgen deprivation**

	Method	Route of administration	Advantages	Limitations	Effect on serum testosterone (T) and estrogen (E)
Surgical castration					
	Orchiectomy	Trans-scrotal surgery	Fast time to castrate levels of T Inexpensive Little morbidity, outpatient procedure	Psychological impact Irreversible Does not address adrenal androgens	↓T ↓E
Medical castration					
	Estrogens	Oral	Inexpensive Effectively reduce serum T Prevents loss of bone mineral density	Significant risk of thromboembolic event Gynecomastia Not considered first line treatment	↓T ↑E
	LHRH agonists	Injection	Effective without cardiovascular risk of DES Reversible	Requires repeated dosing Induces "surge" and "flare" phenomena	↓T ↓E
	LHRH antagonists	Injection	No "surge" or "flare"	Risk of anaphylaxis Withdrawn by manufacturer	↓T ↓E
	Nonsteriodal antiandrogens	Oral	Can prevent tumor "flare" when given with LHRH agonists Preserves libido/ potency in some men Can be used as monotherapy or in addition to other agents for combined androgen blockade	Dosing varies from daily 3 times/day dependingon formulation Preserves libido/potency Potential lethal side effects (uncertain mechanism) Cost	↑T ↑E
	Steroidal antiandrogens	Oral	Widely used in Canada and Europe	Not recommended for use as monotherapy due to increased cardiovascular risks Not available in United States	↓T ↑E

The side-effects associated with each method of ADT are due to (and can be predicted by) their impact on serum T and E. Reproduced with permission from Expert Opinion on Pharmacotherapy. E. A. Singer, D. J. Golijanin, H. Miyamoto, E. M. Messing. Androgen deprivation therapy for prostate cancer. 2008;9(2):211-228.[60]

TABLE 2. **Androgen deprivation regimens**

Method	Indications	Advantages	Limitations
Combined androgen blockade	Locally advanced and metastatic disease	Small survival advantage over LHRH or surgical castration alone	Increased frequency of side effects, added cost
Sequential androgen blockade	Uncertain	May improve sexual function in some men	Investigational
Triple androgen blockade	Uncertain	Most complete androgen deprivation May target stromal AR	Investigational
Antiandrogen monotherapy	Locally advanced	More favorable side effect profile over castrative therapies	Not indicated for localized disease
Antiandrogen withdrawal syndrome	Increasing PSA while on NSAA	Can cause a temporary decrease in PSA	Response usually only lasts weeks to months
Intermittent androgen deprivation	Locally advanced and metastatic disease	May prolong time to progression in the face of ADT Improved quality of life during off periods Decreased cost of treatment	Investigational

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[LHRH] agonists or antagonists); depot formulations permit patients to receive treatment only several times per year.[5] Medical castration may also be stopped, allowing for intermittent ADT. Medical or surgical castration may be combined with antiandrogens in order to block adrenal androgens (combined androgen blockade), or with agents that block the conversion of testosterone to dihydrotestosterone (sequential androgen blockade), or with both of these classes of agents (triple androgen blockade), Table 2.

Timing of ADT

"When to initiate ADT?" is one of the most challenging questions facing all physicians who treat prostate cancer. Traditionally, ADT was reserved for men with symptomatic advanced or metastatic prostate cancer.[6,7] Published in 1997, the MRC study indicated that earlier initiation of ADT, particularly for men without metastases, could prolong survival in patients who had advanced local regional disease.[8,9] Subsequently, ADT as a primary treatment for localized disease became increasingly popular.[10,11] However, mounting evidence has shown that primary ADT (PADT) is not usually beneficial for men with cancer confined to the prostate.[12-14] Lu-Yao and colleagues recently reported that in their population based cohort study of more than 19,000 men over 66 years of age (median 77 years) with clinically localized prostate cancer, PADT was not associated with a cancer specific survival advantage compared to watchful waiting but did expose all the subjects to the side effects and financial costs associated with androgen deprivation.[15] The likely reason for this is that most of these patients had a limited life expectancy and localized prostate cancer rarely grows rapidly enough to be lethal over a 5 to 10 year time horizon, well longer than the overall life expectancy of these men. It is for these reasons that the American Urological Association did not include PADT among its recommended therapies for clinically localized prostate cancer in 2007.[16] In a man with locally advanced prostate cancer, however, the issue is less settled and two large, prospective, randomized, phase III trials (MRC and EORTC) have reported overall survival advantages for early PADT.[8,17]

Early ADT is given in the adjuvant setting soon after definitive therapy for small volume, local regional disease. Late, or deferred, ADT is not implemented until symptomatic or radiographic metastases are present, which is essentially the classic time for initiating this therapy.

In the surgical arena, early ADT has been shown to improve overall, cancer specific, recurrence free, and biochemical recurrence free survivals in men with node positive disease after radical retropubic prostatectomy/pelvic lymphadenectomy (EST 3886).[18,19] Men receiving early hormonal therapy also experienced fewer complications such as pain, urinary retention, and pathologic fractures.[6,8,20] When using PSA thresholds in men with biochemical recurrence after radical retropubic prostatectomy as a trigger for initiating ADT, early treatment improved progression free survival and prostate cancer specific survival compared to deferred ADT.[21-23] Radiation oncologists have also seen improved overall survival by combining external beam radiation with ADT, with the greatest benefit seen in high risk patients with high Gleason grade tumors.[17,24-27]

Based on the current literature, early ADT prolongs survival in men with high risk, localized/regional prostate cancer. Two important considerations that may explain these findings are the burden of disease and life expectancy at the start of hormonal therapy. For example, the subjects in EST 3886 trial had such minimal disease after surgery that 80% of the men in each arm had undetectable PSA levels and their life expectancy was greater than 10 years in order to be surgical candidates to begin with.[18,19] It is uncertain if the same results would be seen in men with a greater amount of residual cancer or worse comorbidities. However, using early ADT in men with low and intermediate risk disease has not shown the same benefits (although there may be a role for neoadjuvant ADT plus external beam radiotherapy in intermediate risk patients[28]).

Therefore, the men most likely to benefit from early ADT are those at high risk to die from their prostate cancer within 10-12 years, but not from their competing medical comorbidities, as death due to non-cancer causes should be relatively low during this period.[19,29] Even if an appropriate candidate is treated with early ADT and receives its expected benefits, a subset will progress despite castrate levels of serum androgens. Once this occurs, median survival is only 18 months.[30] New insights into the molecular biology of the androgen receptor and prostatic homeostasis provide opportunities for new strategies to prolong the beneficial effects of ADT.

Androgens and the androgen receptor

Circulating androgens bind to the androgen receptor (AR), which has been traditionally thought to function as a ligand inducible transcription factor, resulting in prostatic cellular growth.[31,32] In addition to androgens, other sex steroids (estrogens, progestin) and adrenal steroids (glucocorticoids, mineralocorticoids), reninoids, vitamin D, thyroid hormones, and fatty acids have the potential ability to activate the AR, but rarely do so.[32-35] Coregulator molecules modulate AR transcription events by affecting ligand selectivity and DNA binding capacity.[36-39] Despite ADT's initial efficacy in treating nearly all men with prostate cancer, when patients develop androgen independent or hormone refractory disease, which is hallmarked by rising serum PSA levels and tumor growth despite medical or surgical castration, alterations in the AR are often thought to be at work.[40] It is important to note that "androgen independence" does not necessarily mean independence from the AR. The exact mechanism that allows prostate cancer to escape the control of hormonal therapy is unclear, but several models offer intriguing potential explanations.

Transformation into androgen independent disease

One hypothesis is that the AR becomes "superactive," meaning that tumor cells possess more androgen binding sites than their androgen sensitive cohorts and that the AR may be transcriptionally active despite a paucity of testosterone and dihydrotestosterone.[41-44] Additionally, since prostate tumor cells have higher levels of androgens than those in the serum or surrounding benign tissue, the laboratory definition of "castrate" may not be clinically adequate. Evidence also exists indicating that recurrent prostate cancer, in the presence of ADT, can synthesize androgens from cholesterol or adrenal androgen precursors.[45] Agents that block androgen synthesis, such as abiraterone, may play an increasingly important role in the treatment of androgen independent prostate cancer.

A second mechanism involves the liberation of AR activation from rigorously restricted ligand binding. Molecules other than androgens, including cytokines, interleukins, and protein kinases, have been shown to activate the AR, allowing protein translation and cellular proliferation in the absence of traditional ligands.[46-48] These growth factors have been found in increased concentrations in the primary prostate tumor and metastatic sites of men with androgen independent disease,[49-51] strengthening their potential

link as a nonandrogen stimulus for tumor progression via the acetylation or phosphorylation of the AR.[52,53]

Third, as seen in some patients treated with combined androgen blockade, antiandrogens may paradoxically stimulate tumor growth while antiandrogen withdrawal will bring about a temporary decrease in disease burden and PSA. Point mutations in the AR have been identified that allow it to recognize antiandrogens as agonists.[54,55] Additionally, alterations in AR coregulator function can facilitate the AR's use of antiandrogens and nonandrogenic steroid hormones as agonists.[56-58]

A new view of the androgen receptor

The role of the AR, as a promoter of both benign and malignant cellular growth, is more complex than initially believed. In an elegant series of experiments, Niu and colleagues have found that the AR acts as both a tumor suppressor and proliferator in prostate cancer.[59] By creating a mouse prostate cancer model that lacks the AR in its prostatic epithelium only, gain and loss of function studies were able to be performed in epithelial stromal cell cultures and with coimplantation experiments in order to determine the impact of the AR on prostate cancer progression and invasion. In the prostatic epithelium the AR can function as a tumor suppressor preventing invasion and metastases, while in the stroma it can function as a promoter of cancer invasion and progression. The loss of epithelial AR expression, therefore, may be a poor prognostic indicator (and unintended consequence of conventional ADT which lowers androgen levels throughout the body, suppressing AR activity in both the epithelium and stroma) as tumor cell invasion was seen in both *in vitro* and in *vivo studies*. Such dual functioning of the AR is not unique to the prostate, as the AR in the skin of the scalp induces hair loss while the AR in the skin of the face induces hair growth.

Conclusions and new directions

ADT will continue to be a vital weapon in the urologic oncologist's armamentarium against prostate cancer. However, all current hormonal treatments focus on ligand binding and not on the function of the AR itself. As elucidated by Niu and colleagues, the AR is a more complex entity than previously recognized. New treatments for prostate cancer, both hormone sensitive and androgen independent, will need to selectively target the AR itself in specific tissues (targeting the prostatic stromal AR while sparing the epithelial AR). Prostate cancer specialists of all disciplines will need to renew their commitment to prospective, multicenter, collaborative trials in order to realize the potential benefits of new androgen/AR targeted approaches for men with advanced prostate cancer.

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Management of refractory overactive bladder in adults

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Urologists experience frustration in the treatment of refractory overactive bladder for a multitude of reasons. Clinical failure experienced in managing these patients can lead to long office interactions and feelings of inadequacy for both patient and provider. With newer, technically straightforward interventions, this population can be approached with confidence. Appropriately timed diagnostics are essential in identifying neoplastic, neurogenic, and infectious causes for refractory overactive bladder. When approached in an efficient, stepwise fashion, outcomes can be highly satisfactory for both the patient and the provider.

Key Words: overactive bladder, anticholinergic, refractory, treatment failure

Introduction

Overactive bladder (OAB) syndrome, also known as urge syndrome or urgency frequency syndrome, is a symptom complex defined by the International Continence Society as "urgency, with or without incontinence, usually with frequency and nocturia.'[1] The most important management consideration is the fact that the syndrome is a symptom complex - the etiology varies widely. The most common cause remains "idiopathic". Benign causes include increasing age, pelvic floor spasm, atrophic urethritis, and irritants such as tobacco abuse, caffeine, or diet sodas. Causes warranting further work-up need to be considered at every step in management. These include neurologic disease, diabetes, bladder stones, infection, bladder or adjacent organ cancer, fistula, as well as obstruction by the prostate, pelvic organ prolapse, or prior surgery.

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Initial management of OAB after a benign history, physical exam, post void residual, and urinalysis (negative for blood or infection), includes behavioral and medical therapy. When these initial interventions fail, it is advisable to seek a more complex or ominous cause. If further pathology is not identified, effective third line tools are available to help even the most severe of patients. The goal of this discussion is to provide a brief guide for initial management of overactive bladder followed by an in depth discussion of refractory overactive bladder.

Bladder function

Complex voiding dysfunction can be understood in the context of the bladder's simple functions. The role of the bladder is to store and to empty urine.

Storage: the bladder should store urine at low pressures allowing for easy antegrade efflux from the kidneys down the ureters into the bladder. Storage should occur without leakage or bothersome bladder sensations.

Emptying: When it is a convenient time to urinate, bladder emptying should be initiated voluntarily by the cerebral cortex, through the pontine micturition

center, the bulbospinal tracts, and the sacral reflex arc. The detrusor should contract, the pelvic floor should relax, and the bladder should empty fully without reflux to the kidneys.

Bladder dysfunction

Interruption of the neural, vascular, anatomic, and muscular mileu of the bladder can lead to irritating frequency, urgency and urge incontinence, diminished quality of life, loss of work role, infection, and in severely compromised systems, renal failure or death. In addition, some causes of OAB have their own distinct ramifications. This manuscript aims for pragmatism in identifying the dangerous bladder (e.g. high pressure storage) and serious etiologies of OAB (e.g. multiple sclerosis). It should be emphasized that although psychological overlay can exist in this population, it is extremely risky to recommend psychological consultation as the only intervention.

History

The interview is often painstaking due to the subjectiveness of urinary symptoms, poor recall for a habitual activity, and the extraneous unwanted detail elicited during the discussion (e.g. what time the patient wakes up). Intake forms, standardized measures, and voiding diaries can save time and add accuracy in the initial and follow-up visits. Active questioning should characterize prior surgeries, bowel function, history of pelvic organ prolapse, presence of neurological disease, and adherence to routine health screening, e.g. colonoscopy (a current exam decreases suspicion of fistula). The voiding diary can identify excess fluid or caffeine intake, or nocturnal polyuria (> 35% of daily urine production occurring at night[2]).

Physical exam

In addition to the standard physical exam, a few details add minutes to the initial visit but can save hours in patient care. Ambulatory status, body mass index, and hygiene are obvious at first glance. More subtle findings include shuffling gait (suggestive of Parkinson's), fear of the physical exam (pelvic floor spasm), atrophy of calf muscles (tethered cord), and pedal edema (nocturnal polyuria). Genitourinary examination must include evaluation for prolapse in women, Figure 1, most specifically an obstructing cystocele. The standing position should be considered at the end of the exam to further characterize apical descent, as vault or uterine prolapse significantly

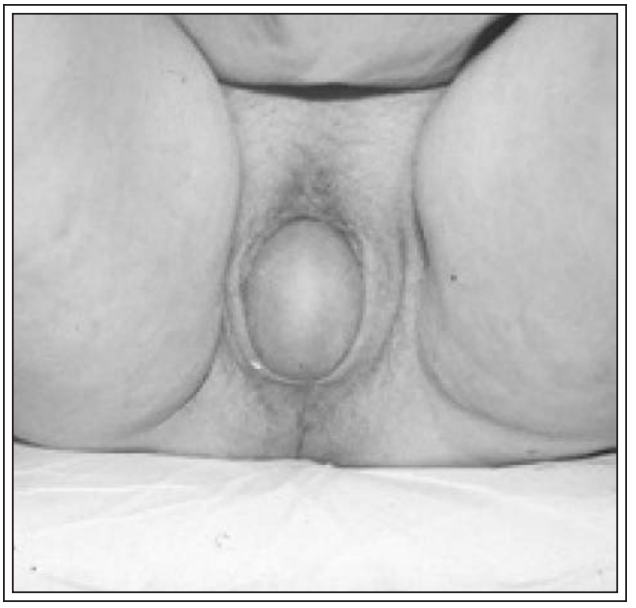

Figure 1. Pelvic organ prolapse, unspecified compartment.

impact surgical management options for cystocele. The apex can be characterized by asking the patient to maximally strain while holding the fingers gently on the vault or cervix. Examination of the levator muscles in both men and women is straightforward. The muscles can be appreciated posterolaterally during digital vaginal or rectal exam. The puborectalis, for example, passes posterior to the rectum close to the perineal body. Manual pressure is perceived as uncomfortable and can reproduce symptoms experienced clinically. Digital rectal examination will also reveal the presence of hypotonic sphincter tone, impacted hard stool, or, in women, a lax perineal body.

Neurological exam is performed to a level of detail commensurate with index of suspicion. Sensation of the perineum derives from S3-5, the anterior scrotum and labia from thoraco-lumbar roots, and the posterior scrotum and labia from sacral roots. The bulbocavernosus reflex tests the integrity of the sacral 2-4 central and peripheral pathways. The cremesteric tests L1-L2. The abdominal reflex tests T6-L2 and is only present if there is an upper motor neuron lesion. The anal wink interrogates S2-5.

Chart review

Prior creatinine, PSA, urine samples, upper urinary tract imaging, cystoscopy, urodynamics, and interventions should be noted or archived at the first visit. Many patients with refractory OAB present with a string of

prior physicians due to non-resolution of symptoms. Imaging and operative notes are documented at multiple sites and the patient's recall for prior medications may be incomplete. Some of this information may save time or improve patient care in later visits. Efforts to find the information should match projected relevance (e.g. a medication previously worked but the patient could not afford it).

Coexisting diagnoses

Incontinence and infection

Incontinence and urinary tract infection (UTI) directly impact the workup. Incontinence can be characterized as urge urinary incontinence (defined as an involuntary leakage accompanied by or immediately preceded by urgency), stress urinary incontinence (involuntary leakage on effort or exertion), and mixed urinary incontinence (a combination of the latter two).[1] In addition, overflow incontinence denotes overflow of urine from a poorly emptying bladder when the bladder reaches maximum capacity, and unawares incontinence refers to leakage perceived only once the skin or clothing is wet. Incontinence can often help point toward a particular diagnosis in OAB. For example, in detrusor overactivity with hypocontractility, the bladder fails to store (overactivity) and fails to empty (hypocontractility). Leakage is both urge and overflow. Diagnosis is by urodynamic testing and treatment involves a combination of timed voiding, anticholinergic therapy, intermittent catheterization, or neuromodulation. Adult tethered cord often presents with incontinence.[3]

Infection should be immediately characterized as culture-positive or culture-negative. All symptomatic episodes should be investigated with a catheterized urine culture in women and midstream or catheterized culture in men. Patients with true culture-positive recurrent urinary tract infection and those in whom data is not reconstructable require a work-up. Upper urinary tract imaging (renal mass protocol in those with hematuria), cystoscopy, and assessment of post void residual should be performed to identify stones, tumors, renal duplication, trabeculation, incomplete emptying, fistulae, foreign bodies from prior surgery, or other pathology. Cystogram can identify more subtle fistulae and voiding cystourethrogram can demonstrate vesicoureteral reflux when further suspicion warrants. Urethral diverticulum is an often-missed cause of recurrent UTI in women. Although the classic triad includes post void dribbling, dysuria, and dyspareunia,[4] it presents most commonly as recurrent urinary tract infection, stress incontinence, pain, and incomplete emptying.[5] Magnetic resonance imaging has superior sensitivity for urethral diverticulum[6] and helps guide surgical planning. In neurological patients who self catheterize, review of catheterization technique should be performed. Catheters should be replaced once a week to prevent surface irregularity, cleaned in a clean-rinsing detergent, and left to dry in open air rather than a plastic bag. Confirmation of emptying on self catheterization can be performed as a quick step at the end of fluoroscopic videourodynamics or in conjunction with office ultrasound. Lastly, patients who self catheterize are often colonized with bacteria. It is only in the presence of symptoms that this colonization is deemed to be an infection.

When symptoms of urinary tract infection are not corroborated by cultures, (it is often the case there are one or two truly positive cultures and the rest are negative), immediate diagnostics are not always necessary. All symptomatic episodes should be cultured. Expressed prostatic secretions should be considered in men and vaginal swab for ureaplasma and mycoplasma in women. Exam of the levator muscles is essential in these patients. Symptoms of UTI can derive from pelvic floor muscle spasm due to cross – sensitization (explained to the patient as "cross talk") along the S 2,3,4 nerve pathways.[7] Relaxation of the musculature via biofeedback or pelvic floor physical therapy can lead to resolution of the episodic symptoms as discussed below. If "UTI" symptoms persist, a workup similar to culture – positive recurrent UTI should be initiated while continuing to gather culture data during episodes. Carcinoma in situ, bladder stones, and urethral diverticula are just a few potential findings.

Bladder outlet obstruction

In both men and women, bladder outlet obstruction can lead to irritative voiding symptoms. Treatment of the bladder with anticholinergics often fails in the setting of obstruction. Conversely, treatment of the bladder outlet (via alpha blockers or surgery) does not always resolve the frequency and urgency resulting from a compromised bladder, especially when the obstruction has been of long duration, Figure 2. Chronic injury in the obstructed bladder is characterized by ischemic damage to nerves, synapses and smooth muscle cells within the bladder wall. This occurs due to initial poor blood flow followed by the generation of reactive oxygen and nitrogen species during reperfusion.[8] These reactive species have been shown to damage plasma and subcellular membranes in animal models. In the human model ischemia has been observed in decompensated bladders. Decreased compliance correlates with decreased blood flow in

human cystometric studies[9] as well as in the rabbit and pig bladder outlet obstruction models.[10,11]

Patients who suffer from significant irritative symptoms in the setting of bladder outlet obstruction should undergo urodynamic testing prior to surgical intervention. In order to avoid dissatisfaction with surgery, patients with decompensated bladder function should be counseled to anticipate continued voiding dysfunction after relief of the obstruction. Reassessment 3-6 months postoperatively allows for maximal detrusor recovery and initiation of further treatment directed at the bladder itself. In 40 women undergoing urethrolysis for iatrogenic bladder outlet obstruction, 56% required either anticholinergics or neuromodulation for refractory overactive bladder.[12] It is obvious why appropriate preoperative counseling is important.

Patients with OAB who failed anticholinergic therapy prior to treatment of the obstruction may now experience success. Randomized trials have shown the superior efficacy of combination therapy using alpha blockage and anticholinergic therapy in men with storage and voiding symptoms.[13]

One often-missed diagnosis in the refractory OAB patient is primary bladder neck obstruction (PBNO).[14]

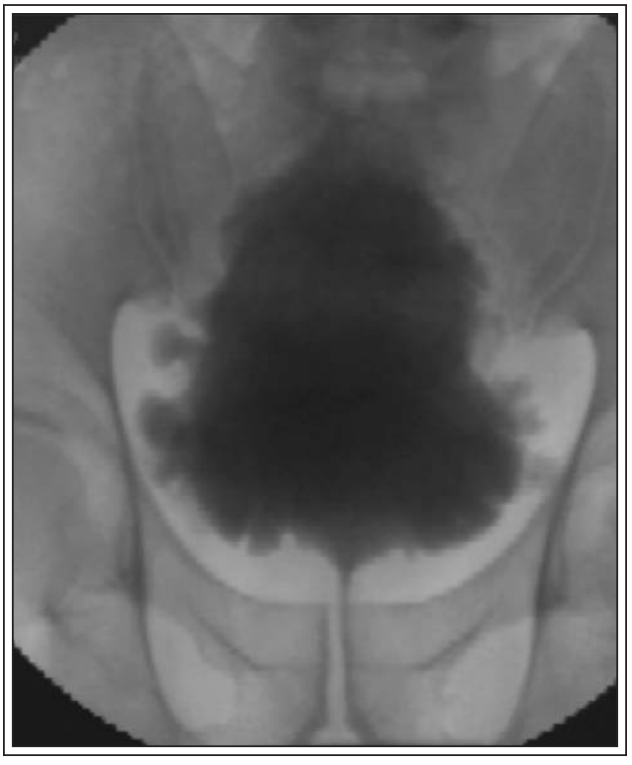

Figure 2. Bladder trabeculation in longstanding obstruction.

This can be present in both men and women, has an early age of onset, and can present with a combination of emptying symptoms (weak stream, hesitancy, intermittency, incomplete emptying) or storage symptoms (frequency, urgency, urge incontinence, or nocturia). Pain (46% of men and 15% of women) and elevated post void residual are common.[14] The bladder neck fails to open during voiding due to either persistent mesenchyme,[15] increased sympathetic tone,[16] or functional extension of the striated sphincter to the bladder neck.[17] Data is scant and skewed as it is comprised of retrospective reviews of referral populations. In the referral centers, PNBO is present in 33%-54% of men under 55 with LUTS.[18-20] In one large urodynamic series of women with LUTS, PNBO was present in 4.6%.[14] Cystoscopic evaluation should always include specific comment on the bladder neck in patients with voiding dysfunction. Trabeculation is not an uncommon finding. However, diagnosis is truly made by fluoroscopic urodynamic testing. The exact criteria for obstruction have not been standardized, but diagnosis is suggested by a relatively high pressure, low flow void with isolated bladder neck obstruction on fluoroscopic urodynamics.[14] Diagnosis is more difficult in patients with "shy bladder" as a history and during testing, who can have PNBO. There is no literature to guide diagnosis without a successful void on pressure flow study. Since the risks of treatment are permanent, the diagnosis should be made carefully. Treatment of PNBO is based on retrospective data. An initial attempt can be undertaken with alpha blockade, which is successful in a small proportion of patients.[21] Bilateral bladder neck incision led to an 87% improvement in symptoms but a 27% retrograde ejaculation rate in 18 men studied retrospectively.[21] Unilateral bladder neck incision in another study of 31 men allowed for preservation of antegrade ejaculation.[22] Bladder neck incision is also successful in women with PNBO. De novo stress urinary incontinence should be counseled as a definite risk.[23]

Pelvic organ prolapse

Pelvic organ prolapse can lead to bladder outlet obstruction by kinking the urethra. Evaluation of urinary and defecatory symptoms preoperatively is essential to creating appropriate expectations postoperatively. Urodynamic testing with and without vaginal packing can characterize improvement in urgency or emptying ability with reduction of the cystocele and can identify occult stress urinary incontinence. A pessary trial can prognosticate response to surgery in real time, and can serve as a long term intervention in the elderly. Kinking of a cystocele over a prior sling should be specifically sought in

patients with relevant surgical history as the prolapse may be more subtle. Obstruction should be suspected and sought on urodynamics in prolapse.

Pelvic floor spasm

Many patients with pelvic floor muscle spasm have seen multiple physicians and have been refractory to other interventions. The office interaction is long and sometimes difficult due to anxiety over prior negative experiences. The importance of identifying the hypertonic levator ani complex on physical exam at the initial visit cannot be emphasized enough, as it can save time, effort, and failed interventions. Pelvic floor spasm can be satisfactorily treated with biofeedback, electrical stimulation and pelvic floor physical therapy and ultimately self directed exercises. In addition, treatment of pelvic floor dysfunction identified preoperatively can be helpful in preventing perioperative crises. For example, pelvic floor spasm can lead to retention and excessive pain perioperatively. Sacral nerve stimulation or intramuscular botox injections can be employed for patients with refractory levator spasm when rehabilitative therapies fail.

Nocturia

Nocturnal polyuria (actual increased production of urine at night) can be easily diagnosed based on the history and the voiding diary. This is defined as > 35% of the 24 hour volume being produced during the sleep cycle.[2] Causes of nocturnal polyuria include: increased evening fluid intake, nocturnal diuretic use, excessive resorption (congestive heart failure, venous stasis peripheral edema, hyperalbuminemia, nephritic syndrome, increased salt intake), osmotic diuresis (diabetes mellitus, sleep apnea), abnormal renal regulation (diabetes insipidus, reversal of circadian arginine vasopressin). Treatment for nocturnal polyuria usually includes treatment of the underlying condition in collaboration with the primary care physician and lifestyle changes such as evening fluid modification.

Diabetes

Voiding dysfunction is present in 5%-59% of patients with diabetes.[24] Classic diabetic cystopathy is characterized as an end stage bladder due to years of sensory (and motor) neuropathy. The bladder suffers from impaired sensation, contractility, and emptying. It should be suspected in infrequent voiders (< 5x per 24h). High post void residual heralds the diagnosis and urodynamic testing can confirm it. The classic picture may not be the most common finding seen in diabetic bladders. One group of referral practices reviewed 182 consecutive patients with diabetes and persistent voiding symptoms. Fifty-five percent had involuntary bladder contractions, 23% impaired detrusor contractility, 10% had detrusor areflexia, and 11% "indeterminate findings".[24] Another group found that diabetics have a 50% increased risk of urge incontinence. Microvascular complications affect the innervation of the sphincter and detrusor, the detrusor function, and the overall vascular supply. Damage is related to the duration and severity of diabetes, the glycemic control, and the presence of peripheral neuropathy.[25] Serum glucose should be checked in patients with refractory voiding dysfunction, especially if the urinalysis is suggestive.

Neurogenic bladder

Neurogenic bladder is often already known by the time the patient presents for evaluation. However, approximately 10% of all patients with multiple sclerosis (MS) present with lower urinary tract symptoms as the only complaint. 505-90% of patients with MS complain of voiding symptoms at some time during their neurological illness. This includes frequency/urgency (31%-85%), incontinence (37%-72%), and obstruction/ retention (2% to 52%).[26] Other occult neurological diseases must be kept in mind. Metastatic disease to the spine, spinal stenosis or spinal disc disease, and Parkinson's disease can all present with refractory overactive bladder.

One very challenging diagnosis is Myesthenia Gravis. Not only can myogenic bladder dysfunction be present, but this disorder is treated with procholinergics. Anticholinergics and botulinum toxin are contraindicated due to the effect on the neuromuscular junction. There is no data on sacral neuromodulation in these patients.

The treatment of neurogenic bladder is outside the scope of this paper but low pressure storage and complete emptying (facilitated by intermittent catheterization or diversion if necessary) are the mainstays of therapy. Periodic renal ultrasound, creatinine, and urodynamic testing are performed every 6 months to 2 years depending on stability. Surveillance cystoscopy seeking squamous cell carcinoma of the bladder is controversial, as annual cystoscopy often misses the rapidly progressive cancer.

Treatment of refractory OAB

Lifestyle and behavioral interventions

These interventions should be offered as first line therapy, but often patients arrive at an initial visit already on anticholinergics. Behavioral interventions can augment virtually any other form of therapy.

Reduction or cessation of caffeine, tobacco, and artificial sweeteners should be encouraged. Fluid intake should be quantified with a voiding diary and reduced. Often simply informing patients that "eight glasses of water per day" has never been shown to be healthy can help reduce fluids and symptoms. Weight loss has been shown to reduce incontinence.[27] Treatment of constipation can improve OAB in both idiopathic and neurogenic patients, most likely due to decreased afferent input along S 2,3,4.

Pelvic floor muscle training, biofeedback and electrical stimulation

These interventions can be presented to the patient as teaching the "on-off" switch for the detrusor muscle. Many urologists are not familiar with these therapies, and the literature is sparse regarding the application to overactive bladder. It is best conceptualized by reviewing neural control of the lower urinary tract. Voluntary contraction of the external urethral sphincter via S 2,3,4 somatics (the pudendal nerve) leads to inhibition of the parasympathetics to the detrusor. A 50%-80% reduction in urge and/or stress incontinence episodes and 15%-50% dry rates have been demonstrated in randomized controlled trials.[28,29] Combination therapy with anticholinergic medication shows improvement beyond either intervention alone.[30] In pelvic floor muscle spasm, the purpose of relaxing the levators is to decrease afferent input along the S 2,3,4 pathways and consequent "cross talk" with the bladder (innervated by S 2,3,4 as well[7]). Biofeedback and electrical stimulation are effective in about 70% of women with pelvic floor spasm.[31] In men with chronic nonbacterial prostatitis and chronic pelvic pain syndrome, pelvic floor biofeedback reeducation led to a highly significant decrease in the Chronic Prostatitis Symptom Index (NIH-CPSI) (23.6 to 11.4, $p < 0.0001$).[32] Pelvic floor physical therapy led to moderate to marked improvement in 70% of female patients with interstitial cystitis in one study.[33] These therapies are indispensable in managing a voiding dysfunction referral practice but unfortunately the literature is not yet strong enough to instill confidence in the general urologist. As in any case of refractory overactive bladder, treatment failure should lead to consideration of diagnostic testing.

Anticholinergic failure

When the pathology discussed above has been ruled out, addressed or optimized, anticholinergic medications form the mainstay of therapy. They are not always an option, as in patients with gastric retention, uncontrolled narrow-angle glaucoma, and severe renal or hepatic failure. At the time of presentation, many patients have already tried medications within the class with suboptimal outcome or prohibitive side effects. It is important to determine the dose and name of the prior medication. Increasing a dose or simply changing to another option may improve the response. Whereas some comparison trials exist among anticholinergics,[34] most comparisons are to the immediate release forms of oxybutynin and tolterodine. The change of anticholinergic choice is often empiric. Some basic differences among the medications can help. For example, those who had prohibitive dry mouth on immediate release oxybutynin may be able to tolerate transdermal delivery. Those with hepatic impairment may be permitted to take trospium chloride, which has primarily renal clearance. Lastly, the effect of imipramine hydrochloride may be synergistic with anticholinergics[35] and despite its narrow safety profile is often employed to improve storage pressures in neurogenic bladder. Patients who have previously failed anticholinergic medications may have success after other interventions, e.g. transurethral resection of the prostate.

With the advent of other treatment options for OAB, the central nervous system side effects of anticholinergic medications gain more importance. Klausner and Steers[36] recently reviewed the central nervous system (CNS) side effects, most importantly indicating that data is not available in the most at risk elderly populations. Additionally, CNS side effects are often self-reported and potentially inaccurate. In a 3 week randomized study of healthy subjects greater than age 50, 15 mg or more daily of oxybutynin ER led to impaired moderate and delayed recall, equivalent to 10 years of normal aging. The effect was not seen in darifenacin. The affected subjects were not aware of their deficit.[37] A separate prospective cohort study found mild cognitive impairment in 80% of people taking antimuscarinics for overactive bladder versus 35% of age-matched controls.[38] Another longitudinal cohort study abstract presented at the American Academy of Neurology this year demonstrated that initiation of medications with anticholinergic activity was associated with a more rapid decline in the cognitive performance of normal individuals.[39] Information regarding cognition receives a great deal of attention in the lay press and studies are lacking to answer these concerns.

Sacral neuromodulation

Sacral neuromodulation (SNS, Interstim) is approved by the Food and Drug Administration (FDA) for urgency/frequency, urge incontinence, and idiopathic

urinary retention. Well over 25,000 patients have had the procedure since approval.[40]

SNS is thought to "reset" somato-visceral interactions within the sacral spinal cord by modulating sensory processing and micturition reflex pathways in the spinal cord.[40-42] Inhibition of guarding reflexes can allow for correction of idiopathic urinary retention. Inhibition of afferent interneuronal transmission as well as direct inhibition of bladder preganglionic nerves are theorized to impact detrusor overactivity.[40,42]

Technique: Peripheral nerve evaluation (PNE) is test stimulation with a temporary lead, placed percutaneously. Lead migration can occur and it is difficult to know whether failure is due to technical factors or the patient's potential for responding. PNE has largely been replaced by the two stage technique which involves the initial percutaneous minimally invasive tined lead[43] and, if successful, the subsequent implantation of the generator. The cross-hair technique for fluoroscopic localization is extremely simple. In the AP view, the inferior margin of the sacroiliac joint forms a horizontal line and the midline processes the vertical.[44] It is also helpful to mark the diagonal lines along the medial side of the foramen, and to insert the spinal needle into the skin along this line 2 cm above the intersection with the horizontal line, Figure 3. Lateral imaging is useful, the goal being to place lead 0 and 1 anterior to the sacral cortex and leads 2 and 3 within. A > 50% improvement on a carefully collected voiding diary is considered a successful trial.

Most surgeons perform unilateral testing. Bilateral SNS was investigated in a randomized crossover clinical trial of unilateral versus bilateral temporary lead testing of SNS in 33 patients.[45] Eight patients had lead migration. Of the remaining 12 patients with urge incontinence and 13 patients with idiopathic urinary retention, there was no statistically significant difference in success. Other non-randomized studies have shown benefit to bilateral stimulation. More research is necessary.

Sacral nerve stimulation, in its initial multicenter randomized controlled trial, is reported as curing urge incontinence in 47% of refractory patients with benefit in an additional 29%.[46] Fifty-six percent of patients with refractory urgency–frequency returned to normal voiding (4-7 times per day) or were at least 50% improved.[47] Sixty-nine percent of patients with idiopathic retention were able to discontinue CIC.[48] Many of these data should be interpreted for patients as including only those who did well with the percutaneous test trial and who went on to implantation of the permanent lead and generator. Therefore the true denominator of non-responders is much greater. Five year data is now published for the initial FDA approval trials. Only those who passed the test trial were enrolled. For urge incontinence, mean number of leaks per day decreased from 9.6 to 3.9. For those with urgency frequency, voids per day decreased from 19.3 to 14.8. For those with retention, number of catheterizations per day decreased from 5.3 to 1.9.[49] Unfortunately the dry rates and the catheter free rates were not reported. Surgical revision rates are reported as high, but have been decreasing over time with better technology to avoid lead migration, errant stimulation, and pain. Battery life is 7-10 years for the Interstim I generator and 4-5 years for the newer, smaller Interstim II generator with more programming options.

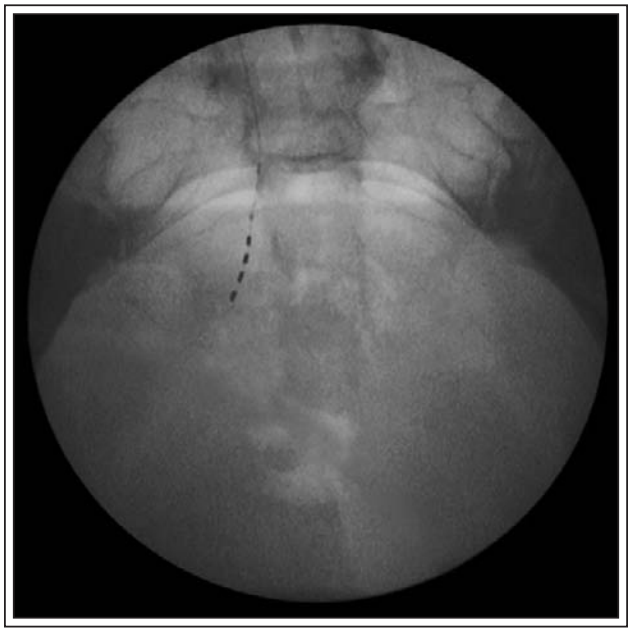

Figure 3. Cross-hair technique and outline of sacral foramen for localization of third sacral neural foramen.

SNS is not approved for neurogenic bladder, interstitial cystitis, pelvic pain, bowel dysfunction, or orgasmic dysfunction, although research continues for these indications.[40] In nine patients with neurogenic urge incontinence, five patients were completely dry at 43.6 months follow-up, with the average number of leaks per day decreasing from 7.3 to 0.3, frequency from 16.1 to 8 voids per day, and mean volume improving from 115 ml to 249 ml.[50] However, other larger studies contradict these results. A prospective randomized trial of 42 children with neurogenic dysfunction noted no significant improvement.[51] Seventeen of 25 patients with interstitial cystitis who went on to implantation had positive results in a prospective non randomized study. Frequency decreased from 17.1 to 8.7 and

nocturia from 4.5 to 1.1. Voided volume increased from 111 cc to 264 cc. Perhaps most surprisingly, pain decreased from 5.8 to 1.6 on a scale of 1-10, and significant decreases were seen in the IC Symptom and Problem Index scores. All results were significant to $p < 0.01$. Six of ten patients with isolated pelvic pain had improvement at 19 months.[52] A recent review details more studies regarding pelvic pain.[53] A review of heterogeneous literature on faecal incontinence found total continence in 41%-75% and improvement in 75%-100% of patients, with only limited data available for constipation.[54] A more rigorous review from 2008 identifies the need for better quality studies.[55] Small studies have investigated SNS in female sexual dysfunction with report of benefit.[56,57]

Neuromodulation can be performed in the form of percutaneous tibial neurostimulation (PTNS). Treatment involves percutaneous access to the posterior tibial nerve and once a week treatments for 12 weeks. Literature is limited, but generally a 20%-35% reduction in frequency, nocturia and UUI can be seen at 12 weeks while still undergoing treatment. Long term data and randomized placebo-controlled trials are not available. Pudendal nerve stimulation is another technology on the horizon holding promise. A summary of this literature is provided by Toby Chai.[58]

Chemodenervation of the bladder using botulinum toxin

Botulinum toxin (BTX) prevents acetylcholine release at the neuromuscular junction by inhibiting exocytic neurotransmitter vesicle fusion[59] or formation[60] in peripheral motor neurons. It is reversible, easy to inject, and can be employed for idiopathic or neurogenic detrusor overactivity. BTX – Type A is most commonly used in the United States (Botox, Allergan, Inc. Irvine, California) and will be referred to as BoNT-A. Botox Type B is available in the United States and two other formulations of type A are marketed in Europe. BoNT-A has been used for less than 5 years but level-one evidence is in support of its efficacy.

The largest prospective studies in idiopathic OAB each had 100 patients and were not randomized. In Rapp's series, there was resolution of urgency in 82% and of incontinence in 86%. Frequency was reduced by half, nocturia by 2/3, and urodynamic capacity increased from 241 cc to 381 cc after 100 U.[61] In Schmid's series, 100 units of BoNT-A were injected at 30 detrusor sites in 100 patients. Urgency had resolved completely at 4 weeks in 72% and incontinence in 74%. Capacity increased by 56%. Benefits lasted 6 months. Poor response was noted in 8%.[62] Two randomized studies of idiopathic detrusor overactivity have shown benefit. Sahai et al randomized 16 patients to 200 U of BoNT-A and 18 to placebo. Impressive differences were observed in frequency, urgency and urge incontinence. Capacity increased by 145 cc at 3 weeks and 96 cc at 12 weeks. Benefit persisted at 24 weeks. Temporary but prolonged intermittent catheterization was necessary in 37.5% of patients.[63] In a study by the Pelvic Floor Disorders Network, 28 patients were randomized to 200 U BoNT-A in 15-20 injections and 15 patients were randomized to placebo. Sixty percent showed improvement based on the Patient Global Impression of Improvement scale. Seventy-two percent of the BoNT-A patients experienced a 75% or more decrease in the number of incontinence episodes. Perhaps most importantly, 43% experienced a PVR of 200 cc or greater.[64] Poor responders to 200 U in a small non-randomized prospective series were found to have high maximum detrusor pressures (> 110 cm H_20) preoperatively.[65] The potential for clean intermittent catheterization should be carefully counseled and taught preoperatively. Dosing of 100 U versus 200 U can be based on the patient's weighted concerns.

In neurogenic detrusor overactivity the best resource is an extensive review by Karsteny et al.[66] Two randomized controlled trials are included. In one study of placebo versus BoNT-A 200 U and 300 U, incontinence was reduced by 50% and capacity increased by 25%.[67] In a study of 75 patients randomized to 300 U BoNT-A versus resiniferatoxin, incontinence in the BoNT-A group decreased by 77%, versus 57% in the resiniferatoxin group. Seventy-three percent became completely continent.[68] Duration of effect in the Karsenty review is at least 12 to 39 weeks, with no outer limit characterized as of yet. In none of the studies reviewed by Karsenty were serious adverse events reported. UTI, hematuria, urinary retention, and injection site pain were the only complications.

Results can be impressive in individual patients, Figure 4a and 4b. Repeat injection of Botox is necessitated every 4-9 months or longer and insurance coverage can be a major issue depending on locality. Long term results are not available, but industry-sponsored randomized controlled trials are underway with an aim to FDA approval.

Open or laparoscopic surgery

Bladder augmentation, autoaugmentation, and urinary diversion are options of last resort, and rarely necessary for idiopathic OAB given the newer options described above. These are primarily employed as the gold standard in patients with neurogenic detrusor overactivity who have failed medical management,

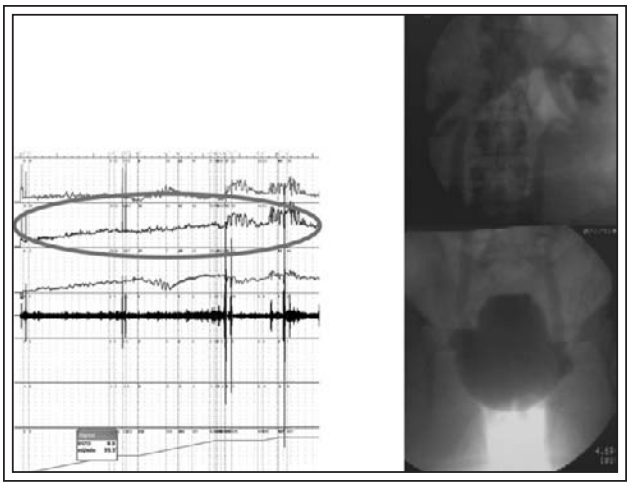

Figure 4a. Poor compliance, elevated creatinine, and reflux failing anticholinergics prior to botox.

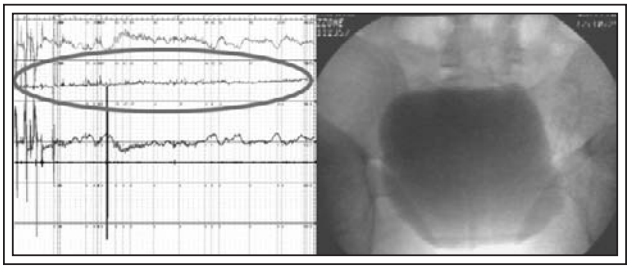

Figure 4b. Same patient as in 4a after Botox. Markedly improved compliance. Rectal contractions contribute artifact.

Figure 5. Randomized controlled trials of outcomes and complications do not exist, but benefits have been reported across the board. In one series of 59 neurogenic patients, improvements were seen in increased bladder capacity (220 cc to 531 cc), decreased end-filling pressures (48.9 cm to 15.8 H_2O), and better continence (67% dry and 29% with only mild incontinence). There was good patient satisfaction with 58/59 patients willing to repeat surgery and 59/59 >= mostly satisfied.[69] Detubularized ileum is considered superior to sigmoid.[70] In Greenwell's extensive review of the literature, neuropathic patients experienced a 92% success rate, defined as dry with stable renal function.[71] Another study reporting patient reported outcomes found 96% of patients with an improved quality of life.[72]

Complications include metabolic acidosis (alkalosis with stomach), mucus and stones, rupture (a fixed rate that does not decrease with time), cancer (11% with ureterosigmoidostomy, unknown for other segments), and incontinence. In Herschorn's study, complications occurred in 24 (40.6%): small bowel obstruction in 1, sling erosion in 1, a fluid collection in 1, deep venous thrombosis in 1, and late bladder perforation in 1, as well as need for reintervention in 21 (median time 10 years, e.g. laparotomy for rupture in 1, cystolitholopaxy in 6, stomal revision in 4, percutaneous nephrostolithotomy in 2, ureteral reimplant in 2, and further intervention for stress incontinence in 12). Greenwell reviewed complications in 1135 patients in 18 series including his own of 267. Early complications included small bowel obstruction in 3%-6%, wound infection in 5%-6%, ventriculo-peritoneal shunt infection in 0%-20%, and prolonged ileus in 5%. Late complications included failure to correct the lower urinary tract in 5%-42% largely due to the idiopathic patients in the series. Perforation occurred in 0%-9%.[70]

There is not a great deal of literature on augmentation in idiopathic detrusor overactivity. The literature that exists is heterogeneous. One report with 83% idiopathic patients reported that 78% of the group were "happy". Eleven of thirty used intermittent catheterization to empty. [70] In Greewell's review, symptomatic success was reported in only 53%-58% of patients with idiopathic detrusor instability.[70]

Autoaugmentation for idiopathic DO has had as much as a 70% reported success with some authors.[73] However, others have not reported the same results and the procedure is not used commonly.

Indwelling suprapubic tube is sometimes the option of compromise in elderly or debilitated patients. Surgical intervention is typically not reversible and should be approached with caution in non-neurogenic OAB.

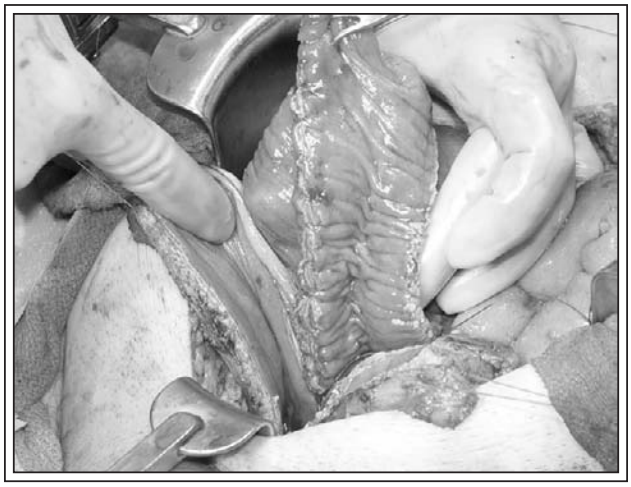

Figure 5. Augmentation Ileocystoplasty.

Conclusion

The patient with refractory overactive bladder can be managed in a stepwise fashion. Careful consideration of each step above can lead to an ordered, safe, and successful approach in this difficult patient population. Due in part to availability of the newer interventions, outcomes can be highly satisfactory for patient and provider alike.

Disclosure

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