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The Evolving Role of Chemotherapy in Treatment of Prostate Cancer

David Shepherd, MD and Margaret F. Fay, PhD, RN, CCRC

According to the National Cancer Institute Surveillance Epidemiology and End Results (SEER) report, nearly 1.5 million men are currently living with prostate cancer. A review of data compiled by the American Cancer Society, the National Cancer Institute (NCI), and the National Center for Health Statistics (NCHS) confirm the fact that prostate cancer now accounts for 33% of new cases of cancer in men and 10% of all cancer deaths. Its high incidence and low mortality make prostate cancer the second most prevalent form of cancer in the United States. (Table A, page 3).

Over the past decade substantial progress has been made in understanding and managing the disease, yet much remains unknown as to the exact cause of prostate cancer. Recently, researchers found that up to nine percent of newly diagnosed cases of prostate cancer in men under the age of 55 were considered to be inherited. Most hereditary cases appear to be transmitted as autosomal dominant genes found on chromosome 1 or chromosome X. The best clue to a possible familial connection is the patient presenting with a family history of (1) at least three first-degree relatives with the disease; (2) two of these who were diagnosed with prostate cancer before age 55; or (3) three consecutive generations of men with prostate cancer.

As researchers explore causal relationships in prostate cancer, investigators have begun to explore the multi-complex pathways and networks associated with the disease in an effort to develop clinically relevant therapies that will prevent or delay disease progression in patients who fail primary and secondary hormonal therapy.

With the completion of the human genome project and recent advances in genomic and proteomic approaches to biology, physicians are investigating a number of new receptor targets. Aside from the classic androgen receptor target, researchers have identified a number of distinctly different pathways which appear to affect metastatic potential. Among these are the endothelin receptor, the vitamin D receptor, cyclic CMP and the VEGF receptor pathway, all of which are the subject of intense scrutiny with several therapeutic regimens now being studied. A number of new clinical trials are investigating antibody therapy directed against specific epitopes such as PSMA, MUC-1 and PSCA. While early research appears to show great promise, results must still be validated in clinical trials.

Because metastatic prostate cancer is the leading cause of cancer deaths, a great deal of effort is being directed at discovering how metastases occur. To produce metastasis, a tumor cell must complete a series of sequential steps. The sequential steps include detachment, invasion, and survival in circulation, reattachment, extravasation, and proliferation, creation of neovasculature and evasion of host defense mechanisms. The successful metastatic cell must be able to complete each step in sequence; any interruption in the process prevents the cell from developing into a metastasis. As a growing body of literature supports the theory that progression from a benign to a malignant tumor is associated with acquisition of a set of genetic and epigenetic alterations that provide the phenotypic characteristics necessary to drive malignancy, researchers are seeking ways of preventing cell transformation by blocking these sequential steps.

Most current therapy is delivered by the urologist until the prostate cancer cells become hormone resistant. Initial treatment of prostate cancer is determined by the characteristics of the tumor at the time of diagnosis. Early-stage disease is treated with curative intent that is, using either radical prostatectomy or radiation therapy. However, as the disease progresses, hormonal therapy (the gold standard because prostate tumor cells depend upon the presence of testosterone to proliferate and survive) is often prescribed.

The goal is to achieve androgen ablation, either by surgical castration or medical castration with lutenizing hormone releasing hormone agonists. Additionally, flutamide, bicalutamide and nilutamide (antiandrogen compounds that are capable of inhibiting the binding of androgen to cell receptors) are employed to

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EDITORIAL

In this issue, we review new horizons in Urology. Topics such as sexual dysfunction among women, urine markers as screening tools for bladder cancer and therapeutic alternatives for hormonal refractory prostate cancer serve as testimonials to the evolving and progressing nature of our specialty.

Medicine in general and Urology in particular, are witnessing dramatic changes in the way we diagnose and manage these problems. In times past our specialty placed emphasis on surgical intervention, the urology office was simply an entrance gate to the hospital and/or the operating room.

Similarly, clinical research was almost exclusively conducted within the University or Academic setting rather than in community based Urological practices where most patients are seen.

Today the face of medicine has changed (the result of increasing societal demand for improved access to care and payer pressure to deliver less invasive and less costly treatments), so has the field of urology.

Moving beyond the office and outpatient surgery setting, today's urologist has incorporated clinical research into the practice. Seeking newer, more effective treatment options for cancer patients, urologists are leading the way in improving cancer care for bladder and prostate cancer patients. By participating in research studies, urologists are destined to see improved quality care as a result of trial participation.

While there are no guarantees that a clinical trial will produce positive results for any one person, those who do participate can be assured they will receive quality care while making a major contribution to future patients by aiding in the development of improved treatments.

Carefully monitored trials, which are now considered standard practice, have resulted in major advances in cancer care, sexual function disorders, and overactive bladder disorders.

Physicians participating in clinical trials are leading the way in improving urology care for everyone. The topics discussed in this Newsletter and the academic and clinical endeavors of the physicians who are participating in this publication are the proof of their commitment to developing newer and more effective treatments for all urology patients.

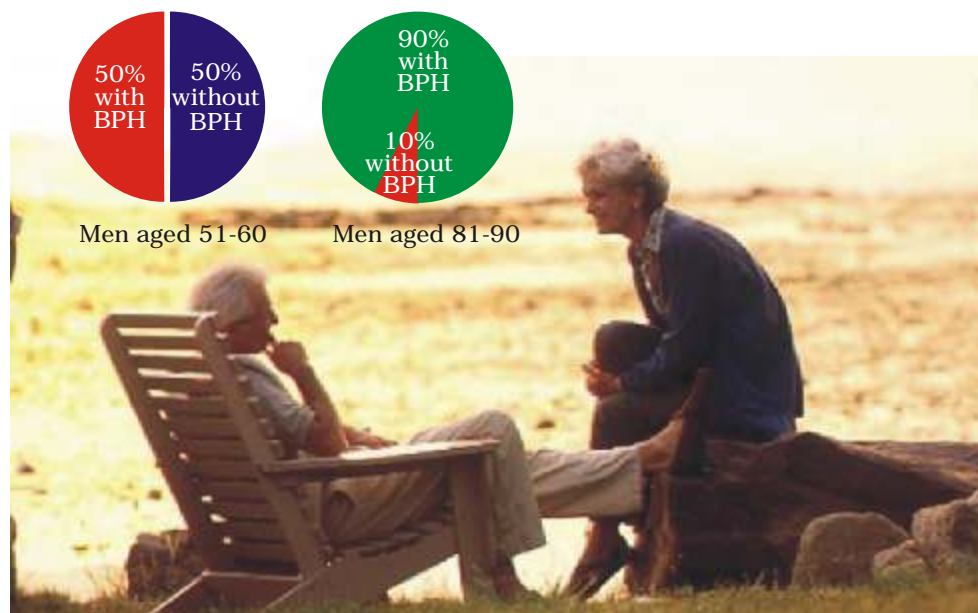
Yitzhak Berger, MD, Editor

Men's Health: BPH and Sexual Dysfunction

Benign prostatic hyperplasia (BPH) is a progressive enlargement of the male prostate gland. Frequently it is associated with lower urinary tract symptoms (LUTS).

Obstructive signs and symptoms related to increased prostate size may include a decrease in urine stream, hesitancy in urination, abdominal straining, dribbling, incomplete voiding, and intermittency. Often men develop symptoms of frequency, urgency, urge incontinence, painful urination and nocturia.

Symptoms Increase with Age



Medina JJ, Parra RO, Moore RG. Benign prostatic hyperplasia (the aging prostate). *Med Clin North Am.* 1999; 83:1213-1229.
Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. *J Urol.* 1984; 132:474-479.

Research studies have shown a correlation between severity of LUTS and increased sexual dysfunction. The relationship between poor sexual function and LUTS is attributed to the discomfort, anxiety, and sleep disturbance that accompanies the distress related to these symptoms. Some researchers believe that sexual dysfunction may be caused by many of the same physiologic factors that cause BPH.

To achieve satisfactory penile erection there must be relaxation of smooth muscle tone in the penis. The increased sympathetic activity that accompanies LUTS contributes to both Ejaculatory Dysfunction and Erectile Dysfunction (ED). In addition, psychological factors can play a role in sexual dysfunction. Studies confirm anxiety and depression can severely impact sexual desire and performance.

Data presented at the 2002 AUA in Orlando, Florida, suggest that men with benign and malignant prostate disease experience lower sexual desire and pleasure than men in the general population. In a multi-national study of 13,000 men aged 50-80 (throughout the USA and Europe) researchers found that while sexual activity decreased with age, the severity of ED and EJD were strongly associated with severity of LUTS independent of key comorbidities.

Recent studies have shown that 5 α -reductase inhibitors prevent the conversion of testosterone to the hormone dihydrotestosterone inducing prostate gland involution. Over time, these drugs alleviate symptoms by reducing the size of the hyperplastic prostate.

To learn more about managing these symptoms, talk to your doctor or visit www.prostatedisease.org.

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Rosen R, O'Leary M, Altwein J, et al. Ejaculatory disorders are frequent and bothersome in ageing males with LUTS: a worldwide survey (MSAM-7). *Eur Urol.* 2003; 2(suppl):94. Abstract 368.
Levine LA. Diagnosis and treatment of erectile dysfunction. *Am J Med.* 2000; 109 (suppl 9A): 3S-12S.

Evolving Role of Chemotherapy in the Management of Prostate Cancer

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achieve total androgen blockage.

When relapse occurs following local therapy, the inherent heterogeneity of the tumor demands a therapy that can impact both the androgen-dependent and independent components if survival differences are to be achieved. The goal is to find combination therapies that will decrease tumor proliferation while maintaining castrate levels of testosterone.

While most patients initially respond to androgen blockage, after 18-24 months many patients tend to develop progressive androgen-resistant disease for which there is currently no effective treatment.

Over 80% of these patients will develop metastases to the bone, the most common site to which prostate cancer metastasizes. Once a patient develops metastases, significant morbidity follows including debilitating pain, pathologic fractures and spinal cord compression.

Recurrences of cancer may be local or disseminated, and based on the particular scenario, additional surgery, radiation, hormonal therapy, adjuvant chemotherapy may be indicated to prevent disease progression, to control pain, prevent pathologic fractures or spinal cord compression.

Among chemotherapeutic agents that have shown promise are anthracyclines (doxorubicin and mitoxantrone); alkylating agents (cyclophosphamide); platinum compounds (cisplatin and carboplatin); taxanes (Docetaxel and paclitaxel); suramin, an antiparasitic agent with antineoplastic activity; estramustine an alkylating agent and estrogen analog; vinca alkaloids (vinblastine and vinorelbine); and

topoisomerase-II inhibitors (etoposide).

These chemotherapeutic agents have been useful for palliation of bone pain in patients with metastatic prostate cancer, in delaying disease progression, lowering PSA levels, shrinking metastases and prolonging survival.

In recent years clinical trials have shown that chemotherapy may play a significant role in the management of Hormone Refractory Prostate Cancer (HRPC). In 1996, mitoxantrone became the first chemotherapy drug to be approved by the U.S. Food and Drug Administration (FDA) for treatment of prostate cancer.

In June 1998, Docetaxel (Taxotere) was approved by the FDA for treatment of patients with advanced or metastatic breast cancer after failure of any prior chemotherapy. More recently, single-agent and combination therapy with adjuvant drugs have shown evidence of therapeutic activity in bladder and prostate cancers.

Hormone Refractory Prostate Cancer has traditionally been regarded as a chemo-refractory disease. However several phase I and II trials have demonstrated that Taxotere has significant anti-tumor activity in HRPC. Administered on a weekly basis, the treatment has been well tolerated by most patients with few side effects.

Taxotere/estramustine combinations have also shown activity in patients with HRPC and the side-effect profile of this regimen was largely found to be tolerable.

Alone or in combination with estramustine or mitoxantrone, Taxotere is a tolerable neoadjuvant therapy in patients at high risk for disease recurrence following definitive therapy

for localized or locally advanced prostate cancer.

Preliminary results from new studies suggest that the use of Taxotere based chemotherapy in hormone sensitive patients produces PSA response in patients with rising PSA following prostatectomy or radiotherapy. Further clinical evaluation is needed to determine the short and long term effects of the early use of Taxotere based regimens in patients with prostate cancer.

Calcitriol is another promising adjuvant agent for Docetaxel/Taxotere. At supraphysiologic concentrations, this natural ligand for the vitamin D receptor (VDR) or its analogs exerts significant antiproliferative activity on prostate cancer cell lines and in animal models of prostate cancer. Calcitriol enhances the antitumor activity of several cytotoxic agents.

While the mechanism by which Calcitriol inhibits cancer cell proliferation is unknown, researchers have shown that it down regulates Bcl-2, causes dephosphorylation of the retinoblastoma protein, inhibits angiogenesis and induces apoptosis.

Today the argument for evaluating chemotherapy in both early stage and advanced prostate cancer is based on several factors. These include the heterogeneity of the disease, the inability of hormonal therapy to completely eradicate all prostate cancer cell clones, and the knowledge that patients with clinically relevant biochemical failure have no effective therapeutic alternatives.

Recently a new and potentially important activity of the taxanes has been evaluated in prostate cancer patients. The ability of taxanes to induce apoptotic death in susceptible cells by effecting changes in Bcl-2, a protein that is part of the apoptosis mechanism in many cancer cells, has demonstrated that high levels of this protein inhibit apoptosis by heterodimerizing with the BAX protein, an apoptosis initiator. In its activated state, BAX initiates release of cytochrome c from mitochondrial cells resulting in activation of the capase cascade. Phosphorylation of Bcl 2 decreases its antipoptotic effects and leads to cell death. Taxanes are known to stimulate the phosphorylation of Bcl-2. For that reason, renewed interest in combination therapy including Docetaxel and Calcitriol, Docetaxel and estramustine because these combinations decrease Bcl-2 levels through antisense gene transfection, resulting in cell sensitivity to drug induced apoptosis.

There is growing optimism in the field of uro-oncology with improvements in the prevention, early detection and treatment of prostate cancer. As our understanding of the biology of prostate carcinoma increases, new

Table A: 2003 Estimated New Cancer Cases US Ten Leading Cancer Types and Deaths in Men

Estimated New Cases = 675,300 Estimated Deaths = 285,900

Prostate (220,900)	33%	Lung and Bronchus	31%
Lung and Bronchus	14%	Prostate (28,900)	10%
Colon and Rectum	11%	Colon and Rectum	10%
Urinary Bladder	6%	Pancreas	5%
Melanoma of the Skin	4%	Non-Hodgkin Lymphoma	4%
Non-Hodgkin Lymphoma	4%	Leukemia	4%
Kidney	3%	Esophagus	4%
Oral Cavity	3%	Liver	3%
Leukemia	3%	Urinary Bladder	3%
Pancreas	2%	Kidney	3%
All Other Sites	17%	All Other Sites	22%

Note: Percentages may not total 100 percent due to rounding. Includes in situ carcinoma of urinary bladder.

Source: Estimates of new cases are based on incidence rates from 1979 to 1999. National Cancer Institute Surveillance, Epidemiology and End Results program. Estimates of deaths are based on data from US Mortality Public Use Data Tapes, 1979 to 2000. National Center for American Cancer Society Surveillance Research, 2003.

Bladder Cancer and Urine Markers

Kevin M. Tomera, MD and Miles Standish

Bladder cancer is a common malignant disease that is characterized by frequent recurrences. To effectively plan patient treatments at the time of diagnosis the physician must first determine the stage of disease .

While cystoscopy remains the “gold standard” for identifying bladder cancer, it also has its drawbacks; it is expensive, invasive and for many people it is uncomfortable. A urine test is far easier and more acceptable to patients.

Among urine tests, urine cytology is the most commonly used test for bladder cancer. Microscopically it identifies the presence of abnormal, malignant cells, which are shed into the urine in patients with bladder cancer. While the method has high specificity (i.e., few false positives), it has other drawbacks.

Specifically, it has low sensitivity (i.e., many false negatives, especially in superficial and low-grade tumors). The results are not immediately available and results are interpreter-dependent (subjective). While quite accurate in detecting high-grade bladder cancer and carcinoma in situ, its ability to detect low-grade cancer is limited.

To assist the urologist in early diagnosis and treatment, considerable effort has been directed at developing an array of immunohistological or molecular markers to aide in characterizing tumor stage and clinically relevant subclasses of bladder cancer.

The new laboratory based tests utilize hierarchical cluster analysis surrounding three major stages of cancer, Ta, T1, T2-4, with the Ta tumors further classified into subgroups. The classifier methods provide physicians with additional predictive information on disease progression in Ta tumors compared to conventional staging which may help define tumor's biological properties and assist in understanding new potential targets for evolving treatment therapies.

These newer tests are more accurate in detecting low-grade bladder cancer, so they are useful in monitoring for recurrence, may significantly improve and simplify workup, diagnosis and follow-up, and hopefully allow for detection of disease at an earlier stage, thus improving the chances of curative therapy.

SENSITIVITY AND SPECIFICITY

In order to understand what these tests are about it's helpful to have an understanding of

the terms Sensitivity and Specificity.

A diagnostic test is one that predicts the presence of a disease. An ideal diagnostic test would always give the right answer, with a positive result in everyone with the disease and a negative result in everyone else. It would be quick, safe, simple, painless, reliable, and inexpensive, as well.

Since no current diagnostic test is ideal, there is a need to evaluate each of them for their clinical usefulness. In practice for any diagnostic test there is a trade-off between sensitivity and specificity. In cancer diagnosis, the need for this trade-off is rooted in the fact that cancer arises from human tissues. It is not completely “foreign” like a virus or bacterium that invades the body.

Sensitivity is the ability of a test to correctly identify a positive specimen; it tells the physician how good the test is at identifying the disease. Statistically, it's the proportion of patients with the disease that have a positive result, that is, the number of “true positives” out of all the situations where the disease is present.

Specificity is the ability of a test to correctly identify a negative specimen, and it tells the physician how good the test is at identifying when the disease is absent. The statistical way of looking at this is the proportion of patients without the disease who have a negative test, that is, the number of “true negatives” out of all the situations where the disease is not present.

Both sensitivity and specificity are very important indicators, because both can be influenced by various factors, such as the characteristics of the population tested or the value used as a cut-off for the test (above which the test is positive and below which it is negative).

A test with low sensitivity and many false

negative results will fail to detect the tumor in a large portion of the patients being tested, while a test with low specificity with many false positive results may lead to unnecessary invasive or expensive procedures and cause undue alarm for the patient.

When a diagnostic test is run, there are four possible results:

True positive when the test is positive and the patient does have the disease

False positive when the test is positive but the patient does not have the disease

True negative when the test is negative and the patient does not have the disease

False negative when the test is negative but the patient does have the disease

BTA STAT TEST, BTA TRAK ASSAY

BTA tests detect a human complement factor H-related protein (hCFHrp) which has been shown to be produced by several human bladder cancer cell lines, and by human bladder cancers, but not by other epithelial cell lines (Kinders, *Clin Cancer Res*4:2511, 1998).

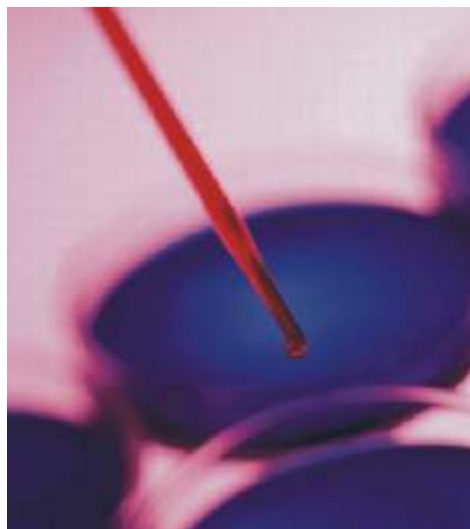
It is thought that factor H acts to protect the tumor cell from the body's natural immune system (Corey, *J Biol Chem* 275:12917, 2000). Both the BTA Stat and the BTA TRAK tests can provide valuable but slightly different information for the bladder cancer patient and the doctor.

The BTA Stat Test is a qualitative (positive or negative) test provided in a disposable format similar to a home pregnancy test. It uses five drops of urine and can be read in five minutes. The appearance of a colored line in the *patient window*, and a colored line in a “*check window*” indicates the test is working properly.

This test has been cleared in the US for use by clinical laboratories. The physician or his staff are able to perform the test right in the office. In some cases the bladder cancer patient may be asked to check his/her urine at home (with a physician's prescription). Besides being highly sensitive, fast and easy to use, with a unique availability to be run by the physician and/or the patient, this test is significantly less costly than other diagnostic tests or cytology.

The BTA TRAK Assay is a quantitative immunoassay test that provides a numerical result of the hCFHrp level. The urine must be sent to a reference laboratory where the test is performed by professional technologists. An advantage of the BTA TRAK test is the ability to rise or fall of hCFHrp.

For additional information about the BTA stat test, the web site is <http://www.btastat.com>.



Bladder Cancer and Urine Markers continued

NMP22

NMP22's core technology is based on the level of nuclear matrix proteins (NMPs) that are detected in body fluids.

These levels are correlated to the presence of early-stage cancerous abnormalities which have been validated in multiple clinical studies. The technology was discovered at the Massachusetts Institute of Technology and it is licensed to Matritech.



The NMP22® Test Kit which uses immunological markers, was found to be twice as sensitive as routine urine cytology. The test appears to be better than the BTA test, which until recently had been the only other FDA approved urine marker test other than cytology.

The NMP22® test showed a sensitivity of approximately 70% versus 50% for the BTA and/or 30% to 40% for routine cytology. However, 25% to 30% of low-grade tumors are not detected by this assay.¹

Daniel B. Rukstalis, MD, Chief of Urology at Medical College of Pennsylvania, one of the many researchers involved in early clinical trials of NMP22® found that a low NMP22® value ten days after surgery will give a near-90 percent certainty that there will not be malignancy found at three-month follow-up visit.

Conversely, an elevated NMP22® value ten days after surgery gives a high degree of certainty that a recurrence will be found at the three-month follow-up cystoscopy. With this information, treatment strategies can better be defined.

The NMP22® Test Kit is a quantitative, laboratory-based test that was approved by the FDA in 1996 for use in monitoring patients after surgery for bladder cancer to identify occult or rapidly recurring bladder cancer. It was also approved in 2000 as an aid in diagnosing patients at risk for bladder cancer.

A point of service version of the NMP22®, the BladderChek™ was recently approved (July 2002) for monitoring patients with a history of bladder cancer. It is currently under review by the FDA for use in the initial diagnosis of bladder cancer.

These NMP22® products are the *only* urine tests approved for *Diagnosis*. All the others are cleared for monitoring indications only. NMP22® is one of only two tumor markers ever approved by the FDA for diagnosis – the other being PSA.

In patients at risk for the initial diagnosis of bladder cancer, Alaska Clinical Research Center compared cystoscopy, cytology, and a new CLIA-waived office test – NMP22® BladderChek™.

Methods. 248 patients with risk factors were evaluated for urothelial cancer. A voided urine specimen was obtained for each patient prior to cystoscopy. Four drops of urine were applied to the NMP22® BladderChek™ and the result was recorded after 30 minutes.

The remainder of the urine was sent to a central laboratory for cytological analysis. Results of both adjunctive tests were analyzed for agreement with cystoscopy and final pathological diagnosis. (See table 1 for results).

LURN Physicians in Bladder Cancer Trial

All seven LURN practices served as clinical trial centers. The total number of patients enrolled for the NMP22® BladderChek™ clinical trial for monitoring bladder cancer recurrence was 668, and for initial diagnosis was 1,331. Of these, 328 monitoring patients,

and 997 diagnosis patients were enrolled by LURN sites.

FISH

Vysis® UroVysion is the first FDA-cleared, noninvasive, genomic DNA-probe test for monitoring recurrence of bladder cancer.

Vysis® UroVysion Bladder Cancer Recurrence Kit (UroVysion Kit), takes a Cellular Genomics approach to disease management by detecting genomic changes (chromosome abnormalities) in bladder cells that are indicative of cancer. As few as four abnormal cells identified with the UroVysion Kit indicate the presence of cancer.

“The FISH method detected cancerous cells in the urine of 81 percent of the patients with bladder cancer,” said Kevin Halling, MD, a Mayo Clinic pathologist and lead researcher on the study. “By comparison, urine cytology detected cancerous cells in only 57 percent of the patients with bladder cancer. Most importantly, the FISH test picked up more than 95 percent of the high grade cancers, which are classified the most dangerous and important group of bladder cancers because they have a high probability of progressing to a potentially incurable muscle-invasive bladder cancer.

“With only one exception, the only cancers the test missed were low-grade tumors, which are less dangerous and have only a 3 to 5 percent chance of progressing to a higher stage tumor over five years. The FISH test also detected recurrence of the cancer three to six

ALASKA CLINICAL RESEARCH CENTER STUDY RESULTS
SCREENING HIGH RISK PATIENTS FOR UROTHELIAL CANCER
TABLE 1

Item	Bladder CA	Ureteral CA	% CA Detected	No CA
# of Patients	17	1	-	230
Cystoscopy +	15	-	83%	-
BladderChek™	10*	1	61%	26
Cytology +	2	1	18%	0

*BladderChek™ detected all three + cytologies and 4/6 atypical cytologies in Cancer Patients.

In the 7 cases of high-grade transitional cell cancers (TCC), BladderChek™ correctly identified 6 (86%) whereas initial cysto identified 5 (71%) and cytology only confirmed 2 (28%). In 5 cases of invasive cancer, BladderChek™ and a cysto exam identified all 5 (100%) but cytology confirmed only 1 (20%). Of the 230 patients determined not to have bladder cancer, 204 (89%) were correctly confirmed by BladderChek™ whereas 217 (99%) were correctly confirmed by cytology (11 no reports). Overall, BladderChek™ improved the detection rate of cysto to 94%.

Conclusions: NMP22® BladderChek™ was more valuable than cytology as an adjunct to cystoscopy in the diagnosis of urothelial cancers in high-risk subjects. Combined with cystoscopy, BladderChek is a simple office test that should be performed before or at the time of a cystoscopy visit to aid in the identification of occult or upper tract urothelial cancers.²

Bladder Cancer and Urine Markers continued

months earlier than by the cytology," says Dr. Halling. "This earlier detection capability should allow treatment to be initiated earlier and possibly give the patient a greater chance for survival."³

Recently, a new commercial test (VYSIS) was developed to aid in evaluating urine cytology. In this test, 4 probes are simultaneously evaluated on a per cell basis on a single cytospin. A pilot study tested the efficacy of the new FISH test and compared it to standard urine cytology; results showed that the multi-colored FISH probe test was more sensitive than cytology, easily performed and yielded a high number of cells with numerical chromosomal aberrations.**

IMMUNOCYT

ImmunoCyt is a qualitative direct immunofluorescence assay intended for use in conjunction with cytology to increase the overall sensitivity for the detection of tumor cells exfoliated in the urine of patients previously diagnosed with bladder cancer.

ImmunoCyt is a noninvasive, highly sensitive test for detecting transitional cell carcinoma of all grades and stages. When combined with conventional urine cytology, it may replace cystoscopy in select patients, especially in follow-up protocols of low-grade transitional cell carcinoma.

ImmunoCyt contains a cocktail of three monoclonal antibodies labeled with fluorescent markers. The cocktail of antibodies has been shown to react with a mucin glycoprotein. It also demonstrates specificity to a glycoform of CEA. The test is able to detect cellular markers specific for bladder cancer in exfoliated cells isolated from urine samples.

This non-invasive test, when coupled with urine cytology may prove to be more sensitive than urine cytology alone or other currently available tumor markers.



ImmunoCyt is carried out in parallel with cytology to improve cytology's sensitivity at detecting tumor cells in the urine of patients, especially those with low stage, low grade tumors.

The concomitant use of classical cytology and ImmunoCyt can substantially improve the detection of bladder cancer.

Studies have shown that a sensitivity of 97.7% can be obtained when both cytology and ImmunoCyt are used together.

<http://www.dakousa.com/immunofactr/immcyt6inf.htm> Dakos website, manufacturers of ImmunoCyt.

FDP FIBRIN/FIBRINOGEN DEGRADATION PRODUCTS

FDP has shown high sensitivity even for low-grade and non-invasive tumors. The FDP test detects the presence of fibrin and fibrinogen degradation products in urine. It is a simple test that can be performed in the office, and results are available in about 10 minutes.

Fibrin and fibrinogen degradation products are protein fragments generated by the action of the fibrinolytic system on fibrin and fibrinogen. Plasma proteins leak from blood vessels in tumors into the surrounding tissue.

Clotting factors rapidly convert the fibrinogen in the plasma into an extravascular fibrin clot, which is then degraded by plasmin and activated by urokinase.

The FDP test can detect these degradation products and is positive in two thirds of patients with bladder cancer. The FDP assay is more accurate than urine cytology and has high specificity (negative in 96% of healthy subjects).

Telomerase is another substance currently being assessed for its potential usefulness in diagnosing transitional cell cancer (TCC) and in monitoring for recurrence. It will soon be made available to doctors and patients. Telomerase is a ribonucleoprotein enzyme responsible for production of telomeres, which are DNA sequences that occupy the ends of chromosomes and protect their integrity during DNA replication: they are also thought to be involved in the immortalization of a cancer cell.⁴

Within each tumor grade and stage, telomerase had the strongest association with bladder cancer among all tests (69% overall concordance). Telomerase was positive in 91% of the patients (10 of 11) with carcinoma in situ. The combination of sensitivity and specificity (70 and 99% respectively) was the highest for bladder cancer screening in these patients.

It was the strongest predictor of cancer with superior accuracy in patients with grade 1 and noninvasive tumors (Ta), and was extremely useful in patients with carcinoma in situ. Telomerase outperformed cytology, BTA stat, NMP22, FDP, chemiluminescent hemoglobin and hemoglobin dipstick in the prediction of

bladder cancer.⁵

Robert H. Getzenberg, PhD, Director of Research at the Prostate and Urologic Cancer Center of the University of Pittsburgh Cancer Institute, and colleagues have identified several components of the nuclear matrix, one of which is called BLCA-4, that can differentiate human bladder tumor cells from normal bladder cells.

Normal samples from unaffected individuals did not react with the antibody, and more importantly, BLCA-4 appears to be present throughout the bladder (i.e., in both normal and tumor areas) in bladder cancer patients. This "field effect" permitted development of a urine immunoassay for BLCA-4 that detects the presence of tumor anywhere in the bladder, regardless of stage or grade. The BLCA-4-urine immunoassay has a specificity of 100% and a sensitivity of 95%.

This test was withdrawn from the market due to stability problems.¹³

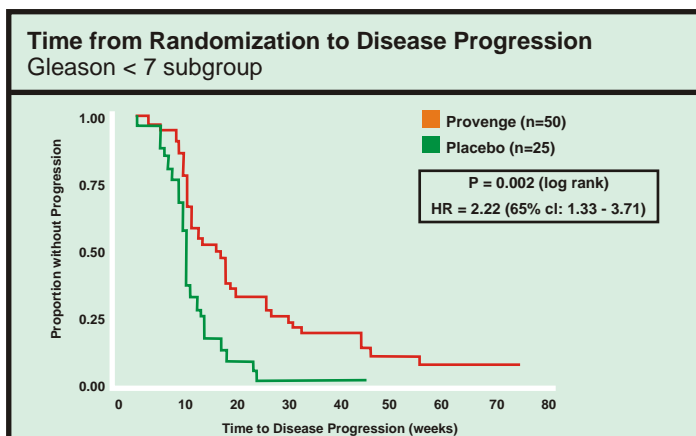
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D-9901 Trial Results Show Promise; Gleason Scores Figure Prominently

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Editor of Provenge® Update, Highlights from a Clinical
Advisory Board Meeting, Dendreon Corporation

Provenge delayed both time to disease progression (TTP) and time to onset of disease-related pain in a subset of all randomized patients with a Gleason Score of 7 or lower. For patients in this group (n= 75), median time to progression was 9 weeks for placebo and 16 weeks for Provenge. The log-rank p-value was 0.002, corresponding to a hazard ratio of 2.22 (95% confidence interval 1.33-3.71) and a 78% treatment effect.



In the analyses of time to onset of disease-related pain, the log-rank p-value of 0.019 and corresponding hazard ratio of 2.22 were consistent with the TTP analyses. In the Gleason < 7 subgroup, the patients treated with Provenge had more than a twofold higher probability of remaining free of both progression and cancer-related pain than did men treated with placebo.

As for the trial's pro-specified primary endpoint (TTP in the full intent-to-treat population), the log-rank p-value approached but did not reach statistical significance (p= 0.085).

Members of the Advisory Board considered the trial results promising and recommended further studies.

Call 1-866-4-PROSTATE to find out about current clinical trials for PROVENGE, an investigational product for prostate cancer.

Prostate Cancer Clinical Trials

All prescription medications must be tested in a rigorous series of studies regulated by the Food and Drug Administration and supervised by medical and scientific experts.

For prostate cancer patients, there are a plethora of new investigational drugs currently in the pipeline. You may wish to consider enrolling in a study.

By participating in a clinical trial, you could potentially benefit from a product not otherwise available. You could also play a role in advancing the understanding of prostate cancer and how to treat it. Even if you are not currently interested in enrolling in a trial, please read on. By staying informed about the latest approaches to treating prostate cancer, you will become more knowledgeable and, ultimately, more empowered.

If you qualify to participate in a clinical trial, a "study doctor" (a physician involved in conducting the trial) will explain the trial in detail and answer all of your questions. Then you will make your decision about whether or not to participate. If there is a reason you should not be in the trial, the study doctor will explain that as well.

If you do enter a clinical trial, you have several important rights. Study doctors and nurses will follow your response to the treatment very carefully. You will have the right to leave the clinical trial at any time.

Before participating in a clinical trial, you should talk with your doctor about the trial and whether you should participate.

As with other anti-cancer therapies, an investigational product may not benefit you and may cause side effects. These side effects could be severe or even life-threatening. There may be side effects that are not known or predictable at this time, but that may occur at the time of treatment or later. You should discuss these risks with your physician or a study doctor.

Clinical trials may present a new treatment option for you and your doctor to consider. By enrolling in a clinical trial, you could potentially be one of the first people to benefit from a new treatment. In a broader sense, you would also be contributing to efforts to understand prostate cancer and treat the disease more effectively.

Even if you are not currently interested in enrolling in a clinical trial, it is important to stay informed about the latest prostate cancer treatments. The more you know, the more empowered you will be in managing your own health.

LURN Clinical Sites

For more information on Clinical Trials please contact the Linked Urology Research Network Medical Directors or Study Nurses listed below:

Kansas City Urology Care, PA
Gary Leifer, MD, FACS
Shannon Cone, CRC
Rockhill Medical Plaza North
6650 Troost Avenue, Suite 206
Kansas City, MO 64131
816-333-5433 • Fax: 816-333-0231

Associates in Urology, LLC
Yitzhak Berger, MD, FACS
Kit Murtha, LPN, CRC
741 Northfield Ave, Suite 206
West Orange, NJ 07052
973-325-6100 • Fax: 973-325-1616

Carolina Urologic Research Center
Neal Shore, MD, FACS
Stacey Harrelson, RN, CRC
823 82nd Parkway, Suite B
Myrtle Beach, SC 29572
843-449-1010 • Fax: 843-497-5627

Urology Associates of North Texas
Delbert Rudy, MD, FACS
Madelon Petersen, RN, CRC
1325 Pennsylvania Ave., #540
Fort Worth, TX 76104
817-332-8595 x60 • Fax: 817-332-8599

Atlantic Urological Associates
Martin Dineen, MD, FACS
S. Warrington, CCRC, CMA
Research Department, 545 Health Blvd
Daytona, FL 32114
386-239-8500 • Fax: 386-239-8530

Excellence in Urology Research



LURN was established to address an urgent priority, ensuring that safe devices, drugs and biologics are developed in accordance with regulatory guidelines, tested appropriately in qualified participants, and carried out in an environment of compassionate care. LURN is the ideal partner for sponsors who share the same commitment to quality care. Perhaps it's why LURN physicians are always among the nation's top enrollers; or it's because sponsors know they can rely on LURN sites for quality data and protocol compliance.

Mission Statement

The Linked Urology Research Network is dedicated to providing sponsors, patients and regulatory agencies with the finest investigative and clinical services available. This goal is achieved through quality assurance audits, continuous quality improvement, patient education and investigator training.

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OUR COMMITMENT TO EXCELLENCE

With over 100 years of combined research experience, LURN founders have diligently worked to construct an organization that delivers quality care. Our team of highly qualified professionals has a proven record of performance, **we are always among the top 5% of study enrollers**. Sponsors acknowledge site excellence and integrity in all aspects of our performance by giving us repeat business. The Linked Urology Research Network is a coalition of independently owned, geographically diverse, highly experienced Urology Research Centers of Excellence. Incorporated as an LLC in 1999, LURN Centers of Excellence focus on a single therapeutic specialty – **Urology**. It is a physician network that is privately funded by member partners. LURN is not a site management organization (SMO). Members have no alliance or contractual obligations with any Study Broker, CRO, or SMO. Each partner/member has a full time clinical research team and separate research department.



THOUGHT LEADERSHIP

LURN investigators are leaders in their specialty and have expertise in designing and conducting clinical trials for the pharmaceutical industry and device manufacturers. LURN physicians assist industry in negotiating with the FDA for development plans and trial designs to meet the special needs of urology patients.



ETHICAL ISSUES AND CREDIBILITY

Clinical trials involving pediatric and geriatric patients require additional consideration to protect this vulnerable population. LURN's approach to facilitating the Institutional Review Board (IRB) process starts with an appropriate protocol design and builds in safeguards for trial participants. LURN's medical director reviews every protocol to ensure acceptability of trial design. The independence and reputation of LURN investigators provide strong credibility with sponsors and regulatory authorities. Our ability to appropriately enroll subjects, deliver clean data, maintain protocol compliance is evident in repeat business from sponsors.

ACCESS TO POTENTIAL STUDY PARTICIPANTS

Appropriate site selection is crucial for a successful trial. LURN has experience working with our own physician owned network of investigative sites. Through our screening process, LURN works with investigators/study coordinators that are well trained and experienced in the conduct of urology protocols. Their knowledge of practice population, familiarity with participant history shorten enrollment times.



SERVICES

LURN coordinates and supports clinical trials aimed at improving outcomes and enhancing knowledge about the medical care of urology patients. LURN facilitates the conduct of clinical trials; disseminate new therapies into community based practices; and serving as an advocate through its interactions with industry and regulatory authorities. LURN has the resources to coordinate and manage clinical trials involving new or existing drugs, biologics, vaccines or medical devices.



Our full range of services include:

- Assistance in trial design and review
- Protocol writing
- Advisory board physician consultant services
- Develop shadow charts and tracking tools
- Manage study timelines
- Measure site performance
- Track project budget
- Facilitate sponsor and project team communications
- Negotiate, prepare and execute site contracts
- Process site payments
- Process regulatory documents
- Identify investigators according to interest and expertise.

Female Sexual Dysfunction:

A primer for the physician

Eric Seaman, MD

Before the current surgical and pharmaceutical treatments for erectile dysfunction (ED) were available, the majority of impotence was attributed to psychological factors and psychotherapy was the mainstay of therapy. It therefore comes as no surprise that until recently, psychological and personality abnormalities have been thought to be responsible for most of what is referred to as "female sexual dysfunction" (FSD).

However, given that risk factors for sexual dysfunction are similar for both sexes, the notion that FSD may reflect underlying organic pathology has become increasingly popular.

RISK FACTORS FOR FSD

Organic risk factors for FSD are similar to those for ED and include heart disease, peripheral vascular disease, hypertension, prior surgery on the reproductive organs, neurologic disorders, history of tobacco use and/or substance abuse.

Certain medications have been associated with FSD. These include: antihistamines, antihypertensives, antiandrogens, anticholinergics, antidepressants, sedatives and antiestrogens.

Psychological risk factors are similar for both disorders (ED and FSD). They include: stressors in the marital relationship, job or financial stress, family stressors, depression and a history of sexual abuse. As with ED, FSD likely affects a substantial portion of the female population. FSD can be further divided into disorders of desire, arousal, orgasm, and sexual pain.

CATEGORIES OF SEXUAL DYSFUNCTION

Hypoactive sexual desire disorder: refers to a lack of sexual thoughts and receptivity to sexual activity. This dysfunction also causes personal distress. Sexual aversion disorder is a subcategory of this.

Sexual arousal disorder: refers to an inability to attain or maintain sexual

excitement. This includes poor vaginal lubrication, decreased genital sensation and poor vaginal relaxation.

Orgasmic disorder: refers to a loss of ability to achieve orgasm after adequate sexual stimulation and arousal.

Sexual pain disorder: refers to genital pain associated with non-coital sexual stimulation which causes personal distress. Dyspareunia and vaginismus are subcategories of this disorder.

HISTORY AND PHYSICAL EXAMINATION

The problem should be defined in terms of onset and duration and whether the problem is situational to a specific partner, or setting. Asking the patient what they think is causing the problem can be helpful. A history should also include questions about sexual orientation. Gender identity conflicts can be a cause of sexual dysfunction.

Physical examination should include a pelvic examination to look for evidence of an organic etiology such as findings of vaginal atrophy and/or dryness. The use of a cotton swab can be helpful to elicit findings of areas that trigger pain and signs of vulvar vestibulitis. A speculum examination may be appropriate in patients with deep dyspareunia.

Endocrine evaluation in select patients may include serum FSH, LH, estradiol, testosterone, and prolactin levels. Other measurable parameters to consider include: vaginal pH, genital blood flow, vaginal wall compliance, and vaginal engorgement pre- and post-stimulation.

TREATMENT

Considerations in modifying lifestyle, general health, limiting substances of abuse and examining current medications are good first steps with which to approach the problem. Patients with depression may respond favorably to a reduction or change in their medication.



In particular, patients who are taking a selective serotonin reuptake inhibitor, may be able to use sildenafil to counteract some of the side effects of the antidepressant. Although sildenafil has been noted to be beneficial in this limited context, studies have not proven its efficacy in larger patient populations.

In postmenopausal women, hormone replacement therapy may be helpful for treating vaginal atrophy, decreasing sexual pain and improving clitoral sensitivity. The decrease in estrogen levels during menopause is likewise associated with a decrease in circulating androgens.

Low levels of circulating testosterone associated with arousal disorder may be amenable to testosterone therapy; however, testosterone administration does have associated risks including alopecia, acne, and hirsutism.

Vaginismus is often related to sexual phobias or prior abuse history. Treatment usually includes use of a vaginal dilator to achieve gradual vaginal muscle relaxation.

Use of a therapeutic clitoral device for women was recently approved by the FDA. The device includes a small soft plastic cup that is applied to the clitoris to exert a negative pressure or vacuum. The vacuum stimulates the clitoris and increases cavernosal blood flow, and engorgement, and vaginal lubrication. It may be beneficial for arousal and orgasmic disorders.

SUMMARY

Just as the field of ED has achieved significant gains in the understanding of the underlying pathophysiology and in the ability to provide adequate treatment, FSD is now beginning to receive new attention in efforts to achieve similar accomplishments. New classification of subtypes of the disorder likely represent only the beginning of the path doctors will take in the acquisition of more knowledge and ability in this new and exciting field.

SEXUAL DYSFUNCTION CLINICAL STUDIES

LURN physicians are actively involved in clinical research trials for both female sexual disorders and male erectile dysfunction. To learn more about these studies visit our web site at www.lurn.org or contact the LURN research offices listed below:

Urology Associates of North Texas	Madelon Petersen	817-332-8595 x 60
Associates in Urology Research Center	Kit Murtha	973-325-6100
Kansas City Urology Care Research Center	Shannon Cone	816-333-5433
Atlantic Urological Associates Research Center	Sandy Warrington	386-239-8535
Grand Strand Urology Research Institute	Stacey Harrelson	843-449-1010 x 268

Table B
Summary of Recent Trials of Patients with HRPC Treated with Taxotere

Patient Number	Treatment	Efficacy		Selected Grade 3/4 Hematologic	Toxicities Nonhematologic
		PSA Decline > 50%	Measurable Disease Reduction		
Single-Agent Trials					
Picus¹³	35 Taxotere 75 mg/m ² q 21 days	46%	24%	Neutropenia (43%)	Infections (23%) Hyperglycemia (63%)
Berry¹⁴	61 Taxotere 36 mg/m ² /week x 6 out of 8 weeks	41%	33%	Anemia (7%) Neutropenia (3%)	Asthenia (10%) Diarrhea (10%)
Beer¹⁵	25 Taxotere 36 mg/m ² /week x 6 out of 8 weeks	43%	60%	Neutropenia (16%) Leukopenia (16%)	
Trials with Taxotere/Estramustine					
Savarese²⁰	47 Taxotere 70 mg/m ² on day 2 Estramustine 10 mg/kg/day on days 1-5 Hydrocortisone 30 mg (a.m.) and 10 mg (p.m.) p.o. daily q 21 days	69%	23%	Leukopenia (58%) Granulocytopenia (50%) Lymphopenia (48%)	Infection (15%) Hyperglycemia (17%) Malaise/Fatigue (16%) Phlebitis/Thrombosis (5%)
Petrylak²⁵	37 Taxotere 70 mg/m ² on day 2 Estramustine 280 mg, t.i.d. on days 1-5 q 21 days	68%	55%	Neutropenia (62%)	Hyperglycemia (19%) Vascular Events (11%) Edema (8%)
Sinibaldi²²	36 Taxotere 70 mg/m ² Estramustine 280 mg q 6 hours x 5 doses q 21 days	42%	22%	Neutropenia (74%) Febrile neutropenia (6%)	Fatigue (68%) Hyperglycemia (12%)
Copur²⁶	20 Taxotere 35 mg/m ² /week Estramustine t.i.d. X 3 days 420 mg for 4 doses 280 mg for 5 doses q week x 2 of 3 weeks	70%	50%	Grade 1-3 neutropenia (10%) No grade 4 neutropenia	

Evolving Role of Chemotherapy in the Management of Prostate Cancer

continued from page 3

therapeutic targets are being identified and novel biologic agents in combination with chemotherapeutic agents are being evaluated for activity in the disease.

Some novel strategies showing promise in clinical trials are signal transduction receptor inhibitors, angiogenesis and growth factor inhibitors, endothelin receptor antagonists, cell cycle inhibitors, immunotherapeutic vaccines and activators of cell death.

However, determining the proper combination of drugs, sequence of therapeutic interventions and appropriate patient population will continue to require careful, well-designed, multi-center clinical trials to prove efficacy, safety and effectiveness.

Currently, the pharmaceutical industry is partnering with community based urologists in an effort to complete quality studies that will establish benefit of the therapy and deliver data to support FDA approval for new anti-cancer drugs. For prostate cancer patients, these investigative trials offer new hope; the value and potential benefit of clinical trial participation cannot be over emphasized and patients should be encouraged to explore these options.

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Celsion Treats First Patient in Clinical Trial of Thermodox™ for Prostate Cancer



Celsion Corporation has treated the first patient in its Phase I clinical trial to investigate the use of Thermodox™ with focused-heat for the treatment of prostate cancer. The technology, developed by Dr. David Needham, Professor of the Department of Mechanical Engineering and Material Science at Duke University, was licensed exclusively to Celsion.

Thermodox™, which is the first drug developed by Celsion using its proprietary heat-sensitive liposome, is a compound encapsulating Doxorubicin, a well-established chemotherapeutic drug.

In this trial, Celsion's Microfocus® BPH800 Urethroplasty™ System provided the focused heat required to trigger the release of the Doxorubicin. The first patient was treated at Regional Urology in Shreveport, LA.

Dr. Davie Price, Principal Investigator for the site in this study on prostate cancer, commented, "Physicians in my practice had an excellent experience working with Celsion in the pivotal trial for its BPH technology. What makes the BPH technology intriguing is its potential application in conjunction with Celsion's heat-sensitive liposomes in treating prostate cancer. I'm hopeful that as we gain experience by treating additional patients, we can establish the basis for a new, effective therapy for patients with prostate cancer and its potential usage with other cancers in the future."

Dr. Price was an assistant professor at Duke's Medical School for seven years and participated with Dr. Needham in the development of Thermodox™.

According to Dr. Augustine Cheung, Celsion's Chief Executive Officer, "This treatment represents another milestone in the process of establishing Celsion's portfolio of cancer therapies. Application of Thermodox™ to prostate cancer is the first of what we believe will be multiple trials evaluating its use in the treatment of different types of solid cancer tumors. Moreover, our heat-activated liposome technology provides a platform which may be applied to other drug encapsulations."

We're moving!

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