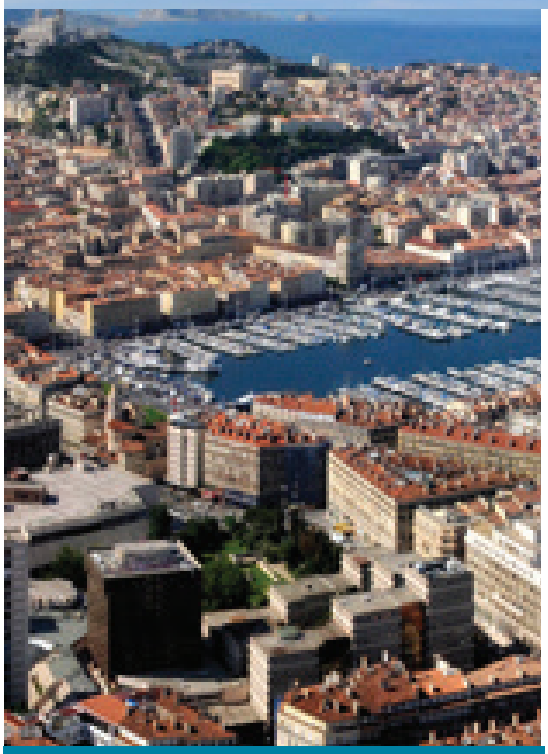
The Prostate Net

In The Know

Confronting Prostate Cancer

December 2013

EMUC 2013 5th European Multidisciplinary Meeting on Urological Cancers



In This Issue

Risk Stratification in Prostate Cancer

Prostate Specific Antigen (PSA) has been the primary biomarker used in the potential diagnosis of prostate cancer. Normally an "elevated" level indicated the need for a biopsy to determine the actual presence of cancer cells. However other factors such as PSA density, PSA velocity, PSA fluctuation as well as the number of biopsy cores taken and the volume of prostate cancer in each core influence the staging of the disease for treatment. Further, post-treatment PSA levels serve as an indicator of treatment failure and disease progression. Clearly there is a compelling need for better biomarkers.

Jack A Schalken PhD

Dr. Jack Schalken, from Radboud University in the Netherlands, in his EMUC presentation presented an overview of the current landscape of tools available to better identify patients that 1) should be screened, 2) need a biopsy, 3) should be treated or not and 4) how their risk for lethal disease can be stratified.

The general categories of protocols can be seen as:

- Diagnostic: used in combination with clinical parameters in risk stratification
  - PSA
  - PCA3 – gene-based urine test to determine biopsy needs
  - ConfirmDX – predictor of positive repeat biopsy
  - ETS-Gene-Fusion to measure androgen expression (no established value yet in risk stratification)
  - Immunohistochemistry (IHC) – molecular cellular analysis of factors

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EDITORIAL

"Everybody wants to go to heaven, but nobody wants to die!" Strategies for patient advocate partnerships in the healthcare marketplace.

In this article, the founder and president of The Prostate Net, Virgil Simons, presents his ideas on how pharma companies can come up with a strategy in order to achieve successful patient advocate partnerships.

Too often we've seen those situations wherein the wishes of success are maximized, but without the concomitant due diligence and hard work necessary to achieve them. This condition is the manifest reality as exemplified in the title of this article. How easy it would be to conjure up exceeding sales goals and market objectives by just wishing it could be.

Such is the situation faced today in the world of pharmaceutical and medical device companies. There is the emphasis on the *"patient"*, in creating *"patient-centric"* standards of care, improving *"patient services"* and the big one; *"empowering the patient"*. So, given these imperatives, why have global pharma not become more engaged with the patient?

Obvious to all are the regulatory statutes preventing direct-to-consumer contact, but yet somehow our colleagues in the US have managed to achieve just that. How? The answer is simple: they talked with the *"right"* patients. Globally, pharma is concerned with achieving certainty be it in drug efficacy, market share, etc. but drug regulatory guidance is far from certain in delivering it. We have seen greater engagement in the US by individual pharma companies such as Sanofi's *"Partners in Patient Health"*, GenZyme's *"Patient Advocacy Team"*, and virtually all others with senior level managers of Advocacy Relations.

The response from pharma might be that we talk to patients now, through our contacts with physicians, with some patient support groups, with advocacy organizations. But, again the question must be asked: "Do we have the right partners in place and do we have true dialogue with them?"

In reality communication amongst pharma, physicians, public health and health service agencies is deficient when attempting to engage with patients. Each of these entities is bringing its own agenda to the process, which treatment would then be viable.

Thus, now more than ever, the patient must assume a more equal, and decisive, role in the management of his disease: firstly, gaining a real understanding of his clinical status (need for action); understanding the treatment options available, the relative odds of success for each one, the potential side-effects – both immediate and delayed, the possibility for progression of the disease and which treatment would then be viable.

No longer is it acceptable to see a doctor and accept his choices; it is OUR disease and OUR lives, and the choice must be OURS!

Risk Stratification…

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contributing to prostate cancer and its progression
- Ki67
- E-cadherin

- Prognostic: measuring the natural biological potential
  - OncoTypeDx Prostate – indicator for Active Surveillance candidacy
- Predictive: response to therapy, either localized or advanced stage
  - Prolaris – potential for aggressive disease
  - Decipher – predictor for post-surgical metastasis
- Therapy monitoring: measuring effectiveness of the agent
  - Circulating Tumor Cells (CTCs)
  - Cell Search

However, though we have many tools available, we are still a long way from having vehicles that can be used across the full spectrum of patients. Key is dialogue with the doctor as to those tests that have the potential to deliver real clinical value.

From an EMUC presentation by: Jack A. Schalken, PhD, Department of Urology, Radboud University Medical Center, Nijmegan, Netherlands

NOTE: Jack A Schalken PhD was trained as a biochemist at the Radboud University Nijmegen (Netherlands), where he also obtained his PhD degree (1987). He did his post doc with Dr. John T Isaacs at Johns Hopkins Hospital (Baltimore, MD). Since then he is director of urological research at the Radboud University Medical Center. In 1996 Dr. Schalken was appointed as full professor of experimental oncology at the University of Utrecht. Since 2001 he is professor of experimental urology at the Radboud University. His research has a strong translational component, i.e. conducting life sciences research to accelerate healthcare outcomes.

EMUC 2013

Developments in personalized therapies for cancers and how these can be used and further refined in the treatment of urological cancers were the key topics in the 5th European Multidisciplinary Meeting on Urological Cancers (EMUC) held in Marseille, France from November 15 to17, 2013.

The most significant area of relevance for patients and their physicians is the reality that "prostate cancer" is not just a single disease, but probably closer to 20 different mutations based on the molecular reactions, interactions and clonal activity of progressive disease. No longer is it sufficient to identify Pca as an ardenocarcinoma, but now we have seen variations that are oligometastatic, neuroendocrine among others.

Compounding the situation is that we now have approximately 10 therapeutic agents to treat advanced stage disease, but questions remain as to what patient will benefit from them and in what sequence should they be administered. This can be exemplified by the emergent immunotherapies that have been approved for late-stage prostate cancer, but recent data show these protocols best benefit overall survival for patients with healthier immune systems, suggesting a need for earlier stage use.

In other presentations:

- Proficiency in Robotic Prostatectomy
- Image Guided Radiation Therapy
- Surgery for treating patients with High-Risk
- Patients with Bone Fractures
- Multi-Disciplinary Therapy

In a ten year study of surgeon proficiency in robotic prostatectomy, it was determined that a median number of 1,000 procedures needed to be done to maximize patient outcomes. In the U.S. 80% of surgeons average about 10 per year! Take home message: high volume centers offer better results.

Image Guided Radiation Therapy (IGRT) with high dose radiation therapy (78gy) achieved higher rates of overall patient survival than the conventional IMRT protocol using 68-70gy.

The use of surgery for treating patients with High-Risk Localized / Locally Advanced prostate cancer is increasing versus the previous protocol of radiation therapy. Studies have shown that generally low level disease has been treated too aggressively (surgery/RT), while high-risk disease has been treated too conservatively (hormonal therapy+radiation).

Patients with bone fractures have increased mortality from prostate cancer versus those who don't. 90% of patients with Castrate Resistant Prostate Cancer develop bone metastases.

Results of the STAMPEDE trial evaluating newly-diagnosed metastatic (M1) prostate cancer patients on androgen deprivation therapy (ADT) showed:

- Survival, and particularly Failure-Free Survival, remains relatively poor (median time 20 months) despite access to docetaxel and other newer therapies
- Patients with lymph node-only disease have significantly better outcomes than those with bone-only disease
- Patients with bone and lymph node disease have significantly worse outcomes than bone-only disease
- Men with M1 disease will now spend more time in a state of Castrate Resistant Prostate Cancer (CRPC)
- Better first-line therapies are needed

Major challenges in managing patients with mCRPC:

- Prolonging overall survival
- Delaying the onset of Symptomatic Skeletal Events
- Palliation of symptoms, particularly pain
- Improving Quality Of Life

The key point of emphasis throughout the conference was that Multi-Disciplinary Therapy (MDT) is essential to appropriate patient care because of the complexity of the disease and the diversity and appropriate sequencing of new therapeutic agents.

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The Prostate Net

Evolutionary Dynamics Of Carcinogenesis And Why Targeted Therapy Does Not Work

By Virgil Simons

With this provocative title, Robert Gillies, PhD, Daniel Verduzco, PhD, and Robert Gatenby, MD, cancer researchers at the Moffitt Cancer Center in Florida, sought to provide an entirely different perspective on the concept of "Targeted or Personalized Therapy" that is emerging as the new focal point in managing cancer in a published study done in Nature Reviews

(Nature Reviews Cancer 12, 487-493 (July 2012) | doi:10.1038/nrc3298).

Central to their arguments are the points that:

- The process of carcinogenesis requires genetic instability and highly selective local microenvironments
- Malignant cancers are dynamically evolving clades of cells living in distinct microhabitats that almost certainly ensure the emergence of therapy-resistant populations
- Cytotoxic cancer therapies also impose intense evolutionary selection pressures on the surviving cells and thus increase the evolutionary rate

A review of these principles can be seen in previous interviews done with Dr. Ken Pienta and Dr. Cory Abate-Shen that support the fact that the current " androgen receptor targeted therapies" are not the solution to achieving long-term prostate cancer survival.

Further support for the hypothesis was provided by Robert Vessella, PhD, at the recent Prostate Cancer Biorepository Network Workshop in a presentation that said: "When cancer cells have disseminated from the primary tumor to distant sites, these can be the seeds of metastatic disease and the lethal phenotype. Once signs of local recurrence or metastatic growth are observed, androgen ablative therapy is usually initiated. This **treatment induces the cells to begin a second phase of adaptation**…over time and through a number of molecular events, the cells progress to a state of castration resistance…and truly portray the lethal phenotype because no current therapies have substantially prolonged survival."

In essence, what is happening is the manifestation of a Darwinian model wherein the strongest, and most lethal, of the cells survive the therapy, adapt their molecular structure and find new environments in which to grow and ultimately kill the patient.

Robert Gatenby, MD

Robert Gillies, PhD

We have the pleasure of gaining more specific knowledge on the subject directly from Drs. Gatenby and Gillies. We have broken the very extensive interview with them into segments that capture the key points of their article and the challenge to way "targeted therapy" is being implemented today. The video segments can be found at:

Why Targeted Therapy Doesn't work!

http://www.youtube.com/watch?v=U_xKb3Hvxd8&list=UUS70Rw6g91je95VmNBIQJZg

Understanding the Mechanics of Therapeutic Response.

http://www.youtube.com/watch?v=1kOcbb_Fgno&feature=c4-overview&list=UUS70Rw6g91je95VmNBIQJZg

Imaging for Personalized Therapy

http://www.youtube.com/watch?v=ve88vjvbWqc&feature=c4-overview&list=UUS70Rw6g91je95VmNBIQJZg

Creating Personal Biomarkers

http://www.youtube.com/watch?v=qV9nyVx1O4k&list=UUS70Rw6g91je95VmNBIQJZg

Clinical Imperatives for Personalized Therapy

http://www.oncologytube.com/index.php?page=videos&section=view&vid_id=1032370

The data we've seen from other researchers would suggest that the cancers are re-programming themselves to adapt to the therapeutic agents being used. However, Gillies and Gatenby believe that the genetic and epigenetic variants for lethal disease have already been in place and are merely being selected by the therapy. They agree with other scientists who hypothesize that the cancers have been "pre-determined to be resistant or not." But, the earlier the disease can be diagnosed and treated, the lower the probability that broad variances will become present.

Further, they believe that in prostate cancer that genetic and epi-genetic variance can be reduced in developing cancers by diet and lifestyle changes which can result in reducing the stressful microenvironments.

Their research is currently looking at hormone sensitive and refractory

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A New Standard of Patient-Centered Care

by Josefina Rodriguez

The European Board of Urology recently certified the Urology Department of the Hospital del Mar in Barcelona as a urological training center. This hospital traces its history from the 16th century and is located on the Mediterranean coast of Barcelona. The hospital has an ambitious project that started in 2008 with plans to be finished in 2017. The main goal of this project is to improve the building and equipment to provide more efficient health solutions for an older population. The Hospital del Mar is linked to Pompeu Fabra University and the Universidad Autonoma in Barcelona.

Dr. Albert Frances

The Urology training program, RTPU (Resident Training Program in Urology), takes about five years in Spain. There is also an interdisciplinary medical research program called IMIM. Urologists have an opportunity to perform basic research at the Hospital del Mar Medical Research Institute. Two main research areas, The Cancer Research Program and the Inflammatory and Cardiovascular Disease Program, are collaborating with other institutes.

We met with Dr. Albert Frances, Chief of Medical Staff of the Urological Department, Hospital del Mar, Barcelona, Program Director of Residency Training Program in Urology, Associate Professor, Universidad Autonoma, Universidad Pompeu Fabra/Barcelona, to discuss what this certification means to the overall standard of practice in Europe and the potential benefit to patient services.

JR: How will the creation of this center improve the training of physicians and how do you envision this changing the current standard of care?

AF: Firstly, because we are primarily a public hospital, most of our patient referrals come from the thirteen Centers of Ambulatory Patient Services (CAPS), which in the U.S. would be comparable to your Primary Care Physicians. Based on the referral clinical diagnostics, the patient would be assigned to a Patient Navigator within each of the functional units (Urology, Radiology, Oncology) whose responsibility is to coordinate with the appropriate physicians for necessary follow-up testing, biopsies, etc. Each week a Review Committee meets to discuss each patient's results and makes recommendations for appropriate follow-up treatment (active surveillance, surgery, radiotherapy, hormonal/chemo therapy, etc.) The Navigator meets with each patient to explain the information and possible options, then schedules the patient for the selected therapy and continues to manage the patient's progress through treatment and after.

JR: You mentioned that the thirteen CAPS centers are the primary conduit for a patient's introduction to your system. What are the needs/concerns relative to this first threshold of care?

AF: Initially we need to deal with cultural issues relating to a diagnosis of cancer. Because there is such a negative perception attached to the word "cancer," we are encouraging a greater use of the word "tumor" in those initial patient<=>physician conversations. There continues to be a lack of patient information and informed discussion. But we realize that the general practitioner is an essential part of the early detection equation, so we are working to increase their overall awareness of education and early intervention.

JR: To that point, Dr. Frances, you spoke of a "Rapid Diagnostic Unit". Exactly what is this and how does it work?

AF: Actually Dr. Jose Antonio Llorente, Medical Staff of the Urological Department, Hospital del Mar, Urological Cancer Functional Unit Coordinator, heads this unit and is best able to answer this question.

JAL: The Rapid Diagnostic Unit is a unit created to detect patients with a high possibility of prostate or bladder cancer. These are the two most likely urological cancers in our environment. This circuit starts with the General Practitioner and is carried out by a Patient Navigator. Patients and relatives are accompanied during the whole diagnostic process.

JR: We've seen statistics, Dr. Frances, that you're seeing more incidents of prostate cancer among younger men. Would you please comment on possible causes for this?

AF: Yes, it is true that there has been an increase in the incidence of prostate cancer among men under 50 years of age. Surely rising PSA determination in this age group is one of the causes of this increase. We do not have a figure for that and we cannot say if the incidence is higher than the U.S. or other countries. We can speculate that dietary and environmental conditions are significant agents, but we need more research to fully understand the situation.

JR: Do you believe that the increasing use of genetic and prognostic tests will be of value in early detection?

AF: It is still too soon to make a clear affirmation about this subject. Promising results with clinical applicability are appearing lately. However, we are convinced that in the future there might be personalized tests adapted to the individual characteristics of each patient.

JR: In summary, Dr. Frances, do you envision the Urological Cancer Functional Unit here at Hospital del Mar setting a new standard of patient-centered care in Barcelona and the rest of Europe?

AF: We do believe that Urological Functional Units are the best way to attend to oncology patients. Early diagnosis is basic for these diseases, which make it essential to have a Rapid Diagnostic Unit. One of the strengths of Functional Units is the multidisciplinary approach we give to the patients. Having all the different specialists involved in these oncological diseases helps every single patient choose the best treatment.

JR: Thank you, Dr. Frances, for your time and insights. If our viewers want more information on the programs here at Hospital del Mar, where can they go to obtain it?

AF: For additional information, you can contact us at:

--www.urologia-hmar.com --TLF: +34 93 248 32 31

NOTE: A video of Dr. Frances speaking about the program can be viewed at: http://www.oncologytube.com/index.php?page=videos&section=view&vid_id=1034672

Active Monitoring, Radical Prostatectomy, Or Radiotherapy For Localized Prostate Cancer: Best Choice for Patients?

Uncertainties about population screening, the risk of over-treatment, and concern about what is the most effective treatment protocol led researchers in 2001 to initiate the ProtecT trial.

The study aims to investigate the clinical and cost-effectiveness of active monitoring, external beam conformal radiotherapy and radical prostatectomy surgery for men with PSA-detected clinically localized prostate cancer.

10-year data have presented some indications, but final outcomes are not expected until 2016. Information on the study can be found at: http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)70361-4/abstract

Evolutionary Dynamics Of Carcinogenesis…

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breast cancer in developing the concept of "Adaptive Therapy", wherein the emerging phenotypes of potentially resistant disease can be modified toward a less aggressive state. The parallels with, and potential therapeutic agents for, prostate cancer are obvious.

For more information on Robert Gillies, PhD, see:

http://www.moffitt.org/research--clinical-trials/individual-researchers/robert-j--gillies-phd

For more information on Robert Gatenby, MD, see:

http://www.moffitt.usf.edu/research--clinical-trials/individual-researchers/robert-a--gatenby-md

For more information on the Department of Cancer Imaging and Metabolism at Moffitt, see:

http://imaging.moffitt.org/members.aspx

The Impact Of Repeat Biopsies On Infectious Complications In Men With Prostate Cancer On Active Surveillance.

In an article in the Journal of Urology, results of a study on complications in the management of patients on active surveillance were reported.

Prostate biopsy related infectious complications are associated with significant morbidity. The risk of infectious complications in patients with prostate cancer on active surveillance remains under studied.

In this study a total of 591 consecutive men who underwent prostate biopsy were prospectively enrolled in a study evaluating prostate biopsy related complications between January 2011 and January 2012. Of these men 403 were previously diagnosed with prostate cancer and were included in this study. They underwent a 14-core transrectal ultrasound guided prostate biopsy as part of an active surveillance regimen.

The results concluded that in men with prostate cancer on active surveillance the number of previous prostate biopsies is associated with a significant risk of infectious complications and every previous biopsy increases the risk of infectious complication. Men with prostate cancer on active surveillance should be informed of the risks associated with serial prostate biopsies.

Details on the research can be viewed at:

http://www.ncbi.nlm.nih.gov/pubmed/24018237

Use Of Aspirin, But Not Other Non-Steroidal Anti-Inflammatory Drugs Is Associated With Decreased Prostate Cancer Risk At The Population Level.

A growing body of evidence suggests that aspirin reduces the risk of some types of cancer, including prostate cancer. A new meta-analysis found that men who regularly used aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) are 13 percent less likely to develop prostate cancer.

Researchers compared long-term cancer rates among patients who used aspirin, NSAIDs, or both, to rates among patients who used neither.

Even when it comes to something as common as aspirin, there's no across-the-board recommendation. That's because even aspirin carries health risks — notably, gastrointestinal bleeding. A review of the literature showed that because of the relatively small benefit NSAIDs provide, the risk of stomach bleeding was high enough that doctors shouldn't advise male patients to take aspirin for cancer prevention alone.

Details of the study can be seen at:

http://www.ncbi.nlm.nih.gov/pubmed/23079475

Death From High-Risk Prostate Cancer Versus Cardiovascular Mortality With Hormonal Therapy: A Decision Analysis.

The role of androgen deprivation therapy (ADT) in combination with radiotherapy for high-risk localized and locally advanced prostate cancer has been shown to decrease prostate cancer-specific mortality.

However, in other patient groups, evidence has suggested an increase in cardiovascular morbidity or death in men who receive ADT. No link was found between ADT and heart-related deaths among men with no risk factors for heart problems after a median follow-up of 4.8 years.

However, among men with congestive heart failure or prior heart attacks, there was a 3.3-times increased risk of death from heart problems. Heart-related deaths occurred in 7.01% of men in this subgroup who were receiving ADT, compared with 2.01% of men not receiving ADT.

Details of the study can be viewed at:

http://www.ncbi.nlm.nih.gov/pubmed/23400678

FATHER...
BROTHER...
HUSBAND...
SON...

EVERY MAN IS AT RISK
FROM

The Prostate Net® is a non-profit patient education and advocacy organization founded 17 years ago by Virgil Simons, a 19-year survivor of prostate cancer and a patient advocate. The Prostate Net has become an international organization that uses a matrix of informational techniques to address disease risk awareness and early disease interdiction.

The core objective of The Prostate Net's mission is to:

1. Educate consumers most at-risk from a diagnosis of prostate cancer
2. Inform the community on other diseases and conditions of negative impact
3. Motivate consumers to make informed choices as to healthcare and lifestyle management
4. Provide on-going health care interaction between patient and professional communities
5. Create an interactive network to maximize actionable healthcare messages

The strength of The Prostate Net's mission is aided by organizations with which we are associated: American Society of Clinical Oncology, Department of Defense Prostate Cancer Research Program, American Association for Cancer Research and European Association of Urology among others.

Our active initiatives include, but are not limited to:

Education:

- Patient and professional Website - www.theprostatenet.org
- Spanish language site - http://theprostatenet.org/espanol/
- Educational Symposia - http://theprostatenet.org/Symposium.html

Research:

- Continuing partnerships with university based community studies
- Consulting relationships to local government agencies; materials for patient education/recruitment; training of agency staff, etc.

Community Interventions:

- Gentlemen, Check Your Engines TM, focuses on Men's & Women's health issues featuring on-site health education and testing - http://theprostatenet.org/programs.html

Through the 17 years of our existence we have expanded our reach throughout the U.S. and to more than 50 countries. Our overarching objective is to continue to provide service to an expanding range of consumer, healthcare, government, university and service agencies to aid in reducing health disparity through education, research and community intervention. We inform to fight.

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