

Letters to the Editor

RE: MALIGNANT EXTRAGASTROINTESTINAL STROMAL
TUMOR OF BLADDER

*M. Krokowski, D. Jocham, H. Choi, A. C. Feller and
H.-P. Horny*

J Urol, **169**: 1790–1791, 2003

To the Editor. This is an interesting article about an extragastrointestinal stromal tumor that resulted in death. Whereas we rarely come across a case of gastrointestinal stromal tumor (GIST), its extragastrointestinal manifestation represents a real curiosity. We would like to add some thoughts to this article because in case of GIST, which is immunologically and genetically a well-defined disease, effective therapy (specially targeted molecular therapy) is a reality.

Even the scientific literature offers us the opportunity to read about the treatment of the urological manifestation of GIST.¹ The effect of the treatment is based on tyrosine kinase of c-kit inhibition as well as the disruption of signal transduction at mitosis. Joensuu et al first reported the successful treatment of GIST with STI571 (imatinib) in 2001.² Blanke,³ van Oosterom⁴ and Demetri⁵ et al have defined this excellent antimitotic therapy, thus, revolutionizing the treatment of sarcomas. This method is often used in case of CD117 and CD34 GIST tumors.

Amazed by the new development of modern medicine, we are obliged to comment, especially in the case of rare tumors, when urologists must be well informed of all the possible treatment methods. Also there is a need for our urological patients to receive the best possible treatment.

Respectfully,
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Reply by Authors. We described a patient with malignant extragastrointestinal stromal tumor of the bladder. Hübler and Szántó indicate that effective therapy for this tumor entity is available and that urologists should be informed about these treatment options. We are certainly well aware of the first publication of Joensuu et al² in 2001, describing treatment effects of the tyrosine kinase inhibitor STI571 in a patient with metastatic GIST, and of the following clinical studies. Imatinib treatment is indeed a particularly encouraging approach showing potent activity against metastatic GIST. As a matter of fact, at our institution several patients with other metastatic malignancies have already been referred to imatinib treatment. However, our published report clearly stated that the patient died shortly after initial diagnosis due to cardiac failure, before any treatment could be applied. Therefore, the comment of Hübler and Szántó is an interesting point of general knowledge but is not directly related to our case.

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DOI: 10.1097/01.ju.0000112917.79903.60

RE: HISTOLOGICAL CHANGES OF MINIMALLY INVASIVE
PROCEDURES FOR THE TREATMENT OF BENIGN
PROSTATIC HYPERPLASIA AND PROSTATE CANCER:
CLINICAL IMPLICATIONS

B. T. Larson, D. G. Bostwick, A. G. Corica and T. R. Larson

J Urol, **170**: 12–19, 2003

To the Editor. I read this article with great interest. I am one of the early users of water induced thermotherapy (WIT) using the Thermoflex system (Argomed, Inc., Cary, North Carolina). I also use office based interstitial laser coagulation (Indigo, Ethicon Endo-Surgery, Cincinnati, Ohio).

The advantages of WIT are not properly described in the article. This is the **only procedure** available today out of all the ones described and compared in this article where the patient is kept supine for the entire period. I have successfully used this method for patients with severe edema of the lower extremities, deep vein thrombosis, those who refuse to stop using their anticoagulants for fear of another stroke and patients with severe respiratory disease, some even carrying an oxygen tank to the room. Patients with severe hip joint problems will benefit from the use of this modality, although I have not had to use it in this situation. Of course, I also offer WIT to healthy patients who want to undergo an office based, minimally invasive procedure.

The only drawback I find to the WIT procedure is that the catheter tip is straight and stiff. As seen on followup cystoscopies, for some unrelated reasons an open channel is created by this method. Interestingly, I also found only one article on the procedure mentioned in the reference list.¹

Respectfully,
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1. Corica, F. A., Cheng, L., Ramnani, D., Pacelli, A., Weaver, A., Corica, A. G. et al: Transurethral hot-water balloon thermoablation for benign prostatic hyperplasia: patient tolerance and pathologic findings. *Urology*, **56**: 76, 2000

DOI: 10.1097/01.ju.0000110461.09373.4f

RE: DIAGNOSTIC POTENTIAL OF SERUM PROTEOMIC
PATTERNS IN PROSTATE CANCER

*L. L. Bañez, P. Prasanna, L. Sun, A. Ali, Z. Zou, B.-L. Adam,
D. G. McLeod, J. W. Moul and S. Srivastava*

J Urol, **170**: 442–446, 2003

To the Editor. Bañez et al evaluated serum proteomic patterns for diagnosis of prostatic carcinoma and concluded that this method has potential. This technology has recently received much attention and, admittedly, little criticism.^{1–3} Despite the hype, careful analysis of all available data pinpoints significant problems and serious inconsistencies, summarized recently by myself³ and others.⁴

Previously, 2 groups reported the diagnostic value of serum proteomic patterns for prostate cancer in 3 separate studies.^{5–7} A meta-analysis of the data indicated that despite the reported impressive results, the discriminatory peaks were different, even when the methods used were the same.³ I have updated the data with inclusion of information from the article under discussion (see table). The current study used surface enhanced laser desorption/ionization time of flight (SELDI-TOF) mass spectrometry chips similar to those used by Adam⁵ and Qu⁶ et al. Yet the previously published sensitivities and specificities (83% to 100%) were not reproduced. Instead, these authors report sensitivities between 63% (weak cation exchange array [WCX2]) and 66% (immobilized metal affinity capture-copper array [IMAC3-Cu]) at specificities of 77% (WCX2) and 38%

Comparison of 4 reports for prostate cancer diagnosis based on SELDI-TOF technology

References	% Diagnostic Sensitivity and Specificity	Chip Type	Distinguishing Peaks, Mass-to-Charge Ratio*
Adam et al ⁵	83, 97	IMAC-Cu	4,475, 5,074, 5,382, 7,024 , <u>7,820</u> , 8,141, 9,149, 9,507, 9,656
Petricoin et al ⁷	95, 78–83	Hydrophobic C16	2,092, 2,367, 2,582, 3,080, 4,819, 5,439, 18,220
Qu et al ⁶	97–100, 97–100	IMAC-Cu	Noncancer vs cancer: 3,963, 4,080, 6,542, 6,797, 6,949, 6,991, 7,024 , 7,885, 8,067, 8,356, 9,656 , 9,720; healthy vs benign prostatic hyperplasia: 3,486, 4,071, 4,580, 5,298, 6,099, 7,054, <u>7,820</u> , 7,844, 8,943
Bañez et al	63, 77 66, 38	WCX2 IMAC-Cu	3,972, 8,226, 13,952, 16,087, 25,167, 33,270 3,960, 4,469, 9,713, 10,266, 22,832

* Mass-to-charge ratios were rounded to whole numbers for simplicity. Ratios in bold represent those identified by Adam⁵ and Qu⁶ et al for differentiating cancer from noncancer cases. Underscored ratios represent peak identified by Adam et al⁵ for differentiating cancer from noncancer cases and by Qu et al⁶ for differentiating healthy individuals from those with benign prostatic hyperplasia.

(IMAC3-Cu). Only when a new trick was used (combination of data from the 2 chips) were the sensitivity and specificity increased to 85%. The reason for the different discriminatory peaks between groups is obscure and may suggest that this method is inconsistent.

These data were obtained by using the widely applied “training set-test set” bioinformatic approach, which favors generation of the best possible data. I predict that when the algorithm is used blindly in unknown series of patients the performance will deteriorate further and, possibly, to a degree that is no better than 2 simple and cheap serological tests for prostate cancer, ie, total prostate specific antigen (PSA) and percent free PSA.

Respectfully,
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Reply by Authors. We would like to indicate that the evaluations of serum proteomic profiles using SELDI-TOF as a more specific prostate cancer (CaP) detection modality represent a new paradigm in cancer diagnostics. Comparison of this approach to PSA is rather hasty as numerous versions of the serum PSA test have been evaluated and reevaluated for more than a decade now. There is no doubt regarding the value of serum PSA testing in the detection of CaP.⁸ However, low specificity of the serum PSA test is also generally accepted, and, therefore, new CaP detection strategies such as protein profiling by SELDI-TOF showing higher specificity of CaP detection are highly encouraging.

There are only a handful of publications on this topic to date. The data generated from this approach are highly complex and bioinformatics driven, and represent a new paradigm for diagnostic testing.^{5,6,9–11} As with other high throughput genomics and proteomics based assays such as cDNA arrays, 2-dimensional protein gels, etc, it is premature to demand a high level of robustness so early in the developmental stage. We agree that standardization of the technology and validations from different laboratories are warranted. We have already addressed many of the issues raised by Diamandis in our article.

Diamandis raises concerns about the validity of the SELDI-TOF assay due to the differences in the discriminatory protein or peptides elucidated in each of the 3 CaP articles, including the current study.^{5,9} One reason for these documented discrepancies may lie in the 3 different chips (IMAC3-Cu, C16 and WCX2) used by the different laboratories, with each chip having different protein binding properties. Another reason for the differences in protein markers may be variations in the methodology used for processing of serum, and conditions used for the binding of proteins to chip surfaces. Although Adam et al⁵ and we used IMAC3-Cu chips, there were differences in the experimental procedures used. Furthermore, the SELDI-TOF process itself can be fine-tuned by changing settings in the data acquisition parameters in the Protein Biological System II ProteinChip Reader (CIPHERGEN Biosystems, Inc., Fremont, California), the mass spectrometer used to generate the proteomic profiles from chip bound serum proteins. Different instrument protocols were used with a different number of averaged shots, laser intensities and detector sensitivities, which would give different spectral data even if the same serum sample is used and the same method of chip processing is followed.⁵

Importantly, the bioinformatic tools used to analyze the SELDI-

TOF data differed from institution to institution. Adam et al used a custom-made program called PeakMiner to cluster the protein peaks in the 2 to 40 kD mass range, then did feature selection using area under the ROC.⁵ As a followup, Qu et al used boosted decision tree analysis to augment their previous analysis.⁶ Petricoin et al used the raw spectral data in ASCII format, and analyzed them using genetic algorithm and cluster analysis as described in their ovarian cancer article.⁹ We used software packages from Ciphergen Biosystems, Inc., including Biomarker Wizard, to cluster peaks between the 2.5 and 50 kD mass range for IMAC3-Cu and WCX2 arrays, then combined the clustered peak data and conducted pattern matching using Biomarker Patterns Software.

Furthermore, protein peaks were defined differently among the published reports. Adam et al⁵ and our study measured peaks directly, and Petricoin et al⁹ derived peaks mathematically using a deconvolution technique. Differences in data analysis algorithms will likewise produce differing results.

Despite these issues, what is most intriguing is that all of the published reports still show high sensitivity and specificity of CaP, suggesting that multiple prostate cancer specific proteins or peptides may exist in serum that are able to discriminate cancer serum from control serum. This is where the paradigm shift may be more apparent when using SELDI-TOF profiling as a diagnostic tool when one is looking at numerous protein patterns rather than 1 or 2 specific proteins. It is also possible that some of the peptides with different masses may be related and may be products of proteolysis of a given protein. Therefore, the level of criticism by Diamandis is appropriately high.

To provide a relevant assay that will be easily transportable to the clinic and will impact the diagnosis, prognostication and eventually management of CaP, standardization of procedures and methodologies will have to be achieved and the reproducibility of data across multiple institutions will have to be assured. To address these issues, Eastern Virginia Medical School (Dr. O. John Semmes, Principal Investigator) is leading a multicenter validation study of the National Cancer Institute–Early Detection Research Network, and our group is a participant in this study. The results of such studies will shed more light on the clinical relevance of SELDI-TOF serum proteomic profiling.

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DOI: 10.1097/01.ju.0000112784.51142.bd

RE: PROSTATE SPECIFIC ANTIGEN BASED BIENNIAL SCREENING IS SUFFICIENT TO DETECT ALMOST ALL PROSTATE CANCERS WHILE STILL CURABLE

J. Hugosson, G. Aus, H. Lilja, P. Lodding, C. G. Pihl and E. Pileblad

J Urol, **169**: 1720–1723, 2003

To the Editor. This study, part of the European Randomized Screening for Prostate Cancer trial, attempted to determine the safe interval of prostate cancer screening using prostate specific antigen (PSA) alone. With a sample size of 9,972 and 9,973 in the screening and control arms, respectively, it showed that biennial screening is safe in men with a PSA of less than 2 ng/ml, while in men with PSA greater than 2 ng/ml a shorter screening interval is suggested. Significantly, the authors argued convincingly that the omission of digital rectal examination as part of the screening tools did not have much impact on cancer detection in this group of subjects with low PSA. However, the authors did not elaborate on the control arm and the way cancers were detected. It would be important to know if there was a significant problem with “contamination” with the control subjects self-initiating PSA testing.

One observation that needs to be highlighted is the fact that of 378 men with PSA more than the cutoff of 3 ng/ml and negative biopsy at the first screening 52 (13.8%) had cancer detected at the second screening after an interval of 2 years. This number constituted 46.8% (52 of 111 men) of cancers detected at the second screening. Undoubtedly, this result testifies to the high false-negative rate of the current transrectal ultrasound guided prostate biopsy technique as reported in the literature.^{1,2} In other words, the success of PSA as a screening tool has not been matched by the current biopsy methods for histological confirmation. The traditionally used sextant biopsy has been found to be inadequate in this PSA era, and different biopsy methods, either increase in the number of cores per biopsy or targeting of different sites of the gland, resulted in better yields.^{3,4} Indeed, the major obstacle to an effective prostate cancer screening program, despite an excellent initial screening test like PSA as shown in this study, is an ineffective biopsy technique giving rise to high false-negative rates.

The number of cores per biopsy used in this study was sextant, the inadequacy of which was partly compensated for by directing the biopsy laterally. However, it should be noted that the 52 men with cancers missed at first biopsy typically had larger prostates, indicating a possible sampling error as rightly suggested by the authors. Then it would seem more appropriate to consider increasing the number of cores per biopsy in general for screening purposes, and specifically for men with increased PSA and negative initial biopsy undergoing repeat biopsy. At my institution we not only preferentially biopsy the far lateral zone, but we also have increased the number of cores per biopsy from 6 to 10. This 10-core peripheral zone biopsy technique has improved the positive predictive value of cancer detection from the previously reported 8.9% to 24.6% for PSA ranging from 4 to 20 ng/ml.⁵ Currently, the issues of optimal number of cores per biopsy, site of biopsy, pre-biopsy and peri-biopsy imaging modality, and needle delivery technique are the subjects of intense research. Until a more effective biopsy technique is found, any screening program will run the risk of producing an undesirable

“by-product”—a group of anxious men with abnormal PSA but uncertain diagnosis.

Respectfully,
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DOI: 10.1097/01.ju.0000112980.38944.7f

RE: IMPROVED CLINICAL STAGING SYSTEM COMBINING BIOPSY LATERALITY AND TNM STAGE FOR MEN WITH T1c AND T2 PROSTATE CANCER: RESULTS FROM THE SEARCH DATABASE

S. J. Freedland, J. C. Presti, Jr., M. K. Terris, C. J. Kane, W. J. Aronson, F. Dorey and C. L. Amling for the SEARCH Database Study Group

J Urol, **169**: 2129–2135, 2003

To the Editor. In this article the SEARCH Database Study Group proposed a new clinical staging system for prostate cancer incorporating positive biopsy laterality into clinical stage based on digital rectal examination findings to classify patients with clinically organ confined disease. The new clinical staging groups were T1c/T2a with unilateral positive biopsy (low risk), T1c/T2a with bilateral positive biopsy (intermediate risk) and T2b/T2c (high risk). The justification for this grouping appears to be based primarily on univariate differences in biochemical failure (BF). While the authors showed that biopsy laterality was an independent predictor of adverse pathological findings after prostatectomy in multivariate analysis (MVA), no such test was described using BF as the end point. Biopsy laterality was not found to predict for BF independent of prostate specific antigen (PSA), biopsy Gleason score and palpation T stage. Multivariate analysis of the proposed staging risk groups demonstrated an association with BF. However, this result may be due mainly to the T stage subgrouping used.

In contrast to the results of the SEARCH group, those of our recently reported series of more than 1,000 patients with prostate cancer treated with radiotherapy revealed bilateral biopsy positivity was not associated with a significantly higher BF rate compared to unilateral positivity for any T stage.¹ For the purpose of this discussion, we performed MVA on the same cohort with pretreatment PSA, Gleason score, T stage and radiation dose included as covariates. Positive biopsy laterality (dichotomous variable) was not significantly associated with BF ($p = 0.17$, Cox regression model). The significant covariates in our analysis were pretreatment PSA, Gleason score, radiation dose and T stage. Moreover, Freedland et al also reported, in a separate MVA using the SEARCH Database, that positive biopsy laterality was not associated with BF when other factors associated with tumor burden (eg percentage of positive diagnostic prostate biopsy cores) were included as covariates.²

There are no convincing data that biopsy laterality should be incorporated into routine clinical staging. More promising are other