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Contents

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PATHOLOGY & DIAGNOSTICS Percent Of Biopsy Cores That Are Positive Improves Prediction:

There is general agreement that when choosing data on which to base predictions of pathology and treatment outcome the percent of biopsy cores that are positive is more informative than the clinical stage. The percent positive figure can replace clinical stage in the predictive trio that includes Gleason sum and PSA. It's intuitive that clinical stage T1c hides a wide spectrum of pathology. As we move further into the PSA era, it is not surprising that the clinical stage is becoming less of an independent predictor of pathologic stage since the majority of men are currently presenting with clinical stage T1c at the time of diagnosis and earlier tables are based on older data. "There is less spread in clinical stage categories making the traditional Partin table less accurate" (Gancarczyk, UROLOGY, March 2003). It had been rumored that Michael Kattan, PhD, was going to augment the new Partin tables by adding "percent positive" data, but in personal communication with Dr. Kattan, I was referred to his article "Prediction of Progression: Nomograms of Clinical Utility (Clinical Prostate Cancer, September, 2002) where Kattan and Scardino conclude "We recently examined the impact of adding percent of cores positive to our preoperative nomogram. We found this variable to be statistically significant ($P < 0.001$), knocking out clinical stage, which became statistically insignificant ($P > 0.05$). However, the concordance index for this new monogram was identical to the original nomogram, suggesting no improvement in overall predictive accuracy after inclusion of percent of positive cores."

Two consortiums, however, have introduced "percent positive" figures into their predictive models. The SEARCH Database data (J UROL, June, 2003) based on 1094 men treated in four California centers stratified their data into categories wherein <34%, 34%-50%, and >50% of cores were positive, and for them "percent positive" data was an independent predictor of PSA recurrence post prostatectomy. The second article (Gancarczyk, ibid) presented the data from The Center for Prostate Disease Research (CPDR) based on the correlation of 1510 prostatectomy specimens and preoperative biopsy findings and incorporated their results in a nomogram predicting pathologic stage after RP. Their nomogram stratifies data into groups with >30%, 30%-59%, and >60% positive biopsies and their results differ from the Partin table predictions in quite a few categories.

It would seem that this "percent positive" data would be most relevant to clinical decision making in instances where patients with seemingly low risk (i.e. T1c) may present with a spectrum ranging from one or two cores positive compared to (say) all cores positive. Conversely, for those men with features of high risk disease, where the probability of involvement of nodes and seminial vesicles might influence the choice of management, it may be useful to consult the CPDR tables. The Gancarczyk article offers an example from the low risk category: A 62 year old man, PSA 4.1 ng/ml, biopsy Gleason sum 6, with 6 of 10 cores positive: probability of organ confined disease - 52%; capsular invasion - 39%, +SV - 5%, and +N - 5%. Comparable parameters entered into the new Partin tables (T1c, Gleason 6, PSA 4.1 ng/ml) indicate probabilities of OC 80%, Cap+ 19%, SV+ 1%, N+ 0%. An example in the higher risk category: CPDR data - PSA 15, Gleason sum 8, 3 of 12 cores positive: OC 33%, Cap+ 35%, SV+ 25%, N+ 8%. The new Partin data (UROL, December, 2001), which uses clinical stage instead of "percent positive" cores predicts for PSA 15, Gleason sum 8, T2b (TNM'92): OC 7%, Cap+ 46%, SV+ 19%, N+ 27%.

BOTTOM LINE: No predictive model can be expected to be perfectly accurate. Now that the number of biopsy cores that are positive is routinely included in pathology reports, clinicians might want to consult **both** the Partin and CPDR tables when making disease management decisions.

CLINICAL TRIALS & PROTOCOLS — Dendreon Launches A New Vaccine Protocol For Men With Metastateic Hormone Refractory PCa With Gleason Sums ≤ 7

Encouraged by establishing "proof of principle" in their recently completed protocol, D9901, Dendreon has opened a new protocol with similar design but limited to men whose Gleason sum ≤ 7. The D9901 protocol utilized the Dendreon product "Provenge", a fusion protein combining GMCSF with prostatic acid phosphatase to create a vaccine, administered in three intravenous applications, and designed to stimulate a dendritic cell mediated immune response against prostate cancer cells (Discussed in PCa Commentary, December 2002). Treatment effectiveness was evident, but only in the subset of patients with Gleason sums of ≤ 7 (n=75) of which 50 men had received "Provenge" and 25 received a placebo. A major study end points was time to disease progression (TTP). Progression developed at a similar rate in both the treated and control groups (during which 50% of each group experienced progression) until about 8 - 10 weeks at which time a trend of better outcome favored the treatment group. This initial period of superimposed decline preceding the separation of the TTP graphic curves for the two groups was thought to result from the time required for the development of an effective immune response. The percent remaining free from progression in the treated v. control groups at 6 months was 34% v. 4%, at 12 months l0% v. 0%, and at 18 months 6.7% v. 0%. The numbers are small, but encouraging, and hence the new protocol, D9902B.

D9902B is now open for enrollment and is aiming for 275 participants. TTP progression and time to first occurrence of cancer related pain are the primary endpoints. As in the prior study, the randomization is 2:1 favoring treatment. For study entry contact Drs. Tia Higano (U of W) or John Corman (Virginia Mason Clinic).

The sister study of similar design (P11) remains open for enrollment. This study accepts patients experiencing their first PSA failure post radical prostatectomy and who are free of metastatic disease

on imaging studies. For patient entry contact either Dr. Higano, Dr. Corman, or Dr. Jack West, Swedish Cancer Institute.

BOTTOM LINE: Enrollment of men into these early vaccine trials is a vital first step toward the development of effective vaccine therapy for prostate cancer.

PATHOLOGY & DIAGNOSTICS Lymph Node Metastases: Observed And Occult - The Next Wave Of Attack

Despite the current trend of detection of prostate cancer at an earlier stage, about 15 to 40% of men (estimates vary) with apparently localized disease will have cancer recurrence. Localized cancer transforms into metastatic cancer as PC cell mutations endow cells with new capabilities - to mention only a few - that effect disassociation from the primary tumor, dissolve collagen barriers that prevent cell migration, and create PC cell receptors that respond to the cytokine tug from lymph nodes and the blood stream.

A well done study was reported by Bader and colleagues from the University of Bern (J UROL, March, 2003),"Disease Progression and Survival of Patients with Positive Lymph Nodes after Radical Prostatectomy. Is there a chance of Cure?" By performing meticulous *extended* lymphadenectomies in 367 men with apparently localized disease and examining the lymph nodes in 3 mm slices they observed metastases in 25% of cases. No immunohistochemical stains were used. They cleared the tissue from the external iliac vein to the internal iliac artery and from the femoral canal to the bifurcation of the iliac vessels. A median of 21 nodes (range 6- 50) were retrieved per case, substantially more than are removed in the less aggressive limited resection, which variously yields fewer nodes and finds positive nodes in about 7-12% of cases. The pathologic tumor stage ('97 TNM) and the percent with positive nodes were collated: pT1-pT2b - 13% positive nodes, pT3a - 25%, and pT3b 49%. They subdivided the cases into groups having one, two, or >2 positive nodes. At a median follow-up of 45 months the men in the 1, 2, and >2 nodes positive groups developed asymptomatic PSA rise in 18, 30, and 24% respectively, and symptomatic progression in 44, 60, and 62%. Their conclusion: 1) more nodes harbor metastases than customarily discovered at limited lymphadenectomies, and 2) "In lymph node positive prostate cancer, time to asymptomatic PSA increase, time to symptomatic tumor progression, and time to tumor specific death significantly correlate with the number of lymph node metastases."

Additionally, more sensitive detection techniques reveal micrometastatic deposits that routine H&E staining miss. Shariat in Cancer Research, Aug, 2003, using immunohistochemistry for cytokeratins and PSA, and RT-PCR for kallikrein (closely associated with PSA) found cancer in 7% of H&E negative nodes from pT3N0 patients. Martinez-Pineiro (European Urology Apr, 2003) using the RT-PCR technique found tags indicating mRNA for PSA in 39.5% (57/145) of "pN0" nodes, which were negative with immunohistochemical staining. Undetected nodal positivity must be one of the important factors leading to treatment failure in clinically localized prostate cancer.

Current research efforts are being directed toward identifying cells within the prostate which are members of a population of which some may already have escaped the gland, or cells which, while still in the prostate, display features that indicate the potential to metastasize. Dr. Don Malins, PhD, DSc at the Pacific Northwest Research Institute, Seattle, is developing the use of Fournier transform infrared spectroscopy on fresh prostate tissue to analyze the extent of oxidative and other damage to DNA (a surrogate for mutation) and is able to identify a characteristic pattern of damage associated with metastatic disease. Wang (JNCI, May 7, 2003) presents one of many studies wherein high-density tissue microarrays are used to identify patterns of gene expression associated with disease progression.

Dr. Alvin Liu and colleagues at the Institute for Systems Biology, Seattle, is approaching this issue by homing in on PC cell surface phenotype markers and has identified two cluster designations (CD), CD26 and CD10, which are associated with metastatic spread or the potential to spread. Evaluation for

these CDs can be performed with flow cytometry on fresh tissue, a technique that is easily performed in a good clinical laboratory.

With more accurate information about PC cell behavior - information whose accuracy will in time exceed observational data and the probability estimates based upon currently clinical parameters - comes the desire for effective early intervention. Currently, the clinical management debate revolves around the timing of hormone deprivation, early or late, or a whether a combined chemo-hormonal regimen is appropriate. The next wave, however, will be the early application of effective vaccine therapy; or treatment based on therapeutic antibodies, radiolabled or not, against appropriate CD targets. Stay tuned.

BOTTOM LINE: More accurate information about prostate cancer cell behavior will lead to a clearer definition of management choices.

IN BRIEF

Taxotere Chemotherapy in Men over 70: Chemotherapy is often withheld from men older than 70 years because of considerations of toxicity. In abstract 2996 (2003 ASCO Proceedings) Dr. Beer reported his analysis of the Taxotere experience (36 mg/M2 for 6 of 8 wks) of 34 men <70 yrs v. 52 >70 yrs culled from two published clinical trials. Results: no significant difference in outcome or toxicity. The PSA response rate was 40% in the younger group v. 47% for the older, and the time to disease progression was 19 v. 24 weeks (range for >70: 21-27 wks). Myelosuppression is usually very mild, and tolerance is quite acceptable for this regimen. Although the overall contribution of chemotherapy in this disease is modest, none the less, if treatment results in a response or prolonged disease stability, its tolerability allows long term application.

CORRECTION

In the August PCa Commentary, the IN BRIEF item on 10-year brachytherapy results mistakenly reported that the researchers concluded that the optimum dosage for low risk patients was ≥ 160 Gy when, in fact, the dose should have been reported as ≥ 140 Gy. This error was brought to our attention Dr. Kasra Badiozamani at the Swedish Cancer Institute.