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PRIMARY TX UPDATE: Is External Beam Radiotherapy A Necessary Supplement To Brachytherapy?

The question: "Permanent Prostate Brachytherapy: Is Supplemental External-Beam Radiation Therapy Necessary?" is the title of a review article authored by Drs. Blasko, Wallner, and Merrick in the May issue of ONCOLOGY, and the same issue is discussed in Merrick's "Monotherapeutic Brachytherapy for Clinically Organ-Confined Prostate Cancer, in West Virginia Medical Journal, July/August 2005. The authors share the opinion that the appropriate application of supplemental XRT is best narrowed to instances of high-risk disease predicted to have extensive involvement of the seminal vesicles and/or pelvic lymph node disease. Their collective data indicates that for low- and intermediate-risk, and some carefully selected high-risk tumors, despite a prediction of extra capsular extension, high-quality brachytherapy as a

single modality produces excellent treatment outcomes. The review in ONCOLOGY is particularly informative because it explains the radiobiologic basis of the "favorable biochemical control rates" achieved by optimal implant techniques, which incorporate "intraprostatic dose escalation", "generous periprostatic brachytherapy treatment margins", and scrupulous post-implant CT verification of seed location combined with accurate dosimetric analytic confirmation of the planned dose distribution. Merrick and Blasko report that in their hands 35%-40% of seeds are placed into periprostatic tissue, thereby extending the field of effective irradiation to 5-8 mm beyond the prostatic capsule and covering the proximal 6-10 mm of the seminal vesicles. Blasko points to pathologic data indicating that "the mean extent of extraprostatic extension [is] in the range of 1 to 3 mm; [and] thus brachytherapy margins of 5 mm should encompass all sites of extracapsular extension in 99% of cases". Their CT-based dosimetry demonstrates "post-implant treatment margins of 6.5 mm at the 100% isodose line". The target radiation doses are 140 Gy for I-125 and 100 Gy of Pd-103. The "adverse pathologic features (eg. high Gleason score, perineural invasion and extensive tumor)" become of less consequence in the face of improvements in radiation delivery." Because ... radiation dose decreases by up to 20 Gy/mm at the periphery of the target volume" it is recommended that "patients at significant risk for seminal vesicle and/or lymph node involvement are likely to benefit from supplemental XRT". Merrick claims, with a whiff of hubris that risks over generalization, that in his hands "cancercidal treatment margins [are] substantially larger than those obtainable with radical prostatectomy".

Results: In Merrick's series of 202 men with clinical T1b-T2c disease, with biochemical failure set at PSA > 0.4 ng/mL, the 8 year bPFS (median follow-up 5.2 years) for therapy with Pd-103 and I-125 was: low-risk (143 men), 98.0% and 93.4%; and for a combined intermediate- (51 men) and high-risk (8 men) group, 96.3% and 93.2%, respectively. The data graphs at this stage of maturity show a clear plateau with no failures after the 3 year mark.

Treatment results from the Seattle Prostate Institute have been widely reported. Representative results for men treated with contemporary technique: low-risk patients (I-125, at 10 years) ~ 88% bPFS, with no improved by supplemental XRT; intermediate-risk patients (Pd-103, at 9 years) - 82% bPFS, also not improved by supplemental XRT; and high-risk (PSA > 20ng/mL, Pd-103, at 9 years), bPFS 65%.

The ability to avoid supplemental XRT confers the advantage of avoidance of the 5 weeks required for administration of an additional 45 Gy of XRT to the prostatic bed and adds significant additional cost, which is considerable if IMRT technique is used. Long-term adverse effect on urinary quality of life may occur, but is lessened with experienced brachytherapists. Long-term bowel dysfunction occurs infrequently, but can be a very serious problem.

Not all radiotherapists agree with the strategic recommendations incorporated in the two articles referred to above, and two critical reviews are included in the ONCOLOGY issue. One objection focuses on the heterogeneity inherent in the "intermediate-risk" grouping and maintains that a more careful stratification in this cohort is needed to allow optimally informed individual treatment decisions. Another concern relates to the choice of the treatment modality for high-risk patients, where uncertainty in biopsy-based prognostic estimates of the true pathologic extent of disease might make a strategy external beam XRT alone the safest choice. Another caveat is that these excellent reported results come from work by very experienced brachytherapists, results that may not be achieved by physicians earlier in their learning curves.

All parties agree that the information that will emerge from RTOG Trial 0232, designed to investigate the usefulness of XRT supplemental to brachytherapy, will provide clarity in these areas of controversy.

PCa SCREENING: Theme And Four Variations:

"AGE-Adjusted PSAV and Prostate Cancer Screening" - Abstract No. 1 at the 2006 Prostate Cancer Symposium:

Dr. Judd Moul and colleagues presented data that adds useful sophistication to the decision of whom to biopsy. They analyzed pre-biopsy PSA velocity in three age groups and correlated PSAV with biopsy outcomes and identified PSAV thresholds in each group above which there is greater likelihood of detecting cancer than biopsies triggered by the traditional threshold of concern, > 0.75 ng/mL/y. . The analysis was based on 11347 men (145593 tests) followed at Duke University between 1988 and 2005. The data was limited to those men whose PSA was <4 ng/mL and PSAV <0.75 ng/mL/yr. In the two younger groups the detection rate was 35% for men ages 40-49 whose PSAV exceeded 0.25 ng/mL/yr (compared to 19% if cut-off of > 0.75 ng/mL/yr was used); 57% for men in the age range 60-69 whose PSAV exceeded 0.50 ng/mL/yr (compared to 25% for traditional threshold). In these two groups, the sensitivity values were 0.519 and 0.398, respectively, compared to 0.265 and 0.306 for the traditional cut-off of 0.75 ng/mL/yr, while retaining nearly the same specificity. The threshold of 0.75 ng/mL/yr was retained for the >70 year old group. Dr. Moul's recommendations for thresholds: >0.40 ng/mL/yr of age 40-49; >0.60 ng/mL/yr for age 60-69; and >0.75 for more over age 70.

"Prostatitis Confounds The Use of PSA Velocity for Prostate Cancer Detection" - Abstract No. 4:

Catalona et al. presented data from a small study that adds statistical support to the awareness, current among clinicians, that a rapid rise of PSA during the year preceding a proposed biopsy may be due to prostatitis. Their data was based on an analysis of "ranges of PSAV and their association with prostate cancer on first biopsy (quadrant or sextant biopsies) and the probability of prostate cancer during the following two years" in a cohort of 1797 men with normal DREs who were followed in a community based cancer screening program. Results: when the PSAV (ng/mL/yr) was <0, 0-1.99, 2-3.99, and >4 cancer was found on the first biopsy in 30%, 28%, 22% and 13% respectively. Cancer was found within 24 months (using the same PSAV groupings) in 39%, 36%, 28%, and 15%, and prostatitis histologically present in 5%, 6%, 8%, and 13%, respectively. All p-values were <0.001.

"A Model of the Natural History of Screen-Detected Prostate Cancer, and the Effect of Radical Treatment on Overall Survival" - Abstract 5:

Clinicians are well aware that PSA screening introduces "lead time" bias into the diagnosis of prostate cancer, and are also aware that radical treatment of screen-detected cancer may not yield an improvement over delayed intervention or, in some instances, no primary therapy. This study represents a valid effort to quantify these difficult to pin down issues by comparing data from a variety of peer-reviewed, highly regarded sources. While estimates can vary among investigators and analytic methodologies may be challenged, the results presented in this abstract are provocative and informative:

1) Based on biennial PSA screening the lead-time estimates for men, aged 55-59 years, diagnosed by PSA screening were 14.1, 9.3, and 5.0 years for men with Gleason scores <7, 7, and >7.

2) "Estimates of 15-year prostate cancer mortality for conservative management of screen-detected prostate cancer ranged from 1% for Gleason scores <7, 7-20% for Gleason score 7, and from 23-68% for Gleason scores >7."

3) "For men aged 55-59 at diagnosis, the predicted absolute 15-year survival benefit from curative treatment of screen-detected prostate cancer was 0%, 11% and 23% for men with Gleason scores <7, 7, >7, respectively". Their conclusion: "The case for curative treatment, rather than conservative management, of screen-detected localized prostate cancer is strongest in men with high grade disease".

Washington State Legislation on Prostate Cancer Screening:

A bill passed by the House and Senate and signed by Governor Gregoire, effective June 7, 2006, is now a law "offering coverage for prostate cancer screening ... to public employees and their covered dependents ... provided that the screening is delivered upon the recommendation of the patient's physician, advanced registered nurse practitioner, or physician assistant". Interestingly the letters "PSA" do not appear in the bill, and the initiative for "recommending" still rests with the health professional, but this bill, lobbied for by the Washington State Prostate Cancer Coalition, can easily be construed as a sign of increasing official support for PSA screening.

PREDICTING OUTCOME OF PRIMARY TX: NOMOGRAM UPDATE: "Preoperative Nomogram Predicting the 10-year Probability of Prostate Cancer Recurrence After Radical Prostatectomy"

Michael Kattan and colleagues published a nomogram update (JNCI , May 17, 2006;98:715-7) extending the preoperative predictions to 10 years as compared to the frequently used earlier version (1998) with its 5 year predictions. The 1998 nomogram that so many clinicians consult on their Palm Pilots or the Web has served as "the most widely used disease-specific prediction tool in oncology" - for patient counseling, clinical trial design, or decisions regarding adjuvant therapy. The important new features are the inclusion of "prognostic information of systemic biopsy results" (number of positive and negative cores) and entry of the year of surgery, an acknowledgment of progressive improvement in surgical technique. Alternative versions that did not include the percentage of cores positive "had less predictive accuracy in external validation" The data is based on the post surgical outcomes of 1978 men who were treated by high-volume surgeons at Baylor and MSKCC between 1983 and 2002. This population reflects the significant changes in tumor grade and the stage migration that have been seen in more recent years as the findings from PSA screening programs have become the indication for prostate biopsy. The extension of observations to 10 years is additionally informative "because a substantial number of men will experience disease recurrence after maintaining an undetectable PSA level for 5 years or more after radical prostatectomy", whereas only 3% will relapse after that period of apparent disease control. As before, disease progression was "defined as a serum PSA value of 0.4 ng/mL or greater (confirmed by a second PSA value higher than the first by any amount), secondary therapy, clinical recurrence, or aborted radical prostatectomy for lymph node metastases". The final nomogram functioned well when it was validated by comparison with 1545 patients operated by different surgeons. A unique feature of the current nomogram allows the option "to estimate the probability of recurrence at any point in time from 1 to 10 years after radical prostatectomy". Michael Kattan indicated (personal communication) that this new data will shortly be incorporated into their existing Web-available preoperative nomogram.

PREDICTING OUTCOME OF PRIMARY TX: Epigenetic Molecular Markers: A New Tool For Segregating Aggressive From Indolent Prostate Cancers.

Susan Cottrell, senior scientist at the Seattle branch of the biotech company, EPIGENOMICS, presented her group's findings at the 2006 AACR Symposium showing that quantitative real-time PCR analysis of the methylation status of five molecular markers yielded valid predictions of prostate cancer aggressiveness. Also studied was a sixth marker, PITX2, also prognostic for breast cancer outcome, and the results were impressive for predicting outcome for prostate cancer: "The methylation of PITX2 provided information beyond what is already provided by traditional prognostic indicators such as Gleason analysis, pre-surgical PSA, staging, and a nomogram". "PITX2 positive patients have a 5-fold higher risk for PSA recurrence within 10 years."

Their study was performed on 605 formalin-fixed, paraffin-embedded RP specimens, and analyzed the extent to which the candidate markers were aberrantly methylated, and correlated the results with post surgical outcomes. The addition of methyl groups to cytosine/guanine dinucleotides, usually targeted to the promoter region of a gene, is an important epigenetic mechanism that impedes the normal transcription process resulting in alteration of gene expression and cellular behavior.

"Hypermethylation of all six markers were correlated with poor survival, but three markers (PITX2 [p=0.00017], GPR7 [p=0.0096], and an EST ['expressed sequence tag'] on chromosome 3 [p=0.035] were statistically significant when the median methylation level was used for cut-off", showing "strong separation of good and poor prognostic groups".

It is anticipated that after further validation this test will become commercially available and contribute useful additional information for treatment selection. Additionally, "Prostatectomy patients testing positive for hypermethylation of these markers would be an ideal sub-group for clinical trials on the efficacy of early adjuvant therapy".

HORMONAL INTERVENTION: Testosterone Recovery After Cessation Of LH-RH Agonist Therapy

Although LH-RH agonist products carry marketing designations of 3, 4, or 12 months duration, clinicians are well aware that the duration of testosterone suppression usually lasts far longer than the implied period. A March 2006 report in PROSTATE from Japan quantified the prolongation of suppression that followed a 30 month median duration of treatment in 32 men who exhibited castrate levels at the end of therapy.

Testosterone and lutenizing hormone levels were measured at 3 months intervals. Results: "Median duration of castrate T levels following cessation was 6 months. Median time to normalization of T levels was 24 months", whereas LH levels recovered in 3 months. Men older than 65 recovered at a slower rate [some never recovering fully].

Abstract No.90 presented at the 2006 Prostate Cancer Symposium reported on "the time course of recovery of serum testosterone levels after a short course of LH-RH analogue and radical radiotherapy to the prostate". Fifty nine men were measured at baseline, and at 6 weeks, 12, 18, 24 and >40 weeks after the last injection. The median treatment period was about 3 months. Conclusion: at 6 weeks after LH-RH cessation no patient showed testosterone recovery. Recovery was seen in 35% at 12 weeks, 85% at 18 weeks, 89% at 24 weeks, and 96% at 1 year, and "the mean testosterone level at 52 weeks was similar to the baseline level".

Both studies offer perspective to the interpretation of PSA levels following treatment with LH-RH agonists.

ANDROGEN INSENSITIVE DISEASE: "Intermittent Chemotherapy in Metastatic Androgen-Independent Prostate Cancer (AIPC): Initial Results from ASCENT." Abstract #216, 2006 Prostate Cancer Symposium

The ASCENT clinical trial compares Taxotere plus high-dose vitamin D to Taxotere alone in a 250 man phase III study. Built into the schema is an option for men to suspend treatment "if they had confirmed $\geq$ 50% reduction in serum PSA and a serum PSA $\leq$ 4 ng/mL". "Treatment was resumed when the serum PSA rose by $\geq$ 50% and $\geq$ 2 ng/mL, or for other evidence of disease progression". Twenty percent of the combined treatment patients and 16% taking only Taxotere met the criteria and chose to enter a "treatment holiday". The median duration of the "off" period was 16 weeks (range 4-74+), and upon re-treatment 50% again showed a $\geq$ 50% reduction in serum PSA, 35% had PSA stability, and 15% progressed.

Dr. Beers concluded: "This strategy results in a meaningful duration of chemotherapy holidays and can be offered to a minority (18%) of patients".