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PRIMARY TX UPDATES: A Consortium Of Expert Brachytherapists Publish State-Of-The-Art Results.

Optimal outcomes for seed brachytherapy are importantly dependent upon the skill and experience of the operator. Dr. Greg Merrick, Schiffler Canter Center, Wheeling, WV, leading a group of BT practitioners (including Dr. Kent Waller, Group Health Cooperative, Seattle, WA) has demonstrated that with scrupulous dosimetry and meticulous placement of some seeds beyond the physical boundary of the prostate in Gleason score (GS)7 disease they have been able to neutralize the adverse consequences of a major Gleason pattern 4. This pattern is considered more inherently aggressive and likely to metastasize than pattern 3 and is associated with a greater extent of extracapsular extension. Dr. Merrick's team treated 530 men, 300 with GS 3 + 4, and 230 with 4 + 3. His report, "Primary Gleason Pattern Does Not Impact Survival After Permanent Interstitial Brachytherapy for Gleason Score 7 Cancer", appeared in CANCER July 15, 2007.

The results of their work challenge the notion "that Gleason score 7 can be stratified into prognostic categories by dominant histologic grade." This report is important, additionally, as being illustrative of the excellent outcome that can be achieved by state-of-the-art technique. Since the management strategies applied ADT and EBRT differently according to individual patient risk factors, it is difficult to compare the results with other primary modes of therapy.

An important collateral observation arose from analysis of the causes of death in the study: "...cardiovascular/pulmonary disease and second malignancies accounted for 46 of the 57 deaths (80.7%), with only 5 of the deaths (8.8%) attributable to prostate cancer (0.9% of all patients) [at a median follow-up of 5.7 years]. This 9.6 fold increase in non-cancer related deaths suggests the need for counseling prostate cancer patients to optimize healthy life-style choices. Overall in this study "Patient age, diabetes, and tobacco usage were the strongest predictor of OS [overall survival, as opposed to CSS]."

What were the demographics of the 530 men in the study? The two groups were comparably composed: median age, 67 years; median pretreatment PSA, 6.8 ng/ml; prostate volume, 33.5 cc; percentage of positive biopsies, slightly higher in the Gleason 4 + 3 group (50% vs. 36.9%); and the dosimetry was similar with a median D90 of 118.9 Gy. Pd-103 was used in 93.2% and 6.8% received I-125. The clinical stage was T1b-T2b in 94.3% of the Gleason 3 + 4 group (n=283) vs 87.4% (n=201); and was T2c-T3 in 5.7% (n=17) for men with GS 3 + 4 vs 6.1% (n=14) for GS 4 + 3 men. Patients with PSA values > 10 and/or stage $\geq$ T2c received a staging pelvic CT and bone scan. "No patient underwent seminal vesicle or pathologic lymph node sampling."

What variation of adjuvant treatments were used to address the differing risk categories among the men? EBRT (45 Gy) was given (before BT) in 77.7% and applied to a similar extent in both Gleason groups, with a larger pelvic treatment field given to those whose risk of lymph node involvement was judged to be more than 10%. ADT ($\leq$ 6 months) was given to 23.4% pre-BT to address the suboptimal geometry of large glands; and 10% (n=53) received prolonged ADT (> 6 months) for poor prognosticators. The overall median duration of ADT was 4 months.

Practitioners treating prostate cancer will recognize that the population under treatment in this study reflects the current community demographics of men who present for prostate cancer treatment, and that the management regimens in this study correspond to accepted high-grade radiotherapy practice.

The results: "At 10 years, Gleason 3 + 4 versus 4 + 3 did not predict for CSS (96.7% vs. 93.3%), bPFS (97.0% vs 92.9%5), or OS (77.0% vs 78%). Clinical stage and radiation dose predicted for CCS; and clinical stage, pretreatment PSA, and prostate volume predicted for bPFS.

Dr. Merrick would argue that his study gives credence to aggressive therapy (EBRT and permanent seeds) in these mostly intermediate risk patients.

PRIMARY TX UPDATES: Long-Term Prognostic Significance of Primary Gleason Pattern in Patients With Gleason Score 7 Prostate Cancer: Impact on Prostate Cancer Specific Survival, J Urol, Feb 2006.

This article by Tollefson et al. from the Mayo Clinic presents the 10 year outcome data based on 1688 men treated with radical prostatectomy and pelvic lymphadenectomy for Gleason Score 7 prostate cancer and is an appropriate counterpoint to the brachytherapy article above. Comparison of the details in the two articles also highlights the difficulty of comparing data

from these two primary treatment modalities even when the populations under study are defined as carefully as possible.

The executive summary: With respect to cancer specific survival (CSS) at 10 years there was no significant difference between the CSS in the two studies: for BT the 10 year CSS for biopsy Gleason score (GS) 3 + 4 vs GS 4 + 3 was 96.7% vs 93.3%; and for the Mayo study the figures were 97% vs 93% for pathologic GS 3 + 4 vs. 4 + 3.

It is possible, however, that because of the larger number of men in this Mayo Clinic study (1688 vs 530) the CSS outcome difference between the two Gleason Scores under study in the Mayo trial reached statistical significance, p=0.013. It's tricky to try to factor into these comparisons the 25% or more upgrading that is known to result in the transition from biopsy GS to pathologic GS, but conceivably moving some of the postulated "undergraded" primary GS 4 cancer in the Merrick brachytherapy study from the GS 3 + 4 column into the 4 + 3 group might have increased the spread between the two categories in the BT study.

What were the differences between the details of the Merrick and Mayo trials? No men in the Mayo study received ADT either neoadjuvantly or in the immediate postoperative period. PSA failure threshold was O.4 ng/ml in both studies, but the Mayo article does not specify how many men ultimately received XRT or ADT leading into their calculation of CSS. However, in the BT study only 10% of men received post treatment ADT for longer than 6 months

The ultimate arbiter of Gleason score is the histology in the surgical specimen. In the Mayo study pathologic examination of the surgical specimen diagnosed seminal vesicle involvement in 15.2% of the GS 3 + 4 group vs 22.7% in the GS 4 + 3 cohort; and positive surgical margins were found in 34% vs 40%, respectively. There was no mention as to the frequency of extracapsular extension. These pathologic features could be expected to be about the same in the Merrick study. And since 77% of patients in the BT study received adjuvant XRT, these adverse pathologic features would have been unknowingly treated initially. The Mayo study excluded men found at surgery to have lymph node involvement.

The ultimate rate of 10 year estimated progression free survival in the BT study was 97.0% vs 92.9% (primary GS 3 vs 4). Progression-free survival from initial surgery in the Mayo study was 48% vs 38% (GS 3 vs 4), which rose to a CSS outcome of 97% vs 93% with the aid of adjuvant XRT. The difference in PFS between the two studies clearly indiicates the beneficial effect of early adjuvant XRT treatment in the BT series, whereas the ultimate similarity in CSS data between the studies indicates that subsequent adjuvant XRT therapy effectively "salvaged" many men with early biochemical progression in the Mayo study.

Because of the inherent nature of the two modalities, there is no way to resolve the these difficulties which prevent a perfect comparison between the two. Each of the two modalities of primary therapy has its inherent strong points. The Merrick study would suggest that their technique of radiation delivery overrides any adverse influence on CSS resulting from the more aggressive primary Gleason pattern 4, whereas the Mayo analysis concludes that their study continues to support "pathological Gleason pattern 4 as an independent predictor of survival in patients with GS 7 prostate cancer. Overall, however, both studies show that when BT and RP are carried out by skilled practitioners, the cancer specific survival for men with GS 7 cancer can be encouragingly favorable.

ADJUVANT / NEOADJUVANT TX: "Adjuvant Radiotherapy for Pathologically Advanced Prostate Cancer"

This study, SWOG 8794, coauthored by Drs. Ian Thompson, Jr., Edward Messing, David Crawford et al.(JAMA Nov 15, 2006) assesses the effectiveness of immediate adjuvant radiotherapy following a prostatectomy in men with pT3 N0 M0 cancer and is a companion piece to the JCO, May 2007, article by Stephenson et al. (reviewed in the PCa Commentary, June 2007), which analyzed the timing of the application of radiotherapy as "salvage" for PSA progression after prostatectomy. This SWOG trial, conducted between August 1988 and January 1997, randomized 425 men after radical prostatectomy and pelvic lymphadenectomy (excluded in some lower risk patients) to either immediate adjuvant XRT, 60 to 64 Gy, to the pelvic fossa (n=214), or to "observation" (n=211), with XRT upon PSA relapse defined as a PSA rise above 0.4 ng/ml. The extent of disease was well balanced between the two study groups, each having ECE/SM+, 68%; SV+ 22%; both, 22%. Adjuvant ADT was not part of the study regimen.

The feature that makes this trial interestingly different from others is the study objective: "To determine whether adjuvant radiotherapy improved metastasis-free survival in patients with stage pT3 NO MO prostate cancer," with the end point defined as the first objective evidence of metastatic disease or death from any cause. This goal was chosen for its practical clinical appeal "because the development of metastatic disease generally leads to morbid therapies," i.e. ADT with its associated toxicity, and morbid events such as pathologic fractures, ureteral obstruction or neurologic complication.

Unfortunately, the hoped for benefit from immediate adjuvant radiotherapy was not achieved: there was no statistically significant improvement in either metastasis-free survival or overall survival resulting from immediate radiotherapy.

A gratifying observation did emerge, however, during the median follow-up of 10.6 years. At the time of study design it had been anticipated that the median metastasis-free survival for the observation group would be 6 years, but the actual result was a 13.2 years, "with 5- and 10-year metastasis-free survivals of 84% and 63%, respectively." For the immediate XRT cohort the result was a median metastasis-free survival of 14.4 years, not significantly different.

The clarity of comparison between these two treatment strategies, however, was constrained by the usual clinical necessity, i.e. a requisite crossover XRT option was available to men in the observation group who experienced PSA failure. A total of 70 men in the "observation" group eventually received XRT because of PSA relapse or objective recurrence. There was no data presented to indicate the timing of the XRT intervention in these crossover patients and its possible effect on outcome.

The now well-recognized postponement of PSA relapse that results from early versus late adjuvant intervention was clearly seen in this study. The median PSA relapse-free survival for the XRT group was 10.3 years vs 3.1 years for the observation cohort. The authors candidly undervalued this "benefit" for early XRT by stating, "Currently, there is debate as to whether a PSA response to treatment can serve as a surrogate for disease-related outcomes; thus, the implications of a reduced risk of PSA relapse after radiotherapy are unknown."

How did the tally sheet of benefits and liabilities stack up at the final analysis?

Pros: 1) At the present time with patients hypersensitive to their PSA levels, postponing PSA relapse postpones anxiety.

2) LHRH agonists, currently the major method of androgen deprivation, have significant toxicity, and in this study "adjuvant radiotherapy significantly reduced the risk of receiving adjuvant hormonal therapy." By five years 21% of the observation group had received ADT vs 10% for the XRT arm.

Cons: 1) "A significant reduction in metastatic disease was not demonstrated."

2) Radiotherapy was associated with an increased complication rate: in total 23.8% for adjuvant XRT vs. 11.9%, "observation." Proctitis and rectal bleeding occurred in 7/214 (3.3%) men receiving XRT vs none in the observation group; urethral strictures developed in 38/214 (17.8%) vs 20/210 (9.5%); and "total urinary incontinence" occurred in 14/214 (6.5%) vs 6/211 (2.8%), respectively. The crispness of these comparisons was impaired by the 33% of men in the "observation" arm who ultimately received XRT at crossover and who likely experienced these side effects at a rate similar to the immediate XRT men.

The study planners' intention to make the study end point meaningful by focusing on clinically significant events such as "death from any cause" and metastasis-free survival was undercut by the now familiar observation that in a disease with such a long course as prostate cancer, non-cancer deaths predominate. In this study 68.9% (115/167) of deaths were from other causes. By removing these cancer-unrelated deaths from the calculation, good news again emerges regarding the long term outcome for treatment of men with pT3 N0 MO prostate cancer. For the combined groups in this study it was determined that "at 13.2 years, the metastasis-free survival estimate would be 78%."

Considering the "lack of a statistically significant improvement in metastasis-free and overall survival in the 2 study groups" the authors allow that a strategy of initial observation and XRT upon PSA relapse "may be reasonable." [See the PCa Commentary review of the Stephenson article on "salvage" XRT for discussion of the optimal timing of XRT delivered upon PSA relapse following surgery.]

The final conclusion was balanced, and rather neutral: "The results of this study may provide guidance for clinicians and patients considering options for adjuvant therapy for pathologically advanced disease."

NEW AGENTS FOR TX: Update: "*Provenge*", Dendreon's Prostate Cancer Vaccine

Patients and physicians are interested to know the current status of FDA licensing approval of *Provenge* for use in metastatic HRPC. The short answer: approval has been deferred pending analysis of mature survival data from three Phase III trials, and a decision may be delayed possibly until as long as 2010, although an interim analysis scheduled for 2008 might be the basis of an earlier approval. Two completed Phase III trials and a third, the 500 man Phase III IMPACT study (IMmunotherapy for Prostate AdenoCarcinoma Treatment), recently closed to registration, will be the basis for the evaluation of efficacy.

Dr. Eric Small, a principle investigator in these studies, presented a complete review of the development of *Provenge* (generic name: sipuleucel-T) and a summary of the trial findings in Expert Opin Biol Ther (2007)7(8).

In brief, the preparation of *Provenge* begins with an ex-vivo incubation of a patient's mononuclear cells with a fusion molecule combining the prostate membrane antigen PAP (prostatic acid phosphatase) with GM-CSF (granulocyte-macrophage colony stimulating factor). GM-CSF targets this fusion product to developing dendritic cells, which mature from mononuclear precursors during the 40 hours of incubation. This preparation of sensitized

dendritic cells (*Provenge)* is administered intravenously to the patient where they home to lymph nodes, take up residence, and proceed to educate the patient's T lymphocytes to recognize and destroy the prostate cells bearing the PAP target.

Initially seven small (~20 or so patients each) Phase I and II studies were carried out in prostate cancer patients, three involving men with hormone-sensitive PC showing serologic progression, and four in men with metastatic hormone refractory disease. These trials established that *Provenge* was capable of eliciting the desired T-Cell immunologic response in 100% of the subjects in three trials. Important declines in PSA values were seen in a substantial number of patients. The safety of *Provenge* was established; and side effect were well-tolerated - essentially infusion reactions such as rigors, pyrexis, tremors and feeling cold.

Encouraged by these early findings, Dendreon sponsored and completed two Phase III randomized, placebo controlled, trials (D 9901 and D 9902), comprised of men with hormone-insensitive, asymptomatic metastatic disease - a total of 147 treated with *Provenge* compared to 78 placebo controls. The primary end-point for these trials was TTP (Time To disease Progression, defined as objective progression or the development of pain). In one of the studies there was a nonsignificant improvement in TTP for treated men, 11.7 weeks vs. 10 weeks for controls. Survival was not a designated study end-point. However, at 3 years the survival for the treatment group was 34% vs. 11% for the control cohort; and the median overall survival comparison was 25.9 months vs. 21.4 months, respectively. These median survival data were among the materials presented to the FDA for the combination of the two studies: 23.2 months for *Provenge* treated patients vs 18.9 months for controls; and the median survival at 36 months was 33% vs. 15%, respectively.

The lack of sufficient mature data establishing a statistically supported survival benefit for *Provenge* was the basis for the FDA withholding its approval. When the FDA conducts its future review it will have more mature survival data from the first two studies, and additionally, data from the now-closed IMPACT trial.

A study of perhaps greater relevance to treatment options in the management of prostate cancer is the now closed P-11 study, in which 175 men with minimal serologic progression after primary therapy were randomized to *Provenge* vs control in a 2.1 ratio. Since there is a general consensus that an effective prostate cancer vaccine would most likely be optimally applied in a setting of low tumor burden, P-11, if positive, would hold great promise. It could nicely be introduced into a niche in the early progression of prostate cancer where hormone intervention can be judiciously withheld.

If the FDA approves *Provenge* for clinical use, a unique and important non-toxic treatment will have been added to our armamentarium.