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Contents

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PRARY TX UPDATES: "Salvage Radiotherapy for Recurrent Prostate Cancer: The Earlier the Better"

The quote above is the title of the editorial accompanying the recent JAMA article (March 17, 2004 -Vol. 291, 1325) jointly authored by 16 leading prostate cancer gurus retrospectively analyzing the outcome of 501 men treated with "salvage" radiotherapy (SRT) after PSA relapse following radical prostatectomy. The data base represents pooled information from five leading institutions. Although much has been written on this subject, this study is the largest and most comprehensive to date and provides an excellent reference for clinicians. A second worthy reference is the review, "Salvage radiotherapy following radical prostatectomy" by Catton and Milosevic, writing from the Princes Margaret Hospital and University of Toronto (World J Urol (2003)21: 243-252). Both articles conclude that salvage radiotherapy to the prostatic fossa is underused (and too often offered too late), and should be considered for all men who present with a PSA relapse. The treatment is considered well tolerated and is the only potentially curative modality available for this group of men. Of particular interest is that both groups offer data supporting an expansion of the customary parameters that heretofore have been considered requisite for the optimal chance of success.

Not surprisingly, the basic recommendations from prior studies remain reinforced: the optimal outcome from SRT is achieved in men with Gleason scores of <8, the PSA doubling times (PSADT) of >10 months, whose PSA relapse occurs >2 years post RP; and in situations where the surgical margin s positive, and

there has been no invasion of seminal vesicles or lymph nodes. The optimal pre-SRT PSA is between 1 and 2 ng/ml. (ASTRO recommends <1.5 ng/ml). The JAMA data found that men who had all of the favorable features enjoyed a 77% freedom from PSA relapse at 4 years median follow-up. Relapse was designated at a PSA >.1 ng/ml. above post SRT nadir, and confirmed by a second consecutive rise or by continued rise in PSA after treatment. The rate of progression following SRT is significantly greater (<0.001) when SRT was initiated at PSA values >2 ng/ml. The authors conjecture that the frequency of initially isolated local recurrences may be underestimated, and that early application of SRT offers the possibility of preventing progression to metastatic disease for even some patients at highest risk. In their outcome analysis they found that "for patients with the poor prognostic features of either high Gleason score or a short PSADT, early treatment (i.e. before the PSA level reached 2 ng/ml) more than doubled the 4-year progression free survival." During the 4 year median follow-up of the 501 men, 50% experienced progression, 10% developed metastases, 4% died from prostate cancer, and 4% died of other causes. The median time to progression after SRT was 12.5 months and 92% of these relapses occurred within 4 years.

What is the major new concept that emerges from the JAMA analysis? The researchers discovered that a positive surgical margin is a favorable finding that "suggests a greater likelihood that recurrence is due to residual pelvic disease...even for patients with aggressive features such as Gleason score of 8 to 10 or a rapid PSADT". Early SRT for this group of men with positive margins and Gleason scores 8-10 achieved a 4 year freedom from PSA relapse of 81% if the PSADT was > 10 months, but only 37% for a shorter PSADT. The rapidity of the PSA rise is a very significant indicator for risk of PSA failure. For example, when SRT was commenced at PSA <2 ng/ml in men whose Gleason score was 4 to 7 and whose PSADT was <10 months, those with positive margins had a 4-year PSA control of 64% compared to 22% control for men with negative margins. The article provides a very clear graphic algorithm that sets out the four-year actuarial progression-free survival after SRT and charts all the various permutations of the major risk parameters so that a clinician could easily identity the likely outcome from SRT for any individual patient. The authors acknowledge that "no comparative study has shown that SRT improves survival or prevents metastatic disease", but they believe that SRT can offer the possibility of cure for even some high risk for recurrence patients who heretofore would not have been considered promising candidates for SRT, or at least SRT can alter the natural history of the disease.

The Catton article addresses treatment complications with the following comment: "Acute complications of diarrhea, urinary frequency and urgency were reported as common events, but no grade 3 or 4 acute morbidity was reported. Late grade 3 and 4 complications were identified in less than 2% of the patients."

Bottom Line: The JAMA authors conclude: "patients with positive surgical margins who experience relapse after radical prostatectomy should be strongly considered for salvage radiotherapy, even those with high grade disease [Gleason sum 8 - 10] and/or rapid [< 10 month] PSADT.

PRIMARY TX UPDATES: High Dose Rate Conformal Brachytherapy - "The Other Brachytherapy": A Three Institution Consortium Reports Long Term Outcome

Most times when prostate brachytherapy is mentioned the technique that comes to mind is the permanent placement into the prostate of radioactive seeds, either with the isotope Iodine 125 or Palladium 103 as the source. The prefix "brachy-" stems from the Greek meaning" short". High dose rate brachytherapy (HDR-BT) involves the delivery of radiation to the prostate and to as far as 5mm beyond the capsule through 12 or more temporarily placed catheters. Each catheter becomes a conduit through which a wire tipped with an Iridium 192 radiation source delivers a planned dose and is then withdrawn. The length of time that the source remains at its target site determines the dose to that location. Each catheter is employed sequentially. HDR-BT is accompanied by treatment with external beam radiotherapy (EBRT). Multiple authors working in Germany, Michigan, and Seattle (including Drs. Tim Mate and Steve Eulau) have reported treatment outcome data at a median follow-up of five years in their article: "Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression of localized prostate cancer" (Int. J. Radiation Oncology Biol Phys, Vol. 58(4) 1048-1055, 2004). There is considerable overlap in the tumor characteristics of patients undergoing treatment for prostate cancer with surgery, permanent seeds, HDR-BT, or EBRT. However,

with regard to men being considered for treatment with radiation therapy, an imperfect generalization would suggest that low to intermediate risk patients thought to have organ confined disease are optimal candidates for treatment with permanent seeds, and HDR-BT and EBRT are a better fit for intermediate and high risk patients. For patients with significant medical comorbidities, large prostate glands, significant urinary obstructive symptoms, or prominent TURP defects, EBRT may be the better modality. The practitioners of HDR-BT cite advantages for this technique principally stemming from the positive control over radiation distribution and the customized dose intensity that this modality affords. Once the catheters are placed, the HDR delivery system allows varying the intensity of radiation dose to different areas within the prostate to as to address varying locations of tumor. They claim that 94% of the targeted areas get 100% of the planned radiation and consider their technique especially well suited to tumors with a high likelihood of multifocal disease and extracapsular extension, since the radiation may be tailored to extend up to 5m beyond the capsule. Even after the HDR-BT has been completed, further dose targeting can be customized, if needed, in the EBRT phase. They assert excellent radiation coverage base to apex, and point out that by carefully shaping the dose distribution radiation to the urethra can be minimized. The flexibility to customize the radiation dose afforded by HDR-BT, and the possibility of delivering higher total doses to the prostate with the HDR-BT/EBRT combination than can be safely achieved by EBRT alone lead to fewer treatment side effects, proponents believe. A negative feature for HDR-BT is that it is heavily labor intensive. As currently practiced in Seattle, HDR-BT requires an overnight hospitalization during which two applications of 8 to 9 Gy of irradiation are delivered via the catheters (only one catheter implant procedure required). This HDR-BT dose is approximately the equivalent of 40 to 50 Gy if delivered by standard EBRT. After HDR-BT, an additional 45 to 50 Gy EBRT is delivered, for a combined EBRT dose equivalent of 85 to 90 Gy. The total treatment time is approximately 6 to 7 weeks. EBRT to pelvic nodes is only offered in situations where the likelihood of nodal spread is considerable, i.e. estimated to be at a risk greater than 15%.

What are the results of the HDR-BT/EBRT treatment? The article by Mate, Eulau, et al. presents the outcome of 593 patients categorized into three risk groups: Group I (low risk, 46 men) stage < T2a (UICC'92), Gleason score < 6, and initial PSA < 10 ng/ml; Group II (intermediate risk, 188 men) comprising men who had one of the following higher risk features, clinical stage > T2b, Gleason score > 7, or iPSA > 10, replacing a Group I element; and, Group III (high risk, 359 men) comprising men with two or three of the higher risk features. The biochemical control rate (as defined by ASTRO) at a mean follow-up of 5 years for Groups I, II, and III were 96%, 88%, and 69% respectively. The cancer specific survival was 100%, 99%, and 95% and the overall survival 88%, 86%, and 85%, again respectively.

How do these results compare to EBRT alone? Kupelian et al. recently reported treatment outcome of a series of 1352 men with T1-T3 disease treated at the Cleveland Clinic with EBRT alone (CANCER, March 15, 2004. pp 1283-1292)? The risk groups were generally similar. However, although the ultimate goal for comparison between studies is "apples to apples", but most times it's more like Macintosh to Granny Smith. The biochemical relapse free survival at a median of 5 years follow-up for the low, intermediate, and high risk groups was 93%, 83%, and 71% respectively. Their analysis allowed this encouraging observation: "The most remarkable observation in the current series was that, among patients who actually experienced biochemical failure after RT, only 28% developed a clinical failure (either local or distant) at 10 years after the failure date." Just as the Vanguard investment guru, John Bogle, constantly stresses, "cost matters", so in radiotherapy for prostate cancer, "dose matters". The HRT-BT dose has gradually increased to a near maximum effectiveness. The total dose delivered by monotherapy with permanent seed implantation is approximately equivalent to 120 Gy EBRT. The results I've cited from the Kupelian study are for only those men who received > 72 Gy, since lesser doses clearly yielded inferior results. Current doses with conformal 3-D and IMRT technology are pushing into the 80 and 90 Gy. and local control is steadily improving with increased irradiation dosage.

Bottom Line: High dose rate brachytherapy is an effective technique for prostate cancer treatment and is especially suited for selected patients.

HORMONE INTERVENTION: Early Androgen Deprivation Benefits Men In High Risk disease category Who Have PSA Relapse After Radical Prostatectomy

"Early Versus Delayed Hormonal Therapy For Prostate Specific Antigen Only Recurrence Of Prostate Cancer After Radical Prostatectomy" (J UROL; Vol 171, March 2004 pp. 1141-1147) by Judd Moul et al. is an important contribution to evidenced based decision making about the management of men with PSA relapse (PSAR) after RP. The findings of this study were amplified by Dr. Moul, the Director of the Center for Prostate Disease Research, in his excellent talk at the recent Swedish Hospital symposium on Prostate Cancer. The study results were based on the retrospective analysis of 1352 men who experienced PSA failure (PSA >0.2 ng/ml) after prostatectomy. The analysis categorized the men into two groups based on an estimate of either high or low risk for clinical recurrence, and then recorded the time to the development of clinical metastases that was associated with the early use of androgen deprivation (AD) versus no AD in both groups. Although most clinicians would intuitively assume benefit for early AD, this is first study to statistically demonstrate which disease characteristics merit consideration of early AD treatment, and calculate the extent of that benefit in this PSA only relapse population.

What were the features of the high risk group for which the study found benefit? They designated as "high-risk" men with a Gleason score >7, a PSA doubling time (PSADT) of <12 months, and men in whom the prostate capsule was positive and the pathological Gleason sum was >6; or positive surgical margins, lymph nodes, or seminal vesicles. The low risk group, which gained no benefit from early AD, had organ confined disease, or "extracapsular extension only and negative surgical margins with Gleason sum <6." This low risk group was considered "curable" by the Johns Hopkins' definition. The authors chose the PSA threshold for PSA relapse at 2 ng/ml so as to match the same value chosen by Pound in his 1999 study of time to metastatic disease after a post RP PSA relapse when no AD was given (his finding: a median of 8 years to metastatic disease). However, it was conceded that perhaps a better choice would have been the .4 ng/ml threshold suggested by Amling (Mayo Clinic), since "this cut point was associated with an approximate 75% chance of further biochemical and/or clinical progression during the next 3 years." The calculation of the PSA-DT was based on a minimum of 2 PSA values that exceeded 0.2 ng/ml separated by 3 months; the median number of PSA tests was 5. The median follow-up after PSAR was 4.7 months and treatment included LH-RH agents alone or combined with an antiandrogen, or orchidectomy. The results in the early AD group were further categorized as to the PSA level at the initiation of AD treatment. The analytic end point of the study was the development of clinical metastases. Results: It was ONLY in the high-risk group that early AD conferred benefit. The hazard ratio for benefit was 2.1, p = <0.01. My non-statistical observation of their graph showing the "event tics" concludes that at eight years after PSA relapse, if AD was commenced at PSA level <5 ng/ml., approximately 80% of men in the high risk early AD group were free of clinical metastases versus 60% for the high-risk no-treatment group. This graph will, of course, change with further follow-up. It is interesting that the freedom from clinical metastases at this eight year point degrades only to 75% for the high-risk treated group if the start of AD was at PSA < 10 ng/ml. There was no benefit to early AD in the low risk group. The authors clearly point up that the ultimate clinical value of early AD in the high-risk category is unknown, since AD will surely be administered upon clinical relapse to the men in the "no-treatment" group. But many clinicians will conclude there is value to the postponement of clinical metastases by the early administration of AD as long as the associated adverse treatment consequences are acceptable to the men involved.

This study was not designed to encompass the additional associated and relevant issue of how this data can be applied to a cohort of men who have undergone salvage radiotherapy? (See first article in this commentary.) It would seem that the study's information is not explicitly transferable since the distribution of PSA producing disease, i.e. From local relapse versus distant disease, will of necessity be different between these two situations. But the Moul study very likely may offer useful guidance in the decision about AD intervention when PSA failure follows the use of salvage radiotherapy, and a rapid PSA-DT might serve as a possible linking bridge to the Moul data.

Bottom Line: The Moul article concludes: "We now demonstrate that in the risk stratified setting of high-risk disease [pathologic Gleason sum >7 or PSA-DT 12 months or less] early use of AD was a significant and independent predictor of delayed clinical metastases." This information can be useful in patient counseling.