SEATTLE PROSTATE INSTITUTE

PCa Commentary
Vol. 24: September 2004

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ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE

Salvage Cryotherapy For Recurrent Prostate Cancer After Radiation Therapy.

Recent improvements in technique have upgraded the performance and outcome of cryotherapy to become a reasonable salvage option for carefully selected patients failing primary radiotherapy for prostate cancer. Follow-up for cryotherapy as **primary** therapy for newly diagnosed patients, especially follow-up for patients who have undergone treatment with "3rd generation" technique, is too short to usefully compare primary cryotherapy outcomes to the 15+ year data for the three major treatment modalities. However, cryotherapy as salvage after radiation failure is emerging to fill a special niche where currently the only available options are watchful waiting, hormone deprivation, or salvage prostatectomy with its well recognized technical challenges and high complication rate.

3rd generation technique utilizes gas driven ultra-thin 17G cryoprobes (1.5 mm.), first introduced in 1997, which allow the direct transperineal penetration of up to 15 probes guided by a template similar to those used in brachytherapy. This 3rd generation evolution employs argon gas for the

freezing cycle and helium for thawing, as opposed to liquid nitrogen as used in 2nd generation technique. Two freeze/thaw cycles are used, and tissue is cooled to a minimum of < 40 degrees C. for at least 3 minutes, followed by a rapid thaw. These recent improvements build on the prior development of TRUS guidance, which allows close real-time monitoring of probe placement, visualization of the rectum, and real-time control of the size of the ice ball. Urethral warming techniques were developed which significantly reduced the incidence of urethral sloughing. Pre-cryotherapy androgen deprivation is generally used to shrink prostates larger than 40 cc., and special maneuvers may be employed to assure optimal treatment to the apices of especially long glands (> 27 cm.). Thermocouples monitor the temperatures at the neurovascular bundles to assure adequate freezing, which is a requisite of success, and unfortunately nearly always (90% to 100%) leads to impotence. The major researchers cited in this article advise against cryotherapy for potent men who wish to maintain performance. Salvage cryotherapy after permanent seed brachytherapy presents a special difficulty for TRUS interpretation due to conflicting echoes arising from the indwelling seeds. In selected cases cryotherapy may be repeated.

Because the 3rd generation techniques promise improvements in outcome and reduction in morbidity compared to earlier procedures, it is appropriate to restrict current analysis to those reports incorporating the most recent developments. And since new developments in this field are rapidly emerging, any reports must be viewed as initial and preliminary data in this evolving field.

"Salvage Cryotherapy for Recurrent Prostate Cancer After Radiation Therapy: A Seven-Year Follow-up" (Bahn et.al, Clinical Prostate Cancer, Sept. 2003) reports on a retrospective analysis of outcome and morbidity in 59 men, clinical stage T1-T3, with biopsy proven recurrence treated with 3rd generation technique. The threshold for recurrence was set at PSA >0.5 ng/mL. 69% had Gleason scores of $\leq$ 7; 36% had a PSA values < 4 ng/mL and 41% had PSA values between 4 and 10. The clinical stage was T2 in 63% of men, the remaining being T3 or T4. The median F/U after cryotherapy was 82 months. In their study group the bDFS was 61%, 68%, and 61% for low, intermediate, and high-risk patients. The reported incontinence rate was 4.3% and rectal fistula formation, 3.4%. In the opinion of these authors the optimal candidates are men with PSA < 10 whose pre-RT clinical stages was T1 or T2.

[Editorial note: Although the small numbers and short duration of F/U for men treated with 3rd generation cryotherapy technique prevents acquiring the required comparable data, none the less there is no reason to think that the degree of success for salvage cryotherapy would not be determined by the same parameters (pre-treatment Gleason score and PSA, and rate of PSA rise) that select for the optimal results for RT salvage after RP.]

Han et.al (UCLA) in "Third-generation cryotherapy for primary and recurrent prostate cancer", BJU Int, 93: pp. 14-18, 2004, reported on 29 men who had undergone salvage cryotherapy. Seven percent reported the use of pads and none had recto-urethral fistulae. Ghafar (J. Urol 2001), using the argon system for locally recurrent prostate cancer after radiotherapy, reported follow-up data on 38 men with biopsy proven recurrent prostate cancer after radiation therapy failed (PSA > 0.3 ng/mL above post-RT nadir). Biochemical RFS was 86% at one year and 74% at 2 years. 86% of their patients had a PSA of $\leq$ 0.1 ng/mL at a mean F/U of 20 months. Complications included rectal pain, 39.5%; incontinence 7.9%; and scrotal edema, 10.5%. There were no instances of rectourethral fistula or urethral sloughing.

Perspective on the pathologic outcome of cryotherapy was provided by Chin, "Serial Histopathology Results of Salvage Cryoablation For Prostate Cancer After Radiation Failure", J Urol Oct. 2003. Fifteen of 106 patients (14.2%) were found to have positive biopsies, 73.9% of

which were found within one year following cryoablation. Han regarded this result acceptable, but "vigilant long-term" follow-up was warranted.

Bahn concluded "that his data further supports cryoablation as a safe and efficacious salvage treatment for radiation-resistant prostate cancer with durable results". Although Han acknowledged that longer term F/U is needed ,he offered the opinion that "in patients who present after failure of radiation therapy ... salvage cryotherapy may offer a more attractive alternative than salvage prostatectomy, hormone deprivation, or watchful waiting".

Bottom Line: Salvage cryotherapy with 3rd generation technique has become a reasonable treatment option for carefully selected men who have biochemical failure after primary radiotherapy.

ADJUVANT AND SALVAGE TX FOR PRIMARY TX FAILURE

Adjuvant and Salvage Radiotherapy After Prostatectomy: Starting Treatment at PSA < 1 ng/mL Unifies Outcome of Two Management Strategies

It is very satisfying when basic tumor biology serves to link two major radiotherapy strategies: immediate adjuvant irradiation (AR) for management of high risk of recurrence cancer found at prostatectomy, and salvage radiotherapy (SR) applied at the time of rising PSA post surgery. Such a link was reported by Hagan et. al, "Comparison of adjuvant versus salvage radiotherapy policies for post prostatectomy radiotherapy", Int.J.Rad.Oncol.Bio.Phys.,Vol.59(2), 2004. The unifying biological premise is that the level of the PSA is proportional to the bulk of cancer from which it arises. Hagan emphasizes that the radiotherapy goal is to irradiate the prostatic bed with the lowest practical postoperative tumor burden, and presents evidence demonstrating that there is a very ìnarrow range of PSA values [0 to < 1 ng/ml] which results in durable control.

Their major findings was that with either policy **if** radiotherapy was initiated when the PSA was < 1 ng/mL the outcome was not statistically different whether measured as OS (p = 0.26), disease-specific survival (p = 0.82), or the time to the appearance of metastatic disease (p = 0.34). The 5-year bRFS% (analyzed from the date of surgery) when comparing pre-RT PSA values of < 1 was 70% for AR and 79% for SR (p = 0.36). When RT was started when the PSA was > 1 ng/ml the 5 year bRFS figures were 36% vs 31% for AR and SR, respectively. Of interest is the lack of outcome difference for post-op adjuvant treatments started when the PSA was undetectable vs. < 1 ng/mL. Since some patients in the AR group did not achieve an undetectable post-op PSA value it was possible to make further comparisons between the AR and SR policies in cohorts where the PSA values were >1 to < 2, > 2 to < 4, and > 4. The declining outcomes were not statistically different for AR vs. SR.

This study was based on the experience of 158 men (AR, 50; SR, 118) from two institutions. At the University of Florida the predominant policy was adjuvant treatment prompted by considerations of microscopically positive surgical margins (63%), seminal vesicle involvement (50%), extracapsular disease (57%), or a combination of these factors, (62%). The median time from surgery to AR was 2.9 months, and the median pre-RT PSA was .86 ng/mL. At the Medical College of Virginia a policy of salvage radiotherapy was followed, applied in the setting of a rising, but not uniform, value PSA value. For this group the median time to RT was 40.3 months and the median pre-RT PSA value was 4.5 ng/mL. Of the AR group 47% were low-moderate grade cancers and 53% high grade, and in the SR group the breakdown was 66% and 34%, respectively. Seminal vesicle vesicle involvement was higher in the AR cohort, 50% vs.14%, as was extracapsular extension, 57% vs. 30%. The salvage group was more likely than the adjuvant group to have received a radiotherapy dose of > 64 Gy, 73% vs. 18%, but all received a minimum dose of > 60 Gy. Both groups were free of nodal metastases. The 5-year actuarial

survival for the adjuvant group was 87%, which was not significantly different from 81% for the salvage group.

Bottom Line: The unifying message: (1) adjuvant and salvage radiotherapy after prostatectomy achieve similar outcomes **if** RT is initiated when the pre-RT PSA is < 1 ng/mL.; and, (2) outcomes for both strategies significantly, and progressively decline when RT is commenced as PSA values rise above > 1 ng/mL.

DIAGNOSTICS: The Biopsy Gleason Score: Only An Estimate Of The Final Pathological Gleason Score, But The Best Estimate We Can Get.

It is not a new finding that the Gleason score based on core biopsies may differ significantly from the Gleason score based on whole mount analysis of the prostatectomy specimen. A recent report is a useful reminder of this fact: "Limitations of biopsy gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer", J Urol July 2004, by a group from University of Miami School of Medicine. They evaluated 531 cases in which the core biopsies were assigned 3 + 3 = 6 followed by a full analysis of the whole mount prostatectomy specimen. Concordence was found in only 51%. The RP Gleason score was higher in 41% and lower in 8%. Among the upgraded scores 36% were raised to Gleason score of 7, 4% to 8 and 1% to 9. They summarized their review of this subject and stated, "Concentrating on the most common Gleason score of 6, 30% to 70% of cases are undergraded with the majority having a Gleason 7 tumor on analysis of the entire prostate". In the upgraded specimens as compared to those that remained Gleason 6, extraprostatic tumor extenseion was found in 22% vs. 4% and seminal vesicle involvement in 9% vs. 2%.

At the median follow-up 55.1 months, the outcome showed that "The risk of biochemcial recurrence was three times higher in patients upgraded following radical prostatectomy, 6% vs. 18%. There was no improvement of prediction accuracy when the cores were analyzed in terms of number of cores positive nor maximum percent of tumor on biopsy.

Unfortunately the extent of tumor heterogeneity and the random distribution of multiple foci understandably escape complete detection by random core biopsies. The underlying prostate pathology that confounds the sampling process is nicely described in the article "Heterogeneneity of Gleason Grade in Mulitfocal Adenocarcinoma of the Prostate", R. Arora et. al, Indiana School of Medicine, CANCER, June 1, 2004. Not unlike findings of other researchers, this group found that among 115 RP specimens multiple foci of cancer were found in 100 (87%); 2 foci were found in 20 specimens; 3 foci in 33; 4 in 17; 5 in 13; and >5 in 17. Just as with the reporting policy of the Dynacare pathologists, the reported global Geason score was based on the largest ("index") tumor. Arora found that "The primary grade of the index tumor was the same as the overall primary grade [of the multiple foci] in 97% of specimens whereas the secondary grade of the index tumor the same as the overall grade in only 68% of specimens. Gleason grade 4 or 5 pathology was found in 19 specimens whose overall Gleason scores of $\leq$ 6, and in these instances could be reported as "tertiary". However, only in 3 these instances was the "tertiary" high grade patterns found in the non-index tumors. Although this study had only a small number of "tertiary" high grade elements, their importance of tertiary elements is emphasized by Arora by noting that "the existence of a high-grade component, even if it accounts for a small percentage of a tumor, had a marked adverse influence on the biologic behavior of the tumor."

Bottom Line: The full extent of tumor heterogeneity and multifocality that can only be appreciated by examination of the entire prostate specimen, and the limitation of random biopsies in fully reflecting this complexity points up the challenge faced by physicians in counseling patients about treatment choices and outcome based on core biopsy information.