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OUTCOME OF PRIMARY TX: Comparison Of Outcomes Of Three Modalities Of Primary Treatment:

"Monotherapy for Stage T1 - T2 Prostate Cancer: Radical Prostatectomy, External Beam Radiotherapy, or Permanent Seed Implantation" - Radiotherapy and Oncology 71 (2004)

Carefully done "apples-to-apples" comparisons of outcomes for different types of treatment of clinical localized prostate cancer are welcome informative. This article by Potter, Klein, Kattan, Kupelian et al. analyzes a study cohort of 1819 men with clinically localized disease - 1178

from the Cleveland Clinic Foundation (746-RP, 340-RT, 91-PPB) and 641-PPB (permanent prostate brachytherapy) treated at Memorial Sloan Kettering between 1992 and 1998. The median follow-up time was 58 months. This data builds on the Cleveland Clinic analysis reported in JCO, August 2002, comparing outcomes of RT and EBRT for cT1 and cT2 cancer. "The [current] study excluded all patients who received any neoadjuvant or adjuvant therapy". Of surgical cases 75% had pelvic node dissection [not further described] and 1.5% were positive, compared nodal biopsies in 3% of EBRT patients where none were positive.

The median dose of EBRT was 74 Gy (range 70.0-83.0 Gy), 94% delivered with 3DCRT technique. I-125 implants were dosed at 144 Gy and Pd-103 at 136 Gy, a comparable dose. The final pathologic status of the 746 RP surgery cases showed organ confined disease in 59%; specimen confined disease in 16%; and seminal vesicle invasion, 8%.

The PSA failure point for RP patients was set at two consecutive values greater than 0.2ng/mL, with time-to-failure recorded as the first elevation. For radiation patients the ASTRO definition was used: "three consecutive rising PSA levels from nadir with a 2-year minimum follow-up", and failure was assigned at midway between the nadir and the first elevation above the nadir. The mean initial PSA was 9 ng/mL (RP-8.8; EBRT-9.5; PPB-9.15).

The high credibility of this data lies is the well-matched clinical characteristics of the men in the three cohorts. Clinical stage comparison: Stage T1 - 55%, 53%, 53% for RP, PPB, EBRT ; T2a - 41%, 41%, and 40%; and T2b - 4%, 6%, and 7%, respectively. Gleason score comparison: Gleason score 2 to 6 - 77%, 77%, 71%; Gleason score 7 - 20%, 20% and 25%; and 8%, 2%, and 4% for Gleason score 8 and 9, respectively.

Results: The 7-year freedom from biochemical relapse rates for RP vs PPB vs EBRT were 79, 74, and 77% respectively, with no significant difference. The disease specific survivals were: 99%, 100% and 98%, again respectively.

Bottom Line: Paraphrasing Dr. Peter Carroll's remark at the 2005 8th Annual Brachytherapy Conference, This battle is over.

HORMONE INTERVENTION: Androgen Deprivation Therapy - What Method Do Men Choose?

Androgen deprivation of prostate cells currently can be achieved by two basic methods: 1) castration and LHRH analogues, which reduce serum testosterone; and 2) anti-androgens which block androgen signaling through the androgen receptor, and are associated with a slight rise in the serum testosterone. This elevation raises the serum level of estrogen by means of steroid conversion leading to symptoms of hyper-estrogenemia. Each method effects its own "side-effect" profile. [The lowering of intraprostatic DHT by 5-alpha-reductase inhibition will not be discussed here.]

Two articles report on the selections men make between these options. The article "Preferences of healthy men for two different endocrine treatment options offered for locally advanced prostate cancer", in Current Medical Research and Opinion, Sept 2005, reported the choices made by 180 men in the UK who had *no evidence of prostate cancer.* They were given a week to consider the method of delivery and the side effects for these two equally effective options. Some side effects were shared by both treatments, although to different extents. For an LHRH agonist the major listed consequences were: reduced erectile function and sexual interest in 9 of 10 men and hot flushes in 7 of 10, compared to 2 of 10 and 1 of 10 for high-dose, non-steroidal antiandrogens (NSAA), respectively. Drug specific side-effects for LHRH

agonists were an increased risk of fractures and osteoporosis, and a loss in all men of physical strength. Whereas for antiandrogens breast tenderness and pain occurred in 7 of 10 men.

Results: 86% of men chose NSAA, 7% chose LHRH and 7% could not decide. The main reason for avoiding LHRH agonist was its method of administration, whereas "those who chose NSAA therapy cited avoidance of the side effects associated with the LHRH agonists. This study highlights the importance of a full disclosure about treatment consequences. Since it was performed in England, the financial aspects of therapy did not influence the treatment choice.

The second UK study, reported in BJU International, Nov. 2005, reported the *actual* choices made by 150 men with advanced prostate cancer. A week period was provided for consideration of the differing side-effect profiles. Results: 42% chose high-dose bicalutamide; 34% chose an LHRH agonist, and 24% orchiectomy. When evaluated three months after the initiation of treatment, the men reported satisfaction with their chosen therapies in 87%, 84%, and 94% respectively. The authors concluded that when men are provided with full information about treatment options "they are satisfied with their decision 3 months later."

Of special note regarding high-dose Casodex: Unpublished data from the Early Prostate Cancer trial comparing 150 mg/day of Casodex vs. placebo showed an increase in deaths in the Casodex arm of the portion of the Scandinavian study segment which compared Casodex to placebo in a "watchful waiting" regimen. I queried Dr. Lawrence Klotz, Chief of Urology, University of Toronto about this issue. He was aware of unsubstantiated information that the increase was due to cardiac causes, and for this reason the drug has been de-registered in Canada and Belgium. This issue is in need of clarification.

DIAGNOSTICS: Lymphoscintigraphy And Radio-Guided Surgery For Sentinel Lymph Node Identification In Low-Risk Clinically Localized Prostate Cancer.

The venerable paradigm that has serviced breast cancer management for years is the understanding that the risk of systemic spread of breast cancer is proportional to the number of involved lymph nodes. This tenet has been honed to the point that metastatic disease in a single node warrants adjuvant therapy in addition to treatment of the primary tumor. Sentinel node mapping in breast cancer has been verified as a reliable method to identify the node that most likely is metastatically involved. The status of that node serves as a surrogate, accurate in <95% of instances, for *any* cancer spread to lymph nodes. Two recent articles suggest that prostate cancer management may be traveling the same pathway.

"Is There a Need for Pelvic Lymph Node Dissection in Low-Risk Prostate Cancer Patients Prior to Definitive therapy?" by Weckermann from Augsburg, Germany (European Urology 47; 2005) states at the onset: "Approximately 60% of lymph nodes would be missed limiting the field of resection to the obturator fossa instead of performing a meticulous lymph node dissection along the external iliac vein, obturator nerve, and internal iliac (hypogastic) vessels". Their study demonstrated that radio-guided (intraoperative) pelvic lymph node dissection allowed the identification of one or more "sentinel nodes (SLN)". On the basis of this identification a biopsy (possibly a laparoscopic biopsy), can be targeted to only the radio-positive nodes, thereby avoiding the morbidity of a "full" dissection, while at the same time detecting positive nodes that might otherwise be missed.

Their study focused on men with clinically localized, low-risk disease (PSA < 10 ng/mL; Gleason score ≤6), of whom 8.5% (16 of 187) had positive prostate biopsies from only in one lobe, and another 10.7% (9 of 84) who were biopsy-positive in both lobes. "A median of 6 SLN

and 5 NSLN were dissected from each patient. All men with positive nodes had a single positive SLN." The location of positive nodes was: obturator fossa, 9; external iliac, 5; internal iliac, 12; presacral, 1. Two patients were positive in non-SLN. The Gleason score was upgraded in 24% of the RP specimens.

In an accompanying editorial Heidenreich, who has authored several articles on this subject, referred to his own extended pelvic lymphadenectomy series in which no positive nodes were found in 13 men with PSA levels of <10 ng/mL and Gleason scores of 2-4. However, positive nodes were found in 10% (11 of 111) of men whose PSA levels were <10 ng/mL, but had Gleason scores of 5-7. His conclusion was that "The data further underline the inadequacy of the currently used preoperative nomograms such as the Partin tables to accurately predict pelvic lymph node disease."

Weckermann points out that the overall 6.8% of nodal positivity in his study is three times as high as predicted in the updated Partin tables, which give an estimated positivity of 0-2% for men with cT2b disease, PSA ≤10 and a biopsy Gleason score ≤ 6; and 0-3% for cT2c patients with the same PSA and Gleason score. "With the standard lymph node dissection which is limited to the obturator fossa and the external iliac nodes, 13 of 25 men would have been left with positive lymph nodes in this low-risk group", with the consequence that the underdiagnosed men would likely not have been offered the long term androgen suppression that was found beneficial in the Messing study.

A second article, "Limited pelvic lymphadenectomy using the sentinel lymph node procedure in patients with localized prostate carcinoma", European Journal of Nuclear Medicine and Molecular Imaging, June 2005, investigated the location of sentinel nodes using the radio-tracer technique. In 77% (21/27) cases a SLN was identified along the initial centimeters of the hypogastric (internal iliac) artery, a region not normally included in the standard limited dissection; 40.7% (11/27) were located in the obturator fossa; and 18.5% (5/27) in the external iliac area. "Four patients had lymph nodes metastases, all in SLN; two in the hypogastric area and two in the obturator fossa". No metastases were found in non-sentinel nodes.

A review by Wawroschek (Urol Int 2003:709(4) of 350 cases studied with SLN technique found metastatic deposits in 24.7% when the specimens were step sectioned. And in an extension of the series (Eur Urol, Feb 2003), the number increased to 26.8% positive nodes in these men with clinically localized prostate cancer. As his experience developed, he eliminated pathologic examination of non-SLN. By sampling only nodes in the obturator fossa 44.2% of positive nodes would have been missed, by adding sampling of the external iliac region the sensitivity was increased to 65.4% of the total of positive nodes found in the full dissection. Conclusion: "Limiting the number of lymph nodes to the one with the highest probability of bearing lymphatic spread (SLN) makes the use of extensive histopathological techniques more feasible."

Bottom Line: The sentinel lymph node radio-guided biopsy technique offers the promise of identifying the important minority of node-positive, low-risk patients with clinically localized prostate cancer who might benefit from adjuvant therapy.

The November Issue of the Journal of Clinical Onocology Was Entirely Devoted to Prostate Cancer. Here are "Cliff notes from 2 of 18 reviews.

HORMONE INTERVENTION: "Early Versus Delayed Androgen Deprivation for Prostate Cancer: New Fuel for an Old Debate" - Charles Ryan and Eric Small

The article presents a succinct summary of the three major trials (Bolla, Pilepich, and Messing,) which each employed 30 plus months of hormone therapy, and the D'Amico trial using 6 months of androgen suppression (AS). They all compared immediate AS to delayed use associated with radiotherapy or surgery for localized disease with high-risk features (Gleason score ≥ 7, T3 or T4 primary tumor, or lymph node metastasis). In each a significant benefit in disease specific and overall survival was found.

Since there have been no randomized trials for the study of timing of androgen suppression at the time of PSA relapse from primary therapy, retrospective analyses must serve. The retrospective study by Judd Moul of 4967 surgically treated men in the CPDR observational database showed that "for the group as a whole there was no *overall* advantage in terms of metastases-free survival for those undergoing early AS. However, a subset analysis found that patients with Gleason score ≥ 7 or a PSADT of < 12 months experienced a delay in time to metastasis.

CAPSURE data on 2671 post-RP men found that androgen suppression given at a deferred time after PSA relapse versus immediately upon relapse increased the comparative likelihood of death by as high as 10.86 times. Deferred AS was studied in cohorts of PSA values > 1, or > 10 ng/mL, or a PSA higher than the median for the group as a whole.

Perspective on the timing of events after PSA relapse was presented at the 2004 ASCO meeting by Bianco et al. Of 4958 men treated with AD at the time of a rising PSA (without metastases) the median time to hormone insensitivity was *10.9 years*, followed by a median period of 9.5 months to metastatic disease. The median survival after "castrate biochemical recurrence" was 26.2 months.

ADJUVANT / NEOADJUVANT TX: High-Risk Localized Prostate Cancer: A Case for Early Chemotherapy - Martin Gleave and Kevin Kelly

The bottom line of this review is that "there are no adequately powered randomized studies that have been completed using adjuvant or neoadjuvant chemotherapy in conjunction with surgery or radiotherapy" and the "use of early chemotherapy remains investigational". Dr. Gleave has pioneered the study of the induction of the "stress-activated cytoprotective chaperones, clusterin and Hsp27 [which prevent apoptosis] that are upregulated and begin to increase immediately following androgen deprivation therapy (ADT). He envisions early chemotherapy as a possible means of addressing their emergence.

The article lists ongoing or planned protocols. SWOG 9921 is active and compares neoadjuvant to neoadjuvant ADT + Mitoxanthrone v. neoadjuvant ADT alone before RP in high-risk patients. Planned studies include: NCI/CALGB/NCICanada - 6 cycles nADT + Docetaxel v. nADT both prior to surgery in high-risk localized disease, a Sandofi-Aventis study of the same design prior to irradiation; and NCI/RTOG - 3DCRT/IMRT followed by 24 months ADT v. 24 months ADT + 6 cycles Docetaxel/Prednisone for localized high-risk prostate cancer. The authors point out that an advantage of employing adjuvant therapy *after* surgery

lies in “limiting the morbidity of additional therapy to only the highest-risk patients” as indicated by their pathology specimens.

CLINICAL BRIEFS:

Hormone Intervention:

Dutasteride: Many men are taking this agent for relief of symptoms of BPH. They would be interested to know that in a study of 4325 men (UROLOGY 64: 537, 2004) randomized between 0.5 mg Dutasteride vs. placebo, the cumulative incidence of prostate cancer at 27 months was 1.2% favoring Dutasteride vs. 2.5% for the placebo. Whether Dutasteride therapy is associated with higher Gleason scores will only be know when the REDUCE trial is reported.

Diagnostics:

Is PSA Response To Therapy A Reliable Indictor Of Outcome In Androgen Sensitive And Hormone Refractory Metastatic Disease?

The European Organization for Research and Treatment of Cancer (JCO, Sept, 2005) says “NO” for hormonally treated patients: “Overall survival cannot be predicted with a high degree of precision from observed treatment effects [e.g. % PSA decline]on PSA end points”. Comparisons of time-to-disease-progression (TTDP) are potentially more informative.

Howard Scher (ASCO Educational Presentation, 2005) comes to the same conclusion with regard to chemotherapy trials in HRPC: “A *decline* in PSA levels [usually stated as > 50% or > 75%] should not by itself be used as a surrogate of clinical benefit in patients with metastatic prostate cancer.” Mario Eisenberg also suggests focusing instead on differences in TTDP.

However, a PSA *nadir of <0.2 ng/mL* does count. Drs. Moul, D’Amico, Scher et al (JCO Sept 20, 2005) reported in “Prostate-specific antigen nadir and cancer-specific mortality following hormonal therapy for prostate-specific antigen failure” that men receiving androgen suppression who failed to achieve a PSA nadir of <0.2 ng/mL by 8 months accounted for 75% of deaths in their study.

Roach had already reported (UROLOGY 62(3)2003) that the post-RT PSA nadir was also informative as to progression free survival in low- and intermediate-risk patients: nadirs of <.3, 0.3-<.6, O.6-1.2, and >1.2 ng/mL were associated with 5 year PFS of 83%, 72%, 58% and 33% respectively.

Autoantibody Signature In The Diagnosis Of Prostate Cancer. (NEJM Sept 26,2005) The various permutations of PSA analysis have been only minimally helpful in improving the specificity of the PSA test for the early diagnosis of prostate cancer. Serum proteomic and biopsy tissue microarray analysis are under investigation. Enter a new candidate: identification of serum autoantibodies against peptides derived from prostate cancer tissue. Very early work with this technique showed it to be diagnostically superior to PSA with an “area under the curve” of .93 compared to .80 for the PSA test.