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ADJUVANT AND SALVAGE THERAPY: Adjuvant vs. Deferred Radiation for Locally Advanced PCa after Prostatectomy: Further Refinement of a Controversial Management Decision.

There is strong clinical trial support that establishes that adjuvant radiation therapy (RT) given as soon as feasible following surgery improves outcome among men with pT3 prostate cancer as compared to no radiation. Management decisions for this stage of cancer are frequently encountered since "After prostatectomy pathologically advanced disease is detected in 38% to 52% of patients," (Ganswindt Eur Urol. 2008 Sep)

In JAMA 2006 Nov Ian Thompson et al. reported the initial results at a median follow-up of 10.6 years of the randomized clinical trial, SWOG 8794, comparing RT to observation in men with stage pT3 pN0 M0 cancer. Adjuvant RT produced a significant prolongation of freedom from PSA relapse (set at >0.2 ng/ml), which occurred at median 10.3 years for RT v. 3.1 years for observation, usually followed by hormone therapy, clearly demonstrating that "immediate" RT *delays* the need for androgen deprivation therapy. Hormone therapy in this study was administered after PSA relapse at clinicians' discretion.

When this study was updated later (J Urol, 2009 Mar) with the longer median follow-up of 12.7 years, the data showed a significant benefit for RT for metastases-free survival (14.7 v. 12.9 years), and a comparative benefit in median overall survival of 1.7 years (15.2 v. 13.3). However, one-third of the observation group received salvage RT, rendering the comparison less definitive.

Wiegel et al. in a multicenter German study (JCO May 2009) addressed the same issue - adjuvant RT v. observation in men with pT3N0M0 prostate cancer who all achieved undetectable PSA (<0.2 ng/ml) levels after surgery. At five years 72% in the RT cohort remained free of PSA progression compared to 54% in the observation group.

A crucial issue that is embedded in the decision regarding radiation management policy is the timing of deferred ("salvage") radiation in the observation groups. A meaningful analysis of the outcome of delayed radiation has been most times frustrated by the lack of uniformity - or absence - in the reporting of the PSA values at which salvage RT is given.

Haugen et al. usefully addressed this important issue (Int.J.Oncol.Bio.Phys. Vol. 59(2) 2004) by demonstrating that in pT3 disease "if radiotherapy was initiated when the PSA was <1 ng/ml the outcome was not statistically different whether measured as overall survival, disease-specific survival, or the time to the appearance of metastatic disease. When RT was administered within this narrow window the 5-year freedom from PSA relapse was 70% for the adjuvant group and 79% for salvage (p=0.36).

The optimal window of opportunity for radiation for PSA relapse after RP was further narrowed in a report by Stephenson et al.(J Clin Oncol 2007 May) in which the best outcomes were achieved when salvage RT was given at a PSA of ≤0.5 ng/ml. In their study of 1540 men with a rising PSA after surgery, 48% treated within this range were disease free at 6 years. The January 2011 issue of the European Association of Urology guidelines now endorses administering salvage RT at this PSA level of ≤0.5 ng/ml.

As clinicians are well aware, not all men with pT3 relapse (perhaps 35%-45% exhibit PSA failure), and some who do relapse have experienced disease control for quite long periods. The risk factors predisposing to relapse include seminal vesicle involvement, a high pre-surgical PSA, Gleason sum ≥8, positive surgical margins (extensive more so than focal), perineural invasion, and a post-op PSADT variously faster than 9 months. Immediate radiation therapy in a select group of men with pT3 disease *lacking* these adverse features would likely be "overtreatment." But how can those men be identified? (Stephenson's article includes a nomogram predicting the risk of failure after salvage radiation.)

AND NOW THE REFINEMENT - The SWOG 8794 trial could be interpreted as concluding that adjuvant radiotherapy should be standard of care for all localized prostate cancers following surgery.

The "refinement" comes from an article by D'Amico, Moul, et al. "Adjuvant versus salvage radiation therapy for prostate cancer and the risk of death." (BJU Int 2010 Mar), which explores the question of who among the men found to have pT3 prostate cancer benefit from early adjuvant radiotherapy, and in whom can this therapy be safely deferred, thereby avoiding the potential toxicity of radiation as long as possible.

The study presents outcomes for 1638 men with "unfavorable-risk [pT3] prostate cancer, i.e., PSA >20 ng/ml or Gleason score 7-10 or pT3 disease, whose lymph nodes were negative, and whose postoperative PSA was "undetectable" [<0.2 ng/ml]. The pathologic features for analysis were seminal vesicle involvement, extracapsular extension and positive surgical margins (R1); the clinical parameter followed was the post surgical PSADT. PSA failure was defined as ≥0.2 ng/ml and salvage radiation was given *within one year of a detectable PSA*. Hormone therapy was withheld until after failure following salvage radiotherapy. The study endpoint was all-cause mortality (ACM) and the prime question was whether post surgical pathologic parameters could predict a slow, post-op PSADT of >10 months, which in their study identified a cohort in whom radiation could be safely deferred.

THE FINDINGS: "In the present study, we found that men who received salvage RT for a slow PSA DT had a risk of ACM that was not significantly different from men who underwent adjuvant RT." As noted

above salvage RT was administered "within one year after the first measurement of a detectable PSA [≥ 0.2 ng/ml]. Salvage RT in men with PSADT of shorter than 10 months showed 3.5X worse ACM than adjuvant therapy in this group. By examining the relationship of pathologic findings and post-op PSADT, the study analysis allowed a very good prediction of which men would have a PSADT of longer than 10 months and, based on their analysis, avoid immediate RT.

Of the total study group of 1638 men, 18.4% had this slow PSADT, and of those men 81.6% had displayed the pathologic findings of a Gleason score of ≤7 and ***either*** pT2R1 or pT3R0, which is the group for which radiation could be might be deferred until after PSA relapse.

An excellent reference addressing all aspects of "Neoadjuvant and Adjuvant Therapies in Prostate Cancer" by Schultz and Oh appeared in Uro Clin N Am 37 (2010) 97-104.

BOTTOM LINE: "Radiation therapy after PSA failure [salvage RT] as compared with adjuvant RT was not associated with an increased risk of ACM in a group of men with Gleason scores ≤7 and [*either*] pT3R0 or pT2R1 disease. By withholding RT in this select group, 81.6% of them could avoid RT or at least have it delayed. By combining this study's findings with those of SWOG 8794, D'Amico and Moul advise that "adjuvant RT in men with any two or all three adverse features (i.e. pT3, Gleason score 8-10, positive surgical margins), should receive adjuvant (early) RT in order the secure the survival advantage seen in SWOG 8794.

"UNDETECTABLE" PSA - A Receding Target

In the studies cited above regarding adjuvant and salvage radiation the criteria for an "undetectable" PSA following a radical prostatectomy was <0.2 ng/ml. But these were studies designed and commenced in late 1980s and early 1990s. In recent years the goal post for achieving an "undetectable" PSA has been unofficially moved to a more stringent target. The new "undetectable" is now considered by many surgeons to be a PSA value of <0.01 ng/nl, utilizing the more recently available "ultra-sensitive" PSA. Obviously, many of today's post surgical PSA values above 0.01 ng/ml but lower than 0.2 ng/ml would have been termed "undetectable" by the earlier standard.

A Question Arises: Many studies confirm that men with a PSA Doubling Time (PSADT) shorter than 9 months after a prostatectomy are at increased risk for metastatic disease (as opposed to local recurrence), a poor response to salvage RT, and an increased risk of prostate cancer-specific mortality at 10 years. Can these adverse prognoses based on a rapid PSADT calculated in the PSA range >.2 ng/ml be usefully applied in the ultra-sensitive PSA range between >0.01 and 0.2 ng/ml, the latter value usually considered the point of PSA failure? The answer depends on two factors: the accuracy of PSA measurement in the ultra-sensitive range and published research on this issue.

The issue of PSA precision in this low range was kindly addressed by Dr. Ron Tickman, lead GU pathologist at Cellnetix, Seattle, Washington, and Art Zebelman, Ph.D, technical director of Laboratory Corporation of America. Repeated tests (to evaluate "within run imprecision") were run on a specimen in the ultra-sensitive range and established that the coefficient of variation around a value of 0.028 ng/ml was 8%. "Between run" variation (i.e. testing the specimen on different days) was about twice that value. For example, a test value of 0.033 ng/ml might vary +/- of 0.002 ng/ml. The biologic variation, if there is truly residual tissue present, might be considerably more than that.

Published research is scanty on the issue of management decisions based on PSADTs in the ultra-sensitive range. The most informative article comes from Teeter, Presti, Amling et al., BJU Int. 2009 Dec. They investigated whether the early PSADT (ePSADT) calculated in the ultra-sensitive range correlated with the standard PSADT calculated after PSA relapse at >.2 ng/ml.

The Findings: "...only 39% of men with the shortest ePSADT (<3 months) had a PSADT of <9 months [after PSA relapse]. Their conclusion: "... a long ePSADT correlated well with a long PSADT and is thus useful in identifying men at low risk for prostate cancer-specific mortality very early in their biochemical recurrence."

THE LOWLY ASPIRIN - Beats an Apple A Day

It's no longer front page news: the lowly aspirin has gained "apple-a-day" rank in keeping the doctor at bay. Daily low-dose (i.e. 81 mg.) aspirin reduces the *risk* of prostate cancer, slows disease *progression*, and reduces *mortality*. These benefits are greater with longer duration usage. Very credible evidence from many studies supports these assertions, and the good news is that aspirin might at the same time reduce the risk of other cancers as well, e.g. the death rate from colorectal cancer was reduced by more than a third by daily low-dose aspirin (Rothman, Lancet.)

The most authoritative and extensive information about aspirin and prostate cancer risk comes from Stanford et al.(Fred Hutchinson Cancer Research Center): "Use of Aspirin and Other Nonsteroidal Anti-inflammatory Medications in Relation to Prostate Cancer," Am J Epidemiol 2010. Their study compared 1001 men diagnosed with prostate cancer with 942 age-matched controls. Aspirin had been taken by 43.3% of the patients and by 47.7% of controls. The extent of recent exercise and smoking was evenly matched between the groups.

Their major finding: daily use of low-dose aspirin for 5 years *lowered the risk of prostate cancer by 29%!* That represents more effective chemoprevention than finasteride or dutasteride. The risk reduction did not vary substantially by disease aggressiveness. "There were no associations between use of nonaspirin NSAIDs and prostate cancer risk."

A second major study by Rothman et al. was published in Lancet Jan 2011: "Effect of daily aspirin on long-term risk of death due to cancer ..." For prostate cancer the 20-year risk of death was reduced by 10%. "Benefit was unrelated to aspirin dose (75 mg and upwards)..." There was a latent period of 10-15 years before the effect of death reduction for prostate cancer was realized. This would suggest the need to start taking daily low-dose aspirin between ages of 40 to 50 years.

Kevin Choe, MD (University of Texas) presented Abstract 270 at 2010 meeting of ASTRO: "Aspirin use and the risk of prostate cancer death in men treated with prostatectomy or radiotherapy: Results from the CaPSURE database." The study analyzed disease *recurrence* and *disease-specific mortality* of a total of 5295 men with localized disease and compared outcomes for the 1649 aspirin users with nonusers.

The findings: the risk of recurrence for the aspirin users was 22% at 5 years and 33% at ten compared to 26% and 43% for the controls. For aspirin users the prostate cancer-specific mortality was 1% at 7 years and 2% at ten versus controls, 4% and 10% respectively.

What might explain these benefits of low-dose aspirin? The Fred Hutchinson authors cite the increasing evidence indicating a role for inflammation in the development of prostate cancer. They point to two enzymes essential for an inflammatory response, enzymes that are inhibited by apsirin/NSAIDs. "Through their inhibition of these enzymes, aspirin/NSAIDs block the synthesis of proinflammatory prostaglandins.

CAVEAT: The benefits of low-dose aspirin are not gained without incurring risk of bleeding, albeit minimal. Aspirin, in addition to being anti-inflammatory, is anti-platelet therapy, i.e. aspirin decreases the adhesiveness of platelets that is essential for clot formation. Fortunately the anti-platelet effect is dose dependent and is least at the usual low-dose of 81 mg. This anti-platelet effect dissipates over 7-10 days after cessation. There is no evidence that higher doses are more effective.

Serebruany et al. (Am J Cardiol 2005 May) analyzed the risk of bleeding complications in 192,036 patients in 31 randomized controlled trials. In summary they concluded, "Despite substantial differences in the reporting patterns of bleeding complications, low-dose ASA was associated with the lowest risk, and moderate doses [100-200 mg/day] caused a relatively high hemorrhagic event rate, especially with regard to minor, gastrointestinal and total bleeding, and stroke." The overall risk in a healthy population lies somewhere between 1% and 0.1% per year. Some conditions merit caution: peptic ulcer disease, diabetes, renal failure, concomitant NSAID usage, and chronic use of corticosteroids.

BOTTOM LINE: The lowly aspirin packs an outsized benefit for men with prostate cancer. For those men not yet diagnosed it is effective as a chemopreventive agent lessening the risk of a diagnosis. When used after a diagnosis low-dose ASA slows disease progression, and reduces the risk of disease-related mortality. This is information that clinicians should share with all their patients.

EXERCISE (Actually, Exercise!) - The story is quite simple …

... "Men with ≥3 hours per week of vigorous exercise had a 61% lower risk of PCa death ... compared with men with less than 1 hour per week of vigorous exercise;" and ≥3 hours of vigorous activity leads to a 46% lower risk of all-cause mortality. These were the major results of a *prospective* analysis, "Physical Activity and Survival after Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study," Kenfield et al. JCO Jan 2011. Of the 51,529 men in the health professionals study observed from 1990 to 2009, 2705 were diagnosed with prostate cancer 548 died, with 20% dying of the disease. The median follow-up time was 9.7 years.

Periodic questionnaires prospectively collated the exercise activities of the men using MET units (Metabolic Equivalent Task) as a comparator with sitting at rest - assigned 1 MET unit. Examples of MET values: bicycling (including stationary machines), 7; jogging slower than 10 min/mile, 7; jogging faster, 12; lap swimming, 7; calisthenics, rowing, stair or ski machines, 6; heavy outdoor work such as digging or chopping, 5.5; and walking 2-2.9 mph, 3, 3- 3.9 mph 4, and ≥4, 4.5 METs. "Non-vigorous activities were those with a MET value of ≤6, and vigorous activities were those with a MET value of ≥6." Using these examples as guides a man can calculate a program for himself and relate to the findings of the study.

Study findings:

1. "Both vigorous and non-vigorous activity were associated with significantly lower overall mortality."
2. "Men with ≥3 hours per week of vigorous activity had a 49% lower risk of all-cause mortality," ..."and had a 61% lower risk of PCa death, compared men with less 1 h/wk of vigorous activity."
3. "Men exercising vigorously before and after diagnosis had the lowest risk."
4. "Only vigorous activity was associated with reduced PAc mortality."
5. For non-vigorous activity, those men achieving 5 to <10 MET h/wk showed a 28% reduction in all-cause mortality, while ≥10 h/wk yielded a 51% risk reduction - but no reduction in prostate cancer related death.

In his column "Exercise is Medicine," highlighting the "The anti-inflammatory effects of high intensity exercise," Jade Teta, ND (and much additional scientific research) gives biologic support for the need to exercise vigorously to obtain maximum benefit. He cites research that indicates that muscle contraction liberates the anti-inflammatory cytokine, Interleukin-6. The more intense the exercise, the greater muscle production of IL-6. "High intensity short duration movement that is tailored to the individual that uses short rest periods and engages the whole body may be the chief means of attaining anti-inflammatory effect from exercise." "The most efficient way to generate an ample IL-6 response is to combine resistance training and aerobic exercise in one workout."

What biologic mechanisms explain these benefits of exercising? Possibilities abound - lower serum insulin, increased insulin sensitivity; lower inflammatory factors (such as IL-6), an increase in anti-inflammatory cytokines; a bolstering of the innate immune system and improved natural killer cell cytolytic activity; and others. The future research will be fascinating.

BOTTOM LINE: ...but for now, find the time, commit to an exercise program and grab the established benefit from regular exercise.

IMAGING FOR BONE METASTASES: A Seattle Nuclear Medicine Protocol: 18F-Fluoride PET bone scan versus 99mTc-MDP scan - a comparison of accuracy and efficiency.

Several studies to date have found that the 18F-Fluoride PET bone scan is more sensitive and accurate than the venerable work-horse, the Technetium scan. (Reviewed in detail in PCa Commentary, Vol. 51 May-June 2008). Drs. David Djang, Director, and Co-Protocol Director, David Haseley, Seattle Nuclear Medicine, have launched a protocol to further evaluate this comparison: "18F-Fluoride PET bone scans versus traditional 99mTc-MDP gamma camera bone scans for the diagnosis of bone metastases: A blinded, prospective trial." Details are available at www.clinicaltrials.gov.

An ancillary study goal that adds value to the study is to "measure and compare the number of equivocal or uncertain findings that would have caused additional testing, particularly additional imagining studies, to confirm" the findings on either scan.

The population for study is Medicare patients diagnosed with of *any* type of cancer who are referred for study to Seattle Nuclear Medicine. Those persons will be contacted by phone prior to their appointments and offered entry into and a discussion of the protocol. It is hoped that after learning of the goals of the study, these patients would be willing to return within two weeks and have - free of charge - the alternative scan not ordered by their physician. The scan type for which they were referred will be the study reported to their physician. The results of the alternative scan will be used in the research.

"After a period of least six months, each patient and all of his available clinical data will be reviewed to determine the veracity of each scan's findings." The referring physician will be queried regarding the impact of the scans on management decisions.

The enrollment goal is 300-400 Medicare patients. For information about the study and to request scanning for a patient contact either Dr. Djang or Dr. Haseley at 206-386-6900.