PRIMARY TX UPDATES: Primary Androgen Deprivation for Prostate Cancer

Older, yes; "old" - no way! As demographics relentlessly shove more men into the upper age brackets, their prevailing claim is a humble origin in Lake Wobegon, where "everyone is above average". Unfortunately, however, mortality statistics have a way of gaining the upper hand, and therein lies the clinicians’ dilemma in guiding e.g. a newly diagnosed 75 year-old through a balanced discussion of management options for his prostate cancer. Suppose he is active with no other health issues, Stage T1c, PSA 22 ng/mL, and Gleason score 8. Actuarial life tables soberingly indicate a median longevity for this age group of 9.8 years. Although generally useful, the Kattan nomogram does not take age and co-morbidities into account in its projections. What does the literature report about the outcome of primary androgen deprivation therapy (PADT), as opposed to ADT combined with radiation therapy or prostatectomy for high-risk localized cancer in this older age group?

The most informative data comes from Japan, where almost half of patients with localized prostate cancer are treated with androgen deprivation, regardless of disease stage. i.e. 57% of all patients, and 46% of those with T1c to T3 disease. CaPSURE data likewise shows that primary androgen deprivation
for men at high-risk for recurrence is increasingly being chosen as an option - increased to 48.2% in 2001 as opposed to 32% in 1989 (Sweeney, C. "The Case for Systemic Therapy Alone for Prostate Cancer" J Urol. 2006, Dec 176 , 6 Pt 2). Three area are covered below: 1) PADT versus surgery plus ADT; 2)combined androgen blockade (CAB) versus LHRH monotherapy; and 3)classification of response to PADT according to subsets of patient characteristics.

1. "Efficacy of primary hormone therapy for localized or locally advanced prostate cancer: results of a 10 year follow-up" was reported by Akaza et al. in BJU Int. 98(3):2006 Sep. Their trial evaluated whether prostatectomy added benefit to ADT as monotherapy. They studied two groups of men with T1b, T1c or T2-3. Group 1 involved 176 men (mean age 67.2 years) who underwent prostatectomy followed by an LHRH agonist; in Group 2, 151 men (mean age 75.5 years) had no surgery but only an LHRH agonist or combined androgen blockade. Results at a median follow-up of 10.4 years: for Group 1 the 10-year overall survival (OS) was 73% and the 10-year cancer-specific survival (CSS) was 86%, versus OS of 41% and CSS of 78% in Group 2. Their conclusion: "With primary hormone therapy or prostatectomy, the men had a life-expectancy similar to that of the normal [age-matched] population," and "There was no difference between studies in cause-specific survival."

2. "Global update on defining and treating high-risk localized prostate cancer with leuprolelin: a Japanese perspective - the effect of primary androgen deprivation therapy on stage C prostate cancer", ( Akaza BJU Int 2007; 99, Supp. 1, 10-12) reports a significant superiority in progression-free survival for combined androgen blockade (CAB) in 78 men, compared with monthly Lupron alone for 73 men. The median follow-up was 10 years. Hormone therapy was administered for two years with continuation at the physicians' discretion. Mean patient age was ~75 years. In the Lupron arm 43% had T3 disease; and in the CAB arm, 47%. Patients were stratified by PSA, Gleason score, and T Stage. The graphic presentation shows progression-free survival for CAB at six years of 60%, and 30% for Lupron monotherapy (p=0.05). There was no difference in overall survival among any of the stratified risk groups. In this study the antiandrogen was chlormadinone.

Akaza's article included the second interim report of an ongoing study of men with advanced stage C and D disease that found that CAB ( LHRH agonist plus bicalutamide 80 mg/day; 102 men ) produced a significantly longer time to disease progression (p=<0.001) compared to LHRH monotherapy (101 men) in the subset of stage C patients receiving PADT. The final results are pending.

3. The most informative report for clinicians confronting this management decision for older men is "Global update on defining and treating high-risk localized prostate cancer with leuprolelin: an Asian perspective," Akaza et al. BJU Int 2007; 99, Supp. 1, 6-9. This study of 628 men suggests a practical treatment algorithm which incorporates stratification into modified D'Amico risk groups and uses the PSA nadir after 6 months of PADT as a decision point at which to continue ADT or add irradiation. Once again CAB proved significantly (P=0.037) more effective in extending CSS then LHRH agonist monotherapy.

"The results showed that, even if a patient is classified as 'high-risk', a good prognosis could normally be predicted based on certain variables: if his initial prostate-specific antigen (PSA) level was <20 ng/mL, his Gleason score was <6, and his PSA decreased to <0.2 ng/mL within 6 months of HT." High-risk was defined as PSA > 20 ng/mL, a Gleason score of >8 or stage >T3, and 376 men in their study met one or more of these criteria. Of the high-risk patients, 60% had relapsed before 10 years. "However, 40% did not relapse by 10 years, so the focus of our studies should be on how we can identify this subgroup and treat them accordingly."

Their suggested management algorithm: Initiate therapy with six months of CAB. Those men who show a PSA nadir of <0.2 ng/mL and achieve this level within 6 months, i.e. "good responders", may continue on CAB (or intermittent CAB), but if these criteria are not met, then combined therapy with CAB and some type of radiation therapy can be considered.

**Bottom Line:** The efficacy of primary therapy with combined androgen blockade for older men with localized or locally advanced prostate cancer has been sufficiently validated so that it may be included in the discussion of management options.
CLINICAL BRIEFS 1, 2

1. Testosterone Recovery After Androgen Suppression: Researchers from the NCI and six other sites studied 98 men to ascertain the time to testosterone (T) recovery following adjuvant administration of two 3-month GnRH-Agonist treatments after primary therapy, beginning the counting of time to recovery at 12 weeks after the second injection. "The median time to increase in T greater than 50 ng/dl was 12.9 weeks" (range 9 to 66.7); and the median time to achieve serum T > 212 ng/dl (the median pretreatment baseline for the group) was 16.6 weeks, "with more than 80% achieving this level by 24 weeks." (Gulley et al. J UROL May 2005)

2. Androgen Deprivation Monotherapy for PCa: Abstract 4610, ASCO 2006, by Beer, Graff, et al. reports a 5-year 66% overall survival (OS) and cancer specific survival (CSS) of 91% in 276 men with localized cancer treated within 6 months after diagnosis with androgen deprivation only. The median age at diagnosis was 75 (50-88) and the median follow-up was 7.6 years. The Gleason score >7 was the only independent predictor CSS (p=0.040); and having a PSA > 20 approached significance as an adverse predictor

PREDICTING OUTCOMES OF PRIMARY TX: Nadir PSA after Radiation Therapy and Androgen Deprivation for Metastatic Disease

Not surprisingly, the lowest PSA nadirs after radiation therapy and androgen suppression are associated with the longest freedom from biochemical recurrence and prostate cancer-specific survival. Here’s the data.

1. EBRT for T1 - T2 Cancer: The outcome of radiation therapy (76 Gy) in 1000 men was reported by Pino et al. from Fox Chase Cancer Center, "Prostate-Specific Antigen Nadir Within 12 Months of Prostate Cancer Radiotherapy Predict Metastases and Death", CANCER Jan 1, 2007. The analysis reported the outcome for men who achieved a PSA of <2 ng/mL during the 12 months after treatment versus those who did not.

This discriminant was chosen as opposed to the actual PSA nadir, which often is delayed to a median of 3 years - "even as long as 8-10 years" after EXRT; and in this study the median nadir was reached at a median of 35.2 months. "The 1-year time point [nPSA12] was investigated because we reported previously that the overwhelming majority of the drop in PSA after RT is during the first year." In this 1000 man study the median PSA during the first post-treatment year was 1.2 ng/mL. Median study follow-up was 58 months. "Dichotomized nPSA12 (<2 versus > 2 ng/mL) was independently related to distant metastases (DM) and cancer-specific mortality (CSM)." Results: biochemical failure at 5- and 10-years for nPSA12 <2 ng/mL was 26% and 30%versus 36% and 46% for nPSA12 >2 (p=0.0015); distant metastases at 5 and 10 years for nPSA12 <2 ng/mL was 2% and 4% versus 8% and 19% for >2 (p=<0.0001). Overall survival projected to 10 years was not significantly different: 26% (<2) vs 35% (>2). The hazard rate for cause-specific mortality was 3.9 for those men with a nPSA12 of >2 ng/mL. Conclusion: nPSA12 was recommended as a strong predictor of outcome after RT and would serve to identify patients at high risk for progression.

2. Androgen Deprivation In Metastatic (D2) Disease: PSA nadir after 7 months of ADT in metastatic prostate cancer is the best factor for predicting overall survival.

It has been canonical that in D2 disease that the duration of response for ADT clusters around 18 to 24 months. Abstract 4517 (reporting SWOG Trial 9346), ASCO 2006 provides OS data usefully categorized into cohorts based on the PSA achieved after 7 months of Zoladex/Casodex therapy, and allows a finer focus on predicting outcome from ADT. The range in OS was surprisingly broad, 13 to 75 months. The study was based on 1134 men (85%) of the study-eligible 1345 men, median age 70 years, baseline PSA > 5 ng/mL, whose PSA became ≤4 ng/mL during the study period. Results: Median OS was 75 months for the 45% of men achieving a PSA of ≤0.2 ng/mL after 7 months of ADT induction; 44 months for the 33% whose PSA fell between 0.2 and 4.0 ng/mL; and 13 months for those whose PSA was > 4 ng/mL at the end of the induction period. "Survival was defined as time to death after 7 months of ADT." A poor response to ADT was associated with co-morbidity (performance status of 2 or 3), bone pain at initiation of ADT, and Gleason score > 8.
3. Brachytherapy And High Dose EBRT- Equivalent Results [in low- and intermediate-risk patients]: (Abstract #38, 2006 ASCO Prostate Cancer Symposium). Drs. Shipley, Zietman, et al (MGH) reported an analysis of well-matched cases in two cohorts each of 132 patients (T1-2, PSA < 15); one treated with brachytherapy and the other with EBRT (79.2 Gy). Case matching was based on T-stage (T1, 75%; T2 25%); Gleason score (GS 6, 85%; GS 7, 13%; GS 8-10, 2%; PSA (median PSA, 6.1 for EBRT; 5.5 for BT); and age. Results: 5 year overall survival and distant metastases-free survival was 98% for both groups; freedom from biochemical failure at 5 years - EBRT, 88%; BT, 90%.

4. External Beam Radiotherapy and Prostatectomy - Equivalent Results: (Abstract #4607, interim report, 2006 ASCO Prostate Cancer Symposium). An Italian study of patients with clinically localized cancer (RP, n=70; EBRT, n=67) at a median follow-up of 67 months reported biochemical progression in 31% (RP) and 32% EBRT, and local progression in 15.8% (RP) and 17.9% (EBRT). The median time to local progression was 65 months for RP and 64 months for EBRT. Distant failure was seen at a median time of 67 months (RP) and 66 months (EBRT). At 2 years RP showed worse urinary function (p<0.001), but better bowel function (p<0.001). "Sexual dysfunction was more prevalent in the RP than in the EBRT group (70.2% versus 61.2%)." Additional accrual and long-term follow-up data is planned.

[The findings reported in these two abstracts, #38 and #4607, are in line with the overall conclusions of equivalence in outcome in a non-randomized comparison among 1819 patients treated with RP, BT, and EXRT reported by Kupelian et al., "Monotherapy for stage T1-T2 prostate cancer: radical prostatectomy, external beam radiotherapy, or permanent seed implantation", Radiation and Oncology 71 (2004).]

PREDICTING OUTCOMES OF PRIMARY TX: Adverse Prognosis Associated With "Detectable" PSA Following Prostatectomy

The "Natural History of Disease Progression in Patients Who Fail to Achieve an Undetectable Prostate-Specific Antigen Level after Undergoing Radical Prostatectomy" (CANCER Dec 1, 2004) is defined in a classic article by Alan Partin et al. in a study of 160 men whose PSA remained above 0.1 ng/mL 3 months after surgery. The study cohort had clinically localized disease, T1 to T3a, and had staging pelvic lymphadenectomies. This retrospective analysis assessed the percentage of men who developed clinically evident metastatic disease without any prior adjuvant intervention, mainly based on a positive bone scan. "The probability of distant metastases-free survival was 68% at 3 years; 49% at five years; and 22% at 10 years," and the median time to distant metastases was 5 years. (The classic estimate by Walsh of 8 years was measured from a rising PSA after surgery to clinical metastases).

Partin's analysis utilized the parameters of Gleason score, and involvement of seminal vesicles and/or lymph nodes to create three predictive subgroups: 1) Gleason score 6 and 7 (3+4) and SV-/LN- or SV-/LN+; 2) Gleason score 7 (4+3); and 3) Gleason score 8-9 or Gleason score 6 and 7(3+4) and SV-/LN+. In group 1 the median time to the development of distant metastases was 9 years; in group 2, 6 years; and in group 1 the interval was 4 years.

The determination of PSA "undetectability" can be made at six weeks post surgery, but PSA interpretation can be confounded by remaining normal prostate tissue, which Partin acknowledges can account for a PSA up to 0.3 ng/mL. However, this level should be stable over time. Hence the diagnostic importance of the measurement of the rate of any upward change in the PSA value during the ensuing 3 - 13 months after surgery, i.e. the graphic "slope" of the PSA over time. Partin regards this observation as "the best predictor of time to distant metastases." The critical breakpoint is >0.05/yr, which is associated with a median time to metastases of 3.5 years, compared to 13 years for a PSA slope <0.05/yr.

This retrospective analysis is an important contribution to the conceptual data on which adjuvant therapy is founded.
5. **Pomegranate Juice, 8 Ounces Daily - What's The Data** ... Someone will ask you. From a Phase II UCLA 22 month study comes a report finding a prolongation of the PSA Doubling Time after RT or RP from a baseline of 15 months to 54 months (P<0.001). The juice was started following a rising PSA (>0.2 ng/mL, but < 5.0) in men with Gleason score < 7. The effect was ascribed to antioxidants and was supported by cell culture data showing decreased cell proliferation and increased apoptosis. (Pantuck, AJ. Clin Cancer Res. 2006 July 1)

6. **Of Mice (And Hopefully) And Men: CANCER RESEARCH, FEB 2007.** Several combination diets consisting of 50% broccoli and tomato powder, or lycopene were compared to castration or finasteride as to the effect on the growth of prostate tumors implanted into mice. Castration reduced tumor weight by 62%, lycopene by 18%, broccoli by 42%, and tomato powder by 34%. The combination of tomato and broccoli led to a 52% decrease, and "tumor growth reductions were associated with reduced proliferation and increased apoptosis". So,... as they say, if the 99% genetic homology between mice and men counts for anything, eat your veggies.

7. **Prostate Cancer Risk Calculator Available On The Web:** The NCI Early Detection Research Network offers a very straightforward calculator that provides an estimate of the risk of a biopsy-diagnosed prostate cancer, based on parameters of age, race, family history, PSA, DRE, and prior prostate biopsy (yes or no). The risk of any grade of cancer is given with a 95% CI, and also specifically provides an estimate of the risk for high-grade cancer. The broad application of this tool was validated by Ian Thompson et al. (UROLOGY 2006, DEC). In the validation study the "observed prostate cancer rates increased with increasing PCPT [Prostate Cancer Prevention Trial] risk." "Cancer was diagnosed in 15.7%, 39.0%, 48.8% and 100% of men for a PCPT risk calculator value of <25%, 25% to 50%, 50% to 75%, and >75%, respectively." The URL is [http://compass.fhcr/edrmnci/bin/calculator/main.asp](http://compass.fhcr/edrmnci/bin/calculator/main.asp); but it can be more easily found as the first hit on Google by entering "prostate cancer risk calculator."