

## Recommendations for Defining and Treating High Risk Localized Prostate Cancer

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This supplement to *The Journal of Urology*® contains the proceedings of a conference held in San Francisco, California, on November 4–5, 2005, which was convened to develop consensus recommendations for the identification and treatment of patients whose apparent organ confined prostate cancer has high risk features for recurrence such as a high Gleason score or a rapid prostate specific antigen recurrence after therapy. The conference format combined brief presentations with extended periods of open discussion, which are included as excerpts with these published proceedings, and was structured into the 3 distinct sessions of identifying high risk patients, management of high risk localized prostate cancer and management of high risk recurrent or advanced prostate cancer.

Perhaps not surprisingly, given the lack of high quality data for many of the issues discussed, there could be no “consensus” on a number of points. It is nonetheless hoped that the articles and discussions in this issue will offer urologists, radiation oncologists, medical oncologists and other health care professionals useful insights and recommendations on monitoring and treating the patient with high risk prostate cancer.

### IDENTIFYING PATIENTS WITH HIGH RISK DISEASE

High risk disease is considered as localized prostate cancer for which monotherapy will likely be insufficient to eradicate the disease. Risk should be understood as significant likelihood of progressive, symptomatic disease or death from prostate cancer. However, many of the pre-treatment risk stratification schemes assess risk of biochemical recurrence rather than risks of clinically significant recurrent disease as defined previously. It is evident from a number of studies that PSA recurrence, as currently defined, often does not predict clinically significant recurrent disease or a need for further treatment. Only a minority of patients with PSA failure will die of prostate cancer.

Pound et al reported the long-term outcomes of 1,997 men treated with radical prostatectomy only.<sup>1</sup> PSA recur-

rence (0.2 ng/ml or greater) was experienced by 15% of patients (315) but only a third of these men (34%, 103 of 304) had progression to clinical metastasis. Median time was 8 years from biochemical recurrence to metastasis and 5 years from metastasis to death. Among these men predictors of metastasis-free survival included PSA recurrence greater than 2 years after radical prostatectomy, Gleason sum less than 8 and PSA doubling time greater than 10 months.

Freedland et al similarly followed the history of 379 men with PSA recurrence (0.2 ng/ml or greater) following radical prostatectomy.<sup>2</sup> Median survival was not reached after 16 years of followup. The authors evaluated various PSADT cut points and reported that a cut point of less than 3 months identified those most in need of early aggressive salvage therapy (median survival 6 years) while placing 94% of patients into the low risk category. Gleason score (7 versus 8–10) and time from surgery to biochemical recurrence (3 versus greater than 3 years) were also significant risk factors for time to prostate specific mortality.

The conference included considerable discussion of existing risk stratification and staging systems, and their use in separating high from low or intermediate risk patients. Conference participants agreed that a system with continuous variables is preferable to one relying on cutoff values. The current TNM staging system needs revision to be more useful in determining risk, and should include PSA and Gleason score, among other variables.

Although PSADT has been determined to be a powerful prognostic factor, identification of the high risk patient needs to consider other variables as well, including baseline Gleason score, PSA level, prediagnosis PSA velocity and clinical T category. PSA velocity the year before diagnosis (greater than 2 ng/ml per year) identifies a group of patients more likely to have recurrence, as discussed in the paper by D’Amico et al (page 000) in this issue. On the topic of PSA and its use in prognosis, conference participants reiterated the point that PSA recurrence alone is not a good end point because the underlying tumor biology is too heterogeneous. Many men with PSA failure will not have aggressive disease and will die of other causes. Clinicians should inform patients early that a PSA recurrence does not necessarily lead to symptomatic prostate cancer or death from prostate cancer. The risk of over treatment in this group of patients is high. A risk strati-

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fication for PSA failure needs to be developed to guide clinicians and patients and to avoid over treatment in this large and growing patient population. Risk stratification also needs to be comprehensible and useful to patients; in general, patients overestimate risk of disease and underestimate risks of treatment.

### **MANAGEMENT OF HIGH RISK LOCALIZED DISEASE**

The conference was planned to present opposing views on the role of surgery in high risk disease. Montie (page 000) argued that, in current practice, the patients who need treatment the least are considered the best candidates for radical prostatectomy by many. Given that surgery may be an effective therapy for eliminating large volumes of cancer, the potential advantages of a multimodality approach that includes surgery followed by radiation and androgen deprivation (and perhaps novel therapy) should be investigated for high risk patients with suspected high volume disease. Sweeney (page 000) presented an opposing view that local therapy does not manifestly add benefit, given that 75% of high risk patients will experience disease recurrence and may be best served with systemic therapy alone. Clearly, there is a need to improve our ability not only to identify high risk disease, but to describe its biology, differentiating patients with probable micrometastases from those with local/regional disease only.

Patients with prostate cancer and multiple high risk disease features, such as tumor in multiple biopsies, a high serum PSA, high Gleason score, or a digital rectal examination or imaging consistent with T3 disease, are often managed by radiation rather than surgery. However, there is an increasing consensus that it is inappropriate to treat such patients with radiotherapy alone using conventional doses (less than 70 Gy) and techniques. Patients with intermediate and high risk disease treated with external beam radiotherapy should also receive hormonal therapy. Studies have shown improved local and distant control with variable effects on survival using 70 Gy radiation with androgen ablation. Dose escalation with further refinement on timing may yield improved results.

The optimal duration of the hormonal therapy is not established. Adjuvant hormonal therapy has been used for durations of 2 years, 3 years and lifelong in phase III trials in men with high risk disease. The emerging issue concerns the cardiovascular risk of long-term hormonal therapy administered either in conjunction with radiotherapy or during disease relapse. In the Radiation Therapy Oncology Group 9202 trial, which randomized 1,500 patients (median age 70 years) to either long-term hormonal therapy or 4 months of hormone therapy there was no overall survival advantage and, in fact, patients without high risk disease in the long-term hormone therapy arm had a worse overall survival. Thus, it is crucial to consider the systemic effects of these therapies in an aging population with other significant risk factors. Hormonal therapy has often been used far too indiscriminately, for example, for increasing PSA in an elderly or low risk patient.

Combining external beam radiotherapy with low dose permanent implant or high dose temporary implant is another option for men at high risk of disease recurrence and progression. However, the rectal toxicities are sub-

stantially increased with the combination versus either modality alone. Gleason score, PSA, and the findings on digital rectal examination and imaging would be the main considerations in determining whether the patient is at sufficient high risk to warrant combination therapy. Further progress may be attainable by combining the 3 modalities of androgen ablation, chemotherapy and radiation therapy, although again the toxicity will be significantly increased as well. A quality of life component should be incorporated into studies of combination modalities and also considered in the benefit/risk assessment of the individual patient's treatment.

The role of adjuvant therapy in the high risk population following either surgery or radiotherapy needs systematic study. A substantial proportion of these patients may be presumed to have micrometastases at presentation; micrometastases are more susceptible to hormonal or chemotherapy eradication than established bulky disease. High risk patients can be identified by clinical, biochemical or molecular techniques, providing a sufficiently well-defined target population for testing adjuvant treatment. The efficacy of adjuvant chemotherapy is well established for other common epithelial cancers (eg with survival benefit in lung, colorectal, breast). The Southwest Oncology Group 9921 trial is attempting to examine this question but is currently accruing slowly.

A major disconnect between clinical guidelines and clinical practice lies in the status of primary hormone therapy for nonmetastatic prostate cancer. In the United States, and even more so in Japan where it is the treatment of choice, men with locally advanced or localized prostate cancer often receive androgen ablation therapy as primary treatment. There are few prospective data to indicate whether androgen ablation is effective as a primary treatment with surgery or radiation. Some recent data, discussed by Akaza et al (page 000) in this issue, suggest that the efficacy of androgen deprivation is greater in early stage prostate cancer than in late stage disease, where its effects are generally palliative. In Japan a large, prospective study of more than 26,000 patients is now under way evaluating progression-free survival, overall survival and cancer specific survival in patients receiving androgen deprivation as primary, adjuvant or neoadjuvant therapy. If this and other trials provide evidence of disease control, clinical guidelines for early stage prostate cancer should be revised to include primary androgen deprivation as an option. Once again, however, the morbidity of this treatment requires careful study.

Neoadjuvant therapy is another option for patients diagnosed with high risk local/regional disease. Currently, there are 2 randomized trials, the Veterans Administration CSP 553 and Cancer and Leukemia Group B 90203 studies, looking at neoadjuvant hormones plus chemotherapy versus none, examining outcomes in terms of local and systemic control.

### **MANAGEMENT OF HIGH RISK RECURRENT DISEASE**

As noted, not all PSA failures following local treatment indicate high risk, and treating them all may mean unnecessary exposure to toxicity. PSADT has better usefulness in assessing the risk and the appropriate manage-

ment steps. Although few data describe the natural history of the disease in these patients, some general guidelines can be provided. Those patients with a rapid PSADT of less than 6 months are candidates for continuous or intermittent androgen blockade, or for clinical trial enrollment as they are at high risk for development of metastases and prostate cancer death. For PSADT of 6 to 12 months, a patient can be offered salvage radiotherapy, intermittent androgen blockade, high dose bicalutamide, combined flutamide/finasteride or participation in an appropriate clinical trial. For a slow PSADT of greater than 12 months, salvage radiotherapy can be considered along with clinical trial participation but, unless the patient is highly anxious despite education on his risk level, active surveillance is an option. While the standard of care for a rising PSA is salvage radiation, there is still an unanswered question regarding whether immediate postoperative radiation is more beneficial than waiting until some specified increase in PSA in high risk patients as defined by margin status and T stage.

There is as yet no established role for chemotherapy in androgen sensitive high risk disease, but a rationale can be offered for investigating its benefit in this setting on the assumption that it might allow the early elimination of androgen independent clones while retaining sensitivity to androgen blockade as a subsequent therapeutic maneuver. One concept for exploring this hypothesis would be to select a cut point PSA nadir as a trigger point for chemotherapy. Such a cut point has been associated with higher risk of death from prostate cancer in several studies. Preclinical models do not show antagonism between chemotherapy and hormone therapy, but the optimal schedule for administering chemoradiation is unclear, whether concomitant or sequential, and whether chemotherapy would be given as a fixed number of cycles or determined by response. Accurate identification of risk is essential to the proper design of early chemotherapy trials.

A trial of antiandrogen withdrawal should generally be the first step after failure of combined androgen blockade. The proportion of patients responding to antiandrogen withdrawal is 10%, with a median duration of 3 to 5 months. No clear features are predictive of who will respond. Tumor heterogeneity results in varying degrees of sensitivity to secondary hormonal maneuvers in patients who have a diagnosis of "hormone refractory" disease. Secondary hormone therapy is appropriate in patients with minimal symptoms, lower disease burden and disease that is not rapidly progressing. Secondary hormonal options include a second antiandrogen (eg bicalutamide or megestrol after flutamide), adrenal androgen ablation with ketoconazole, or estrogen treatment. Diethylstilbestrol has efficacy in androgen independent prostate cancer, with PSA decreases of less than 50% reported in 30% to 40% of patients. Transdermal estrogen preparations appear to avoid the cardiovascular toxicity noted with oral preparations. The phase III CALGB 9583 study showed lower efficacy for ketoconazole than expected from phase II studies, but there appear to be subgroups of patients who benefit substantially, such as those with higher levels of androstenedione at baseline. These patients frequently achieve a prolonged and clinically meaningful response. These patients with increasing PSA levels and hormone refractory disease constitute a large population that may benefit psychologically and clinically from clinical trial participation.

## **NATIONAL CLINICAL TRIALS AND RESEARCH PRIORITIES FOR HIGH RISK DISEASE**

In the last 2 years 2 major cooperative group phase III trials in high risk recurrent prostate cancer have closed due to poor accruals: the RTOG 0014 trial, which was to examine the benefit of early chemohormonal therapy in patients with a rising PSA after primary treatment, and the Eastern Cooperative Oncology Group (ECOG) 1899 study, which was to evaluate second line hormonal therapy (ketoconazole) versus chemotherapy (docetaxel) in men with an increasing PSA after hormonal therapy. At least 2 major trials are currently suffering from slow accrual rates: the CALGB 90202 zoledronate trial, which has enrolled 63 of 680 subjects, and the SWOG 9921 study of adjuvant chemotherapy in high risk prostate cancer, which has recruited 828 of 1,350 subjects since opening 6 years ago (see Appendix). The failures of RTOG 0014 and ECOG 1899, as well as the slow accrual rates of other major intergroup trials, have raised concerns within the leaderships of the cooperative groups and the Cancer Therapy Evaluation Program about the feasibility of designing and performing future clinical trials in prostate cancer. Accordingly, the conference included extensive discussion aimed at identifying the causes and remedies for poor accrual to clinical trials in high risk patients with prostate cancer.

Physicians and patients must be aware of a trial's existence and its eligibility criteria well in advance of management decisions that might exclude the patients from participation. Compared to patients with breast cancer, men with prostate cancer are much less likely to actively seek information on clinical trial participation. Potential reasons for poor accrual include referral patterns in urology and radiation oncology, where patients frequently do not see a medical oncologist who could put them on trial or offer secondary therapy until relatively late in the disease course. At the same time, medical oncologists may not be opening these trials because they see too few patients with prostate cancer who would meet study entry criteria.

In some instances there may be trial design issues that discourage participation. Often the major intergroup trials are designed to add to our knowledge incrementally, asking such legitimate questions as the benefit of early institution of chemotherapy versus chemotherapy at time of measurable disease progression, or addressing management controversies, such as the role of adjuvant radiation before chemotherapy, choice of chemotherapy and the role of androgen ablation. However, physicians and patients may have already formed an opinion on the preferred treatment strategy in these settings. For example, slow accrual for the SWOG 9921 trial may be related to the perception that the mitoxantrone plus prednisone regimen is less active than docetaxel based chemotherapy. Patients are also frequently unwilling to accept randomization to trials that feature discordant treatment arms, since they may have already decided which therapy they want or do not want to receive. Finally, some studies may set entry criteria that conflict with community. All of these issues point to a need to test study concepts in a focus group setting before trial launch to determine if the questions and the design are as interesting and relevant to the community practitioners as they are to the academic physicians planning the trial.

From the perspective of a busy practitioner, trial participation may simply be impractical, and intellectual interest may be an inadequate inducement. The fact that industry trials such as TAX 327 (which required only 18 months to recruit) have accrued rapidly also points to the issue of the funding supplied for patient enrollment and followup. In addition to offering substantially higher per patient reimbursement, industry trials often provide clinical research infrastructure to manage trial data. In some instances, particularly when long followup and onerous record keeping are required, the physician may decide that he or she simply cannot afford to participate even when the trial addresses an interesting and important question.

In the modality focused specialties of urology, radiation oncology and medical oncology there needs to be improved

mechanisms for collaboration and sharing of patients so that patients can more readily access clinical trial opportunities without being formally referred from one specialist to another. Study entry criteria should not be set so as to preclude patients from participating in subsequent trials after disease progresses. Currently, for example, patients receiving adjuvant chemotherapy who then have progression are often not eligible for the next trial of national priority. Priorities should be established, since in many instances the studies are competing against each other for a limited pool of interested and eligible patients. Given the number of major trials now open, better communications among patients, community physicians and trialists are urgently needed if these important trials are to succeed.

## APPENDIX

Phase III National Trials				
Group/Number	Trial Therapy	Disease Stage	Accrual Goals	Primary End Points
RTOG 0232	RT + brachytherapy vs brachytherapy	Local therapy for intermediate risk disease	1,520	OS
CALGB 90203	Neoadjuvant docetaxel (8 cycles or less) + RP versus RP alone	High risk newly diagnosed prostate cancer	610	5-yr DFS
VA CSP 553	Adjuvant docetaxel	High risk disease post-prostatectomy	636	PFS
SWOG 9921	Adjuvant CAB (2 yrs goserelin/bicalutamide) ± chemotherapy (6 cycles 12mg/m <sup>2</sup> mitoxantrone + prednisone)	High-risk disease post-prostatectomy	1,360	OS, DFS
TAX 3501	Adjuvant AA (18 mos leuprolide 1-month depot) ± docetaxel* vs observation	High risk disease post-prostatectomy	1700	Time to biochemical recurrence
RTOG 0521	AA (2 yrs luteinizing hormone releasing hormone + initial antiandrogen) + RT ± post-radiation docetaxel/prednisone	Localized, high risk prostate cancer, no prior treatment	600	OS
CALGB 9593	CAB ± pelvic irradiation	Locally advanced prostate cancer	1,200	OS, TTP
TAX 3502	AA (leuprolide 24 mos) ± docetaxel	Rising PSA following definitive local therapy, PSA doubling time less than 9 mos, minimum PSA 2	800	PFS
PARADIGM (E1805)	PROSTVAC®-VF/granulocyte-macrophage colony-stimulating factor vs granulocyte-macrophage colony-stimulating factor	Nonmetastatic HRPC	700 (not yet open)	TTP
DAHRT (S0421)	Docetaxel/prednisone + placebo vs docetaxel/prednisone + atrasentan	HRPC with bone metastases	706 (not yet open)	TTP
VITAL-1	Randomized open label: GVAX® vs docetaxel	Asymptomatic metastatic HRPC, no prior chemotherapy	600	OS
VITAL-2	Randomized open label docetaxel ± GVAX®	Symptomatic metastatic HRPC, no prior chemotherapy	600	OS
ASCENT II	Docetaxel ± calcitriol (45 mcg/day)	Metastatic HRPC, no prior chemotherapy (except estramustine)	900	
CALGB 90202	AA + zoledronate (every 4 wks) vs AA + placebo then open label zoledronate at disease progression or a skeletal related event	Bone metastasis, prior AA only if 6 mos or less + greater than 1 yr previously, or 3 mos or less since start of AA	680	Time to first skeletal related events
CALGB 90401	Docetaxel/prednisone + bevacizumab vs docetaxel/prednisone + intravenous placebo	Metastatic HRPC, no prior chemotherapy	1,020	OS
SWOG 9346	Intermittent vs continuous CAB	Metastatic stage IV (stage D2), 6 mos or greater since start of CAB, greater than 1 yr since any prior AA of 4 mos or less	1,500	OS, QOL
CHAARTED (E3805)	AA vs AA + docetaxel	Extensive metastatic prostate cancer, patients stratified by age, PA, prior CAB/AA, bisphosphonate	568 (not yet open)	TTP, OS

\* Docetaxel regimen = docetaxel q 21 days × 6 cycles, unless otherwise stated.

**Abbreviations and Acronyms**

AA	=	androgen ablation
CAB	=	complete androgen blockade
CALGB	=	Cancer and Leukemia Group B
DFS	=	disease free survival
ECOG	=	Eastern Cooperative Oncology Group
HRPC	=	high risk prostate cancer
OS	=	overall survival
PFS	=	progression free survival
PSA	=	prostate specific antigen
PSADT	=	PSA doubling time
QOL	=	quality of life
RP	=	radical prostatectomy
RT	=	radiation therapy
RTOG	=	Radiation Therapy Oncology Group
SWOG	=	Southwest Oncology Group
TTP	=	time to disease progression
VA	=	veterans administration

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