

## PERSPECTIVES ON PROSTATE CANCER DIAGNOSIS AND TREATMENT: A ROUNDTABLE

MICHAEL K. BRAWER, THOMAS A. STAMEY, JACKSON FOWLER, MICHAEL DROLLER, EDWARD MESSING, AND WILLIAM R. FAIR (MODERATOR)

### ABSTRACT

This roundtable was held September 30, 2000. It addressed, first of all, the accuracy and proper interpretation of the available prostate-specific antigen assays. Dr. Brawer presented data to demonstrate the specificity of the complexed prostate-specific antigen assay. Dr. Stamey counterpoised evidence that pretreatment prostate-specific antigen levels less than 9 ng/mL are attributable to benign prostatic hyperplasia and therefore are of little value as an indicator of when to initiate treatment for prostate cancer. The other roundtable participants offered reviews and new data regarding hormonal therapy as primary or adjunctive treatment of prostate cancer. Dr. Fowler presented a large retrospective series of men with locally advanced prostate cancer for whom androgen ablation was the primary therapy. Dr. Droller discussed his center's experience in integrating hormonal therapy with brachytherapy. Finally, Dr. Messing reviewed and critiqued the evidence that the combination of hormonal and radiation therapy improves survival. *UROLOGY* 58: 135–140, 2001. © 2001, Elsevier Science Inc.

### DR. MICHAEL K. BRAWER: ADVANCES IN PROSTATE-SPECIFIC ANTIGEN TESTING FOR PROSTATE CANCER

Early on in the development of prostate-specific antigen (PSA) testing, it was recognized that PSA was limited with respect to specificity. The serum PSA at established cutoffs has a sensitivity of 70% or 80%. Consequently, much research has been directed at making PSA a better marker by enhancing the specificity.

A number of the so-called PSA derivatives, including PSA velocity, age-specific PSA, PSA density, transition zone density, and PSA doubling times have been advocated. Although these various

approaches showed some improvement over total PSA in the initial reports, most of them have fallen into disfavor, primarily because outside a rigorous protocol, their utility in enhancing specificity has never been definitively shown. Then Stenman *et al.*<sup>1</sup> and Christensson *et al.*<sup>2</sup> did some very interesting work with Scandinavian patients. They showed that a proportion of PSA is complexed to alpha-1-antichymotrypsin (ACT) and several other protease inhibitors in the serum and that the proportion of free PSA is higher in men without prostate cancer.

Virtually every study of free and total PSA testing has shown an enhancement of test specificity relative to total PSA of 20% to 30%. Perhaps the definitive study was the multicenter trial reported by Catalona and colleagues,<sup>3</sup> in which a cutoff of 25% free PSA enhanced specificity by 20% in men with a normal prostate. That appeared to be a major advance, but not all manufacturers have adopted the calibration standard of the Second Stanford Conference,<sup>4</sup> and without that standardization, very different results have been reported.<sup>5</sup>

Jeffrey Allard was the lead scientist in our efforts to develop an assay for complexed PSA. He preincubated sera with an antibody that recognized a specific epitope for free PSA, leaving the PSA complexed with ACT noninhibited. Thus, with the Immuno 1 cPSA assay, we had a specific assay for the

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*From the Northwest Prostate Institute, Seattle, Washington; Stanford University Medical Center, Stanford, California; Mississippi Medical Center, Jackson, Mississippi; Mount Sinai Medical Center, New York, New York; University of Rochester Medical Center, Rochester, New York; Memorial-Sloan Kettering Cancer Center (Emeritus), New York, New York*

*Reprint requests: William R. Fair, M.D., 435 L'Ambiance Drive, Suite 806, Longboat Key, FL 34228*

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**TABLE I. Comparison of PSA pairs in Kaplan-Meier survival analysis (Wilcoxon) (626 of 695 PZ cancers with PSA follow-ups\*)**

PSA (ng/mL)	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11.9	12-16.9	17-21.9	>22
n (with follow-up)	50	44	62	64	52	65	31	42	58	77	34	47
2-3	—	0.2660	0.1691	0.2978	0.4776	0.0205	0.3614	0.0008	0.0034	<b>0.0001</b>	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
3-4	—	—	0.9657	0.8495	0.9012	0.2603	0.9382	0.0501	0.0768	0.0091	<b>0.0001</b>	<b>&lt;0.0001</b>
4-5	—	—	—	0.9838	0.6927	0.1648	0.9633	0.0156	0.0266	0.0016	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
5-6	—	—	—	—	0.7297	0.1757	0.9889	0.0619	0.0318	0.002	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
6-7	—	—	—	—	—	0.1238	0.6927	0.0149	0.0237	0.0019	<b>&lt;0.0001</b>	<b>&lt;0.0001</b>
7-8	—	—	—	—	—	—	0.4121	0.2447	0.3415	0.0836	0.0010	<b>&lt;0.0001</b>
8-9	—	—	—	—	—	—	—	0.1035	0.5446	0.0353	0.0019	<b>&lt;0.0001</b>
9-10	—	—	—	—	—	—	—	—	0.8539	0.6803	0.0640	<b>&lt;0.0001</b>
10-11.9	—	—	—	—	—	—	—	—	—	0.4755	0.0226	<b>&lt;0.0001</b>
12-16.9	—	—	—	—	—	—	—	—	—	—	0.0677	<b>&lt;0.0001</b>
17-21.9	—	—	—	—	—	—	—	—	—	—	—	0.015
>22	—	—	—	—	—	—	—	—	—	—	—	—
Insignificant pairs per column (%)		100	100	100	100	100	100	100	100	89	50	9

KEY: PSA = prostate-specific antigen; PZ = peripheral zone.

\* Mean 4.94 years; median 4.66 years after radical retropubic prostatectomy. The Bonferroni correction for 132 pairwise comparisons changes the usual statistical significance of  $P = 0.05$  to  $0.0004$  (ie,  $0.04/132$ ).

Reprinted, with permission, from Stamey TA: Preoperative serum prostate-specific antigen (PSA) below 10  $\mu\text{g/L}$  predicts neither the presence of prostate cancer nor the rate of postoperative PSA failure. *Clin Chem* 47: 631-634, 2001.

ACT form of PSA. In our initial study, we had about a 25% enhancement in the performance with increased specificity relative to total PSA. We looked at serum samples from 300 men with 25% of those samples from men with cancer. Using the Hybritech 4.0 ng/mL total PSA cutoff as a standard, we avoided about 20% of the negative biopsies that result from using this threshold.<sup>6</sup> In a large series of some 600 men, at cutoffs yielding 95% sensitivity, we had 18% specificity for total PSA, 23% for free/total PSA, and 24% for complexed PSA.<sup>7</sup> Thus, in these studies we saw about a 25% overall enhancement in the specificity with complexed PSA.

The information that one gets from complexed PSA is best for total PSA levels ranging from 3 to 5 ng/mL. The information from the free/total ratio, probably because it is a better surrogate of prostate size, is better with PSA levels greater than 6 ng/mL. When we look at the assay performance in the 4 to 10-ng/mL range in our combined multicenter database, at the 95% sensitivity level once again, we found total PSA, free/total PSA, and complexed PSA had a specificity of 7%, 17%, and 18%, respectively.

*Dr. Fair:* At this point, the goal for various forms of PSA testing is to increase the specificity and sensitivity in diagnostic screening. Is it fair to say that there does not seem to be any benefit for these other forms of PSA as follow-up for a man who has had a radical prostatectomy?

*Dr. Brawer:* In following up a patient with established disease, all PSA assays are probably equivalent.

*Dr. Messing:* The irradiated prostate still has be-

nign glands producing PSA. Would this assay be of some theoretical value in distinguishing whether the PSA rises in benign versus cancerous glands?

*Dr. Brawer:* We were thinking for a while that the complexation may actually occur in the prostate, and benign acini did not have the machinery to change the molecule to allow it to complex to ACT. But what is going on in the prostate is basically irrelevant if the complexation occurs systemically. The data are just not in.

#### DR. THOMAS A. STAMEY: SERUM PSA LESS THAN 12 ng/mL IS UNRELIABLE AS A PREOPERATIVE PREDICTOR OF PROSTATE CANCER PROGRESSION AFTER RADICAL PROSTATECTOMY

A series of 626 men with peripheral zone cancers underwent radical prostatectomy at Stanford between 1984 and 1997 with PSA follow-up measurements for a mean of 4.94 years (median 4.66). As shown in Table I, we grouped their preoperative serum PSA levels at 1-ng/mL intervals between 2 and 12 ng/mL, and then at 12 to 16.9, 17 to 21.9, and 22 ng/mL or greater. The Bonferroni correction for 132 pairwise comparisons changes the usual statistical significance of  $P = 0.05$  to  $P = 0.0004$  (ie,  $0.05/132$ ), a correction that avoids falsely detecting differences where none exist. These data suggest that serum PSA is not a reliable predictor of biochemical PSA failure rates between 2 and 12 ng/mL. Our data indicate that PSA at these levels is largely attributable to increasing prostate size (benign prostatic hyperplasia [BPH]).

As to Dr. Brawer's advocacy of complexed PSA in prostate cancer, we reported in 1994 that serum PSA was 94% to 96% complexed at all volumes of prostate cancer varying between 4 cm<sup>3</sup> and gross metastatic, untreated disease.<sup>8</sup> The same high rate of complexation was found in men in whom radiation therapy or hormonal therapy failed and in transition zone cancers. Only BPH had a lower percentage of complexation (83%). The amount of complexed PSA showed no relationship to increasing cancer burden; it is clearly not cancer specific. In terms of specificity, Dr. Brawer's current data show a very restricted range of usefulness for complexed PSA (4 to 6 ng/mL) with a limited specificity of 20% to 25%. Our recent data<sup>9</sup> show that if one knows the transition zone volume, it is equivalent to the free/total PSA ratio, inferring that BPH nodules liberate a lot of nicked PSA into the serum, leading to high proportions of free/total PSA.

*Dr. Fair:* What do your data tell us in terms of the hazards of using PSA as an indicator for when to initiate therapy in a patient who is opting for watchful waiting? If it goes from 3 to 5 ng/mL, do you treat?

*Dr. Stamey:* No, I think PSA is largely proportional to the volume of BPH between 2 and 12 ng/mL.

*Dr. Fair:* So you are saying that, in terms of watchful waiting in the hormone-naïve patient, the practicing urologist can gain no information as to when to start treating if the PSA changes within the range of 2 to 12 ng/mL?

*Dr. Stamey:* Essentially, yes, and absolutely if the PSA range is 2 to 7 ng/mL in peripheral zone cancers.

*Dr. Fair:* In the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER) data, almost 30% of men with prostate cancer are opting for watchful waiting. There is a tremendous problem in just following up these men if we cannot use serum PSA levels to help us decide when to intervene.

*Dr. Droller:* This whole issue of PSA anxiety, which is so troubling for the patient and the doctor, needs to be addressed. We have this dilemma of being forced to make a diagnosis in situations in which it is not going to make a difference, really, in longevity, but making the diagnosis can seriously influence the quality-of-life issues—not only from the treatments that we apply, but from the patient's psychological burden of feeling that he has cancer.

*Dr. Stamey:* I believe that when the final chapter on this disease is written, which is unlikely to be in my lifetime, never in the history of oncology will so many men have been so overtreated for one disease. After all, we have a very small death rate from prostate cancer, which is much less than 1%. Yet, if you take men with any borderline PSA level (2 to 4

ng/mL) or elevation (4 to 10 ng/mL) and biopsy them, you'll get a monotonous 25% or better positive biopsy rate. Clearly, we are overdiagnosing this cancer.

*Dr. Droller:* I do not think you can make it cause and effect, just because you are seeing the same morphology, that PSA levels are equivalent.

*Dr. Stamey:* We have two pieces of data. First, you cannot show a reliable relationship between serum PSA and the volume of Gleason grade 4/5 cancer, and this relationship is especially poor for the 85% of men whose largest cancer is in the peripheral zone. Second, you cannot show a statistically significant difference in cancer cure rates between a serum PSA of 2 to 3 and at least 7 ng/mL. There is a definite break in cure rates at 9 ng/mL. So all we are saying is that a man is no more incurable with a PSA of 7 ng/mL than he is at 3 ng/mL.

#### DR. JACKSON FOWLER: HORMONAL THERAPY AS PRIMARY THERAPY FOR LOCALLY ADVANCED DISEASE

We encounter a large number of men with locally advanced prostate cancer. Many have significant comorbid disease and in most cases we recommend primary hormonal therapy. Between January 1991 and September 2000, we treated 200 men with Stage T3-4 prostate cancer with hormonal therapy. Our extent-of-disease evaluations include a physician examination to stage the primary tumor and a bone scan. In most cases, we have not performed computed tomography and, therefore, the stage is T3-4 NXM0. In these patients, the median PSA was 46.4 ng/mL (range 8.2 to 763) and 86% had Gleason score 7 to 10 cancers. The median age was 73 years; 74% were black and 26% were white.

Altogether, 58% of the patients were treated with primary androgen ablation only; 35% were treated initially with primary androgen ablation but received secondary antiandrogen therapy; and 3% were treated initially with total androgen blockade, usually because of patient preference. Other indications for secondary antiandrogen therapy are a PSA nadir greater than 1.0 ng/mL or a PSA increase to greater than 1.0 ng/mL after a nadir of less than 1.0 ng/mL. The median potential follow-up was 71 months (range 3 to 115). The outcome measures were biochemical disease-free survival, cause-specific survival, and all-cause survival. Table II summarizes the patient status as of September 2000.

*Dr. Fair:* Given these data, it looks as though survival might almost be comparable to men without prostate cancer. We used to think in terms of a 2 or 3-year survival if hormonal therapy was started, and your data suggest this is not the case.

**TABLE II. Status of 200 patients with locally advanced prostate cancer treated with hormonal therapy**

Status	Patients (n)
Alive without PSA elevation	96 (48)
Dead without PSA elevation	58 (29)
Alive with PSA elevation	23 (11.5)
Dead with PSA elevation	9 (4.5)
Dead from cancer	11 (5.5)
Lost to follow-up	3 (1.5)

KEY: PSA = prostate-specific antigen.  
Numbers in parentheses are percentages.

*Dr. Fowler:* The actuarial cause-specific survival at 5 years was 95%, which suggests that the primary tumor and subclinical metastases can be well controlled with hormonal therapy. However, the actuarial all-cause survival at 5 years was only 59%. This was not unexpected, because many of the patients were not particularly healthy. Nonetheless, the 5-year actuarial all-cause survival was comparable to the 52% 5-year all-cause survival reported in the Medical Research Council study.<sup>10</sup> It is also remarkably similar to the actuarial 5-year all-cause survival reported by the Radiation Therapy Oncology Group for patients treated with radiation therapy alone or with radiation plus 4 months of hormonal therapy, both 60%.<sup>11</sup> The latter suggests that in selected men primary hormonal therapy may be equivalent to integrated radiation and hormonal therapy in terms of the most important endpoint in prostate cancer therapy—overall survival.

*Dr. Fair:* If you just showed the radiation plus hormone data to someone who knew nothing about the issue in question, it would indicate that the addition of hormonal therapy improves survival over radiation therapy alone. It does not tell us whether we could get the same results with hormones alone.

*Dr. Fowler:* To my knowledge, the study by Bolla *et al.*,<sup>12</sup> in which men were treated with radiation therapy alone or with radiation therapy and 3 years of hormonal therapy, is the only randomized trial that has demonstrated an overall survival advantage for men who received integrated radiation and hormonal therapy rather than radiation therapy alone. However, when the study was published, a large number of men were still receiving hormonal therapy and the true impact of radiation therapy on the survival of these patients is difficult to determine.

*Dr. Messing:* I have the Bolla data for 5 years, and the data are probably closer to yours now. It is still a positive study.

*Dr. Fair:* The view that the combination of long-term hormonal therapy with radiation statistically

improves survival still holds. The problem is that these men, with a mean age of 73 years, do very well with hormonal therapy alone.

#### DR. MICHAEL DROLLER: ROLE OF HORMONAL THERAPY BEFORE BRACHYTHERAPY

The observations that I describe are based largely on studies performed at the Mount Sinai Medical Center and reported in several recent publications.<sup>13–15</sup> We have suggestive but no definitive evidence that hormonal therapy in combination with brachytherapy may improve disease-free survival. These data are for 4 to 5 years in all risk categories, particularly PSA biochemical survival data in the moderate-risk category (defined as PSA greater than 10 ng/mL, grade greater than 7, and clinical Stage T2b to T2c), and in the high-risk category (defined as PSA greater than 15 ng/mL, Gleason grade greater than 8, and Stage T2c to T3c).

Recent univariate analyses of a series of 192 implanted patients demonstrated that hormonal therapy, radiation dose, PSA level, and risk group were significant predictors of outcome. In a multivariate analysis, hormonal therapy was the strongest significant predictor of freedom from biochemical failure. The 5-year freedom from biochemical failure rate was 79% in patients treated with hormonal therapy versus 58% in those treated without hormonal therapy. Observations in moderate-risk patients indicated a 5-year freedom from biochemical failure rate of 92% with neoadjuvant hormonal therapy versus 76% without hormonal therapy. The corresponding 5-year freedom from biochemical failure rate in high-risk patients was 76% with hormonal therapy versus 50% in the implant-alone group.

*Dr. Fair:* In the early days of radiation therapy for prostate cancer, it was almost axiomatic for radiation therapists that proliferating tissue will respond better to radiation. Yet here we are saying that if you put those cells into G<sub>0</sub> with hormonal therapy, they seem to respond better to radiation. Is it purely a matter of reducing the size of the gland?

*Dr. Droller:* Yes, the only concrete observation to explain the apparent survival advantage is that pretreatment with hormonal therapy decreases the size of the prostate, which facilitates the seed placement and presumably enhances the dosimetry. Subsequent data looking at patients who had a higher dose delivered show that they seem to do better in terms of biochemical failure-free survival. Synergistic effects of hormonal ablation and radiation on apoptosis have been suggested but remain to be proved. We do not yet know whether we are

**TABLE III. Androgen deprivation and radiotherapy vs. radiotherapy and deferred hormonal therapy for locally advanced prostate cancer**

Study	n	Stage	Before	During	After	Type	Survival	Deferred Hormones (%)	Hormones (%)	P Value
Zagars <i>et al.</i> <sup>16</sup>	82	T3,4a	—	—	+ permanent	DES	5 yr 10 yr 15 yr	73 50 33	68 42 25	0.58
Pilepich <i>et al.</i> <sup>17</sup>	945	T2-4a, N0	—	—	+ permanent	LHRH agonist	7 yr  Gleason ≥8, no surgery	71	75	0.37  0.05
Bolla <i>et al.</i> <sup>12</sup>	415	T2,3	—	+	For 3 yr	LHRH agonist	5 yr	63	78	0.001
Granfors <i>et al.</i> <sup>19</sup>	91	T2-4 PN+ (43%) PN0 (57%)	+	+	+ permanent	Orchiectomy	9.1 yr	47	63	0.02
Hanks <i>et al.</i> <sup>20</sup>	1520	T2-4a	+ in both arms	+ in both arms	2 yr in hormone arm only	LHRH agonist	5 yr actuarial  Gleason ≥8	79  69	78  80	0.90  0.02

Key: DES = diethylstilbestrol; LHRH = luteinizing hormone-releasing hormone; + = hormones.

truly seeing an increased cure rate, and that information will only come with longer follow-up of these patients. Now, that is not to say that there is not a benefit to the patients in terms of the PSA anxiety issue.

*Dr. Fair:* Dr. Droller, on the basis of these data, are you sending patients to radiation therapists for whom you formerly would have recommended surgery?

*Dr. Droller:* If they are equally good candidates for surgery versus radiation, my preference for organ-confined disease remains surgery. With high-risk patients, although surgery may benefit some, by and large they fail, and those are the groups that fail with radiation as well, so then the issue of potential morbidity comes in.

*Dr. Fair:* Dr. Stamey, in light of these data on hormonal therapy in combination with radiation, have you changed your view in recommending radical prostatectomy versus radiation therapy, or would your indications still be the same?

*Dr. Stamey:* I do not think my indications have changed in terms of surgery versus radiation, but I am very concerned that we are treating far too many patients with either one of these modalities of therapy.

*Dr. Fair:* This discussion brings up the point that Dr. Whitmore made, that probably more people are making a living from prostate cancer than are dying from it.

#### DR. EDWARD MESSING: POSTRADIATION HORMONAL THERAPY

If you are going to look at the long-term impact of this treatment, you have to look at survival (Table III). Looking first at the M. D. Anderson study, a small study of 82 patients with Stage T3-T4, there was no difference in survival after 14.5 years median follow-up for those patients who received diethylstilbestrol (DES) at completion of radiation therapy versus those who did not.<sup>16</sup> The early data from the Radiation Therapy Oncology Group 85-31 study, started in 1985, showed a delay in recurrence.<sup>17</sup> But, when you look at the survival data, there was virtually no difference between the treatment arms with a median follow-up of 8 years ( $P = 0.37$ ). They claimed that the Gleason score 8 to 10 subgroup did have a survival advantage, but these types of subgroup analyses are highly suspect.<sup>18</sup>

The Bolla data recently presented at the European Organization for Research and Treatment of Cancer (EORTC) meetings have a median follow-up of just more than 5 years and show about 78% survival for men who received early hormonal therapy plus radiation.<sup>12</sup> However, many of these men had lower stage tumors, Stage T2 rather than large T3. I think there is an advantage in that the gland presents a smaller target if you give hormonal therapy at the beginning of treatment, and perhaps this explains whatever benefit is seen.

The two arms of the study by Granfors *et al.*<sup>19</sup> were orchiectomy plus radiation versus radiation plus observation, with the orchiectomy group receiving radiation 1 month after orchiectomy. There was a statistically significant survival advantage, but it was only achieved at a little more than 9 years out. So, you could say there was a modest benefit in this small study for people who received hormonal therapy before and during radiation.

In the Radiation Therapy Oncology Group 92-02 study with more than 1500 patients, it has been accepted that early hormonal therapy helps radiation.<sup>20</sup> The group was randomized to 2 months before radiation and during radiation; then one half of the group continued hormonal therapy for 2 years and one half stopped hormonal therapy at the completion of the radiation. There was clearly no difference in the actuarial survival at 5 years in the whole group, only in the subgroup of selected high-risk patients. This was a small subgroup analysis of a larger study; when that sort of analysis is at odds with the results of the entire study, and the specific subgroup is retested alone with a study of appropriate size, the results almost invariably support those of the original study as a whole, and not the subgroup analysis. They were claiming the study to be positive because of the local control and PSA data. When you actually get to the overall survival, there was no difference.

*Dr. Droller:* The headlines in the *Urology Times* state that hormonal therapy remarkably improves radiation therapy outcomes.

*Dr. Messing:* If there is a benefit with hormonal therapy and survival with radiation, it is probably only true if you get it before and during radiation treatment. That is how I read the five studies on the issue. I know the radiation therapists do not agree with that. I agree with Dr. Droller that there are circumstances in which you need the downsizing before therapy. I think there is little doubt that if you have a large gland, hormonal therapy will make radiation more effective by downsizing the prostate.

#### REFERENCES

1. Stenman UH, Leinonen J, and Alfthan H: A complex between prostate-specific antigen and alpha1-antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostatic cancer: assay of the complex improves sensitivity for cancer. *Cancer Res* 51: 222–226, 1991.
2. Christensson A, Laurell CB, and Lilja H: Enzymatic activity of prostate-specific antigen and its reactions with extracellular serine proteinase inhibitors. *Eur J Biochem* 194: 755–763, 1990.
3. Catalona WJ, Partin AW, Slawin KM, *et al*: Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. *JAMA* 279: 1542–1547, 1998.

4. Stamey TA: Second Stanford Conference on International Standardization of Prostate-Specific Antigen Immunoassays: September 1 and 2, 1994. *Urology* 45: 173–184, 1995.
5. Roth HJ, Christensen-Stewart S, and Brawer MK: A comparison of three free and total PSA assays. *Prostate Cancer Prostatic Dis* 1: 326–331, 1998.
6. Brawer MK, Meyer GE, Letran JL, *et al*: Measurement of complexed PSA improves specificity for early detection of prostate cancer. *Urology* 52: 372–378, 1998.
7. Brawer MK, Cheli CD, Neaman IE, *et al*: Complexed prostate specific antigen provides significant enhancement of specificity compared with total prostate specific antigen for detecting prostate cancer. *J Urol* 163: 1476–1480, 2000.
8. Stamey TA, Chen Z, and Prestigiacomo A: Serum prostate specific antigen binding alpha 1-antichymotrypsin: influence of cancer volume, location and therapeutic selection of resistant clones. *J Urol* 152: 1510–1514, 1994.
9. Stamey TA, and Yemoto CE: Examination of the 3 molecular forms of serum prostate specific antigen for distinguishing negative from positive biopsy: relationship to transition zone volume. *J Urol* 163: 119–126, 2000.
10. The Medical Research Council Prostate Cancer Working Party Investigators Group: Immediate versus deferred treatment for advanced prostatic cancer: initial results of the Medical Research Council Trial. *Br J Urol* 79: 235–246, 1997.
11. Pilepich MV, Krall JM, al-Sarraf M, *et al*: Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of the Radiation Therapy Oncology Group. *Urology* 45: 616–623, 1995.
12. Bolla M, Gonzalez D, Warde P, *et al*: Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 337: 295–300, 1997.
13. Stock R, Stone, NN, and Yeghiahhan R: Neoadjuvant androgen suppression and permanent radioactive seed implantation in the treatment of stage T1-T2 prostate cancer. *Mol Urol* 2: 121–126, 1998.
14. Stock RG, and Stone NN: Permanent radioactive seed implantation in the treatment of prostate cancer. *Hematol Oncol Clin North Am* 13: 489–501, 1999.
15. Stone NN, and Stock RG: Neoadjuvant hormonal therapy improves the outcomes of patients undergoing radioactive seed implant for localized prostate cancer. *Mol Urol* 3: 239–244, 1999.
16. Zagars GK, Johnson DE, von Eschenbach AC, *et al*: Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: long-term results of a prospective randomized study. *Int J Radiat Oncol Biol Phys* 14: 1085–1091, 1988.
17. Pilepich MV, Caplan R, Byhardt RW, *et al*: Phase III trial of androgen suppression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85-31. *J Clin Oncol* 15: 1013–1021, 1997.
18. Yusuf S, Wittes J, Probstfield J, *et al*: Analysis and interpretation of treatment effects in subgroups of patients in randomized clinical trials. *JAMA* 266: 93–98, 1991.
19. Granfors T, Modig H, Damber JE, *et al*: Combined orchiectomy and external radiotherapy versus radiotherapy alone for nonmetastatic prostate cancer with or without pelvic lymph node involvement: a prospective randomized study. *J Urol* 159: 2030–2034, 1998.
20. Hanks GE, Lu J, Machtay M, *et al*: RTOG protocol 92-02: a phase III trial of the use of long term androgen suppression following neoadjuvant hormonal cyoreduction and radiotherapy in locally advanced carcinoma of the prostate. *Proc Am Soc Clin Oncol* 19: 327a, 2000.