



Faith Krucina. *Spirit of the Mentor*. Acrylic on canvas, 48" × 36". Courtesy of Artistic Images by Faith, Dunedin, Fla.

*The efficacy of neoadjuvant androgen ablation in reducing prostate tumor bulk prior to definitive local therapy is being investigated*

# Neoadjuvant Androgen Ablation in Localized Carcinoma of the Prostate

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**Background:** An increased awareness of prostate cancer has led to a rise in the detection of this disease at a clinically localized stage at presentation. This article discusses the role of neoadjuvant hormonal ablation at this earlier stage to decrease tumor bulk and thus enhance survival.

**Method:** Outcomes from each primary modality for localized treatment of prostate cancer with and without neoadjuvant androgen deprivation (NAAD) are reviewed.

**Results:** Survival benefit using NAAD has not yet been demonstrated from prostatectomy. Long-term hormonal deprivation provides an improved time to progression and has decreased distant metastatic and biochemical failure for poor-risk patients undergoing external-beam radiation. The toxicities of brachytherapy can be decreased with NAAD.

**Conclusions:** NAAD with radical prostatectomy is considered to be investigational. The duration of NAAD needs to be delineated for poor-prognosis patients who are treated with external-beam radiation therapy, but the approach improves the local toxicity of brachytherapy.

## Introduction

The end of the 20th century was a seminal time for prostate cancer. Heightened awareness and attention

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have led to a rise in detection and incidence but, more importantly, to prolific attempts to ameliorate the final outcome. The widespread use of prostate-specific antigen (PSA) assays for early detection has caused a stage migration away from gross distant disease at presentation to clinically localized disease at presentation.<sup>1</sup> Thus, an issue for consideration is the role of neoadjuvant hormonal ablation in clinically localized disease. Localized prostate cancer is understaged clinically in 35%-50% of cases.<sup>2</sup> Can effectively downstaging and decreasing tumor bulk affect the time to progression and ultimate survival?<sup>3</sup> The following discussion presents the data to date and justifies upcoming new trials.

## Surgical Treatment: Localized Disease

As early as 1991, Fair and Heston<sup>4</sup> discussed the high rate of positive surgical margins in patients undergoing radical prostatectomy for presumed localized disease. They compiled data from five series consisting of 1,500 patients with clinical T1-T2 disease who had had radical prostatectomies. Only 680 (47%) had organ-confined disease.<sup>5</sup> Thus, in 53% of cases, the basic surgical tenet of Walsh and Jewell<sup>6</sup> (ie, in order to cure carcinoma of the prostate with surgery, all tumor must be excised) was not met. With extracapsular disease, most patients will evidence biochemical or clinical failure within 5 years of follow-up.<sup>5</sup> Tumor beyond the prostate at radical prostatectomy is associated with earlier prostate-specific antigen (PSA) relapse. This early biochemical failure will eventually translate into clinical evidence of disease, although the PSA failure may present up to 8 years earlier.<sup>7</sup> The concept of utilizing presurgical hormonal therapy emerged in an attempt to improve the rate of organ-confined disease. Theoretically, this would allow for depletion of hormone-sensitive cells and allow surgery to remove the presumably hormone-insensitive cells.<sup>7</sup>

In an early pilot study,<sup>8</sup> 55 patients with prostate adenocarcinoma were treated with diethylstilbestrol (DES) daily for 8 weeks prior to radical prostatectomy. Eighteen patients had stage T2c disease, 27 had stage T3, and 10 had stage D0 (10 patients). A reduction in PSA was seen in 54 patients, but only 18 patients had pathologically confined disease. No real effect on disease status was observed.

Fair et al<sup>9</sup> in 1997 undertook a prospective, non-randomized trial for patients with clinically locally advanced disease (T1b-T3). Patients were treated with goserelin and flutamide for 12 weeks. Of the 75 patients entered, 69 actually completed the trial. Another 72 patients who did not participate in the trial were used as controls, and they were treated with surgery only. Of those receiving neoadjuvant androgen deprivation (NAAD), 48 (70%) of 72 patients had organ-confined T2 disease compared with 35 (48%) of the 72 patients in the surgery-only group ( $P<0.05$ ). Seventy-one percent of patients in the treatment group were clinical stage T2, while only 45% of those in the surgery-only group were clinical stage T2. The margin-positive rate for the study group was 10% compared with 33% for the control group.<sup>7</sup> PSA results after a median 57 months showed no difference in relapse rate.<sup>9</sup>

A follow-up phase III trial in clinically localized (T1-T2) disease randomized patients to surgery alone vs 3 months of goserelin and flutamide followed by surgery. Of the 66 patients in the surgery-only arm, 39 (59%)

had organ-confined disease compared with 52 (70%) of 74 patients in the combined-treatment arm ( $P=0.17$ ). The positive-margin rate was lower in the combined arm (19%) compared with the surgery-only arm (37%) ( $P=0.023$ ). Median follow-up of 35 months showed no difference in PSA relapse rate.<sup>9</sup>

Does improvement in pathologic staging (specifically, decreasing margin positivity) translate into increased disease-free survival? Labrie and colleagues<sup>10</sup> were among the first to attempt to answer the question with a randomized, prospective trial using flutamide and leuprolide prior to radical prostatectomy vs radical prostatectomy alone. The goal was to increase the rate of negative margins and thus improve survival. Patients were fairly well matched; the majority were clinically staged B1-B2. Cancer-positive surgical margins were found in 25 (38.5%) of 65 control patients and in only 10 (13%) of 77 study patients ( $P=0.006$ ). Improvement in stage was observed in 35 (42.9%) of 77 neoadjuvant patients compared with only 5 (7.7%) in the control group. Histopathologic examination revealed upstaging in 53.8% of the control group, whereas downstaging occurred in 23.4% of the combination treatment group. The authors concluded that although the long-term effect was not yet apparent, a downstaged patient with organ-confined disease should anticipate the life expectancy of a patient without prostate cancer. The authors postulated that potentially increased benefit might be obtained if the luteinizing hormone-releasing hormone (LHRH) agonist was continued for a longer period of time.

Soloway et al<sup>11</sup> performed a randomized, prospective trial of combined androgen blockade preceding radical prostatectomy vs radical prostatectomy alone for clinical stage T2b NX M0 patients. The combined-therapy arm included 138 patients, and the surgery-alone arm included 144. Patients who received androgen deprivation preoperatively had significantly lower rates of capsule penetration (47% vs 78%,  $P\leq 0.001$ ), positive surgical margins (18% vs 48%,  $P\leq 0.001$ ), and tumor at the urethral margin (6% vs 17%,  $P\leq 0.001$ ). Follow-up of PSA values at 12 months following prostatectomy revealed PSA  $>0.4$  ng/mL in 16% of pretreated patients and in 12% of patients who had radical prostatectomy alone ( $P=0.0473$ ).<sup>12</sup> Similarly, a study by Goldenberg and colleagues<sup>13</sup> utilizing cyproterone as the neoadjuvant ablation treatment vs radical prostatectomy alone showed no difference in PSA failures at 24 months, despite improvement in positive margins with hormonal treatment. Protracted follow-up is needed to determine actual effectiveness with regard to PSA failure and survival.

Dalkin et al<sup>14</sup> performed a preprostatectomy hormonal ablation trial in which patients were randomized

to either 12 weeks of an LHRH agonist preoperatively or to surgery alone. Of 61 patients entered on the trial, 56 patients were evaluable. Patients were clinical stage T1c, T2a, and T2b. The authors noted no differences between the two arms in either pathologic outcome or the percentage organ-confined disease. This study was hampered by the small number of patients.

In a randomized trial, van der Kwast and colleagues<sup>15</sup> evaluated 3 months vs 6 months of combined androgen deprivation with an LHRH agonist and flutamide in 40 patients undergoing radical prostatectomy. In previous studies, 3 months of similar combined androgen blockade was noted to cause a decrease in margin positivity of specimens.<sup>10,11</sup> Three months of hormonal deprivation also coincides with a low or undetectable PSA reading in most patients. This PSA decrease is associated with a reduction of both tumor and prostate volume.<sup>16-18</sup> Of the 40 patients who entered the trial, 32 (80%) were clinical stage T2; 31 of the 40 patients remained so following treatment. Prolonging hormonal ablation to 6 months led to a 60% reduction in prostate volume compared with a 40%-50% reduction after only 3 months. This 60% decrease in volume was associated with a decrease in positive margins of 9.1% compared with a 3-month treatment positive margin rate of 27.8%, which was not statistically significant ( $P=0.2$ ).<sup>15</sup> The pathology specimens of the patients treated with 6 months had a lower MIB-1 than did those at 3 months, but this was not statistically significant.

Gleave et al<sup>19</sup> evaluated 50 patients with presumed clinically localized prostate cancer with 8 months of neoadjuvant androgen withdrawal prior to radical prostatectomy. As noted previously, the 3-month studies showed decreases in tumor volume and positive margins. Serum PSA, however, does not always become undetectable in all patients by 3 months. The decrease of serum PSA levels after beginning androgen ablation is due to a cessation of the androgen-regulated PSA gene expression and of apoptosis.<sup>20-22</sup> Goldenberg et al<sup>22</sup> noted that maximal PSA response (nadir) and soft-tissue regression occurred after 8 months of intermittent androgen blockade in advanced stages C and D2. Thus, in this trial by Gleave and colleagues,<sup>19</sup> 50 patients with predominantly clinical stage T2b disease underwent androgen ablation either by an LHRH agonist plus flutamide or DES or by cyproterone acetate for 8 months. The rate of positive margins was only 4%, with 68% organ confined. PSA nadirs were lower in organ-confined disease. PSA levels are dependent on androgen levels and tumor volume.<sup>20,23,24</sup> Serum PSA levels decrease rapidly by 84% after 1 month of ablation. A more gradual 52% decrease in PSA levels occurs with 3 months of treatment.<sup>19</sup> By 8 months, 84% of patients have reached their nadir. The continued

decrease in PSA is due to a decrease in tumor volume. Apoptotic cell death causes an initial decrease in PSA, and subsequent diminution of tumor proliferation produces a continued decrease.<sup>19</sup>

Does androgen ablation merely postpone an unchanged failure pattern?<sup>24</sup> The long-term effect on cure rate by neoadjuvant hormonal manipulation remains unclear and therefore should be regarded as investigational in the surgical setting.<sup>20</sup> In addition, hormonal ablation is associated with shortcomings, particularly long-term effects (anemia, hot flashes, diarrhea, decreased libido), as well as substantial cost.<sup>25</sup> Another issue is the return to potency after radical prostatectomy in the absence of androgens.<sup>23</sup> The reversibility of the effect on libido and potency after long-term androgen ablation needs to be examined systematically. Postoperative serum testosterone levels returned to normal in only 15 of 50 patients tested in the study by Gleave et al.<sup>19</sup> Oefelein<sup>26</sup> reported that the median duration of castrate levels of testosterone in patients after one 22.5-mg leuprolide injection (the 3-month depot formulation) was 6 months. Lack of long-term follow-up precludes a definitive statement regarding the role of neoadjuvant hormonal deprivation with radical prostatectomy.

## Radiation Treatment

External-beam radiation therapy is a well-established and potentially curative treatment modality for patients with small-volume tumors and no distant metastases. The long-term locoregional control rates and survival are comparable to those seen with a radical prostatectomy,<sup>27</sup> although a prospective, randomized trial comparing the two has not been conducted. Patients with T3-T4 disease have a poorer prognosis, even with external-beam radiation therapy. Thus, the evaluation of neoadjuvant hormonal deprivation prior to irradiation is an attempt to change outcome.<sup>26</sup>

In 1997, Bolla and colleagues<sup>28</sup> published data from the European Organization for Research and Treatment of Cancer (EORTC) stating that neoadjuvant hormonal deprivation, when used with external-beam radiation, improved local control and survival. Patients included were clinical stage T1-T4 without nodal disease. They received conventional external-beam radiation therapy plus treatment with goserelin given subcutaneously every 4 weeks, starting on the first day of pelvic irradiation and continuing for 3 years. Cyproterone acetate was used to block the flare. A total of 415 patients entered, with 208 receiving radiation therapy alone and 207 receiving combined treatment. Median duration of follow-up was 45 months. Overall survival at 5 years was 79% for combined therapy and 62% for radiation

Table 1. — RTOG 85-31: Summary of Efficacy Endpoints

Endpoint	Arm	Number of Patients	Number of Failures	Estimated 5-Year Rate (%)	P
Local failure	1	477	78	16	<.0001
	2	468	135	29	
Distant metastases	1	477	82	17	<.0001
	2	468	136	30	
NED survival	1	477	206	60	<.0001
	2	468	343	44	
NED survival with PSA <4.0 ng/mL	1	438	187	57	<.0001
	2	429	302	28	
NED survival with PSA <1.5 ng/mL	1	438	206	53	<.0001
	2	429	343	20	
Absolute survival	1	477	131	75	.52
	2	468	138	71	

Arm 1: adjuvant therapy (goserelin) plus radiation therapy  
 Arm 2: radiation therapy alone

From Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppressions 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.* 1997;15:1013-1021. Reprinted with permission.

therapy alone ( $P=0.001$ ). Disease-free 5-year survival for the combined therapy group was 85% compared with 48% for the radiation therapy alone group ( $P\leq 0.001$ ).

A review of the extensive Radiation Therapy Oncology Group (RTOG) prostate cancer database revealed that hormonal therapy and definitive radiation might have a beneficial effect on overall disease-free survival.<sup>29</sup> Concurrently, data from postprostatectomy patients with neoadjuvant hormone deprivation also purported improved survival and a delay in disease progression.<sup>30,31</sup> These factors were part of the basis for the design of the study RTOG 85-31, which included T1-T2 patients with pelvic nodes and T3 patients with or without pelvic nodes. Also included were patients who had positive nodes, either radiographically or histologically, following prostatectomy. These patients received definitive conventional radiation with or without goserelin. Goserelin was started the last day of radiation therapy and continued indefinitely. The adjuvant arm included 477 patients, and 468 were entered in the radiation therapy-alone arm.<sup>30</sup> There was a remarkable improvement in 5-year disease-free survival for the hormonal arm (60% vs 44%,  $P<0.001$ ), and other parameters also improved (Table 1). The overall 5-year survival rate was

75% on the adjuvant arm and 71% on the control arm ( $P=0.52$ ). However, in patients with a Gleason score of 8-10, the difference of 66% vs 55% was statistically significant ( $P=0.03$ ).

Earlier RTOG trials using androgen ablation and external-beam radiation established the safety of short-term hormonal ablation in regard to acute reactions to pelvic radiation and the preservation of potency posttra-

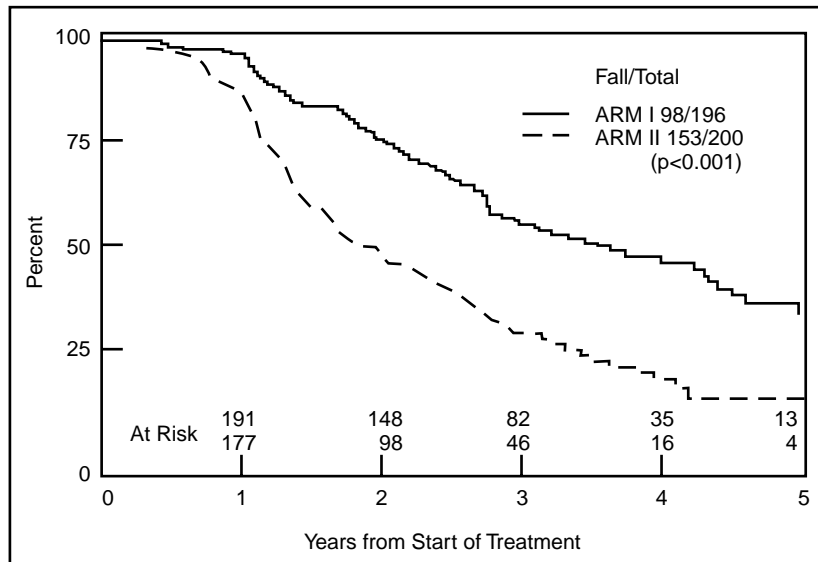


Fig 1. — Progression-free survival by treatment group. Arm I is goserelin and flutamide plus radiation therapy; arm II is radiation therapy alone. RTOG 86-10. From Pilepich MV, Krall JM, al-Sarraf M, et al. Androgen deprivation with radiation therapy compared with radiation therapy alone for locally advanced prostatic carcinoma: a randomized comparative trial of Radiation Therapy Oncology Group. *Urology.* 1995;45:616-623. Reprinted with permission.

Table 2. — Subset Analysis of RTOG Trials 85-31 and 86-10

	All Patients			Duration of Hormones			LTH (85-31)		
	RT	RT+H	Significance	LTH	STH	Significance	RT	RT+H	Significance
bNED Control	14%	41%	<0.0001	52%	27%	<0.0001	18%	52%	<0.0001
DMF	39%	28%	0.0001	24%	34%	0.0002	34%	24%	0.0008
CSF	24%	18%	0.06	15%	23%	0.007	18%	15%	<0.0001

bNED = biochemical disease-free survival  
 DMF = distant metastases failure  
 CSF = cause-specific failure  
 RT = radiation therapy  
 RT+H = radiation therapy + hormones  
 LTH = long-term hormones  
 STH = short-term hormones

From Horwitz EM, Winter K, Hanks GE, et al. Long-term outcome for patients with locally advanced non-metastatic prostate cancer treated with adjuvant hormones and radiation therapy versus radiation therapy alone: subset analysis of RTOG 85-31 and 86-10. Proceedings of the American Society of Therapeutic Radiology Oncology (ASTRO), San Antonio, Tex. *Int J Radiat Oncol Biol Phys.* 1999;45:142. Abstract. Reprinted with permission.

diation therapy.<sup>31,32</sup> In addition, the apoptotic regression occurring with androgen deprivation suggested that radiation cell kill could be enhanced.<sup>33</sup> Thus RTOG 86-10 was conducted to evaluate short-term androgen ablation and radiation vs radiation alone.<sup>34</sup> In arm I, goserelin and flutamide were given for 2 months prior to and during the radiation therapy course. Arm II consisted of standard external-beam radiation therapy. Clinically confined disease included T2b, T2c(B2), and T3-T4(C) disease, with no disease beyond regional nodes. Patients were stratified for stage and tumor grade, and 401 patients were entered in the trial. Seventy percent of the evaluable patients in each arm were stage T3-T4(C). There was a statistically significant improvement in 5-year cumulative incidence of local progression — 46% in arm I compared with 71% in arm II. Progression-free survival also improved for arm I ( $P \leq 0.001$ ) (Fig 1). However, there was no difference in overall survival.

A reanalysis of RTOG 85-31 and 86-10 was published by Horwitz et al<sup>35</sup> in 1999. Patients with positive lymph nodes and those with postradical prostatectomy were excluded from analysis. From the RTOG 85-31 trial, 575 patients with T3 N0 M0 disease were included (280 patients treated with adjuvant hormones plus radiation therapy and 295 patients treated with radiation therapy alone). From the RTOG 86-10 trial, 418 patients with T2b-T4 N0 M0 disease were included (210 patients treated with radiation therapy plus adjuvant hormones and 208 patients treated with radiation ther-

apy alone). Patients in the RTOG 85-31 trial had received hormonal treatment from the last week of radiation therapy and continued indefinitely (LTH). Patients in the RTOG 86-10 trial had received hormonal treatment for 2 months prior to and during radiation therapy (STH). Radiation treatment in both studies was 44-46 Gy to the prostate and regional lymphatics, followed by a 20-25 Gy boost to the prostate. The evaluated endpoints were 8-year overall survival, cause-specific failure, distant metastatic failure, and 5-year biochemical no evidence of disease (bNED) rate. bNED was defined as a posttreatment PSA of less than <1.5 ng/mL for more than 1 year following randomization. The median follow-up was 71 months (0.6-129

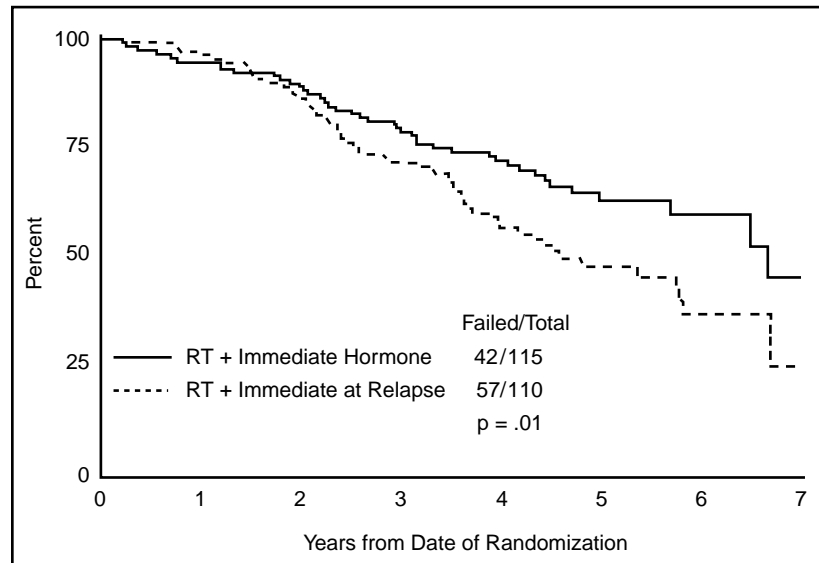


Fig 2. — Survival for patients without prostatectomy and centrally reviewed Gleason score 8 to 10. From Pilepich MV, Caplan R, Byhardt RW, et al. Phase III trial of androgen suppressions using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group protocol 85-31. *J Clin Oncol.* 1997;15:1013-1021. Reprinted with permission.

months). LTH produces statistically significant differences for bNED, distant metastatic failure, and cause-specific failure (Table 2). The benefit of the LTH was specific for patients with locally advanced nonmetastatic prostate cancer with a Gleason score of 7, and 8-10 (Fig 2). Since LTH was lifelong, was the hormonal treatment in the RTOG 85-31 trial truly neoadjuvant?

RTOG 92-02 was a prospective, randomized trial of androgen suppression and external-beam radiation in patients with locally advanced prostate cancer (T2c-T4) and PSA less than 150 ng/mL.<sup>36</sup> All patients received androgen suppression consisting of goserelin and flutamide given 2 months prior to radiation and continuing for 2 months during radiation. Patients were then randomized to 24 months of additional goserelin alone (arm 1) or to observation (arm 2). Of 1,554 patients entered, 1,520 were eligible. Patients in arm 1 showed significant improvement in disease-free survival (54% vs 34%,  $P=.0001$ ), local progression (6% vs 13%,  $P=.0001$ ), distant metastasis (11% vs 17%,  $P=.0001$ ), and biochemical failure (21% vs 46%,  $P=.0001$ ). However, 5-year survival was not appreciably different (78% vs 79%). A subset analysis including all patients with Gleason scores of 8-10 from RTOG 92-02 was compared to a subset analysis of RTOG 85-31. Five-year survival was significantly better with long-term androgen deprivation (80% vs 69%,  $P=0.02$ ).<sup>36</sup> Thus, androgen deprivation in addition to local radiation is recommended for all high-risk patients.<sup>36,37</sup>

An ongoing trial (RTOG 94-08)<sup>38</sup> is studying endocrine therapy used as a cytoreductive and cytostatic agent prior to radiation therapy. Eligibility requirements include clinical T1b-T2b disease with no involved nodes, no distant metastases, and a PSA of  $\leq 20$ . Goserelin and flutamide are administered as in RTOG 86-10 for a finite period along with standard external-beam radiation vs radiation alone.

## Brachytherapy

The role of neoadjuvant hormone ablation in brachytherapy of prostate cancer is not to achieve an adjuvant effect, but rather to reduce the size of the gland to allow for greater technical ease in performing a transperineal implant. Zelefsky et al<sup>39</sup> have shown an improvement in local pelvic geometry after NAAD prior to external-beam radiation therapy to allow better exclusion of the rectum and bladder from high-dose regions and thus decrease local toxicity.

In a retrospective study by Potters et al,<sup>40</sup> 132 patients were treated for 3-8 months with NAAD to achieve a reduction in tumor volume prior to transper-

ineal interstitial permanent prostate brachytherapy (TIPPB). These patients were matched with 131 patients who had TIPPB only. The actuarial PSA relapse-free survival at 5 years was 86.5%. The 5-year relapse-free survival for patients with NAAD was 87.1% compared with 86.9% for those without NAAD. Patients who received NAAD tended to receive external-beam radiation as part of their treatment. There was no difference in PSA disease-free survival for these groups with or without external-beam irradiation. This demonstrated no significant advantage in PSA relapse-free survival by adding TIPPB.

D'Amico et al<sup>41</sup> noted that the addition of NAAD to TIPPB in a retrospective analysis improved biochemical survival in patients with a Gleason score of 7 compared with TIPPB alone.

A current study by the Prostate Brachytherapy Research Group is investigating NAAD in a prospective, randomized trial for patients with T1-T2 prostate cancer who are at high risk for extracapsular extension and local failure. Those factors are PSA of 10 or greater and a Gleason score of 7 or higher (unpublished data, Sarah Cannon Cancer Center, 1999).

The present role of NAAD in brachytherapy is to ameliorate radiation side effects. There is no evidence to date to support an effect on biochemical or regional failure.

## Conclusions

The role of hormonal therapy for the treatment of advanced prostate cancer has been known since Huggins described the effects 50 years ago.<sup>42</sup> Androgen deprivation remains as first-line therapy for metastatic disease, but what about earlier disease? Is there a role for neoadjuvant hormonal therapy? In the preceding discussion, each primary modality for localized treatment has been examined with and without hormonal deprivation. Surgical treatment in the form of radical prostatectomy has shown limited benefit with decreases in positive margins and tumor downsizing but has produced no effect on PSA relapse.<sup>42</sup> There is no definitive answer regarding overall survival, which remains the overriding issue.

Hormonal deprivation is not risk free. Primary changes in libido and potency are lifestyle consequences that must be justified by demonstrated benefit. In addition, the changes that occur with protracted androgen deprivation (eg, decreases in muscle mass and exercise tolerance, anemia, hot flashes and sweats) can take from 6 months to 1 year to reverse.<sup>26</sup> Thus, in

the surgical setting, neoadjuvant hormonal therapy should be considered investigational.<sup>25</sup>

Local therapy with radiation is often hampered by more advanced disease and patient comorbidities. However, Bolla et al<sup>28</sup> noted improved overall survival for patients treated with radiation therapy and hormonal therapy. The period of androgen ablation was 3 years, which may not be much different than permanent ablation. Recovery of testicular androgen production after 3 years is doubtful and may not occur at all.<sup>36</sup>

The RTOG trials 85-31, 86-10, and 92-02 demonstrated improvements in progression-free survival, distant metastatic failure, and biochemical failure, especially for patients with a Gleason score of 7 or higher utilizing long-term androgen ablation.<sup>35,37,42</sup> Subset analysis in RTOG 92-02 of patients with a Gleason score of 8-10 improved 5-year survival.<sup>37</sup>

Duration of therapy remains an issue. Long-term therapy in the RTOG studies that decreased biochemical and distant metastatic failure varied from 2 years to lifelong.<sup>35,37</sup> Perhaps a more scientific approach would be to use PSA nadir to define the length of treatment and the timing of local therapy.<sup>43</sup> This approach would require fewer lifestyle changes, limit side effects, and reduce exorbitant costs. NAAD is investigational with radical prostatectomy. It is recommended with external-beam radiation therapy for poor-risk patients and with brachytherapy to limit toxicities. Studies are ongoing to determine the role of NAAD in lower-risk patients and the appropriate length of that treatment. Other potential markers and prognostic indicators may be of value.

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