

# EVOLUTION OF THERAPEUTIC APPROACHES WITH LUTEINIZING HORMONE-RELEASING HORMONE AGONISTS IN 2003

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## ABSTRACT

The role of hormone therapy in the current era of widespread testing for prostate-specific antigen (PSA) continues to evolve. Although still used in patients with metastatic disease, the most common uses of luteinizing hormone-releasing hormone (LHRH) agonist therapy are in the adjuvant and neoadjuvant settings with radiotherapy and sometimes with radical prostatectomy, as well as in the treatment of PSA-only recurrence. Immediate (adjuvant) hormone therapy after prostatectomy may provide a survival advantage relative to deferred treatment in high-risk patients, whereas the survival benefit of adjuvant therapy with radiation is clearer. Combined androgen blockade with an LHRH agonist and a nonsteroidal antiandrogen provides a very modest but statistically significant survival benefit relative to LHRH agonist monotherapy in patients with metastatic disease, but it has not been proved in those with less advanced disease. Intermittent hormone therapy appears to be effective in maintaining disease control for several years, but randomized studies are needed to determine if survival is at least equivalent to continuous therapy. Finally, LHRH agonist therapy is commonly used in the setting of biochemical or PSA-only recurrence. However, there are no randomized controlled trials to prove a survival benefit over observation. In summary, hormone therapy now plays a more important role at earlier stages of disease, consistent with the changing epidemiology of prostate cancer. Additional studies are needed, however, to define how to optimally use hormone therapy across various patient types. *UROLOGY* 62 (Suppl 6A): 20–28, 2003. © 2003 Elsevier Inc.

The role of hormone therapy in the treatment of prostate cancer has evolved over the last decade in conjunction with changes in disease epidemiology. As illustrated by the Department of Defense Center for Prostate Disease Research (CPDR) national database, prostate cancer is now being diagnosed at earlier stages, at younger ages, and in men with lower prostate-specific antigen (PSA) levels.<sup>1</sup> During the 1990s, the percentage of men diagnosed with stage T1c disease increased, but as importantly, the percentage with stage T3 and T4 disease decreased. Moreover, the percentage of men diagnosed in their 50s and the percentage

having PSA levels of 4 to 10 ng/mL increased over the last decade, and in the last several years, the percentage with PSA <4 ng/mL also increased. Similar trends are seen in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.<sup>2</sup> Whereas hormone therapy has been traditionally used in patients with stage D disease, the SEER program shows that only 3% to 5% of newly diagnosed men with prostate cancer have stage D2 disease, and <2% have stage D1.

Leuprolide acetate is the most commonly prescribed luteinizing hormone-releasing hormone (LHRH) agonist in the United States. Although used in patients with stage D1 and D2 disease, leuprolide acetate is currently prescribed more commonly in other settings because of the changing epidemiology. According to market statistics, the most common uses of leuprolide acetate are in the neoadjuvant or adjuvant setting with radiotherapy, in treatment of PSA-only recurrence, and in its emerging role in the adjuvant treatment of high-risk individuals after prostatectomy. This article focuses on the efficacy of LHRH agonists in each of

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these settings and identifies areas of further exploration and questions that remain unanswered.

### IMMEDIATE HORMONE THERAPY VERSUS OBSERVATION

From a historical perspective, the Veterans Affairs Cooperative Urological Research Group (VA-CURG) conducted several studies that laid the foundation for immediate hormone therapy of prostate cancer. In their first study, patients were randomly assigned to observation, orchiectomy, diethylstilbestrol (DES) 5 mg, or both orchiectomy and DES.<sup>3</sup> Orchiectomy did not appear to affect the survival of patients with advanced disease, whereas DES was associated with higher cardiovascular mortality. In a subsequent study, patients were randomized to treatment with placebo or with DES 0.2 mg, 1 mg, or 5 mg.<sup>3</sup> The high-dose group was terminated early because of cardiovascular mortality. Although survival did not differ among treatments, patients receiving DES 1 mg were less likely to progress to metastatic disease compared with those given placebo or DES 0.2 mg, which does not effectively suppress plasma testosterone levels. When the data were subsequently reanalyzed, they suggested that young patients with high-grade tumors had a survival advantage when hormone therapy was initiated at the time of diagnosis.<sup>4</sup>

The Medical Research Council (MRC) subsequently compared immediate and deferred hormone therapy (orchiectomy or LHRH agonist) in patients with locally advanced or asymptomatic metastatic disease.<sup>5</sup> Although the target was to enroll 2000 patients, the study was discontinued early because of decreasing enrollment after 938 patients had been assigned to treatment. Survival of patients with asymptomatic metastatic disease did not differ between immediate and deferred treatment. However, in those with locally advanced disease, immediate hormone therapy delayed disease progression and development of cancer-related complications. At the time of analysis, metastasis or death from prostate cancer had occurred in 38% of men in the immediate-treatment group compared with 59% of those in the deferred-treatment group ( $P < 0.001$ ). It is important to recognize, however, that some of the men in the deferred-treatment arm who died of prostate cancer never received hormone therapy as their disease progressed.

### ADJUVANT HORMONE THERAPY AFTER PROSTATECTOMY IN HIGH-RISK MEN

The role of immediate (adjuvant) hormone therapy in high-risk patients after radical prostatectomy was evaluated by the Eastern Cooperative Oncology Group (ECOG) and Southwestern On-

cology Group (SWOG).<sup>6</sup> In all, 98 men with node-positive disease who underwent radical prostatectomy and pelvic lymphadenectomy were randomly assigned to receive immediate hormone therapy (goserelin 3.6 mg subcutaneously every 28 days or bilateral orchiectomy) or observation until disease progression. After a median follow-up duration of 7.1 years, 3 (6%) of the 47 men receiving adjuvant therapy and 16 (31%) of the 51 men in the observation group died of prostate cancer. Compared with men receiving adjuvant therapy, those in the observation group were at a 6.2-fold higher risk of death from prostate cancer ( $P < 0.01$ ) and a 12.2-fold higher risk of disease recurrence as shown by rising PSA levels, radiographic evidence, or biopsy ( $P < 0.001$ ). Data after a median follow-up time of 10 years continue to show that immediate hormone therapy was associated with better overall (72% vs 49%,  $P = 0.025$ ) and cause-specific (87% vs 57%,  $P = 0.001$ ) survival than observation.<sup>7</sup>

The ECOG/SWOG study has been criticized for being small in size, lacking a central pathologic review to ensure balancing of Gleason scores between groups, and having lower survival of the observation group than encountered in other contemporary studies.<sup>8</sup> Moreover, a larger study by Schroeder *et al.*<sup>9</sup> in Europe did not show a survival advantage of immediate hormone therapy in men with stage D1 disease. Each of these criticisms has been refuted by the ECOG investigators.<sup>10</sup> Survival of patients in the observation arm of the ECOG study was comparable to survival rates for untreated patients with stage D1 disease at the Mayo Clinic (Rochester, MN), as well as at the Johns Hopkins Medical Center (Baltimore, MD). The European study had a major difference in design: the prostate was not removed when surgeons found D1 disease. Nevertheless, immediate hormone therapy showed a trend for being better than observation, but statistical significance was not achieved. Thus, in patients with node-positive disease, debulking by radical prostatectomy and pelvic lymphadenectomy leaves an extremely low volume of residual disease, and in this setting, adjuvant hormone therapy appears to be beneficial.

### ADJUVANT HORMONE THERAPY WITH RADIOTHERAPY

The use of LHRH agonists in conjunction with radiotherapy in locally advanced disease has increased in popularity in the United States. Evidence supporting the use of adjuvant hormone therapy with radiotherapy is derived principally from a study conducted by the European Organisation for Research and Treatment of Cancer (EORTC).<sup>11</sup> A total of 415 patients with locally advanced prostate cancer were randomly assigned to radiotherapy alone or radiotherapy plus adju-

vant LHRH agonist therapy. Patients in the latter group received goserelin every 4 weeks starting on the first day of irradiation and continuing for 3 years. The study population had high-risk disease inasmuch as 34% had Gleason grade 7 to 10 cancers, 92% were at clinical stage C, 89% were node-negative, and 80% had PSA levels >10 ng/mL. Adjuvant LHRH agonist therapy produced better outcomes than radiotherapy alone.<sup>12</sup> As seen in Figure 1, clinical progression occurred after a median of 65.7 months in 90 (43%) of 208 men in the radiotherapy group compared with 27 (13%) of 207 men receiving adjuvant hormone therapy. Notably, adjuvant therapy significantly improved overall survival (hazard ratio, 0.51;  $P < 0.0001$ ) and biochemical disease-free survival (hazard ratio, 0.42;  $P < 0.0001$ ). With adjuvant therapy, 5-year disease-specific survival was 78% compared with 62% with radiotherapy alone ( $P = 0.0002$ ), and 5-year biochemical disease-free survival was 76% versus 45%, respectively ( $P < 0.0001$ ). Despite these findings, it is important to recognize that patients in the radiotherapy-alone group were not treated in a manner consistent with current practice in the PSA era. Most (80%) patients in the radiotherapy group had documented metastatic disease before they started hormone therapy.

#### PSA-ONLY RECURRENCE

Among the most common problems facing clinicians is PSA-only recurrence after prostatectomy, external-beam radiotherapy, or brachytherapy.<sup>13</sup> Clinical trials defining optimal timing of hormone therapy in these high-risk cases are not available. Because of stage and age migration, many men with PSA-only recurrence are relatively young, and its implications are of major concern to both patient and clinician. Unlike the design of the EORTC study,<sup>11</sup> most patients with a rising PSA value do not want to wait for clinical evidence of metastatic disease before starting therapy. SEER statistics suggest that approximately 40% of patients undergoing localized treatment for prostate cancer will eventually experience a PSA-only recurrence. In a cohort of 3208 patients from CPDR who underwent radical prostatectomy, about 40% had a PSA recurrence within 7 years and nearly half within 10 to 12 years.<sup>14</sup> In most cases, perhaps  $\geq 66\%$  of them, the PSA recurrence was a manifestation of systemic disease. If a clinician believes that immediate hormone therapy provides a survival advantage for traditional stage D disease, then by extrapolation, hormone therapy may enhance the survival of men with a PSA recurrence, particularly if it is seen to represent "occult" stage D disease. Several lines of evidence support this concept. First, for many men, there is a short period between PSA recurrence and the development of

bone metastases.<sup>15</sup> Second, salvage radiotherapy to the prostate bed in men with PSA recurrence after radical prostatectomy has low long-term efficacy.<sup>16</sup> Only about 33% of such patients maintain a response at 5 years. Finally, experience with ProstaScint scanning (Cytogen, Princeton, NJ) in patients with PSA recurrence shows a high incidence of occult nodal disease.<sup>17</sup>

In a retrospective review of nearly 2000 men who underwent radical prostatectomy at the Johns Hopkins Medical Center between 1982 and 1997, PSA recurrence was found in 315 (15%) patients.<sup>15</sup> The median time from PSA recurrence to clinical metastases was 8 years, and the median time to subsequent death from prostate cancer was 5 years. Several factors, including recurrence within 2 years of initial treatment, high Gleason sum (8 to 10), and short PSA doubling time (<10 months), were predictive of the probability and time to the development of metastatic diseases. Moreover, the time from prostatectomy to clinical metastases was predictive of the time until death from prostate cancer. The CPDR database includes a total of 4966 men who underwent radical prostatectomy between 1987 and 2002, and 1753 (35%) had PSA recurrence with levels >0.2 ng/mL.<sup>18</sup> Overall, 57% of these recurrences occurred in the first 2 years after surgery, and 86% occurred in the first 5 years. However, only 170 patients, or 10% of those with PSA recurrence, had progressed to metastatic disease after a 5-year follow-up interval. In many of these cases, hormone therapy was provided at PSA recurrence. The relation between use of hormone therapy at PSA recurrence and subsequent disease progression in the CPDR database still needs to be evaluated.

Multiple prognostic factors may help to predict which patients with clinically localized disease are at high risk of recurrence and, thereby, to better direct multimodal therapy with adjuvant LHRH agonists after radical prostatectomy. Several nomograms have been used, and it is unclear whether a particular nomogram is superior to another. The CPDR and Cancer of the Prostate Strategic Urologic Research Endeavor (CPDR/CaPSURE) risk-of-recurrence equation is based on 4 independent prognostic factors: pretreatment PSA level; Gleason score (worst sum) of the primary tumor; pathologic stage; and patient ethnicity.<sup>19</sup> The CPDR/CaPSURE equation stratifies patients into 4 risk groups: very low, low, high, and very high. Findings showed that 7-year disease-free survival correlated with risk group in a group of >1500 patients (Figure 2). This information is useful for educating patients about their risk—whether surgery had a high likelihood of addressing their prostate cancer or whether they have high or very high

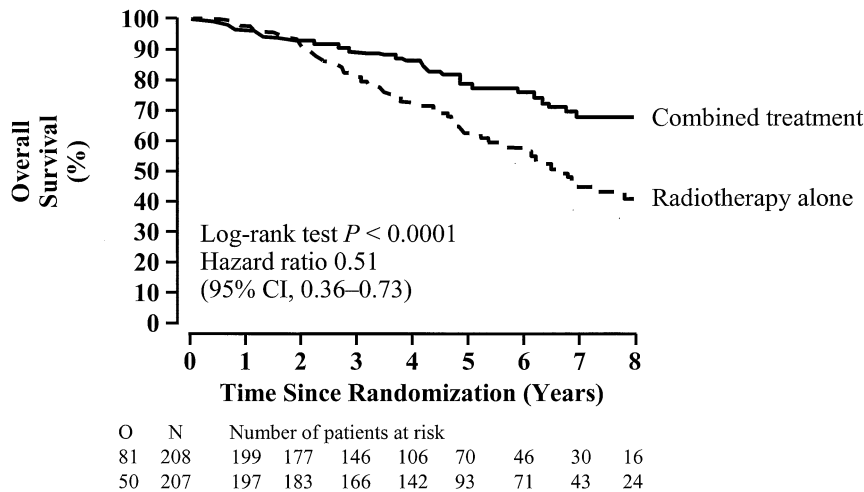


FIGURE 1. Kaplan-Meier estimates of overall survival in European Organisation for Research and Treatment of Cancer trial of adjuvant luteinizing hormone-releasing hormone and antiandrogen therapy with radiotherapy versus radiotherapy alone in patients with locally advanced prostate cancer. CI = confidence interval; N = number of patients; O = number of deaths. (Adapted from Lancet.<sup>12</sup>)

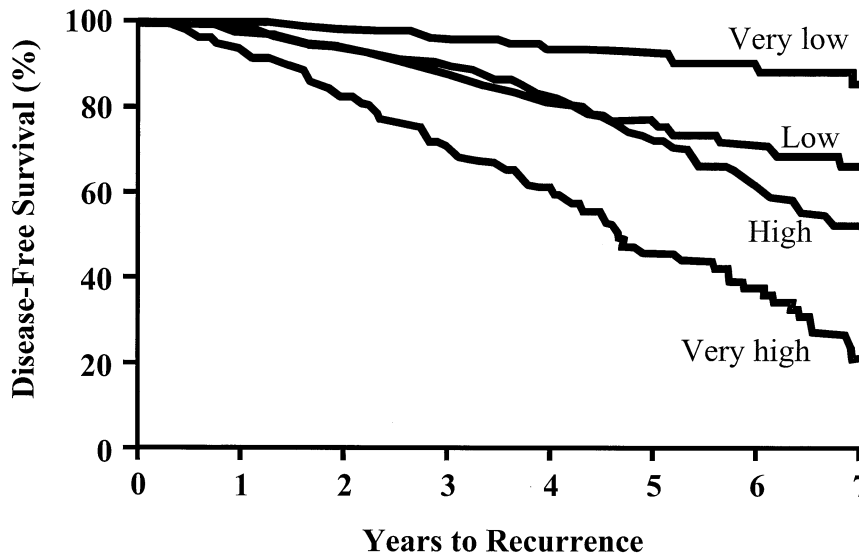


FIGURE 2. Relation between risk groups according to the Center for Prostate Disease Research/Cancer of the Prostate Strategic Urologic Research Endeavor equation and disease-free survival. (Reprinted from J Urol.<sup>19</sup>)

risk of recurrence and, therefore, should consider adjuvant treatments.

The concern about immediate hormone therapy, whether in the adjuvant setting or for PSA recurrence, is the possibility that patients will develop an earlier hormone-refractory state and have a diminished survival. Immediate therapy may improve metastasis-free survival, but patients will be hormone refractory when metastases develop. Treatment that delays the appearance of bone metastases is likely to be favorable, particularly because better therapies might become available in the future for hormone-refractory disease. Nevertheless, survival is the ultimate end point, and data are needed to show whether immediate hormone

therapy for PSA recurrence actually improves survival. Moreover, the optimal PSA threshold or doubling time for initiating such therapy needs to be determined.

#### MONOTHERAPY VERSUS COMBINED HORMONAL THERAPY

The role of combined hormonal therapy in advanced prostate cancer has been controversial since flutamide was approved by the US Food and Drug Administration (FDA) in 1989 and since bicalutamide and nilutamide were approved in the mid 1990s. Early studies suggested that combined hormonal therapy with an LHRH agonist and an

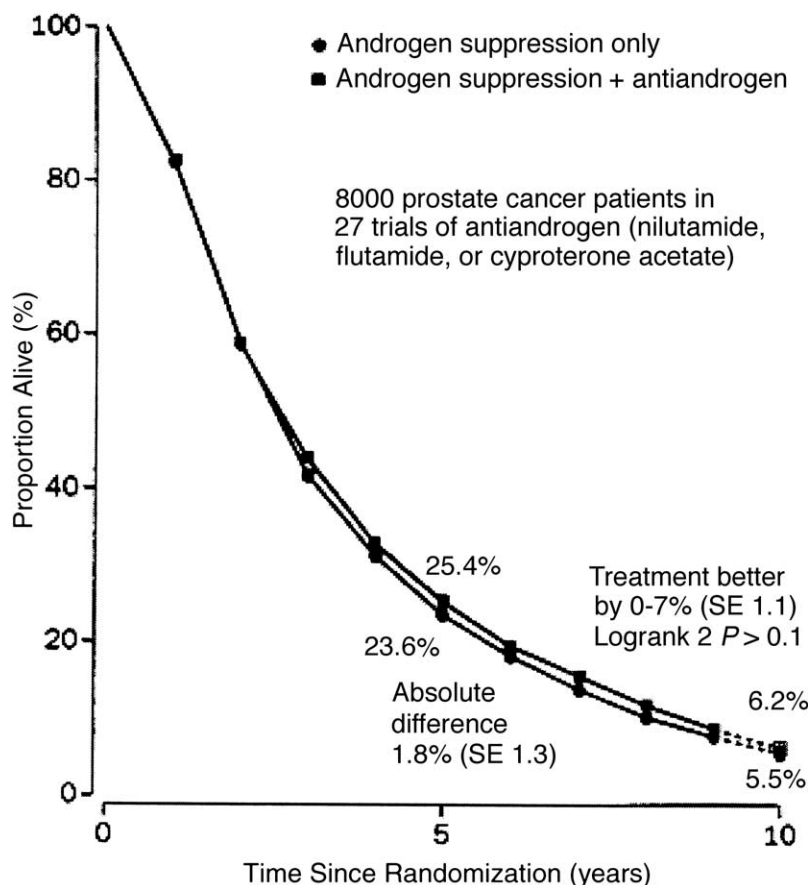


FIGURE 3. Meta-analysis of 10-year survival of patients with prostate cancer (88% with metastatic disease and 12% with advanced disease) after combined androgen blockade as compared with monotherapy with a luteinizing hormone releasing hormone agonist or orchiectomy. (Reprinted with permission from Lancet.<sup>26</sup>)

antiandrogen provided a modest survival benefit in stage D2 disease. In the Intergroup Trial (INT) 0036 patients were randomly assigned to leuprolide alone or in combination with flutamide.<sup>20</sup> Median duration of progression-free survival was significantly prolonged from 13.9 months for patients treated with leuprolide alone to 16.5 months for those receiving combined therapy ( $P = 0.039$ ). Overall survival was also prolonged from 28.3 to 35.5 months. The benefit of combined hormonal therapy in this study was particularly evident in patients with minimal disease and better performance status. Similarly, EORTC 30853 showed that a goserelin implant plus flutamide improved survival compared with bilateral orchiectomy in newly diagnosed patients with metastatic disease.<sup>21</sup> However, no differences in survival were seen in a large study of orchiectomy with or without flutamide in patients with metastatic disease<sup>22</sup> or in a number of smaller studies of LHRH analogs with or without an antiandrogen.<sup>23-25</sup>

The most recent meta-analysis of monotherapy versus combined therapy was published in 2000.<sup>26</sup> It evaluated 27 randomized trials involving 8275 patients, including 4803 patients treated with flutamide (usually at 750 mg/day), 1688 patients with

nilutamide (usually at 300 mg/day), and 1784 patients with cyproterone acetate (usually at 150 to 200 mg/day). This meta-analysis included updated information on 13 previously analyzed trials and results from 5 trials including INT 0036, which had not been included in the previous meta-analysis. Most patients (88%) had metastatic disease, whereas 12% were classified as having locally advanced disease. Overall, 5-year survival was 25.4% with combined hormonal therapy compared with 23.6% with either orchiectomy or LHRH agonist alone—the absolute difference being 1.8% ( $P = 0.11$ ; Figure 3). The effect of the pure nonsteroidal antiandrogens flutamide and nilutamide differed from that of cyproterone acetate. Combined therapy involving flutamide or nilutamide provided a small, but statistically significant, benefit on 5-year survival (27.6% vs 24.7%,  $P = 0.005$ )—the absolute difference being 2.9%. In contrast, combined therapy involving cyproterone acetate produced somewhat lower 5-year survival rates than monotherapy (15.4% vs 18.1%,  $P = 0.04$ ). In the subgroup of 1000 patients with locally advanced disease, survival was slightly, but not significantly, better with combined hormonal therapy.

Some clinicians advocate using combined hormonal therapy based on the modest survival advantage shown in the meta-analysis, but a comparable number prefer monotherapy for the very same reason. The dilemma is how to use this information: whether to call it a statistically significant, albeit modest, benefit or a clinically insignificant difference. In either case, it is probably advisable to present the data to each patient and have him participate in the decision-making process.

### INTERMITTENT VERSUS CONTINUOUS HORMONAL THERAPY

The rationale for intermittent hormonal therapy (IHT) is to allow androgen-dependent cells to repopulate the tumor when treatment is withdrawn and thereby compete with the growth of androgen-independent cells.<sup>27,28</sup> Although conceptually attractive, clinical efficacy remains unproved, and the underlying process is based solely on experimental models. For example, the mean time to androgen independence increased from 50 days with continuous hormone therapy to 150 days when the androgen-dependent Shionogi carcinoma was sequentially transplanted into male mice who were castrated only when the tumor reached a pre-defined size.<sup>29</sup>

IHT offers several potential benefits, but it has an equal number of drawbacks.<sup>28</sup> It may reduce the adverse physiologic effects associated with continuous hormone therapy (eg, loss of libido, erectile dysfunction, and hot flashes) and provide periods of improved quality of life when the patient is off treatment. Additionally, IHT should be less costly than continuous therapy, although the costs of closely monitoring patients during periods off treatment may minimize any cost advantage. Finally, IHT is usually patient directed and thereby gives patients a feeling that they are in control of their disease. On the other side of the equation, it remains to be established whether survival with IHT is equivalent to continuous therapy. Another unanswered question is whether the significance of PSA levels after treatment remains comparable to those before treatment. For example, PSA levels may be much lower when bone metastases develop than when a patient with a stage T3 or T4 tumor is started on hormone therapy.

IHT is optimally used in younger men with PSA recurrence after prostatectomy or radiotherapy and in older men at low risk who want treatment rather than observation. There are no well-established guidelines for treatment withdrawal and re-institution. Patients are started on hormone therapy with an LHRH agonist alone or in combination with an antiandrogen. If a PSA nadir is achieved

after 8 to 12 months, then hormone therapy is discontinued and PSA levels and/or testosterone levels are monitored every 1 to 2 months. In our opinion, the PSA nadir should be  $<1$  ng/mL and preferably undetectable after the initial hormonal therapy in patients with PSA recurrence after primary therapy who are offered IHT. Hormone therapy is resumed when PSA levels and/or testosterone levels increase to a predetermined level or with evidence of clinical progression. If an acceptable PSA nadir is not achieved, then patients should probably receive continuous hormone therapy.

Several groups have reported on their experiences with IHT. Prapotnich *et al.*<sup>30</sup> treated 233 patients with advanced prostate cancer or PSA recurrence after primary therapy for a 10-year period. A 3-month LHRH subcutaneous implant was used in combination with a nonsteroidal antiandrogen during the treatment periods. Hormone therapy was discontinued when PSA levels decreased to  $<4$  ng/mL and was resumed with a PSA  $>20$  ng/mL, when PSA velocity over the previous 3 months was  $>5$  ng/mL per month, or with recurrence of pain or urinary symptoms. Patients were observed for a median duration of nearly 3 years, with the mean duration of an on-treatment/off-treatment cycle being 14 months. As the number of cycles increased, the on-treatment duration decreased as did the off-treatment duration. During each treatment cycle, patients spent about 30% of the time on treatment whether treated for advanced disease or PSA recurrence. The investigators concluded that IHT provided good disease control over a 3-year period and was not associated with major complications.

In a study by De La Taille *et al.*,<sup>31</sup> IHT was used to treat 146 men: 74 men with PSA recurrence after prostatectomy or radiotherapy as primary treatment, and 72 men with localized, locally advanced, or metastatic disease. Hormone therapy was continued for 6 months after PSA became undetectable or reached a nadir, and it was reinstated when PSA levels increased to  $>4$  ng/mL for those who had previously undergone prostatectomy or to  $>10$  ng/mL for all others. Patients were observed for a mean of 45.6 months, and overall 5-year PSA recurrence-free survival was estimated to be 68%. In a multivariate analysis, the strongest predictors of biochemical progression were a Gleason score  $\geq 8$ , locally advanced or metastatic disease, and age  $<70$  years.

Although these reports are encouraging, randomized clinical trials are needed to demonstrate if IHT provides equivalent progression-free and overall survival, compared with continuous therapy. An INT is in progress to address this issue.

**TABLE 1. Prospective randomized studies of hormone therapy in conjunction with radiation therapy**

Study	Treatment Arm	Difference in 5-Year Survival: P Values				Subgroup Analysis
		PSA	Metastatic Disease	Cause-Specific	Overall	
RTOG 8531 <sup>33</sup>	Continuous LHRH agonist (adjuvant)	<0.0001	<0.0001	0.23	0.36	Gleason 8–10: CS <i>P</i> = 0.02; OS <i>P</i> = 0.04
RTOG 8610 <sup>34</sup>	LHRH agonist for 4 mo (neoadjuvant)	<0.0001	0.04	0.05	0.10	Gleason 2–6: CS <i>P</i> = 0.0002; OS <i>P</i> = 0.02
RTOG 9202 <sup>35</sup>	LHRH agonist for 2 yr (after neoadjuvant)	0.0001	0.001	0.07	NS	Gleason 8–10: CS <i>P</i> = 0.007; OS <i>P</i> = 0.02
EORTC 22863 <sup>12</sup>	LHRH agonist for 3 yr (adjuvant)*	<0.0001	<0.0001	0.001	0.0002	

CS = cause-specific subgroup; EORTC = European Organisation for Research and Treatment of Cancer; LHRH = luteinizing hormone–releasing hormone; NS = not significant; OS = overall survival subgroup; PSA = prostate-specific antigen; RTOG = Radiation Therapy Oncology Group.

\* Most (80%) patients in control arm did not receive hormone therapy until there was evidence of metastatic disease.

### NEOADJUVANT VERSUS ADJUVANT HORMONE THERAPY

The activity of adjuvant therapy after radical prostatectomy was shown in the ECOG/SWOG study described previously.<sup>6</sup> Neoadjuvant hormone therapy before prostatectomy was evaluated in 61 patients with stage T3 or T4 tumors by the SWOG in a phase 2 study.<sup>32</sup> Patients received goserelin monthly and flutamide daily for 4 months before undergoing surgery. The incidence of positive surgical margins was 30%, which was considered remarkably low, given the extent of disease. Nevertheless, the lower incidence of positive surgical margins may be artificial because of the difficulty of identifying cancer exposed to hormone therapy. In the SWOG study, the 5-year progression-free and overall survival rates were 70% and 90%, respectively, which compare favorably with studies of neoadjuvant therapy with radiation therapy.

Several studies conducted by the Radiation Therapy Oncology Group (RTOG) show that hormone therapy integrated with radiation therapy increases local disease control and lowers the risk of PSA recurrence, but it does not prolong overall survival (Table 1).<sup>33–35</sup> In general, these studies enrolled high-risk patients with stage T2, T3, or T4 disease. In RTOG 8531, 977 patients were randomly assigned to continuous adjuvant LHRH agonist therapy or radiotherapy alone with hormone therapy at PSA recurrence.<sup>33</sup> Patients were observed for a median duration of 5.6 years. Adjuvant hormone therapy reduced the rate of local failure at 8 years from 37% to 23% (*P* < 0.0001) and distant metastasis from 37% to 27% (*P* < 0.0001), and it significantly improved disease-free survival (*P* < 0.001). Importantly, cause-specific (16% vs 21%, *P* = 0.23) and overall (49% vs 47%, *P* = 0.36) survival at 8 years

did not differ between the groups receiving adjuvant hormone therapy versus radiotherapy alone. However, in a subset analysis of patients with Gleason scores of 8 to 10, adjuvant hormone therapy significantly improved cause-specific (*P* = 0.019) and overall (*P* = 0.036) survival. RTOG 8531 used a similar design as the EORTC study discussed previously,<sup>11</sup> except that LHRH agonist therapy was given continuously instead of stopping after 3 years, and in the control arm, patients usually received hormone therapy at PSA recurrence rather than waiting for evidence of metastatic disease.

RTOG 8610 evaluated neoadjuvant hormone therapy in 471 patients with clinical stage T2 to T4 tumors with or without evidence of lymph node involvement.<sup>34</sup> In the neoadjuvant arm, patients received goserelin and flutamide for 2 months before and 2 months during radiotherapy. In the other arm, patients were treated with radiotherapy alone and then hormone therapy at recurrence. Patients were observed for a median duration of 6.7 years. At 8 years, neoadjuvant therapy significantly reduced the rates of local failure from 42% to 30% (*P* = 0.016) and distant metastasis from 45% to 34% (*P* = 0.04), and it improved the rates of disease-free survival (21% vs 33%, *P* = 0.004) and cause-specific mortality (23% vs 31%, *P* = 0.05). Overall survival, however, did not differ significantly between the 2 groups (*P* = 0.10). In a subset analysis, the benefit of neoadjuvant therapy was seen in patients with Gleason scores of 2 to 6, where all end points including overall survival were significantly improved. A secondary analysis was conducted to determine if neoadjuvant therapy compromised the activity of salvage hormone therapy at relapse.<sup>36</sup> Notably, disease-specific and overall survival rates at 5 years after salvage therapy were identical for patients who had initially

been treated with neoadjuvant hormone therapy or radiotherapy alone. Thus, patients receiving neoadjuvant therapy remain sensitive to subsequent androgen ablation.

In RTOG 9202, all patients received neoadjuvant hormone therapy with goserelin and flutamide for 2 months before and 2 months during radiation therapy, and then patients were randomly assigned to receive the LHRH agonist for 24 months after irradiation or regular monitoring.<sup>35</sup> Although the group that continued to receive hormone therapy had significantly better local control of disease ( $P = 0.0001$ ), a lower incidence of metastases ( $P = 0.001$ ), and a trend for better cause-specific survival ( $P = 0.07$ ), a difference between treatments in overall survival was not observed. As in RTOG 8531, this study showed significantly better cause-specific ( $P = 0.007$ ) and overall ( $P = 0.02$ ) survival with adjuvant hormone therapy in the subgroup of patients with Gleason scores of 8 to 10.

It is reasonable to believe that the potential benefit of using hormone therapy with radiotherapy results from a reduction in tumor volume. Eradication of subclinical distant metastasis is another possibility, but lack of efficacy of neoadjuvant therapy with radical prostatectomy argues against this concept. The optimal duration of neoadjuvant therapy remains unknown, and treatment for periods  $>3$  to 4 months may be necessary to show a good survival advantage. Indeed, treatment for 12 to 24 months before and after radiotherapy may be needed to obtain the maximal benefits of hormone therapy. For selected patients, particularly those who are healthy, who are in their late 40s to mid 50s, and who have significantly elevated PSA levels and locally advanced disease, radical prostatectomy may be appropriate after completion of a period of neoadjuvant therapy. If the pathology proves unfavorable, then possibly radiotherapy and adjuvant hormone therapy would be offered after surgery.

## CONCLUSION

The role of hormone therapy in the management of prostate cancer continues to evolve. Immediate hormone therapy after radical prostatectomy was shown to improve cause-specific and overall survival of high-risk patients in an ECOG/SWOG study,<sup>6</sup> and the benefit of hormone therapy with radiotherapy is quite clear. Although the EORTC study showed a survival benefit with adjuvant hormone therapy after radiotherapy, most patients in the control arm were not treated in a manner consistent with current clinical practice in the PSA era.<sup>12</sup> In RTOG 8531, control patients received treatment on PSA recurrence according to the discretion of the treating physician, and in this study,

adjuvant therapy improved disease control but did not prolong survival.<sup>33</sup>

Combination hormone therapy may provide a statistically significant, but very modest, survival advantage over monotherapy with an LHRH agonist based on the results of the most recent meta-analysis.<sup>26</sup> The benefit of combination therapy was restricted to the use of nonsteroidal antiandrogens and was seen in patients with metastatic disease but not in those with locally advanced disease.

IHT may be feasible for patients with PSA recurrence and for older patients who prefer treatment to observation. Reports by several investigators suggest that this approach is effective in maintaining disease control over periods of several years.<sup>30,31</sup> However, randomized clinical trials are needed to ascertain if cause-specific and overall survival with IHT are equivalent to those with continuous hormone therapy.

Finally, neoadjuvant hormone therapy improves disease control when used with radiotherapy in men with clinical stage T2 to T4 disease, but it has been shown to improve survival only in certain patient subsets.<sup>34</sup> Neoadjuvant therapy with radical prostatectomy has, by and large, been abandoned by the urologic community, although prolonged treatment for 12 to 24 months in young healthy men with clinical stage T3 and T4 tumors probably deserves systematic investigation. In summary, hormone therapy now plays a more important role at earlier stages of disease, consistent with the changing epidemiology of prostate cancer. Additional studies are needed, however, to define how to optimally use hormone therapy across various patient types.

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