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## IMMEDIATE HORMONAL THERAPY COMPARED WITH OBSERVATION AFTER RADICAL PROSTATECTOMY AND PELVIC LYMPHADENECTOMY IN MEN WITH NODE-POSITIVE PROSTATE CANCER

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### ABSTRACT

**Background** Because the optimal timing of the institution of antiandrogen therapy for prostate cancer is controversial, we compared immediate and delayed treatment in patients who had minimal residual disease after radical prostatectomy.

**Methods** Ninety-eight men who underwent radical prostatectomy and pelvic lymphadenectomy and who were found to have nodal metastases were randomly assigned to receive immediate antiandrogen therapy, with either goserelin, a synthetic agonist of gonadotropin-releasing hormone, or bilateral orchiectomy, or to be followed until disease progression. The patients were assessed quarterly during the first year and then semiannually.

**Results** After a median of 7.1 years of follow-up, 7 of 47 men who received immediate antiandrogen treatment had died, as compared with 18 of 51 men in the observation group ( $P=0.02$ ). The cause of death was prostate cancer in 3 men in the immediate-treatment group and in 16 men in the observation group ( $P<0.01$ ). At the time of the last follow-up, 36 men in the immediate-treatment group (77 percent) and 9 men in the observation group (18 percent) were alive and had no evidence of recurrent disease, including undetectable serum prostate-specific antigen levels ( $P<0.001$ ). In the observation group, the disease recurred in 42 men; 13 of the 36 who were treated had a complete response to local treatment or hormonal therapy (or both), 16 died of prostate cancer, and 1 died of another disease. The remaining men in this group were alive with progressive disease at the time of the last follow-up or had had a recent relapse. Except for the treatment group (immediate therapy or observation), no clinical or histologic characteristic significantly influenced the outcome.

**Conclusions** Immediate antiandrogen therapy after radical prostatectomy and pelvic lymphadenectomy improves survival and reduces the risk of recurrence in patients with node-positive prostate cancer. (N Engl J Med 1999;341:1781-8.)

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ANDROGEN-ablation therapy has been a mainstay of treatment for prostatic adenocarcinoma since the pioneering work of Huggins and coworkers nearly 60 years ago.<sup>1,2</sup> However, its role as a primary therapy for early stages of prostate cancer and the timing of its administration in advanced disease have been the subjects of considerable debate. Indeed, since the clinical trials of the Veterans Administration Co-operative Urological Research Group, which were conducted during the 1960s and early 1970s, the concept that early hormonal therapy retarded disease progression but did not prolong survival has been part of the dogma of prostate-cancer therapy.<sup>3,4</sup> In recent years, the availability of alternative forms of hormonal therapy<sup>5-7</sup> and the indications that radiotherapy or cryosurgery can be highly effective when directed at relatively small targets<sup>8-10</sup> have renewed interest in the use of androgen ablation in early disease.<sup>10-17</sup> In 1997, a randomized phase 3 study showed that early hormonal therapy combined with external-beam radiation prolonged survival in patients with locally advanced disease.<sup>12</sup> Hormonal therapy may well have provided its benefit by reducing the size of the prostate gland and prostate tumor, which were the targets of radiotherapy, rather than by controlling minimal residual disease after radiotherapy.

We studied men who appeared to be free of disease after radical prostatectomy and pelvic lymphadenectomy but who still had residual cancer cells be-

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cause they had nodal metastases. We compared the survival of men who started antiandrogen therapy shortly after surgery and continued it indefinitely with that of men who received such treatment only after the appearance of disease progression. Specifically, we tried to confirm reports of the benefits of early hormonal therapy in these men<sup>18,19</sup> by means of a randomized, prospective trial conducted by the Eastern Cooperative Oncology Group.

## METHODS

Between 1988 and 1993, we enrolled 100 men who had undergone radical prostatectomy and bilateral pelvic lymphadenectomy for clinically localized disease (no more than stage T2) but who were found on review of the histologic slides to have nodal metastases. All the men were randomly assigned to receive immediate antiandrogen therapy, with either goserelin (Zoladex, Zeneca Pharmaceuticals, Wilmington, Del.) at a dose of 3.6 mg subcutaneously every 28 days or bilateral orchiectomy, or to be followed until there were signs of progression other than newly detectable or rising levels of serum prostate-specific antigen (PSA). Goserelin is a synthetic agonist of gonadotropin-releasing hormone that inhibits the secretion of testosterone. Since this study was initiated before the widespread appreciation of the value of PSA levels as a marker of prostate cancer, we did not use PSA levels in our study criteria for eligibility or recurrence or as a reason for initiating antiandrogen therapy in patients who were assigned to the observation group. However, serum PSA was measured in most patients at most clinical visits. None of the patients had evidence of metastases on radionuclide bone scans or chest x-ray films obtained before prostatectomy, and none had received hormonal therapy before randomization. Each institution's institutional review board approved the study, and informed consent was obtained from each patient before entry into the study.

Patients underwent randomization within 12 weeks after prostatectomy. During the first year of follow-up, physical examinations and measurements of serum prostatic acid phosphatase levels (and, ultimately, PSA levels) were performed quarterly, and bone scanning was performed semiannually. Subsequently, serum acid phosphatase measurements and physical examinations were performed twice a year, and bone scanning was conducted once a year. There was no centralized review of pathological findings, so the diagnosis of nodal metastases and the stage and grade of disease were based on the interpretations of the pathologists at each institution. If only local recurrence was documented in patients who were assigned to the observation group, a treatment such as external-beam radiation was strongly preferred according to the protocol to antiandrogen therapy.

When patients died, the cause of death was determined by the treating physicians and corroborated by a review of study reports, death certificates, and when available, autopsy findings. All men who were identified as having died of prostate cancer had progressive, widely disseminated, and highly symptomatic metastases at the time of death.

Descriptive statistical analyses were used to provide an overview of the patients' characteristics at entry. The log-rank test of Peto and Peto<sup>20</sup> was used to compare survival and the time to recurrence according to treatment and according to selected characteristics of the patients at base line. Stratified log-rank tests<sup>21</sup> were used to control for differences attributable to the choice of hormone therapy. The Cox proportional-hazards model<sup>22</sup> was used to assess whether there were differences in the response to treatment according to race or ethnic group. Survival was estimated according to the method of Kaplan and Meier.<sup>23</sup> The method developed by Mehta et al.<sup>24</sup> for exact inference with the type of ordered categorical data was used to compare adverse effects in the two groups. An intention-to-treat analysis was conducted that included all eligible patients as originally randomized.

## RESULTS

Of the 100 men who underwent randomization, 2 were found to be ineligible. One patient did not undergo prostatectomy, and another did not undergo lymphadenectomy. The initial accrual goal of 220 patients was not achieved, primarily because the importance of the serum PSA level in the monitoring, staging, and early detection of prostate cancer was recognized during the study. For this reason, progressively fewer men who were undergoing prostatectomy were found to have nodal metastases.<sup>25-27</sup> During this time there was also growing reluctance among patients with prostate cancer and their physicians to ignore the serum PSA level in making management decisions. Seven patients had stage T1b prostate cancer (cancer detected by means of transurethral resection of the prostate in which more than 5 percent of the resected tissue consisted of malignant cells), and 91 had stage T2 disease (a nodule or induration palpable on digital rectal examination and believed to be confined to the prostate). Because there was no centralized pathological review, postoperative tumor grades were determined on the basis of the Gleason scores assigned by the individual pathologists at each institution.

The characteristics of the patients at entry into the study are summarized in Table 1. Serum PSA levels were measured in 53 patients before prostatectomy, and the median value was 19.2 ng per milliliter. Serum PSA levels after prostatectomy, although not required for study entry, were available for 93 of the 98 men (Table 1). Eighty percent of these patients had undetectable serum PSA levels after prostatectomy, according to the standards of assays in use at the time.

After a median follow-up of 7.1 years (range, 3 to 10), survival was significantly better among the men in whom antiandrogen therapy was initiated immediately than among those who were assigned to be observed ( $P=0.02$ ) (Fig. 1A). Of the 18 patients in the observation group who died, 16 died of prostate cancer (Table 2). The remaining two men died of other causes but had distant metastases at the time of death. Of the seven men in the immediate-therapy group who died, three died of prostate cancer and four died of seemingly unrelated causes; each of these four had undetectable serum PSA levels and negative findings on bone scanning and physical examination within five months before death. Two of the four died of unrelated cancers, one of cerebral vascular disease, and one of ischemic bowel disease. Of the three patients in this group who died of prostate cancer, one declined hormonal therapy until symptomatic osseous metastases occurred 24 months after randomization. He died 17 months later and was included in the intention-to-treat analysis. He was the only man in this group who did not begin antiandrogen therapy immediately after randomization. Prostate-cancer-specific survival is shown

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE MEN WITH PROSTATE CANCER.

CHARACTERISTIC	IMMEDIATE-THERAPY GROUP (N=47)	OBSERVATION GROUP (N=51)	ALL PATIENTS (N=98)
Age			
Median (yr)	65.1	66.6	65.6
Range (yr)	52-75	45-78	45-78
≤65 yr (%)	49	43	46
>65 yr (%)	51	57	54
Serum PSA detectable (%)*			
Yes	22	19	20
No	78	81	80
Serum prostatic acid phosphatase elevated (%)*			
Yes	16	8	12
No	84	92	88
Median estimated tumor volume (cm <sup>3</sup> )†	18	8.1	12.5
Positive surgical margins (%)			
Yes	69	61	65
No	31	39	35
Positive seminal vesicle (%)			
Yes	58	62	60
No	42	38	40
Gleason score (%)			
3	0	6	3
4	9	3	6
5	6	3	4
6	17	26	22
7	54	41	48
8-10	14	21	17
Median Gleason score	7	7	7
Median no. of nodes examined	11	14	12
No. of positive nodes			
Median	2	2	2
Range	1-19	1-20	1-20

\*The levels of prostate-specific antigen (PSA) and prostatic acid phosphatase in five patients (two in the immediate-therapy group and three in the observation group) were unknown at base line, after prostatectomy. The limits of detectability of PSA and elevated levels of prostatic acid phosphatase were defined separately at each institution.

†The tumor volume, which was based on the gross and microscopic inspection of specimens by the pathologists at each institution, was unknown in the case of 59 patients (28 in the immediate-therapy group and 31 in the observation group).

in Figure 1B ( $P=0.001$  for the difference between groups).

Recurrence was defined as the detection of local or disseminated disease (or both) on a computed tomographic scan, a chest x-ray film, a bone scan, physical examination, or biopsy. Recurrence-free survival was significantly better in the immediate-therapy group than in the observation group ( $P<0.001$ ) (Fig. 1C). At the time of the last follow-up visit, only eight men in the observation group (16 percent) were alive without having had a recurrence and had undergone no additional treatment (according to the definition of recurrence that we used or on the basis of a detectable serum PSA level). One additional man (2 percent) had requested and received immediate hormonal therapy and had not had a recurrence. Another 13 men in the observation group (25 percent) had

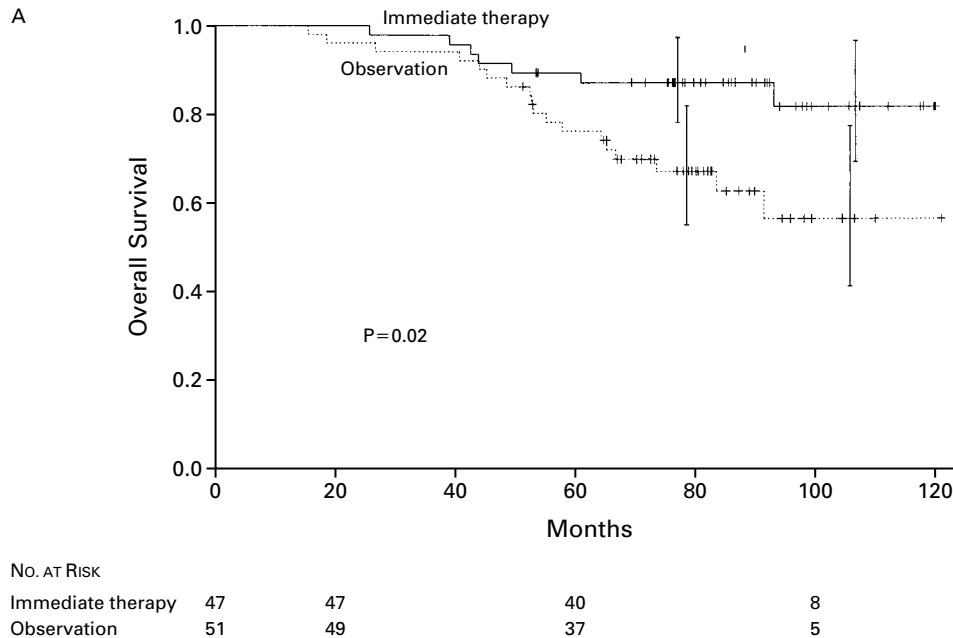
had complete and durable responses to hormonal therapy (11 patients), local salvage radiotherapy (1 patient), or a combination of the two (1 patient) on recurrence. Thus, at the time of the last follow-up, 22 men in the observation group (43 percent) were alive and had no evidence of disease (including detectable serum PSA levels). By contrast, 36 men in the immediate-therapy group (77 percent) were alive without evidence of recurrence (including detectable serum PSA levels) at the time of the last follow-up. None had discontinued treatment with goserelin. The outcomes are summarized in Table 2.

Four men relapsed in the immediate-therapy group and received additional therapy. At the time of the last follow-up, three men had died and one man was alive with progressive disease.

We analyzed various characteristics, including serum levels of PSA or acid phosphatase before prostatectomy or randomization, histologic grade, local extent or volume of the tumor, number or proportion of positive nodes, type of immediate antiandrogen therapy (33 received goserelin, 13 underwent bilateral orchiectomy, and 1 refused either treatment), and race or ethnic group within each group and in the group as a whole. None of these characteristics had a statistically significant effect on overall survival, prostate-cancer-specific survival, or progression-free survival.

A total of 37 men in the observation group received hormonal therapy. Three men received hormonal therapy relatively early; two requested and received it immediately after randomization, and one received it along with radiotherapy of the prostate bed on the basis of a rising serum PSA level alone. Two of these three men were free of detectable disease at the time of the last follow-up; the third was alive but his disease status was unknown because he declined to undergo further follow-up examination. Of the 34 men in the observation group who received hormonal therapy for a local recurrence (1 patient) or a systemic recurrence (33 patients), 17 (50 percent) had substantial reductions in disease burden on imaging studies, physical examination, or both and undetectable levels of serum PSA for more than six months. In 6 of these 17 men, the cancer recurred or progressed; 4 of the 6 subsequently died of prostate cancer. The length of follow-up in the case of three men who received hormonal therapy on progression was too brief to assess their response. The remaining 14 men who received hormonal therapy on progression had either no response or a brief response, and all but 1 had died at the time of the last follow-up. The median time from randomization to the initiation of hormonal therapy in the observation group was 20 months (range, 2.7 to 69), and the median serum PSA level at the start of such treatment was 14 ng per milliliter (range, 0.6 to 162).

The adverse effects reported in each group are



**Figure 1.** Kaplan–Meier Estimates of Overall Survival (Panel A), Prostate-Cancer–Specific Survival (Panel B), and Progression-free Survival (Panel C).

I bars are 95 percent confidence intervals. The log-rank test was used to calculate P values.

listed in Table 3. One patient who received goserelin had a myocardial infarction, and in another, severe leukopenia and thrombocytopenia developed, but the relation of these problems to treatment is uncertain. No man in the immediate-treatment group had symptoms serious enough to require cessation of therapy. Because many men had locally advanced disease (Table 1), only 16 underwent potency-sparing prostatectomies (11 reported that they were potent at randomization). A significantly higher proportion of men in the immediate-treatment group than in the observation group had increases in urinary frequency (7 vs. 1) and nonspecific symptoms of irritable voiding (22 vs. 6). Serious incontinence occurred in only 3 of the 98 men, whereas minor gynecomastia, hot flashes, night sweats, weight gain, and gastrointestinal symptoms (minimal nausea or loose bowel movements) were, as expected, more common in the immediate-treatment group. Transient peripheral neuropathy, rashes, and superficial (nonsurgical) infections also occurred more frequently in the immediate-treatment group (data not shown), but these effects almost entirely resolved within six months. Persistent, minor voiding problems usually responded to anticholinergic drugs.

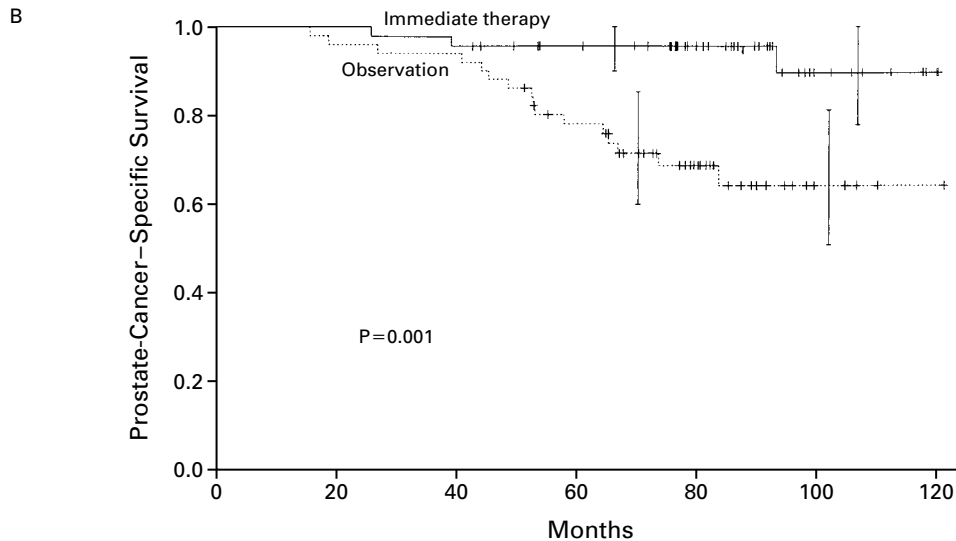
## DISCUSSION

In this prospective, randomized comparison of immediate and delayed androgen suppression after radical prostatectomy and pelvic lymphadenectomy in

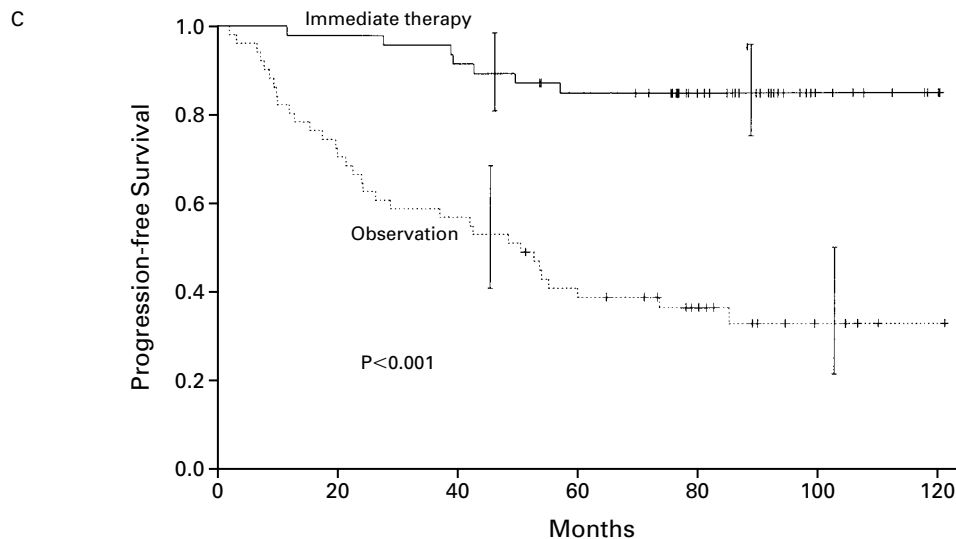
men with node-positive prostate cancer, we found that early treatment significantly improved survival. We must stress that these results are applicable only to the particular subgroup of patients in our study — namely, men who underwent radical prostatectomy and lymphadenectomy and were found to have metastatic prostate cancer in the excised lymph nodes.

Our findings confirm those of others, including investigators at the Mayo Clinic.<sup>18,19</sup> In their series, however, only patients with tumors that consisted of DNA diploid cells had a survival advantage with immediate therapy, and this advantage was evident only after 10 years of therapy. The conclusions of the Mayo Clinic group have been questioned further,<sup>25</sup> because their study was retrospective and there were major differences in the number of men in the treatment and observation groups.

Bolla et al. found that patients with clinical stage T2 or T3 prostate cancer who received goserelin during external-beam radiotherapy and for three years thereafter had significantly higher survival rates than similar patients who received radiotherapy alone.<sup>12</sup> However, this effect could have been due to a reduction in the size of the primary tumor and the entire prostate gland, which would thereby improve the efficacy of radiotherapy without necessarily eliminating or suppressing micrometastases. Furthermore, numerous other studies of immediate and delayed antiandrogen therapy in conjunction with radiation have reported that the combination delays disease progression



No. AT RISK					
Immediate therapy	47	47	40	8	
Observation	51	49	37	5	



No. AT RISK					
Immediate therapy	47	46	38	8	
Observation	51	36	19	5	

but does not increase survival.<sup>10,11,13-15,28</sup> In one study, survival rates were significantly higher ( $P=0.036$ ) in the subgroup of men with Gleason scores of 8 to 10 who received adjuvant therapy with goserelin, but for the entire cohort of 945 men with data that could be analyzed, there were no significant differences in survival ( $P=0.36$ ) after a median follow-up of 5.6 years.<sup>28</sup> Since this subgroup included less than one

third of all participants,<sup>11</sup> the advantages of early anti-androgen therapy in combination with radiotherapy remain to be fully elucidated.<sup>29</sup>

Our findings challenge the conclusion of the Veterans Administration Co-operative Urological Research Group that estrogen therapy or orchiectomy should be withheld until the symptoms become severe and that treatment earlier in the course of the disease not

TABLE 2. OUTCOME AFTER A MEDIAN FOLLOW-UP OF 7.1 YEARS.

OUTCOME	OBSERVATION GROUP (N=51)	IMMEDIATE-THERAPY GROUP (N=47)	HAZARD RATIO	P VALUE*
Dead	18	7	3.0 (1.2–7.3)	0.02
Death from prostate cancer	16	3	6.2 (1.8–21.5)	<0.01
Death from other causes	2	4		
Any recurrence, including recurrence based on PSA levels	42†	7	12.2 (5.1–29.1)	<0.001
Alive	33	40		
Without recurrence	9‡	36	9.7 (4.5–21.0)	<0.001
With recurrence§	24	4		
Treated for recurrence	36	4		
Alive after treatment	19¶	1		
Dead after treatment	17	3		

\*The log-rank test was used to calculate P values.

†For the nine patients in the observation group with consistently detectable serum PSA levels after prostatectomy, a recurrence based on PSA levels was defined as an increase of at least 0.1 ng per milliliter on three consecutive measurements conducted at least one month apart.

‡Eight of the men had received no hormonal or local therapy after prostatectomy and lymphadenectomy, and one requested and received hormonal therapy immediately after randomization.

§Two men in the immediate-therapy group had progressive disease at the time of the last follow-up, and the disease status of the other two was unknown. Of 24 men in the observation group, 13 were free of detectable disease (including detectable serum PSA levels), 7 had progressive disease (4 had not yet received any treatment for recurrence, and 3 had continued progression while receiving hormonal therapy), 3 had received hormonal therapy on progression but follow-up was too brief to assess their response, and 1 requested and received hormonal therapy immediately after randomization but his disease status was unknown at the time of the last follow-up.

¶Thirteen men were free of detectable disease after treatment, three had progressive disease despite hormonal therapy, and three had insufficient follow-up to be assessed for a response to therapy.

||This group includes all 16 men who died of prostate cancer and 1 who died of another disease but who had metastatic prostate cancer and who was receiving hormonal therapy when he died.

only is unlikely to be beneficial, but also may cause considerable damage.<sup>3</sup> Perhaps the use of hormonal treatments with fewer vascular side effects than diethylstilbestrol (which was used in those studies)<sup>3,4</sup> and the relatively good health of our patients (all of whom had successfully undergone major surgery immediately before entry) could in part explain the discrepancies between their results and ours.

In a randomized study comparing immediate with delayed antiandrogen therapy in patients with advanced local, regional, or systemic metastatic disease, immediate orchiectomy offered a small but statistically significant survival advantage over delayed treatment.<sup>30</sup> However, the chief benefit of immediate therapy in this study was the prevention of catastrophic complications of metastatic prostate cancer, such as pathologic fractures, paraplegia, renal impairment, and hydronephrosis.

Of the 51 patients in our study who did not receive antiandrogen therapy immediately after surgery, 8 (16 percent) had no detectable prostate cancer (defined as normal findings on physical examination and bone scanning, and undetectable serum levels of PSA) after a median follow-up of 7.1 years without ever receiving antiandrogen or other therapy. As in the case of patients with nodal metastases from other

solid tumors, patients with prostate cancer may sometimes be cured by surgical excision of regional nodes and primary lesions alone. Thus, some men may have had no residual prostate cancer at enrollment. More important, all but 20 percent of our patients had no detectable evidence of disease at randomization. Although the serum PSA level has limitations as a direct reflection of the extent of prostate cancer, as a predictor of disease progression or recurrence, and as an indicator of the efficacy of treatment, in the absence of androgen suppression after radical prostatectomy, an undetectable serum PSA level remains an accepted indicator of the presence of minimal — if any — residual prostate cancer.<sup>31,32</sup> We therefore believe that our patients had much less residual cancer (if any) than patients in other randomized studies comparing early and delayed antiandrogen therapy, including the two that showed only a small survival benefit with early treatment.<sup>12,30</sup>

In other studies, survival rates were higher among patients treated with hormonal therapy who had disease in a relatively early stage than in those with more advanced disease.<sup>6,30</sup> This observation and our findings suggest that antiandrogen therapy may be particularly effective when the tumor burden is minimal. We do not mean to imply, however, that anti-

TABLE 3. ADVERSE EFFECTS REPORTED IN EACH GROUP.\*

ADVERSE EFFECT	IMMEDIATE-THERAPY GROUP (N=46)			OBSERVATION GROUP (N=50)			P VALUE
	GRADE 1 OR 2	GRADE 3	GRADE 4	GRADE 1 OR 2	GRADE 3	GRADE 4	
Myocardial infarction	0	0	1	0	0	0	0.33
Hematologic effects	7	1	1	2	0	0	0.02
Gastrointestinal effects	12	0	0	3	0	0	<0.01
Nonspecific genitourinary effects	22	0	0	5	1	0	<0.01
Incontinence	19	1	0	13	2	0	0.22
Frequency	6	1	0	1	0	0	0.05
Nocturia	6	0	0	2	0	0	0.15
Hot flashes	23	4	0	0	0	0	<0.001
Gynecomastia	10	0	0	1	0	0	<0.01
Weight gain	8	0	0	1	0	0	0.05
Fatigue	2	0	0	0	0	0	0.23

\*Data on adverse effects were not available for one patient in each group. A grade of 1 indicates mild adverse effects, a grade of 2 moderate effects, a grade of 3 severe effects, and a grade of 4 life-threatening effects.

androgen therapy should be the primary treatment for localized early lesions, which are often cured by local treatment alone. Even patients with such localized disease have more detectable cancer cells than those we studied had at entry, and for this reason, they are unlikely to derive the same survival benefit from early antiandrogen therapy. Early antiandrogen therapy should not be accepted as the standard of care for early prostate cancer without being tested in properly designed clinical trials.

Complete excision by radical prostatectomy and bilateral pelvic lymphadenectomy and, in one man, subsequent prostatic-bed radiotherapy, resulted in sustained disease-free survival in nearly 18 percent of our patients. In conjunction with immediate antiandrogen therapy, this treatment resulted in long-term remissions and survival in another 59 percent of patients. We do not know whether antiandrogen therapy alone (without prostatectomy) would have been as effective in our patients with regional lymph-node metastases as the combination of antiandrogen therapy and surgery. An attempt to answer this question by means of a clinical trial was not successful, because of low enrollment.

In the face of minimal disease, does antiandrogen therapy provide a survival advantage even if it is not continued indefinitely? The results of the study by Bolla et al., in which goserelin was stopped after three years, imply that it does, but in that study the hormonal treatment was administered during radiotherapy, and thus its primary benefit may have been to improve the control of local disease.<sup>12</sup> Therefore, the need to continue hormonal suppression remains unclear.

We cannot extrapolate our findings to other forms of hormonal therapy or treatment protocols. We do

not know whether our results would have been similar if we had used total androgen ablation,<sup>6,7,33-35</sup> treatment with antiandrogens alone,<sup>35,36</sup> suboptimal hormonal therapy (such as treatment with 5 $\alpha$ -reductase inhibitors),<sup>37,38</sup> or intermittent hormonal therapy.<sup>39</sup> Similarly, we do not know whether the outcome would have been improved in the observation group if the patients had been treated sooner or instructed on dietary modifications<sup>40-42</sup>; the use of vitamin,<sup>43</sup> herbal,<sup>44</sup> and nutritional supplements<sup>45-49</sup>; and other lifestyle changes that are now often made by patients with prostate cancer.<sup>49</sup>

It is unlikely that it will be feasible to repeat our study. Were it to be carried out today, there would be fewer eligible men because widespread use of serum PSA testing has led to earlier diagnosis of prostate cancer.<sup>25-27</sup> Physicians' and patients' preferences concerning the timing of antiandrogen therapy — and the value of PSA measurements in disease monitoring and treatment decisions — would further limit participation and lead to protocol violations that would be likely to invalidate the results. In the future, the availability of molecular techniques for identifying nodal micrometastases may well increase the relevance of early antiandrogen therapy.<sup>50-52</sup>

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