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Since 1941 when Huggins and Hodges (1) demonstrated that carcinoma of the prostate is a hormonally responsive tumor, castration or other methods of hormonal ablation have been the mainstay of treatment for advanced adenocarcinoma of the prostate. While orchiectomy remains the gold standard for hormonal manipulation, alternative treatment methods include diethylstilbestrol (DES), luteinizing hormone-releasing hormone (LHRH) agonists, and antiandrogens.

## Orchiectomy/DES

Despite much early hope, numerous clinical trials over the past four decades have shown that cures and improved survival with castration and DES are unlikely. The largest series included studies by Nesbit and Baum (2) in the 1940s and early 1950s and the Veterans Administration Cooperative Urological Research Group (VACURG) studies in the 1960s (3).

The cooperative study by Nesbit and Baum (2) in 1950 compared patients with metastatic disease treated by either orchiectomy, DES (1 to 5 mg/day), or a combination of DES and orchiectomy. These 263 patients were followed for five years and compared to a control group of 231 patients followed between 1925 and 1940 who received no hormonal manipulation. Results revealed differences in ultimate survival between the hormonally treated group and the control group at five years (17% versus 6%). Patients treated with orchiectomy or a combination of DES and orchiectomy had the highest survival rate (20% and 21%, respectively), whereas no difference was observed between the DES and control groups (10% versus 6%). However, because the control group was a historical series and not concurrent with the study group, it was difficult for the investigators to conclude, in that preantibiotic era, that the increase in survival was totally due to hormonal manipulation even though it occurred in late and not early stages of the disease.

In the VACURG study (3) 772 patients were randomly placed in four treatment groups: placebo, orchiectomy, DES (5 mg/day), or a combination of orchiectomy and DES. All patients were followed for five years. Results revealed no statistical difference in survival between the four groups and showed that hormonal manipulation is palliative. The results also indicated that ultimate survival is apparently independent of the timing of hormonal manipulation. Although this study forms the basis for current clinical use of hormonal manipulation, it was not well designed. Patients were evaluated based on the original group to which they were assigned even if their treatment had been changed because they did not do well with the assigned method of treatment. The results, therefore, are extremely difficult to interpret.

Nonetheless, these results were corroborated in 1982 by Lepor et al (4) who also used a historical control group to compare ultimate survival to a group of patients with metastatic disease who received standard hormonal therapy. The results showed no significant difference in ultimate survival between the two groups.

Based on the preponderance of evidence, the timing of hormonal intervention is not significant in asymptomatic patients with advanced stage D-2 prostate carcinoma. The only question remaining concerns the significance of early hormonal intervention in patients with stage D-1 disease and questionably minimal stage D-2 disease (5). In stage D-2 disease palliation is the only definitive indication for the use of hormonal ablation. Unfortunately, the decision to hormonally ablate an asymptomatic patient with stage D-2 disease is often made without consideration of quality-of-life issues, such as the individual's sex life. In these circumstances physicians undoubtedly provide a disservice to these patients.

Orchiectomy remains the gold standard for hormonal manipulation in adenocarcinoma of the prostate. It is definitive, alleviates concerns about patient compliance, has the fewest long-term side effects, and is performed easily with the patient under local anesthesia. In my practice the majority of men are not troubled by the notion of castration or related body image changes when they understand all the treatment options and why orchiectomy is necessary in their case.

The main alternative to castration is DES. The VACURG study (3) proved that 3 mg/day of DES is the safest dose that provides a persistent and well-defined therapeutic response. However, the side effects from DES are substantial. The Leuprolide Study Group (6) found a 31% overall severe complication rate in patients on DES and a 27% severe complication rate in asymptomatic patients with no prior cardiac history. De Voogt et al (7) and Henriksson and Edhag (8) found similar significant complication rates with DES. This significant morbidity and mortality should relegate DES to a secondary role in the management of prostate cancer.

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## LHRH Agonists

Despite its significant side effects, DES was the only alternative to castration until this decade when a new class of drugs was developed. These LHRH agonists include naferelin, leuprolide, buserelin, and zoladex (6,9). Although only leuprolide is clinically available, the other drugs are in various stages of study. Leuprolide differs from true LHRH by a change in the 6 position from gly to D-leu and in the 10 position from gly-$NH_2$ to $NH_2$ $NHCH_2CH_3$. The site of action is the pituitary. The substance is an agonist of gonadotropin releasing hormone, but paradoxically with chronic use is antagonistic to normal LHRH effects and achieves castrate testosterone levels within one month. The Leuprolide Study Group (6) evaluated 199 patients with new stage D-2 prostate cancer who received either 3 mg/day of DES or 1 mg/day of lupron injected subcutaneously. At two years the progression and survival rates were not significantly different. The increased cardiovascular morbidity and mortality suffered by patients on DES was significant.

The principal side effects of LHRH agonists include hot flashes (up to 90%), fluid retention (2%), and gynecomastia (3%). Of more than 75 patients at Henry Ford Hospital receiving leuprolide, none have had any difficulty or shown any reluctance in giving themselves injections. Leuprolide's associated morbidity and its similar efficacy to DES make it the best alternative to orchiectomy in the management of advanced carcinoma of the prostate.

## Antiandrogens

The antiandrogens used for hormonal manipulation consist of three groups: steroidal, nonsteroidal, and those that inhibit steroidogenesis (10).

The steroidal agents have both central and peripheral effects: centrally they decrease the LH levels, and peripherally they compete with dihydrotestosterone. The three major steroidal antiandrogens are cyproterone acetate (CPA), megestrol, and medroxyprogesterone acetate (MPA). CPA, which has generated the most interest, acts by blocking the uptake of dihydrotestosterone by the prostate (7,11). While use of megestrol is fairly common, in time it becomes ineffective due to a central escape phenomenon whereby the body overrides the competitive blockade at the pituitary level. The central escape phenomenon is also associated with CPA, but the drug's strong peripheral effects compensate for this effect. In a phase III trial comparing CPA, MPA, and DES, Jacobi et al (11) found five-year survival rates to be 38% for DES, 32% for CPA, but only 14% for MPA. They also found that at three years the progression rate was 55% for DES, 80% for CPA, and 90% for MPA. Thus, DES was significantly better than either CPA or MPA in retarding progression. However, the cardiovascular toxicity was 35% for DES patients and only 10% for CPA patients. Although antiandrogens have a limited role as primary hormonal ablaters, if orchiectomy is impossible they are of value because of the significantly lower cardiovascular toxicity compared to DES.

Nonsteroidal antiandrogens have significant peripheral effects. They are especially acceptable as a primary treatment because serum testosterone does not decrease and sexual potency is usually preserved. However, the primary response rate is only 60% to 70%, which generally is not prolonged due to incomplete androgen blockade by these medications (12).

**Table**
**Summary of Initial Objective Response Rates***

| Treatment | Number of Patients | % Objective Response | Range |
|---|---|---|---|
| DES/Orchiectomy | 177 | 83% | 80.7-100 |
| Antiandrogens | | | |
| Cyproterone acetate | 51 | 80% | 65.0-100 |
| Flutamide | 179 | 85% | 53.8-100 |
| Ketoconazole | 53 | 79% | 72.5-100 |
| LHRH analog | 191 | 83% | 78.2-86 |

*From Schulze H, Isaacs JT, Coffery DS. A critical review of the concept of total androgen ablation in the treatment of prostate cancer. In: Murphy GP, ed. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc, 1987:1-19.

The nonsteroidal antiandrogens include flutamide and RU-23908, a new drug currently under study. The side effects of flutamide include severe diarrhea (30%), nausea and vomiting (30%), and gynecomastia (36%). In clinical use diarrhea is the primary side effect but usually resolves with dose modification. RU-23908 has a greater range of toxicity including night blindness, interstitial pneumonitis (which is reversible but occasionally fatal), and alcohol intolerance. Although not yet available clinically, its associated side effects will limit its use.

The nonsteroidal antiandrogens should not be considered for primary hormonal ablation. They are currently used only in an attempt to achieve further palliation in patients whose initial hormone treatment failed. They are also being evaluated in clinical trials in conjunction with orchiectomy or chemical castration in order to achieve "total" androgen ablation as a primary treatment.

The two most important antiandrogens that inhibit steroidogenesis are aminoglutethimide and ketoconazole (13-16). Ketoconazole impairs the activity of cytochrome P450-dependent enzymes (15) and induces a rapid and sustained decrease in testicular and adrenal androgen production. Castrate levels of testosterone are usually achieved within four to eight hours after an initial dose of 400 g. The usual dosage is 200 to 300 mg every eight hours. The principal side effect is nausea (20%), but hepatotoxicity, which is reversible, can occur although rarely (1/16,000) (15).

Ketoconazole is a popular treatment option for patients in whom hormonal manipulation has failed. There is marked subjective response (relief of pain, increased appetite, and improved sense of well being) to treatment in about 50% of patients. Trachtenberg and Pont (14) suggest that this symptomatic improvement is probably mediated through a combination of diminishing androgen levels and also by the effects on the cytochrome P450 system.

A summary comparison of initial objective (complete and partial) response rates for these various treatment modalities is presented in the Table.

## Total Hormonal Ablation

In 1985 Labrie et al (17) reintroduced the concept of total androgen ablation in the primary management of metastatic or lo-

cally advanced adenocarcinoma of the prostate. After the initial work of Huggins and Hodges (1), investigators believed that the adrenal gland produced more androgen after orchiectomy and that the increased androgen levels were responsible for reactivation of prostate carcinoma in patients whose hormonal therapy failed. Recent studies, however, revealed that androgen levels remain normal in hormonally treated patients (18). Schulze et al (19) reviewed the results of hypophysectomy and adrenalectomy for therapeutic response in those patients whose standard hormonal therapy failed. In their summary of the results of seven studies of bilateral adrenalectomy, the 89 evaluable patients showed only a 5.6% objective response rate. The 209 patients from the seven studies of hypophysectomy yielded only a 6.7% response rate.

These studies indicate that removal of circulating androgens after failure of hormonal treatment has no significant impact on the prostate carcinoma. However, this does not negate the hypothesis of Labrie et al (17) that total hormonal ablation at the time of initial treatment for metastatic disease will have a more significant impact than sequential therapy. Animal research has been performed to test this hypothesis. Studies of rat prostate cancer by Ellis and Isaacs (20) and by Redding and Schally (21) showed no significant difference in tumor response to castration versus castration plus antiandrogens or LHRH treatment versus LHRH plus antiandrogens. Both studies reported a similar response for castration/LHRH agonists alone or in combination with antiandrogens. In clinical trials comparing orchiectomy and CPA, Giuliani et al (22) found one- and two-year survival rates equal to those found by Murphy et al (23) with DES and orchiectomy. Schroeder et al (24) reported these same results when comparing LHRH agonist versus LHRH plus CPA.

These studies strongly indicate that combined initial therapy for metastatic disease provides no treatment or survival advantage. Early results from a National Cancer Institute sponsored double-blind intergroup study comparing leuprolide plus placebo to leuprolide plus flutamide suggest a slightly increased disease-free period of approximately 11 weeks for those on combined treatment (personal communication, E.D. Crawford). However, until survival data are available, this mode of therapy cannot be considered superior.

## Conclusions

Orchiectomy remains the gold standard for treating advanced carcinoma of the prostate. Estrogen therapy is an effective alternative, but its significant cardiovascular side effects should relegate this mode of therapy to a secondary role. LHRH analogs are excellent alternatives to orchiectomy, are well tolerated, and therefore should be considered as the next best alternative to orchiectomy. No evidence exists to support the concept of total androgen ablation. While antiandrogens are effective modalities of treatment, they are not superior to standard therapy and thus should remain secondary to primary hormonal ablation. Their possibly more important role is to provide symptomatic relief for patients in whom primary hormonal therapy has failed.

## References


1. Huggins C, Hodges CV. Studies in prostatic cancer: The effects of castration, estrogen and of androgen injection on serum phosphatase in metastatic carcinoma of the prostate. Cancer Res 1941;1:293-7.

2. Nesbit RM, Baum WC. Endocrine control of prostatic carcinoma: Clinical and statistical survey of 1818 cases. JAMA 1950;143:1317.

3. Byar DP. Proceedings: The Veterans Administration Cooperative Urological Research Group's studies of cancer of the prostate. Cancer 1973;32:1126-30.

4. Lepor H, Ross A, Walsh PC. The influence of hormonal therapy on survival of men with advanced prostatic cancer. J Urol 1982;128:335-40.

5. Elder JS, Catalona WJ. Management of newly diagnosed metastatic carcinoma of the prostate. Urol Clin North Am 1984;11:283-95.

6. The Leuprolide Study Group. Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med 1984;311:1281-6.

7. De Voogt HJ, Smith PH, Pavone-Macaluso M, et al. Cardiovascular side effects of diethylstilbestrol, cyproterone acetate, medroxyprogesterone acetate and estramustine phosphate used for the treatment of advanced prostatic cancer: Results from European Organization for Research on Treatment of Cancer trials 30761 and 30762. J Urol 1986;135:303-7.

8. Henriksson P, Edhag O. Orchiectomy versus oestrogen for prostatic cancer: Cardiovascular effects. Br Med J 1986;293:413-5.

9. Denis L, Keuppens F, Mahler C, et al. Long term therapy with a depot LHRH analogue (zoladex) in patients with advanced prostate cancer. In: Murphy GP, ed. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc, 1987:221-7.

10. Sogani PC, Fair WR. Treatment of advanced prostate cancer. Urol Clin North Am 1987;14:353-71.

11. Jacobi GH, Altwein JE, Kurth KH, Basting R, Hohenfellner R. Treatment of advanced prostatic cancer with parenteral cyproterone acetate: A phase III randomised trial. Br J Urol 1980;52:208-15.

12. Jacobo E, Schmidt JD, Weinstein SH, Flocks RH. Comparison of flutamide (SCH-13521) and diethylstilbestrol in untreated advanced prostatic carcinoma. Urology 1976;8:231-3.

13. Crawford ED, Ahmann FR, Davis MA, Levasseur YJ. Aminoglutethimide in metastatic adenocarcinoma of the prostate. In: Murphy GP, ed. Prostate cancer. Part A: Research, endocrine treatment and histopathology. Progress in clinical and biological research. Vol 243A. New York: Alan Liss, Inc, 1987:283-9.

14. Trachtenberg J, Pont A. Ketoconazole therapy for advanced prostate cancer. Lancet 1984;2:433-5.

15. Trachtenberg J. Hormonal management of stage D carcinoma of the prostate. Urol Clin North Am 1987;14:685-92.

16. Mahler C, Denis L, DeCoster R. The endocrine effect of high dose ketoconazole. In: Murphy GP, ed. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc, 1987:291-7.

17. Labrie F, DuPont A, Belanger A. Complete androgenic blockade for the treatment of prostate cancer. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott, 1985:193-217.

18. Catalona WJ, Scott WW. Carcinoma of the prostate. In: Campbell MF, ed. Campbell's Urology. 5th ed. Philadelphia: WB Saunders Co, 1986; 2:1463-1534.

19. Schulze H, Isaacs JT, Coffery DS. A critical review of the concept of total androgen ablation in the treatment of prostate cancer. In: Murphy GP, ed. Prostate cancer. Part A: Research, endocrine treatment and histopathology. New York: Alan Liss, Inc, 1987:1-19.

20. Ellis WJ, Isaacs JT. Effectiveness of complete versus partial androgen withdrawal therapy for the treatment of prostatic cancer as studied in the Dunning R-3327 system of rat prostatic adenocarcinomas. Cancer Res 1985; 45:6041-50.

21. Redding TW, Schally AV. Investigation of the combination of the agonist D-Trp-6-LH-RH and the antiandrogen flutamide in the treatment of Dunning R-3327H prostate cancer model. Prostate 1985;6:219-32.

22. Giuliani L, Pescatore D, Giberti C, Martorana G, Natta G. Treatment of advanced prostatic carcinoma with cyproterone acetate and orchiectomy—5-year follow-up. Eur Urol 1980;6:145-8.

23. Murphy GP, Beckley S, Brady MF, et al. Treatment of newly diagnosed metastatic prostate cancer patients with chemotherapy agents in combination with hormones versus hormones alone. Cancer 1983;51:1264-72.

24. Schroeder FH, Lock TM, Chadha DR, et al. Metastatic cancer of the prostate managed with buserelin versus buserelin plus cyproterone acetate. J Urol 1987;137:912-8.