

A Further Analysis of European Organization for Research and Treatment of Cancer Protocol 30805

Orchidectomy versus Orchidectomy plus Cyproterone Acetate versus Low-dose Diethylstilbestrol

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This study, European Organization for the Research and Treatment of Cancer protocol 30805, is a randomized, phase III clinical trial comparing surgical orchidectomy to surgical orchidectomy plus cyproterone acetate (100 mg, three times daily) and diethylstilbestrol (DES; 1 mg, daily). In 1980, when this protocol was written, orchidectomy, although long considered a standard therapy for prostate cancer, had never been studied in a prospective phase III clinical trial. The decision was made to compare surgical castration alone to orchidectomy plus cyproterone acetate, because Bracci,¹ in a study that was not randomized, considered this combination therapy superior to orchidectomy. A third treatment arm of DES (1 mg, daily) was added, because Byar² had reported in 1980 that this dose of DES was as effective as a dosage of 5 mg per day but caused less cardiovascular toxicity.

Patients

Three hundred, fifty-one patients have been entered into the study, of whom 328 were eligible for analysis. All have had newly diagnosed, histologically confirmed metastatic prostate cancer. Table 1 lists the 16 European institutions that have participated in the trial. The patients were followed up every 3 months during the first year of the study, and every 6 months thereafter.

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Evaluation Criteria

At the time this study was initiated, before modern imaging techniques were universally available, it was considered difficult to measure the primary lesion and distant metastases of carcinoma of the prostate objectively; therefore, a decision was made to make the end points of the study the time to progression of metastatic disease and survival, including death from any cause. The criteria of progression that have been accepted are the appearances of new hot spots on a bone scan that are confirmed by a second scan 4 weeks later, the radiographic confirmation of a new bone metastasis, or the appearance of new visceral or soft tissue metastases.

Table 1. Patients Entered by Each Institution

Institution	No. of patients
St. James, Leeds	49
York	41
PR, Hull	40
Pontefract	32
Vub, Brussels	30
Do Desterro, Lisbon	27
Freeman, Newcastle	20
Huddersfield	19
CS La Paz, Madrid	18
Solihull	11
Baviere, Liege	10
Palermo	9
OLVG, Amsterdam	7
Ramazzini, Carpi Modena	7
Bradford	5
San Antonio, Porto	3
Total	328

Table 2. Progression

	ORCH	ORCH + CPA	DES	Total
None	27	34	35	96 (29%)
Objective	68	59	50	177 (54%)
Death of malignant disease	8	11	8	27 (8%)
Only subjective	5	5	8	18 (6%)
After off study	2	2	6	10 (3%)
Total	110	111	107	328

ORCH: orchidectomy; CPA: cyproterone acetate; DES: diethylstilbestrol.

Results

Patients were entered into the study between April 1981 and March 1986. The median duration of follow-up at the time of this analysis was 4 years. Of the patients in the study, 54% had objective progression according to protocol criteria and 8% died before objective progression for them could be recorded. Of the patients who were removed from the study, 6% were removed because they showed evidence of subjective progression before there was objective evidence of metastases, and 29% died from causes other than prostate cancer or are still alive (Table 2).

The time to progression or death from malignant disease, whichever came first, is shown in Figure 1, and the duration of survival is shown in Figure 2.

Cardiovascular side effects have been recorded

carefully. The incidence of hypertension, cerebrovascular accidents, ischemic heart disease, and angina were similar in all three treatment arms. There was, however, a greater incidence of ankle edema, deep vein thrombosis, and dyspnea in patients who received DES. Nine of the 108 patients who had an orchidectomy, 12 of the 112 patients who had an orchidectomy and received cyproterone acetate, and 16 of the 108 patients who received DES died of cardiovascular disease. Therefore, even with the small dose of DES used in this study, there was an increased risk of cardiovascular toxicity. Death from malignant disease was observed in only 61 patients who received DES compared with 73 who had an orchidectomy.

Discussion

The data analyzed in this study are now mature, and the results clearly demonstrate that, according to the protocol criteria of progression and survival (death from any cause), there was no difference among the three treatment arms. The combination of orchidectomy and cyproterone acetate as a form of total androgen blockade has not proved to be beneficial. Diethylstilbestrol was shown to be as effective as orchidectomy and had the added advantage of causing slightly fewer deaths related to malignant disease and slightly more due to cardiovascular causes. These conclusions are similar to those made at the time of the preliminary report of this study 5 years ago.³

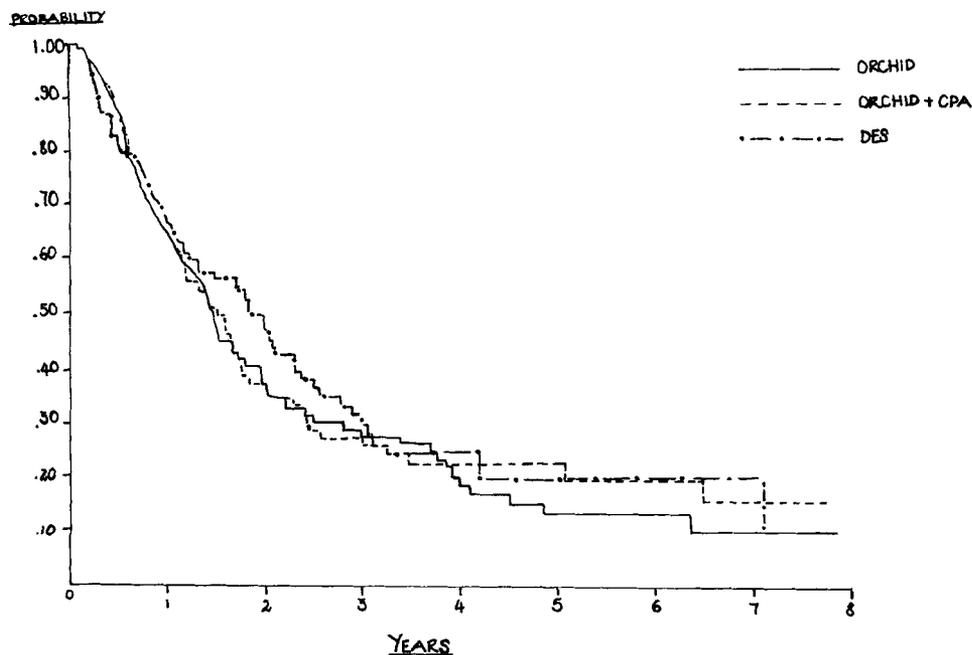


Figure 1. Time to study progression or death from malignant disease.

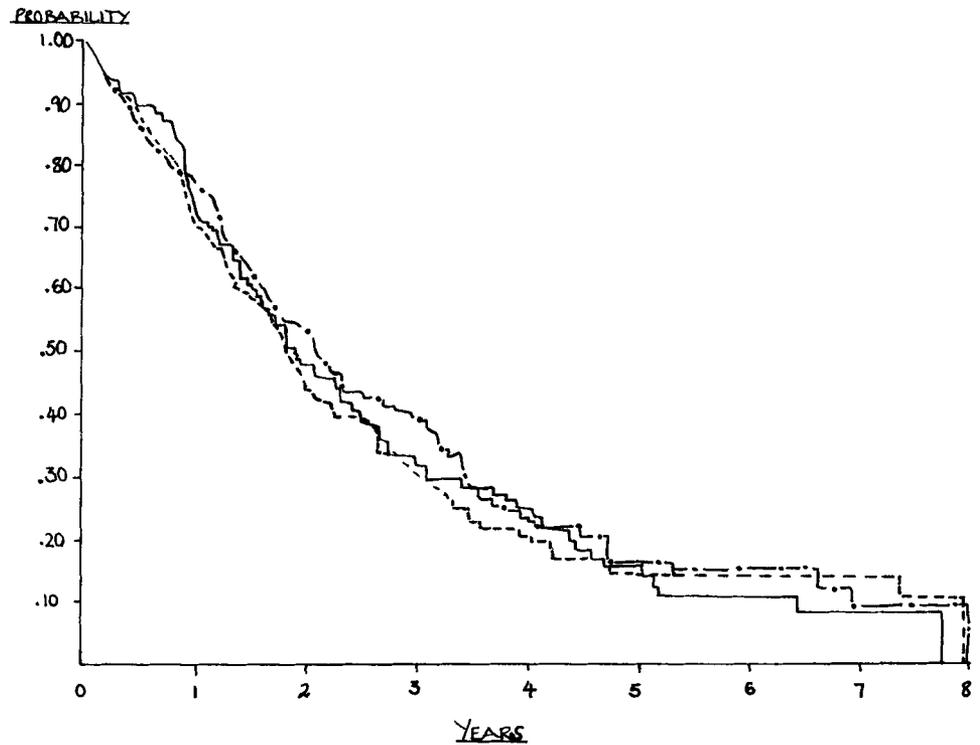


Figure 2. Duration of survival, death from any cause.

References

1. Bracci U. Present procedures in the treatment of prostatic cancer. In: Bracci U, Di Silverio F, editors. *Hormonal therapy of prostatic cancer*. Varese, Italy: Coffese-Palermo, 1977:177-92.
2. Byar DP. Review of the Veterans Administrative studies of cancer of the prostate: the new results concerning treatment of stage 1 and T1 tumours. In: Pavone-Macaluso M, Smith PH, Edsmyr F. *Bladder tumours and other topics in urological oncology*. New York: Plenum, 1980:471-92.
3. Robinson MRG. EORTC protocol 30805: a phase III trial comparing orchidectomy versus orchidectomy and cyproterone acetate and low dose stilboestrol in the management of metastatic carcinoma of the prostate. In: Pavone-Macaluso M, Smith PH, editors. *Management of advanced carcinoma of the prostate and bladder*. New York: Alan R. Liss, 1988:101-10.