Orchidectomy versus Goserelin plus Flutamide in Patients with Metastatic Prostate Cancer (EORTC 30853)

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A total of 327 patients with metastatic prostate cancer were randomized to receive bilateral orchiectomy or treatment with Zoladex and flutamide. The trial aimed to evaluate subjective and objective time to progression, survival, and incidence and duration of response. Strict quality control and evaluation by independent ad hoc committees were organized.

Progression was assessed for each of 13 parameters. The time to subjective and objective progression was in favor of the combination treatment, with statistical significances of $P = 0.009$ and $P = 0.008$, respectively. This delay in objective progression resulted in increased survival in favor of the combination treatment for death by cancer ($P = 0.02$) or overall survival ($P = 0.05$). Survival differences were more marked in the patients with better prognostic factors. The clinical significance of these differences for the individual patient requires detailed assessment. ***Cancer*** **1993; 72:3863–9.**

The urologic group of the European Organization for Research and Treatment of Cancer (EORTC) initiated three randomized trials between 1979 and 1989 to test the hypothesis that maximal androgen blockade is superior treatment to surgical or medical castration. The third phase III trial, EORTC 30853, was initiated to test the results of a phase II study claiming that treatment results for a combination treatment with luteinizing hormone-releasing hormone agonist and an antiandrogen[1] were superior to those achieved with historic controls. The treatment scheme of EORTC 30853 evaluated the time to progression and survival in patients treated by either bilateral orchidectomy or goserelin (Zoladex R, Zeneca Pharmaceuticals, Macclesfield, Cheshire, England) depot and flutamide (Eulexin R, Schering-Plough, Kenilworth, NJ). The analyzed data on side effects and efficacy of treatment are presented in this report.

Patients and Methods

The study was initiated in March 1986 and closed after enrolling 327 patients for randomization in May 1988. The list of the participating centers is presented in Table 1. A strict quality-control program of the EORTC trials necessitated a management structure, which is presented in Table 2, in which independent committees controlled and evaluated a number of trial aspects, such as pathology, bone scan, response criteria, markers, endocrine aspects, and quality of life.

The treatment regimen consisted of a 3.6 mg goserelin depot injection given once every 4 weeks. Flutamide (250 mg, three times daily) was given after meals starting on the first day of treatment. Orchidectomy was performed either as a total bilateral orchidectomy or as a subcapsular procedure. Treatment was to be continued for a minimum of 3 months and to progression whenever possible.

Concurrent therapy consisting of sedatives, analge-

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Table 1. Patient Entry by Institution: EORTC 30853

AZ VUB, Brussels-Antwerp	43
ST. James Hospital, Leeds	33
St. Maria, Lisbon	32
Princess Royal, Hull	30
OSP Civils, Varese	27
St. Rafael, Leuven	21
Normanton Hospital, Castleford	21
Hop de Baviere, Liege	19
OLV Aalst	13
Hosp de Strasbourg	13
Hosp Desterro, Lisbon	12
Freeman Hospital, Newcastle	11
St. Joseph's, Oostende	11
District Hospital, York	10
Univ. St. Luc, Brussels	9
Univ. de Palermo	5
St. Radboud, Nijmegen	5
AZ Gent	5
Barmherz, Bruder, Munchen	4
Hospital Curry Cabra, Lisbon	2
Groot Zoekengasthuis, Hertogenbosch	1
Total	327

sics, antibiotics, palliative radiotherapy, and surgery for relief of lower urinary tract obstruction was allowed.

The pretreatment studies and the clinical evaluation studies are presented in Table 3.

Patient Selection

Patients were eligible for inclusion if: (1) they had histologically proven prostate cancer; (2) they had been assigned a tumor, node, or grade category (those with M1

Table 2. Management Structure: EORTC 30853

Coordination committee	
Study coordinator	L. Denis (B)
Co-coordinators	M. Robinson (UK)
	C. Mahler (B)
Study data manager	P. Ongena (B)
Secretary	R. Denie (B)
Independent ad hoc committees	
Central pathology	P. Spaander (NL)
Bone scan	P. Smith (UK)
Response criteria	D. Newling (UK)
Markers (PSA)*	T. Cooper (UK)
Endocrine aspects*	C. Mahler (B)
Quality of life*	F. Calais da Silva (P)
Data management	
Statistician	R. Sylvester (B)
Data manager	M. De Pauw (B)
Data analyst	K. Vermeylen (B)

* Optional.

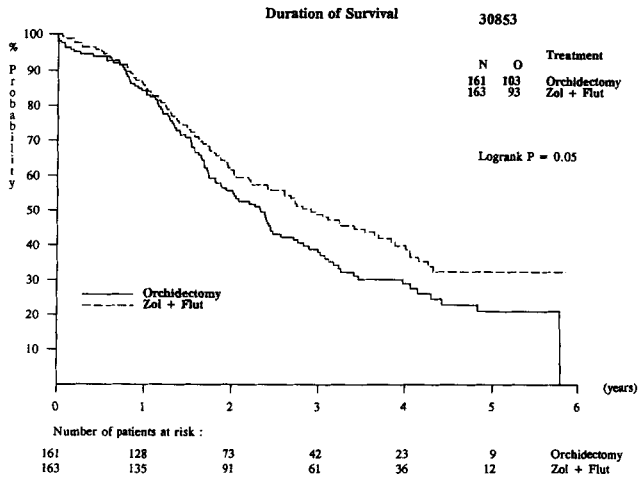

Figure 1. Duration of survival including all causes of death.

category disease who had not had previous systemic treatment also were excepted); (3) they had bone metastases that were diagnosed by bone scan and/or x-ray (biopsies were preformed on questionable metastases); and/or (4) they had a World Health Organization (WHO) performance status of 0–2, with a minimum life expectancy of at least 3 months.

Patients were excluded from the study if: (1) they had had previous hormonal and/or chemotherapy; (2) they had had previous surgery (total prostatectomy or transurethral resection); (3) they had undergone radiotherapy and their progressive metastatic disease did not fall outside the field of radiation; (4) they had another neoplasia (excluding skin cancers); (5) investigators expected them to be difficult to follow-up because of psychiatric disorders or marked senility or because they lived too far from the investigator's center; (6) they had obvious liver disease (at least twice normal serum glu-

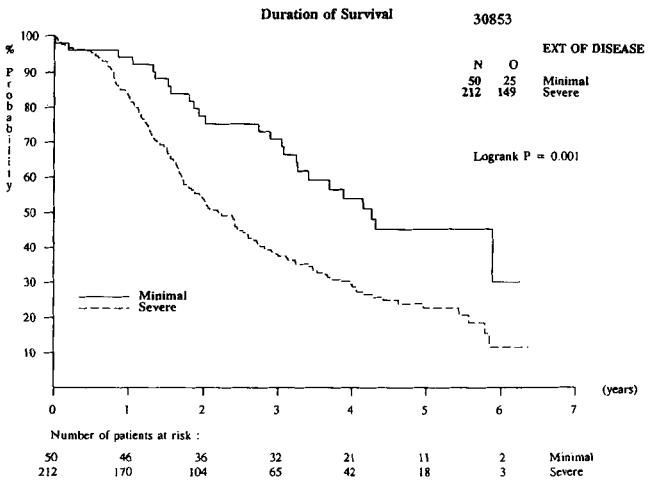

Figure 2. Duration of survival (including all causes) in patients with minimal and severe disease.

Table 3. Study Plan for Patients With Stage M1 Prostatic Cancer (Two Treatment) Arms

Duration of TRT	Before therapy			During TRT period					
Date				First year				After first year	
Weeks	0	4	8	12	24	36	48	Every 12 weeks	
Visit	1	2	3	4	5	6	7	7	8
Informed consent	+								
Anamnesis (complaints, side effects, medication)	+	+	+	+	+	+	+	+	
Physical examination	+	+	+	+	+	+	+	+	
Laboratory									
Hematology	+			+	+	e	+	+	
Blood chemistry	+			+	+	+	+	+	
Acid/alkaline phosphatase	+			+	+	+	+	+	
General urinanalysis	+								
Endocrinology Testosterone	+	+		+	+	+	+	At time of progression	
								Every 48 weeks and at time of progression	
Radiology									
Specific skeletal lesions	+				+		+	+	
Bone scan	+				+		+	+	
IVP	+						+*	If indicated	
CAT scan	+*				+*			+*	
Ultrasound of prostate	+*				+*			+*	
Chest x-ray	+						+	+	
Ultrasound of liver	+*							+*	
Histology primary									
Tumor	+								
Cytology	+*							+*	

* Optional.

tamic oxaloacetic transaminase or serum glutamic pyruvic transaminase values); or (7) they were over 80 years of age.

Evaluation

This trial compared the toxicity and efficacy of both treatment arms in delaying subjective and/or objective progression and in prolonging survival. The incidence and duration of response for each treatment arm also were determined. A general scheme of the criteria for progression is outlined in Table 4.

The following were considered objective criteria for progression: (1) new hot spots on a bone scan or/and x-ray changes; (2) new soft tissue lesions that were palpable or confirmed by computer tomography and/or biopsy; (3) evidence of new pulmonary or liver metastases; and (4) an increase of more than 25% in any *measurable* metastatic lesion. Note that an increase in the intensity of hot spots or increase in size was *not* accepted as progression.

Local progression was defined as an increase of more than 50% of the product of the two maximum perpendicular diameters of the primary tumor by rectal examination or ultrasound. Because very small changes in small-volume glands would fulfill the above criteria, they were acceptable only in patients whose tumors measured at least 9 cc at entry. Transurethral resection of the primary lesion necessitated the discontinuation of the use of the primary lesion as a parameter for progression. Patients who fell into this category were kept in the study, and evaluation of all of their other parameters continued.

The following were considered non-specific and subjective criteria of progression: (1) the observation of an increase in the acid phosphatase level (measured by biochemical or immunologic methods) on two successive occasions; (2) a change in performance status; (3) a change in the amount pain and the use of analgesics; (4) changes in urinary symptoms; (5) a decrease in hemoglobin; (6) a weight loss of at least 10%; (7) an increase in the alkaline phosphatase level noted on two successive occasions.

Subjective deterioration in a patients's general condition alone was *not* a reason to withdraw the patient from the study. Similarly, an improvement of the performance status after radiotherapy of metastatic lesions was not regarded as a criterion for response. Spontane-

Table 4. Criteria of Subjective and Objective Progression

Subjective criteria of progression
- WHO performance status
- Pain score
  - Progression: increase of 2 categories (from the lowest value)
- Weight
  - Progression: ≥ 10% decrease within 1 yr
- Urologic symptoms
  - Progression: appearance of severe symptoms requiring surgical relief or catheterization
- Hemoglobin
  - Progression: decrease of > 25% from the highest value.
- Alkaline phosphatase
- Prostatic acid phosphatase
  - Progression: increase of 2 categories or from 3 to 4

Phosphatases	Pain Score	
< 1.25 × N	None	no analgesics
1.26–2.5 × N	Mild	nonnarcotic analgesics occasionally required
2.6–5 × N	Moderate	nonnarcotic analgesics regularly required
5.1–10 × N	Severe	narcotic analgesics occasionally required
> 10 × N	Intractable	narcotic analgesics regularly required
	Urological Symptoms	
	NED	No treatment required
	Moderate	Requiring treatment
	Severe	Reg. catheter/surgical relief

Objective criteria of progression
- Digital examination of the primary tumor
  - Progression: increase of > 50% (from lowest value) of the product of the largest perpendicular diameters; patients with a product of < 9 cm^2 at entry were excluded
- Regional lymph nodes
- Distant lymph nodes
- Lung metastases
- Liver metastases
  - Progression: increase of ≥ 25% of the sum of the products of the largest perpendicular diameters or the appearance of new metastases
- Bone metastases
  - Progression: appearance of new hot spots on the bone scan or new lesions on x-ray

or

  - Progression (osteolytic lesions): increase of ≥ 25% of the sum of the products of the largest perpendicular diameters

ous fracture of bone was not considered evidence of progression.

The disappearance of all signs and symptoms of prostatic cancer for a period of at least 12 weeks was considered *complete* remission. The disease was considered to be in *partial* remission if there was no progression and any of the following occurred: (1) an x-ray showed normalization of bone scan and recalcification of lytic lesions; (2) there was more than a 50% decrease in metastatic measurable lesions in the sum of the products of the two maximum perpendicular diameters of all lesions; (3) there was a decrease of more than 50% of the product of the two maximum perpendicular diameters of the primary tumor identified by rectal examination or ultrasound, where one of these diameters measured at least 3 cm; or (4) the prostatic acid phosphatase level decreased to normal in cases in which the elevated level had been at least twice the normal level.

No change was observed when the patient was not classified as having progression, complete response, or partial response.

To complete data on survival time, we followed all patients until death.

Results

Patient and Disease Characteristics

As of July 1989, 184 patients have been removed from the study, two thirds of whom were removed for disease progression.

Table 5. Patient Characteristics (307 Patients)

Age	
< 65 yr	63 (21)
65–74 yr	150 (49)
> 75 yr	94 (30)
WHO performance status	
0	107 (35)
1	131 (43)
2	69 (22)
Pain	
None	117 (38)
Mild	100 (33)
Moderate	58 (19)
Severe	25 (8)
Intractable	7 (2)
Urologic symptoms*	
None	43 (14)
Minimal	137 (45)
Moderate	34 (11)
Severe	93 (30)
Chronic diseases	
Cardiovascular	127 (41)
Respiratory	46 (15)
Paget disease	5 (2)
Musculoskeletal	26 (8)
Other	31 (10)

Values in parentheses are percentages.

Patient characteristics at the time of entry on study —age, WHO performance status, pain, urologic symptoms, and associated chronic disease—are presented in Table 5. Disease characteristics at entry on study—tumor category, node category, grade, sites of metastases, disease extent, and alkaline and acid phosphatase levels coded according to WHO guidelines—are given in Table 6.

The distribution of the extent of disease at entry on study is given for those patients whose bone scans were subjected to an extramural review at entry or who had lung or liver involvement at entry. Patients were divided into two categories according to the criteria given by Crawford et al.[2] Of the patients studied, 25% had minimal disease and 75% had severe disease.

Side Effects

The frequencies of the incidence of hot flushes at any time during follow-up (± 60%) and gynecomastia (± 10%) were different in the two treatment arms. Side effects requiring treatment modification were reported in 12 of 149 patients (8%) who received the combination treatment and in 1 patient (1%) who underwent orchidectomy. As presented in Table 7, the side effects experienced most frequently in patients in the goserelin plus flutamide group were liver toxicity (five patients) and gastrointestinal disturbances (three patients). These side effects can be attributed to flutamide. Table 8 presents the frequency of changes in liver function tests in patients who went from WHO level 0 at entry to at least WHO level 2 (more than 2.5 normal) during follow-up. A slightly higher incidence of serum glutamic pyruvic transaminase elevation was noted in the Zoladex plus flutamide group (10% versus 3% in the orchidectomy group, $P = 0.06$).

Reviews by Ad Hoc Committees

Interesting data came out of this quality and analysis control, among which the most remarkable is the pre-

Table 6. Disease Characteristics (307 Patients)

T category	
0	5 (1)
1	20 (7)
2	53 (17)
3	148 (48)
4	81 (26)
N category	
0	45 (15)
1	4 (1)
2	8 (3)
3	6 (2)
4	37 (12)
Unknown	207 (67)
Histology grade	
1	49 (16)
2	157 (51)
3	96 (31)
Unknown	5 (2)
Lung metastasis	14 (5)
Liver metastasis	3 (1)
No bone metastasis	9 (3)
N4M0	6 (2)
Disease extent	
Minimal	46 (25)
Severe	141 (75)
No bone scan rev	120
Alkaline phosphatase	
< 1.25 N	127 (41)
1.26–2.5 N	78 (25)
2.6–5 N	48 (16)
5.1–10 N	24 (8)
> 10 N	21 (7)
Unknown	9 (3)
Acid phosphatase	
< 1.25 N	90 (29)
1.26–2.5 N	49 (16)
2.6–5 N	50 (16)
5.1–10 N	47 (15)
> 10 N	69 (22)
Unknown	2 (1)

N: upper limit of normal.

Table 7. Side Effects Necessitating Treatment Modification

Side effect	No. of patients
Zoladex + flutamide	12/149 (8%)
Liver toxicity	5
Gastrointestinal	3
Estrogens for hot flushes	2
Increase of weight	1
Persistent diarrhea	1
Orchidectomy	1/148 (1%)
+Estrogens for hot flushes	1

liminary conclusion that the value of repeated bone scans during follow-up in randomized trials of prostate cancer should be questioned.[3] This finding is remarkable in view of the fact that the appearance of new hot spots generally was accepted as an objective sign of progression in most studies.

The sites of bone metastases in patients at entry reviewed by the bone scan committee are given in Table 9. The pelvis was involved in 73% of the reviewed bone scans. The relationship between pain and lumber bone metastases is presented in Table 10.

Response

No statistical differences in response were noted in respect to any of the parameters except for serum acid phosphatase levels. The combination treatment normalized these levels in patients who initially had elevated levels (79 of 113 patients (70%); $P = 0.005$).

Time to Progression

Progression was assessed for each of the 13 parameters (6 objective and 7 subjective), which are presented in Table 11. The highest progression rate was seen with the pain score for evaluation of subjective progression. Here, the pain categories of 37% of the patients increased by two. The combination treatment had a better effect on preventing increases in pain (Table 12). The difference in median progression between the two groups was 35 weeks.

Table 8. Changes in Liver Tests From WHO-0 at Entry to at Least WHO-2 During Follow-up

	Orchidectomy	Zoladex + flutamide
Gamma GT	4/63 (6)	6/69 (9)
SGPT*	4/118 (3)	11/115 (10)
SGOT	5/116 (4)	5/113 (4)

Values in parentheses are percentages.
* $P = 0.06$.

Table 9. Site of Bone Metastases at Entry on Study (178 Patients)

Site	%
Pelvis	73
Dorsal	63
Lumbar	62
Ribs	61
Cervical	51
Femur	40
Skull	28
Sacrum	25
Humerus	24

The highest progression rate for the objective parameters occurred with respect to new bone metastases. Here again, the combination treatment was more effective than orchidectomy in preventing the development of new bone metastases (Table 12). The difference in median progression between the two groups was 48 weeks. The advantage of the combination therapy was confirmed by the recording of any first subjective or objective progression with a difference of 25 weeks (Table 12).

Survival

The median duration of follow-up was approximately 4 years. In that time, two thirds of the patients have died —103 who underwent orchidectomy and 93 who received the combination treatment. The difference is significant ($P = 0.05$), and combination therapy offered a 7-month extension of survival (Figure 1, Table 12). Based solely on death by cancer, this difference increases to 15 months ($P = 0.02$; Table 12).

A survival analysis based on extent of disease showed a statistical difference in favor of patients with minimal disease ($P = 0.001$). However, the numbers of

Table 10. Relation Between Pain at Entry On Study and Lumbar Bone Metastases

Pain score	Lumbar metastasis		Total
	No	*Yes*	
0	36 (54)	32 (30)	68 (39)
1	18 (27)	43 (40)	61 (35)
2	9 (14)	21 (20)	30 (17)
3	2 (3)	8 (7)	10 (6)
4	1 (2)	3 (3)	4 (2)
Total	66 (38)	107 (62)	173

Values in parentheses are percentages.
$P = 0.001$.

these patients are limited and should be evaluated with caution. The curves are shown in Figure 2.

Discussion

After 4 years of follow-up, we have found that the combination treatment significantly delays the time to progression and survival as compared with orchidectomy. This finding is in contrast with our previous publication, which reported that after a 2-year follow-up, no difference in survival could be detected.[4]

Similar results were observed in the large collaborative study in the United States (National Cancer Institute trial 036), in which combination luteinizing hormone–releasing hormone agonist plus flutamide treatment was compared to treatment with a luteinizing hormone-releasing hormone agonist and placebo control.[2] In addition, in this study, the benefits of the combination treatment were most evident for patients with minimal disease. However, this study also showed that the numbers of patients involved were too small to allow definite conclusions.

Because patients with severe disease do not seem to benefit from combination treatment, we will have to look for the patients or tumors that benefit most from this type of therapy.

Both of these studies stand in contrast to other studies, including two by the EORTC that used cyproterone acetate with either orchidectomy or a luteinizing hormone-releasing hormone agonist. In these studies, no long-term benefit has been observed with the combination treatment.[5–8]

The quality control of our data revealed problems in defining response and even in progression in analysis of these events.[2] We expect that other trials face the same problem and contradictions between phase III trials are not abnormal.

Table 11. Parameters for Progression

Objective	Subjective
Primary tumor	Performance status
Regional lymph nodes	Pain score
Distant lymph nodes	Weight
Bone metastasis	Urologic symptoms
Lung metastasis	Hemoglobin
Liver metastasis	Alkaline phosphatase
	Acid phosphatase

Table 12. Advantages for Combination Treatment: EORTC 30853

Time to	*P* value	Hazard ratio	95% CI
Subjective progression	0.009	1.50	1.11–2.02
Objective progression	0.008	1.57	1.13–2.20
First progression	0.002	1.56	1.18–2.06
Death	0.05	1.33	1.00–1.76
Death by cancer	0.02	1.45	1.06–1.98

We hope that the analysis of the randomized trials coupled with the prognostic factors finally will answer the question regarding the extent of the advantage offered by combination treatment. Further confirmation or negation could derive from a phase III trial with high enough enrollments to answer both this question and the more important question of which patients profit most from combination treatment.

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