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ORCHIDECTOMY VERSUS ZOLADEX® PLUS EULEXIN® IN PATIENTS WITH METASTATIC PROSTATE CANCER (EORTC 30853)

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Summary—A total of 327 patients with metastatic prostate cancer have been randomized to either orchidectomy or treatment with goserelin (Zoladez®) 3.6 mg depot preparation combined with flutamide (Eulexin®) 250 mg t.i.d. in a phase III study (EORTC 30853). A small but statistically significant difference in time to subjective and objective progression of disease was found in favour of the combination treatment. However, time from objective progression to death was longer in the group initially allocated to orchidectomy. Thus no difference was found in overall survival between the two treatment groups. The clinical significance of these differences requires further follow up and analysis.

INTRODUCTION

The measurable presence of the adrenal androgen metabolites in the plasma and prostatic tissues of patients after first line hormonal treatment for prostate cancer could possibly lead to further stimulation of tumour growth [1]. Past treatments utilizing adrenal ablation or blocking adrenal hormone production by cortison treatment failed to bring worthwhile clinical improvement to these patients [4]. The introduction of the anti-androgens blocking the androgen receptor sites in prostatic tissue offered a more acceptable treatment to test the hypothesis of adrenal androgen tumour stimulation.

The Urological Group of the EORTC started two randomized phase III trials, one in 1980 and one in 1984, where combination treatment of orchidectomy and cyproterone acetate was compared to various forms of monotherapy leading to castrate levels of serum testosterone. Remarkable and widely published results of a phase II study [3] prompted a third randomized trial comparing orchidectomy versus goserelin, a depot LHRH agonist, and flutamide (Table 1). The results of the latter study are presented in this report.

PATIENTS AND METHODS

The objective of this study was to compare the side-effects and efficacy of orchidectomy versus a gonadotrophin hormone-releasing hormone (Zoladex®) combined with flutamide (Eulexin®). Treatment efficacy was assessed with respect to time to progression and duration of survival.

The study was initiated in March 1986 and closed after randomizing 327 patients in May 1988. The list of the participating centres is presented in Table 2. The strict quality control programme of the EORTC trials necessitates the management structure presented in Table 3 where independent committees control and evaluate a number of trial aspects as pathology, bone scan, response criteria, markers, endocrine aspects and quality of life.

Treatment regimen and treatment studies

The treatment regimen consisted of a 3.6 mg Zoladex depot injection once every four weeks. Flutamide 250 mg t.i.d. 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

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Table 1. Overview of three consecutive EORTC phase III studies on maximal androgen withdrawal

30805 Study Coordinator M. Robinson
Bilateral orchiectomy
Bilateral orchiectomy + CPA 50 mg 3 × /day
Des 1 mg daily
Closed 351 patients
30843 Study Coordinator H. De Voogt
Bilateral orchiectomy
Buserelin + CPA 50 mg 3 × /day 14 days
Buserelin + CPA 50 mg 3 × /day
Closed 353 patients
30853 Study Coordinator L. Denis
Bilateral orchiectomy
Zoladex + flutamide 250 mg 3 × /day
Closed 327 patients

a minimum of 3 months and to progression whenever possible.

A total of 19 (6%) of the patients was ineligible and an additional 14 (4%) of the patients was not evaluable for toxicity but evaluable for survival. Concurrent therapy consisting of sedatives, analgesics, 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 4.

Patient selection

Criteria for inclusion. All patients had histologically proven carcinoma of the prostate.

All patients with all T, N and G categories were accepted with M1 category disease without previous systemic treatment. Patients in Mo N4 category were accepted as M1 Lym. Bone metastases were diagnosed by bone scan and/or X-rays but questionable metastases had to be biopsied. If there was doubt, the bone scan committee was consulted by the participants. All patients had performance status WHO 0–2

Table 2. Patient entry by institution EORTC 30853

A. Z. VUB, Brussels-Antwerp	43
St James' Hospital, Leeds	33
St Maria, Lisbon	32
Princess Royal Hospital, Hull	30
Ospedale Civils, Varese	27
St Rafael, Leuven	21
Normanton Hospital, Castleford	21
Hôpital de Baviere, Liege	19
O.L.V., Aalst	13
Hôpital de Strasbourg	13
Hospidale Desterro, Lisbon	12
Freeman Hospital, Newcastle	11
St Joseph's, Oostende	11
District Hospital, York	10
Université St Luc, Brussels	9
Univ. De Palermo	5
St Radboud, Nijmegen	5
A. Z. Gent	5
Barmherzigen Brüder, München	4
Hospidale Curry Cabra, Lisbon	2
Groot Ziekengasthuis hertogenbosch	1
Total	327

Table 3. Management structure EORTC 30853

Coordination Committee	
Study coordinator	: L. Denis (B)
Co-coordinators	: M. Robinson (U.K.), C. Mahler (B)
Study data manager	: P. Ongena (B)
Secretary	: R. Denie (B)
Independent *ad hoc* Committies	
Central pathology	: P. Spaander (NL)
Bone scan	: Ph. Smith (U.K.)
Response criteria	: D. Newling (NL)
Markers (PSA)*	: T. Cooper (U.K.)
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.

with a minimum life expectancy of at least 3 months.

Criteria for exclusion. Patients with previous hormonal and/or chemotherapy were excluded. Prior surgery (total prostatectomy or transurethral resection) and radiotherapy were not a cause for exclusion if there was proven progressive metastic disease outside the field of irradiation.

Patients with another neoplasia (except skin, excluding melanoma) were excluded.

Expected difficulties of follow up relating to psychiatric disorders, marked senility, or too large a distance between patients home and investigator's centre were criteria for exclusion. Patients with obvious liver disease (at least twice normal SGOT and SGPT values) and patients over 80 years of age were also excluded.

Randomization, data management and statistical considerations

Randomization. All patients were centrally randomized at the EORTC Data Center by telephone or by electronic mail connection to the Data Center computer. The randomization was done using a minimization technique with stratification for institution and the WHO performance status.

Data management. Forms for this trial were designed at the Data Center in collaboration with the study coordinator. The forms were filled out at the participating institutions and returned to the Data Center for verification and processing by the data manager. While the Data Center had no direct access to patient medical records, the EORTC-GU Group conducted site visits in member institutions during which the quality of transfer of data from the medical records to the EORTC forms was verified.

Table 4. Study plan for patients with stage M1 prostatic cancer (two treatment) arms

Duration of treatment	Before therapy							During treatment 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	+			+	+	+	+	+
Blood chemistry	+			+	+	+	+	+
Acid/alkaline phosphatase	+			+	+	+	+	+
General urine analysis	+							
Endocrinology	+	+		+	+	+	+	At time of progression
Testosterone								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								
Tumour	+							
Cytology	+*							+*

*Optional.

Five different types of forms were used in this study:

1. An On Study Form which contains information on eligibility checks, pretreatment studies as defined in the protocol, and prognostic factors.
2. A Follow Up Form providing the follow up data required by the protocol (symptoms, laboratory data, tumour status, side effects).
3. An Off Study Form giving information on progression and survival.
4. A Progress Report Form which provides survival information on patients who are off study.
5. An Evaluation Form which is filled out by the study coordinator after the patient goes off study.

These forms were the only source of information to perform quality control and to provide interim reports and statistical analysis.

Data quality control was carried out in 4 steps:

1. Protocol verification by the data manager based on forms received: patient eligibility, protocol and treatment compliance, missing or unclear information. If necessary, forms were returned to the investigator for clarification.
2. Computerized verification: range checks, cross checks within one form or between different forms.
3. Review of patient files by the study coordinator: eligibility, compliance, endpoints.
4. Computerized verification by the statistician for errors and/or inconsistencies.

Interim reports were prepared by the data manager for presentation at the 6 monthly meetings of the GU Group. Such reports contained general administrative information (patient accrual, eligibility, patient characteristics, problems in running the trial) and data on toxicity.

Statistical considerations. Except when missing data made their inclusion impossible, all patients have been included in the statistical comparisons of treatment efficacy. Ordered categorical data was compared using the χ^2-test for linear trend. Time to progression and duration of survival curves were calculated using the Kaplan–Meier technique and compared using the logrank test. Retrospective stratification was used in order to adjust for prognositc factors. Statistical comparisons of treatment efficacy were presented by the statistician only once the trial was closed to patient entry.

Evaluation

This trial compared the efficacy and toxicity of both treatment arms in delaying subjective and/or objective progression and in prolonging survival.

Table 5. 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: $\geqslant 10\%$ decrease within 1 year
Urological symptoms
Progression: appearance of severe symptoms requiring surgical relief or catheterization
Haemoglobin
Progression: decrease of $\geqslant 25\%$ from the highest value
Alkaline phosphatase
Prostatic acid phosphatase
Progression: increase of 2 categories or from 3 to 4

Phosphatases	Pain Score	Urological Symptoms
$\leqslant 1.25 \times N$	None = No analgesics	NED = No treatment required
$1.26–2.5 \times N$	Mild = Non-narcotic analgesics occasionally required	Moderate = Requiring treatment
$2.6–5 \times N$	Moderate = Non-narcotic analgesics regularly required	Severe = Requiring catheter/surgical relief
$5.1–10 \times N$	Severe = Narcotic analgesics occasionally required	
$>10 \times N$	Intractable = Narcotic analgesics regularly required	

Objective criteria of progression
Digital examination of the primary tumour
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 $\geqslant 25\%$ 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 lesion on X-ray or
Progression (osteolytic lesions): increase of $\geqslant 25\%$ of the sum of the products of the largest perpendicular diameters

The incidence and duration of response for each treatment arm were also determined.

A general scheme of the criteria for progression are listed in Table 5.

Objective criteria for progression. New hot spots on a bone scan or/and X-rays changes. New soft tissue lesions which were palpable and/or confirmed by CAT-scan and/or biopsy. New pulmonary or liver metastases. Increase in any *measurable* metastatic lesion by more than 25%. Note that 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 tumour by rectal examination or by ultrasound scanning. Since very small changes in small volume glands would lead to the above criteria being fulfilled, they were only acceptable in patients whose tumour measured at least $9\,cm^2$ at entry. TUR of the primary lesion necessitated discontinuation of the use of the primary lesion as a parameter for progression. The patient was kept on study and evaluation of all other parameters continued.

Non-specific and subjective criteria of progression. Increase of acid phosphatase (measured by biochemical or immunological methods) noted on two successive occasions. Changes in performance status. Changes in pain and use of analgesics. Changes in urinary symptoms. Decrease in haemoglobin. Weight loss of 10% or greater. Increase of alkaline phosphatase (noted on two successive occasions). It should be noted that subjective deterioration in a patient's general condition alone was *not* a reason to withdraw the patient from the study. Likewise an improvement of the performance status after radiotherapy of metastatic lesions was not regarded as a criterion for response. Spontaneous fracture of bone was not evidence of progression.

Other criteria of response

Complete remission. Disappearance of all signs and symptoms of prostatic cancer maintained over a period of minimum 12 weeks.

Partial remission. No progression was allowed and any of the following criteria: Normalization of bone scan and re-calcification of lytic lesions on X-ray. Decrease in metastatic measurable lesions more than 50% in the sum of the products of the two maximum perpendicular diameters of all lesions. Decrease by more than 50% of the product of the two maximum perpendicular diameters of the primary tumour by rectal examinations or by ultrasound scanning where one of these diameters measured at least 3 cm. Decrease of

elevated serum prostatic acid phosphatase to normal where the evaluation was at least twice normal.

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

Survival time. All patients were followed until death.

RESULTS

Patient and disease characteristics

As of July 1989, 184 patients have gone off study, two thirds for disease progression. A new analysis is planned for May 1990.

Table 6 provides patient characteristics at the time of entry to study: age, WHO performance status, pain, urological symptoms, and associated chronic disease.

Disease characteristics at entry to study are given in Table 7: T category, N category, G grade, sites of metastases, disease extent, alkaline and acid phosphatases coded according to the WHO.

The distribution of the extent of disease at entry to study is given for those patients having either an extramural review of the bone scan at entry on study (187 patients) or those with lung or liver involvement. Patients have been divided into 2 categories according to the criteria given by Crawford *et al.* [4]. Twenty-five percent of the patients had minimal disease and 75% had severe disease.

The distribution of patient and disease characteristics was well balanced in the two treatment groups, except that a higher percentage of patients on orchidectomy had severe extent of disease, 80 vs 71%. This was due to the fact that 11 of the 14 patients with lung metastases received an orchidectomy.

Table 6. Patient characteristics (307 patients)

Age (yr)	
<65	= 63 (21%)
65–74	= 150 (49%)
⩾75	= 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%)
Intact	= 7 (2%)
Urological symptoms	
None	= 43 (14%)
Minimal	= 137 (45%)
Moderate	= 34 (11%)
Severe	= 93 (30%)
Chronic disease	
Cardiovascular	= 127 (41%)
Respiratory	= 46 (15%)
Paget's disease	= 5 (2%)
Musculo-skeletal	= 26 (8%)
Other	= 31 (10%)

Table 7. 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%)
X	= 207 (67%)
Histology grade	
1	= 49 (16%)
2	= 157 (51%)
3	= 96 (31%)
X	= 5 (2%)
Lung metastases	= 14 (5%)
Liver metastases	= 3 (1%)
No bone metastases	= 9 (3%)
N4 M0	= 6 (2%)
Disease extent	
Minimal	= 46 (25%)
Severe	= 141 (75%)
No bone scan review	= 120
Alkaline phosphatase	
⩽1.25 N	= 127 (41%)
1.25–2.5 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.

Side effects

The incidence of hot flushes at any time during follow up is given by treatment group in Table 8. The incidence of gynecomastia is reported in Table 9. For neither of these variables is there a difference in frequency in the two treatment groups.

Side effects requiring treatment modification were reported in 12/149 patients (8%) on Zoladex + flutamide and in 1 patient (1%) on orchidectomy. As presented in Table 10 the most frequent reasons on Zoladex + flutamide

Table 8. Hot flushes during follow up

	Orchid	Zol + flut
None	63 (43%)	51 (34%)
<3 × per day	54 (37%)	60 (40%)
>3 × per day	31 (21%)	38 (26%)
Total	148	149

Table 9. Gynecomastia during following up

	Orchid	Zol + flut
None	137 (93%)	129 (87%)
Not painful	10 (7%)	17 (11%)
Painful	1 (0%)	3 (2%)
Total	148	149

were liver toxicity in 5 patients and gastro-intestinal disturbances in 3 patients. Except in patients for whom estrogens were added, treatment with flutamide was stopped.

Table 11 presents the frequency of changes in liver function tests from WHO 0 at entry to at least WHO 2 (more than 2.5 N) during follow-up. A slightly higher incidence of SGPT elevation was noted on Zoladex + flutamide, 10 vs 3%, $P = 0.06$.

Reviews by ad hoc committees

The reviews for pathology, testosterone, response to treatment, quality of life, markers and bone scan are in progress and will be a subject of separate reviews.

Interesting data came out of this quality and analysis control among which the most remarkable is the preliminary conclusion that the value of repeated bone scans during follow up in randomized trials of prostate cancer should be questioned [5]. Remarkable in view of the fact that the appearance of new hot spots was generally accepted as a very objective sign of progression.

The site of bone metastases at entry is given in Table 12 and the relationship between pain and lumber bone metastases has been described in Table 13.

Time to progression

Progression was assessed for each of the 13 parameters (6 objective and 7 subjective) as presented in Table 14.

Subjective progression. The number of parameters for which subjective progression occurred is given by treatment group in Table 15.

The differences is significant at $P = 0.01$ in favour of Zoladex + flutamide. Fifty percent of the patients having an orchidectomy and 40% of the patients receiving Zoladex + flutamide progressed with respect to at least one parameter. The highest progression rate for the subjective parameters occurred with respect to the pain score with 28% of the patients having an increase of 2 or more categories.

Objective progression. The number of parameters for which objective progression occurred is given by treatment group in Table 16. The difference is marginally significant at $P = 0.04$ in favour of Zoladex + flutamide. Only 17 patients showed an objective progression with respect to more than one parameter since patients normally left the trial at the time of the first objective progression. Thirty-nine percent of the patients having an orchidectomy and 31% of the patients receiving Zoladex + flutamide progressed with respect to at least one parameter.

Table 10. Side effects necessitating treatment modification

Zoladex + flutamide: 12/149 patients (8%)	
Liver toxicity	5 patients
Gastro-intestinal	3 patients
Estrogens for hot flushes	2 patients
Increase of weight	1 patient
Persistent diarrhea	1 patient
Orchidectomy:	1/148 patients (1%)
+ Estrogens for hot flushes	1 patient

Table 11. Changes in liver tests from WHO-0 at entry to at least WHO-2 during follow-up

	Orchid	Zol + flut
Gamma GT	4/63 (6%)	6/69 (9%)
SGPT*	4/118 (3%)	11/115 (10%)
SGOT	5/116 (4%)	5/113 (4%)

*$P = 0.06$.

Duration of survival

The median duration of follow up for the 320 patients with follow up data is 1.5 yr.

Figure 1 presents the duration of survival by treatment group based on all causes of death. Approximately one third of the patients entered have died, 52 on orchidectomy and 55 on Zoladex + flutamide. There is no significant difference between the curves, $P = 0.89$. The median duration of survival is approximately 2.5 yr.

If one considers just those patients entered prior to June 1987 (and for whom the median duration of follow up is approximately 2 yr), there is likewise no difference between the curves, $P = 0.58$.

The cause of death is presented by treatment group in Table 17. Among the 107 patients who have died, malignant disease has been

Table 12. Site of bone metastases at entry to study (178 patients)

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

Table 13. Relation between pain at entry to study and lumbar bone metastases

Pain score	Lumbar metastases No	Yes	Total
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

$P = 0.001$.

Table 14. Parameters for progression

Objective	Subjective
Primary tumour	Performance status
Regional lymph nodes	Pain score
Distant lymph nodes	Weight
Bone metastases	Urological symptoms
Lung metastases	Haemoglobin
Liver metastases	Alkaline phosphatase
	Acid phosphatase

Table 15. Number of parameters with subjective progression (%)

Parameters	Orchid	Zol + flut	Total
0	81 (50)	99 (60)	18 (55)
1	26 (16)	23 (14)	49 (15)
2	19 (12)	18 (11)	37 (11)
3	14 (9)	18 (11)	32 (10)
4	14 (9)	5 (3)	19 (8)
5	7 (4)	1 (1)	8 (2)
6	2 (1)	0 (0)	2 (1)
Total	163	164	327

$P = 0.01$.

Table 16. Number of parameters with objective progression (%)

Parameters	Orchid	Zol + flut	Total
0	100 (61)	114 (69)	214 (65)
1	52 (32)	44 (27)	96 (29)
2	11 (7)	6 (4)	17 (5)
Total	163	164	327

$P = 0.04$

listed as the cause in 83 patients (78%) and cardiovascular disease in 11 patients (10%).

The duration of survival according to the levels of the various prognostic factors at entry of study is as expected quite significant. An example is presented in Fig. 2 where survival of patients with minimal disease is compared to survival of patients with extensive disease.

Adjustment of the treatment comparison for the prognostic factors does not in any way modify the overall conclusions of no treatment difference with respect to the duration of survival. In addition, there is no evidence that any differences in the duration of survival by treatment may exist within any subgroups of these factors. The number of patients is, however, too small to draw separate conclusions within the various subgroups.

CONCLUSIONS

The combination treatment significantly delays the time to progression (subjective,

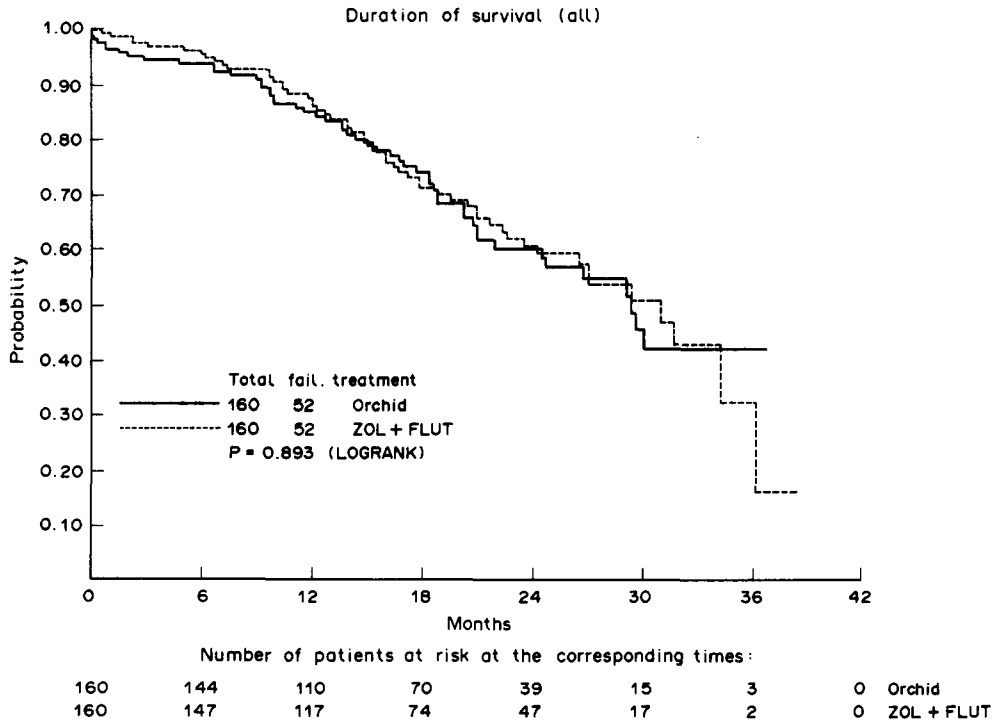

Fig. 1. Duration of survival.

Table 17. Cause of death (%)

	Orchid	Zol + flut	Total
Alive	111 (69)	109 (67)	220 (68)
Malignant disease	43 (26)	40 (24)	83 (25)
Cardiovascular disease	6 (4)	5 (3)	11 (3)
Infection	1 (1)	2 (1)	3 (1)
Chronic disease	0 (0)	1 (1)	1 (1)
Other/unknown	2 (1)	7 (4)	9 (2)
Total	163	164	327

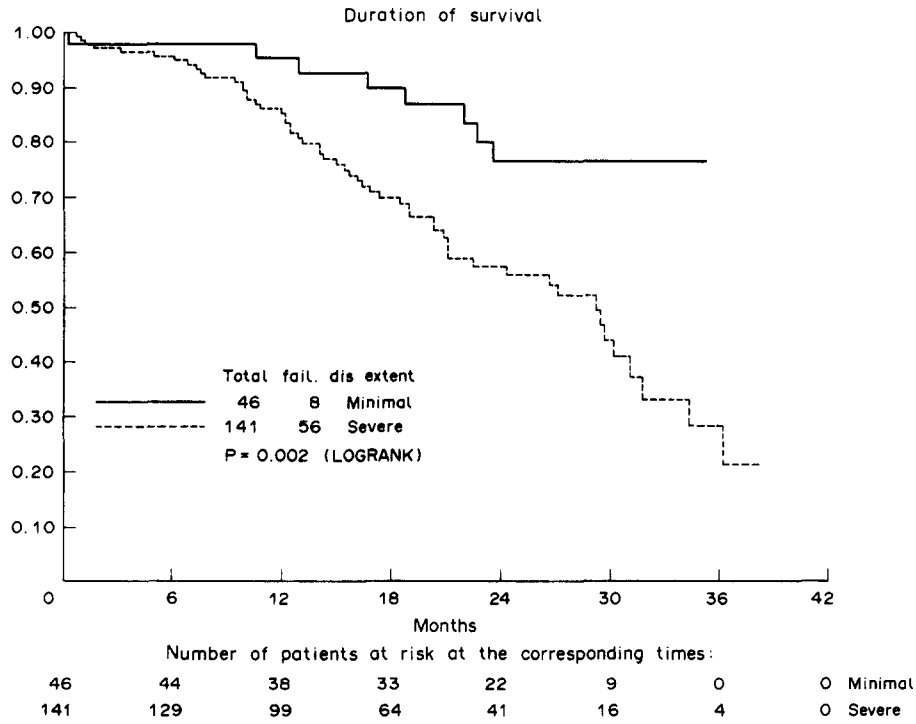

Fig. 2. Duration of survival.

objective, first progression) as compared to orchidectomy, however, no difference in survival (all causes, malignant disease) could be detected. Thus a delay in the appearance of progression has not resulted in an improved survival. In fact the duration of survival after progression tends to be shorter on Zoladex + flutamide, especially after an objective progression ($P = 0.02$). There is thus no evidence to suggest any survival benefit with Zoladex + flutamide. The number of patients is too small to draw separate conclusions within any subgroups.

The quality control revealed discrepancies between local data and data reviewed by the independent *ad hoc* committees. This of course raises questions concerning the applied criteria and the clinical significance which has to be matched with the results of response. Unfortunately it was impossible to blind the trial due to the nature of the treatment. The survival results are valid but further analysis on more mature data is mandatory.

Apparent contradictions between phase III trials are not abnormal and require quality control and subset analysis. Now more than ever is there a need to continue close collaboration on data exchange to reach definitive conclusions on the clinical, human and public health significance of the cited statistical significance in treatment efficacy. A feasibility on a meta-analysis of all randomized trials in prostate cancer should be studied as a means to come to the truth of the matter.

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