# Orchiectomy versus Goserelin and Flutamide in the Treatment of Newly Diagnosed Metastatic Prostate Cancer

## Analysis of the Criteria of Evaluation Used in the European Organization for Research and Treatment of Cancer—Genitourinary Group Study 30853

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**This European Organization for Research and Treatment of Cancer (EORTC) trial 30853 is the fifth EORTC—Genitourinary Group randomized phase III trial of endocrine treatment for patients with newly diagnosed metastatic prostate cancer. Special attention was given to the assessment of response and/or progression. Each of the following factors was assessed separately as nonspecific and subjective criteria of response or progression: performance status, pain, alkaline and acid phosphatase, hemoglobin, urinary symptoms, and prostate-specific antigen (PSA). Objective progression was based on measurable disease. The observed sequence of progression was: (1) protein-specific antigen; (2) bone; (3) pain; and (4) performance status. Protein-specific antigen, an optional parameter, was the first sign of progression in more than 50% of patients whose disease had progressed. *Cancer* 1993; 72:3793–8.**

The European Organization for Research and Treatment of Cancer—Genitourinary Group has just completed a further analysis of its study number 30853. This study is its fifth[1–4] prospective multicenter randomized phase III clinical trial of hormonal treatment for newly diagnosed metastatic prostate cancer. Previous analyses[5] have shown the benefit of treatment with a combination of goserelin and flutamide in terms of a lengthening of the time to progression. There is now a clear trend in terms of a longer duration of survival in this group of patients as well.

The assessment of response to treatment and/or progression of metastatic prostate cancer has been difficult in all previous phase III studies.[6] In this study, detailed information has been requested from the investigators to allow us to analyze the types and patterns of progression. In particular, this study investigated the prognostic significance of the different forms of progression. An analysis of these criteria is presented in this paper.

## Material and Methods

This prospective randomized phase III study was performed to compare the efficacy and side effects of orchiectomy with those of goserelin-flutamide therapy in the treatment of newly diagnosed metastatic prostate cancer. The principal end points of the study were time to progression and duration of survival, both overall and cancer-related.

### *Patient Selection Criteria and Treatment Regimen*

All patients under the age of 80 with a good performance status (World Health Organization 0-1-2) and proven metastatic prostate cancer (M+/N4 M0) were eligible for inclusion in this trial. The patients needed to have an anticipated life expectancy of >3 months and to have received no prior hormonal or cytotoxic treatment for their tumor. Prior surgery and prior radiotherapy were allowed, provided the metastatic disease to be evaluated was outside the field of radiation.

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**Table 1. Response Criteria**

Digital examination of the primary tumor
- Response: decrease of ≥ 50% (from the initial value) of the product of the largest perpendicular diameters
- Patients with a product of < 9 $cm^2$ at entry were excluded from this analysis

Bone metastases
- Response: complete resolution of the bone scan (complete response), clearance of one site (partial response 1), clearance of one lesion (partial response 2), visual improvement (partial response 3), no change or progression (see Table 2) as determined by an independent review of the bone scans

WHO performance status improvement to performance status 0

Pain score
- Response: decrease of 2 categories (from the initial value)

Alkaline phosphatase

Prostatic acid phosphatase
- Response: decrease of 2 categories (from the initial value); decrease to normal (not normal at entry on study)

| Phosphatase | Pain score | Meaning |
|---|---|---|
| ≤ 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 |

Orchiectomy could be either total or subcapsular. A 3.6 mg depot of goserelin was administered subcutaneously every 28 days. A dosage of one 250-mg tablet of flutamide three times a day was begun on the same day as the patient received the first goserelin injection. Treatment was continued for a minimum of 3 months.

### *Patient Assessment*

Each patient underwent a full physical examination which included an assessment of performance status, pain score, and micturition problems. The primary tumor was assessed regularly and, when possible, by rectal ultrasound. The routine laboratory examinations included hemoglobin, assessment of liver function, and creatinine and alkaline and acid phosphatase measurements. Prostate-specific antigen (PSA) levels were measured when possible. Serum testosterone levels also were measured. The radiologic investigations included a bone scan, intravenous pyelogram, ultrasound of the liver, x-ray of hot spots, and chest x-ray. Histology of the primary tumor had to be made available to the referee pathologist.

Clinical evaluations were performed after 4 weeks of treatment, 3 months after treatment began, and every 3 months thereafter. A physical evaluation was performed with these evaluations. Serum acid and alkaline phosphatase, testosterone, and PSA levels, when available, were repeated every 3 months, and radiological examinations were repeated every 6 months.

The parameters of progression as originally defined in the protocol, which were used as end points in this study, were changes in the primary tumor, lymph node, lung or liver metastases, and bone metastases (objective progression).[7] Progression in regard to certain nonobjective parameters was not regarded as an end point, and the patient normally remained on protocol treatment until objective progression as defined above was reached. These nonobjective parameters were performance status, pain, weight loss, urologic symptoms, alkaline phosphatase level, acid phosphatase level, hemoglobin, and PSA level, when available.

### *Criteria of Evaluation*

Definitions for each type of response and progression were established retrospectively for 13 different parameters independently of the definition of response and progression in the protocol. Date of response and progression were calculated independently for each parameter based on data available in the patients' files.

Response to treatment was assessed for each of six different parameters: bone metastases according to central bone scan review, performance status, pain, primary tumor, alkaline phosphatase level and acid phosphatase level. For the last two parameters, two different definitions of response were applied (Table 1). Progression was assessed for 13 parameters, 6 of which were objective and 7, nonobjective. The objective parameters (Table 2) were the primary tumor, regional lymph nodes, distant lymph nodes, bone metastases, and lung and liver metastases. If progression was noted in any of these parameters, the patient left the protocol to receive further treatment at the investigator's discretion. The nonobjective parameters (Tables 3,4) were performance status, pain score, weight loss, urologic symptoms, hemoglobin, alkaline phosphatase level, acid phosphatase level, and, where possible, PSA level.

Patients were assessed with respect to their response to treatment, the time to first progression, time to nonobjective progression, time to objective progression, and overall duration of survival starting from the date of entry into the study.

### *Statistical Methods*

Except when missing data made their inclusion impossible, all patients have been included in the statistical comparisons of treatment efficacy. Categoric data were compared with the chi-square test for proportions, and ordered categorical data were compared with the chi-

**Table 2. Progression Criteria: Objective Criteria of Progression**

| |
|---|
| Digital examination of the primary tumor |
| Progression: increase of > 50% (from the lowest value) of the product of the largest perpendicular diameters; patients with a product of < 9 $cm^2$ at entry were excluded from this analysis |
| 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 lesion on X-ray; new hot spots had to be confirmed by x-ray or a subsequent bone scan |
| **or** |
| Progression (osteolytic lesions): increase of ≥ 25% of the sum of the products of the largest perpendicular diameters |

square test for linear trend. Time to progression and duration of survival curves were calculated with the Kaplan–Meier technique and compared with the log-rank test. Retrospective stratification was used to adjust for prognostic factors.

## Results

Between March 1986 and May 1988, 327 patients from 22 institutions were admitted to this study. Eighteen patients (6%) were ineligible. By September 1991, 251 patients (74%), 164 of whom had died, were no longer in the study.

**Table 3. Progression Criteria: Nonobjective Criteria of Progression**

| |
|---|
| Weight |
| Progression: ≥ 10% increase with 1 year |
| WHO performance status |
| Deterioration by two scores |
| Pain score |
| 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 |
| Phosphatases |
| ≤ 1.25 × N |
| 1.25–2.5 × N |
| 2.6–5 × N |
| 5.1–10 × N |
| > 10 × N |

**Table 4. PSA**

| |
|---|
| Response |
| To be eligible for response the value at start and the value at 3 mo or 6 mo are necessary |
| Response = PSA > 10 at start and to ≤ 10 at (3 mo or 6 mo) |
| Progression |
| To be eligible for progression it is necessary to have the value at start or at 3 mo or at 6 mo |
| Progression is defined as 1 or 2 |
| 1. If PSA ≤ 10 at start or at 3 mo or at 6 mo and increase to > 10 (respectively, after entry, after 3 mo, after 6 mo) |
| 2. If PSA >10 at start, 3 mo and 6 mo (if available) |
| Increase by 100% compared with the original value (original value may be value at start or at 3 mo or at 6 mo) |

### *Patient Characteristics*

Except for the fact that 11 of the 14 patients who had lung metastases underwent orchiectomy, the patients were matched evenly between the two treatment arms. Based on the number and site(s) of metastases and the extramural review of the bone scans of 243 patients on their entry into the study, it was found that a higher percentage of patients in the orchiectomy arm had "a severe extent of disease" compared with those in the combination goserelin-flutamide arm (84% versus 76%). Pretreatment PSA values were available for only 92 patients.

### *Response to Treatment*

According to follow-up bone scans subjected to independent review, 60% of the patients in both arms showed at least some visual improvement (Table 5). The overall variability of partial responses, which were considered together in earlier studies, led to a the development of a number of separate categories of partial response in this analysis. A number of categories of partial response are new to this study and cover a wide variability of bone scan interpretation. With regard to the other parameters of response, except for acid phosphatase level, there was no statistical difference between the two arms; again, approximately 60% of the patients showed a response in one or another of the five other parameters. In this study, patients who received combination goserelin-flutamide treatment showed a higher response rate, as measured by acid phosphatase levels, than did those in the orchiectomy only arm (48% versus 36%). In the assessment of response of the PSA level to treatment, the numbers are too small for us to draw any meaningful conclusions. The response as defined above occurred in 22 of 34 of the patients who underwent orchiectomy (65%) and in 32 of the 38 patients who received combination treatment (88%). The response in the pain score required a diminution of 2

**Table 5. Prognostic Importance of Progression**

| Type of progression | % progress | Median survival (wk) | Relative risk* | Median time to progression (mo) |
|---|---|---|---|---|
| PSA | 45 | 52 | 1.93 | 24 |
| Bone | 40 | 41 | 1.39 | 30 |
| Pain | 37 | 32 | 2.51 | 34 |
| Performance status | 32 | 24 | 2.57 | NYR |
| Acid phosphatase | 24 | 43 | 1.62 | NYR |
| Hemoglobin | 18 | 22 | 2.40 | NYR |
| Alkaline phosphatase | 17 | 35 | 1.79 | NYR |
| Urologic symptoms | 9 | 48 | 1.51 | NYR |
| Weight | 6 | 12 | 4.26 | NYR |
| Lung | 4 | 11 | 2.04 | NYR |
| Regional lymph nodes | 3 | 28 | 1.61 | NYR |
| Liver | 2 | 10 | 5.42 | NYR |
| Distant lymph nodes | 2 | 33 | 1.15 | NYR |

NYR: not yet reached.
* Relative risk of death in patients progressing.

grades to be classified as a response. This change occurred overall in a total of 60 patients, and there was no significant difference between the two arms.

### *Progression on Treatment*

Objective progression, according to the criteria given in Table 2, occurred in 52% of the patients who underwent orchiectomy and in 46% of the patients who received goserelin-flutamide therapy. The difference in time to progression between the two groups was significant ($P = 0.008$).

Nonobjective progression, according to the criteria in Table 3, occurred in 65% of the patients who underwent orchiectomy. Of those patients who received the combination goserelin-flutamide therapy, 55% progressed in at least one of the nonobjective parameters. The difference in time to progression between the two groups was significant ($P = 0.009$). Progression with respect to the pain score was the most common type of nonobjective progression, with 37% of the patients overall progressing according to the criterion noted previously.

If the time required to reach for patients the first objective or nonobjective progression is compared, there was again a significant difference between the two arms in favor of the goserelin-flutamide arm ($P = 0.002$).

The individual criteria for progression, both objective and nonobjective, have been assessed separately with a view to their frequency, the duration of survival after progression associated with them, and their prognostic importance (Table 5).

## Objective Progression

Forty percent of patients showed progression of their bone metastases. There was no difference between the two arms in the time to progression in 171 follow-up scans. The median survival for all patients after progression of bone metastases was 41 weeks. The patients who showed progression of their bone metastases have a relative risk of dying that was 1.39 times higher than that of patients who did not show this type of progression.

The number of patients with lung metastases at the beginning of the study was small (14). Their progression represents only a small percentage of the overall progressions (4%) but carries a poor prognosis with a median survival of only 11 weeks. The relative risk of death of a patient with lung metastases progression over one who does not show signs of lung progression was 2.04.

Patients with liver metastases also showed a very shortened survival after progression—only 10 weeks. Overall, however, liver metastases were not seen commonly at patients' entry into the study, and liver progression represents only 2% of all progressions. In patients with liver metastases progression, the relative risk of dying was 5.42 times greater than that for patients who did not show evidence of liver progression.

A very small number of patients had lymph node metastases, and lymph node progression took place in a total of 5% of these patients. The median survival after regional lymph node progression was 28 weeks, and that after distant lymph node progression was 33 weeks. The relative risk of dying for someone with regional lymph node metastases progression was 1.61, and for distant lymph nodes, 1.15.

Progression of the primary tumor also occurred in a small number of patients. Early in the study it seemed that there were problems regarding the certainty of measurements recorded, i.e., whether they represented the tumor or the prostate gland itself; therefore, this form of progression was used rarely as an indication for patient withdrawal from treatment and was not thought to be reliable enough to analyze in regard to its prognostic importance.

## Nonobjective Progression

Performance status progression occurred in 32% of the patients over both arms. Deterioration of performance status by two levels (World Health Organization scale) suggested a poor prognosis with a median survival after

progression of 24 weeks. The relative risk of dying for those who progressed in performance status as opposed to those who did not was 2.57.

The pain score employed in this study appears to have worked satisfactorily. Progression of the disease as represented by a deterioration in the pain score by at least two points was recorded in 37% of the cases. A median survival of 33 weeks from the time of recording the pain progression was observed. The relative risk of death was 2.51.

Progression according to the parameter of urologic symptoms was recorded in 9% of the cases. The median survival after this progression was 48 weeks, and the relative risk of death 1.51.

Deterioration in weight by 10% suggested a poor prognosis. Although it was only recorded in 6% of the cases as a progression, the median survival following this progression was only 12 weeks. The relative risk of death was high—4.26.

Progression measured by a fall in the hemoglobin was noted in 18% of the cases. These patients had a median survival after progression of 22 weeks, and their relative risk of dying compared with those who did not show this progression was 2.40.

Progression as defined by alkaline phosphatase levels occurred in 17% of the cases, i.e., considerably less than the 40% of cases in which objective progression was seen on the bone scan. Median survival after progression of alkaline phosphatase level was 35 weeks, with a relative risk of death of 1.79.

Progression in acid phosphatase level was seen in 24% of patients and was followed by a median survival of 43 weeks. The relative risk of death, therefore, was 1.62.

Measurement of PSA was not available universally in all centers at the beginning of this study. Therefore, this information was gathered retrospectively, and regular follow-up measurements were available for only 126 patients. Nevertheless, from this information progression as measured by a rise in the PSA level was the most frequently seen form of progression among either the nonobjective and objective measurements. It occurred in 45% of the 126 patients, as shown in Table 5. The median survival after progression of PSA level was 52 weeks, with a relative risk of dying of 1.93.

Among the patients with PSA progression, 68% had bone progression. In 50 of the 57 patients with PSA progression, PSA progression appeared as the first evidence of progression. Progression in bone metastases appeared in 5 of the 57 patients before the PSA level rose. Overall, patients showed progression in either bone metastases, pain, performance status, or a combination of two of these without evidence of a rising PSA.

The relative figures of progression are included in Table 5.

## Discussion

The importance of a parameter of progression in malignant disease is to indicate a failure of contemporary treatment; hopefully, this type of progression will indicate a need for an available new treatment before the patient's general condition has deteriorated. A good measurement of progression therefore must indicate with certainty that if the cancer is left untreated, further progression will occur, leading to the patient's death. The parameter also should indicate a time frame within which either disease progression or death will happen.

Of the objective parameters examined in this study, progression of lung or liver metastases clearly implies an extremely poor prognosis, with median survival of 11 and 10 weeks, respectively. The apparent long median survival (28 and 32 weeks) after progression in regional and distant lymph nodes may be a little misleading in view of the very small number of cases involved. Clear evidence of progression in bone metastases, occurring as it did in this study in 40% of the patients with a bone scan review, has only a modest impact on survival. Although measured in less than 50% of the patients, the PSA level progression appears to be the first sign of treatment failure.

From this analysis, it seems the first and most common form of progression in patients treated for newly diagnosed metastatic prostate cancer by hormonal therapy is a rise in PSA, usually followed by changes on the bone scan, and then an increase in pain and a deterioration of the performance status. Once the latter two conditions appear, it is probably too late to consider changing therapy, because the only available therapies in second line treatment of prostate cancer are not very effective and are still highly toxic.[8] The relative risk of dying once there has been deterioration of the patient's pain score, performance status, hemoglobin, and weight is so high, and the survival so short, that it is probably unjustifiable to use the second line therapies presently at our disposal.

It therefore might be suggested that a rise in the level of PSA within the limits, defined in the criteria for progression, might be an indication for a change in therapy. This change, in turn, might allow the use of full-dose cytotoxic agents or other experimental therapies to be tried at a time when the patient's general condition is good and widespread changes in the peripheral blood or bone marrow do not preclude the use of any cytotoxic or cytostatic agents.

Although the most common objective progression as defined in this protocol was in bone, this frequently occurred some time before a deterioration in the patient's pain occurred, and, based on our present information concerning the median time to progression after therapy, an even longer time before the patient's perfor-

mance status deteriorated. It is unclear from the information already analyzed in this study whether progression in bone metastases automatically led to a change in therapy.[9] In terms of the assessment of the overall efficiency of one treatment or another, perhaps the best criterion might be not when an individual progression occurs but when, in the opinion of the investigator, a therapy has to be changed. Subsequent evaluations must address further the relative prognostic importance of a significant biochemical response indicated by a rapid fall in the PSA.

## Conclusions

The response rates, as reflected by improved bone scans, in patients with metastatic prostate cancer treated with orchiectomy or combination hormone therapy (goserelin-flutamide) were similar in the two treatment arms (60%). This study again has highlighted the problems of measuring response to hormonal therapy in metastatic prostate cancer. In a phase III study of the treatment of prostate cancer, because all patients ultimately progress but not all patients are show a response based on the criteria used, progression is a more sensitive indicator than response to identify differences in treatment efficiency than response.

Although not measured in all patients, a rise in the level of PSA appears to be the first sign of progression after treatment. This rise is followed most commonly by the appearance of new metastases on the bone scan, and later by an increase in pain score and the deterioration of performance status. Later signs of progression, such as a reduction in weight and the appearance of lung or liver metastases, indicate a uniformly poor prognosis, with a median survival after progression in most cases of approximately 12 weeks. Once there has been a marked increase in pain, and certainly once performance status deteriorates, the expected duration of survival is usually too short for the clinician to consider changing the patient's therapy. For any of the existing or foreseen new therapies in prostate cancer to be used ethically and with any chance of success, it seems logical that progression evidenced by a rise in the level of PSA should be taken as a genuine indication of treatment failure and of the need for a new therapeutic strategy.

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