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# IS THE EFFICACY OF HORMONAL THERAPY AFFECTED BY LYMPH NODE STATUS? DATA FROM THE BICALUTAMIDE (CASODEX) EARLY PROSTATE CANCER PROGRAM

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## ABSTRACT

**Objectives.** To report an exploratory subgroup analysis assessing the extent to which the overall benefit found in the Early Prostate Cancer program is dependent on lymph node status at randomization. The program is ongoing, and the overall survival data are immature. The first combined analysis of the bicalutamide (Casodex) Early Prostate Cancer program at 3 years' median follow-up showed that bicalutamide, 150 mg once daily, plus standard care (radical prostatectomy, radiotherapy, or watchful waiting), significantly reduced the risk of objective progression and prostate-specific antigen (PSA) doubling in patients with localized/locally advanced prostate cancer.

**Methods.** Men (n = 8113) with localized/locally advanced disease received bicalutamide 150 mg or placebo once daily, plus standard care. The time to event data (objective progression, PSA doubling) was analyzed by lymph node status at randomization.

**Results.** Compared with standard care alone, bicalutamide significantly reduced the risk of objective progression, irrespective of lymph node status, with the most pronounced reduction in patients with N+ (hazard ratio [HR] 0.29; 95% confidence interval [CI] 0.15 to 0.56) compared with those with N0 (HR 0.59; 95% CI 0.48 to 0.73) and Nx (HR 0.60; 95% CI 0.50 to 0.72) disease. The largest decrease in risk of PSA doubling with bicalutamide was observed in N+ disease (HR 0.16; 95% CI 0.09 to 0.29), with significantly reduced risks seen in N0 (HR 0.45; 95% CI 0.40 to 0.51) and Nx (HR 0.38; 95% CI 0.33 to 0.44) disease.

**Conclusions.** The greatest reduction in the risk of objective progression and PSA doubling with bicalutamide was seen in patients with N+ disease. However, bicalutamide also provided a statistically significant benefit in those with N0 and Nx disease. UROLOGY **63:** 928–933, 2004. 

The ongoing bicalutamide (Casodex) Early Prostate Cancer (EPC) program is investigating the value of adding bicalutamide, 150 mg once daily, to the standard care of patients with localized or locally advanced prostate cancer.[1,2] In the first protocol, combined analysis of the program (at 3

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years' median follow-up), bicalutamide had significantly reduced the risk of objective progression by 42% (hazard ratio [HR] 0.58; 95% confidence intervals [CI] 0.51 to 0.66; $P < 0.0001$).[2] Overall, bicalutamide was well tolerated, with breast pain and gynecomastia the most frequently reported adverse events.[2]

Lymph node involvement is an established risk factor for disease progression in prostate cancer.[3–5] Some studies have demonstrated survival benefits with hormonal therapy (adjuvant or alone) in men with positive lymph nodes (N+).[6–8] To explore the extent to which the benefit of bicalutamide is dependent on lymph node status (negative [N0], N+, or unknown [Nx]) at randomization, we performed a subgroup analysis of the EPC program data.

## MATERIAL AND METHODS

The methods for the EPC program have been previously published[1,2] and are summarized in brief.

### *Study Design and Treatment*

Three ongoing, randomized, double-blind, placebo-controlled trials are being conducted in North America (Trial 23; n = 3292); Europe, South Africa, Australia, Israel, and Mexico (Trial 24; n = 3603); and Scandinavia (Trial 25; n = 1218) in accordance with the Declaration of Helsinki. The local ethics committee or institutional review board approved the trial protocol. All patients provided informed consent. Eligible patients were randomized (1:1 ratio) to receive either bicalutamide 150 mg or placebo once daily plus standard care (radical prostatectomy, radiotherapy, or watchful waiting). The protocol duration of randomized therapy was 2 years in Trial 23 and 5 years or more in Trials 24 and 25.

### *Patients*

Men aged 18 years or older with Stage T1b-T4, any N, M0 prostate cancer were eligible for enrollment. Some differences exist among the three trials that reflect international variation in clinical practice. In Trial 23, patients were required to have undergone radical prostatectomy or radiotherapy, and patients in Trials 24 and 25 were required to have received therapy of primary curative intent or to have been considered eligible for watchful waiting. In Trial 23 only, patients with N+ disease were excluded, because these patients in North America would normally receive additional therapy and thus could not routinely be randomized to placebo. Patients with Nx in Trial 23 were required to have a prostate-specific antigen (PSA) level of less than 20 ng/mL and a Gleason score of less than 7 to ensure a low risk of recruiting patients who actually had N+ disease. In the event of objective progression, as defined in the protocol, patients were to stop the randomized therapy and receive appropriate treatment at the investigators' discretion. However, investigators could decide to stop the trial therapy and institute other treatment for other reasons, including a rising PSA level or adverse events.

### *Assessments and Endpoints*

Nodal status was determined before trial entry either histologically or by imaging. No overall minimal evaluation of nodal category was defined in the protocol. PSA levels, clinical disease progression, and adverse events were assessed every 12 weeks. Bone scans were scheduled at 96-week intervals. After treatment withdrawal, patients were followed up every 24 weeks until death. The time to objective progression was defined as the number of days between randomization and the earliest occurrence of objective progression (confirmed by bone scan, magnetic resonance imaging, ultrasonography, or computed tomography scan) or death without progression. The time to PSA doubling was defined as the number of days between randomization and the earliest occurrence of PSA doubling from baseline, objective progression, or death in the absence of progression.

### *Statistical Analysis*

The time to event data were analyzed on an intent-to-treat basis using Cox proportional hazards regression analysis. For each lymph node status (at randomization) subgroup (N+, N0, and Nx), HRs and 95% CIs were calculated, providing 30 or more events had occurred across both randomized groups.

## RESULTS

### *Patients*

The EPC program recruited 8113 patients; 4052 were randomized to bicalutamide and 4061 to placebo, plus standard care. The two treatment groups were well matched with respect to demographic characteristics at baseline.[2] At randomization, 150 patients (2%) had N+ disease, 4806 (59%) had N0 disease, and 3157 (39%) had unknown nodal status (Nx).

The use of lymphadenectomy or lymph node dissection in patients was recorded. However, it was unknown how many underwent disease staging using other techniques to confirm nodal status, because this information was not routinely recorded. Of the patients who were assessed as N+ or N0 at trial entry, 86 (57.3%) of 150 and 3263 (67.9%) of 4806, respectively, had evidence of histologic confirmation from lymphadenectomy or lymph node dissection. In the radiotherapy and watchful waiting groups, 10 (71.4%) of 14 and 43 (69.4%) of 62 patients with N+ disease had undergone lymph node dissection, respectively. Separate lymph node sampling procedures were recorded in fewer than 50% of patients with N+ disease who underwent radical prostatectomy. This apparently low figure probably reflects that investigators did not record lymph node dissection done at radical prostatectomy as a separate procedure. We assumed that most radical prostatectomy patients with N0 or N+ disease were assessed at surgery, suggesting that most patients with N+ disease had a histologically confirmed nodal status. Imaging techniques such as computed tomography scans were probably the method of determining nodal status in the remainder.

The demographic characteristics by nodal status are shown in Table I. The median follow-up was 3 years, and patients received randomized therapy for an average of 2 years. Fewer bicalutamide patients withdrew from randomized therapy owing

**TABLE I.** *Patient demography by nodal status*

| Characteristic | Nodal Status N+ (n = 150) | N0 (n = 4806) | Nx (n = 3157) |
|---|---|---|---|
| Age (yr) | | | |
| Mean | 64.6 | 64.9 | 70.1 |
| Range | 52–84 | 38–89 | 42–93 |
| Median baseline PSA (ng/mL) | 22.8 | 8.9 | 10.5 |
| Disease stage (%) | | | |
| T1 | 28.7 | 63.6 | 75.2 |
| T2 | 65.3 | 35.4 | 22.7 |
| T3 | 6.0 | 1.04 | 2.0 |
| T4 | 0.0 | 0.0 | 0.1 |
| Gleason score (%) | | | |
| Well differentiated (2–4) | 14.7 | 15.3 | 32.8 |
| Moderately differentiated (5–6) | 40.0 | 44.3 | 44.6 |
| Poorly differentiated (7–10) | 42.0 | 39.8 | 21.4 |
| Not known | 3.3 | 0.6 | 1.3 |
| Standard care received (%) | | | |
| Radical prostatectomy | 49.3 | 82.6 | 13.0 |
| Radiotherapy | 9.3 | 9.1 | 29.1 |
| Watchful waiting | 41.3 | 8.3 | 57.8 |

*Key: PSA = prostate-specific antigen.*

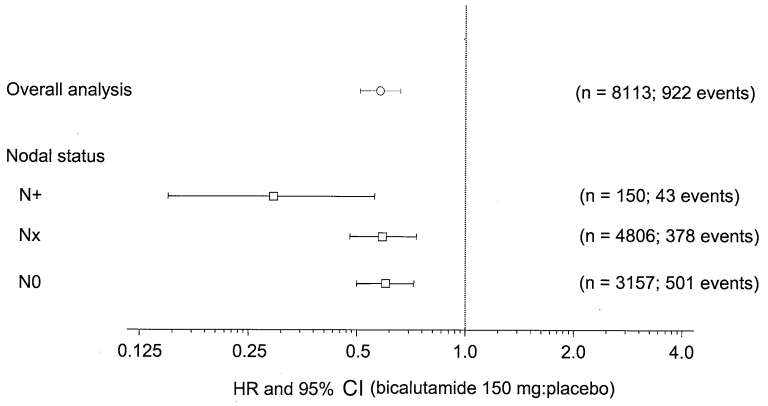


FIGURE 1. *HRs and 95% CIs for time to objective progression for overall population and by nodal status at 3 years' median follow-up.*

to disease progression than placebo patients in the N+ (19.7% versus 39.7%), N0 (1.8% versus 6.0%), and Nx (5.0% versus 16.6%) groups. The proportion of patients withdrawing because of adverse events was similar for the patients with N+ disease in the bicalutamide and placebo groups (11.8% versus 11.0%), but was greater for those with N0 (30.0% versus 8.5%) and Nx (23.7% versus 9.5%) in the bicalutamide group. The most common second-line therapies were luteinizing hormone-releasing hormone agonist therapy and maximal androgen blockade; antiandrogen alone was also frequently used in the placebo group.

### *Objective Progression by Nodal Status*

Bicalutamide significantly reduced the risk of objective progression compared with placebo, regardless of lymph node status (Fig. 1). The greatest benefit of bicalutamide treatment was seen in patients with N+ disease (HR 0.29; 95% CI 0.15 to 0.56; $P = 0.0002$) compared with those with N0 (HR 0.59; 95% CI 0.48 to 0.73; $P < 0.0001$) and Nx (HR 0.60; 95% CI 0.50, 0.72; $P < 0.001$) disease.

A lower percentage of patients with N+ disease experienced objective progression with bicalutamide compared with placebo in the radical prostatectomy (11.4% versus 30.8%) and watchful waiting (26.5% versus 57.1%) subgroups (Fig. 2). Because of the small numbers of patients with N+ disease in each primary therapy subgroup, too few events occurred to calculate the HRs. Only two objective progression events (with placebo) occurred in patients with N+ disease who received radiotherapy.

Compared with placebo, bicalutamide significantly reduced the risk of objective progression in

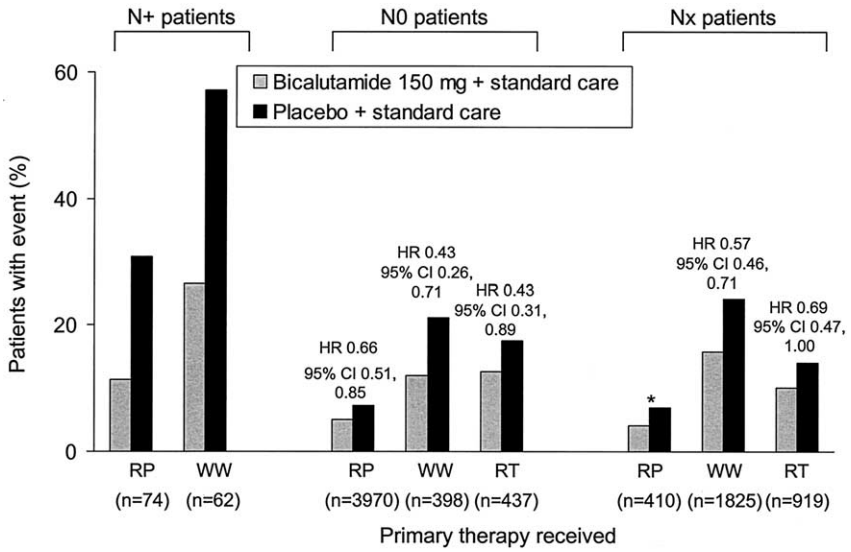


FIGURE 2. *Objective disease progression by primary therapy received for those with N+, N0, and Nx disease at 3 years' median follow-up. RP = radical prostatectomy; RT = radiotherapy; WW = watchful waiting. *Too few events to calculate HR.*

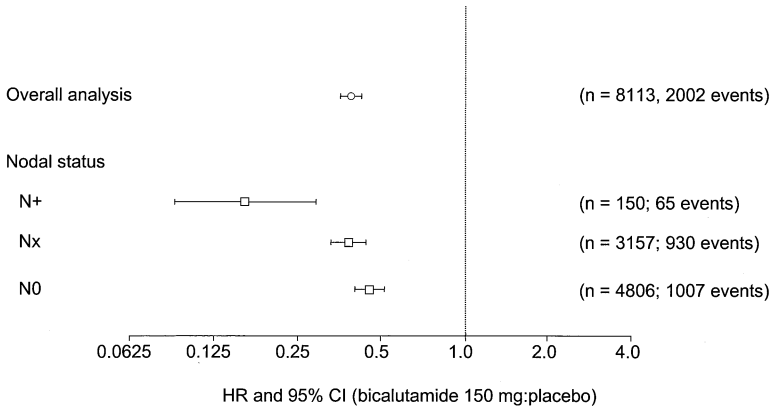


FIGURE 3. *HRs and 95% CIs for time to PSA doubling for overall population and by nodal status at 3 years' median follow-up.*

patients with N0 disease irrespective of the primary therapy received (radical prostatectomy [HR 0.66; 95% CI 0.51 to 0.85], watchful waiting [HR 0.43; 95% CI 0.26 to 0.71], or radiotherapy [HR 0.53; 95% CI 0.31 to 0.89]; Fig. 2). Bicalutamide also reduced the risk of objective progression in patients with Nx disease regardless of the primary therapy (Fig. 2). This reduction was statistically significant for patients with Nx disease who received watchful waiting (HR 0.57; 95% CI 0.46 to 0.71) and just failed to reach conventional statistical significance for patients with Nx disease who received radiotherapy (HR 0.69; 95% CI 0.47 to 1.00). Although too few events occurred to calculate an HR for patients with Nx disease who underwent radical prostatectomy, the incidence of objective progression was lower among those who had received bicalutamide (4.1% versus 7.0%).

### *PSA Doubling by Nodal Status*

Bicalutamide significantly reduced the risk of PSA doubling in patients with N+, N0, and Nx disease (Fig. 3). Again, the greatest benefit of bicalutamide was observed in patients with N+ disease (HR 0.16; 95% CI 0.09 to 0.29; $P < 0.0001$) compared with those with N0 (HR 0.45; 95% CI 0.40 to 0.51; $P < 0.0001$) and Nx (HR 0.38; 95% CI 0.33 to 0.44; $P < 0.001$) disease.

For patients with N+ disease, a statistically significant decrease occurred in the risk of PSA doubling in the radical prostatectomy subgroup (HR 0.11; 95% CI 0.04 to 0.30). A reduced risk was also seen in the radiotherapy (14.3% versus 57.1%) and watchful waiting (29.4% versus 67.9%) subgroups, but, because of the population size, too few events occurred to calculate the HRs. Irrespective of the initial treatment, bicalutamide significantly reduced the risk of PSA doubling in patients with N0 disease (radical prostatectomy, HR 0.50; 95% CI 0.43 to 0.58; watchful waiting, HR 0.26; 95% CI 0.17 to 0.39; radiotherapy, HR 0.33; 95% CI 0.22 to 0.51). Similar results were obtained in patients with Nx disease (radical prostatectomy, HR 0.57; 95% CI 0.37 to 0.87; watchful waiting, HR 0.33;

95% CI 0.27 to 0.39; radiotherapy, HR 0.46; 95% CI 0.35 to 0.60).

## COMMENT

This exploratory subgroup analysis of preliminary EPC program data showed that immediate bicalutamide, in addition to standard care, reduces the risk of objective progression and PSA doubling in men with localized or locally advanced prostate cancer, irrespective of lymph node status at randomization.

The decreased risk of objective progression and PSA doubling was most pronounced in patients with N+ disease, and numeric benefits from bicalutamide therapy were apparent regardless of the standard care received. These results are consistent with the findings of other studies.[6–9] Messing *et al.*[6] investigated the effects of immediate versus deferred hormonal therapy (goserelin [Zoladex] or surgical castration) in 98 men with cT1-T2, pN1-N3 disease who underwent radical prostatectomy and bilateral pelvic lymphadenectomy. At a median follow-up of 7.1 years, immediate hormonal therapy was associated with statistically significant improvements compared with deferred therapy in terms of both overall (85% versus 65%, $P = 0.02$) and recurrence-free (77% versus 18%, $P < 0.001$) survival.

Another study randomized 234 patients with N+ disease (who did not undergo local treatment) between immediate and deferred castration-based hormonal therapy.[8,9] An early analysis in a subgroup of patients demonstrated a statistically significant reduction in the risk of developing distant metastases with immediate versus deferred therapy.[9] At 8.7 years' median follow-up, a 23% nonstatistically significant survival advantage was noted in favor of immediate therapy.[8]

Granfors *et al.*[7] evaluated adjuvant orchiectomy plus radiotherapy versus radiotherapy alone in 91 men with T1-T4N0-N3 disease, of whom 39 (43%) had positive lymph nodes. After 9.3 years' median follow-up, statistically significant differences were found in favor of adjuvant therapy with respect to mortality (38% versus 61%, $P = 0.02$) and disease progression (31% versus 61%, $P = 0.005$). When the data were analyzed by lymph node status at study entry, these differences were statistically significant in patients with N+ disease only ($P < 0.001$ and $P = 0.001$, respectively).

In contrast, in the present study, statistically significant reductions in the risk of objective progression and PSA doubling with bicalutamide were seen in patients with N0 and Nx disease, regardless of the primary therapy. As expected, at this stage of the EPC program, relatively fewer events in proportion to the size of the patient population had been observed in the N0 and Nx groups compared with the N+ group. Additional follow-up is needed to assess the benefits in these groups.

The most reliable method of determining lymph node status is by histopathologic examination after pelvic lymphadenectomy. The studies by Messing *et al.*[6] and Granfors *et al.*[7] used this method. Although histologic findings were used for most patients in the N+ group, a potential concern is that patients with N+ disease may have been misclassified as having N0 or Nx disease. Misclassified patients with N+ disease could, therefore, have been driving the statistically significant benefit seen in the patients with N0 disease. However, the statistically significant result, which was observed in the patients with N0 disease who underwent radical prostatectomy and, therefore, were more likely to have undergone histopathologic confirmation, provides reassurance that this was not the case.

The endpoints reported here are not proven surrogates for survival, and mature survival data are awaited with interest. Nevertheless, a reduction in risk of disease progression is important, because disease progression may be associated with clinical symptoms, anxiety, and/or the initiation of additional treatment.

## CONCLUSIONS

Irrespective of lymph node status, bicalutamide significantly reduced the risk of objective disease progression and PSA doubling in patients with localized or locally advanced prostate cancer when given in addition to standard care. One of the most important findings was the marked benefit of bicalutamide in patients with N+ disease. This result suggests a benefit of early endocrine therapy in patients with N+ disease. Mature survival data are awaited.

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