

GYNECOMASTIA AND BREAST PAIN INDUCED BY ADJUVANT THERAPY WITH BICALUTAMIDE AFTER RADICAL PROSTATECTOMY IN PATIENTS WITH PROSTATE CANCER: THE ROLE OF TAMOXIFEN AND RADIOTHERAPY

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ABSTRACT

Purpose: We investigated the role of tamoxifen and radiotherapy (RT) for the prevention and treatment of gynecomastia and breast pain during adjuvant bicalutamide monotherapy after radical prostatectomy (RP) in patients with prostate cancer. Also, we evaluated their effects on patient hormonal status, quality of life (QOL), sexual function and prostate specific antigen relapse-free survival.

Materials and Methods: This was a multicenter prospective trial. From January 2002 to February 2004, 102 patients who had undergone RP for localized or locally advanced prostate cancer were recruited and randomized into 3 groups, namely group 1—those receiving only 150 mg bicalutamide as adjuvant hormonal therapy, group 2—those receiving bicalutamide and 10 mg tamoxifen, and group 3—those receiving bicalutamide and RT. Patients in group 1 in whom gynecomastia or breast pain developed were subsequently randomized to receive tamoxifen or RT soon after symptoms started. Gynecomastia, breast pain, prostate specific antigen, QOL, sexual function and hormonal levels were assessed. Minimum followup was 12 months.

Results: Of group 1 patients 67% had gynecomastia compared with 8% in group 2 and 34% in group 3. Breast pain was more frequent in group 1 than in groups 2 and 3 (58% vs 7% and 30%, respectively). Differences were significant between groups 1 and 2 (OR 0.12 $p < 0.001$), and groups 1 and 3 (OR 0.52 $p < 0.01$). In patients in group 1 who had gynecomastia or breast pain a significant decrease in symptoms was achieved in those receiving tamoxifen ($p < 0.05$). Treatments were well tolerated in the 3 groups. No differences in QOL between groups 2 and 3 were found. At a median followup of 26 months we observed 12 biochemical relapses.

Conclusions: Gynecomastia and breast pain induced by bicalutamide monotherapy after RP can be prevented and treated. Tamoxifen has been shown to be more effective and safe than RT in this setting. QOL and sexual function are not negatively influenced by these 2 treatment options.

KEY WORDS: prostate, prostatectomy, quality of life, gynecomastia, pain

A treatment option in patients with early prostate cancer (PCa) is radical prostatectomy (RP) and most men undergoing this surgical treatment have an excellent outcome.¹ However, a significant proportion of patients can experience disease recurrence and prostate specific antigen (PSA) progression is the earliest evidence of persistent or recurrent disease after primary therapy with curative intent.²

In previously untreated patients with nonmetastatic PCa 150 mg bicalutamide monotherapy has been shown to be equivalent to castration in terms of the survival rate at a median followup of 6.3 years, offering quality of life (QOL) advantages with respect to sexual interest and physical capacity.^{3,4} The value of adding 150 mg bicalutamide daily to standard care for early PCa is being investigated in the

bicalutamide early prostate cancer (EPC) program, which is the largest international clinical trial of early PCa therapy to date.^{5,6} The EPC program is ongoing and data on the effect of treatment on mortality are still missing. Followup will provide further clarification on the role of bicalutamide in this setting.

To date 150 mg bicalutamide monotherapy has not been Food and Drug Administration approved for use in the United States. Nonetheless, it has been licensed in some European countries as adjuvant treatment for early PC. Notably in Italy based on EPC program toxicity data 150 mg bicalutamide should be prescribed with caution as adjuvant treatment in patients at low risk who have not received any primary treatment with curative intent

In the EPC program the incidence of gynecomastia and breast pain is 68.3% and 73.6%, respectively, with symptoms developing in the majority of patients within the first 6 to 9 months of bicalutamide therapy.⁶ Controlled trials have demonstrated the efficacy of prophylactic estrogen therapy

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Study received approval from the ethics committee at each participating center.

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and prophylactic breast irradiation for gynecomastia and breast pain caused by bicalutamide monotherapy.^{7,8}

We investigated the role of 10 mg tamoxifen daily and 12 Gy electron beam radiotherapy (RT) for preventing and treating gynecomastia and breast pain during 150 mg bicalutamide monotherapy in adjuvant setting after RP. The effects of these 2 treatment options on patient hormonal status, QOL, sexual function and prostate specific antigen (PSA) relapse-free survival were also evaluated.

MATERIALS AND METHODS

Patient recruitment. This multicenter, randomized trial was done between January 2002 and February 2004. The study population consisted of men with histologically confirmed prostate cancer without distant metastases (T1-T3, any N, M0) and no evidence of current gynecomastia or breast pain. All patients had received RP with or without a nerve sparing (NS) procedure as primary therapy.

Exclusion criteria were previous hormonal therapy for PCa, metastatic disease, evidence of biochemical relapse after RP, any comorbid condition that could contraindicate trial drugs, or hematological (hemoglobin 10 gm/dl or less, white blood count less than 3,000/ μ l and platelet count less than 100,000/ μ l), renal (creatinine 2.2 ng/nl or greater) or liver (transaminase and bilirubin 50% of normal or greater) dysfunction.

The trial was performed in accordance with the 1964 Declaration of Helsinki. Each patient provided written informed consent. The protocol was approved by the ethics committee at each participating center.

Study design. Treatment was assigned on a randomized basis according to a 1:1:1 ratio. Randomization was performed centrally at Pascale Cancer Institute of Naples using a stratified, permuted randomization algorithm that was balanced within institutions. Stratification factors were disease stage (T1-T2 vs T3), NS procedure (yes vs no), lymph node involvement (N+ vs N- vs NX), Gleason score (less than 7 vs 7 or greater) and PSA (less than 10 vs 10 ng/ml or greater). All randomly assigned patients were included in efficacy and safety analyses.

All patients were divided into 3 groups (fig. 1). Group 1 patients received only 150 mg bicalutamide daily. Those presenting a gynecomastia score of 3–4 or moderate-severe breast pain were successively randomized to receive 10 mg tamoxifen daily for 24 weeks or a single 12 Gy dose of RT. Group 2 patients were treated with 150 mg bicalutamide daily and 10 mg tamoxifen daily for 24 weeks. Group 3 patients were treated with 150 mg bicalutamide daily and a single 12 Gy dose of RT. RT was administered as an electron beam directed to irradiate a 5 cm diameter circle of tissue centered around each nipple.

Oncological followup. Physical examination, hematology and serum biochemistry evaluations, including total PSA, were performed every 3 months. Radiological assessments, ie computerized tomography, bone scan, abdominal ultrasonography and chest x-ray, were performed when disease progression was suspected based on PSA. PSA progression was defined as 2 consecutive PSA increases (greater than 0.04 ng/ml).

Gynecomastia/breast pain assessment. Calipers were used to measure gynecomastia. The severity of gynecomastia was scored based on the largest diameter, including grade 1–2 or less, grade 2—between 2 and 4, grade 3—between 4 and 6, and grade 4—greater than 6 cm. Breast pain was evaluated via direct patient questioning at each visit. It was arbitrarily scored according to severity as none, mild, moderate or severe. Gynecomastia and breast pain were evaluated monthly.

QOL assessment. QOL was evaluated using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire, which was developed by the EORTC to measure QOL in patients with cancer in clinical trials.⁹ The questionnaire was administered at baseline and at 3-month intervals during treatment.

Erectile function assessment. Erectile function was evaluated only in patients who had undergone NS RP using the abridged 5 item version of the International Index of Erectile Function (IIEF-5) questionnaire.¹⁰ The study population consisted only of patients with normal erectile function (score 21 to 25) or mild erectile dysfunction (score 15 to 20), as assessed before surgery. In these patients rehabilitation therapy was

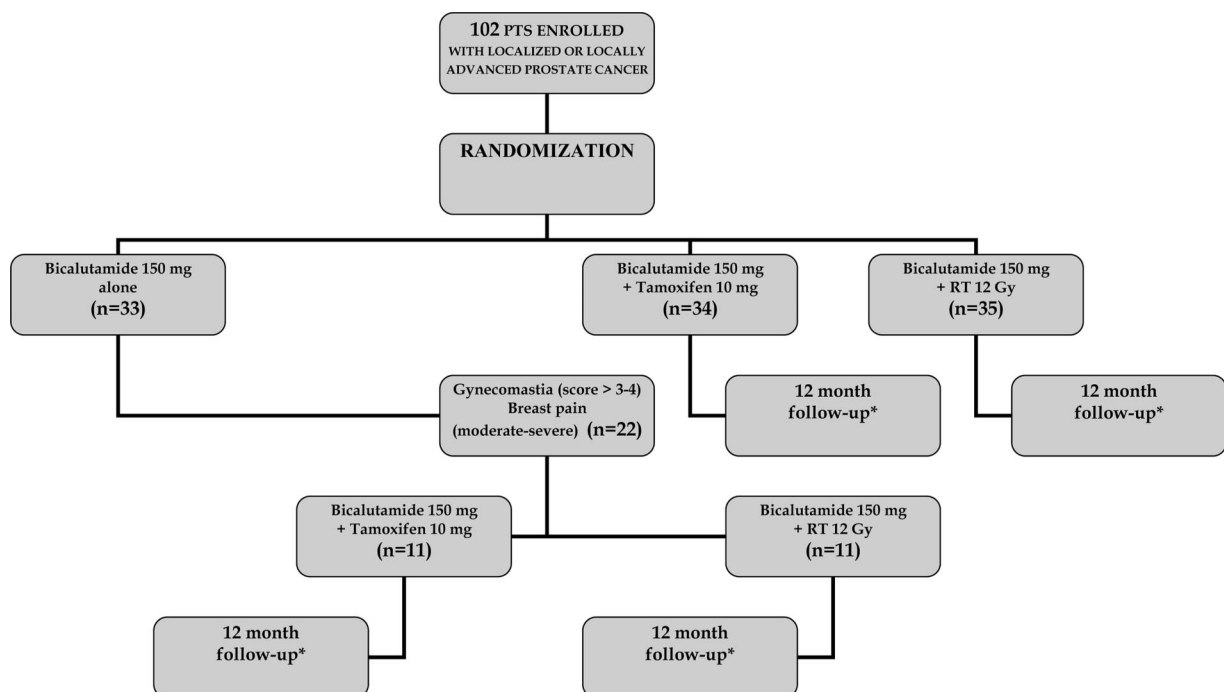


FIG. 1. Study design. Asterisk indicates monthly assessment with breast pain/gynecomastia evaluations, and 3-month assessment with PSA, laboratory examinations, QOL and IIEF-5 questionnaires.

TABLE 1. Patient demographics

	Group 1	Group 2	Group 3	Totals
No. pts	33	34	35	102
Age:				
Median	65.5	67.5	67.5	66.8
Range	50–75	57–74	50–73	50–75
No. stage:				
T1–2	22	22	22	66
T3	11	12	13	36
No. Gleason score:				
Less than 7	20	20	21	61
7 or Greater	13	14	14	41
No. PSA before RP (ng/ml):				
Less than 10	20	20	22	62
10 or Greater	13	14	13	40
No. node status:				
N+	1	2	2	5
N–	25	26	26	77
Nx	7	6	7	20
No. RP:				
NS	22	23	22	67
No NS	11	11	13	35

tween groups 1 and 2, and 1 and 3. PSA relapse-free survival was estimated with the Kaplan-Meier product limit method.¹¹ All p values are 2-sided and only p ≤0.05 is shown in the tables.

RESULTS

Overall 102 patients were randomized and included in the analysis. Patients and disease characteristics were well balanced among treatment groups (table 1). Minimum followup was 12 months (median 26, range 13 to 35) in all patients.

Efficacy. Figure 2 shows the incidence of grade 3–4 gynecomastia and moderate-severe breast pain after 6 months in each group. In group 1, 67% of patients had gynecomastia compared with 8% in group 2 and 34% in group 3. The difference was statistically significant between groups 1 and 2 (OR 0.12, 95% CI 0.10 to 0.15, p <0.001), and groups 1 and 3 (OR 0.52, 95% CI 0.49 to 0.54, p <0.01). Breast pain was more frequent in group 1 than in groups 2 and 3 (58% vs 7% and 30%, respectively). Differences in breast pain were statistically significant between groups 1 and 2 (OR 0.13, 95% CI 0.10 to 0.16, p <0.001), and groups 1 and 3 (OR 0.44, 95% CI 0.41 to 0.47, p <0.025).

Considering that 67% and 58% of group 1 patients had grade 3–4 gynecomastia and breast pain, respectively, 22 were successively randomized to receive tamoxifen (11) or RT (11). These patients included 19 with breast pain who were successively treated with tamoxifen (10) or RT (9).

A significant decrease in gynecomastia was achieved in patients receiving tamoxifen (p <0.05). In fact, after 6 and 9 months gynecomastia was reported in only 1 of 11 of these patients (9%), while 6 of 11 (54%) treated with RT still reported gynecomastia (fig. 3). Figure 4 shows breast pain relief results. A higher decrease was reported by patients in the tamoxifen group than in the RT group (p <0.05). In fact, after 6 and 9 months breast pain were reported in only 2 of 10

started at randomization using intracavernous injection with 10 µg alprostadil twice weekly for month 1 and with type 5 phosphodiesterase inhibitors thereafter at the maximum dose available, ingested on demand. Patients were encouraged to have sexual activity. The IIEF-5 questionnaire was administered at baseline (at randomization) and at 3-month intervals during treatment.

Pharmacodynamic assessment. Blood samples were obtained at baseline, and 3 and 6 months, Testosterone, free testosterone and prolactin were assessed by radioimmunoassay.

Statistical methods. The chi-square and Fisher’s exact tests were used to compare groups in respect to the incidence of gynecomastia, breast pain, adverse effects, QOL and IIEF-5 scores, and pharmacodynamics, showing the OR be-

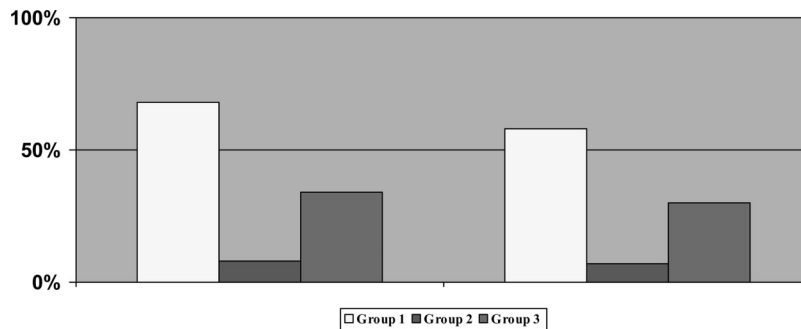


FIG. 2. Incidence of grade 3–4 gynecomastia (left) and moderate-severe breast pain (right) in 3 groups after 6 months. Differences in gynecomastia incidence were significant between groups 1 and 2 (OR 0.12, 95% CI 0.10 to 0.15, p <0.001), and groups 1 and 3 (OR 0.52, 95% CI 0.49 to 0.54, p <0.01). Differences in breast pain were statistically significant between groups 1 and 2 (OR 0.13, 95% CI 0.10 to 0.16, p <0.001) and groups 1 and 3 (OR 0.44, 95% CI 0.41 to 0.47, p <0.025).

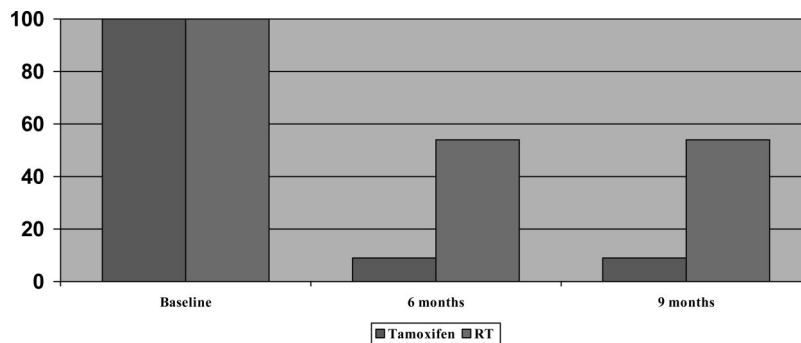


FIG. 3. Results of tamoxifen treatment or RT in 22 group 1 patients who had gynecomastia. Significant decrease in gynecomastia was noted in patients receiving tamoxifen (p <0.05).

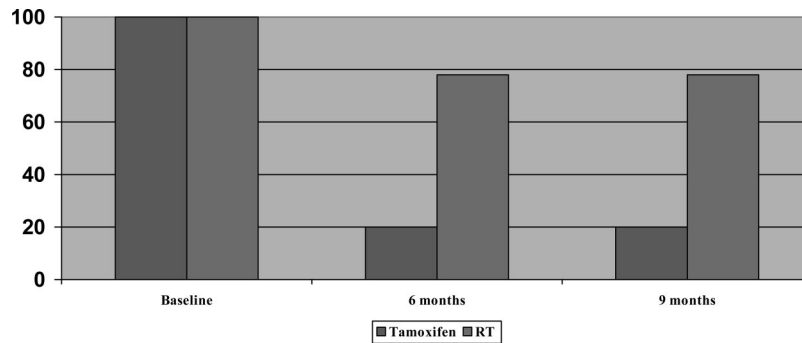


FIG. 4. Results of tamoxifen treatment or RT in 19 group 1 patients who had moderate-severe breast pain. Breast pain was more decreased in tamoxifen group ($p < 0.05$).

TABLE 2. Side effects

Side Effects	% Group 1	% Group 2	% Group 3
No. pts	33	34	35
Rash/nipple erythema*	31	3	40
Skin irritation*	0	0	40
Pruritis	3	6	3
Anemia	0	2	0
Fever	0	2	2
Myelotoxicity	2	0	4
Asthenia	3	3	6
Cardiovascular events	3	6	6
Neurological events	3	3	3
Constipation	6	9	6
Diarrhea	6	6	6
Hot flashes	6	6	6

* Difference among groups statistically significant ($p < 0.05$).

men (20%) receiving tamoxifen, while 7 of 9 (78%) treated with RT still reported breast pain.

Adverse events. Treatments were well tolerated in the 3 groups (table 2). All RT related adverse events resolved and were short-lived with a median duration of 4 weeks.

QOL. Figure 5 shows global health scores in the 2 groups. Table 3 lists functional and symptom scales only in the 2 prevention arms, ie groups 2 and 3. Those data showed no differences between the groups.

Erectile function. A total of 52 patients were included in the analysis of sexual function. Figure 6 lists IIEF-5 scores. We found an increase in mean IIEF-5 scores at 6 and 12 months in all 3 groups without any significant differences among them.

Pharmacodynamics. Testosterone increased in all groups at 6 months without differences among the groups (fig. 7). Similarly free testosterone increased at the same time in

patients in groups 1 ($p < 0.05$) and 3 ($p < 0.05$), while in group 2 patients it remained substantially unchanged (fig. 8). Prolactin remained unchanged in groups 1 and 3, whereas there was a trend toward decreased levels in group 2 ($p < 0.065$, fig. 9).

PSA relapse. Overall 88% of the patients were disease-free at a median followup of 26 months (range 12 to 35). Figure 10 shows PSA relapse-free survival according to the Kaplan-Meier estimate in the study population. It seems that there were no differences among the 3 groups since there were 4 PSA relapses in each of groups 1 to 3.

DISCUSSION

Recently the large international EPC program indicated the progression-free survival benefits of immediate 150 mg bicalutamide treatment given in addition to standard care (RP, RT or watchful waiting) compared with standard care alone in patients with locally advanced PCa.⁶ Gynecomastia and breast pain are commonly reported adverse events of bicalutamide monotherapy and they may cause some patients to withdraw from treatment. Several interventions have been used as prevention, including surgery, hormone therapy and radiation.^{7,8}

Data from old studies of patients with PCa who were treated with the estrogen antagonist tamoxifen⁷ are today supported by recently published trials confirming that hormonal treatment can be used to restore the balance of estrogen and androgen.^{12,13} Boccardo¹² and Saltzstein¹³ et al recently reported 2 randomized trials of the role of tamoxifen and anastrozole for the prevention of gynecomastia and breast pain.

Studies of prophylactic breast irradiation before estrogen or antiandrogen therapy have shown success in a high pro-

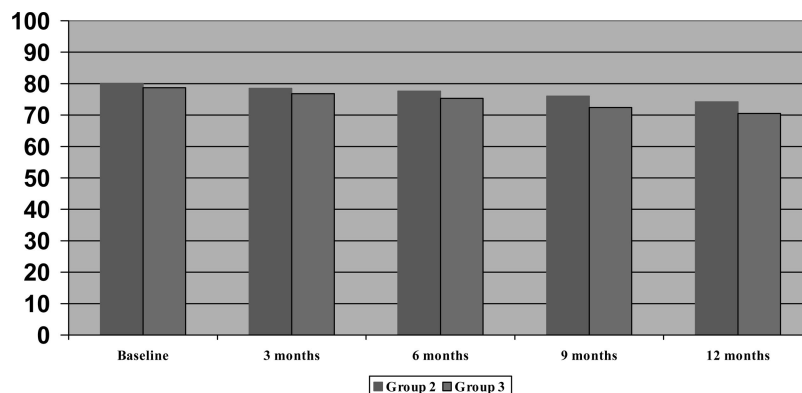


FIG. 5. Mean EORTC QLQ-C30 global health scores in 2 prevention arms (data presented as mean value). Score range was 1—very poor to 7—excellent. For analysis raw questionnaire scores were transformed into 100 point scale. Calculated scores were 0 to 100 with higher scores representing higher level of functioning.

TABLE 3. EORTC QLQ-C30 functional and symptom scales in 2 prevention groups

Item	Mean Group 2					Mean Group 3				
	Baseline	3 Mos	6 Mos	9 Mos	12 Mos	Baseline	3 Mos	6 Mos	9 Mos	12 Mos
Functional scales:										
Physical	84.2	80.2	79.2	78	77.4	83.8	82.2	81.1	78.3	77.6
Role	77.4	77.2	76.5	76.7	76.1	76.9	76.4	75.8	76.5	74.6
Emotional	79.4	80.0	80.5	80.7	81.3	79.4	79.6	79.6	78.3	79.7
Cognitive	88.1	88.9	90.3	90.1	89.8	88.9	88.0	89.8	88.7	88.7
Social	76.6	76.0	76.5	76.3	76.0	76.2	75.9	75.5	75.2	75.3
Symptom scales:										
Fatigue	25.5	23.8	22.6	22.6	23.4	25.2	24.6	23.8	24.2	24.1
Pain	18.2	17.4	18.7	19.1	21.4	18.0	17.3	18.8	20.2	22.5
Sleep disturbance	24.4	24.0	25.4	25.7	26.0	24.2	24.3	25.9	26.8	26.6
Constipation	22.6	21.8	21.6	22.0	22.8	23.1	22.3	22.8	23.0	23.6
Diarrhea	20.6	21.1	21.6	22.5	22.4	21.0	21.4	22.1	22.0	22.3

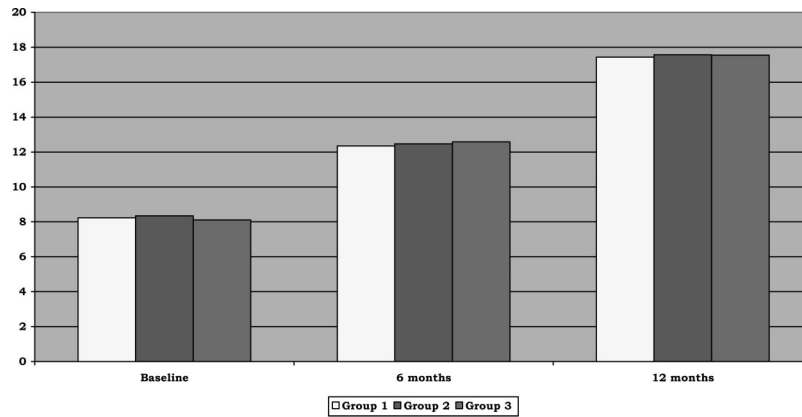


FIG. 6. Mean IIEF-5 scores in 52 evaluable patients. No significant differences were found between groups

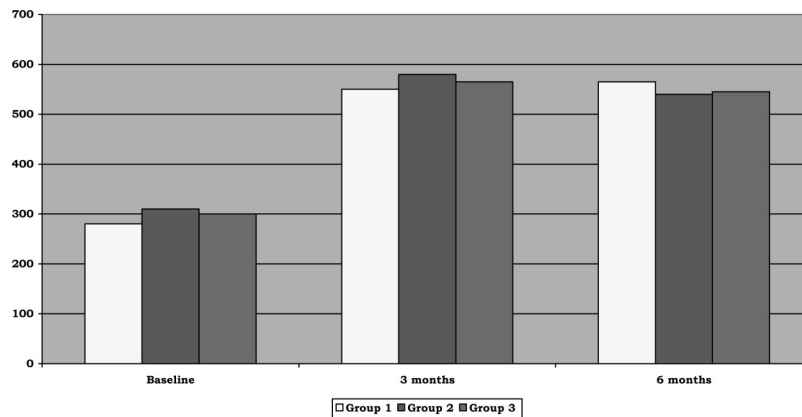


FIG. 7. Mean testosterone in ng/dl in 3 groups. No significant differences were found between groups

portion of patients.⁸ Tyrrell et al recently observed that prophylactic breast irradiation is an effective and well tolerated strategy for preventing bicalutamide induced gynecomastia.¹⁴ In this trial a single 10 Gy dose of electron beam RT significantly decreased the incidence of gynecomastia to 52% of patients. Van Poppel et al evaluated the efficacy of localized RT of 2, 6 Gy fractions in 51 patients receiving 150 mg bicalutamide.¹⁵ Therapeutic RT improved the intensity of bicalutamide induced gynecomastia and/or breast pain in approximately a third of patients.

To our knowledge no randomized trials comparing RT and hormone therapy as treatment and prevention options for bicalutamide induced gynecomastia and breast pain have been reported to date. We performed such a comparative study to investigate the efficacy of tamoxifen and RT for gynecomastia and breast pain due to bicalutamide mono-

therapy. The incidence of gynecomastia in the current study was similar to that in the EPC program but lower than that in the study of Boccardo et al (67%, 68.3% and 73%, respectively).¹²

Tamoxifen was more effective than RT for preventing bicalutamide induced gynecomastia and breast pain. Our positive findings are in agreement with prior studies with different treatment schedules, such as those of Boccardo¹² and Saltzstein¹³ et al, who administered 20 mg tamoxifen daily, and those of Eaton et al, who administered 20 mg weekly.¹⁶

The incidence of gynecomastia in our trial was 34% after RT, lower than that reported by Tyrrell et al, who noted gynecomastia in 52% of the RT group,¹⁴ and similar to that reported by Widmark et al, who observed gynecomastia in 28% of irradiated patients.¹⁷ These differences in the results can be probably attributed to the difference in the radiation

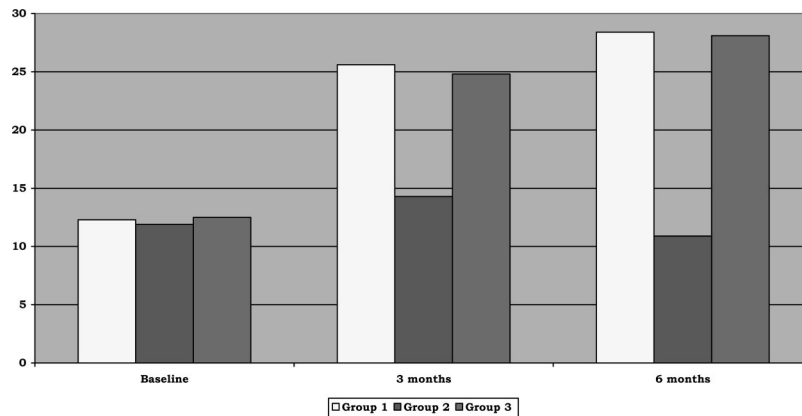


FIG. 8. Mean free testosterone in pg/ml in 3 groups. Level was increased in groups 1 and 3 (each $p < 0.05$), while in group 2 it was substantially unchanged.

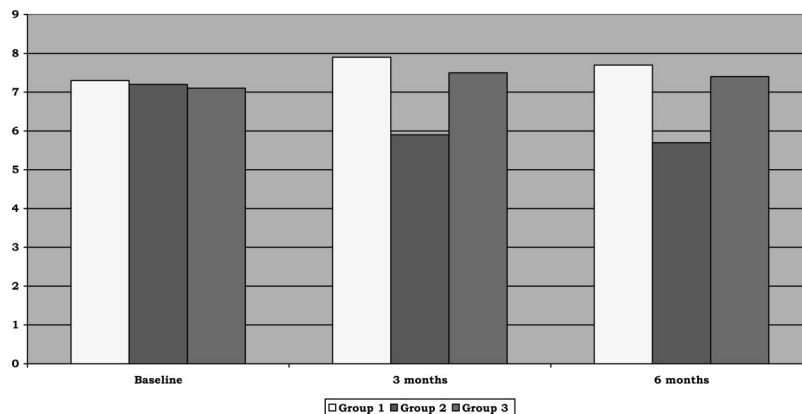


FIG. 9. Mean prolactin in ng/ml in 3 groups. Levels remained unchanged in groups 1 and 3, whereas there was trend toward decreased levels in group 2 ($p < 0.065$).

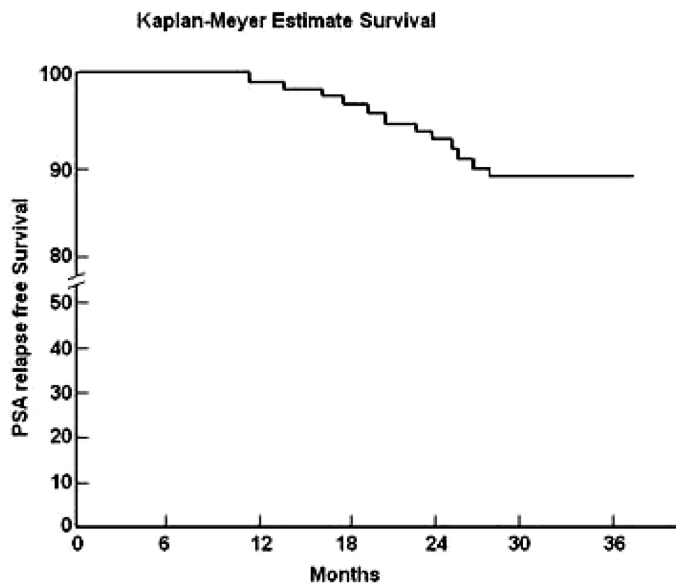


FIG. 10. PSA relapse-free survival according to Kaplan-Meier estimate in study population.

dose. We are aware that this is only an assumption. However, we did not have the possibility of performing a comparative study evaluating different radiation dosing or schedules. Moreover, to our knowledge there are no such comparative studies in the literature.

Considering that 22 of 33 patients (67%) in group 1 had

grade 3–4 gynecomastia, we further randomized them to receive tamoxifen or radiotherapy. Results were better with tamoxifen.

Our result is better than that reported by Van Poppel et al, who observed improvement in gynecomastia in a third of their patients.¹⁵ This difference may have been due to the difference in the number of RT fractions (12 Gy as a single fraction vs 2 fractions of 6 Gy each).¹⁸

RT related adverse events were seen in 40% of 35 patients and they were similar to those observed in previous studies,^{14,15} All were transient and resolved spontaneously. When designing this trial, the aim was to minimize the risk of adverse events and also minimize patient inconvenience by administering a single low dose of radiation. To date there have been no reports in the literature of secondary malignancy associated with a single 10 to 12 Gy dose.¹⁹

QOL evaluation and erectile function recovery after surgery were not negatively influenced by either treatment option.

The current study confirms that bicalutamide monotherapy causes an increase in testosterone and free testosterone. However, there were differences between groups in free testosterone at 6 months with significant increases in groups 1 and 3 ($p < 0.05$ and $p < 0.05$ vs baseline, respectively) but not in the tamoxifen group. The maintenance of free testosterone in the tamoxifen group could suggest potential antitumor efficacy by antiestrogen.

The use of tamoxifen in prostate cancer is experimental and it is unclear what influence tamoxifen could have on progression and survival in these patients. For this question this supposed antitumor efficacy currently needs confirma-

tion. In this respect after 26 months of median followup only 12 relapses were observed. It is reassuring that no differences in PSA relapse were recorded among the 3 groups.

CONCLUSIONS

Gynecomastia and breast pain induced by bicalutamide monotherapy after RP can be prevented and treated. Tamoxifen has shown to be more effective than RT in this setting without increasing adverse events and without compromising QOL, erection recovery after surgery and PSA relapse-free survival. However, the results of our study are preliminary and they should be considered with caution. More appropriate trials are needed to investigate the safety and efficacy of tamoxifen in combination with bicalutamide in patients with PCA.

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