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DOES PROPHYLACTIC BREAST IRRADIATION PREVENT ANTIANDROGEN-INDUCED GYNECOMASTIA? EVALUATION OF 253 PATIENTS IN THE RANDOMIZED SCANDINAVIAN TRIAL SPCG-7/SFUO-3

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ABSTRACT

Objectives. To examine the development of antiandrogen-induced gynecomastia and breast tenderness in the first 253 patients in a randomized Scandinavian trial (SPCG-7/SFUO-3) with a 12-month complete follow-up evaluation performed by both doctors and patients.

Methods. In this study, the treating doctor and patient decided whether prophylactic irradiation (RT) of the breast should be given to prevent antiandrogen-induced gynecomastia. At each visit, the doctor evaluated the occurrence of gynecomastia and breast tenderness. Questions about gynecomastia and breast tenderness were also included in the study quality-of-life questionnaire (Prostate Cancer Symptom Scale).

Results. Mammary RT with mostly single fraction (12 to 15 Gy) electrons was given to 174 (69%) of the 253 evaluated patients. At the 1-year follow-up visit, the doctor evaluations indicated some form of gynecomastia in 71% and 28% ($P < 0.001$) of the nonirradiated (no-RT) and irradiated (RT) patients, respectively. The patient evaluations at 1 year showed some form of breast enlargement in 78% and 44% ($P < 0.001$) of the no-RT and RT patients, respectively. The doctors reported some form of breast tenderness at 1 year in 75% and 43% ($P < 0.001$) of the no-RT and RT patients, respectively. The patient evaluations of breast tenderness show an expected significant increase in the RT arm at the 3-month follow-up, which was probably due to skin reactions. At 1 year, significantly more patients who marked "very much" on the Prostate Cancer Symptom Scale were seen in the no-RT group. A weak correlation between the doctors' and patients' detection of breast problems was observed.

Conclusions. The results show that, with high significance, prophylactic RT of the breast decreases the risk of antiandrogen-induced gynecomastia and breast tenderness. UROLOGY **61:** 145–151, 2003. © 2003, Elsevier Science Inc.

Gynecomastia is a condition that increases the proliferation of the glandular part of the male breast and is probably caused by an increase in the ratio of estrogen to androgen activity.[1] Estrogen treatment of prostate cancer often causes gynecomastia; 60% to 70% of the patients develop this problem.[2–4] Today, an increased number of patients with prostate cancer are treated with nonsteroidal antiandrogens (bicalutamide, flutamide, nilutamide). The development of gynecomastia after antiandrogen treatment is an increasing problem; 40% to 80% of these patients develop gynecomastia.[4–6]

The use of ionizing radiation to prevent breast enlargement in experimental animals was demonstrated in the early 1900s.[7,8] In addition, it was accidentally discovered that hypoplasia or aplasia of the female breast occurred after roentgen or radiotherapy (RT) of the breast in childhood,[9,10]

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which showed that RT could prevent breast enlargement.

In 1962, Larsson and Sundbom[11] published the first results of breast RT to prevent estrogen-induced gynecomastia in men with prostate cancer. Two weeks before the start of estrogen treatment, they gave 10 to 15 Gy with 190 kV, 0.5-Cu filter to the right breast, and the left breast was sham irradiated. In the RT-treated breast, no gynecomastia developed within 6 months. In the left, sham-treated breast, however, 4 of 6 patients developed gynecomastia. One patient later underwent surgery 5 months after RT after developing a fivefold increase in breast mammary gland volume in the untreated breast. Histologic examination showed a clear reduction in the number of ducts in the irradiated breast compared with the sham-treated control breast. Less effect was seen on the epithelium. Alfthan and Kettunen[12] showed a similar beneficial effect of RT to prevent estrogen-induced gynecomastia. They also showed that RT was less effective when started 1 or 4 months after the beginning of estrogen treatment.

In the Radiation Therapy Oncology Group 8307 study, Pilepich and coworkers[13] showed that if no prophylactic breast RT was given, 55% of estrogen-treated patients (diethylstilbestrol) developed gynecomastia; only 7% in the progesterone (megestrol) arm developed gynecomastia. Estrogen-induced gynecomastia was slightly lower than reported by some.[2–4] The differences could have been due to varying definitions of gynecomastia.

Waterfall and Glaser[14] showed in a dose-response study that 9 Gy could prevent estrogen-induced gynecomastia. A very low frequency of side effects was reported at 4 years of follow-up,[15] showing no difference in efficacy between 12 and 15 Gy.

Chou and coworkers[16] reported a good effect on pain in established gynecomastia (mammalgia) with almost 100% complete relief of pain when evaluated 6 months after treatment. Regarding the effect of RT on established gynecomastia, only 3 of 7 patients reported a significant decrease in volume. Two sex offenders treated with cyproterone acetate for a few months developed gynecomastia and breast tenderness. Irradiation prevented further development of gynecomastia and reduced the pain and tenderness.[17]

During the late 1990s, antiandrogens were introduced as monotherapy for the treatment of prostate cancer. Gynecomastia developed in about 60% of the patients, and it has become one of the major obstacles to the treatment of prostate cancer with antiandrogens (see Tyrrell[18] and McLeod and Iversen[1]).

The present study evaluated whether mammary RT can prevent the development of antiandrogen (flutamide)-induced gynecomastia in patients participating in a Scandinavian trial (SPCG-7/SFUO-3) of locally advanced prostate carcinoma.

MATERIAL AND METHODS

Patients

In the SPCG-7/SFUO-3 trial, all patients with locally advanced, nonmetastasized prostate cancer were treated with 3 months of neoadjuvant total androgen block (TAB), Procren Depot (leprolin) 11.25 mg, and Eulexin (flutamide) 250 mg × 3. After 3 months of TAB treatment, all patients continued with antiandrogen treatment only until progression. In the randomized study, one arm was treated with RT to the prostate after the 3-month TAB period.

Because of the high risk of gynecomastia after antiandrogen treatment, it was recommended in the protocol that the patient should be given RT to the breast before starting hormonal treatment. The treating doctor and the patient, however, decided whether breast RT should be performed. By June 2000, 540 patients had been included in the study. Of these, 407 (75%) received RT to the breast. We chose to analyze only patients with a minimal follow-up of 1 year and 3 months from inclusion, which resulted in 335 patients by June 2000. For 264 (79%) of the 335 patients, complete information about gynecomastia and breast tenderness and information at specific follow-up times (3, 6, and 12 months) was available. Among the 264 patients with complete information, 185 (70%) were given RT to the breasts. For 11 of the 185 irradiated patients, the RT was given more than 1 month after the start of antiandrogen treatment. They were therefore excluded from the analysis, resulting in 253 patients (174 [69%] irradiated and 79 [31%] not irradiated) available for analysis. Fourteen of 16 units used electrons (6 to 9 MeV) and 2 units used the roentgen (190 kV plus 0.5 mm Cu). The targets were mostly between 4 and 6 cm in diameter. Ten of 16 RT units gave 12 to 15 Gy, mostly 15 Gy as a single fraction; the others gave the same dose in 3 fractions.

The ethics committee approved the study, and the patients gave informed consent to participate in the study.

Evaluation of Side Effects

The treating physician evaluated the grade of gynecomastia and breast tenderness according to the definitions presented in Table I.

In the study quality-of-life questionnaire, the Prostate Cancer Symptom Scale (PCSS[19]), the patients were asked two questions regarding their breast symptoms: "Have your breasts increased in size?" and "Have you felt tenderness in your breasts?" The answer was marked on a 10-grade modified linear analog scale between 0 (not at all) and 10 (very much). No symptoms were recorded if the answer was marked as 1 or less, and if the answers were marked greater than 1 to 10, the marks were divided into three equal parts: a little, quite a bit, and very much.

Statistical Analysis

To test for different distributions of gynecomastia and breast tenderness between the nonirradiated and irradiated patients, the likelihood ratio chi-square test was used. To measure the degree of agreement between the doctor and patient evaluations, kappa values were computed.

RESULTS

This study included 253 patients, 174 RT patients and 79 no-RT patients. All these patients had

TABLE I. ***Distribution of gynecomastia and breast tenderness in study population***

	Entrance		3 mo		6 mo		12 mo	
	no RT	RT	no RT	RT	no RT	RT	no RT	RT
Gynecomastia/breast enlargement								
Doctor evaluation								
None	79 (100)	170 (98)	68 (86)	150 (86)	41 (52)	131 (75)	23 (29)	126 (72)
Slight	0 (0)	4 (2)	9 (11)	21 (12)	32 (41)	31 (18)	40 (51)	33 (19)
Moderate	0 (0)	0 (0)	2 (3)	3 (2)	5 (6)	12 (7)	14 (18)	14 (8)
Severe	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	2 (3)	1 (1)
Total	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)
P value†	0.082		0.908		0.001		<0.001	
Patient evaluation								
None	77 (97)	165 (95)	63 (80)	122 (70)	45 (57)	93 (53)	17 (22)	97 (56)
A little	2 (3)	7 (4)	13 (16)	41 (24)	19 (24)	62 (36)	26 (33)	56 (32)
Quite a bit	0 (0)	2 (1)	3 (4)	9 (5)	12 (15)	17 (10)	17 (22)	16 (9)
Very much	0 (0)	0 (0)	0 (0)	2 (1)	3 (4)	2 (1)	19 (24)	5 (3)
Total	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)
P value†	0.387		0.290		0.133		<0.001	
Breast tenderness								
Doctor evaluation								
None	79 (100)	174 (100)	66 (84)	143 (82)	38 (48)	106 (61)	20 (25)	99 (57)
Sometimes	0 (0)	0 (0)	13 (16)	26 (15)	33 (42)	55 (32)	44 (56)	54 (31)
Often, but tolerable	0 (0)	0 (0)	0 (0)	3 (2)	7 (9)	11 (6)	10 (13)	17 (10)
Always, but tolerable	0 (0)	0 (0)	0 (0)	2 (1)	1 (1)	2 (1)	5* (6)	4 (2)
Total	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)
P value†	–		0.280		0.301		<0.001	
Patient evaluation								
None	79 (100)	163 (94)	74 (94)	107 (61)	38 (48)	65 (37)	12 (15)	63 (36)
A little	0 (0)	8 (5)	2 (3)	34 (20)	11 (14)	57 (33)	17 (22)	53 (30)
Quite a bit	0 (0)	2 (1)	3 (4)	27 (16)	19 (24)	38 (22)	21 (27)	38 (22)
Very much	0 (0)	1 (1)	0 (0)	6 (3)	11 (14)	14 (8)	29 (37)	20 (11)
Total	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)	79 (100)	174 (100)
P value†	0.037		<0.001		0.009		<0.001	

KEY: RT = radiotherapy.
Data presented as the number of patients, with the percentage in parentheses.
** Included 1 patient with very troubling breast tenderness.*
† Test for different side-effect distributions between no-RT and RT patients, likelihood-ratio chi-square test.

complete data on the doctor's evaluation, as well as complete data to the questions about breast enlargement and breast tenderness in the PCSS questionnaire from the beginning of treatment and at the 3, 6, and 12-month follow-up visits.

GYNECOMASTIA

As early as 6 months after the start of hormonal therapy, 1 to 2 months after testosterone recovery, the doctors' reports showed a significant difference in the development of gynecomastia. By this time, a slight increase was seen in 41% in the no-RT group compared with 18% in the RT group. At 12 months, the difference in the development of gynecomastia was more than doubled in the no-RT group compared with the RT group. By 12 months, the doctor evaluations reported some form of gynecomastia in 71% of the no-RT patients and 28% of the RT patients (Fig. 1A). During the first 2 years, serum testosterone was measured, and no difference in serum testosterone recovery was seen between patients who developed gynecomastia and those who did not (also in no-RT patients).

Breast enlargement was evaluated by the patients with the question "Have your breasts increased in size?" No significant difference between the RT and no-RT patients was reported before the 12-month follow-up (Fig. 1B and Table I), although more serious problems were noted at the 6-month follow-up in the no-RT group. By 12 months, 78% of patients in the no-RT group and 44% in the RT group ($P < 0.001$) reported some form of breast enlargement (greater than 1 on the 10-grade scale; Fig. 1B). In the no-RT patients, 46% reported "quite a bit" or "very much" breast enlargement compared with 12% of the RT patients.

BREAST TENDERNESS

Increased breast tenderness was reported by the doctor at the 12-month follow-up in 75% of the

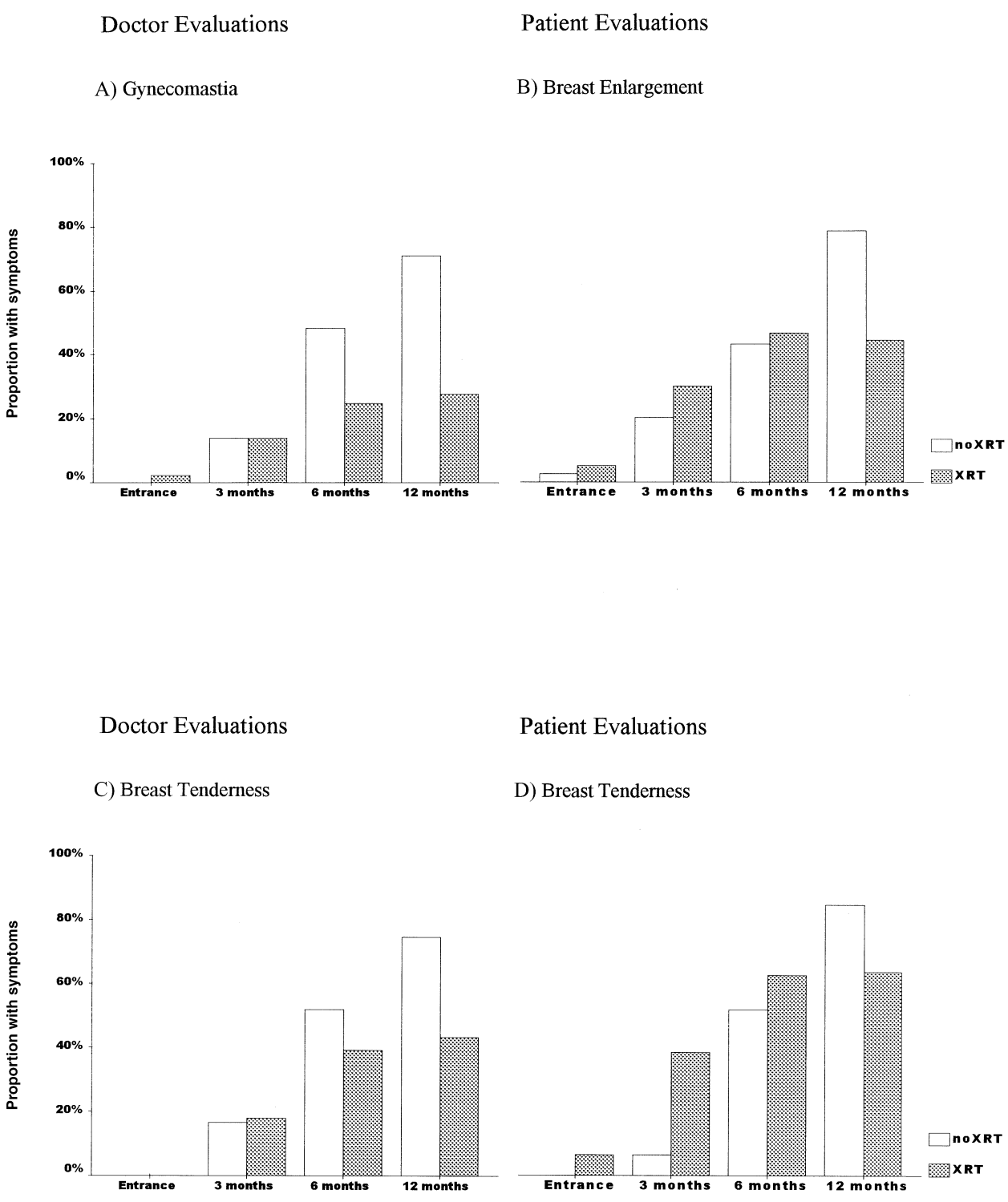

FIGURE 1. *Number of patients with gynecomastia according to (A) doctor and (B) patient evaluations of breast enlargement. Number of patients with breast tenderness according to (C) doctor and (D) patient evaluations at the beginning of the study and at 3, 6, and 12 months of follow-up after the start of hormonal treatment. Bars indicate percentage of no-RT (open) and RT (shaded) patients.*

no-RT patients compared with 43% of the RT patients ($P < 0.001$, Fig. 1C).

By using the question "Have you felt tenderness in your breast?" the patient evaluated breast tenderness (Fig. 1D and Table I). Because of RT-induced skin reactions (soreness) in many patients, more problems were reported in the RT arm (39%) than in the no-RT arm (6%) at the 3-month follow-up evaluation. At the 12-month follow-up assessment, more than three times as many patients reported "very much" problems in the no-RT group than in the RT group. At the 12-month fol-

low-up evaluation, some form of breast tenderness (Fig. 1D) was reported by 85% of the no-RT and 64% of the RT patients.

Agreement Between Doctor and Patient Evaluations

The level of agreement between the doctor and patient evaluations was higher than expected by chance, although the level of agreement was rather poor when all grades were compared (kappa value at the 12-month follow-up of 0.24 and 0.16 for gynecomastia and breast tenderness, respectively). However, when the comparison only included whether any symptoms were present, the kappa value at the 12-month follow-up was 0.495 and 0.465 for gynecomastia and breast tenderness, respectively.

COMMENT

To date, this is the only study with both doctor and patient prospective evaluations of antiandrogen-induced gynecomastia that investigated the efficacy of RT in the prevention of breast problems. The present study showed an obvious effect of prophylactic RT, with a significant decrease in gynecomastia/breast enlargement and breast tenderness independently evaluated by both the treating physician and the patient using a symptom scale (PCSS).

Gynecomastia

A small increase in breast problems during the first 3 months was seen in the RT patients; some patients experienced skin irritation (soreness) at the 3-month follow-up visit because of the RT. At the 12-month follow-up assessment, the doctors reported that more than 70% of the no-RT group (compared with less than 30% in the RT group) had some kind of breast enlargement. In the present study, RT was an efficient technique for the prevention of the development of antiandrogen-induced gynecomastia. Similar rates of prevention were also reported in studies using RT to prevent estrogen-induced gynecomastia,[12,14–16,20] suggesting a similar degree of efficacy of prophylactic RT for the prevention of antiandrogen-induced gynecomastia as for estrogen-induced gynecomastia.

The use of antiestrogens (tamoxifen) to prevent antiandrogen-induced gynecomastia has been tested in 6 cases and showed a good prophylaxis in these cases.[21] Whether more potent second-generation aromatase inhibitors will be efficient remains to be seen. Some concerns have been raised regarding the use of antiestrogens because of their influence on prostate cancer and because their interaction with the antiandrogens might influence the inhibitory effect on cancer.[1]

The present results suggest that when the antiandrogen-treated patients recover after TAB and testosterone increase, the difference in breast problems between the RT and no-RT groups becomes obvious. During the TAB period, when no testosterone is available, very few problems with the breasts are seen. Recovery of normal testosterone was accomplished in 85% of the patients at 6 months. With normal testosterone levels, but under continuous antiandrogen treatment, the conversion of testosterone to estrogen will occur and, as shown in this study, will clearly influence the development of gynecomastia and breast tenderness. By 6 months, a significant difference in breast enlargement was detected by the doctors, but was not reported by the patients.

In the present study, the doctor evaluations of gynecomastia seemed to be more sensitive than the patient evaluations of breast enlargement. This was probably because of the difficulty for the patient to notice the discrepancy between breast enlargement and the development of real breast tissue (gynecomastia). On the whole, the correlation between the doctor and the patient was good as to whether a breast problem was present, but not so obvious when grading the magnitude of the problem was compared.

Breast Tenderness

The doctor detected a significant difference in breast tenderness between the no-RT and RT patients only at the 12-month follow-up. With the patient evaluation in the PCSS questionnaire, higher sensitivity was seen. The RT patients reported significantly more problems at the 3-month follow-up than did the no-RT patients. This was probably because of the well-known acute side effects (ie, skin reactions and soreness) after breast RT. However, at the 12-month follow-up, 85% of the no-RT patients compared with 64% of the RT patients ($P < 0.001$) reported some form of breast tenderness. Fass and coworkers[15] reported no mammalgia in 83% of patients after prophylactic RT before diethylstilbestrol treatment. However, mammalgia is probably more comparable with "very much" breast tenderness in the present study.

RT to prevent breast problems after antiandrogen (and estrogen) treatment has high efficacy and is of clinical benefit. However, the efficacy seems to be higher in preventing gynecomastia than in preventing breast tenderness. Longer follow-up and more patients will add additional information. Further studies should also evaluate the optimal dose, fractionation, and volume in relation to side effects. A small risk of secondary malignancies has been reported in children after RT for pubertal gynecomastia.[22] Patients with estrogen-treated me-

tastasized prostate cancer who underwent breast RT probably did not live long enough for the detection of secondary malignancies; however, the present use of antiandrogens in nonmetastasized men might have the potential to show this risk.

CONCLUSIONS

The results of the present study showed a clear prophylactic effect of breast RT for the prevention of gynecomastia and breast tenderness in patients treated with antiandrogen (monotherapy) for a longer time. Increased use of antiandrogens for the treatment of patients with prostate cancer could over time create severe problems for the patients. Prophylactic RT of the breasts is a simple treatment with few side effects that will undoubtedly contribute to a better quality of life for these patients.

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APPENDIX

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