ELSEVIER

# GYNECOMASTIA IN PATIENTS WITH PROSTATE CANCER: A REVIEW OF TREATMENT OPTIONS

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Gynecomastia is a condition characterized by proliferation of the glandular component of the male breast and is caused by an increase in the ratio of estrogen to androgen activity. The condition occurs mainly in three age groups: newborn, adolescent, and elderly men. The prevalence of gynecomastia in men (aged 17 years or older) varies between 32% and 65% in different studies,[1] with a higher prevalence of 72% found in hospitalized male veterans (aged 50 to 69 years).[2] However, gynecomastia can also be caused pathologically, for instance as a side effect of drug treatment, chronic disease (eg, chronic liver disease due to alcohol abuse) or, occasionally, a tumor (eg, choriocarcinoma). To date, approximately 10% of cases are drug induced, with a wide range of drugs being implicated in the pathogenesis, including compounds that increase estrogenic or inhibit androgenic activity.[1]

## DIAGNOSIS OF GYNECOMASTIA

In the early stages of gynecomastia, there is a proliferation of the glandular ducts, epithelial hyperplasia, expansion of stroma, increased vascularity, and periductal edema. However, when gynecomastia has been present for a substantial time, at least 1 year, a reduction in epithelial proliferation is seen, and hyalinization and fibrosis of the stroma occur—processes that are usually irreversible.

Although gynecomastia is common there is no consensus on which methods to use for defining and grading the severity of this condition. International agreement on grading of gynecomastia and definitions of response to treatment would greatly facilitate research in this field. The criteria used for diagnosis may vary between centers; for example, gynecomastia may be confirmed histologically or by palpation of a subareolar mass with a diameter of at least 2 cm.[1] Gynecomastia is often staged according to the Marshall Tanner breast stages for pubertal changes in girls.[3]

Gynecomastia usually presents as a firm disk of tissue underlying the nipple and is bilateral in most cases, although initially the condition may be apparent in one breast. Initially, patients should be examined physically to eliminate the possibility of carcinoma or pseudogynecomastia due to fat deposition. In addition, breast tenderness, breast and nipple pain, and the course of onset should be assessed. Awareness of the possible causes of gynecomastia and prompt recognition of the condition will enable early treatment before the irreversible processes of fibrosis and hyalinization occur. Treatment at such an early stage of the disorder may avoid unnecessary patient discomfort and distress, and improve the long-term cosmetic outcome.

## PROSTATE CANCER TREATMENTS ASSOCIATED WITH GYNECOMASTIA

The premise underlying endocrine therapy for prostate cancer is that testosterone stimulates the growth of the cancerous tissue. Therefore, the aim of treating prostate cancer patients with hormone manipulation is to eliminate circulating androgens, and/or to block their effects on cancer tissue. However, changes in the hormonal milieu induced by such manipulation can alter the ratio of circulating estrogens to androgens, and thereby increase the likelihood of developing gynecomastia. The effect of prostate cancer treatments on the estrogen-to-androgen balance is illustrated in Figure 1.

A simplified view of the hypothalamic–pituitary–gonadal axis controlling testosterone and estradiol secretion in male humans is shown in Figure 2. Luteinizing hormone-releasing hormone (LHRH) stimulates the secretion of luteinizing hormone

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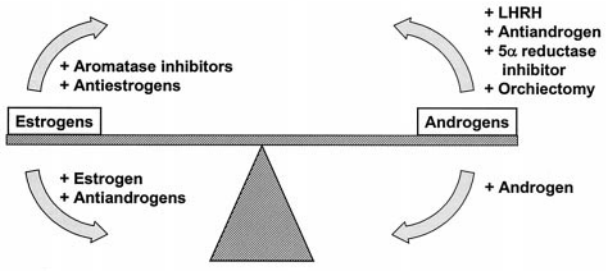


FIGURE 1. *The effect of prostate cancer treatments on the balance between circulating estrogens and androgens. An increase in the estrogen-to-androgen ratio may lead to gynecomastia.*

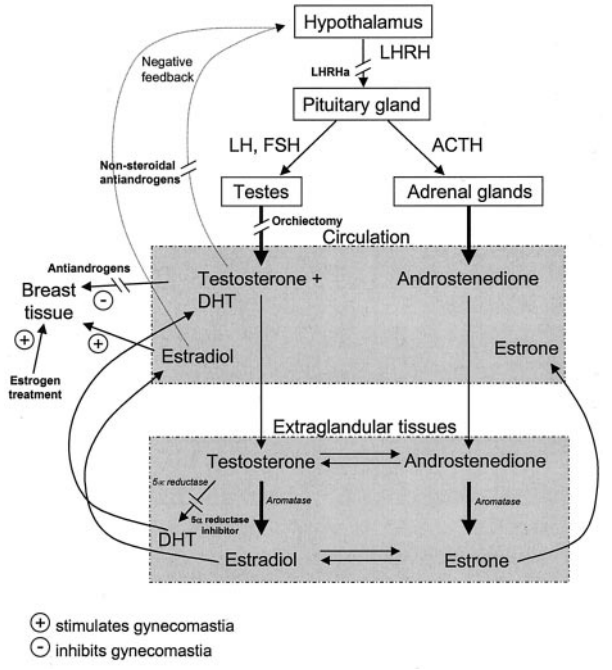


FIGURE 2. *Glandular and extraglandular origins and interrelations of the androgens, testosterone, DHT, and androstenedione, and the estrogens, estradiol and estrone, and their effect on breast tissue. The effect of prostate cancer treatments on these pathways is also shown. Thick arrows denote the major sources of the hormone.*

(LH), follicle-stimulating hormone (FSH), and adrenocorticotropic hormone (ACTH) from the pituitary gland, which stimulate the testes and adrenal glands to secrete androgens. Testosterone itself inhibits LHRH release through negative feedback at the hypothalamic level. Testosterone then undergoes reduction to 5α-dihydrotestosterone (DHT) (the intracellular mediator of most of its actions) or is aromatized peripherally to estradiol, in a ratio of approximately 100:1.

The range of incidences of gynecomastia following various treatments for prostate cancer is shown in Table I[4–18]; the varying incidence with a particular treatment option is most likely due to differences in diagnosis or reporting methods. Eliminating circulating testosterone by removing the primary source of testosterone (orchiectomy) or by blockade of LHRH receptors in the pituitary gland (LHRH agonists) increases the ratio of estrogen to androgen and can lead to gynecomastia in some patients with prostate cancer (Fig. 2). Following orchiectomy, estradiol is produced by the peripheral aromatization of plasma androstenedione to estrone and subsequent conversion to estradiol, with minimal formation of testosterone from androstenedione. Estrogen treatment directly stimulates the growth of breast tissue, often resulting in severe gynecomastia, and is associated with the highest incidence of gynecomastia. Both steroidal and nonsteroidal antiandrogens block androgenic activity at the breast, thereby removing an inhibitory effect on estrogenic stimulation. Moreover, nonsteroidal antiandrogens also block androgen receptors at a central level, inhibiting the negative feedback effect of circulating testosterone, thereby causing a reflex increase in levels of testosterone. This leads to higher estrogen levels, by peripheral aromatization.

## TREATMENT OF GYNECOMASTIA

Three forms of treatment have been used effectively to alleviate or prevent the development of gynecomastia and/or breast pain: radiation, surgery, and medical therapy.

### *Radiation*

A number of small studies, from as early as 1962, have shown that pretreatment with prophylactic irradiation effectively prevents gynecomastia in most patients (Table II[19–21]). A review of several small studies showed that 89% of patients with prostate cancer who received breast irradiation before estrogen treatment had no or minimal breast changes after such treatment.[19]

Radiation therapy can also provide effective relief from breast pain due to gynecomastia, although it has minimal effect on breast size (Table II[22,23]).

Two AstraZeneca trials have started recruiting patients to assess the efficacy and tolerability of radiotherapy, both prophylactically before treatment with bicalutamide and as a treatment after gynecomastia developed.

### *Surgery*

*Prophylaxis.* Surgical prophylaxis of gynecomastia has been described by a number of researchers.[24–26] In the largest series of observations, bilateral subareolar mastectomy prevented gynecomastia in 84% of 78 patients with prostate cancer receiving estrogen therapy.[27]

**TABLE I.** *Incidence of gynecomastia following treatment for prostate cancer*

| Treatment | Reference | No. of Evaluable Patients | Incidence (%) |
|---|---|---|---|
| Orchiectomy | Iversen *et al.*[4] | 125 | 1 |
| | Robinson *et al.*[5] | 101 | 14 |
| | Denis *et al.*[6] | 149 | 8 |
| LHRH agonists | | | |
| Goserelin | Kaisary *et al.*[7] | 168 | 5* |
| | Tyrrell *et al.*[8] | 293 | 1 |
| Leuprolide | Crawford *et al.*[9] | 268 | 13 |
| | Rizzo *et al.*[10] | 44 | 16 |
| Buserelin | Klioze *et al.*[11] | 105 | 3 |
| Estrogens—DES | Pavone-Macaluso *et al.*[12] | 64 | 40† |
| | Robinson *et al.*[5] | 97 | 77 |
| | Chang *et al.*[13] | 42 | 74 |
| Nonsteroidal antiandrogens | | | |
| Bicalutamide | Iversen *et al.*[14] | 314 | 47 |
| Flutamide | Chang *et al.*[13] | 34 | 79 |
| | Narayan *et al.*[15] | 293 | 16 |
| | Oosterlinck *et al.*[16] | 75 | 49‡ |
| | Boccon-Gibod *et al.*[17] | 54 | 30 |
| Nilutamide | Decensi *et al.*[18] | 34 | 79 |
| Steroidal antiandrogens—CPA | Pavone-Macaluso *et al.*[12] | 75 | 6† |
| Combined androgen blockade | | | |
| Flutamide + orchiectomy | Oosterlinck *et al.*[16] | 196 | 14‡ |
| Flutamide + LHRHa | Crawford *et al.*[9] | 264 | 13 |
| | Denis *et al.*[6] | 153 | 22 |
| | Oosterlinck *et al.*[16] | 634 | 19‡ |

*KEY: LHRH = luteinizing hormone-releasing hormone; DES = diethylstilbestrol; CPA = cyproterone acetate.*
* *Breast swelling.*
† *Painful gynecomastia.*
‡ *Breast tenderness.*

*Treatment.* Most cases of gynecomastia can be surgically treated by a subcutaneous mastectomy through an areolar or periareolar incision, a procedure described by Webster.[28] More recently, liposuction to remove excess fatty tissue has been used as an adjunct to surgery to remove glandular tissue. Liposuction may also help the skin to contract, making skin excision necessary only in rare cases in which spontaneous postoperative contraction alone is unlikely to give a satisfactory result. This combined approach enables a smooth chest profile to be obtained and has been associated with a low incidence of postoperative complications and high levels of patient satisfaction.[29,30] Of 62 patients who were treated with such a combined approach, 37 (60%) were very satisfied with the result and 19 (31%) were satisfied.[30] Another recently employed technique, which may be used more widely in the future, is endoscope-assisted mastectomy, which offers the potential to reduce further scarring.[31]

### *Medical Therapy*

Androgens, antiestrogens, aromatase inhibitors, and danazol have been used to treat gynecomastia. However, there is a paucity of published literature and none of these hormonal treatments is registered for use in patients with gynecomastia. Of course, the use of androgens is not an option for patients with prostate cancer.

Antiestrogens should improve gynecomastia by blocking estrogen receptors in target tissues. Indeed, improvement of the signs and symptoms of gynecomastia with tamoxifen, an estrogen antagonist, has been described in several case studies (Table III).[32,34–36] However, only one of these studies included patients with gynecomastia resulting from treatment for prostate cancer.[35] In a larger study, complete regression of idiopathic gynecomastia was seen in 49 (80%) of the patients following treatment with tamoxifen.[33] A number of small studies have also described the use of the antiestrogen clomiphene citrate to treat pubertal gynecomastia with variable results (Table III).[37–39]

Aromatase inhibitors should alleviate gynecomastia by preventing the peripheral aromatization of circulating androgens to estrogens. Treatment with the aromatase inhibitor testolactone (a first generation inhibitor) did result in a decrease in breast size among 22 boys with pubertal gynecomastia (Table III).[40] Other reports on the use of testolactone in cases of gynecomastia tend to be in individual patients with inconclusive results.[41] A

**TABLE II.** *Studies using radiation therapy to prevent or treat gynecomastia*

| Reference | No. of Patients | Treatment for Prostate Cancer | Radiation Therapy | Efficacy Results |
|---|---|---|---|---|
| Prophylactic radiotherapy | | | | |
| Gagnon *et al.*[19] | 262 | Estrogen treatment | 800–1500 cGy prior to estrogen treatment | 234 of 262 (89%) no or minimal breast changes after pre-estrogen breast irradiation |
| Waterfall and Glaser[20] | 47 | Tetrasodium testestrol 100 mg TID or stilbestrol 5 mg TID for 2 weeks followed by stilbestrol 3 mg/day | 3 × 300 cGy on consecutive days prior to estrogen treatment (n = 27) | 17 of 20 (85%) in estrogen-only group developed gynecomastia within 4 weeks; only 3 of 27 (11%) in radiotherapy-pretreated group developed gynecomastia |
| Fass *et al.*[21] | 87 | Diethylstilbestrol | <1200 cGy (n = 5), 1200 cGy (n = 43), 1500 cGy (n = 39) just before or once hormone treatment had started | 67 of 87 (77%) no gynecomastia, 9 of 87 (10%) mild, 11 of 87 (13%) moderate, and 1 of 87 (1%) severe gynecomastia (follow-up ≥1 year); 72 of 87 (83%) no breast pain, 11 of 87 (13%) mild, and 4 of 87 (5%) moderate breast pain |
| Radiotherapy treatment | | | | |
| Chou *et al.*[22] | 11 | Diethylstilbestrol 1–4 mg QID | 2000 cGy in 5 fractions to 4000 cGy in 20 fractions for 1–22 (average 9.4) months after starting diethylstilbestrol (1 patient also received 1000 cGy of radiation 1 day before starting hormone treatment) | 3 of 11 (27%) significant reduction in breast size, 11 of 11 (100%) satisfactory pain relief (follow-up 1–60 months, average 27 months) |
| Alfthan and Kettunen[23] | 25 | Usually polyestradiol phosphate 40 or 80 mg once a month | 2375 cGy (16 patients) or 1425 cGy (9 patients) on the day that hormone treatment started (8 patients) or after the development of gynecomastia (1 month to 6 years after hormone treatment) | Effective relief of soreness and pain in all 17 patients who developed gynecomastia. Eight of 17 (47%) patients with gynecomastia experienced a reduction in breast size. Gynecomastia was prevented in all 8 patients who received prophylactic radiotherapy. |

KEY: *TID = three times a day; QID = four times a day.*

**TABLE III.** *Studies using anti-estrogens and aromatase inhibitors to treat gynecomastia*

| Reference | No. of Patients | Cause of Gynecomastia | Medical Therapy | Efficacy Results |
|---|---|---|---|---|
| Tamoxifen | | | | |
| Parker *et al.*[32] | 10 | Liver disease, alcoholism, or the use of drugs such as cimetidine or digoxin | Randomized, double-blind, crossover design, tamoxifen 10 mg once daily or placebo for 1 month each | 7 of 10 (70%) objective decrease in size of gynecomastia, significant reduction of −2.1 cm in breast diameter with tamoxifen treatment ($P < 0.01$); 4 of 4 (100%) men with painful or tender gynecomastia experienced pain releif within 2 weeks of beginning tamoxifen |
| Alagaratnam[33] | 61 | Idiopathic | Tamoxifen 20 mg/BID for 2 months followed by 10 mg BID if successful or surgery if unsuccessful | 49 of 61 (80%) complete remission of signs and symptoms of gynecomastia within 4 months (30 of 49 [61%] in 2 months). |
| McDermott *et al.*[34] | 6 | Idiopathic | Randomized, crossover design, tamoxifen 10 mg BID or placebo for 2–4 months each | 5 of 6 (83%) pain reduction while receiving tamoxifen ($P = 0.04$); 3 of 3 (100%) with Stage III (Marshall-Tanner grade) gynecomastia had complete resolution of gynecomastia, although no significant size reduction occurred in the 3 patients with Stage IV disease |
| Staiman and Lowe[35] | 6 | Flutamide 250 mg BID and finasteride 5 mg BID for prostate cancer | Tamoxifen 10–30 mg once daily for 1 month | 6 of 6 (100%) pain alleviation, breast size remained stable but was considered less tensely enlarged |
| Serels and Melman[36] | 3 | Orchiectomy | Tamoxifen 10 mg BID | Gynecomastia resolved within 1 month |
| | | LHRH analogues for 2 years | Tamoxifen 10 mg BID | Improvement of gynecomastia and breast pain in ~1 month |
| | | Orchiectomy | Tamoxifen 10 mg once daily | Improvement of gynecomastia and breast pain symptoms within 6 weeks |
| Clomiphene citrate | | | | |
| Stepanas *et al.*[37] | 19 | Pubertal | Clomiphene citrate 50 mg/day for at least 8 weeks, reduced to alternate days if a measurable response | 18 of 19 (95%) breast size decreased with treatment; 8 of 18 (44%) satisfied with response (mean change in size 76%, $P < 0.01$) |
| LeRoith *et al.*[38] | 28 | Pubertal | Clomiphene citrate 100 mg/day for 6 months | 6 of 28 (21%) noncompliant; 14 of 22 (64%) no breast tissue detected; 8 of 22 (36%) no demonstrable change |
| Plourde *et al.*[39] | 12 | Pubertal | Clomiphene citrate 50 mg/day for 1–3 months | Mean breast size decreased by 0%–36%; in 5 of 12 (42%) breast size decreased by >20%; only 1 of 12 (8%) were satisfied with the reduction |
| Aromatase inhibitors | | | | |
| Zachmann *et al.*[40] | 22 | Pubertal | Testolactone 450 mg/day for 2–6 months | Mean breast gland diameter regressed from 4.4 cm to 3.3, 3.2, and 1.7 cm at 2, 4, and 6 months, respectively; in 2 of 14 (14%) there was no subjectively sufficient reduction of glandular tissue after 4 months |

*KEY: BID = twice a day; LHRH = luteinizing hormone-releasing hormone.*

variety of second-generation, more potent, and selective aromatase inhibitors (anastrozole, letrozole, vorozole) may also give good results but no studies have been published to date.

There may be, however, some concerns regarding the use of antiestrogens and aromatase inhibitors in prostate cancer. Although reducing estrogen levels or blocking the effects of estrogen may effectively prevent or treat gynecomastia, the consequences of such treatment are unknown. Indeed, such therapy could be expected to increase androgen secretion by blocking or decreasing the negative feedback of estradiol on the hypothalamic–pituitary axis. Therefore, clinical trials with careful endocrinologic and clinical follow-up of patients receiving hormonal therapy in combination with antiestrogens or aromatase inhibitors are necessary.

Although limited safety data are available on the use of tamoxifen in men with infertility problems and other male cancers, including advanced renal cell carcinoma and metastatic melanoma, no safety data are currently available on the use of tamoxifen or aromatase inhibitors in men with prostate cancer. Efficacy data for tamoxifen use in patients with gynecomastia following treatment for prostate cancer are limited to only 6 patients.[35]

A pilot study to investigate whether the combination of anastrozole or tamoxifen with bicalutamide raises concentrations of testosterone above an acceptable level is currently underway. If no such increases in testosterone concentration are seen, a further trial to compare the effects of bicalutamide plus placebo with bicalutamide plus either anastrozole or tamoxifen on the development of gynecomastia will be undertaken.

## TREATMENT EXPERIENCES

### *Dr. Peter Iversen*

I am increasingly using nonsteroidal antiandrogen monotherapy (bicalutamide 150 mg/day) in the treatment of prostate cancer in my clinic. Patients are routinely offered prophylactic irradiation of the breast, with a single 8-Gy dose. Adverse events are typically minimal, with only a temporary slight skin discoloration. In the absence of randomized data, it is my clinical impression that this regimen almost completely alleviates breast tenderness, and minimizes gynecomastia. However, some lipomastia, a change in fat distribution, may still occur. In our clinic, we have offered surgical treatment of gynecomastia to patients with prostate cancer only rarely in the past. A case study is presented here illustrating the management of such patients at our clinic.

*Case Study*. A 60-year-old male business executive had slight prostatism. He was otherwise healthy. He was physically and sexually active, with a wife 20 years his junior. His prostate-specific antigen (PSA) level was 48 ng/mL. Digital rectal examination showed a slightly indurated left lobe. Sextant biopsies showed Gleason 3+3 in four of six biopsies and a biopsy from the base of the left seminal vesicle showed evidence of carcinoma. A bone scan was normal.

The patient did not want a radical prostatectomy. Radiotherapy preceded by neoadjuvant endocrine therapy was discussed among possible treatment options. The patient, supported by his wife, opted for immediate endocrine therapy with bicalutamide 150 mg daily. An important aspect of this choice was the possibility of continued sexual activity.

The patient was informed thoroughly and, because of the risk for gynecomastia, he wished to have pretreatment irradiation. A total of 8 Gy was administered toward the breasts before the start of therapy.

The patient responded well to treatment and, after 16 months, the PSA level was still below 1 ng/mL. The patient developed slight gynecomastia (or lipomastia), which was reported and registered after 6 months, but there was no breast tenderness. The patient was capable of living a normal life professionally and privately, even though he complained about feeling more tired. This finding disappeared following 6 months of treatment. On the other hand, the patient reported increasing erectile dysfunction, although he was still capable of having intercourse. He claimed he had an unchanged libido.

Treatment with sildenafil 50 mg was started and was highly effective according to the patient, who was again satisfied with his sexual life.

Currently, after 16 months of treatment, the patient's only complaint is loss of body hair on the chest. Bicalutamide 150 mg is being continued.

### *Dr. David McLeod*

At the Walter Reed Army Medical Center we are treating more patients with hormonal therapy earlier in their disease, as opposed to the large number of Stage D2 patients we used to see routinely. A large part of my practice consists of patients with rising PSA levels following definitive treatment for clinically localized disease. Patients treated with an antiandrogen, either as monotherapy or in combination with the 5$\alpha$-reductase inhibitor finasteride, often spontaneously report gynecomastia and/or mammalgia (painful breast tissue) during follow-up visits. The incidence of gynecomastia is probably higher if patients are asked specifically about this condition. These symptoms can be very bothersome to men, particularly if they are physically active and being treated to combat rising PSA

levels and not for metastatic disease. As we are increasingly encountering gynecomastia and mammalgia in men being treated with antiandrogens alone, it has become routine practice to offer pretreatment/prophylactic radiation.

Varying regimens exist for the administration of this prophylactic radiation, but, in general, our standard treatment is 1200 cGy given in three fractions, although some of our radiation oncologists use 1500 cGy in three fractions. Treatments are given usually on three consecutive days to a 6 to 10-cm field centered on each nipple the week before starting hormonal therapy. For patients already on treatment, or for patients who did not initially elect for radiation therapy and subsequently changed their mind, the usual dose is 2000 cGy in five daily fractions (400 cGy/fraction). Mammalgia is usually palliated; however, gynecomastia is less likely to be alleviated after initiation of hormonal therapy. We caution these patients that pain relief may not be tangible for several months. These regimens are based on the work of Fass *et al.*[21] and Chou *et al.*[22] when diethylstilbestrol made up a large portion of the treatment of patients with metastatic prostate cancer.

We have had two patients who, having started on antiandrogen therapy, developed gynecomastia of such significance that the condition interfered with their physical fitness programs. In both patients liposuction achieved good results. Our plastic surgeons normally use liposuction alone for patients who have not had radiation therapy. Of three patients who needed a reduction of their gynecomastia despite post-treatment radiation, a periareolar incision was made and the lump of fatty tissue removed. Liposuction was then used on the surrounding nonradiated tissue to reduce and improve the contour of the breasts.

Thus, with increased awareness on our part, men who are treated with an antiandrogen therapy alone are now afforded the option of radiation therapy before initiation of treatment. In addition, in those patients who have problems following an antiandrogen treatment regimen, radiation therapy can be considered. Liposuction is also an option held in reserve.

## COMMENT

Although gynecomastia is a common side effect of treatment for prostate cancer, especially following estrogen or antiandrogen monotherapy, it is not well documented. Before initiation of hormonal therapy for any stage of prostate cancer, an examination of the breasts should be performed and any enlargement documented: the patient may have pre-existing gynecomastia due to another factor such as aging or excessive alcohol intake. In addition, the possible breast changes that may occur with treatment should be discussed with the patient.

Prophylactic radiotherapy has generally proved successful in the prevention of gynecomastia occurring as a result of estrogen treatment for prostate cancer and is, therefore, also likely to be effective in the prevention of gynecomastia resulting from antiandrogen treatment: clinical trials are ongoing to confirm the effectiveness of this approach. If a patient is reluctant to receive prophylactic radiotherapy, local removal by surgery of bothersome enlargement or painful breast tissue remains a valid option. Medical treatment with tamoxifen or an aromatase inhibitor may also alleviate these sequelae; however, at the present time these treatments are not indicated for gynecomastia or mammalgia. Further, there are a paucity of data available on the usage of these medical treatments, and there are no data on the potential impact of such treatments, if any, on hormonal therapies being used to treat prostate cancer.

In general, patients with advanced prostate cancer will tolerate the side effect of gynecomastia if there is a chance of slowing the disease process. However, wider use of monotherapy in the treatment of early disease is resulting in gynecomastia becoming more of a problem in younger patients, although such pharmacologic events rarely necessitate withdrawal of therapy. Quality of life issues, such as the maintenance of libido and sexual potency, which can be achieved with antiandrogen monotherapy, may be more important in this patient population than in an older patient population and may outweigh the disadvantage of increased gynecomastia. Hopefully, the more widespread use of antiandrogen monotherapy will encourage further research and, ultimately, guidelines for the prevention and treatment of gynecomastia in this setting.

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